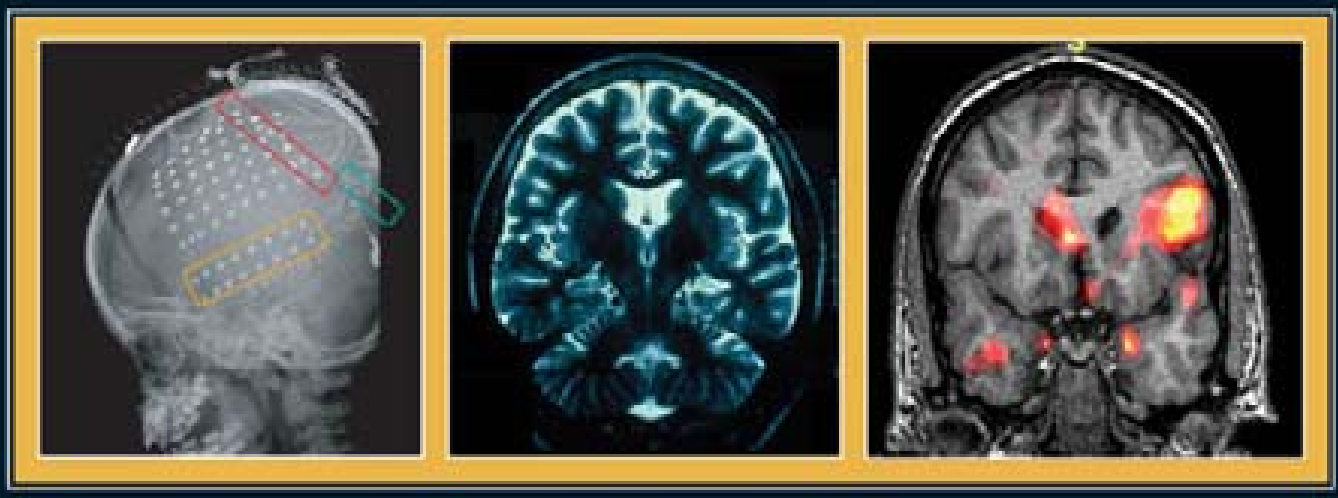

Epilepsy *and* Intensive Care Monitoring

BRUCE J. FISCH

PRINCIPLES AND PRACTICE

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EPILEPSY AND INTENSIVE CARE MONITORING

PRINCIPLES AND PRACTICE

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CONTENTS

PREFACE

Few diagnostic procedures demonstrate their usefulness over long periods of time under the scrutiny of repeated observation and continuing development of competing technologies. EEG is one such test, now over 80 years old. Epilepsy monitoring, now over 40 years old, is another. One of the main limitations to the broader implementation of monitoring is the need for practitioners with special expertise. This book is primarily intended to assist in the education of fellows in clinical neurophysiology and neurology residents, as well as neurologists involved in running or establishing monitoring programs. Because there are few single sources of information on this topic, this book is also likely to become a useful resource for everyone involved in this field, including fellowship and residency directors, adult and pediatric neurosurgeons, ICU physicians, epilepsy and ICU nurses, social workers, hospital and insurance administrators, and those involved in developing healthcare policy. To that end, I have been fortunate to have an outstanding group of authors, who have contributed to the advancement epilepsy care and ICU monitoring, join me in creating an authoritative reference. Essential guidelines, including those of the National Association of Epilepsy Centers and the American Clinical Neurophysiological Society, provide additional useful information that can be found in the appendixes.

Recent surveys indicate that although the benefits of monitoring are clear, monitoring is not available to the majority of patients in need. Moreover, the way in which monitoring is performed, including data analysis and basic safety precautions, varies widely between centers. This may seem surprising because video EEG monitoring is not a new procedure. As often noted by Dr. Robert Gumnit, presurgical epilepsy monitoring, in which a patient undergoes elective medication withdrawal, is one of the few situations in a hospital in which patients are knowingly chosen to be put in harm's way. Even in acute inpatient monitoring situations, the gathering of information carries significant administrative and healthcare responsibilities that are specific to the monitoring process. Although the contributing authors and I would not want this book to promote a consensus in areas that are still evolving, it is my hope that it will help hasten a uniform approach in areas of patient care that are well established as essential for diagnosis and patient safety.

As aptly noted by Michael Carey, an accomplished epilepsy neurosurgeon and a friend and colleague of mine, the life-changing effects of epilepsy surgery make it "the closest a neurosurgeon ever comes to being an obstetrician." EEG and video monitoring is well recognized as a key part of a profound, life-changing—as well as life-saving—process. Although initially intended to identify surgical cases, once introduced, monitoring unexpectedly defined a large population of patients with conditions that mimic medically resistant epilepsy, particularly involuntary psychogenic attacks. Monitoring now has a tremendous impact on such individuals, reducing iatrogenic injury, disability, direct medical cost and caregiver burden. The more recent introduction of video and EEG monitoring into the ICU setting has yet again revealed a similarly unexpectedly large population of individuals in need of treatment in whom frequent subclinical seizures impair consciousness and appear to contribute to secondary brain injury.

In the late 1980's, a clinical neurophysiology fellow at Columbia University, Douglas Labar (who subsequently went on to direct the epilepsy program at Cornell University), worked in my laboratory on a project to determine whether EEG could detect the onset of vasospasm. We combined simple FFT signal processing equipment developed by Richard Moberg (who is still very much involved in the field of ICU monitoring) with subsequent offline signal analysis. We were able to show that quantitative EEG analysis could be used to detect vasospasm following subarachnoid hemorrhage prior to clinical changes observed by neurological ICU nurses and physicians (Labar, Fisch, Pedley, et al, EEG Clin. Neurophysiol. 1991). This has subsequently been verified by others (see Chapter 23, Stroke and Subarachnoid Hemorrhage by Claassen and Hirsch) and helped initiate the latest application of monitoring, quantitative EEG trend analysis in the ICU.

In recognizing those who contributed to this book, I would like to give special thanks to all the chapter authors as well as to my academic mentors, who will always deserve my considerable gratitude. Sadly, during the writing of this book a singular figure in the field of neurology, and an outstanding mentor of mine and of many others, William E. DeMeyer, professor of pediatric neurology at Indiana University, died. I learned many things from him, including the neurological examination and neuroanatomy. But,

above all, he taught rigorous precision of thought in neuroscience, which I have tried to pass on to medical students and residents throughout my career, and which I hope is reflected here. This book was also greatly influenced by my mentors in clinical neurophysiology and epilepsy, a remarkable group of academic leaders who include Donald Klass, Barbara Westmoreland, and Frank Sharbrough at the Mayo Clinic and Timothy Pedley at the Neurological Institute of Columbia University College of Physicians and Surgeons.

I began working on this book around the time of Hurricane Katrina, a disaster that had terrible consequences for the people of the Central Gulf South and for the identity of all Americans. It shattered the infrastructure of my New Orleans medical community. Because of this event the development of this book will always have a special meaning for me, and so I am particularly grateful to all the contributing authors who joined in this effort without hesitation. I began working on it with a very patient and dedicated editor, Craig Percy, who eventually left Demos but who continued to check with me on the book's progress. I remain grateful for his support. Subsequently, I worked with an efficient team at Demos that included Beth Barry, Richard Johnson, Kelly Applegate, and Katy Thompson. As a result of the efforts of all involved, I believe this book will be useful to readers of all levels of expertise, and I hope it will assist them in expanding the practice of monitoring.

Bruce J. Fisch

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EPILEPSY AND INTENSIVE CARE MONITORING

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SECTION

I

EPILEPSY AND INTENSIVE CARE MONITORING: INDICATIONS, PROCEDURES, AND ADMINISTRATION

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PATIENT EVALUATION AND SELECTION FOR ROUTINE AND INVASIVE EPILEPSY MONITORING

KATHERINE H. NOE
GREGORY D. CASCINO

Prolonged video electroencephalography (vEEG) is a method of recording simultaneous clinical behavior and electrographic activity, either from routine scalp or intracranial electrodes. Used correctly, it is an invaluable tool in the diagnosis and management of epilepsy. Long-term EEG recordings are resource-intensive and carry potential risk; therefore, careful selection of appropriate candidates is a critical component of success. Inpatient epilepsy monitoring has traditionally been performed almost exclusively under the purview of tertiary epilepsy surgery programs. Improvements in the technology and costs in recent years, however, have enabled vEEG to be used increasingly in community hospital settings for diagnostic purposes. In order for this greater availability of vEEG to best serve patients, it is important to formally examine the indications for monitoring and selection of candidates.

NON-INVASIVE INPATIENT VIDEO EEG MONITORING

Long-term video EEG monitoring offers significant benefits over routine EEG recordings. First, a prime advantage is the ability to record seizures, a task that can only rarely be managed during routine EEG recordings. Recording a full night of sleep activity can allow the detection of nocturnal interictal activity and of events that would be almost impossible to capture on a routine EEG study. Second, patients can be examined during their typical clinical event. This gives the opportunity not only for assessment of the physical examination, but also for recording of additional physiological parameters of interest using methods such as cardiac telemetry, blood pressure measurements, or pulse oximetry. When indicated, ictal laboratory studies or imaging tests can be obtained. Third, vEEG allows repeated reviewing of events, including subtle behaviors that can easily be missed even by an experienced observer witnessing a seizure "live." Such careful study of seizure semiology is important both for accurate diagnosis of spells and for localization of seizure onset. Fourth, vEEG offers the ability to monitor and/or alter antiepileptic drug therapy. Tapering or withdrawal of antiepileptic medication is helpful in increasing the frequency of recorded seizures, resulting in a decreased duration of admission (1). Extended recording time and antiepileptic drug reduction also increase the yield of observing interictal epileptiform activity. Finally, the prolonged interaction of the clinical staff with the patient and his or her family is beneficial. Longer observation periods often allow identification of psychosocial issues that were missed or suppressed in the outpatient setting.

There are concerns regarding the use of vEEG monitoring that also need to be considered. A significant issue is the expense related to the resources and time needed. An epilepsy monitoring unit requires a specialized team of epileptologists, nursing staff, and experienced EEG technicians who are able to provide care around the clock. The average length of stay is 4 to 7 days, but can continue for up to several weeks if indicated (2,3,1). Efforts to record seizures in a timely fashion may inadvertently lead to unusually severe seizures, seizure clusters, or status epilepticus, with the potential for seizure-related injury and postictal psychosis. In a review of 514 epilepsy monitoring unit admissions to five epilepsy centers, a cluster of three or more complex partial and/or secondary generalized seizures in a four-hour period occurred in 17.8% of admissions, and status epilepticus occurred in 3% (4).

Despite the potential concerns discussed above, when used appropriately vEEG provides invaluable information for patient management. In representative reports from tertiary epilepsy referral centers, useful diagnostic information is obtained in about 75% of all admissions (5,6,7,8). Extended vEEG leads to a change in diagnosis in close to

60% of epilepsy monitoring unit admissions and a change in medical management in about 75% (3). Failure to make a diagnosis usually reflects failure to capture a typical event. Before selecting a case for admission, one must consider the likelihood of recording an event during a routine 5- to 7-day stay. Provocative maneuvers, including medication tapering or withdrawal and sleep deprivation, are commonly used to increase the chance of capturing clinical events. Using such techniques as necessary, the average time to the first recorded seizure is 2 days (4). For patients with highly specific seizure triggers or events that only occur in distinct settings, it is necessary to consider whether the triggering environmental situation can be recreated within the confines of the epilepsy monitoring unit. In some instances, the increased yield for interictal epileptiform abnormalities may be sufficient to increase the certainty of a diagnosis of seizure or of seizure type, even in the absence of a recorded event.

Common Indications for Routine Video EEG Monitoring

The two most common indications for vEEG monitoring are (a) a diagnostic evaluation to determine the nature of a seizure or seizure-like spell, and (b) a presurgical evaluation for medically refractory epilepsy (Table 1-1).

Diagnostic Classification

A history of recurrent, stereotyped spells may suggest a diagnosis of epilepsy; however, many physiological and psychiatric events can be confused with epileptic seizures (Tables 1-2 and 1-3 and Chapters 11, 12, and 13). Accurate diagnosis is important for many reasons, including initiation of appropriate treatment and discontinuation of unnecessary antiepileptic drugs. Recurrent unclassified spells can have a high health care cost, with repeat emergency room visits and hospital admissions—an unnecessary use of medical resources that could be avoided with accurate diagnosis. A definite diagnosis helps to minimize the social, psychiatric, and financial burden that continued spells place on the patient and his or her family. In many cases, a careful history and physical examination, head magnetic resonance imaging (MRI), and routine EEG will allow accurate diagnosis of epilepsy with reasonable certainty. However, when the diagnosis remains uncertain, vEEG monitoring should be strongly considered, particularly if a medication trial has been unsuccessful.

Inpatient video EEG monitoring is of high yield for event classification. In a retrospective review of 274 patients admitted for inpatient vEEG monitoring at Mayo Clinic in Rochester, Minnesota, between 1993 and 1997 for recurrent, unclassified spells, 55% of patients were diagnosed with psychogenic nonepileptic seizures (PNES), 36% with epileptic seizures, and 5.5% with a combination of epileptic seizures and PNES (9). A physiological cause other than epilepsy was established in a small minority at 3.4%. A similar review of 137 adult patients admitted for vEEG monitoring at Mayo Clinic in Arizona in 2006 for the same indication established

TABLE 1-1. COMMON INDICATIONS FOR VIDEO EEG MONITORING

1. Diagnostic evaluation
   a. Determine etiology of recurrent spells
   b. Classify epilepsy type or syndrome
   c. Evaluate seizure precipitants
2. Medication adjustment
3. Quantification of seizure frequency
4. Presurgical evaluation for medically refractory epilepsy

TABLE 1-2. PHYSIOLOGICAL NONEPILEPTIC EVENTS THAT MAY MIMIC EPILEPTIC SEIZURES

1. Cardiac
   a. Vasovagal syncope
   b. Cardiac arrhythmia
   c. Orthostatic hypotension
2. Toxic/Metabolic
   a. Hypo- or hyperglycemia
   b. Drug intoxication
3. Pulmonary
   a. Hyperventilation
   b. Sleep apnea
4. Movement disorders
5. Migraine headache
6. Cerebrovascular disease (transient ischemic attack)
7. Autonomic disorders
8. Sleep disorders
   a. Narcolepsy/cataplexy
   b. REM sleep disorders
9. Vestibular dysfunction
10. Transient global amnesia

TABLE 1-3. PSYCHIATRIC EVENTS THAT MAY MIMIC EPILEPTIC SEIZURES

1. Psychogenic nonepileptic seizures (conversion or somatoform disorder)
2. Malingering
3. Catatonia
4. Panic attack
5. Hallucinations/psychosis
6. Episodic dyscontrol
7. Fugue states
8. Munchausen syndrome/Munchausen syndrome by proxy

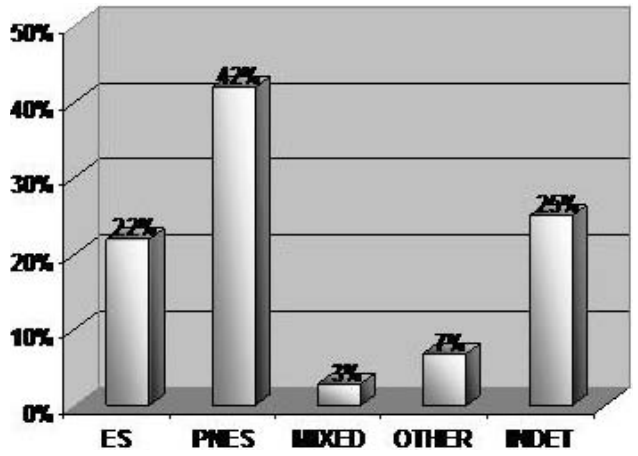

FIGURE 1-1. Discharge diagnosis after long-term video EEG monitoring for spell classification, Mayo Clinic Arizona, 2006. Among 137 adult patients admitted for evaluation of spells that remained of indeterminate etiology following outpatient workup, vEEG monitoring made the diagnosis of epilepsy seizure (ES) in 22%, psychogenic nonepileptic seizure (PNES) in 42%, and mixed epileptic and nonepileptic seizures (MIXED) in 3%. 7% of patients were found to have a physiological cause for the events other than epilepsy (OTHER). In 25%, the etiology of the spells remained indeterminate (INDET). For outcomes related to a mixed pediatric and adult population please refer to the text.

a diagnosis of PNES in 42%, epilepsy in 22%, and a mixture of these in 3% (Figure 1-1; previously unpublished data). A further 7% had physiological events other than epilepsy, including transient ischemic attack, movement disorder, sleep disorder, cardiac arrhythmia, symptomatic hypertension, hypoglycemia, and migraine. A quarter of those admitted for spell classification were discharged without a definite diagnosis, primarily because of failure to capture a typical event. These two series show a remarkable similarity in diagnostic results both over time and between centers.

In comparison, in a retrospective review of 941 monitoring cases that included approximately equal numbers of pediatric and adult patients (University of New Mexico, editor, personal communication) from admissions between 2000 and 2007, admitted for recurrent, unclassified spells, a diagnosis of PNES was established in 15.5%, epilepsy in 30.72%, and both PNES and epilepsy in approximately 1%. A further 5% had events with other diagnoses, 25% had no events recorded and another 14% were discharged without a definitive diagnosis. As in the two series from Mayo Clinic centers, about one-fourth of patients did not have events during recording. A relatively smaller percentage of patients had PNES due to fewer cases occurring in the pediatric population (patients 19 years and younger).

Psychogenic Nonepileptic Seizures

Prolonged video EEG monitoring is the "gold standard" for diagnosis of psychogenic nonepileptic seizures (PNES) (10,11,12). PNES are thought to be highly underdiagnosed. The estimated prevalence is 1.5 per 100,000 in the general population, with all age groups affected based on a study performed in Iceland by Sigurdardottir and colleagues (13). In a more recent EMU based study in North America (University of New Mexico), PNES prevalence rates were estimated to be approximately 22.5/100,000. Although certain clinical and historical features may suggest PNES, no one of these is diagnostic, making accurate diagnosis in the absence of confirmatory vEEG difficult. Twenty percent of cases referred to tertiary epilepsy centers for medically refractory seizures, and 50% referred for vagus nerve stimulator placement, were determined to have PNES (14,8). Although the clinical history and outpatient testing may suggest the diagnosis, even experienced epileptologists have been shown to misdiagnose PNES as epileptic seizures as often as 20% of the time based on confirmatory vEEG evaluation (15). Conversely, epileptic seizures, particularly those arising in the frontal lobe, can also be misclassified as PNES. In one study, 22% of patients referred for vEEG confirmation of suspected PNES were found to have epilepsy or physiological nonepileptic events (16). Misinterpretation of routine interictal EEG studies may contribute substantially to misclassification of epilepsy and PNES (17). Comorbidity of epileptic seizures and PNES in an individual is a potential concern, and where both diagnoses are confirmed by vEEG the rate is reported in the range of 5% to 20% (18,19,20,21).

Confirmation of PNES using vEEG can be an invaluable tool to help patients accept their new diagnosis, and leads to improved outcomes. Sadly, the average delay to correct diagnosis is 7 to 8 years (22,23). Prior to diagnosis, repeated ER visits for acute treatment of seizures are seen, and even "pseudostatus" is not uncommon, leading to unnecessary interventions such as intubation and intensive care unit admission with the potential for significant morbidity (24,25). The disability from ongoing PNES, including the impact on working and driving, is similar to that from refractory epilepsy (26). Excellent outcomes can be achieved after vEEG diagnosis, however. Walczak et al. reported that a year or more after admission to an epilepsy monitoring unit, 35% of patients had full resolution of events, 41% had a greater than 80% reduction in spell frequency, and 72% reported improved functioning (27). In addition, a dramatic (84%) reduction in related medical costs has been described in comparisons of the 6 months before vEEG-confirmed diagnosis with the 6 months after (28).

Seizure Quantification

There are selected instances in which epilepsy monitoring unit admission for quantification of seizure activity can be beneficial. Lack of an accurate seizure count may complicate the therapeutic decision-making process. While most

patients or their caregivers are able to accurately recognize and report seizures, this task may be difficult when seizures are extremely frequent or clinically subtle. Further challenges may arise when patients are cognitively impaired or are amnestic for their events, particularly in the absence of a reliable eyewitness. In patients with an established seizure disorder, the presence of an unexplained alteration of cognitive or behavioral status or a report of frequently disrupted sleep may raise concern that unrecognized seizure or interictal epileptiform activity is the etiological factor. A short vEEG study may be all that is required in order to resolve this clinical question.

Classification of Seizure Type or Epilepsy Syndrome

Misclassification of epilepsy as partial rather than generalized may result in an inappropriate choice of anticonvulsant medication, making patients falsely appear to be refractory to medication. Accurate categorization of seizure type will also help determine the potential for surgical intervention. The interictal EEG may be misleading, leading to a false conclusion of generalized seizures if secondary bilateral synchrony is present, or to the mistaken impression of focal seizures if lateralized fragments of otherwise generalized epileptiform patterns are recorded.

In one review, vEEG monitoring resulted in a change in diagnosis from a partial to generalized epilepsy syndrome in 5% of admissions (3). Prolonged EEG can also be appropriate if there is uncertainty as to whether a patient's typical event is a simple or complex partial seizure. Determination of the presence of loss of awareness during seizures will have important repercussions for working and driving, and may affect therapeutic management decisions. Finally, certain epilepsy syndromes are defined in part by extended EEG findings, particularly during sleep. Examples include Landau-Kleffner syndrome and electrical status epilepticus in sleep (ESES), in which case an overnight sleep recording should demonstrate continuous spike and wave discharges in at least 85% of the record.

Medication Adjustment

Changes in antiepileptic drugs can usually be safely managed on an outpatient basis. However, there are specific clinical situations in which vEEG during medication changeover may be considered. One of the most common indications is for persons with a history of status epilepticus during a prior medication change. The development of a serious adverse drug reaction may necessitate an unusually rapid medication adjustment, and may justify monitoring, particularly in patients with a history of seizures that were difficult to control. Finally, on some occasions it is helpful to assess the effect of acute medical treatments on interictal EEG activity or on frequent clinical seizures.

Evaluation for Epilepsy Surgery

Epilepsy surgery is a potential therapeutic option for patients who have failed to achieve adequate seizure control after a reasonable trial of medication. Among epilepsy patients, 30% to 40% have seizures that are refractory to medical management (29). The burden of uncontrolled seizures includes increased mortality, greater adverse side effects of medication, potential cognitive decline, and impairment of psychosocial functioning adversely affecting mood, interpersonal relationships, and employment (30). Therefore, there is increasing recognition of the importance of early recognition of, and intervention for, medically refractory disease. There are no universally accepted criteria by which refractory epilepsy is defined. However, in a prospective study of 470 adolescents and adults followed from the time of epilepsy diagnosis, only 11% of those who failed to achieve seizure freedom with the first anticonvulsant became seizure-free with subsequent drug trials (29). Based largely on this information, it is generally recommended that persons with epilepsy with partial seizures who have failed trials of two appropriate antiepileptic drugs because of lack of efficacy (not tolerance) should be considered for surgical evaluation. Seizures must be of a severity and frequency that adversely affect quality of life. At a minimum, seizures are considered disabling if the ictal or postictal effects interrupt the patient from being able to perform needed activities or if the ictal events are obvious to others. There is not a firm age restriction for epilepsy surgery, with outcomes in children and selected elderly patients similar to those in other adults (31). Major medical comorbidity and progressive degenerative neurological conditions are generally contraindications to epilepsy surgery. Surgery in individuals with severe psychiatric disorders is often avoided because of potential complications that can include self-inflicted injury, difficulty cooperating with the presurgical evaluation, poor medication compliance, and difficulty in determining seizure frequency.

The goals of a noninvasive presurgical evaluation are to (a) confirm the diagnosis of epilepsy, (b) identify the area of the brain that must be removed to achieve seizure freedom, and (c) determine whether such a resection can be performed without undue morbidity. For patients with medically refractory partial epilepsy, vEEG recording of interictal and ictal activity is an essential component of localization of the epileptogenic zone. Localizing information gleaned from careful review of seizure semiology is extremely important. It is necessary to determine whether seizures arise from more than one brain location or whether there is the rare coexistence of primary generalized and partial seizures. The results from vEEG must be carefully analyzed relative to localizing information obtained from the clinical history and examination, neuropsychological evaluation, and head MRI imaging. Additional testing may include magnetoencephalography or functional imaging

with fMRI, positron emission spectroscopy (PET), single photon emission computed tomography (SPECT), or subtraction ictal SPECT coregistered to MRI (SISCOM).

Surgical outcome is dependent on a complete resection of the epileptogenic zone. Potentially curative procedures include lesionectomy, focal cortical resection, and lobectomy. There is clear evidence that for intractable mesial temporal lobe epilepsy, anterior temporal lobectomy results in greater seizure freedom and improved quality of life compared to continued medication trials (32,33). In a pooled analysis of previously published surgical series, 65% of patients were seizure-free after this procedure at 1 and 5 years, and another 20% had improved seizure control (33,34). For patients with neocortical epilepsy, seizure-free rates after focal cortical resections are 50% overall, with better outcomes in cases where the MRI demonstrates a clear lesion (33). For patients where resective surgery is not a reasonable option, whether because of the involvement of eloquent cortex, the extent of involved tissues, or the underlying epilepsy syndrome, palliative procedures such as multiple subpial transaction, hemispherectomy, corpus callosotomy, or vagus nerve stimulation are potential options.

In some instances, noninvasive presurgical evaluation may provide sufficient localization for surgical resection. This is most often the case in patients with a clearly identified epileptogenic lesion seen on MRI, such as unilateral mesial temporal sclerosis, with concordant localizing findings from the rest of the presurgical evaluation and localization away from eloquent cortical regions (35,36,37,38). For other patients, concordant findings from these studies will be used to identify a potential target for intracranial EEG monitoring.

INVASIVE EEG MONITORING

Invasive EEG monitoring with intracranial electrodes is indicated when the noninvasive presurgical evaluation does not adequately localize seizure onset or when necessary to carefully define cortical function in an area of planned surgical resection (Table 1-4). Compared to scalp recording, implanted electrodes have the advantage of improved signal-to-noise ratio, increased sensitivity, and improved spatial resolution (39). Invasive electrodes can also be used for stimulation studies in mapping cortical function. For lesional cases, intracranial recording may be used to tailor the extent of a cortical resection or to map local eloquent cortex. For nonlesional cases, the site of implantation is determined by results from the noninvasive testing often guided by EEG, behavioral semiology and MEG. SISCOM abnormalities may also serve as a target, particularly in nonlesional extratemporal cases, and have been shown to correlate with surgical outcome (40). Monitoring can be continued for up to several weeks in order to allow recording of both interictal and ictal activity. There are potential risks, including infection, hemorrhage, and cerebral edema, that may result in either transient or permanent neurological deficit. In addition, intracranial recording provides only a limited assessment of cerebral electrographic activity restricted to the focal area of electrode coverage. If the implantation is remote from the true epileptogenic zone, the area of ictal onset may be missed or falsely localized because of propagation from regions beyond the recording electrodes. The implantation strategy, therefore, must be carefully considered.

TABLE 1-4. COMMON INDICATIONS FOR INVASIVE INTRACRANIAL EEG MONITORING

1. Lateralization of seizure onset when non-invasive presurgical evaluation suggests possible bilateral mesial temporal onset
2. Localization of seizure onset when head MRI is non-lesional
3. Localization of seizure onset when head MRI shows more than one lesion
4. Localization of seizure onset when results of non-invasive presurgical evaluations are inadequate or contradictory
5. Discrimination of mesial versus neocortical temporal onset
6. Identification of eloquent cortical regions that should not be resected
7. Refinement of limits of epileptogenic zone to allow tailoring of a focal cortical resection

Choice of Invasive Recording Electrode

Implantation strategy involves determination not only of where to implant electrodes, but also of what to implant. Commonly used invasive recording devices include depth, strip, and grid electrodes, used alone or in combination. Intracranial electrodes are placed with the patient under general anesthesia, either via a burr hole (depth or strip) or craniotomy (strip or grid). Placement with stereotactic guidance is helpful when there is a specific anatomic or functional target defined by MRI or SISCOM. Serious potential complications of intracranial electrode placement include hemorrhage and infection. With grid and strip implantation, cerebral edema with increased intracranial pressure can also occur. Reported serious complication rates for depth electrodes alone range from 2% to 4% (41,42). In a series of reports, complication rates for patients implanted with grids and strips but without depth electrodes range from 2.5% to 19% (43,44,45,46). Complication rates for subdural grids or strips are increased with implantation of large numbers of electrodes, with longer periods of monitoring (>10–14 days), and in older patients (45,46). Several published series have demonstrated a trend toward decreased complication rates over time, suggesting a role for both improved technology (e.g., MRI guidance of depth

electrode placement) and operator experience in optimizing outcomes (46,44,41).

Depth electrodes are often used for lateralization of seizure onset in cases where bilateral mesial temporal onset is of concern. They can also be placed into areas of deep malformations of cortical development, such as a subependymal nodular heterotopia. Grid electrodes have the advantage of providing large areas of neocortical coverage; however, size generally restricts their use to the lateral hemispheric convexities. Strip electrodes can be placed into less easily accessible regions such as intrahemispheric, inferior frontal, or inferior temporal areas.

In some instances, "semi-invasive" foramen ovale electrodes or epidural PEG electrodes may be used. Foramen ovale electrodes can be placed, with the patient under local or general anesthesia, into the subarachnoid space to facilitate recording of activity from mesial basal temporal lobe structures (47,48). They have been used at select centers for the presurgical evaluation of patients with temporal lobe epilepsy, particularly in the presence of unilateral mesial temporal sclerosis, and primarily when scalp recording is not lateralizing or shows independent bitemporal onset (48,49). The goal, then, is to confirm true unilateral localization via improved sensitivity as in depth electrode recording, but with a potentially lower risk of morbidity. Epidural electrodes are inserted via burr hole, and are occasionally used as a means of refining localization in cases where ictal scalp EEG monitoring is nonlateralized or poorly localized in an effort to refine subsequent subdural or depth electrode implantation (50). The method of implantation essentially limits the use of epidural electrodes to regions other than the inferior frontotemporal and intrahemispheric structures.

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2

CONTINUOUS EEG IN THE INTENSIVE CARE UNIT: INDICATIONS AND PROCEDURES

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LAWRENCE J. HIRSCH

It is now possible and practical to continuously record patients' cerebral function. Just as critically ill patients receive continuous monitoring of cardiac function via telemetry, recent technological advances allow for continuous monitoring (or at least recording) of brain function with EEG. Continuous EEG monitoring (cEEG) has been shown to capture significantly more seizures and clinical events than would be captured using routine EEG studies (1,2). The implications of these advancements with cEEG are still being realized. However, it is already well known that the early diagnosis and treatment of nonconvulsive status epilepticus improves outcomes, and cEEG in critically ill patients is a vital tool in diagnosing nonconvulsive status epilepticus and nonconvulsive seizures (2–4).

The cellular mechanisms of neuronal damage associated with status epilepticus (SE)—as well as the metabolic and neurological consequences of these damaging events—have been well demonstrated, particularly in animals. For more than a decade it has been known that convulsive SE mediates neuronal damage via excitotoxic mechanisms (5). More recently, an animal model also showed lasting behavioral and morphological sequelae of nonconvulsive SE (6). The relationship between complex partial SE in humans and significant neurological morbidity and mortality has been demonstrated in several case reports (3,7–9). Associated radiographic findings have been reported, including an increased temporal lobe T2 signal and cortical laminar necrosis in the settings of partial SE and complex partial SE, respectively (10,11). Finally, in human subjects with seizures, increased intracranial pressure, elevated cerebrospinal fluid (CSF) levels of the excitatory amino acid glutamate, and increased serum and CSF neuron-specific enolase (a marker of acute neuronal injury) have been described as markers of seizure activity (12–15). This advancing awareness of the deleterious effects of untreated seizures, particularly in the acutely injured brain, has highlighted the urgent need to determine effective methods to detect and treat seizures—that is, to develop cEEG programs.

The most common indication for initiating cEEG is for the detection of nonconvulsive seizures or nonconvulsive SE. Other possible indications include the characterization of spells in intensive care unit (ICU) patients, the assessment of a patient's level of sedation, the management of burst-suppression in anesthetic coma, prognostication, and the detection of cerebral events such as ischemia or hemorrhage (see Table 2-1). Twenty-four hours is generally a sufficient duration of cEEG monitoring to screen for seizure detection in noncomatose patients, whereas 48 hours or longer may be necessary for comatose patients (2).

The rise of ICU EEG monitoring has brought about new challenges regarding the need for 24-hour hookup availability, as well as an increasing demand for timely interpretation of the large volumes of EEG and video data that are generated. A variety of customized, scaled-down, and "screening" montages have been used, and new types of electrodes allow for rapid hookups and reduced unmonitored time during imaging studies. Food and Drug Administration–approved, magnetic resonance imaging (MRI)–compatible EEG electrodes are now available. These allow for imaging in critically ill patients without prolonged interruption of cEEG monitoring and without the need for an additional time-consuming repeat application of electrodes. Continuing developments in contemporaneous data modalities, including text data-entry, video and audio monitoring, brain oxygen monitors, specific biomarkers, and cerebral microdialysis, are allowing increasingly sophisticated multimodal brain monitoring. Future directions in cEEG will likely include

* Lewis L. Kull is now deceased.

TABLE 2-1. SUMMARY OF POSSIBLE INDICATIONS FOR cEEG Specific indications for initiation of cEEG in ICU settings, including correlating clinical scenarios.

Indication	Clinical Description
Detection of subclinical seizures	Fluctuating mental status Unexplained alteration of mental status Ocular movement abnormalities Persisting altered mental status after convulsive Sepsis-associated encephalopathy status epilepticus
Characterization of spells	Paroxysmal clinical events (posturing, rigidity, tremors, chewing, agitation) Unprovoked changes in blood pressure or heart rate
Assessment of level of sedation and following trends	For patients requiring paralytics Detection and trending of focal EEG findings caused by neurological or general medical conditions
Management of burst suppression in anesthetic coma	Titration of medication doses for elevated intracranial pressure or for treatment of refractory status epilepticus
Detection of ischemia	Detection early, reversible ischemia in patients with cerebral infarction, transient ischemic attack, or subarachnoid hemorrhage During and after vascular neurosurgical or interventional neuroradiological procedures In patients with hemodynamic lesions and borderline flow
Detection of other acute events	Hypoxia, elevated intracranial pressure (including hydrocephalus, hemorrhage, etc.)
Prognostication	In patients with poor-grade subarachnoid hemorrhage After status epilepticus or nonconvulsive seizures

automated real-time detection systems and true continuous neurotelemetry akin to cardiac telemetry, allowing immediate therapeutic neurological interventions and continued improvement in care of the brains of hospitalized patients.

INDICATIONS FOR INITIATION OF CONTINUOUS EEG MONITORING

Detection of Subclinical Seizures

There are an increasing number of reasons to perform cEEG monitoring in the ICU. The most common reason is to detect nonconvulsive seizures or nonconvulsive status epilepticus. The frequency of electrographic seizures in ICU patients with acute neurological conditions has been reported as between 19% and 50% (1,2,16–18). Findings suggestive of subclinical seizures include fluctuating or unexplained alteration of mental status, as well as ocular movement abnormalities, including hippus, nystagmoid eye jerks, repeated blinking, and persistent eye deviation. One study showed a combined sensitivity of 100% for patients with either eye-movement abnormalities or remote risk factors for seizures (19).

Continuous EEG monitoring is also crucial in patients after convulsive status epilepticus (20). In one study, cEEG after clinical control of convulsive SE revealed that 14% of patients were actually experiencing nonconvulsive SE, and 48% of patients had persistent but intermittent electrographic seizures (18). Furthermore, another study showed that the majority of children with nonconvulsive SE had preceding seizures in the acute setting, most of which were brief convulsions as opposed to convulsive SE (21). (Also, see Figures 2-1 and 2-2 for an example of this). Therefore, in practice, every patient with convulsive SE or a single convulsion who does not rapidly return to baseline should be monitored with cEEG.

Characterization of Spells

Continuous EEG monitoring is also used to help characterize spells in ICU patients. Suspicious types of paroxysms include sudden posturing, rigidity, tremors, chewing, agitation, and unprovoked sudden changes in blood pressure or heart rate. In these cases there is a risk associated with empirically starting antiepileptic medications, as they bear risks both to the patient directly and in terms of their numerous medication interactions. Neuronal damage can

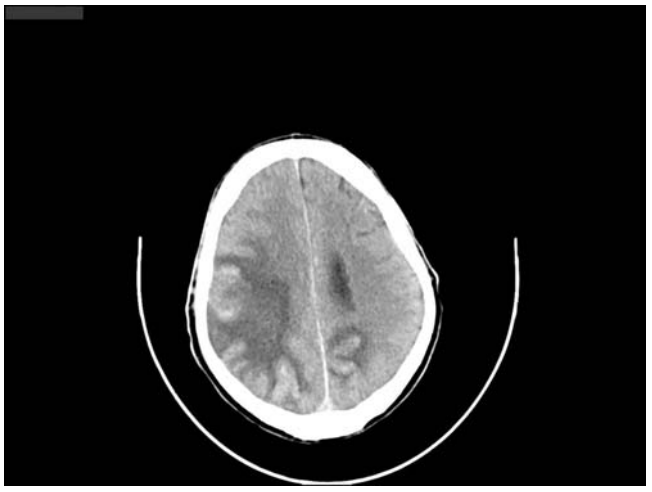

FIGURE 2-1. Poststroke nonconvulsive status epilepticus after an isolated convulsive seizure. Axial head CT showing bilateral hemorrhagic infarcts, much larger on the right *(left side of figure),* in a 67-year-old man with hypertension and atrial fibrillation who presented with dizziness, left hemiparesis, and lethargy. By day 14 of his hospital stay he developed pneumonia, renal insufficiency, and a deep vein thrombosis and had a witnessed isolated convulsion followed by continued impaired mental status and leg twitching. He was given 4 mg of lorazepam and loaded with fosphenytoin 18 mg/kg (20) (continued in Figure 2.2).

occur in patients with untreated seizures, again indicating the need for a thorough assessment of suspicious spells with cEEG. (For further discussion, see Chapter 18, Events that Mimic Seizures during ICU Monitoring).

Assessment of Level of Sedation and Detection of Cerebral Events

In patients who are somnolent or comatose, cEEG can be helpful for assessing the level of sedation and for detecting trends, particularly in patients requiring paralytics in whom the exam cannot be used for this purpose. Similarly, quantitative EEG (QEEG) analysis can detect gradually evolving background changes, which may not be easily identified when reviewing the raw EEG data (see Figure 2-3) (22). For example, increasing slower waveforms, with loss of faster frequency activity or gradual loss of total power, can indicate a dangerous acute or subacute neurological event—such as ischemia or rising intracranial pressure—or a systemic issue such as acidosis. In one recent case, potentially lethal hydrocephalus caused by lumbar drain failure was diagnosed early, and successfully reversed, because of electroencephalographer recognition of progressive diffuse attenuation and loss of reactivity on cEEG monitoring. Likewise, increased slowing was detected on cEEG of another patient, prompting emergent clinical evaluation that revealed respiratory failure with significant acidosis (Figure 2-4).

For patients in anesthetic coma, cEEG is instrumental in both monitoring and managing burst suppression. When

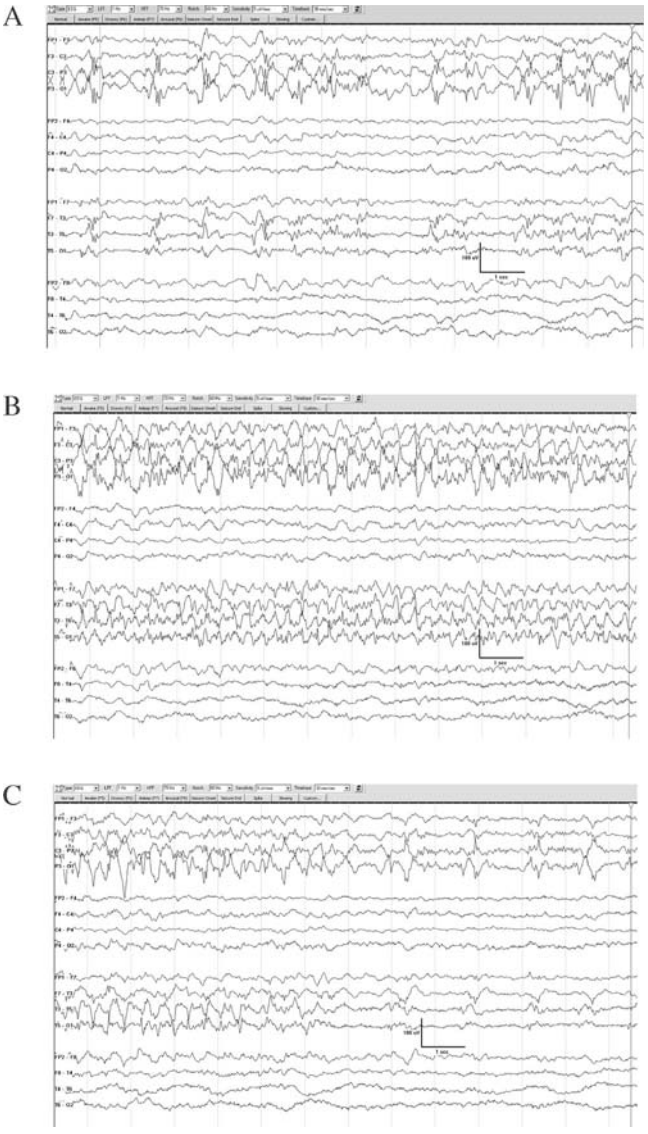

FIGURE 2-2. Detection of nonconvulsive seizures. Urgent EEG in the patient from Figure 2-1 showed nearly continuous seizures from the left posterior quadrant, lasting up to 4 minutes each with only a minute between seizures. There was no clinical correlate to any of these seizures, and thus EEG monitoring played an important role in following his nonconvulsive seizures. (A) Start of typical seizure from left posterior quadrant. (B) Middle of seizure, almost 2 minutes after first EEG, now involving entire left hemisphere. (C) End of seizure, 1 minute after second EEG. After seizure offset, EEG activity shows periodic lateralized epileptiform discharges recurring at just under 1 per second, also maximal in the left posterior quadrant (20).

pentobarbital is used to manage increased intracranial pressure in traumatic brain injury patients, cEEG is a key tool to help monitor the depth of sedation. However, high pentobarbital doses can result in cardiovascular depression; an animal study has demonstrated that further increases in pentobarbital after reaching suppression-burst do not result in further decreases in cerebral metabolic rate, but instead cause cardiovascular depression (23).

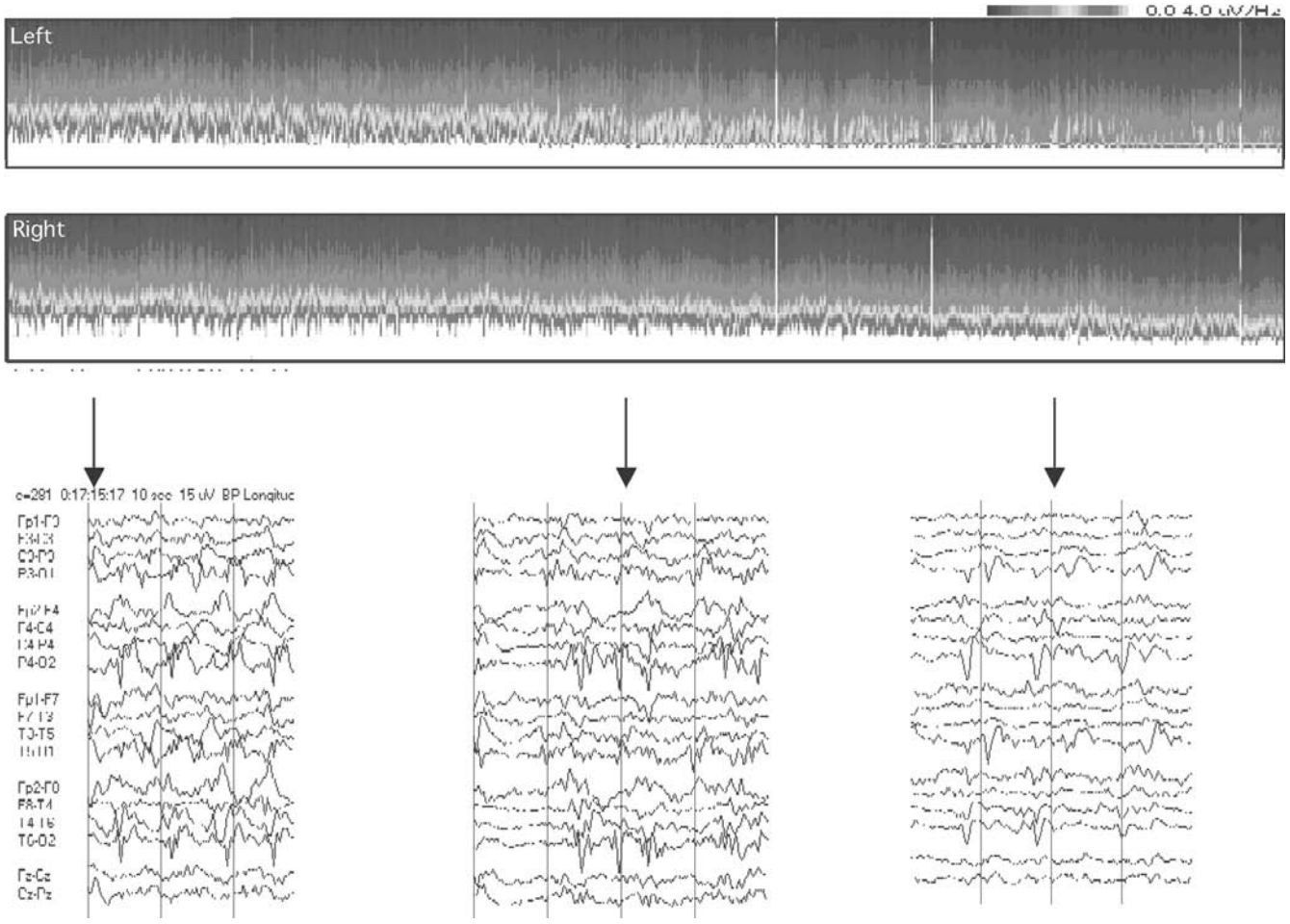

FIGURE 2-3. Resolution of nonconvulsive status epilepticus shown on compressed spectral array (CSA). CSA showing gradual resolution of nonconvulsive status epilepticus over 11 hours. CSA is particularly useful for recognition of such long-term trends. Arrows indicate approximate time periods in the CSA from which the EEG samples were taken. Y-axis: frequency, 0 Hz at bottom, 60 Hz at top. X-axis: time (approximately 11 hours shown). Gray scale (z-axis, typically displayed in color) power of given frequency (scale in upper right; microvolts/Hz) (22). (*See color insert*).

Detection of Ischemia

Continuous EEG monitoring is also useful for the detection of ischemia, and conveys the ability to detect early reversible ischemia in at-risk patients. Prominent EEG abnormalities arise when the cerebral blood flow drops from normal levels of 50–70 mL/100 g/min to 25–30 mL/100 g/min (24). However, cell death does not occur until cerebral blood flow declines below 10–12 mL/100 g/min, when an isoelectric EEG is noted. cEEG has long been used during and after cardiac, neurosurgical, and interventional neuroradiological procedures to detect ischemia, particularly during carotid endarterectomy. Quantitative EEG (QEEG) tools, such as the brain symmetry index (25), have also improved ischemia detection in hemispheric stroke patients, and these may be useful for following patients with hemodynamic lesions and borderline flow. QEEG has also been shown to be effective in detecting the development of vasospasm after aneurismal subarachnoid hemorrhage (26). More recently, Claassen and colleagues (27) found that a specified reduction in the alpha/delta ratio on QEEG proved 100% sensitive and 76% specific for the detection of delayed cerebral ischemia from vasospasm. (For further discussion, see Chapter 23, Stroke and Subarachnoid Hemorrhage).

Prognostication

Finally, cEEG also provides prognostic information. In patients with poor-grade subarachnoid hemorrhage, cEEG monitoring provides independent prognostic information, and specific unfavorable EEG findings include periodic epileptiform discharges, electrographic SE, and the absence of sleep architecture (28). Certain EEG patterns have also been shown to be useful predictors of clinical outcome after SE (29). Compared to critically ill patients without seizures, outcome is worse in critically ill patients with nonconvulsive seizures (3,18,29). In one study, mortality

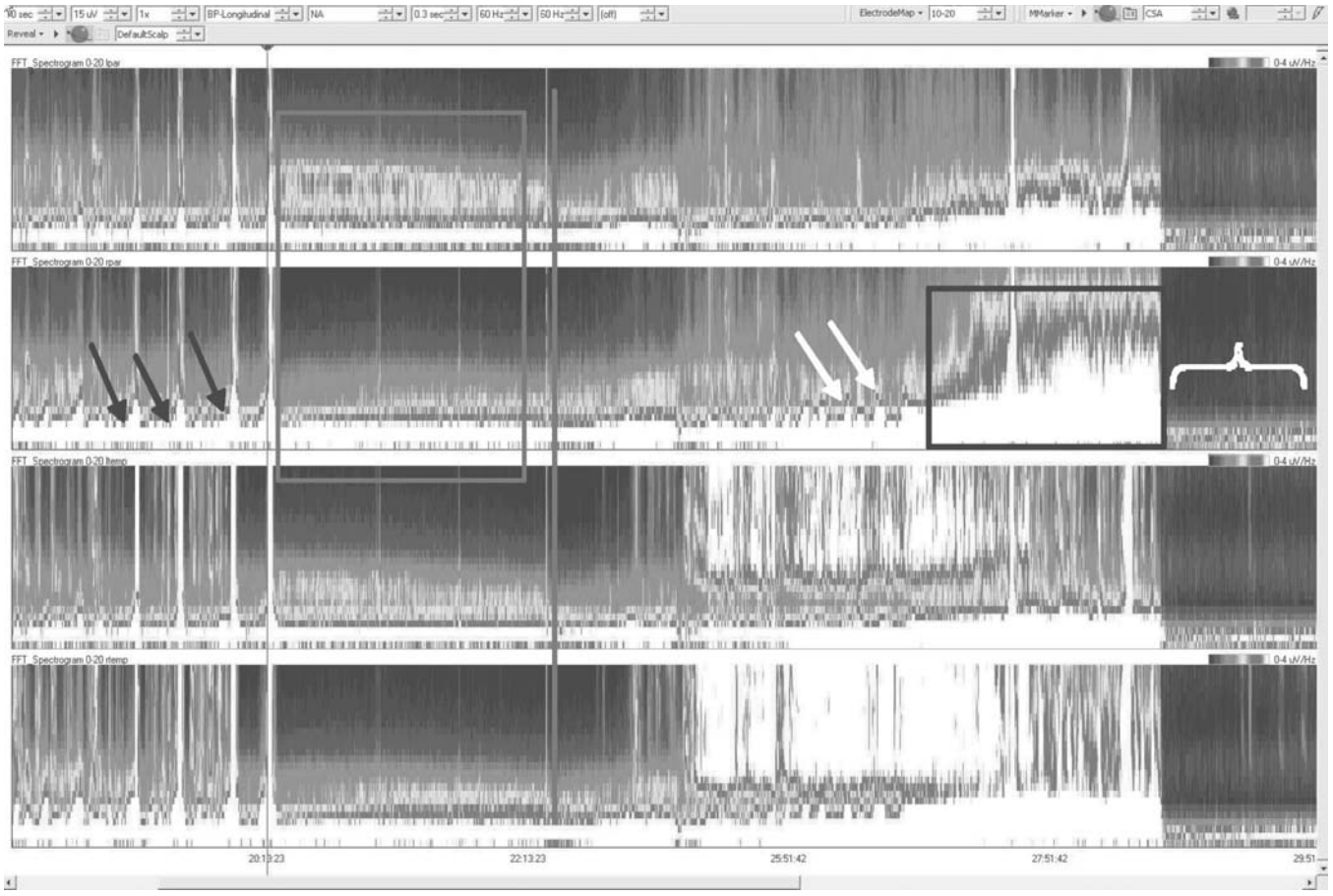

FIGURE 2-4. CSA detection of respiratory failure: a 10-hour case summary. CSA showing 10 hours of EEG in a 76-year-old patient with atrial fibrillation, on warfarin, who was admitted with a small right subdural hematoma. Continuous EEG monitoring was initiated after the patient became lethargic for an unknown reason (there were no clinical seizures). Initially the CSA revealed recurrent right>left hemisphere nonconvulsive seizures (black arrows). Seizures ceased for several hours without any change in antiepileptic medications (taller box). Clinical assessment at that time revealed respiratory failure, with pH 7.1; presumably, the acidosis led to fewer seizures. After intubation (dark line) and improvement of acidosis, CSA activity gradually increased, but was followed by gradual recurrence of nonconvulsive seizures (white arrows), and eventually nonconvulsive status epilepticus (black box). A midazolam infusion was begun (white bracket), with subsequent resolution of electrographic epileptic activity and diminished activity on CSA. Y-axis: frequency, 0 Hz at bottom, 20 Hz at top. X-axis: time (approximately 10 hours shown). Color scale (z-axis): power of given frequency (scale in upper right) measured in microvolts/Hz. (*See color insert*).

in critically ill patients with nonconvulsive seizures was found to be 9%, compared to 57% in those with convulsive SE (3). In general, mortality was strongly linked to duration and delay-to-diagnosis of nonconvulsive SE, and this worsening of outcome was independent of etiology and age (3).

PROCEDURES

Issues Related to Hookups

Many logistical challenges arise in the face of offering cEEG in intensive care units. New programs for ICU cEEG usually siphon off staff resources from the daytime-oriented EEG staff. Night or weekend hookups are naturally more difficult. Many hospitals, even those with busy epilepsy monitoring units (EMUs), do not provide continuous in-house EEG technologist coverage (30). However, the risks incurred by postponing EEG can be significant. One study assessed factors influencing mortality in ICU patients with nonconvulsive seizures and found that only seizure duration and delay to diagnosis were associated with increased mortality (31). Indeed, urgent EEG should be available 24 hours a day, ideally with rapid availability (though this is not feasible in many hospitals from a financial and personnel standpoint).

Several possible solutions for performing emergency EEGs have been developed. These include using trained nonphysicians or housestaff to apply a limited number of electrodes, having EEG technologists on call at a remote location, and having continuous in-house EEG technologist availability. There are also techniques and electrode

products designed to increase the ease of hookups, such as premeasured elastic templates with color-coded electrode positions, and electrode caps. Although useful in the majority of cases, these have limitations insofar as they preclude flexibility in electrode placement often needed to allow for skull defects, surgical wounds, dressings, ICP and other invasive monitors, and ventricular drains. Caps and nets may shift position, with obvious deleterious effects on the reliability of acquired EEG data. Previously, these prefabricated devices were touted as useful for initial brief hookups, such as those completed while a patient awaits MRI. However, with recent FDA approval of MRI-compatible electrodes (see discussion below), this should no longer be a major problem, barring cost limitations.

Finally, close communication between EEG technologists, ICU nursing staff, and physicians is crucial in maintaining efficiency in initiating and maintaining cEEG. Often, EEG hookups are requested on the same day patients are scheduled for other studies or procedures. After initiation of monitoring, EEG-related tasks must often be coordinated with pressing aspects of patient management. Explicit discussions are necessary to aid with scheduling and prioritization of hookups, and to limit costly electrode reapplication and maintenance.

Montages

A variety of montages have been used in ICU recordings, and there is no single optimal choice. As previously noted, postsurgical changes and monitoring equipment often partially dictate the placement of electrodes (17,32). Many groups have studied specific applications using fewer than the standard 21 electrodes, particularly when monitoring is indicated in order to follow generalized EEG patterns (33). For example, Vespa et al. used only 10 electrode positions and structured a 14-channel montage to monitor patients with traumatic brain injury (34).

Screening EEGs, which use a limited number of electrodes, have also been studied as a tool for the hastened detection of seizures (35–38). Kolls and Husain evaluated the sensitivity of hairline EEG for diagnosing nonconvulsive SE, comparing interpretations of three reformatted six-channel "hairline" montages to original conventional EEG interpretations (39). However, even with the best montage, sensitivity for correctly detecting seizures was only 72%. Seizures were frequently misconstrued as more benign patterns, and some benign patterns were interpreted by expert electroencephalographers as seizures. Thus, hairline EEG is not recommended for use as a screening tool, although it is certainly much better than no EEG at all.

Conversely, using a full set of electrodes is ideal for detection of subtle findings and for differentiating artifact from brain activity. A full set of electrodes also allows for functional loss of some electrodes, as is almost guaranteed to happen with prolonged monitoring in ICUs, without compromising the ability to reliably record seizures and other brain events.

Electrodes

Despite remarkable advances in cEEG technology, the electrode itself remains a major limiting factor in the quality of the recording, particularly in the ICU setting. Fortunately, the use of subdermal and MRI-compatible electrodes is beginning to alleviate some of these issues. The two main types of electrodes currently in use are scalp disk electrodes (still the most common by far), and subdermal needle or wire electrodes. These are contrasted in Table 2-2.

Traditional disk electrodes are associated with significant artifacts, which cloud accurate interpretation (including computerized detection and displays) and may lead to erroneous interventions (40). Causes of further disruption of the disk-scalp interface in the ICU are many, and include frequent perspiration and patient movement (either passive or related to patient agitation). While wrapping the head helps keep electrodes in place, disk electrodes require constant attention and need adjustment every 10 to 24 hours (41). The recording quality of surface electrodes starts to deteriorate immediately after being adjusted for ideal impedance, and critical diagnostic information can be missed if the quality of the signal is poor. Finally, disk electrodes can be a significant source of skin breakdown and occasionally superficial infections. They are in a state of constant friction against the scalp, in the setting of nonsterile materials including jell, gauze, injection tips, and the patient's own hair.

Subdermal stainless steel needle electrodes, introduced for EEG recordings in the 1960s, present an attractive alternative to metal disk electrodes in certain situations (32). Application is quick, requiring less than 1 minute, compared with 2 to 3 minutes per standard surface electrode (41). They are well suited for long-term cEEG monitoring because they do not require frequent maintenance and do not cause skin breakdown. This lack of skin abrasion also makes then ideally suited for patients with scalp burns and surgical lesions (42). Their main drawbacks include discomfort for awake patients and the risk of needle sticks to the EEG technologist, other hospital staff, and the patient. For this reason these electrodes are not appropriate for combative patients. Utmost care should always be exercised in preventing entanglement with linens and garments, and only disposable needles should be used. Finally, stainless steel needle electrodes cause attenuation of low-frequency EEG signals; although rarely a problem, interpretation should be conducted with this in mind (30).

Subdermal wire electrodes are essentially a modified version of the stainless steel needle electrodes. Like the subdermal needle electrode, the subdermal wire electrode is inserted below the skin, and once placed does not need further adjustment for days or weeks. After insertion, the

TABLE 2-2. COMPARISON OF SEVERAL EEG ELECTRODE TYPES. Comparison of several types of EEG electrodes on the basis of construction, imaging compatibility, and other general advantageous and disadvantageous features. The term "MRI Safe" used here refers to an item that has been demonstrated to pose no known hazards in a specified MRI environment with specified conditions for use (59).

Electrode	Construction	Advantages	Disadvantages	CT Artifact	MRI Safe	MRI Artifact
Gold cup electrode (with Ives's MRI-compatible wiring system)	Gold-plated	Mass connector (for easy disconnection/ reconnection) Reusable	Skin breakdown Frequent maintenance	Yes	Yes	No
Conductive plastic electrode (with Ives's MRI-compatible wiring system)	Plastic with a coating of Ag/AgCl	Potentially X-ray and angiogram compatible Mass connector Reusable	Skin breakdown? Frequent maintenance	No	Yes	No
Subdermal wire electrode (with Ives's MRI-compatible wiring system)	0.25-mm Ag/ AgCl wire electrode	No skin breakdown Less maintenance Sterile Mass connector	Requires needle for placement Risk of needle sticks Local bleeding upon placement Single use Painful	No	Yes	No
Subdermal stainless steel needle electrode	Stainless steel needle	No maintenance No skin breakdown Sterile Easy to apply	Risk of needle sticks Painful Attenuates low frequency EEG signals Local bleeding upon placement Single use	Yes	No	(NA)
Standard metal cup electrode and wiring	Gold or Ag/AgCl	Reusable Most widely used	Frequent maintenance Skin breakdown	Yes	No	(NA)

disposable, 25-gauge needle is withdrawn and the wire remains hooked in place. This system conveys all key advantages of the needle electrodes described above. In addition, the wire's minimal mass and malleable property make it less vulnerable than standard surface electrodes to patient movement artifact (41). Furthermore, in a study by Young et al., only 1.25% of subdermal wire electrodes showed 60-Hz artifact (a common sign of electrical interference), compared with 37.5% of collodion-applied scalp disk electrodes (43).

Disadvantages of subdermal wire electrodes are few, other than discomfort and minor bleeding during insertion. As with needle electrodes, there have been concerns regarding the risk of needle sticks; however, sticks should be less likely with wire electrodes as needles are only employed briefly during hookup. Although the wire electrode is considered invasive, the track through the skin and into the dermal layer is only a 0.25-mm Teflon-coated wire. Therefore, the actual invasive opening is minuscule and can be more easily monitored than that for gauze-covered cup electrodes, which can create significant erosive wounds. In one study, about 40% of wire electrode placements in human scalp were associated with local bleeding, which was easily stopped with a few seconds of pressure (41). Overall, subdermal wire electrodes may prove to be a valuable alternative electrode type, particularly for use in comatose patients.

One massive inconvenience in ICU cEEG has been the need to remove and replace electrodes for magnetic resonance and computed tomography (CT) imaging. This is labor-intensive for the EEG technical staff and disruptive for the nursing staff, creates a frustrating delay for physicians, and is demoralizing for the EEG technologist who completes the application of electrodes only to remove them a short time later. Fortunately, MRI-compatible systems have been formally introduced and approved by the FDA (personal communication with J.R. Ives, July 1, 2007). There are three types of EEG electrodes: the subdermal wire electrode (also discussed extensively above), the gold or silver/silver chloride cup electrode, and the conductive plastic electrode. All of these are MRI-compatible (i.e., their use with MRI is safe and does not distort images). The MRI safety and compatibility of these electrode systems derives of their construction of nonmagnetic materials; from a wiring system with short, straight wires to prevent heating and burning or catching on the MRI gantry; and

from their minimization of distortion of the MR image from susceptibility (44). All except the gold cup and silver/silver chloride electrode are also CT-compatible (the gold cup electrodes cause significant artifact but are still safe). The conductive plastic electrode may be most well suited overall for use in cEEG. This electrode has a low mass and conductivity, and the thin layer of conductive silver epoxy over the plastic cup results in "excellent" recording characteristics. The thin layer of silver epoxy also makes the conductive plastic electrode equivalent in noise level to the metal cup electrodes (45,46). Further adding to the convenience of the Ives electrode system, the harness and mass connector are interchangeable, allowing disconnection and reconnection for imaging or other procedures to be easily handled by nursing staff (47).

Finally, a noteworthy caveat regarding prolonged cEEG with ICU patients is the issue of skin breakdown. This can be a problem, especially when cup electrodes are used. Varying the sites of electrode placement, or planning for periods of unhooking patients for scalp rest, may be necessary to minimize wounds and permanent scarring in patients who require prolonged (>1 week) cEEG. Another reasonable solution may be to record initially with a full set of electrodes and then reduce the number when clinically appropriate (30). Finally, the use of subdermal (needle) electrodes may be considered in selected cases.

Adhesives

Along with the type of electrode, one must select from a number of options with which to secure the electrodes. Specific features of each adhesive influence this decision, including conductivity, adhesive quality, mechanical stability, ease of use and removal, toxicity, and even odor. For disk or cup electrodes, electrode paste and collodion are the main options. Options to secure wire or needle electrodes in place externally include collodion and Tegaderm. However, for wires or needles the issue is somewhat simplified by the fact that the recording electrode surface is under the skin, and not directly mediated by the intervening adhesive.

Electrode paste, a conductive medium itself, is problematic because electrodes may be easily dislodged, and even vibrating beds can cause them to be loosened. The paste can also smear with electrode movement, thus making the recording area larger, or even causing shunting of activity between electrodes that become close together as a result of the movement. Falco et al. compared the application of gold cup electrodes using EC2 electrode paste (Grass Technologies) with collodion application methods in 40 patients (48). They concluded that in the patient group (20 patients) in which EC2 paste was used, application was less time-consuming and produced better quality EEG recordings than did application for the patient group (20 patients) in which collodion was used. However, their study only evaluated a 24-hour period in a population of patients in a long-term EMU.

The best choice is to glue each electrode in place with an overlying strip of gauze soaked in collodion—a mixture of nitrocellulose dissolved in diethyl ether and ethyl alcohol. Collodion provides excellent mechanical stability and is nonconductive, thus effectively sealing the electrodes. Collodion is also probably the best way to minimize artifacts in long-term EEG studies (30). Several problematic aspects of collodion include its volatility, combustibility, and odor. Because of its ether content collodion vapors can cause flash fires, and it can even combust in solid form. Acetone, the agent commonly used to remove collodion, is also highly combustible (49). For this reason there are very specific requirements for its storage, container compatibility, and ventilation. There is an alternate, alcohol-based formulation, Collodion II (Mavidon Corp.), that is generally less durable and takes longer to dry. With practice, however, this can be as effective as the ether-based collodion as is currently used in the Neuroscience ICU at our center.

Perhaps collodion is most infamous for its offensive and pungent odor, which frequently prompts concern and complaints from patients, their roommates, and medical staff alike. The odor is often perceived to mean that collodion is toxic, and this has been an ongoing source of controversy, with frequent complaints from technologists and nurses including headache, eye strain, and euphoria. Collodion vapors are respiratory irritants, especially when used in improperly ventilated areas. If ventilation in a patient's room is not sufficient it can be supplemented with portable air-filter devices or hood-type systems (49). Some ICU settings are now designed to meet the ventilation specifications, thus eliminating this problem. While more extensive, systematic study of the potential health risks of collodion is needed, including in critically ill patients, one reassuring study did find that the highest concentration of ethyl ether detected by charcoal sampling devices worn by EEG technologists was nearly tenfold lower than the established safety limit (50).

Contemporaneous Data

Along with EEG, other simultaneously acquired data are increasingly part of monitoring in the ICU setting, and can dramatically aid in the interpretation of EEG patterns. As in the EMU, video and audio recording are crucial for analyzing clinical events, identifying sources of artifact, and characterizing seizures. They are also helpful in identifying periods of patient stimulation, and thus help to identify stimulus-induced rhythmic, periodic, or ictal discharges (SIRPIDS), commonly seen in critically ill patients (see Figure 2-5 for an example) (51).

With numerous mechanical sources of potential artifact in the ICU, such as vibrating beds and ventilators (also see Chapter 18, Events that Mimic Seizures during ICU

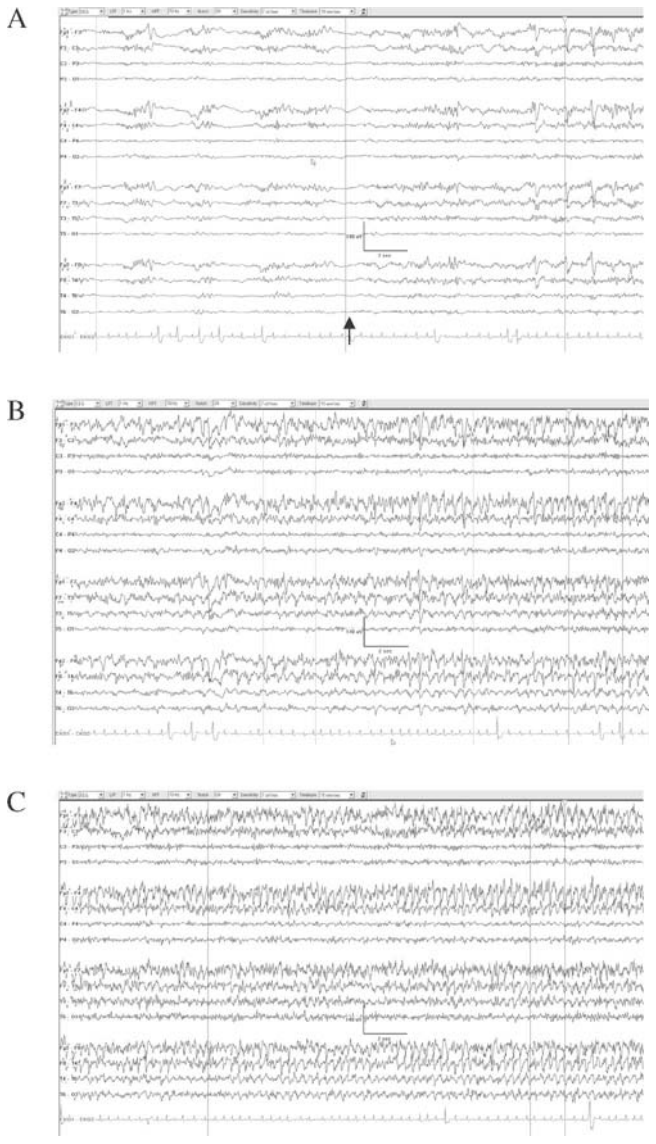

FIGURE 2-5. SIRPIDs on the cEEG of a 72-year-old woman with multifocal, bilateral ischemic infarcts after cardiac arrest. (A) Initial segment reveals a discontinuous pattern. Stimulation via nostril tickling (arrow) results in gradual buildup of electrographic seizure activity on EEG, with rhythmic delta that evolves and spreads (B–C). (Note: for purposes of illustrating cEEG findings here, the timebase has been adjusted to 15 mm/second rather than the standard 30 mm/sec).

Monitoring), video and audio recording help the electroencephalographer correctly interpret otherwise questionable patterns. Electrocardiogram data are also always collected and displayed in tandem (with at least two noncephalic electrocardiogram electrodes to allow recording of pure electrocardiogram data not contaminated by EEG), and this can help correlate EEG findings with various physiological responses or states. Additionally, other data streams can be helpful, including pulse oximetry, blood pressure, and intracranial pressure. Ideally, ICU systems should be designed to automatically passively acquire and merge all relevant physiological, laboratory, and therapeutic data into a single record that is integrated with the EEG record (30). Commercial systems are now available for precisely this purpose.

Perhaps most important are notations entered into the cEEG record by nurses, other staff, and patients' relatives. These help identify and clarify clinical events, mark times of intentional stimulation, and convey changes in therapeutics. Notations assist in establishing the reactivity of a patient's EEG background. A keyboard or other device should be readily accessible to facilitate entering of notations, and ideally should be as simple as possible, not requiring one to turn on an additional computer or enter a password (30). Pushbuttons and handwritten diaries are also useful in some scenarios, primarily when family members are often present. In addition, with continuous video and audio recording, nurses, other staff, and relatives should be encouraged to narrate their observations and interactions with the patient.

Special Considerations Related to ICU cEEG Interpretation

Continuous EEG monitoring in the ICU setting has led to a tremendous time burden required for analysis of the complete data stream. As opposed to the EMU setting, where there is typically an expected and accepted delay in cEEG analysis of paroxysmal events, the ICU setting requires frequent review and analysis of the record to enable prompt interventions (52). There also may be emergency hookups in the ICU during the night, requiring immediate interpretation. In response to these challenges, both new staffing organization and data presentation systems are continually being developed. It will be some time before real-time monitoring of brain function (neurotelemetry) is a widely available service, but select centers have begun to provide this service.

Ideally, EEG data should be continuously monitored by a specially trained person. This may be a physician, a specialized nursing staff, or a specifically trained video EEG neurotelemetry technologist (17). Reliable computer networking to allow for remote viewing from home of the file by electroencephalographers, for example during the night, is crucial for providing detailed, expert analysis. Automated interpretation systems, such as spike and seizure detection algorithms used in EMU settings, are generally of limited use in ICU cEEG in their current forms. This is because seizures in brain-injured or encephalopathic patients often demonstrate lower-frequency rhythmic patterns, as well as more subtle evolution (51). With the development of new programs capable of more complex analysis, ICU-appropriate detection systems should be possible in the future (53,54). One promising possibility is a system that would be capable of recognizing deviations from a previously "learned" patient-specific baseline EEG pattern. Beyond detection of seizures, automated recognition of other patterns, such as alpha-delta ratio fluctuations associated with cerebral ischemia, will be of obvious use in critically ill patients (27).

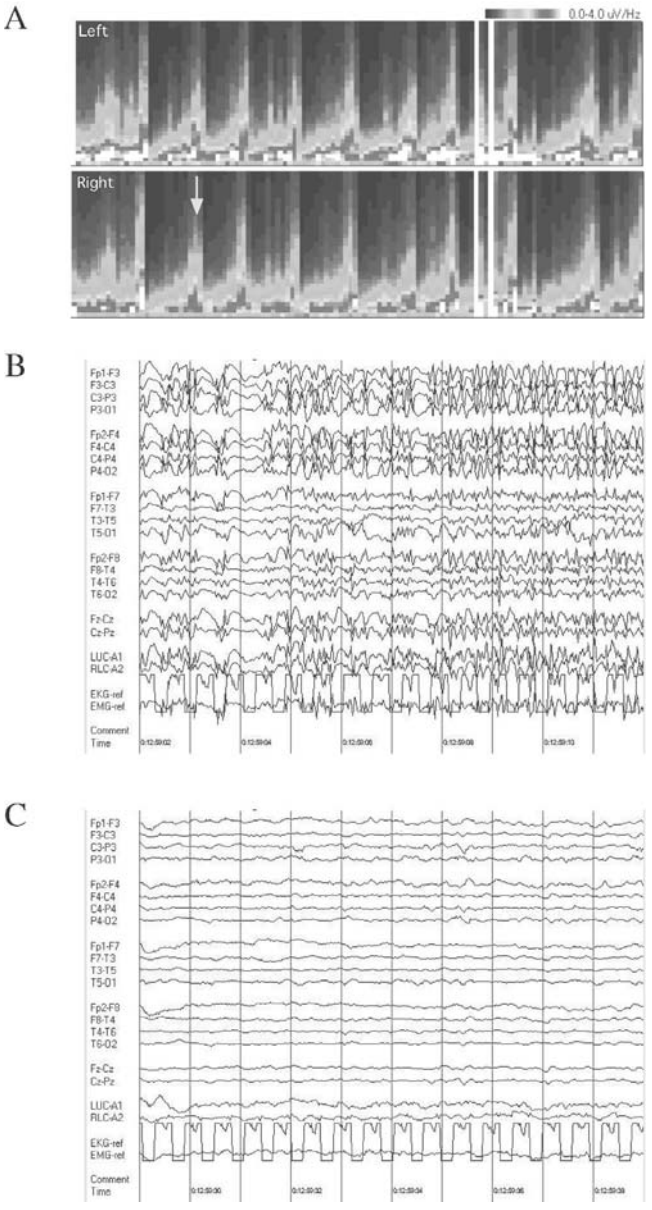

FIGURE 2-6. Cyclic seizures. (A) CSA in a patient demonstrating a cyclic seizure pattern, with a gradual buildup of voltage, followed by the seizure (arrow). This is again followed by seizure offset, which is then followed by the gradual buildup of voltage again. The seizures occur at a rate of approximately one every 3 minutes. (B) Ictal EEG from same patient, corresponding to the peak labeled with the arrow on CSA. (C) Postictal EEG, corresponding with the postictal attenuation of activity on the CSA, just after the arrow (58). (*See color insert*).

In addition to automated detection systems, specialized compressed data representation systems, such as compressed spectral arrays (CSA), have been developed to facilitate review of large quantities of EEG data. These do not, however, substitute for review of the original EEG file, but rather complement it, assisting in highlighting trends or changes over prolonged periods. Ideally, programs should allow for facile movement between any point in the raw EEG file and CSA, or include concurrent display of both. CSA may also be useful to physicians or staff less experienced in EEG interpretation in correlating clinical events, tailoring therapies, or deciding when to seek the expertise of an electroencephalographer. Because these power spectrographic displays compress several hours of recording into a single image, they may assist in revealing patterns, such as periodic recurring seizures, that were otherwise unrecognized (see Figure 2-6).

LENGTH OF cEEG MONITORING

Clinical judgment must be used in tailoring the decision to terminate cEEG for each patient. As a rule, patients with prior status epilepticus or frequent seizures should be monitored until they are seizure-free, ideally for 24–48 hours. Titration of continuous intravenous antiepileptic medications is also a guiding factor. *After the treatment of status epilepticus, patients—even if seizure-free—should be kept on cEEG until all continuous intravenous antiepileptic medications (such as pentobarbital, midazolam, or propofol) are withdrawn and the patient is on appropriate maintenance antiepileptic drugs.* This is crucial to ensure that patients do not develop electrographic seizures during adjustment of medications.

In contrast to patients with seizures, it can be difficult to determine the appropriate length of cEEG monitoring in patients with a nonspecific encephalopathy or with coma of unknown etiology. This problem was assessed in the Columbia series, evaluating time to first seizure in 110 critically ill patients with electrographic seizures (2). Within 24 hours, 87% of patients with seizures had experienced their first seizure. When comatose patients were evaluated separately, it was found that 20% did not have their first seizure detected until more than 24 hours of cEEG monitoring. Furthermore, in 13% of comatose patients the first recorded seizure occurred beyond the first 48 hours of monitoring (see also Figure 2-7). In children results were

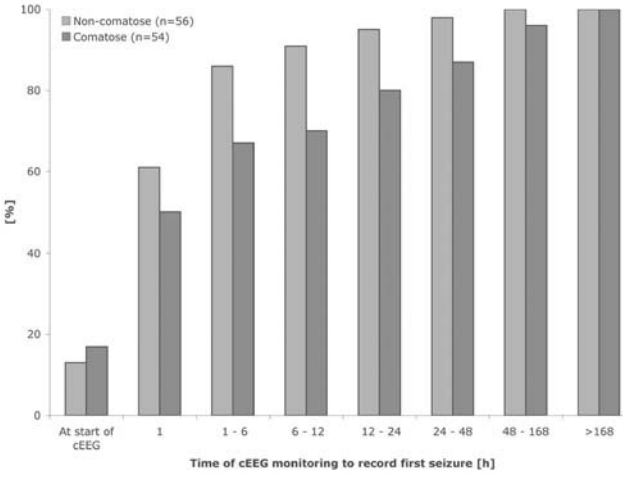

FIGURE 2-7. Time to record the first seizure, comparing noncomatose and comatose patients (2).

similar, with 50% of seizures detected within the first hour of cEEG, and 80% in the first 24 hours (55). In summary, 24 hours of cEEG monitoring is usually adequate to exclude nonconvulsive seizures in noncomatose adult patients, and 48 hours or more is recommended in those who are comatose. In patients with periodic discharges prolonged monitoring is also likely indicated, as they are at higher risk of developing seizures (55).

LEGAL LIABILITY

Despite the broad applicability of continuous EEG monitoring and its potential benefit to patients, some practitioners may be hesitant in their pursuit of cEEG out of fear of legal liability for missing events while recording EEG or for detecting them in a delayed fashion. However, in this rapidly developing field there are aspects of the technology itself and practical staffing issues that still render real-time detection of adverse events impractical, if not impossible, for most centers in the near future. Therefore, failure to detect adverse events in real time, or even to recognize all such events on review of cEEG recordings, cannot be interpreted as either negligence or breach of the "standard of care." With ongoing improvements in both technology and the understanding of EEG patterns in critically ill patients, improved software, and dramatic expansion of technical staff, truly practical, real-time brain monitoring will be possible. In the meantime, it would be wrong to allow any concerns of liability to impede medical advancement, or worse, to threaten the provision of optimal care to critically ill patients. Detecting some events is clearly preferable to detecting none.

CONCLUSIONS

As a result of recent technological advances, continuous recording (and potentially real-time monitoring) of brain function in critically ill patients is now possible with EEG. In ICU patients, cEEG can help create improved clinical care through detection and treatment of nonconvulsive seizures (1–3,18,23,29,31,56,57). For patients at risk of cerebral ischemia, cEEG may help improve clinical outcomes through early detection and prevention of in-hospital stroke. As the application of cEEG in the ICU expands, so does awareness of the variety of detectable neurological illnesses.

Work is underway developing new features of continuous EEG monitoring in the ICU setting. Future directions include the use of depth electrodes inserted into the cerebral cortex, which are already being used to closely monitor dynamic changes within the brain during a variety of acute brain injuries (60). Ancillary parameters—including brain tissue oxygenation levels; microdialysis for brain tissue lactate, pyruvate, glucose, glycerol, glutamate, and more; and biomarkers such as neuron-specific enolase—are being aggressively investigated, and may help determine which EEG patterns in critically ill patients are resulting in ongoing neuronal injury or are associated with obvious intracranial seizure activity. As the understanding of continuous and quantitative EEG in critically ill patients expands, computerized detection systems are being developed for neurotelemetry programs. In the future, such automated systems may allow for immediate recognition and treatment of seizures and ischemia, as well as real-time notification of any ominous developing patterns in the recording. While much remains to be learned regarding EEG in critically ill patients, it is quickly becoming the standard of care in neurological ICUs, and furthermore remains the only option for practical, continuous, noninvasive monitoring of brain function.

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3

EPILEPSY MONITORING UNIT PEDIATRIC AND ADULT MANAGEMENT

JEFFREY RONALD BUCHHALTER

GENERAL CONSIDERATIONS

The utility of inpatient video EEG monitoring for the diagnosis, evaluation, and treatment of paroxysmal disorders (especially seizures) has been well established in children (1,2) and adults (3–6). Patient selection for monitoring as well as technical requirements (video EEG hardware, software, and study interpretation) are described in other chapters of this book. This chapter will focus on the patient management issues that affect the successful completion of the patient-specific admission goals. It should be recognized at the outset that the strategies used to accomplish these goals will vary significantly with the medical setting and resources available.

Although an individual patient is the subject of investigation, it is the rule for children, and a very frequent occurrence for adults, that other individuals (parents, spouses, other family members, significant others, health care workers) are intimately involved in the delivery of care. Therefore, the term *patient/caregivers* will be used to acknowledge the functional unit to which information is delivered. Similarly, it should be acknowledged that multiple health care providers are involved with each epilepsy monitoring unit (EMU) admission. At a minimum these individuals include the physician, office staff, nursing staff, and EEG technologists. Other care providers who frequently become involved include pharmacists, psychiatrists, psychologists, neuropsychologists, social workers, Child Life, as well as speech, physical, and occupational therapists.

The goals of an EMU include, but are not necessarily limited to, the following:

1. Record the typical events that are of concern. These can include seizure and nonepileptic paroxysmal events. Seizure-related issues include quantification, classification, and localization. All require some participation of the patient/caregivers and thus involve management decisions.
2. Perform the monitoring in the most efficient manner possible. The EMU admission is expensive with regard not only to health care resources, but also to the time away from work and family for the patient and caregivers.
3. Perform the monitoring as safely as possible. The importance of safety in the EMU may seem obvious, but there are some key patient management considerations that should be planned for every admission.

Outpatient and Inpatient Education Considerations

Outpatient Education

In order to ensure an optimal EMU experience, the goals and expectations of the admission need to be clear to the patient/caregivers as well as to the staff taking care of the patient in the hospital. The best place for this process to begin is in the outpatient clinic. It is here that the clinical question is identified and the EMU suggested as a means of answering that question. The most common reasons for admission include spell classification, seizure classification, seizure quantification, presurgical evaluation, and medication alteration. The purpose of the admission should be clearly communicated to the patient/caregivers verbally, and provided in writing, either as a summary document at the end of the office visit or as part of the clinic visit note documenting the plan. The latter has the advantage of providing the rationale for the admission to the staff in the EMU. This will avoid a situation in which the patient or doctor is unsure of the reason for the monitoring session.

Another type of information that can and should be conveyed in the outpatient clinic is the expectation of

patient and caregiver responsibility. If a caregiver is required to be in attendance during the EMU admission, this needs to be conveyed so that the caregiver can arrange time off from work and/or child care for siblings for an appropriate number of days. The patient/caregivers need to be informed that the primary goal of the admission can best be accomplished if he or she activates the "push-button" when typical events occur. Small considerations, such as asking the family to bring a comfortable button-down shirt (to facilitate wiring and re-gluing) and familiar toys or games, can greatly enhance the experience for pediatric patients. Caregivers should also be informed as to what arrangements will be available for them with regard to sleeping, hygiene, meals, and taking breaks from the room.

Patient/caregiver education can be supplemented by written material describing the EMU process, which should be as specific as possible for the institution. This can be provided at the end of the clinic visit and/or as part of the information mailed to the patient/caregivers prior to the EMU admission.

Inpatient Education

The education process designed to optimize the EMU admission begins again at the time of patient/caregiver orientation to the EMU. In addition to the customary description of inpatient facilities and services, specific information to facilitate recording the events in question should be provided. This can be done by having the responsible nurse clarify with the patient/caregivers the events to be recorded. This can be accomplished by providing the patient/caregivers with a seizure/event log that is kept on a clipboard at the bedside (see Figure 3-1). This form makes clear the events that should result in activation of the push-button by the patient/caregivers, nurse, or other care providers, provides "backup" (in case the button is not pushed) by recording the time of the event and allows comment regarding the nature of the event. Comments such as "typical," "mild," "not sure," or "longer than usual" can be very useful in the subsequent clinical–electrophysiological correlation, and are used in the daily physician review of the previous 24 hours of video EEG recording.

Other techniques are used to reinforce the verbal information provided by the nurse. A "Frequently Asked Questions" sheet is included in an information folder provided at the time of admission. The example provided (Figure 3-2) is used in a pediatric setting, but can be adapted for the adult population. A laminated set of reminders for the patient/caregivers is posted in each room in English and Spanish. Finally, we have two whiteboards installed in each room. One is used to keep track of the plans for each day—for example, "decrease medication A, increase medication B, sleep deprivation tonight, MRI tomorrow." The list is updated each day during bedside rounds, and provides the patient and family members who may not have been present at rounds an immediately accessible summary of the plan for the next 24 hours. The other whiteboard serves two purposes. The first is to compile a list of questions that have occurred to the patient or caregivers in the preceding 24 hours; these can be written on the whiteboard by the nurses, by family, or by friends. This ensures that patient questions will be answered each day. We encourage the patient/caregivers to keep a notebook of questions asked and the answers provided for future reference. The other purpose of the second whiteboard is to provide space for the physician to draw illustrations based upon the questions asked. Some of the most common drawings generated are related to demonstrating the difference between interictal and ictal discharges, the relationship of clinical events to electrical abnormalities, and the mapping of ictal onset and eloquent function during evaluation for epilepsy surgery.

Another advantage of the EMU admission is that it creates a unique educational opportunity for the patient and their caregivers or family members. This can be accomplished to some degree each day in the course of rounds and reinforced by repeated visits. However, a concerted effort should be made by the care team to provide additional verbal, written, and Web-based materials that will enhance understanding and compliance after discharge. Regrettably, there are few publications available to guide health care workers dealing with methods and/or outcomes of in-hospital, EMU education programs.

Nurse Education

The central role of nursing in patient management is extremely important. In addition to providing direct care, nursing staff frequently manage the scheduling of related diagnostic procedures and are ideally situated to be a major source of education for patients and caregivers. It is axiomatic that care is optimized when delivered by individuals specifically trained for any task. However, the realities of space, personnel, and efficiency dictate that EMUs will be situated in different settings with different nursing models. From the perspective of individual patient care, it is ideal if the EMU is a defined unit within the hospital with dedicated, epilepsy-trained nurses. When necessary, segregation into infant/child and adolescent/adult units allows the needs of each population to be addressed by staff skilled in age-specific manner.

Nursing staff education can be accomplished by a variety of methods. A traditional approach is the in-service lecture. If this format is chosen, a series of lectures will be needed to cover the relevant and necessary topics, which include (but are not limited to): paroxysmal nonepileptic events, seizure types and classification, medication management of seizures, behavioral testing during and after

PHOENIX CHILDREN'S *Hospital*

PEMU
Seizure / Event Log

Apply Patient Label

Seizure/Event Type 1: _____

Seizure/Event Type 2: _____

Date	Time	Type 1	Type 2	Comments

FIGURE 3-1. PEMU seizure log.

Frequently Asked Questions

Q. Can my child shower in the PEMU?

A. No, your child may have a sponge bath due to lead attachment.

Q. Where do parents shower?

A. We have showers available just down the hall from your child.

Q. What type of room are we in?

A. A single patient room with a bathroom, sink, patient bed, parent sleeper, TV-DVD, storage area. We will give a full tour/ welcome on admission.

Q. How are meals ordered for my child? For us parents?

A. We have menus you can order from for your child, and we will give you times that our cafeteria is open. We will assist in watching your child while you are away for meals.

FIGURE 3-2. Questions frequently asked by parents.

seizures, epilepsy surgery evaluation, optimizing video EEG recording (e.g., electrode artifact detection, simple electrode re-gluing), and safety. Another approach is to provide the education in one day. Whatever approach is chosen, some method of written and observational testing should be employed, and it is then necessary to construct competencies that are integrated with other institutional nursing guidelines.

It is desirable to provide durable materials available to nursing staff as reference materials. The construction of a "resource manual" containing the information provided in the lecture series, in addition to other useful information, is useful in concept. However, it does not address the needs of the nurse who does not work every day in an EMU and does not have the time to reacquaint him- or herself with essential knowledge prior to starting the shift. In this circumstance, and in general, it is extremely useful to have a one-page checklist that covers nursing issues in preadmission, admission, and ongoing care (see Figure 1 of reference 7).

Safety

The topic of safety during video EEG monitoring has been the subject of at least one extensive review (8), and is given emphasis in multiple other descriptions of EMUs (6,7,9–11). The local biomedical group should be involved in the acquisition and implementation of all electrical equipment used in the EMU to address potential electrical safety issues. The use of pulse oximeter, heart rate, and muscle activity data in addition to the EEG electrodes should be carefully evaluated to avoid ground loops. Safety-related equipment, such as suction and an oxygen source, should be part of all rooms in which seizures are being recorded (6).

There is currently a national effort in U.S. hospitals to increase safety levels, with fall prevention playing a prominent role. The individual with epilepsy is clearly at elevated risk of a fall when in the hospital. The conditions that have been associated with the greatest risk of falling include difficulty with walking, abnormal mental status, and difficulty with equilibrium (8). These can be caused by a static encephalopathy, by medications, or by increased seizures, to name the most prominent etiologies.

In addition to support by a staff or personal caregiver while a patient is ambulatory, it is reasonable to consider rounded corners on furniture and cork or carpeted flooring as structural methods of decreasing morbidity if a fall were to occur. Bed rails should be padded and elevated to the appropriate height to prevent injury during a motor seizure from striking metal or plastic surfaces and from a fall to the floor. Individuals with nonconvulsive seizures are also at risk, especially if nonpurposeful wandering is part of the ictal or postictal state.

As it is not practical to provide one-to-one nursing coverage, alternative methods are available for patient observation. *The safety goal of observation is to prevent the morbidity and mortality related to untreated status epilepticus, cardiac and/or respiratory arrest, and falls, and to ensure the recording and clinical examination of every event.* The optimal configuration of an EMU to facilitate observation is to have the rooms located in a circular fashion around a central nursing area. When the rooms are arranged along a standard hospital corridor, the video and EEG feed from the patient's room should be displayed on monitors at the EMU nursing station. The location selected for the monitor should reflect the need to maintain patient confidentiality—that is, the monitors should not be viewable from any public area. Modern video EEG systems provide camera control at the nursing and/or EEG technologist areas so that the patient will be on camera at the time of seizures.

The success of observation is dependent upon someone (nurse, EEG technologist, or desk personnel) looking at the monitor. This is best achieved by having a trained

EEG technologist viewing the video and EEG simultaneously. Because of the cost and lack of availability of EEG technologists at many institutions, this role can be filled by specially trained nurses, patient care technicians, or other trained neuro telemetry technicians. Whoever is viewing the monitor can alert the nurse who is providing the primary care to the patient by voice or pager.

Unfortunately, in some hospitals, because of the size of the EMU or lack of funding, this may not be possible. In such cases, if monitoring must be performed, an alternative approach should be undertaken to support patient safety until a neuro telemetry staff can be developed. This alternative approach often involves a combination of the attending nurse watching the monitors in the EMU nursing station and the use of automated alarms triggered by events in the EEG or other physiological monitors.

The software suite included in the video EEG system usually has algorithms for detection of rhythmic sharp activity that conforms to some, but not all, ictal patterns. The utility of this means of seizure detection varies depending on variables that include the specific program, the type of typical ictal onset pattern, and the ability to "tune" the detection parameters for the individual patient. Currently, EEG alarms lack specificity, so if used they are usually set to a high sensitivity that includes false positives, in order to avoid missing true positives. In addition, transducers are available for monitoring heart rate, pulse oximetry, chest respiratory excursion, nasal air flow, and muscle activity. Alarms can be programmed to activate when the high or low parameters of each device are reached. In practice, the heart rate and pulse oximetry alarms need to be set to levels sensitive enough to detect "real" events, but not so restrictive as to result in an excessive number of false alarms. The next issue to consider has to do with informing the attending nurse that a seizure detection, an excessively high or low heart rate, and/or a decline in oxygen saturation has occurred. The seizure detection program can produce a visual alarm on the monitor, if someone is viewing the monitor; and/or an auditory alarm, if it is connected to an acquisition computer with speakers. The pulse oximeter and heart rate alarms can usually be heard within or immediately outside the patient's room. In order to effectively alert the nurse responsible for the patient, the various alarms can be interfaced with a pager, cell phone, or nurse locator device. In addition, the alarms can be interfaced with a light system outside each room and an auditory alarm that can be heard if the nurse is in another room. A look down the corridor will then identify the origin of the room of interest by the light outside.

A final safety issue is the acute treatment of seizures. The most important aspect of acute treatment is effective planning. A "rescue" plan regarding treatment of seizures should be included in the orders. This may consist of an order to call the on-call physician for any seizure or, alternatively, after a specified number, type, and/or duration of seizures. If the covering staff at night includes anyone not on the primary team, they should receive clear guidelines as to the number and type of seizures that can be tolerated prior to intervention (e.g., three complex seizures in 8 hours, or one secondarily generalized tonic-clonic (SGTC) seizure). The type of treatment that may be used should be anticipated, so that the doses of the appropriate medications will be known well in advance of the decision to treat and can be kept in an appropriate, locked pharmaceutical area on the ward for rapid access. A standardized order set can be very useful in this regard and is essential in teaching institutions in which residents and fellows will also be involved in the patient's care (see below).

Pharmacy and Medications

Collaboration with the pharmacy is a key aspect of patient management in the EMU. The time at which medications are given will impact when trough and peak serum concentrations should be obtained. In addition, it is possible to alter the "profile" of medication administration to coincide with decision-making on morning rounds. For example, if the video EEGs are reviewed by 10:00 a.m., it would be reasonable to have a 10 a.m. and a 10 p.m. profile for a twice-a-day medication. This allows the team to alter the medication dose prior to the a.m. dose. The cumulative effect of earlier rather than later medication changes could potentially result in a decreased length of stay, while achieving the desired goals of monitoring.

One means of increasing efficiency, potentially decreasing medication errors, and following evidence-based guidelines is the use of a standardized order set. An example of one is provided in Figure 3-3. The usual orders, as well as seizure-specific orders, can be incorporated into a single form that permits efficient admission procedures that allow video EEG monitoring to begin as soon as possible. In addition, the order set in the example was designed to provide the opportunity for specific antiepileptic drugs (AEDs), which may be needed on an urgent basis, to be placed in the pharmacy medication storage device closest to the patient at the correct dosage. This allows rapid acquisition and administration of medication when needed to effectively treat seizures. The order set also serves as a teaching device for housestaff, if involved in the care of these patients.

The involvement of a pharmacist as part of the EMU team can greatly facilitate patient care. Inaccurate drug doses, uncommon drug interactions, and potential allergic reactions can be reduced by a pharmacist on rounds. Unfortunately, this is a relatively uncommon occurrence in most video EEG monitoring services. The relatively recent advent of more sophisticated automated pharmacy systems, in which medication orders are analyzed with regard to allergies recorded in the medical record and drug interactions, can help to mitigate some of the medication-related safety issues.

Pediatric Epilepsy Monitoring Physician Order Set	Apply Patient label

Mark the **"X"** for desired orders. If ☐ are blank, order is inactive. All pre-printed doses are based on normal renal and hepatic function and must be assessed for adjustment against the individual patient's renal and hepatic function and for interactions with other medications.

Height: cm	Weight: kg
Allergies:	☐ See Medication Reconciliation Form

Indication for EEG monitoring:

Admit with video EEG monitoring and seizure precautions to:

☐ Care Area 1A - PEMU

MEDICATIONS:

Schedule anti-convulsant medications for the following hours:

Daily	10
Twice a day	10 - 22
Three times a day	10 – 16 – 22
Four times a day	10 – 14 – 18 – 22

Drug(s)/Dose/Route/Frequency/Indication

-
-
-
-
-

☐ Hydroxyzine 0.5-1 mg/kg/dose IV or PO Q6H prn itching (maximum dose 25mg)

☐ Topical Lidocaine 2.5% / Prilocaine 2.5% (EMLA) cream for labs/IV start (see back of order set for maximum dosage

☐ Peripheral IV lock.

☐ D5W and 0.45% NaCL with KCL _____mEq/L IV at _____mL/hour.

☐ D5W and 0.2% NaCL with KCL _____mEq/L IV at _____mL/hour.

DIET: ☐ General diet for age. ☐ NPO after _____(time) on _____(date).
☐ Ketogenic diet: _____

ACTIVITY: ☐ Bed rest. ☐ Bed rest with bathroom privileges ☐ Ad lib. ☐ _____

OTHER:

URGENT ANTICONVULSANT THERAPY for PRN use in urgent situation A physician must be present for the initiation of medication (unless stated otherwise below). Administration by an R.N. and until patient is hemodynamically stable. (See back of order set for age definitions)

☐ Lorazepam (Ativan) _____mg IV (Neonates 0.05 mg/kg dose; infants and children 0.1 mg/kg/dose, maximum of 4 mg/dose; adolescents 0.07 mg/kg/dose, maximum of 4mg/dose.) Dilute dose with equal volume of 0.9% NaCL and administer IV push over 5 minutes.
Monitoring includes: respiratory rate, blood pressure, continuous monitoring of heart rate and oxygen saturation (pulse oximetry) during Lorazepam

FIGURE 3-3. Pediatric epilepsy monitoring physician order form.

☐	Fosphenytoin (Cerebyx) _____mg phenytoin equivalents IV (10-20 mg/kg/dose phenytoin equivalents) Administer over _____minutes (1 mg phenytoin equivalents/kg/minute, maximum of 150 mg phenytoin equivalents/minute) using a syringe pump or IV push. Further dilute to 25 mg phenytoin equivalent/mL concentration. The IV line must be flushed with 0.9% NaCL injection before and after administration with a sufficient volume at an equivalent mL/minute rate to clear the line
☐	Phenobarbital_____mg IV. Administer via syringe pump or IV push over _____minutes (10-20 mg/kg/dose) (1 mg/kg/minute, maximum of 30 mg/minute for infants and children, maximum of 60 mg/minute for adolescents greater than 60 kg).
☐	Diazepam Rectal Gel (Diastat) (no dosing guidelines less than 2 years of age; 2-5 years 0.5 mg/kg/dose; children 6-11 years 0.3 mg/kg/dose; children greater than 11 years 0.2 mg/kg/dose. Round dose upward to the next available dose.) ☐ 2.5 mg ☐ 5 mg ☐ 10 mg ☐ 15 mg ☐ 20 mg
☐	Sodium Valproate (Depacon) _____ mg IV. Dilute and infuse over at least 60 minutes. Do not exceed an infusion rate of 20 mg per minute. (10-30 mg/kg/dose) **Call Pharmacy to dispense dose STAT**
NOTIFY:	☐ Kidslink ☐ PNT ☐Neurology ☐Other: • • •

Prescriber's Signature	Prescriber's Pager #:	Service Pager #:
Prescriber's Printed Name:	Date:	Time:

FIGURE 3-3 *Continued.*

Improving Outcomes in the EMU

There are relatively few reports of interventions to improve a variety of outcomes in the EMU setting. One group used a total quality management (TQM) approach to improve communication problems between physicians, EEG technologists, nurses, and patients/caregivers (12). A multidisciplinary team used the TQM process with the result of creating new policies and practices that addressed the communication issues. In the end, it was the impression of the group that unit function had been improved and the TQM team was maintained to address patient care issues.

Another study assessed the role of the acute care nurse practitioner in the EMU (9). The efficiencies introduced by instituting this role in a two-bed EMU resulted in a decreased length of stay and a reduction in the average cost of testing on each patient. The cost savings were almost $100,000 during the first year, and almost $60,000 during the first quarter of the second year. A patient satisfaction survey indicated that 100% of patients were completely satisfied or satisfied with the care received. However, no comparative data were available prior to the study period. Subsequently, four outcomes—comprising patient satisfaction, clinical outcomes (seizures, absence of status epilepticus and injury), functional health status (patient/family education), and cost reduction—were targeted for improvement using the Clinical Value Compass Model (13). Team collaboration involved meetings between the professionals involved in the EMU, including a neurologist, an EEG technologist, a nurse practitioner, a staff registered nurse, a pharmacist, a unit secretary, and the epilepsy clinical trials coordinator. Although the study group was small (n = 22), the results indicated that patient care could be improved and cost savings achieved by carefully analyzing and intervening when possible in each step of the patient care process. This study highlights the importance of a multidisciplinary approach that considers the continuum of patient issues from the time of scheduling the admission to discharge.

A recent study used a questionnaire to query staff nurses as to the perceived efficacy of nurse education interventions to improve their comfort level when working in a pediatric EMU (7). The response of the vast majority of the responders (n = 37, 44% response rate) indicated that lectures and a variety of written resource materials enhanced their experience in taking care of patients in this setting.

Thus, available evidence indicates that a variety of patient and staff outcomes can be affected by targeted interventions. These studies need to be expanded with regard to the total number of participants and the application of more formal measures of outcome, especially those related to patient care.

SPECIFIC PROTOCOLS

In the following section, specific patient management protocols for ictal single photon emission computed tomography (SPECT), withdrawal of antiepileptic drugs, and induction of pseudoseizures will be discussed.

Ictal SPECT

As described in Chapter 24, Neuroimaging Localizing Procedures, SPECT is a well-established nuclear medicine technology for the localization of seizure onset. Although interictal SPECT has a relatively low specificity and sensitivity, ictal SPECT has a much higher yield (14). In theory, a patient with very frequent seizures could have intravenous access obtained and could then wait in the nuclear medicine department until a seizure occurred, at which time the injection could be performed. However, the need to perform the injection within 60 seconds of ictal onset (or sooner) and the unpredictability of seizure occurrence usually require an inpatient EMU admission. The EMU provides the ideal environment in which to have an EEG technologist identify the first clinical or electrographic signs of seizures and perform, or alert the nurse to perform, the ictal injection. In this section, an overview of patient management issues and ictal SPECT–related protocols will be considered.

The patient/caregivers need to be educated as to the rationale for, risks and benefits of, and processes involved in ictal SPECT. They need to understand that SPECT is a blood flow technique for helping to determine the region of seizure onset, most commonly in the evaluation for resective epilepsy surgery. An example of a localizing ictal SPECT that uses pseudocolor to demonstrate the area of hyperperfusion ("hot spot") can be more effective for teaching than the gray-white images of the raw data. It is useful to explain prior to admission that the results of the test may provide information that is not apparent on either the ictal EEG or the MRI, and that by combining all of the results a potential focus for resection or grid placement may become apparent. In terms of risk, the patient/caregivers can be reassured that the dose of radioactivity is minimal, but should understand that obtaining the injection may take several days depending upon seizure frequency. After admission, the patient/caregivers should understand that when a seizure is identified an EEG technologist or nurse will literally run into the room, perform the radionucleotide injection, and arrange transport to the scanner within1 or 2 hours after the injection. It should be communicated to the patient/caregivers that they can facilitate the process by activating the event button at the first observed sign or sensation of seizure onset. Because of the need to have slots available for scanning the patient after injection, all involved need to understand what days of the week and times of the day form the "window of opportunity" for the ictal SPECT. Setting realistic expectations will contribute to patient/caregiver satisfaction, as some may otherwise believe that the test is available at any time of the day or night when a seizure occurs.

Two patient populations require additional testing and information. The first is women of childbearing age, who should have a negative pregnancy test (serum β-human chorionic gonadotropin) confirmed prior to radioactive tracer injection. The second group is small children and older individuals who are not able to remain still for the SPECT imaging. This scenario may require the participation of an anesthesiologist for adequate sedation. The family needs to be informed of the small additional risk associated with general anesthesia, which is sometimes required. The care-providing team needs to coordinate the daily acquisition of the radionucleotide, availability of scanning time in the nuclear medicine department, and availability of an anesthesiologist. In addition, the patient needs to be made *nil per os* (NPO) in anticipation of the injection and anesthesia if required for scanning. Typically, this means placing an intravenous (IV) port the evening prior to the day of the anticipated injection to maintain hydration, beginning NPO after midnight, and hoping that a typical seizure occurs when the radionucleotide is available the next day. However, an IV port is routinely placed in anticipation of the need for acute intervention in the event that convulsions or status epilepticus occurs. Most pediatric patients can tolerate not eating until midafternoon, at which time the window of opportunity ends and the process is repeated for the next day.

The key issues that need to be decided by the time of EMU admission are as follows. *The staff that will be doing the injection needs to be identified.* This will be determined, in part, by state and hospital regulations as to who can handle radioactive material. The group of staff (nurses or EEG technologists) will need to take the appropriate nuclear materials safety course. The *injection time window* will then be defined according to the factors described above. The *location of tracer* in the EMU will be determined by the availability of staff and the seizure type. Complex partial seizures and secondarily generalized tonic-clonic seizures may evolve slowly enough that an individual can run into the patient's room with the tracer from a central monitoring station. However, rapidly secondarily generalized seizures may require an individual to sit by the bedside to perform the injection immediately after onset. The *need for sedation/anesthesia* makes the commitment of colleagues from the departments of nuclear medicine and anesthesia

TABLE 3-1. PROTOCOL FOR ICTAL SPECT INJECTION

Establish IV access with adequate size and location to ensure rapid infusion of tracer with minimal likelihood of subcutaneous infiltration
Consider specifics of IV connections to facilitate rapid and safe infusion of tracer and saline flush
Optimize pathway to infusion site (ensure patient room is close to monitoring station, remove obstacles, remove clothing at IV site)
Place absorbent, plastic-backed pad under IV site
At time of injection, announce "tracer in . . . , flush in" for recording the exact times later
Transport patient to the scanner accompanied by nurse and support for potential seizures
After the patient leaves the EMU to undergo scanning:
Perform radioactivity check in room
Record specifics of injection (see EEG Technologist Worksheet)

essential to ensure that the scan can be performed under optimal conditions when the seizure occurs.

The development of protocols to perform ictal SPECT in the setting of the EMU have previously been described (15,16). The essential elements of a protocol to facilitate ictal SPECT are presented in Table 3-1, and an example of a technologist ictal SPECT worksheet in Table 3-2. However, each epilepsy center will need to determine the best means for accomplishing these steps with the available technical and human resources.

The use of ictal SPECT is enhanced by comparison of the brain perfusion with the interictal SPECT image. Traditional side-by-side comparison between images is significantly augmented by computer algorithms that subtract an interictal SPECT from the ictal SPECT and co-register the subtracted image on an MRI, known as SISCOM (subtracted ictal SPECT co-registered to MRI) (17). The interictal scan can be obtained prior to or after the EMU admission to obtain the ictal SPECT. However, for individuals with frequent, subtle, or electrographic seizures, the best way of knowing that the interictal scan is truly interictal is to use video EEG recording to ensure that no seizures have occurred in the 24 hours prior to the interictal injection. This injection can be performed after medications have been provided following the ictal SPECT, or on a day when no seizures have occurred while waiting for a typical seizure. The latter method optimizes the use of resources, because the tracer ordered for the ictal injection is not wasted if a seizure does not occur.

TABLE 3-2. EEG TECHNOLOGIST WORKSHEET FOR ICTAL SPECT INJECTION

Patient name:
Medical record number:
Date of ictal SPECT injection:
Time of injection in:
Time of flush in:
Seizure clinical onset time: Seizure clinical off:
Seizure EEG onset time: Seizure EEG off:
Time of secondary generalization (if it occurs):

Antiepileptic Drug Reduction

The primary goal of the EMU admission is most frequently to record typical seizures for classification and quantification, frequently in the setting of presurgical evaluation. For individuals who do not have seizures daily or every other day, it is necessary to facilitate the occurrence of seizures. A variety of classical activation procedures exist to make the admission more effective and efficient. Although pharmacological activation has been used in the past, it was found that the focus activated did not always correspond to the one responsible for the typical seizures. This method, and currently used techniques including AED withdrawal, hyperventilation, and sleep deprivation, are described in detail in a comprehensive review of activation procedures (18). Only considerations pertinent to patient management for medication withdrawal will be discussed herein.

Although a standard method of withdrawal is desirable, this is a challenge given the multiple variables involved for each patient, which include seizure frequency, seizure type(s), history of generalized tonic-clonic seizures, use of specific AEDs, and AED levels at the time of admission. One method is to lower an individual AED by $\frac{1}{3}$ to $\frac{1}{2}$ each day until discontinued. If the patient is on multiple AEDs, each can be tapered and discontinued individually, or all AEDs can be decreased by the same percentage each day. The logic for doing the latter is that therapeutic levels of one or more AEDs may prevent seizure occurrence when only one medication is eliminated (19). The reasons for not discontinuing a medication abruptly are concern for precipitating generalized tonic-clonic seizures and the theoretical possibility of producing a rebound seizure that is not a characteristic seizure type (18).

Several studies performed since the introduction of the newer AEDs address some, but not all, of the issues noted above. One prospective study included 20 patients with temporal lobe seizures and 16 patients with extratemporal-onset seizures admitted for video EEG monitoring (20). The dosage of a single AED was decreased by 50% if no seizures occurred during the first 24 hours of monitoring. The dosage of the same drug was then decreased once every 24 hours or until seizures occurred. Then, additional AEDs, if any, were tapered in the same manner. Barbiturates and benzodiazepines were not tapered. Fourteen patients (4 temporal, 10 extratemporal) had seizures within the first 24 hours. Compared with the temporal group, the extratemporal group had a shorter mean time to the first seizure

(2 days versus 4.4) and a greater total number of seizures (5.5 versus 10.4). The reported seizure frequency prior to monitoring was not a predictor of time to first seizure or total number of seizures, but the history of generalized tonic-clonic seizures was associated with the occurrence of these events after AED withdrawal. Another study used a rapid discontinuation paradigm stopping all conventional AEDs on the second day of recording followed by the more recently approved medications on day four at the rate of $\frac{1}{3}$ of the daily dose per day (21). All of the 89 adult patients were selected on the basis of known complex partial seizures. The mean time to the first complex partial seizure was 3.2 days, consistent with other reports. Notably, almost 50% of patients had secondarily generalized tonic-clonic seizures or clusters, including 75% of those who had phenobarbital or primidone withdrawn. This finding, consistent with that found in other rapid discontinuation protocols (22), led the authors to recommend a slower withdrawal of these AEDs.

Recently, a more quantitative approach has been used to evaluate seizure frequency, intensity, and duration. The technique involved 3 days of baseline recording, followed by 3 days of carbamazepine or valproate taper and discontinuation, followed by 3 more days of recording (23). The results indicated that withdrawal of carbamazepine was associated with an increase in seizure frequency, intensity, and duration, whereas only duration significantly increased with valproate discontinuation. The localization of ictal onset and seizure semiology were not affected by the withdrawal of either medication. Similar methods were used to compare the withdrawal of carbamazepine and lamotrigine (24). Significant increases in seizure frequency and duration, but not in intensity, occurred during the withdrawal of medication for patients on monotherapy with either drug and for those on polytherapy with combined carbamazepine and lamotrigine.

In summary, some patients admitted to the EMU will have seizures during the first 1–3 days without reduction of AEDs. When reduction is pursued as an activating procedure, it is reasonable to expect an increase in seizure frequency and duration. IV access should be pursued prior to the time of medication reduction. The elicited seizures will most likely be of the same type and ictal onset as the typical seizures and, therefore, useful for pre-surgical localization. When the discontinuation is very rapid, particularly with barbiturates and benzodiazepines, there will be a risk of precipitating secondarily generalized tonic-clonic seizures and/or clusters of seizures approaching 50% of patients. For all patients in whom medications are being withdrawn, it is prudent to have a clearly defined rescue plan. The plan should state how many seizures of what type will elicit urgent treatment with AEDs. A variety of protocols exist such as giving an oral loading dose of the medication being withdrawn if two or more generalized tonic-clonic seizures occur within 12 hours of each other and an oral or intravenous medication if these occur within a two hour period (18). Another published approach is to administer 2 mg of intravenous lorazepam if two generalized tonic-clonic seizures occur within 1–3 hour and >4 of complex partial seizures in 24 hours (21). The choice of the intravenous medication is limited by the preparations currently available, and includes levitiracetam, lacosamide, valproic acid, phenobarbital, fosphenytoin, phenytoin, and benzodiazepines. Rectal diazepam has been approved for the treatment of serial seizures (25) and thereby provides an alternative when intravenous access fails or has not been previously established.

Induction of Psychogenic Pseudoseizures

A wide range of physiological and nonphysiological events enter into the differential diagnosis of seizures. Examples of physiological events particularly common in children include gastroesophageal reflux, night terrors, attention-deficit hyperactivity disorder, and tics, whereas parasomnias and cardiac and autonomic abnormalities are present across all age groups. The combination of video EEG monitoring and etiology-specific tests (e.g., holter monitoring, tilt table, sleep study) is effective for distinguishing a seizure etiology for most paroxysmal physiological events. The group of nonphysiological events termed "psychogenic/pseudo seizures" is perhaps the most common and problematic type of nonepileptic event encountered in pediatric and adult EMUs. It is this group that has received the greatest attention in the literature given the ethical and technical considerations surrounding how these patients should be managed in the EMU. As no "gold standard" protocol exists for their management, the considerations that each

TABLE 3-3. ADVANCE PLANNING FOR INDUCING NONEPILEPTIC EVENTS

Setting in which to induce events
With or without (video) EEG (clinic vs. lab vs. EMU)
Outpatient versus inpatient
Preferably in an EMU setting to facilitate acceptance and provide subsequent educational and psychiatric support
Induction protocol
Choose specific method of induction
Allow time for a spontaneous event to occur
Choose method of confirming typical event
Consider what to tell the patient
Consider patient's home environment in deciding how to give the diagnosis of a nonepileptic event to the patient and caregiver(s)
Antiepileptic drug management
Neurologist/psychiatrist/mental health follow-up

practice/institution must consider will be discussed. These are presented in Table 3-3, which includes and expands the "principles of eliciting conversion symptoms" previously described (26).

Deciding Whether to Use Induction Techniques

This decision will be made mainly on the basis of the feelings of the care providers (physicians, nurses, EEG technologists) regarding the ethics of attempting to induce possibly nonepileptic events. The frequency with which induction methods are used can be derived from several surveys, the majority of which involve adult patients. In one study, a survey was sent to 60 epilepsy centers, from which 51 responses were returned (27). It was found that 73% of centers use one or more forms of induction, with issues regarding liability and ethics being the most common concerns reported. All centers but one told the patients that the induction procedure had the potential of eliciting an event. Another study surveyed the American Epilepsy Society and received questionnaire responses from 426 individuals, finding that 40% of these individuals used induction methods (28). These two studies were performed in the same year, 1996, and may reflect differences in attitude between individual practices that have EMUs readily available and individual practices without a comprehensive epilepsy center.

The various aspects of the ethics issue have been the subject of recent review (29) and eloquent debate (30,31) in the neurological literature. The fine points of this debate are beyond the scope of this discussion. In summary, the major objection to using induction techniques without the knowledge of the patient is that the process is fundamentally deceptive and dishonest. This could potentially adversely affect long-term trust between the doctor and patient, although no evidence exists that this is a common outcome, and it is extremely unlikely to occur if testing is performed with compassion (editor, personal communication). Another concern is the possibility of precipitating an atypical nonepileptic event that could be misleading. The arguments in favor of induction techniques include the importance of making a correct diagnosis so that unnecessary and potentially dangerous adverse effects of medication can be avoided and appropriate psychologically oriented therapy may begin. The latter is particularly important given the significant incidence of sexual and physical abuse as the root cause of nonepileptic behaviors, particularly in women. In addition, induction methods may be cost-efficient when spontaneous events do not occur at the initiation of monitoring. The ability to record a typical event provoked by an induction technique may make the difference between a monitoring admission that allows a practitioner to arrive at the correct diagnosis and an admission that proves nondefinitive. Some investigators have suggested that if the practitioner uses an induction method that is not a "placebo," the problem of perceived deception is less of a concern (see below); however, this is a somewhat circular argument.

Determining the Setting for the Procedure

The current gold standard for making the diagnosis of a psychogenic seizure is to record the specific behavior during video EEG monitoring (29,32). However, it is conceivable that the behavior could be so obvious or the induction by an external trigger so clear that monitoring is not necessary. In the latter circumstance, observation of the behavior in question either directly or on video without simultaneous EEG may be adequate if the cost of monitoring is prohibitive. Although the inpatient EMU is the most common setting in which video EEG monitoring for spell classification is performed, recent reports (33,34) indicate that outpatient monitoring is an option for some patients. In one report of 74 adult patients who underwent 1–2 hours of outpatient video EEG monitoring, an event was provoked in 69% of patients (33). It is unclear how these patients were selected for outpatient rather than inpatient monitoring, other than on the basis of strong "clinical suspicion" in the outpatient clinic. A similar result was demonstrated in a study of 30 patients recorded in the outpatient setting, in which 66% of 15 patients who were randomized to an induction technique group had typical nonepileptic events (34). The 30 patients in the study were selected based upon clinical suspicion of nonepileptic events, absence of epilepsy, and a history of more than a single potential nonepileptic spell.

Deciding upon an Induction Protocol

It is critical for the neurologist to determine exactly what behavior is the source of the patient's disability and is therefore to be induced in the EMU. This can be accomplished by a careful clinical description prior to admission, with or without seeing the behavior on a home video provided by the patient. Following the recording of the spell in the EMU, it is essential to confirm that it was a typical event. In all cases, with the patient's permission, the video should be shown to someone who has witnessed the patient's typical attack (without disclosing the result of the simultaneous EEG) to verify that the recording demonstrates the type of event in question, unless that person has already witnessed and verified the event at the bedside.

Irrespective of the technique that is used, the clinician has wide latitude as to what to tell the patient prior to application of the induction method. It is possible to state that any of the methods frequently precipitates seizures without revealing that it is being done to elicit a nonepileptic event. Alternatively, one can tell the patient that the psychogenic events are part of the differential diagnosis of seizures and that the test will be useful in discriminating between the two, and obtain consent to do the test (26). The timing, manner, and emphasis of this information can vary signifi-

cantly. Finally, patients were consented in a recent investigation for a study in which they were randomized to either suggestion (hyperventilation and photic stimulation) or no suggestion during outpatient video EEG, after being told that suggestion could precipitate a psychologically based event (34). Notably, there was not a statistically significant difference between event occurrences in the two groups.

A wide variety of specific methods of induction described to precipitate nonepileptic events have been listed in comprehensive reviews of psychogenic seizures (26,30,32,35). The most commonly cited methods include hypnosis, application of a tuning fork to the body, placing of patches or moist material on the skin, saline injection, hyperventilation, and photic stimulation. However, a common feature to all protocols, whether stated explicitly of not, is the power of suggestion. This most frequently used form of suggestion is the "psychological environment" in which the induction takes place. The language that is used is intended to create the *expectation* that an event will take place. The use of phrases such as "this *will* result or is *likely* to result in a spell" is more predisposing than "it is *possible* that a spell will occur" or "*sometimes* a spell happens." Furthermore, the reassurance that it is safe for the event to occur by drawing the patient's attention to the pads on the bed, to the availability of oxygen and suction if needed, and to the attendance of care providers during the procedure, all set the stage for a psychogenic spell to occur. Whatever the specific induction technique, it should be noted that spontaneous typical spells can occur within 24–48 hours of admission, and that an accordingly adequate period should be allowed (34,36,37).

The range of specific methods of induction techniques is best illustrated by saline infusion (37–40) and hyperventilation/photic stimulation (26,34,36). The saline infusion technique has been reported in the studies cited as an effective means of precipitating the event of interest in more than 60% of individuals, although the populations reported differ. It is acknowledged that the technique involves the use of a placebo, and argued that the lack of openness with the patient is justified by the goal of determining the correct diagnosis to guide appropriate therapy. Unlike the other placebo techniques, saline infusion is invasive in that intravenous access must be established. The use of hyperventilation and photic stimulation (individually or in combination) has ethical merit in that both techniques are routinely used to activate epileptic seizures and, therefore, are not strictly placebos.

When the diagnosis of a pseudoseizure has been made, there should be a plan in place to initiate treatment. A variety of options exist involving psychiatric and psychological modalities; in addition, a proportion of patients will stop having events when told of the nonepileptic etiology (41). However, several issues need to be addressed in the EMU, including how the information should be conveyed to the patient/caregivers; what should be done with the AEDs, if these are being used; and what role the neurologist has in relation to the psychiatrist/psychologist. The current state of knowledge does not allow answering these questions based upon carefully designed experimental paradigms testing one approach versus another. Rather, we must be informed by the counsel of experienced clinicians who have given thoughtful consideration to these management issues, which have recently been reviewed (29,42). In 1990, a protocol was described to inform patients that their spells were nonepileptic (43). This protocol emphasizes the importance of discussing in detail the results of the video EEG monitoring session that demonstrates that there is no abnormal electrical correlate to the event. The patient is informed that these types of events can be part of other psychological issues, and the association with a history of sexual abuse can be noted. Finally, the importance of follow-up with a mental health professional is stressed. In an insightful discussion of the issues surrounding the treatment of pseudoseizures (42), Kanner raises the issue of the immediate goal of treatment. Contrary to intuition, he argues that this goal should not be to produce cessation of events, but rather to convince patients and their physicians that the events are not epileptic seizures. This reflects the reality that much of the morbidity arising from pseudoseizures is iatrogenic, resulting from medications, invasive procedures, and hospitalizations. Such morbidity is due, in part, to the reluctance of mental health care professionals to accept the diagnosis based upon video EEG monitoring. This was demonstrated in a recent study in which 70% of neurologists, but only 18% of psychiatrists, endorsed video EEG monitoring as diagnostic of a nonepileptic event (44). It is difficult to justify the continuation of AEDs for the treatment of pseudoseizures, and thus it is reasonable to taper and discontinue these medications in a manner that will not necessarily precipitate withdrawal seizures (a particular concern with barbiturates and benzodiazepines) *However, if there is any possibility of the coexistence of seizures (e.g., the presence of frontal or temporal interictal epileptiform activity), then medications should not necessarily be discontinued at the time of discharge from the monitoring unit.* Up to 12% of patients with epilepsy may not have interictal epileptiform discharges during admission to the EMU (45). Finally, the importance of the neurologist continuing to see that patient after discharge from the EMU has been stressed as a means of maintaining a therapeutic alliance as the transition to the mental health professional is accomplished (42).

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4

EMU DESIGN AND GUIDELINES

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The epilepsy monitoring unit (EMU) is a special environment designed for the evaluation and treatment of people with epilepsy or suspected epilepsy. Usually, the goal of an EMU evaluation is to (a) simultaneously record video and EEG and (b) examine the subject during seizures or other suspicious events. Video monitoring is usually performed for one or more of the following reasons: (a) characterization of events suspected to be seizures, (b) characterization of the epilepsy syndrome, (c) localization of the seizure onset area prior to epilepsy surgery, and (d) quantification of seizure activity. Patients are also often admitted for exacerbation of seizures or for toxicity related to treatment. The design of the EMU, the personnel staffing of the EMU, and the standards of care in the EMU should reflect these basic needs.

The National Association of Epilepsy Centers has defined three levels of specialized epilepsy care (10): third-level medical center for epilepsy, third-level medical–surgical center for epilepsy, and fourth-level center for epilepsy. Third-level medical centers provide a basic range of medical, neuropsychological, and psychosocial services needed to treat patients with refractory epilepsy, but do not perform resective epilepsy surgery. Third-level medical–surgical centers additionally offer resources and personnel needed for noninvasive evaluation for epilepsy surgery and performance of straightforward resective epilepsy surgery. Fourth-level epilepsy centers additionally offer resources and personnel needed for video monitoring with intracranial electrodes, cortical stimulation studies, and the full range of surgical procedures for epilepsy. The design of an EMU, the required personnel, and the standards of care will differ depending on the level of epilepsy care offered. The following discussion considers EMU design, personnel, and standards in terms of the needs addressed by an EMU evaluation and the levels of epilepsy care offered.

EPILEPSY MONITORING UNIT DESIGN

Physical Design

Items Governing Physical Design

A primary function of the EMU is recording seizures and examining patients during those seizures. The physical design of the EMU must therefore follow this function. Four interrelated considerations govern the design of the EMU. First and most important is patient safety. Epileptic seizures, which can result in a host of medical complications, occur several times daily in the typical EMU. Because antiepileptic drugs are usually reduced during evaluation, seizures occurring in the EMU are typically more severe than those the patient usually experiences. An important safety goal is recording a sufficient number of seizures in a timely fashion without precipitating a significant seizure acceleration or overt status epilepticus. Another important safety goal is preventing trauma or other complications of seizures.

A second, related consideration governing design is observation. Patient safety is related to the number and severity of seizures. Patients must be under constant visual and EEG observation so that seizures can be detected, quantified, and treated if they are occurring excessively. A third consideration is access. Once seizures are detected, the patient must be reached quickly so that he or she can be examined and, if necessary, treated. The fourth consideration is the desirability of a normal milieu. Seizure frequency typically decreases following inpatient admission (1), possibly because the demands of daily life are decreased in the hospital. Maintaining normal activity and the usual conditions of daily life may facilitate seizure recording.

Overall Physical Design

The overall layout of the epilepsy monitoring unit should maximize the ability to observe and access monitored

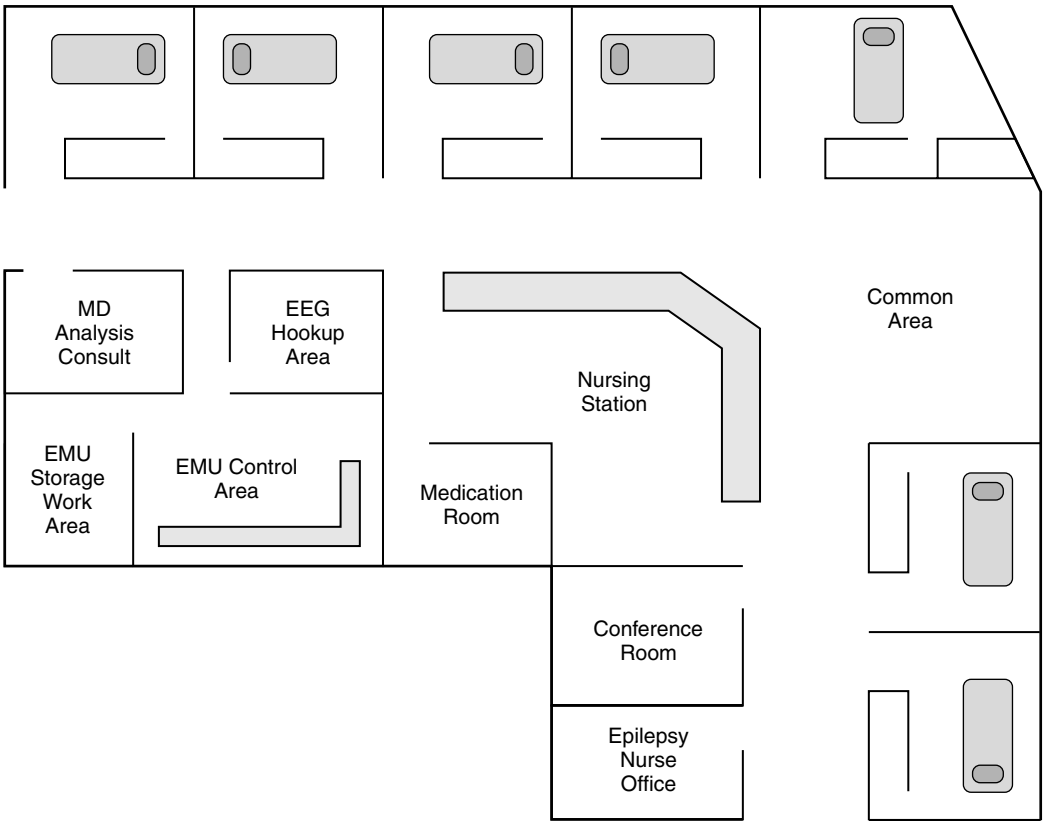

FIGURE 4-1 Typical physical configuration of an epilepsy monitoring unit.

patients. This purpose is served by placing the nursing station at the intersection of two corridors or at a corner of the hospital building, and by placing a patient common area across from the nursing station and encouraging patients to spend most of their waking time in the common area (Figure 4-1). Placing a nursing station at the center of a semicircle of rooms also facilitates observation and access. It should be noted that the prevalence of private hospital rooms in the United States significantly limits access and observation. The older standard of two-patient rooms or a large open ward, while less comfortable to the patient, facilitates observation and access and would likely increase patient safety.

Design should reduce the number of objects with sharp corners that might injure a falling patient; remaining corners should be padded. Some centers prefer carpeted floors to minimize the trauma associated with falls and to promote a normal milieu. Others feel that a carpeted EMU is inappropriate because of the increased risk of rug burns and infection (2). Carpets also increase the risk of static electrical discharges during dry winter months, which may be a concern when intracranial recording is being performed. Padded tile is a reasonable alternative that can be readily cleaned. The ability to temporarily lock down a unit to contain a patient with postictal confusion or running seizures is useful.

Design of Individual Rooms

Safety, observation, and access also govern the physical design of individual patient rooms. Arrangements should ensure privacy when appropriate (e.g., design of the bathroom), but locks should be removed and rapid access must be available at all times. Many seizure-related accidents occur in the bathroom; attention to sharp corners, padded floor tiles, and recessed sinks is especially important here. Temperature-limiting devices should be installed on shower heads, and seating should be available in shower stalls. The windows of the room should be hardened to prevent escape of patients during postictal psychosis or confusion. Larger high-backed chairs with arm rests help to prevent falls when seizures start in the sitting position. In-room accommodations should include a fold-out bed for family or a friend; this allows for an observer familiar with the patient to alert staff to the occurrence of seizures, and decreases the occurrence of injury.

Design of the Common Area

A comfortable, attractive common area in direct view of the nursing station is the centerpiece of maintaining a normal milieu. This should include comfortable furniture, tables, and an abundant supply of games and puzzles. Including

a large-screen television, computers with Internet access, appropriate exercise equipment (and, in Minnesota, several pots of warm coffee) encourages patients to spend time in the common area. Patients should be encouraged to eat meals together in the common area. Laundry facilities are not only practical for longer stays, but also encourage the patient to assist in self-care and prevent regression to a "sick role." Encouraging patients to congregate in the common area during the day has many advantages. First, it increases the likelihood that seizures will be detected. Second, it decreases the isolation associated with epilepsy and promotes interactions with other patients with epilepsy. Relationships formed with other patients during an EMU stay are often an important benefit of an evaluation at an epilepsy center. Third, a group of patients in a common area provides an ideal opportunity for general education regarding epilepsy or facilitated group therapy. Finally, encouraging congregation in a common area increases the semblance of a normal life that may help promote the occurrence of seizures.

Physical Design Concerns for the Level IV Epilepsy Center

In addition to the above, neurodiagnostic equipment and furnishings must meet electrical safety and other standards applicable to intracranial recording (3,4,5).

Design of EMU Information Systems

The required safety and technical features of video EEG monitoring systems, and other technical issues, are addressed in Chapter 8, Special Considerations in Pediatric Monitoring, and in several issued sets of guidelines and recommendations (3,4,5). Here we provide a brief overview of the configuration of information systems necessary to achieve the tasks typically performed in an EMU.

EMU information systems are organized to store video and EEG information, and to transmit it to staff who observe, interpret, prune, and archive relevant portions of that information. Signals recorded in contemporary EMUs are almost uniformly digital. Contemporary digital technology allows efficient recording and manipulation of an overwhelming amount of data, more than could possibly be reviewed by expert physicians or stored in its entirety. Unfortunately, available computerized algorithms do not detect all seizures or epileptiform abnormalities. A combination of human screening, algorithmic detection, and marking of relevant portions of the record by patients or staff is generally necessary. Digitized video and EEG signals are easily transmitted between various computers using network technology. The configuration of such networks is driven by the observation, interpretation, and storage needs that define the function of the EMU.

In a typical EMU, video, audio, EEG, and marking signals are recorded individually for each patient undergoing evaluation. The ability to record video and audio from multiple areas of the unit is important to allow patients free range throughout the EMU and to promote a normal milieu. Continuous real-time video at the nursing station is critical to detect seizures. Additionally, continuous real-time EEG at the EMU control area is important so that subtle seizures or nonconvulsive status epilepticus can be detected and the integrity of the recording maintained. Review stations are necessary offline analysis, pruning, and archiving—both by technical staff in the EMU control area and by physicians, preferably in a separate room. Finally, the capacity to review and archive individual patient information off site, both in real time and offline, is very useful for emergency assessments and to optimize work flow.

The video monitoring systems and network architecture that make the most sense will vary depending on the individual situation. Local needs, institutional resources, available hardware, extent of use, and institutional and public regulations all must be considered. Health Insurance Portability and Accountability Act (HIPPA) issues are not trivial and should be carefully addressed. However, the EMU functions outlined in the paragraph above must receive primary consideration. One configuration fulfilling these functions will serve to illustrate (Figure 4-2). Video and audio signals from various areas of the unit may be linked to a switch prior to processing by the central processing unit (CPU) associated with the patient. Video–audio signals corresponding to the patient's location can then be transmitted to the screen assigned to the patient in the nursing station prior to entering the CPU associated with the patient. Keeping the patient "on camera view" as he or she wanders about the unit is one of the most important (and challenging) duties of EMU staff. Commercially available software synchronizes and processes EEG, video, audio, and marking signals in the CPU associated with the patient; computer algorithms typically perform spike and seizure detection here as well. Processed signal typically "flows through" the CPU and is stored on a server. Server-based video, audio, EEG, marker, and detection files can then be accessed by review stations on a local network. Recorded information can thus be accessed in "real time" for acute assessment, or "offline" for further analysis, pruning, report generation, and archiving. Whenever possible, the EMU network should be independent of the hospital network and "backbone" to minimize down time.

Server-based files can also be accessed off site, either over a dedicated connection (e.g., a fiberoptic line) or over the Internet. The advantages of a dedicated line are security, speed, and bandwidth. The major disadvantage is cost, which is much higher than for an Internet service provider. Accessing server files over the Internet offers maximum flexibility; a computer with the appropriate software can theoretically access EMU server files from any Internet connection at much lower costs. However, the bandwidth of a typical cable modem or digital subscriber line may not

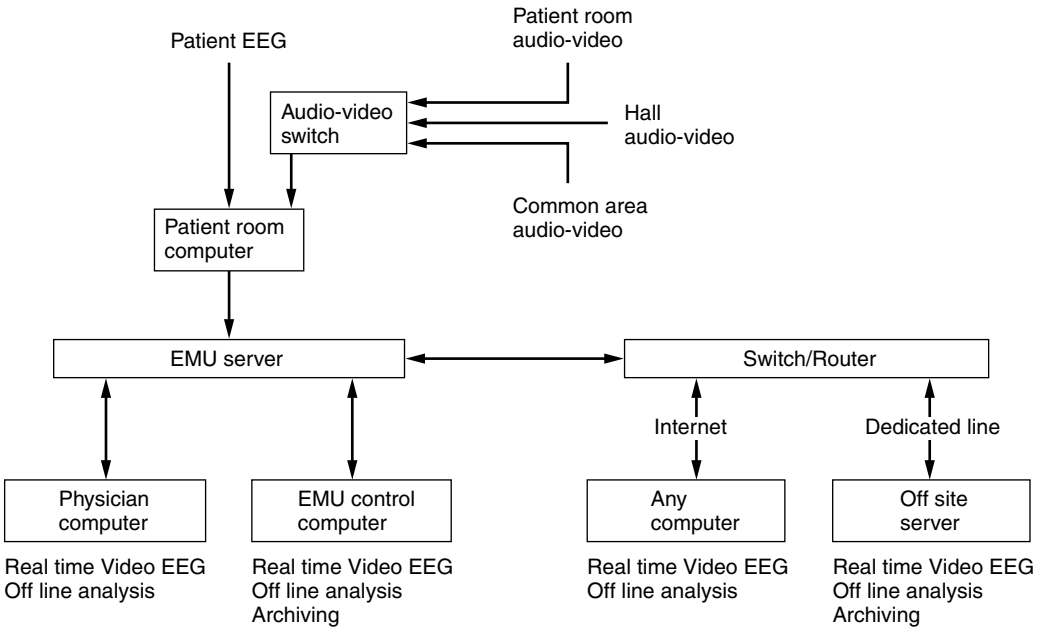

FIGURE 4-2 Information flow in an epilepsy monitoring unit computerized network (see text).

allow real-time video analysis, and patient confidentiality issues must be carefully considered.

System redundancy costs more, but is important so that data are not lost when system components fail. For example, the system configuration in the EMU staffed by the authors offers three levels of redundancy. If the EMU server fails, synchronized and processed files will be stored to the CPU associated with the patient. If the CPU associated with the patient fails, EEG (but not video or audio) data will be stored to the recording unit the patient carries on his or her person. The latter two components can usually store more than 24 hours of data, allowing plenty of time to react to the component failure and make alternative arrangements.

EPILEPSY MONITORING UNIT PERSONNEL

Introduction

Ultimately, information recorded in an EMU must be pruned, analyzed, synthesized, and responded to. Even the best information systems do not help much if the information obtained is not accessed, synthesized, and used by caregivers to benefit the patient. The interface between information systems and personnel is a central preoccupation of contemporary business studies, and these ideas are very relevant to the highly data-driven situation in the EMU. Protocols outlining information flow, analysis, report generation, and archiving are probably as important as the architecture of the information systems. Guidelines regarding who should communicate what to whom and in what circumstances are very helpful, though all staff must understand that guidelines will occasionally need to be ignored when the clinical situation demands this.

The NAEC guidelines (10) list the types and qualifications of required personnel working in the EMU. These vary somewhat depending on the level of epilepsy care delivered. EMU personnel have multiple responsibilities, but two are critical: (a) continuously observing patients to allow examination during seizures, ensure that excessive seizures do not occur, and provide first aid; and (b) ensuring integrity of recording so that vital information is not lost when seizures do occur. The NAEC guidelines state that "continuous observation by EMU staff or epilepsy staff nurses is highly recommended, supplemented as appropriate by frequently reviewed spike and seizure detection. Reliable and appropriately trained family members or nursing assistants may assist in some situations. A higher nurse-to-patient ratio than in standard care is necessary. For video-intracranial EEG monitoring continuous observation by EEG technologists or epilepsy staff nurses is mandatory" (10). This standard is widely followed in EMUs around the world (7). In general, nurses are responsible for patient safety and EEG personnel for recording integrity.

Monitoring Technician

The NAEC guidelines (10) define monitoring technicians as individuals trained in seizure observation and capable of maintaining recording integrity in the absence of an EEG technologist. They should be able to recognize clinical seizures and communicate with other staff as appropriate.

They should be able to recognize artifact, reattach several scalp electrodes, troubleshoot minor system failures, and perform routine system maintenance tasks. They should be certified in basic life support.

EEG Technologists

The duties and required skills for EEG technologists are detailed in the appropriate guidelines (3,10). EEG technologists are able to attach a full complement of electrodes, maintain integrity of the EEG recording, observe for seizures, examine patients during seizures, and operate and troubleshoot equipment. EEG technologists should be able to recognize the clinical and electrographic features of most seizures and alert nursing or physician staff following prescribed protocols. In some units, EEG technologists with further training will screen and "prune" studies into a more manageable file for physician review and archiving; in academic centers these functions are typically performed by physicians undergoing advanced training in epilepsy. EEG technologists are preferably board-eligible or certified by the American Board of Registration for EEG Technology (ABRET). They should be certified in basic life support. Chief technologists should be ABRET-registered and have additional training and experience in long-term monitoring. At least several EEG technologists in fourth-level centers must have experience with long-term monitoring with intracranial electrodes and with the safety and recording issues associated with cortical stimulation.

Biomedical Engineer/Information Systems Support

This individual has at least two responsibilities. The first is to ensure that the video EEG equipment, other electronic equipment, and physical configuration of the EMU pose no electrical danger to patients. This function can often be fulfilled by the hospital biomedical engineering department, but extensive physician input is necessary. Special circumstances pertaining to the EMU must be considered, especially when intracranial recordings will be performed. The second responsibility is information systems support. Because of the pervasiveness of information systems in the contemporary EMU, extensive support is necessary, usually much more than can be provided by staff devoted to general hospital information systems. It is preferable to have at least part-time staff devoted to the EMU; often this individual will also have other administrative responsibilities.

EMU Nursing Staff

Responsibilities of the EMU nursing staff include routine epilepsy patient care, administration of medications, examination during seizures, first aid during seizures, and patient and family education. Nursing staff should have additional experience with epilepsy, medications used to treat epilepsy, psychiatric conditions associated with epilepsy, and psychogenic nonepileptic events. In fourth-level centers, nursing staff should have additional experience with postoperative neurosurgical care, as well as with head dressings and other issues associated with long-term monitoring with intracranial electrodes. High demand for nurses and frequent rotations make retention of an experienced cadre of epilepsy monitoring nurses a major challenge. An ongoing program of training and updating is helpful to promote a uniform approach to patients in the face of constant change in nursing personnel. In this regard, a clinical nurse specialist permanently associated with the EMU is almost essential. This individual should have extensive experience in neuroscience nursing and epilepsy. Responsibilities include coordinating nursing functions and education, organizing patient education, and acting as a liaison between nursing staff and EMU technologists as necessary.

Physicians

Physicians play multiple roles. They are ultimately responsible for all aspects of individual patient care in the EMU. Physicians synthesize the information that continually emerges during the evaluation, generate the required reports, and use the information generated to address the problems that prompted the evaluation. They are responsible for sharing results with the patient and referring physician. NAEC guidelines state that physicians attending in the EMU should be "board certified neurologists with expertise in epilepsy, clinical neurophysiology, video-EEG monitoring, pharmacology of anticonvulsant drugs, and the vagus nerve stimulator. Generally neurologists would have undergone fellowship training in these topics. At least one of these individuals should be board certified in clinical neurophysiology" (10). In fourth-level centers, physicians should have experience in the interpretation of intracranial EEG recordings and in the performance and interpretation of cortical stimulation studies. At least one physician, often the director of the overall epilepsy program, should serve as medical director of the EMU. This individual should have extensive additional experience in video monitoring technology and a good overall command of procedures and administrative issues in the EMU; he or she will often help to administer EMU staff, take the lead on quality assurance, and interact with hospital, nursing, and administrative systems as necessary.

STANDARDS

Generating standards, seeing to their implementation, monitoring the degree of implementation, and changing standards in the overall context of quality assessment is

one of the most important functions of the EMU director and nursing administration. Standardized orders are widely available on contemporary electronic medical record systems and are a powerful tool for implementing standards of care. Thus the EMU director and staff are generally responsible for generating such order sets pertaining to EMU patients. There are no published or widely accepted standards of care for people evaluated in an EMU. The NAEC guidelines (10) state that protocols addressing the following "are useful."

Examination during Seizures

Characterization of seizures and other events is a major purpose of EMU evaluation. EMU staff examination during seizures supplements information provided by clinical semiology and EEG (7). The EMU medical director should devise a standardized protocol for examination during seizures that should be used by all staff as appropriate. The examination protocol should be simple, and should examine the patient's ability to recall information during seizures and examine postictal speech (8,9). Standardizing communication between EMU nursing and monitoring staff, and determining which have primary responsibility in examining a patient, is important. Printed copies of the protocol in patient rooms help ensure that patients are properly examined.

Seizure Numbers or Severity Requiring Notification or Treatment

Medications are often reduced during evaluation in an inpatient EMU to prompt recording of seizures (7). Medication reduction is not recommended in the outpatient setting and should not be done without a physician or an extensively trained nurse clinician on the premises (10). Medication reduction may result in seizure exacerbation, increased seizure severity, or acute repetitive seizures. The numbers and types of seizures requiring physician notification must be clearly documented in patient orders. "Rescue medications" to be administered once seizure number or severity exceeds a documented threshold should be specified. A uniform approach to these needs is important, with the understanding that there will be exceptions. For example, EMU directors should decide whether intravenous access and intravenous benzodiazepines will be the default option for all EMU admissions. Arrangement with a nearby hospital to provide emergency services is mandatory for outpatient EMUs.

General Safety Protocols for Patients Undergoing EMU Evaluation

Seizures may result in falls, trauma, aspiration, or other medical complications. Even death (sudden death in epilepsy (SUDEP)) may rarely occur. These complications are not always preventable, but a uniform approach probably reduces their occurrence (7). The following should be considered: (a) evaluation for fall potential and implementation of preventative measures; (b) padding of bedrails and decision as to how many bedrails (perhaps all) should be up at night; and (c) first aid, positioning, and observation during and following generalized tonic-clonic seizures. Addressing details is important and may result in decreased morbidity over time. For example, turning a patient to the lateral decubitus position during a tonic-clonic seizure appears to increase the risk of shoulder dislocation without decreasing the risk of aspiration; turning a patient following termination of tonic-clonic movements is recommended. Standards in our EMU mandate the wearing of protective helmets in all patients undergoing antiepileptic drug reduction when out of bed. This has essentially eliminated the occurrence of cerebral concussion, though facial trauma still occurs on occasion. There is almost no evidence-based data to support one approach or another. For example, we are not aware of any studies indicating that the widespread practice of padding bedrails actually provides any benefit. The EMU medical director should create reasonable protocols and see that they are consistently applied. The incidence of target events should be reviewed periodically in the context of quality assurance. This will provide information as to whether a set protocol is helpful, and prompt changes if needed.

Intracranial Electrodes

Evaluation with intracranial electrodes introduces additional specialized issues, including the potential for cerebral edema and cerebral infection. Mobilizing the patient is important to prevent postoperative complications. On the other hand, the recording equipment (often recording from more than 100 intracranial electrodes) is cumbersome, and abrupt changes of position occurring during falls or seizures may place excessive traction on electrode cables emerging from the skull, impairing the EEG recording or worse. A severely agitated patient with intracranial electrodes removing the head dressing and pulling on electrode cables may be the EMU nurse's worst nightmare. Again, a systematic protocol-driven approach will prevent or mitigate this possibility.

The physician must assess the patient's ability to tolerate intracranial electrodes before they are placed. The range of activity allowed, care of head dressings, measures to prevent postoperative infections or other complications, number of nurses needed for transfers, mobilization protocols, and restraints to be used while the patient is in bed all should be standardized. Educating the patient and staff prior to implanting intracranial electrodes is critical to ensure that expectations are clear. Given the potential dangers, continuous observation by trained EMU staff is mandatory during video–intracranial EEG monitoring.

Other Protocols

These are not recommended in the NAEC guidelines but are important in appropriate circumstances. A voluminous amount of data is recorded in a busy EMU. A standardized approach to screening, pruning, reviewing, and archiving this information and a standardized approach to generating reports is critical. Guidelines are necessary if trained EEG technologists screen and prune the initial study. Reviewing physicians may not be able to generate reports quickly; rules are necessary to determine how much data should be stored and for how long. Policies addressing which and how much information to archive are needed.

Ictal single photon computed tomography (ictal SPECT) (11) is occasionally useful to determine the location of seizure onset during an evaluation for epilepsy surgery. The goal is to inject a radioactive tracer substance during a seizure, preferably early in the seizure. The resulting information is typically compared to interictal SPECT, either visually or with advanced processing methods such as subtraction ictal SPECT co-registered to MRI (SISCOM). Ictal SPECT injection is almost always performed during video EEG monitoring so that the relationship of the injection to seizure onset and propagation can be fully understood. An ictal SPECT program requires enthusiastic support from all EMU staff, a high degree of organization within the EMU, and good collaboration with the nuclear medicine department. Seizure detection and communication between EMU monitoring and nursing staff are critical. A high degree of physician or nurse training (including formal training on safe handling of radioactive material) and appropriate safety precautions are needed. Again, a systematic protocol-driven approach is necessary.

CONCLUSION: THE PLACE OF THE EPILEPSY MONITORING UNIT IN A SPECIALIZED EPILEPSY CENTER

The ability to achieve clear diagnosis and fully characterize seizures in an epilepsy monitoring unit has revolutionized epilepsy care. It is hard to imagine delivering contemporary epilepsy care without this capacity. Unfortunately, too often tertiary epilepsy care is limited to an EMU evaluation. Given the expense and potential benefits of an EMU evaluation, this is both wasteful and unfortunate.

An EMU evaluation is most useful when the goals of the evaluation are clear prior to admission and the patient and family have learned enough about the process to fully cooperate. The information obtained during the evaluation must be placed in the context of the patient's history and other evaluation. Ideally, therefore, a fair amount of education and evaluation should take place *prior to* the hospital admission. Data from outpatient and inpatient evaluation should be synthesized and used to develop short- and long-term plans to treat and hopefully completely control the patient's epilepsy. Consistent follow-up is needed to ensure that these plans are put into effect. Communicating results with patients and referring physicians, articulating serial plans for treatment, and following up regularly ensures that the information obtained during an EMU evaluation has a maximal positive impact. The important information obtained during an EMU evaluation is best used in the context of a comprehensive approach to epilepsy care.

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ADMINISTRATIVE CONSIDERATIONS IN EPILEPSY AND ICU MONITORING: CODING AND DIAGNOSTIC CLASSIFICATION

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PAUL VESPA
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In the United States, health care public policy systems are in place for coding and reimbursement for all types of medical, surgical, and diagnostic procedures. These systems are peculiar to the United States, although other national health care systems are examining these processes for possible adoption elsewhere.

Much of this chapter is devoted to the specific coding and classification issues found throughout the United States, focusing primarily on epilepsy and ICU monitoring. Several important coding systems include:

Current Procedural Terminology (CPT): a codified listing of medical, surgical, and diagnostic procedures
Evaluation and Management (E/M): a CPT code system for patient visits to a physician
National Correct Coding Initiative (NCCI or CCI) Edits: a list of which pairs of CPT codes cannot be used with each other
International Classification of Diseases (ICD): a codified listing of diagnoses, symptoms, and other conditions that may affect a patient
Linkage tables: an insurance company's listing of which ICD codes are acceptable as reasons for conducting a CPT procedure
Medicare Fee Schedule (MFS): a list of the relative value of each CPT procedure
Outpatient Prospective Payment System (OPPS): a list of relative values for hospital charges for outpatient services
Diagnosis Related Groups (DRGs): a list of payments to hospitals for a hospitalization

Public policy systems use these codes and lists as well as additional regulations. The end results are limits on to whom and how care may be delivered, limits on how much reimbursement will be paid for a procedure or hospitalization, and specifications as to what documentation must be included in the medical record.

CURRENT PROCEDURAL TERMINOLOGY

The American Medical Association publishes *Current Procedural Terminology*, presently in its fourth edition. The publication is updated annually. It lists codes, and their brief descriptions, for all medical, surgical, and diagnostic procedures; the list includes about 8,000 different entries. The codes provide a specific common language about procedures. In theory, this allows for better communication between physicians, patients, and third parties (e.g., insurance companies).

The system gained great popularity in 1983 when the U.S. Health Care Financing Administration (HCFA) adopted CPT as the primary procedural coding system for submitting reimbursement claims to Medicare, the U.S. national health care coverage program for the elderly and disabled. In 1986, the HCFA extended its CPT coding requirement to the Medicaid system, the U.S. national health care coverage program for the poor. Now essentially all insurance companies and health care systems use CPT. An editorial board supervises the system along with an advisory panel representing all branches of organized medicine.

Category I codes are the typical CPT codes for procedures or services. They use a unique five-digit code and descriptor for each procedure. These are for widely used, FDA-approved procedures for which clinical efficacy is well established. CPT codes for epilepsy and ICU monitoring are shown below.

Category II codes identify performance measures for data collection and quality control. They use a four-digit

numeric code plus the letter F. Physicians use these codes to indicate that certain recognized quality services have been performed. For example, for diabetic patients, one code identifies that the HgbA1c level was checked and was within normal limits. There are no specific Category II codes for ICU monitoring at present. A family of codes for ICU stroke care is available, but is beyond the scope of this chapter. A family of Category II codes for epilepsy patient care has been developed. This epilepsy code family now is undergoing the extended process of vetting and obtaining approvals.

Category III codes are used for emerging technologies. They facilitate data collection for an investigational procedure. They use a four-digit numeric code plus the letter T. If a Category III code becomes widely used, it can then be changed into a Category I code. Codes 0160T and 0161T are two Category III codes that are used to indicate therapy with transcranial magnetic stimulation. There are no emerging technology CPT codes for epilepsy or ICU monitoring at present.

The CPT system also contains modifier codes used to indicate variations in a procedure. Modifiers can be appended to the procedure's CPT code number, or reported with a separate five-digit code.

Electroencephalography (EEG) CPT Codes

Category I EEG codes are given below. Codes 95812 through 95822 include hyperventilation and/or photic stimulation when appropriate. The routine EEG codes, 95816 through 95822, include 20 to 40 minutes of recording. Two extended EEG codes, 95812 and 95813, include reporting times longer than 40 minutes.

95812	Electroencephalogram (EEG) extended monitoring; 41–60 minutes
95813	Electroencephalogram (EEG) extended monitoring; greater than one hour
95816	Electroencephalogram (EEG); including recording awake and drowsy
95819	Electroencephalogram (EEG); including recording awake and asleep
95822	Electroencephalogram (EEG); recording in coma or sleep only
95824	Electroencephalogram (EEG); cerebral death evaluation only
95827	Electroencephalogram (EEG); all night recording
95950	Monitoring for identification and lateralization of cerebral seizure focus, electroencephalographic (e.g., 8-channel EEG) recording and interpretation, each 24 hours
95951	Monitoring for localization of cerebral seizure focus by cable or radio, 16 or more channel telemetry, combined electroencephalographic (EEG) and video recording and interpretation (e.g., for presurgical localization), each 24 hours
95953	Monitoring for localization of cerebral seizure focus by computerized portable 16 or more channel EEG; electroencephalographic (EEG) recording and interpretation, each 24 hours
95956	Monitoring for localization of cerebral seizure focus by cable or radio, 16 or more channel telemetry, electroencephalographic (EEG) recording and interpretation, each 24 hours
95957	Digital analysis of electroencephalogram (EEG) (e.g., for epileptic spike analysis)

The awake/asleep EEG code, 95819, is for a planned awake/asleep study with or without sedation. The code also may be used if the technologist tried unsuccessfully to get the patient to fall asleep; the rationale behind that is that the procedure was performed, but the technologist simply didn't get the desired results.

The awake EEG code, 95816, is used if an awake-only study is planned and performed. However, if the patient falls asleep and the recording time is sufficient, one may use code 95819.

The coma/sleep EEG code, 95822, is used for patients who are asleep, anesthetized, or comatose for the whole test.

The prolonged EEG codes, 95812 and 95813, are used for prolonged EEGs, including some in the ICU. A test 40–60 minutes long usually uses code 95812, to distinguish it from the shorter awake and awake/asleep EEG procedures. Code 95813 originally was defined for use with two particular typical circumstances. The first was the neonatal EEG, in which one records for 90–120 minutes to catch both active and quiet sleep. The second was for ICU EEG monitoring, in which a machine is left at the bedside and run intermittently or continuously over many hours. This is one of the codes that still are in use for continuous ICU EEG monitoring.

Digital analysis of EEG, code 95957, is used for additional digital analysis performed on the EEG. That extra procedure requires substantial technologist time and extra physician time. For example, this code may be used for three-dimensional spike source localization, as is occasionally needed on patients evaluated for epilepsy surgery. Documentation must be provided to show a separate procedure, with its own described methodology, results, and interpretation. That documentation can appear in a separate procedure note, or as a separately identifiable part of a larger combined procedure note. Code 95957 is not used for a routine EEG that merely happens to be run on a digital machine. This code also is not used for routine spike and seizure detection during EEG monitoring using monitoring codes 95951, 95953, or 95956.

Most of the monitoring codes, 95950, 95951, 95953, and 95956, are reported for "each 24 hours." These codes are used

if at least 12 hours of monitoring occurred. If the recording time is less than 12 hours, but more than 6 hours, one should bill the appropriate monitoring code with modifier -52 to indicate that the service was reduced, and should indicate the actual number of hours that the study was performed. For example, a patient leaves the epilepsy monitoring unit for several hours while undergoing an MRI; the patient is reconnected to monitoring after the MRI. That patient still is coded as 95951, even though the patient was on monitoring for only 22 hours during that day. (The use of modifiers is further described in the next section.)

Code 95951 describes video EEG for localization of a cerebral seizure focus. It is performed classically as an inpatient procedure at a specialized epilepsy center, for presurgical localization or to otherwise characterize a patient's seizures. It is also performed as part of an in-depth diagnostic evaluation for epilepsy. In recent years, some centers have used this 95951 video EEG code for ICU patients who have seizures, or possible seizures, and are undergoing 24-hour monitoring to identify seizures, regulate seizure therapy, and characterize the seizures (or other seizure-like events).

Video EEG is not performed as the initial diagnostic test for evaluating a patient who presents with a transient undiagnosed episode. Such a patient usually warrants a routine EEG. The use of code 95951 is not justified by the mere addition of a video camera during the course of a routine outpatient EEG. Nor is code 95951 justified in a patient whose clinical situation does not warrant an in-depth evaluation for seizures.

The physician would code 95951 with the -26 modifier when studies are done for hospital inpatients. In general, hospitals use a midnight-to-midnight bed census. For that reason, 95951 is commonly billed for the day of admission up to midnight, subsequently from midnight to midnight, and finally from midnight of the last hospital day to the discontinuation of recording. If the duration of recording on the first and last day is less than 12 hours, 95951 should be coded with a -52 reduced service modifier. Some hospitals prefer to code for the procedure starting at the time of hookup. If so, the hospital should have a procedure policy to describe the coding of this 24-hour service.

A physician should code 95951 with the -26 modifier when the study is done in a hospital outpatient laboratory. As with inpatient testing, the -52 modifier should be used for testing times less than 12 hours. The hospital will bill the technical component or a facility fee. For a Medicare patient, the Ambulatory Patient Classification system is used by the hospital to code EEG with video monitoring under Medicare's Hospital Outpatient Prospective Payment System.

A physician would use the global code 95951, without modifier -26, when EEG with video monitoring is provided in an office or freestanding center. The reduced service modifier, -52, should be used if testing is for less than 12 hours.

For these EEG codes, the service needs to be consistent with the community standards for the codes, as provided by the minimum technical standards and guidelines of the American Clinical Neurophysiology Society. For example, one cannot use these codes for a 3-minute-long EEG or a one-channel EEG recording, because these fail to meet the minimum technical standards for EEGs according to those guidelines. The National Association of Epilepsy Centers (NAEC) also provides some coding guidelines.

Modifier Codes

Modifier codes are appended to the Category I procedure codes to indicate that the service provided differed from the base procedure itself in some way. They can be implemented by adding the two-digit modifier as a suffix to the procedure code, or by listing a second five-digit modifier on the next billing line under the procedure code.

Professional Component: -26 or 09926

Each EEG code has two components, its professional component and its technical component. The hospital will use the modifier code -TC to indicate that it is billing for the technical component.

Modifier -26 is used to indicate the component of a test involving the physician's diagnostic interpretation. It is billed when another entity, for example, the hospital, has provided the procedure's technical component. Modifier -26 is used to indicate interpretations of EEGs performed in hospital outpatient or inpatient EEG laboratories, because the hospital will have billed separately for the technical component.

When an EEG is performed in the physician's office, these -26 or -TC modifiers usually are not used. The absence of the professional component modifier indicates that the physician provided the whole service—that is, paid for the technologist, supplies, equipment, and office overhead associated with running the EEG.

An EEG procedure coded without a -26 or a -TC modifier is called a global service, which includes both the professional and the technical components.

Multiple Procedures: -51 or 09551

This modifier is used in the unlikely event that multiple procedures are performed on the same day by the same provider. Adding modifier -51 indicates that a charge is for an additional procedure, and is not a clerical error of billing twice for the same service. A double procedure might occur when a patient has a routine EEG test in the morning, then another routine EEG in the evening.

Reduced Services: -52 or 09952

Sometimes a service or procedure is reduced or eliminated at the physician's discretion or for technical reasons. This modifier reports that the service was reduced. For example,

an EEG monitoring session may be stopped partway through the day because of a machine problem. This code is more commonly used when a CPT procedure is defined as bilateral, but only a unilateral test is carried out—for example, a unilateral somatosensory evoked potential. That use applies to unilateral somatosensory evoked potential testing.

Discontinued Procedure: -53 or 09953

This code is used when a service is stopped early because of a patient medical problem. If daily monitoring was stopped early because the patient had to be taken to surgery, then this code can show that monitoring was started on that day, but stopped after less than the usual monitoring duration.

Distinct Procedural Service: -59 or 09959

This modifier can be used to indicate that a procedure or service was distinct or independent from other services performed on the same day. However, if another modifier is more appropriate it should be used rather than -59.

Using These CPT Codes in the Epilepsy Monitoring Unit and the ICU

Professional reading for video EEG monitoring in the inpatient epilepsy monitoring unit (EMU) is coded as 95951-26; the hospital codes the technical component of the service as 95951-TC. This applies to EMU video EEG for services of more than 12 hours' duration. Outpatient video EEG recorded in a hospital lab for 6 to12 hours is coded as 95951 plus 09952 and 09926.

Professional interpretation of continuous video EEG monitoring for differential diagnosis of seizures in ICU patients is coded as 95951-26. Such monitoring without video is coded as 95956-26. Continuous ICU EEG monitoring more generally, which is not specifically for differential diagnosis and identification of epileptic seizures, is coded as 95913-26.

EVALUATION AND MANAGEMENT CPT CODING

Evaluation and Management (E/M) codes refer to patient visits with physicians in the office and hospital. The services covered by these codes include taking a history, conducting a physical examination, and developing impressions and plans. E/M constitutes about 40% of all payments for medical services nationally.

E/M codes come in families. New patient office visits are for self-referred patients, or patients referred for ongoing care from, for example, the emergency room. Consults are a request for an opinion, with a report back to the referring physician. Hospital subsequent day E/M codes are used both by the primary physician and by consultants.

The hospital E/M code families are relevant for care for patients on epilepsy and ICU monitoring services. The hospital subsequent day family of codes has three levels of service.

Level 1, code 99231: This is for stable patients with no continuing problems. An example is a stroke patient on a floor bed who is stable and awaiting placement in a rehabilitation facility or nursing home. A note must be made listing the chief complaint and documenting the physician's visit with the patient.

Level 2, code 99232: This is for a patient with one continuing problem that is inadequately controlled, and which requires new physician orders for lab tests, medications, or other services to evaluate or manage the problem that day. Documentation must describe an inadequately controlled problem, and the state of at least one other system. For example, in an epilepsy monitoring unit patient, "Seizure disorder: No seizures since yesterday, no adverse AED side effects, awaiting seizures, will decrease AEDs further."

Level 3, code 99233: This highest level is for patients with a new problem or multiple inadequately controlled continuing problems, where the problem(s) require new physician orders for lab tests, medications, or other services to evaluate or manage the problem(s) that day. Documentation must include the chief complaint, four facts about the current problems, a list of medications, and the state of at least two other systems. For example, in an epilepsy monitoring unit patient, "Seizure disorder: Three partial seizures in 5 hours overnight, began with head turning and posturing to left, lasting 1–2 min., 20 min. post-ictal. New headache, sleepy and fatigue today. Given 4 mg Ativan overnight; will check level and increase AED dose today."

A physician also may use Critical Care E/M codes 99291 and 99292. These are used most frequently in the ICU. The documentation must show that the patient is unstable and critically ill, and that the documenting physician managed the patient's care. It must state the time taken to care for that patient on that day, which must be 31 minutes or more. Otherwise, there are no further details required for using these codes. Two or more physicians may use these codes if both are managing the patient.

CODING FOR MULTIPLE PROCEDURES

While many medical procedures may be carried out on the same day, there are recognized limits to this. For example, an awake and asleep EEG cannot be coded as two procedures, the awake portion and the asleep portion. Coding rules prohibit coding a 95816 (awake and drowsy EEG) together with a 95822 (asleep EEG).

The National Correct Coding Initiative (NCCI) has organized a recognized list of prohibited coding pairs.

Sometimes this process and list are referred to by the shortened name Correct Coding Initiative (CCI).

In general, these prohibited code pairs are meant to make good sense. For EEGs in general, they prohibit more than one procedure on the same day. Providing an E/M on the same day as an EEG is not affected.

Some procedures are included within another. The NCCI recognizes the bundling of those individual services within a bigger, broader service. It then prohibits coding simultaneously for both the broader procedure and the included piecemeal procedures. For epilepsy and ICU monitoring, spike and seizure detection are bundled into the monitoring codes. One cannot code for the monitoring and separately for the spike and seizure detection, because the latter are included as (bundled as) a part of the former. Coding for both a broader inclusive procedure and its separate component parts is called *unbundling*.

Some prohibited code pairs may be allowed if the modifier code -59 is used. For example, if a routine EEG is performed, and a decision is made thereafter to monitor the patient, then one might code for the routine EEG as 95816 and the subsequent monitoring as 95951-59.

The Medically Unlikely Edits (MUE) list is a part of the NCCI process. That list limits the number of identical procedures allowed on the same day. The classic example is a procedure that can be coded once per limb, and for which, therefore, only four units are allowed. For EEGs, generally only one test of each type is allowed daily. Modifier code -51 is used if more than one service is medically necessary on a particular day. For example, if a routine EEG is conducted on a comatose patient in the morning and another is conducted in the evening for good medical reasons, then the first is coded 95822 and the second is coded 95822-51.

Various insurance carriers have their own internal procedures for processing codes with the -51 modifier. Payment results vary among carriers. Some deny payment for the second procedure, no matter how medically necessary it is. In the report of the second procedure, it is good to clearly indicate the reason why the second recording was medically necessary.

INTERNATIONAL CLASSIFICATION OF DISEASES

The International Classification of Diseases (ICD) is a codified listing of diagnoses, symptoms, and other conditions that may affect a patient. The U.S. Medicare administration, known as the Centers for Medicare and Medicaid Services (CMS), oversees a modified version of this international coding system, tailored to the needs of the U.S. medical system. The United States currently uses a Code Modification (CM) of the ninth international system, known as ICD-9-CM.

Other nations have moved on to use the Tenth ICD (ICD-10) for their research and public health reporting purposes. The United States has avoided using the tenth version, because the conversion will require enormous amounts of reprogramming of carrier and physician computers, retraining of all users, and development of a new set of modifications.

The ICD-9-CM codes most relevant for seizure patients are:

Generalized epilepsies

345.00	nonconvulsive epilepsy, not intractable
345.01	nonconvulsive epilepsy, intractable
345.10	convulsive epilepsy, not intractable
345.11	convulsive epilepsy, intractable status epilepticus
345.2	petit mal status
345.3	grand mal status

Localization-related (focal) (partial) epilepsy and epileptic syndromes

345.40	with complex partial seizures, not intractable
345.41	with complex partial seizures, intractable
345.50	with simple partial seizures, not intractable
345.51	with simple partial seizures, intractable
345.6	infantile spasms
345.7	epilepsia partialis continua

Other forms of epilepsy and recurrent seizures

345.80	not intractable
345.81	intractable

Epilepsy, unspecified

345.90	not intractable
345.91	intractable
333.2	myoclonus

Convulsions (as a symptom)

780.31	febrile convulsions
780.33	post-traumatic convulsions
780.39	other convulsions

Alteration of consciousness

780.01	coma
780.02	transient alteration of awareness
780.09	drowsiness, somnolence, unconscious, semi-coma, or stupor
780.2	syncope and collapse

There are two definitions of intractable. In the original definition, a patient was considered intractable when he or she had seizures during the past year. Another common definition is when the patient's seizures interfered with life's activities.

When reporting ICD-9-CM diagnosis codes, use the 345 series codes whenever they accurately describe the patient's diagnosis. The more generic codes in the 780 series are for symptoms where no clear diagnosis can be made, or for a seizure occurring in another medical setting. For example, a patient would be coded as 345.81 for frequent nonepileptic seizures. For a patient with a single convulsion immediately after a head injury, code 780.39 would be used along with codes for the head injury. A patient still having partial complex seizures would be coded as 345.41.

The U.S. government plans to switch diagnostic coding from ICD-9 to ICD-10. That system has a larger number of codes, with greater specificity of site and condition. The date of conversion is set tentatively for 2012.

LINKAGE TABLES

Insurance carriers create policies concerning the ICD diagnoses for which particular CPT codes are considered medically necessary. In this way, they automate the process of deciding when a procedure is "medically necessary." The lists or tables that define such policies are called "linkage tables."

The epilepsy ICD codes are generally listed as reasons justifying providing EEG CPT codes. Other diagnoses are treated variably. As a result, it is important to consider the ICD code used when providing EEG services.

Medicare carriers and other government carriers are required by law to publish the linkage tables. Some states have laws requiring all carriers to make available the rules they use for determination of coverage. Private carriers sometimes consider these linkage tables to be proprietary, but may release some information piecemeal. Careful attention may be needed to which codes a carrier considers medically necessary and which not; after all, a list of applicable diagnoses for a patient is often much longer than the spaces available or convenient to use on a charge document.

These regulations and processes lead to the nonsense appearing on some carrier replies to billing (denials of payment listed on the explanation of benefits), which state that a procedure was "not medically necessary" when it was fully medically necessary by ordinary community standards. The statement "not medically necessary" really means, "That ICD is not on our linkage table for that CPT procedure."

MEDICARE FEE SCHEDULE

Each year, the CMS publishes a fee schedule for all CPT procedures. This has two parts. One is a simple single conversion factor that sets the actual value of services for that year and applies equally to each procedure. Individual CPT codes are ranked according to their relative work and expense, as compared to each other. These are referred to as Relative Value Units (RVUs). There are three types of RVUs: physician work RVUs, practice expense RVUs, and malpractice RVUs.

In theory, a procedure that requires more physician work has a higher physician work RVU than one that requires less physician work. Physician work RVUs for various procedures are ranked by the American Medical Association's Relative Value Update Committee (RUC) from time to time, based upon surveys conducted by each involved specialty. Work is determined by the typical time taken to conduct the procedure, with some times weighted higher when harder or more stressful. For example, critical care time is weighted roughly twice as high per minute as is a routine office follow-up visit. Time includes not only typical face-to-face time, but also an estimate of time between visits for phone calls, writing notes, renewing medications, checking labs results, and so on.

Practice expense RVUs are set based upon the amounts of supplies and equipment, and the numbers of technologists and nurses, typically needed to carry out a procedure.

Malpractice expense for a given procedure is estimated based on the typical malpractice costs for specialties usually carrying out that procedure.

The fee schedule also contains geographic adjustment factors. These generally increase the payments for physicians in many cities, and decrease the payments for rural areas. This reflects the reality that the costs of living, office space, and staffing are higher in certain areas.

The RVU for each procedure is calculated by summing the physician work RVUs, practice expense RVUs, and malpractice RVUs. The payment to a physician is calculated by multiplying the procedure RVUs by the geographic factor and the national conversion factor.

The RVUs for some EEG procedures currently are:

CPT	Procedure Description	RVUs
95813	Extended EEG, >1 hr.	7.33
	Professional Component	2.47
	Technical Component	4.86
	Physician Work	1.73
95816	Awake EEG	5.34
	Professional Component	1.56
	Technical Component	3.78
	Physician Work	1.08
95819	Awake and Asleep EEG	5.00
	Professional Component	1.56
	Technical Component	3.44
	Physician Work	1.08
95951	Video EEG Long-Term Monitoring	
	Professional Components	8.65
	Technical Components	N/A
	Physician Work	5.99
95953	Automated Ambulatory Monitoring	11.42
	Professional Components	4.68
	Technical Components	6.74
	Physician Work	3.30

95956	EEG Monitoring, No Video	19.14
	Professional Components	4.44
	Technical Components	14.70
	Physician Work	3.08

No RVUs are specified for the technical component of 95951. The fee schedule instead suggests that individual carriers set a price for that code.

HOSPITAL OUTPATIENT PROSPECTIVE PAYMENT SYSTEM

Medicare pays for hospital outpatient procedures under an arrangement, different from the Medicare Fee Schedule, called the OPPS. In this system, procedures of roughly equivalent value are lumped together. This system is meant to reduce costs, because a hospital would have no reason to up-code a service to a similar but somewhat higher valued service. OPPS pays the same reimbursement for the somewhat higher intensity service as it does for the lower intensity service within a family of services.

This affects outpatient epilepsy monitoring, such as is used for daytime monitoring of children with frequent daily seizures. The payment for these services varies from year to year, and occasionally there is movement of procedures between categories. The following two categories include most EEGs used in epilepsy and ICU monitoring.

Category #	Codes included	CPT equivalents
209	Polysomnography	95805–95811
	Ambulatory monitoring	95950, 95953
	EEG monitoring	95951, 95956
210	Routine EEGs	95806, 95812–95827
	Wada test	95958

DIAGNOSIS RELATED GROUPS

The DRG program pays hospitals for Medicare inpatient care. The amount of payment depends on the diagnosis. The program lumps together many patients' hospitalizations. Its goal is cost saving, since it provides no incentive for hospitals to add additional costs during the inpatient stay. The amount paid will be the same, irrespective of costs incurred.

For practical purposes, the DRG for inpatient EEG monitoring is DRG #100. It pays a lump sum, which averages to the equivalent of a 3.7-day inpatient stay. That seems short for typical EEG monitoring. This is because the DRG combines hospitalizations for most seizures; as a result, the DRG averages the small number of epilepsy monitoring patients with the larger number of seizure patients admitted for a day or two for out-of-control or new-onset seizures.

Considerable attention has been paid to whether a separate DRG is warranted for epilepsy monitoring. To date, this proposal has not gained acceptance from the CMS. The National Association of Epilepsy Centers continues to pursue that goal.

REFERENCES

CPT is a trademarked product of the American Medical Association. The book *Current Procedural Terminology* is available from the AMA CPT Product Catalogs at www.ama-assn.org/ama/pub/category/3116.html.

Medicare Coverage Information is available at www.cms.hhs.gov/mcd, although the Medicare Web addresses occasionally change. This resource includes a large number of source materials, as well as a search engine to find policies or determinations about particular codes. A particular physician resource area is at www.cms.hhs.gov/physicians/.

National Correct Coding Initiative (CCI) Edits are available at www.cms.hhs.gov/NationalCorrectCodInitEd.

The American Academy of Neurology (AAN), at www.aan.com, publishes a useful ICD coding book specially designed for neurologists. The AAN also publishes other resources for neurologists or their staff to use for coding, available through the online AAN Store.

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SECTION

II

TECHNICAL ASPECTS OF EPILEPSY AND INTENSIVE CARE MONITORING

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6

EEG LOCALIZATION AND INTERPRETATION*

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EEG interpretation is most effectively learned by reviewing EEG records with an experienced, board-certified electroencephalographer (certified by, e.g., the American Board of Clinical Neurophysiology) who can effectively teach the analytic thought process during the learning experience. Not surprisingly, proficiency almost always requires fellowship training. For those not in fellowship programs, learning to interpret EEG is best done in long continuous blocks of time (i.e., months). Like routine EEG, EEG monitoring analysis—in which the main goal is the detection and interpretation of epileptiform activity, electroencephalographic trends, and coma patterns—can only be approached using the basic "tools" of EEG interpretation.

EEG monitoring interpretation follows a sequence of analysis that includes the following steps:

1. The inspection of individual waveforms and patterns
2. The mental reconstruction of the spatial and likely anatomical origins of electrical sources
3. The determination of pathophysiological significance
4. The determination of clinical significance

The main pitfall in learning electroencephalography, other than inadequate instruction, is the tendency to shortcut the learning process by replacing the first two steps with "pattern recognition." This has two unfortunate consequences: (a) the analytic process of EEG interpretation is never mastered, and (b) EEG is conceptualized as a graphic entity, not as brain activity. The most difficult and useful aspect of EEG interpretation that must be mastered initially is the second step, spatial localization. In epilepsy monitoring, one of the most important questions to be answered is, "Where is the seizure actually coming from?" To a great extent, knowledge of waveform morphology and the relationship of EEG findings to clinical findings can be acquired by completing EEG rotations during residency, attending courses, and referring to textbooks and atlases of EEG. Therefore, the main thrust of this chapter concerns spatial localization.

* All figures were provided by Dr. Fisch or can be found in Fisch and Spehlmann's Digital and Analog EEG Primer, Elsevier, Amsterdam, 1999, unless otherwise indicated.

THE ANALYTIC PROCESS OF EEG INTERPRETATION

Operationally, the routine EEG can be defined as the difference in voltage between two or more electrodes placed on the scalp displayed over time. When viewing and discussing EEG, a working vocabulary is needed. All well-trained electroencephalographers use the following terms:

Channel: One line of EEG recording (generated by one amplifier that amplifies the difference between the electrode(s) plugged into input 1 and input 2 of the amplifier).

Derivation: The electrodes representing amplifier inputs 1 and 2 (e.g., the derivation, Fp1 – F3, consists of two electrodes, with Fp1 in 1 and Fp2 in 2 of the amplifier).

Montage: A collection of derivations.

Bipolar derivation or bipolar montage: Adjacent electrodes on the scalp plugged into inputs 1 and 2, respectively (e.g., Fp1 – F3 is a bipolar derivation).

Referential derivation or referential montage: Montage with identical electrode(s) in all channels in input 2. The electrode in input 1 is considered to be the exploring electrode, and the electrode in input 2 is intended to be out of the field of the activity of interest being recorded by electrode 1 (e.g., F7 – Cz is a referential derivation where F7 is intended to be the exploring electrode and Cz is intended to be the reference).

Longitudinal: This refers to the anterior-posterior direction, as in the longitudinal bipolar montage (see below).

Transverse: This refers to the left-right direction, as in the transverse bipolar montage (see below).

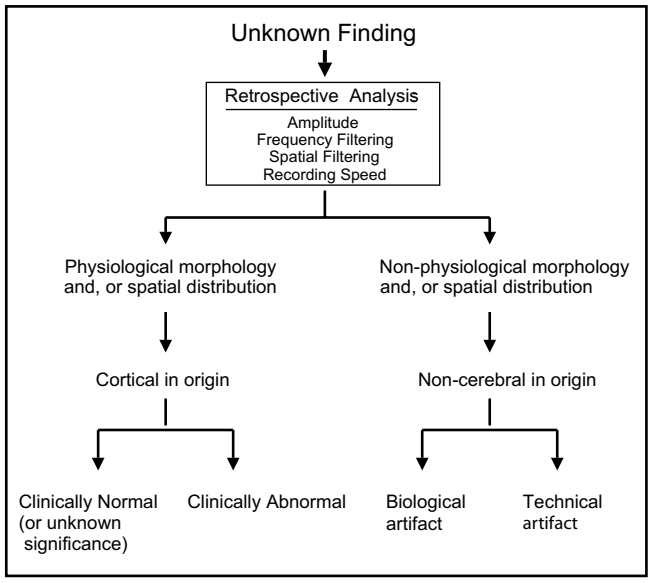

FIGURE 6-1. Electrographic diagnostic decision tree.

The basic analytic process that is followed when encountering unknown patterns is shown in the EEG decision tree (Figure 6-1). The student should apply this thought process for each new pattern and understand why each decision branch is followed.

The features that determine the first decision branch are based on the morphology (waveform shapes) and spatial distribution of the pattern. Concerning the last decision branch for activity that is cortical in origin, it is important to emphasize that statistically "abnormal" EEG findings (i.e., those rarely encountered except in certain individuals) are often considered to be clinically normal. That is one reason why simply identifying a pattern as one you have never seen and concluding that it therefore represents a clinically relevant abnormality is a poor strategy for EEG interpretation.

Morphology refers to the shape of the waveform. Waveform morphology is described using the following terms:

Frequency
Spike
Sharp wave
Complex
Amplitude
Polarity
Phase(s)
Rhythmicity
Reactivity

Frequency

Frequency may be described precisely in hertz (Hz; cycles per second), as waveform duration in milliseconds, or using the frequency band terms delta (<4.0 Hz), theta (4.0 to < 8.0 Hz), alpha (8.0 to 13.0 Hz, inclusive), and beta (>13 Hz). Notice that the borders of the frequency bands have no gaps (e.g., the theta band is often mistakenly described as 4.0 to 7.5 Hz and the alpha band as 8.0 to 13.0 Hz, leaving a 0.5-Hz gap); instead the band frequency ranges *should be seamless*.

Spike, Sharp Wave, Complex

In common practice, the terms "*spike*" and "*sharp wave*" are only used to describe abnormal epileptiform patterns or their normal variants (pseudoepileptiform patterns). Both spikes and sharp waves have the same clinical implication. Abnormal spikes or sharp waves should be referred to as *epileptiform spike(s)* or *epileptiform sharp waves*. Sharply contoured waveforms that are not felt to be abnormal are commonly referred to as *sharp transients*. Vague terms such as *"sharps"* should not be used.

An *epileptiform spike* is a sharply contoured (apiculate) waveform with a duration of 20 to 70 milliseconds that has a physiological field of distribution and morphology consistent with a cortical site of origin.

An *epileptiform sharp wave* is a sharply contoured (apiculate) waveform with a duration of 70 to 200 milliseconds that has a physiological field of distribution and morphology consistent with a cortical site of origin.

The following eight features help to distinguish abnormal epileptiform spikes from other sharply contoured waveforms.

1. Asymmetry. The initial half of the wave (from the baseline to peak) often has a shorter duration (more rapid deflection from the ongoing electrical baseline) than the second half of the wave (from the peak to baseline). In contrast, many nonepileptiform transients are approximately symmetric (e.g., wicket spikes).
2. Associated slower waveform. Epileptiform spikes and sharp waves may be followed by a slow wave. The slow wave is not sharply contoured and it has a longer duration than the predominant background waveforms. The slow wave usually range in frequency from the theta to the delta band.
3. Biphasic or multiphasic. Epileptiform spikes and sharp waves usually have more than one phase (usually two or three), and the duration of each phase differs from the durations of the phases of the surrounding background waveforms.
4. Distinct from ongoing background activity. Epileptiform spikes and sharp waves do not appear as simply an abrupt increase in the amplitude of sharply contoured waveforms that are part of the ongoing background activity.
5. Background disruption. Epileptiform spikes often appear to interrupt the ongoing background beyond the duration of the spike or sharp wave because of the presence

of an aftergoing slow wave or surrounding irregular slower waveforms that may precede and/or follow the spike or sharp wave.

6. Involvement of more than one electrode. Sharply contoured waveforms that are recorded from only one electrode may be related to poor electrode contact, defective electrodes, or other potentials that are noncerebral in origin. Therefore, epileptiform activity usually can be detected at more than one electrode site. When activity is only detected at one electrode, the impedance of that electrode should be tested and one or more additional recording electrodes should be placed adjacent to the active electrode.
7. Clearly distinguishable from benign epileptiform patterns. Pseudoepileptiform patterns frequently confused with abnormal epileptiform spikes or sharp waves include "wicket spikes, small sharp spikes, rhythmic midtemporal discharge, triphasic waves, 6 per second phantom spike and wave, and 14 and 6 Hz positive spikes" (13).
8. Negative polarity. The dominant spike component that appears consistently is usually negative in polarity. Sharply contoured waveforms in which the polarity is primarily positive are less likely to be epileptiform spikes.

When the pattern consists of two or more waves with a distinct form, such as a spike and an aftergoing slow wave, then the waveform pattern is referred to as a *complex*, as in a "*spike and slow wave complex*." Multiple spikes mixed with slow waves are commonly referred to as *multiple spike and slow wave complexes* or *polyspike and slow wave complexes*.

Amplitude

The term *amplitude* refers to the voltage of the waveform or waveform complex. Amplitude in EEG is measured in microvolts, in contrast to electrical signals, measured in millivolts that arise from muscle (ECG, EMG) are measured in millivolts. The degree to which the original signal is amplified is referred to as the *gain* of the amplifier. However, amplitude settings are described in terms of *sensitivity* in microvolts (μV) per millimeter. The sensitivity setting describes the display magnification of the waveforms. Notice that the relationship between sensitivity and gain is inverse. If the sensitivity setting is increased, the size of the waveforms on the monitor is reduced. For example, if the sensitivity setting is increased from 5 to 10 μV/mm, then the size of the waveforms on the monitor will be cut in half.

Amplitude is usually described as an approximation using the terms *low* (under 20 μV), *medium* (20–50 μV), and *high* (over 50 μV). The amplitude of the normal EEG varies according to age. An EEG with all activity less than 20 μV would be abnormal in a child, whereas less than 10 μV is abnormal at any age (5).

It is meaningless to state the μV value without naming the montage, because changing the montage changes the voltage. The closer the scalp distance between the input 1 and input 2 electrodes, the smaller the amplitude. That is because closer-spaced electrodes record similar activity, and the EEG is the difference between input 1 and input 2. If the activity recorded by inputs 1 and 2 is identical, then the output of the amplifier is zero. In contrast, as the input 1 and input 2 interelectrode distance increases, the amplitude of the output signal increases. This holds true up to an interelectrode distance of about 10 cm. After that, little or no amplitude is gained by moving the electrodes farther apart. That is why, for example, in adult brain death recordings interelectrode distances of at least 10 cm are used.

Polarity

The *polarity* of an EEG waveform is referred to as positive or negative. Polarity conventions are discussed below in the treatment of spatial analysis.

Phase

The term *phase* refers to that part of the waveform that begins in one direction and then returns to the baseline. For example, a sine wave has two phases: the initial upward deflection and its return to the baseline is one phase, and the following downward deflection from the baseline and its return to the baseline is the second phase.

Each phase can be described by its polarity (i.e., the direction the waveform begins in), and its duration and amplitude. If the electrode detecting the waveform shows an increase in amplitude in a negative direction and then a turn in a positive direction as it returns to baseline, then the phase of the signal is said to be negative.

If a waveform has more than one phase, the phases are counted according to the number of turns the waveform takes across the zero electrical baseline (changes in polarity direction). For example, a waveform such as a sine wave that goes up, comes down to the baseline, and then goes down and returns up again to the baseline would have two phases and be referred to as *biphasic*. A waveform with three turns would be referred to as *triphasic*.

Rhythmicity, Synchrony, and Symmetry

Rhythmicity refers to the appearance of an uninterrupted series of monomorphic waveforms. A sine wave signal at a fixed frequency would be considered perfectly rhythmical, as would a more complex waveform that repeats in an uninterrupted series without changing its shape. *Irregular* patterns consist of waveforms with continuously varying shapes and durations, such as *continuously irregular focal delta activity,* also referred to as *polymorphic delta activity*. Sometimes the spatial descriptor "asynchronous" is mistakenly used to mean irregular. Patterns that combine varying degrees of rhythmical and irregular repetition intervals are referred to as *semirhythmic*.

The term *synchrony* refers to the simultaneous bilateral left-right hemisphere mirror image appearance of waveforms. *Bisynchronous* activity occurs simultaneously with matching phases over similar areas of the left and right hemisphere. *Asynchronous* activity is left and right hemispheric activity that demonstrates a clear simultaneous phase mismatch between hemispheres. For example, patterns such as FIRDA (frontal intermittent rhythmic delta), OIRDA (occipital intermittent rhythmic delta), and typical spike-and-wave (e.g., 3-Hz spike-and-wave) can be described as bisynchronous because there is no apparent timing difference in the appearance of the waveforms between the left and right hemispheres using routine visual inspection at typical display speeds.

The term *symmetry* refers to the left and right hemisphere amplitude comparison of background activity or specific patterns. For example, normal symmetry of the alpha rhythm means that one hemisphere does not consistently have more than 1.5 times the amplitude of alpha rhythm waveforms of the other.

Reactivity and Activation

The term *reactivity* refers to the degree of change that occurs in the EEG in response to exogenous or endogenous stimulation. For example, the alpha rhythm is defined, in part, by its attenuation or complete suppression in response to sustained eye opening. (Alpha frequency activity and the alpha rhythm are therefore not synonymous). *Reactivity testing should be performed in every routine EEG, and repeatedly in patients being monitored with impaired consciousness.* It should include asking the patient to open and close his or her eyes (to demonstrate the alpha rhythm) and should guarantee the presence of an awake state by asking the patient to answer simple mental calculation questions and orientation questions. If the patient is not fully alerted, then the peak frequency of the EEG background activity and the alpha rhythm may be underestimated. These maneuvers also help to clarify whether background slowing is actually present or whether the patient was merely excessively drowsy during the recording.

In patients in coma not caused by general anesthesia, hypothermia, hypotension, or other reversible causes, an *invariant pattern* (a pattern lacking spontaneous variability) and a complete absence of EEG reactivity are almost always indicative of a poor prognosis for survival.

Abnormal slow waves in toxic and metabolic encephalopathies are often diminished by alerting and enhanced by drowsiness, whereas abnormal slow waves seen in cases of structural lesions usually show less attenuation or blocking during alerting maneuvers. However, in some cases, reactivity in patients with nonstructural encephalopathies appears as a sudden onset of, or increase in, delta frequency slow waves.

Activation refers to the appearance of a particular pattern in response to a stimulating procedure that in susceptible individuals may provoke an interictal epileptiform abnormality or seizure. Routine activating procedures that are performed in every routine EEG, and in all cooperative individuals during monitoring with suspected seizures, include hyperventilation (unless medically contraindicated because of increased intracranial pressure or mass lesions or vascular lesions), photic stimulation, and sleep. Although activating procedures may produce a variety of abnormalities, they are primarily used to increase the detection of epileptiform abnormalities. The presence of activation can only be verified by demonstrating it more than once. Hyperventilation and photic stimulation are useful in triggering generalized epileptiform patterns. Rarely, focal electrographic seizures occur.

SPATIAL DISTRIBUTION

The ability to understand the localization of cortical sources and the topographic distribution of EEG patterns is the single most useful tool the electroencephalographer has for correctly classifying patterns. It is also the single aspect of EEG interpretation in which agreement between electroencephalographers is expected to reach 100%.

The EEG arises from constantly changing electrical currents that flow through the scalp. These currents are generated by the underlying cortex and are intermixed with other noncerebral sources (i.e., artifacts). The anatomical origin of scalp cerebral electrical activity in clinical EEG recording is the cortex. Moreover, the only part of the cortex that is typically recorded is that which is distributed over the convexities of the hemispheres in proximity to the scalp electrodes. Electrical activity deep within sulci or fissures, or from cortex covering the base of the brain (approximately two-thirds of the brain's cortical surface area), contributes little or nothing to the final recording. Subcortical structures do not produce electrical activity reliably recordable at the scalp except in the case of stimulus time-locked averaging, that is, evoked potential recording. For example, epileptiform spikes generated within the hippocampus are not thought to be directly seen in scalp recordings. However, they may evoke cortical spikes transynaptically that are then recorded in the routine scalp EEG. In contrast to scalp electrodes, intracranial electrodes (subdural and depth) record much higher amplitudes, but the activity they record is far more restricted spatially. Intracranial activity that is less than a centimeter away from an intracranial recording electrode often goes undetected, whereas most recordable cortically generated scalp potentials can still be detected even when the scalp electrode is moved several centimeters.

The figure below illustrates differences in amplitude between simultaneous recordings of a seizure from scalp and intracranial electrodes (hippocampal, anterior temporal, neocortical, and overlying scalp electrodes) referenced

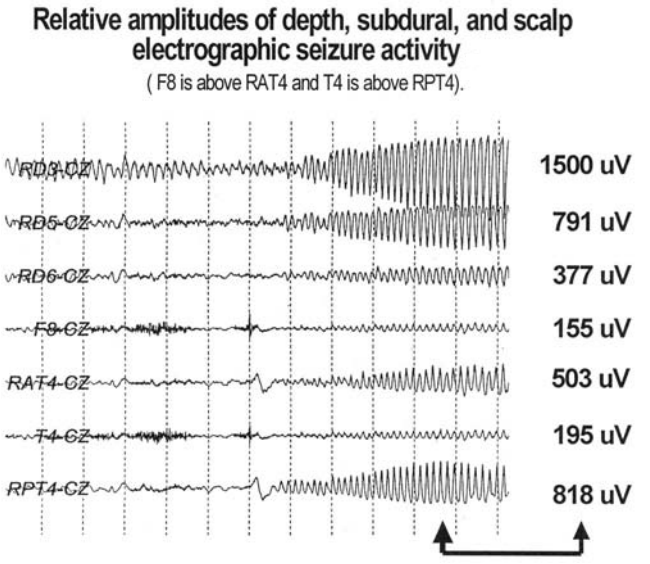

FIGURE 6-2. This figure illustrates differences in amplitude between simultaneous recordings of a seizure from scalp, subdural, and depth electrodes (hippocampal depth, anterior temporal subdural neocortical, and overlying scalp electrodes) all referenced to a scalp needle electrode at Cz. The seizure is initially only seen in the top channel (right hippocampal depth electrode). As it spreads, it next appears in the overlying anterior temporal subdural electrodes recording directly from the cortex (channels 5 and 7), and then finally in the temporal scalp electrodes (channels 4 and 6). The voltage values indicate the highest voltage of the signal (peak to peak) seen in each channel at the time of the upward arrow.

to Cz. The seizure is initially only seen in the top channel (right depth electrode). As it spreads, it next appears in the overlying subdural electrodes recording directly from the cortex (channels 5 and 7), and then finally in the scalp electrodes (channels 4 and 6). The voltage values indicate the highest voltage of the signal (peak to peak) seen in each channel at the time of the upward arrow.

As can be seen in Figure 6-2, the majority of the EEG electrical signal is limited to the intracranial compartment. However, a relatively small fraction penetrates through the meningeal coverings, spinal fluid, and skull to the scalp, where it produces the scalp-recorded EEG.

Volume conduction is the passage of an electrical current through a conducting substance. In clinical biological recording, the conducting substance is the human body. EEG electrical current fields pass from the synaptic cleft of cortical pyramidal cell neurons to the scalp. The EEG electrical currents arise almost exclusively from pyramidal cell inhibitory and excitatory cortical postsynaptic potentials. Although the EEG is a result of individual neuronal potential changes, microelectrode activity from individual cortical cells often correlates poorly with the ongoing EEG activity. This is partly due to the property of emergence, where in a complex system a property can emerge that would not be anticipated from the analysis of the individual contributing components. In the case of EEG, an extremely large number of potentials summate to produce the EEG. Furthermore, the summating effects of volume conduction help to obscure the overlapping contributions (temporal dispersion) of individual neurons.

The cortical electrical activity that is most likely to reach scalp recording electrodes consists of slow, simultaneous, summated postsynaptic potentials generated by large cortical areas oriented in parallel to the cortical surface. Within the cortex, the vertically oriented pyramidal cells form sheets of electrical dipoles that are parallel to each other and perpendicular to the cortical surface. These dipole sheet layers have uniform voltage polarities. For those cortical layers that are parallel to the scalp, the dipole sheet is perpendicular (radial) to the overlying scalp and only one polarity (one end of the dipole, one side of the dipole sheet or layer) is exposed to the view of the overlying scalp electrode. Such voltage dipoles are therefore oriented radially (at a 90-degree angle; i.e., perpendicular) to the scalp at the convexity of the gyrus, with one end of the dipole pointing toward the scalp surface.

The cortical layers in the walls of the sulci are oriented perpendicular to the overlying scalp surface, so that their dipole layers are oriented in parallel (tangentially) to the scalp surface instead of radially. Because tangential dipoles (also referred to as parallel generators or horizontal dipoles) do not strongly project either negativity or positivity to the immediate overlying scalp, they contribute significantly less to the final EEG signal than do radially oriented signals. Moreover, dipole layers in the walls of sulci face each other so that their opposing dipole layers tend to produce a cancelation effect at the scalp overlying the sulcus. Such tangential dipoles are best detected by an entirely different procedure, magnetoencephalography (MEG), whereas radial signals are not. In this sense, the MEG and EEG are complementary procedures, so that in some cases (probably less than 10%), epileptiform activity can be detected by one procedure and not the other.

The electrical activity generated by the cortex does not project to the immediately overlying scalp in a highly focused way. Instead, the electrical current flowing from the cortex spreads out as it meets different layers of electrical resistance. These layers include the brain parenchyma, cerebrospinal fluid, dura, skull, and scalp. Therefore, as the amplitude of the scalp potential increases, it becomes more widespread over the scalp surface. Similarly, the greater the integral of the waveform (i.e., the area between the waveform and the electrical baseline), the more widespread it is over the scalp surface. This is the basis for a fundamental rule of EEG interpretation, for cortical EEG:

$$(\text{Amplitude}) \propto (\text{size of the scalp current field distribution})$$

In practice, this means that for cerebral activity, the distribution over the scalp increases with the change in voltage of the cortical signal. *Therefore, a prominent waveform that*

is only detected by one electrode may be artifact unless it can also be detected by placing an additional adjacent electrode. There are, however, two commonly encountered situations in which a spike may be expected to occur at only one electrode during a routine scalp recording:

1. The recording electrode is located overlying or near a skull defect or missing portion of skull (e.g., from prior trauma or surgery)
2. Recordings in neonates and infants in which the skull is thin and highly localized patterns commonly occur

The best way to improve the spatial resolution of the EEG is to increase the number of recording electrodes. This is analogous to increasing the sampling rate of an analog-to-digital converter. Just as digital sampling involves the conversion of a continuous signal into discrete points, *spatial sampling* involves the conversion of continuous voltage current contours over the scalp into discrete points in space, with each point represented by a recording electrode. If the distance between recording points is longer than the diameter of the activity to be sampled, then spatial undersampling and spatial aliasing occur. It is generally cited that at least 6 cm^2 of cortical area needs to be engaged in a synchronous activity to produce a well-defined potential at the scalp surface (1). In fact, most epileptiform spikes involve the activity of about 1 million neurons and arise from 10–20 cm^2 of cortical surface (2).

For the smallest radially oriented cortical source recordable at the scalp, it is estimated that the sampling error using the 10–20 system of electrode placement (with typical interelectrode distances of about 4.5 cm) is about 6%. The newer modified combinatorial expanded 10–20 system has interelectrode distances closer to 2.0 cm, and is shown below (Figure 6-3). Because it is impractical to routinely apply all of the electrodes shown below, *this system is used for adding electrodes as needed, during monitoring*. Notice that only the four darkened electrodes of the original 10–20 system have to be renamed to adapt the older 10–20 system: T3 and T4 become T7 and T8, and T5 and T6 become P7 and P8.

One of the immediate advantages of the expanded system is that the placement of additional electrodes can be communicated accurately to the technologist and reproduced between laboratories. The figure below (Figure 6-4), showing the typical distribution of the anterior temporal spike, provides an example of why additional electrode placement to the 10–20 system is useful. The routine 10–20 electrodes would not go below the upper edge of the darkest part of the spike field. In contrast, the T10, F10, and FT10 electrodes over the right hemisphere of the expanded system would be placed more directly in the spike field. Similarly, sphenoidal electrodes are inserted under the lower edge of the sphenoidal ridge, in the center of the darkened area.

As noted above, the selection of electrodes for inputs 1 and 2 for any single amplifier channel is referred to as the *derivation*. The combination of multiple derivations is

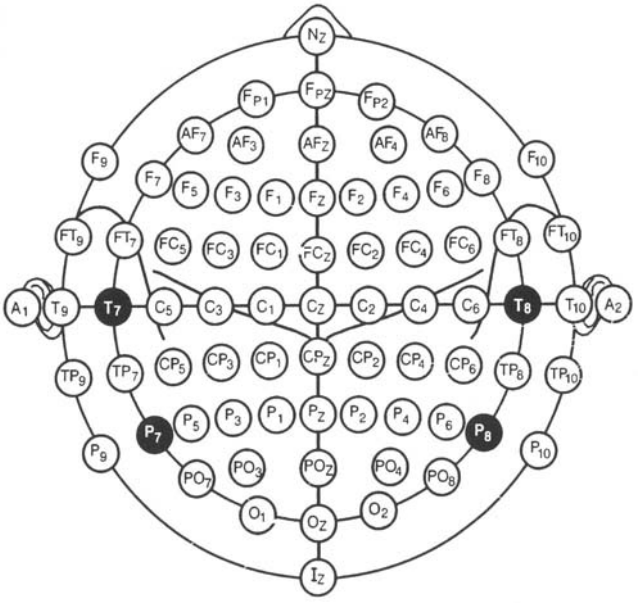

FIGURE 6-3. Modified combinatorial expanded 10–20 system of electrode placement as proposed by the American Clinical Neurophysiology Society. For a description of how the 10–20 electrode measurements are made for electrode placement, the reader is referred to textbooks on EEG, such as *Fisch and Spehlmann's EEG Primer*.

referred to as a *montage*. Montages perform the function of *spatial filtering* because they filter out, to varying degrees, similarly shaped waveforms that are simultaneously and widely distributed over the scalp. To make a simple analogy, changing montages can be compared to varying lens settings in order to focus on specific distributions of EEG activity. Some montages (e.g., bipolar or Laplacian) are best suited for viewing highly localized activity (close-up views), whereas others (e.g., reference montages) are better for viewing widespread potentials (distant views). Because spatial

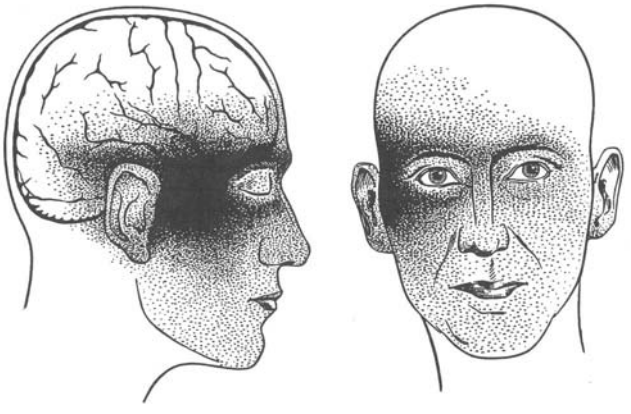

FIGURE 6-4. The stippled area indicates the voltage distribution of a typical anterior temporal lobe epileptiform spike. The darker the area, the higher the peak voltage of the spike. Reproduced from Gibbs and Gibbs (12).

analysis is so important in EEG interpretation, the most important advance in routine EEG technology in the last 20 years has been the application of digital EEG montage reformatting in which the montage can be changed after the recording to bring various signal features into "focus."

There are currently five basic kinds of montages the EEG reader should be familiar with: bipolar, common electrode reference, average reference, weighted average reference, and Laplacian (source derivation). To understand the construction and use of montages, it is essential to understand differential amplification and polarity conventions in EEG.

Field polarity in EEG (and in all biological recording except MEG) is always relative, because it is assigned according to the voltage difference between recording electrode inputs, each of which is attached to a different location on the body. At no time is the difference between body voltage and ground voltage (earth zero voltage; absolute voltage) ever determined.

Differential Amplification

All biological recording uses differential amplification. *Differential amplifiers* measure the difference (hence the term differential) in voltage between two electrodes placed on (or in) the body. The reason differential amplification is used is that it eliminates any electrical noise detected by both amplifier inputs (electrodes), such as 60-cycle interference. If the voltage potential of a particular electrode could be compared to the ground potential (i.e., the potential voltage of the earth (literally an electrode stuck in the ground), then its polarity could be established in absolute terms. This would then be referred to as single-ended amplification. Unfortunately, recording from the body (input 1) and the earth ground (input 2) produces too much electrical interference to be useful.

By convention, a differential amplifier subtracts the voltage in input 1 from that in input 2. Therefore, at any single point in time:

EEG amplified signal = (input 1 voltage) − (input 2 voltage)

Somewhat arbitrarily, it has been decided that if the voltage in input 1 is relatively more negative than that in input 2, then the waveform deflection is upward. If EEG activity in input 1 is relatively more positive than in input 2, then the waveform deflects downward. Remember, polarity in differential amplification is relative. Therefore, a voltage of +30 μV in input 1 and a voltage of +70 μV in input 2 would produce an upward signal deflection, because even though the activity in input 1 is positive, it is negative relative to that in input 2. Again, according to the equation above, the amplified signal would be (+30) − (+70) = +30 − 70 = − 40. Another way to express the EEG polarity convention would be to say that a relative positivity in input 2 compared to that in input 1 produces an upward deflection, whereas a relative negativity in input 2 produces a downward deflection.

Montage Construction and Reformatting

As stated above, montage reformatting is the process of creating a new montage to view the same EEG epoch. It is surprisingly simple to understand reformatting if it is understood that the EEG signal from each channel is created by the subtraction of the activity in the electrode in input 2 from input 1. For example, *when a technologist labels a channel montage as Fp1 – A1, they have actually written a mathematical expression* that states that the signal displayed will be Fp1 minus A1 (input 1 minus input 2).

If a recording has been obtained from Fp1 – A1 and F3 – A1, then Fp1 – F3 can be derived by subtracting F3 – A1 from Fp1 – A1, as follows:

$$(Fp1 - A1) - (F3 - A1) = Fp1 - F3 + A1 - A1 = Fp1 - F3$$

Similarly, if a recording has been obtained from one channel with Fp1-F3 and one channel with F3-C3, then a recording of Fp1-C3 can easily be derived by adding the two channels:

$$(Fp1 - F3) + (F3 - C3) = Fp1 - F3 + F3 - C3 = Fp1 - C3$$

As long as all the electrodes that are to be combined have been somehow referred to each other in the original recording, it is a simple matter to reconstruct any combination of montages, including more complex montages such as the common average reference and Laplacian (e.g., source derivation) montages. For this reason, digital EEG systems store the original EEG signal in a referential montage containing all electrodes. If the original recording montage does not incorporate a particular electrode, then a new montage cannot be derived that contains that electrode. Because montage reformatting is simply a matter of addition, subtraction, multiplication, or division, computers are able to reformat montages nearly instantaneously.

Bipolar Montages

Bipolar *derivations* consist of adjacent electrodes of the 10–20 international system of electrode placement inserted into inputs 1 and 2, respectively. Recommended *bipolar montages* consist of a series of overlapping bipolar derivations in straight lines, either longitudinally (anterior to posterior) or transversely (left to right) across the scalp. They act as spatial filters that remove widespread potentials with similar amplitudes and phases (i.e., coherent waveforms) from the recording. *Bipolar montages are therefore best for analyzing low to medium amplitude waveforms that are highly localized.*

Bipolar montages consist of overlapping bipolar derivations that are arranged in a chain-link fashion so that an electrode at input 2 of one amplifier is in input 1 of the next amplifier, as shown in Figure 6-5 below. There are 2 kinds of bipolar montage: *longitudinal* and *transverse*. An example of a *longitudinal bipolar montage* would be Fp1-F3, F3-C3, C3-P3, and

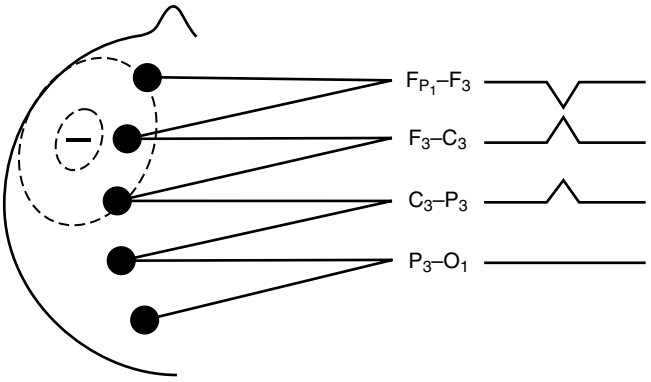

FIGURE 6-5. Longitudinal (anterior–posterior) bipolar recording of a left-hemispheric negative potential demonstrating an instrumental phase reversal between the first and second channels. In each channel, input 1 is anterior to input 2.

P3-O1 (notice that the electrode derivations progress in an anterior-posterior line; refer to Figure 6-3 above showing the expanded 10–20 system). An example of a *transverse bipolar montage* would be T7-C3, C3-Cz, Cz-C4, C4-T8 (notice that the electrode derivations progress in a left-to-right line).

In bipolar montages, cerebral potentials are localized according to the direction of their waveform phase deflections between channels. An identical voltage in input 2 of one channel and input 1 of the next channel in a bipolar chain of derivations causes waveform (or pen) deflections of opposite direction between those two channels. This is referred to as an *instrumental phase reversal*.

Figure 6-5 shows a bipolar montage recording of a relatively negative potential that has an instrumental phase reversal between the top channel and the next lower channel. The top channel shows a downgoing deflection because input 2 is near the negative potential, whereas the next channel, being connected to that electrode through input 1, shows an upgoing deflection. *Recall that, in EEG recording, if the electrode in input 1 is more negative than the electrode in input 2, then the waveform deflection will be upward; if the electrode in input 1 is more positive than the electrode in input 2, then the waveform deflection will be downward.*

The phase reversal (i.e., mirror-image orientation of the potential in channels 1 and 2) shown in the figure above does not indicate an actual reversal of polarity of the cerebral potential from one cortical area to the next (*true phase reversal*). It represents a reversal in the direction of the waveform deflection created by arrangement of the montage derivations (hence an *instrumental* phase reversal). If the potential shown in the figure above was positive instead of negative, the waveforms in the first two channels would then point away from each other instead of toward each other.

In the author's experience, many physicians who are learning to interpret EEG initially develop *three fundamental misconceptions about polarity and phase reversal*. The first is the belief that an upward deflection of the waveform means that the scalp potential that caused the waveform was negative, and that a downward deflection was caused by a positive potential. Remember, a waveform that points up is no more positive or negative than a waveform that points down. Polarity is totally dependent on which input of the differential amplifier the active electrode is in. In a single channel of recording, it is not possible to know whether an upward or downward deflection is negative or positive. Thus, a positive scalp potential in the electrode of input 2 makes an upgoing deflection, and, similarly, a negative scalp potential in the electrode of input 1 makes the same upgoing deflection.

The second misconception is that a phase reversal is always an abnormal finding. This is partly the fault of the teacher, who only invokes the concept of phase reversal in the setting of epileptiform spikes.

The third misconception is that an instrumental phase reversal is the same thing as a true phase reversal. Instrumental phase reversals, like polarity, are simply the by-product of the configuration of the bipolar montage, and prominent normal examples can be found on virtually every page of a bipolar recording. In contrast, *true phase reversals* are generated by different cortical surfaces simultaneously *truly* having different polarity voltages. *A true phase reversal is identified by the presence of a single instrumental phase reversal in a reference montage or two instrumental phase reversals in a bipolar montage. True phase reversals suggest the presence of a tangential voltage source (tangential potential, also referred to as a parallel generator).*

A potential having a maximum exactly between two recording electrodes, as shown in Figure 6-6 below, produces the same potential in both electrodes and therefore causes no deflection in the channel in which they are both connected. However, a potential that is the same in two adjacent electrodes can be detected in a bipolar montage, because these electrodes are also connected in two other channels that will show a phase reversal in relation to each other (channels 1 and 3 in Figure 6-6). This is referred to as "in-phase cancelation."

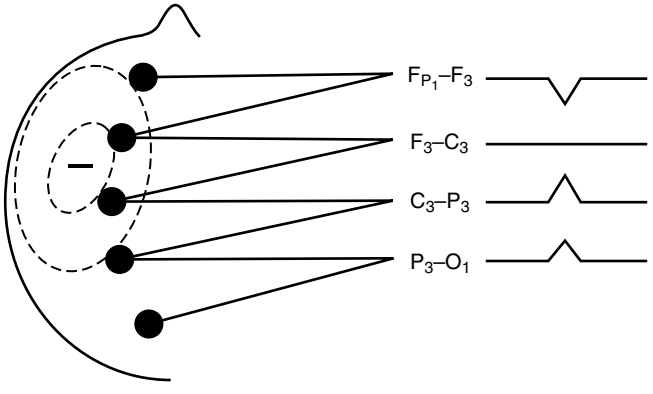

FIGURE 6-6. Longitudinal (anterior–posterior) bipolar recording of a left-hemispheric negative potential demonstrating a phase reversal between the first and third channels and cancelation in the second channel caused by an equal voltage occurring in each of the two electrodes in the second channel. The maximal potential source is therefore between F3 and C3.

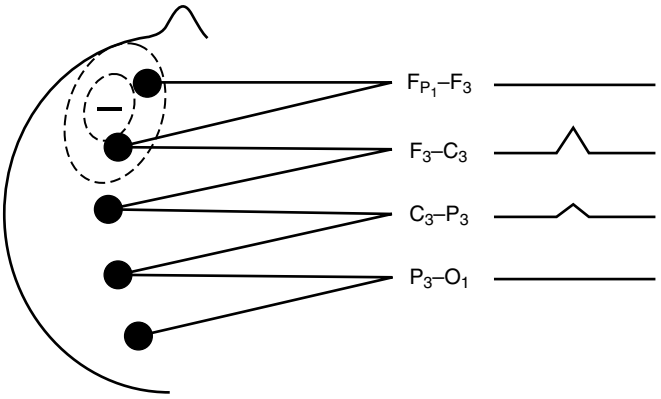

FIGURE 6-7. Longitudinal (anterior–posterior) bipolar recording of a left-hemispheric negative potential, demonstrating localization without an instrumental phase reversal. Cancelation occurs in the first channel because both electrodes of that channel record the same voltage. The second channel records the difference between the two electrodes in that channel, in which the more anterior input 1 electrode records a higher voltage negativity compared to the more posterior input 2 electrode. In the third channel the same occurs, but the negative voltage in input 1 is less than that which occurred in input 1 of the second channel recording.

Potentials that appear with greatest voltage in the last electrode in the chain of electrodes will produce waveform deflections in the chain of bipolar channels that are all in the same direction (i.e., no phase reversal). This is sometimes referred to as the "end of the chain phenomenon."

Cancelation, the end of the chain phenomenon, and phase reversal can occur in various combinations. When a potential occurs between the last two electrodes in a chain and affects them equally, then no output is seen in the channel that contains them both, whereas the remaining channels show waveform deflections in the same direction, as shown in Figure 6-7.

Exceptionally, and as shown in Figure 6-8, widespread potentials may be largely canceled or produce phase reversals in the opposite ends of the chain of channels.

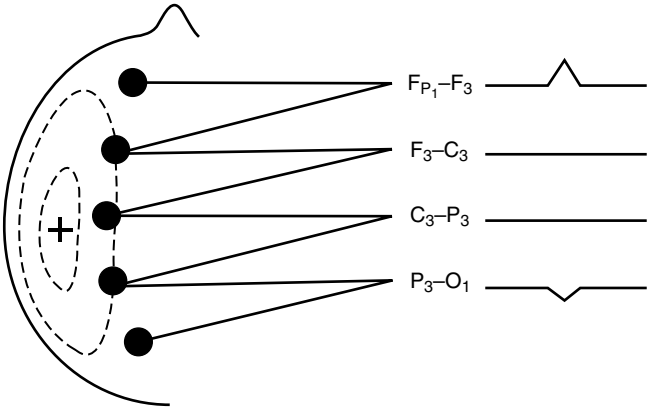

FIGURE 6-8. Longitudinal (anterior–posterior) bipolar recording of a left-hemispheric positive potential in which F3, C3, and P3 are equally involved but Fp1 and O1 are spared.

When uncertainties as to the localization of a voltage source using bipolar montages occur, the electroencephalographer should apply alternate montages to resolve the spatial distribution of the activity in question.

A final cautionary note about bipolar montages is that they are *not reliable for assessing interhemispheric amplitude asymmetries unless the asymmetry is present in both the longitudinal and transverse bipolar montages*. In other words, an artifactual asymmetry may appear in a longitudinal bipolar montage and not in the transverse montage (or the reverse).

Common Electrode Reference Montages

Common electrode reference montages consist of a series of derivations in which the same electrode is used in input 2 of each amplifier. Ideally, the reference electrode in input 2 is at a distance from the source of the activity of interest, in a relatively "quiet" location. Unlike the bipolar montage, the common electrode reference montage does not automatically filter out widespread potentials that have similar amplitudes and phases (i.e., coherent waveforms). It also produces a higher-amplitude EEG recording because of the longer interelectrode distances.

Highly localized low- to medium-amplitude activity that would be easily seen in a bipolar montage may be completely lost in the presence of intermixed, higher-amplitude, widespread activity. There are two main categories of common electrode reference montages that are distinguished according to the placement of the reference electrodes on the body: *cephalic* and *noncephalic*.

Typical cephalic reference electrodes for the common reference electrode montage include A1, A2, and Cz.

Figure 6-9 shows a cephalic ear (A1 electrode) referential montage recording with the same potential as that recorded with a bipolar montage in Figure 6-5.

Note that in the common reference montage, when the reference electrode is far from the scalp area of activity the following statement is true: *In a reference montage, the*

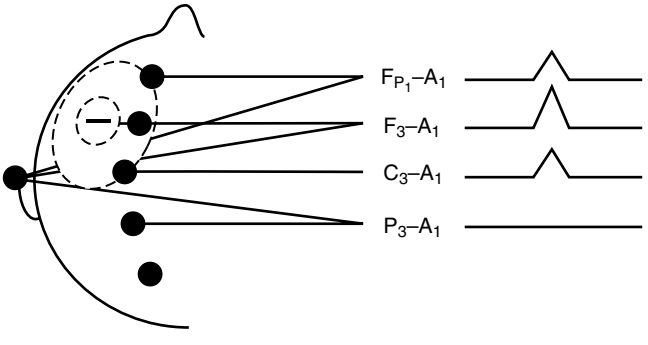

FIGURE 6-9. Ear reference montage of the same potential as that recorded in Figure 6-5. The ear reference electrode is not in the voltage field of the negative potential. Phase reversal does not occur, and F3 in the second channel with the highest voltage is closest to the cortical source.

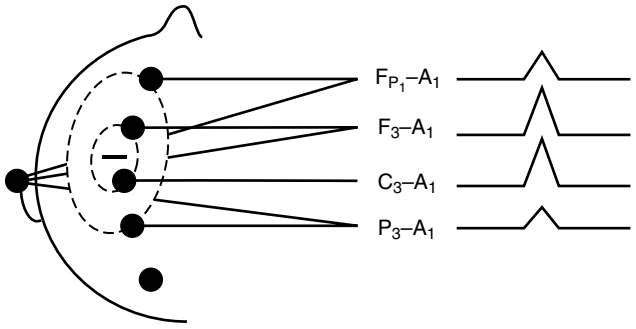

FIGURE 6-10. Ear reference montage recording of the same potential shown in Figure 6-6. The ear reference electrode is not in the voltage field of the negative potential (i.e., not contaminated by the potential). Phase reversal does not occur. The second and third channels show equally large peaks, indicating that their input 1 electrodes (F3 and C3) are approximately equidistant from the center of the scalp voltage field, and closer to it than are the other three electrodes.

location of the maximal potential on the head is usually determined by amplitude, not by phase reversal.

Assuming that the reference electrode is not in the main voltage field of the activity and that the exploring electrodes in input 1 are, then the channel that records the potential of highest amplitude contains the electrode closest to the origin of the potential. If the output of two channels is of equal amplitude, the origin of the potential is usually located an equal distance between each of the two electrodes connected to input 1, as shown in Figure 6-10 for F3 and C3 and for Fp1 and P3.

If several channels show a similar output, the potential usually affects input 1 of all these channels to an equal degree, as shown for F3, C3, and P3 in Figure 6-11.

If all channels show the same output, then the activity is usually coming from the reference electrode itself.

Unlike the bipolar montage, the reference montage can give a better approximation of how the waveform shape might appear in a truly reference-free recording. However, it is sometimes difficult to find a cephalic reference

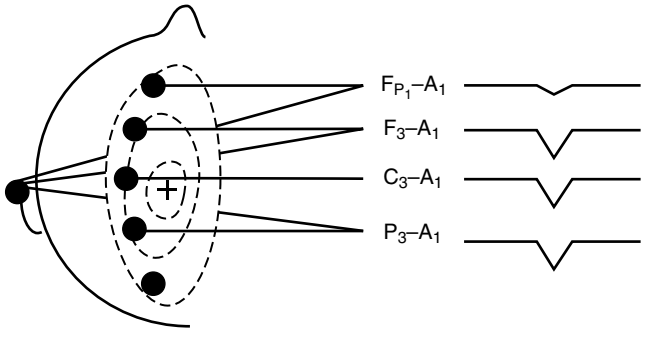

FIGURE 6-11. Ear reference montage recording of a positive voltage field equally involving F3, C3, and P3 with lesser involvement of Fp1 and without involvement of O1. The reference is not in the field of the potential, and so the localization of the potential is determined by the amplitude of the input 1 electrodes.

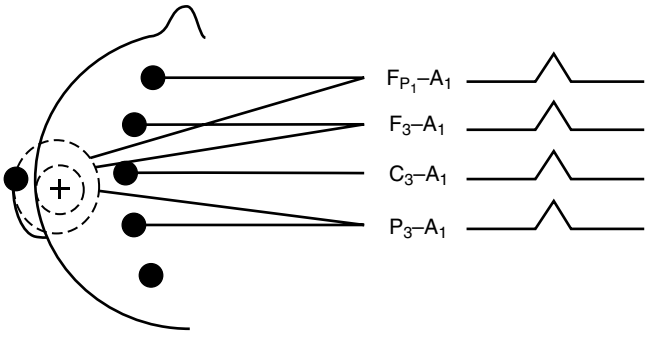

FIGURE 6-12. Ear reference montage recording of a positive voltage field located near the reference. This montage is poorly chosen because the reference is in the field of the activity of interest. The "contaminated" reference is responsible for the spike deflection in each channel, and therefore all the channels record the same approximate peak voltage. Note that because positivity is present in input 2 (in this case the reference electrode), the signal deflection is upward. When all input 2 electrodes appear with similar voltage, the source is localized to the reference electrode.

electrode that is relatively inactive, or free of contamination from the cerebral potential in the input 1 electrodes. Moreover, potentials (cerebral or noncerebral) at the reference electrode may sometimes be large enough to overwhelm all channels connected to that electrode. Difficulties in interpretation that may occur using common cephalic electrode reference montages are summarized as follows:

1. A potential may affect only the reference electrode. For example, activity in the temporal lobe may appear as a transient positive potential at an ear electrode (A1 or A2) reference. This will produce a deflection in all channels connected through input 2 to this electrode, as shown in Figure 6-12.
2. A potential located midway between the reference electrode and a scalp electrode may be canceled in a channel connected to both these electrodes and appear in other channels that are connected to the reference electrode, as shown in Figure 6-13.

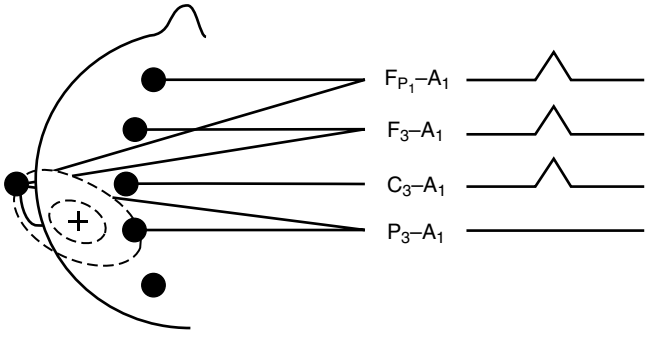

FIGURE 6-13. Ear reference montage recording of a positive voltage field located between the reference electrode and the input 1 electrode (P3) in the last channel. The first three channels record the "contaminated" reference (as in Figure 6-10), whereas the last channel demonstrates cancelation because the reference and the input 1 electrode record the same voltage of the positive field.

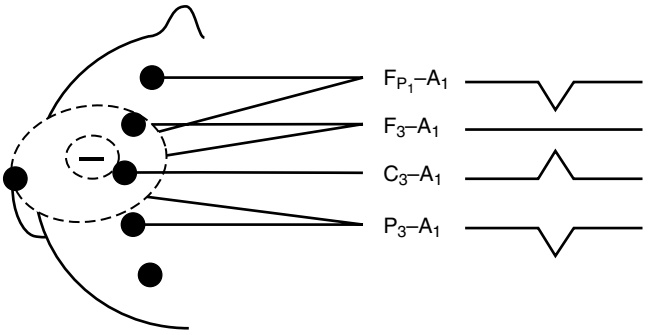

FIGURE 6-14. Ear reference montage recording of a negative voltage field that is located between two of the input 1 electrodes and the reference electrode. This creates a highly complex appearance in which there is cancelation and two phase reversals (one between channels 1 and 3, and one between channels 3 and 4). In channel 1 the negativity in the reference electrode (A1) creates a downward deflection (by convention, negativity in input 2 results in a downward deflection). In channel 2 both the reference and the input 1 electrode F3 record the same approximate negative voltage and therefore cancel each other. In channel 3 there is greater negativity in the input 1 electrode than in the reference electrode, resulting in an upward deflection. In channel 4 the reference electrode records the negative field producing a downward deflection.

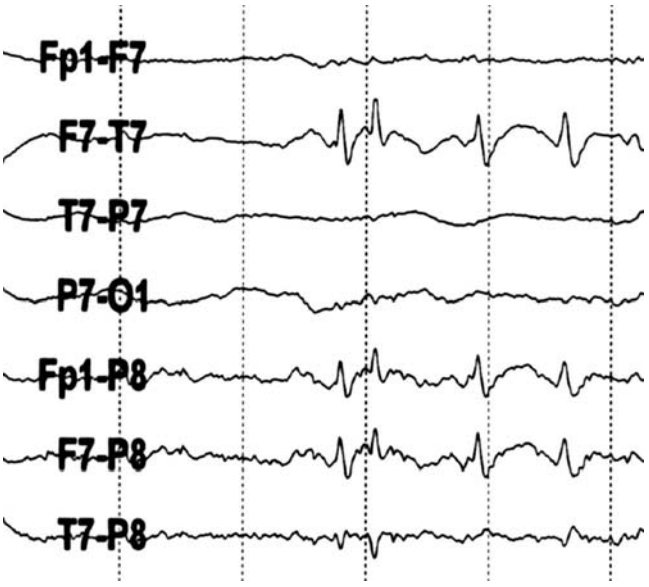

FIGURE 6-15. Longitudinal bipolar montage recording alone does not allow for accurate localization. Localization is easily resolved by adding a reference montage with a reference electrode that is away from the field of interest, reducing the likelihood of reference contamination.

3. A potential may be located between the reference electrode and some scalp electrodes so that, as shown in Figure 6-14, it appears as a contribution by input 1 in one channel (Fp1-A1), cancels between inputs 1 and 2 in another channel (F3-A1), and appears with opposite polarity as a contribution by the reference electrode in the other channels (C3-A1 and P3-A1).

To overcome these potential shortcomings of the reference montage, it is useful to use a reference electrode that is placed off the scalp, and even better, off the head. The most widely used noncephalic reference is the *neck–chest reference.* One electrode is placed at the sternal notch and a second electrode is placed at the base of the back of the neck. In long-term recordings, adhesive stick-on electrodes are superior to collodion glued electrodes. Both electrodes are joined together by a Y connector in input 2. Although this minimizes reference contamination by cerebral potentials, the ECG (which is a millivolt signal) can obscure the EEG signal (which is a microvolt signal) during the QRS complex in many individuals (over 30%). The point of placing one electrode on the neck and another on the chest is to try to cancel out the cardiac current vector, which normally is a positive wavefront moving from an anterior right to a posterior left direction. The neck–chest electrode also serves as a movement monitor, particularly for neck flexion and extension.

With digital EEG, neck–chest electrodes should always be used. This allows the reader the option of applying a noncephalic reference during retrospective analysis.

Figure 6-15 illustrates a complex localization problem that is quickly solved by applying a common electrode referential montage. In the bipolar montage in the first four channels, localization cannot be accomplished by instrumental phase reversal (because none is present). Similarly, it cannot be determined whether the spikes in channel 2 are negative and arising from F7, or whether they are positive and arising from T7.

One solution to this problem comes by retrospectively creating new derivations using a distant reference electrode that is outside the field of the activity in question. All digital systems now allow the reader to rapidly create new derivations or select new reference electrodes. In this case, the P8 electrode is far removed from the activity in question, and thus serves as an indifferent reference to help reveal the true distribution of the spikes. Selecting the P8 reference electrode in input 2 of the bottom three channels reveals that the activity in question is a series of horizontal dipoles with anterior negativity (Fp1 and F7) and posterior positivity (T7).

Average Reference Montages

The *average reference montage* consists of a series of derivations in which all or most of the 10–20 electrodes are added together in input 2 of every amplifier to serve as a reference for each electrode in input 1. If, for example, there are 19 scalp electrodes being used, then all 19 are combined in input 2 of every channel of recording. Each of the 19 electrodes then contributes one-nineteenth of the total activity in input 2. However, one or more electrodes can dominate the final value of the reference. For example, a 200-μV potential in one of the reference electrodes

would dominate the final value of the reference if the inputs from each of the other reference electrodes was 5 μV (18/19 of 5 μ is 4.74 μV, compared to 1/19 of 200 μV, which is 10.52 μV). Because the average reference usually contains all the scalp electrodes, the electrode in input 1 is compared against the other electrodes and itself. In the example of 19 recording electrodes, one-nineteenth of the activity in the input 1 electrode would be subtracted from the final output by the presence of the input 1 electrode in the input 2 common average. In analog and digital instruments, the average reference electrodes are selectable and can be added or removed from the reference. This allows the user to increase the amplitude of activity of selected head regions (or reduce reference contamination from those same head regions) by removing the electrodes of those head regions from the reference. In general, the average reference should contain at least 16 electrodes, but the intent of the montage is best served if all the recording electrodes are used.

Some investigators have referred to the average reference montage as "reference-free." This is true to the extent that the average reference montage does give an accurate reading of the relationship of voltage values between all the electrodes. Moreover, if the correct zero baseline potential at any given head region at any given moment could be known, then an approximation of the true potential values at the different electrode sites could be calculated. Unfortunately, this is, in routine practice, not the case. The average reference montage should not be regarded by clinicians as reference-free because high-amplitude potentials at even a few electrodes can contaminate the reference.

As shown in the example in Figure 6-16, the average reference montage on the left shows a vertex wave during sleep that appears to be negative in the midline but positive over the temporal head regions. However, using the electrocardiogram lead on the chest as a noncephalic reference, it can easily be seen that the vertex wave is negative all over the scalp with a maximum amplitude at Cz. The "upside-down" vertex wave over the temporal head regions actually represents contamination of the average reference. That is most clearly shown in the upper left EKG1-AVG recording channel, in which the negative potential arises from the average reference.

Although a high amplitude or widespread activity can contaminate the reference and produce a confusing picture, it is important to understand that *the channel of the average reference that contains the highest amplitude waveform almost always correctly localizes the cortical activity to the electrode in input 1 of that channel.*

This can be seen in the figures mentioned above. The average reference montage produces a spatial filtering effect that is intermediate between the common electrode reference montage and the bipolar montage; there is less attenuation of widespread potentials than in the bipolar montage, but more than in the common electrode reference montage. Using the lens analogy, the average reference does not give a perfectly focused view of either the whole forest or the individual branches on the trees, but both can often be seen well enough to identify pathological patterns.

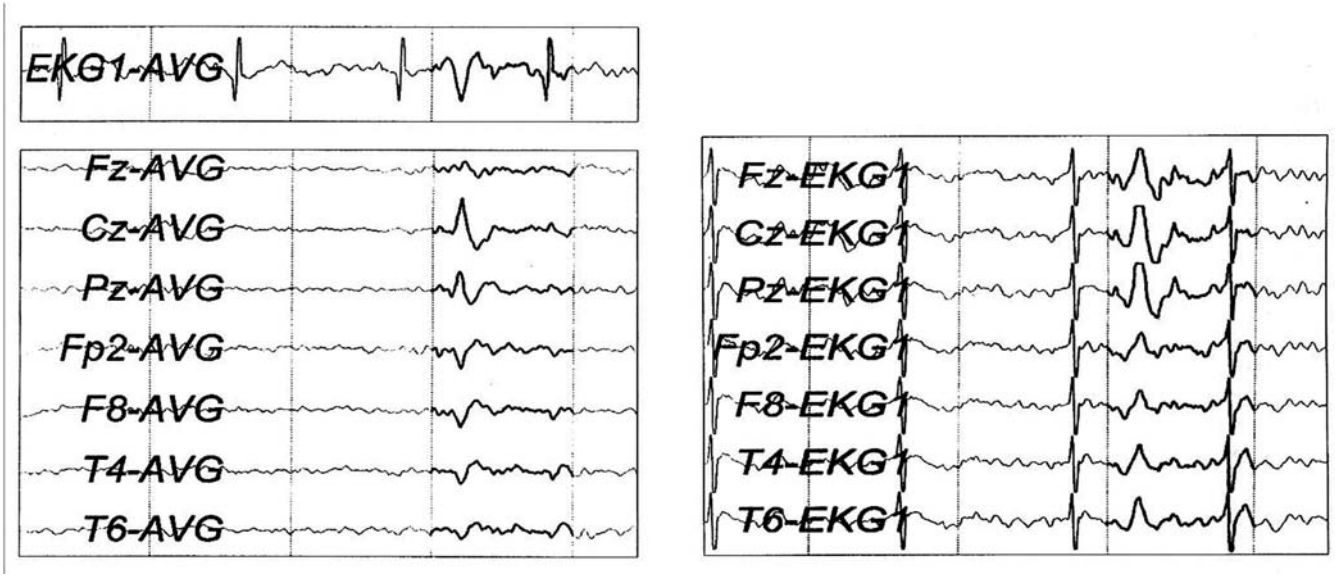

FIGURE 6-16. Average reference montage showing a vertex wave of sleep that appears over the temporal head regions, with reversed polarity from the central head regions caused by reference contamination. The high amplitude of the vertex wave becomes part of the reference in input 2 from contributions from Fz, Cz, Pz, F3, C3, P3, F4, C4, and P4. The contribution of the average reference is shown in the EKG-AVG (ECG input 1 and average reference in input 2) derivation, and the actual distribution of the vertex wave is shown on the right side of the figure using one of the two noncephalic electrocardiogram electrodes as an indifferent reference. See Fisch (13).

Weighted Average Reference (WAR) Montage

The weighted average reference montage is similar to the average reference montage, except that the electrodes in input 2 do not contribute equally to the reference and the input 1 electrode is not included in the reference. The electrodes closer on the scalp to the input 1 electrode contribute more to the reference (have a greater "weight") than do the electrodes farther from the reference. Thus, the relative percentage contributions of the reference electrodes vary from channel to channel depending on which electrode is in input 1. In comparison to the average reference, the weighted average reference reduces the possibility of a widespread activity contaminating the reference of all channels. The intention of the weighted average reference is to better demonstrate localized waveforms without creating reference-contaminated waveforms. This can be enhanced in some cases by using weighting factors based on actual scalp interelectrode distances. The weighting factors are calculated as inverse linear distances. The longer the distance from the input 1 electrode, the less that input 2 electrode will contribute to the reference. This creates a spatial filtering effect that is intermediate between the average reference and bipolar montages (3). The weighted average reference montage as originally described for the 10–20 system can be easily implemented on most commercial digital EEG systems using either spreadsheet input or special vendor-specific programs.

Laplacian Montage

The Laplacian montage design was first implemented by Hjorth (4) who referred to it as the *source derivation montage*. Although the Laplacian equation was originally derived to analyze thermal topography as a continuous process, it has been adapted to the analysis of discrete phenomena such as EEG spatial sampling. As noted above, spatial sampling is similar to analog-to-digital conversion, but instead of creating sampling points of voltage over time, each electrode site is a sample point for sampling voltage over space.

In application, the Laplacian montage design is similar in construction to the weighted average reference, but it typically includes just the nearest neighboring electrodes surrounding the input 1 electrode. Ideally, the input 1 electrode is surrounded in a symmetric fashion by reference electrodes to create a local weighted average reference that approximates the mean potential gradient directed at the central (input 1) electrode. This is not possible for all input 1 electrodes of the 10–20 system, because some are located at the edge of the scalp array and cannot be symmetrically surrounded by reference electrodes. Therefore, like the weighted average reference montage, the Laplacian montage design cannot be uniform for all input 1 electrodes; it is always somewhat limited by so-called "edge effects."

Like the weighted average reference, the contributions of the reference electrodes are linearly "weighted" according to their distance from the input 1 electrode. This creates a more severe filtering of widespread waveforms. The Laplacian montage is therefore intermediate in filtering effects between the bipolar and weighted average reference montages. Most digital EEG instrument vendors now offer some version of the Laplacian montage. As with all other reference montages, confusing pictures can arise because of reference contamination. However, the Laplacian montage is extremely useful for filtering out widespread coherent waveforms and for emphasizing localized waveforms. It is routinely used to localize seizure onset.

Source Localization

Source localization refers to the process of calculating the precise anatomical location of a current source within the brain by using the distribution of potentials recorded from the scalp and other nonintracranial electrodes. It is an attempt to solve the *inverse problem*. The solution of the inverse problem is, not surprisingly, typically referred to as the *inverse solution*. Because any scalp voltage can theoretically arise from an infinite number of intracranial sources, it is theoretically impossible to solve the inverse problem. However, there are certain reasonable, practical assumptions that can be imposed to greatly limit the number of possible solutions. For example, it is already known that all spontaneously recordable scalp EEG signals arise from the underlying cortex (except, as noted above, in the case of evoked potential averaging, in which the signal-to-noise ratio of the desired signal is tremendously increased). Using such constraints, a number of approaches to the inverse problem have been proposed. Each applies assumptions about the anatomy of the volume conductor and about the likely site of the generator(s). Although progress continues in this area of EEG research, the information provided by these methods is considered adjunctive at best, and should not be used in isolation to make important clinical decisions (e.g., to localize the epileptogenic zone of the brain for surgical removal).

Even more progress toward the inverse solution has been made using an alternative technology, magnetoencephalography (MEG). As noted above, MEG records neuronal magnetic currents (as opposed to the extracellular electrical currents recorded by EEG) with reference-free recording (the reference is the magnetic field of the earth), and can accurately localize some sources within the brain. In contrast to electrical fields, the intervening tissues (cerebrospinal fluid, skull, etc.) do not distort the magnetic fields between the cortical generator and the detector. Currently, the widespread application of MEG is limited by its expense. However, it is a useful for: (1) presurgical mapping to avoid post-operative neurological impairment, (2) presurgical anatomical localization of the irritative zone (i.e., interictal epileptiform activity), and (3) planning for the optimum positioning of intracranial electrodes.

Montage Display and Design

There are three basic montage designs: *longitudinal bipolar (LB)*, *transverse bipolar (TB)*, and *reference (R)*. In addition to these three basic montages, there are special situations that require other montages. For example, neonatal recording routinely uses fewer electrodes and includes the monitoring of respiration, submental elecromyography, and eye movements. *In some long-term monitoring situations a reduced number of electrodes may be used, typically after recording with a full set to determine optimum placement with a more limited set of electrodes.* Recording for electrocerebral inactivity requires the use of long interelectrode distances as well as movement and electrical interference monitoring. In many monitoring situations, spontaneous movements are anticipated (e.g., myoclonus, tremor, asterixis, cataplexy). In such cases additional monitors are added to the basic montage (e.g., accelerometers for movement, surface skin electrodes for electromyography and movement, thermistors or airflow sensors, piezoelectric belts for respiratory effort, etc.).

RETROSPECTIVE ANALYSIS

There are four different ways in which the digital EEG can be reconstructed during the review of the record. Each of these approaches has its advantages and disadvantages that the electroencephalographer must be fully aware of.

In comparison to older analog pen-and-paper EEG, these aspects of digital EEG review actually adds considerable time and complexity to the work of the electroencephalographer, and shift some of the burden of EEG analysis from the technologist to the physician. This is true for routine EEG as well as monitoring.

Amplitude Adjustment

Many patients have normal background activity that is best viewed with sensitivity settings of 3 or 5 μV/mm, whereas the most commonly used standard recording sensitivity is 7 μV/mm. Activity in the beta frequency range is relatively lower in amplitude than is activity in the lower frequency ranges. An attenuation of beta waveforms is highly specific for an underlying cortical dysfunction. Conversely, skull defects are typically associated with an increase in beta amplitude. A sustained beta amplitude asymmetry greater than 35% (i.e., the activity over one hemisphere is more than 1.35 times that of the other) is significant and often most easily seen by increasing the amplitude of the recording. In some instances, rhythmic electrographic seizure activity may be easier to identify by either by increasing or decreasing the overall amplification of waveforms.

Frequency Adjustment

Both high- and low-frequency artifacts frequently obscure the EEG. In the high-frequency range, muscle artifact and 60-Hz interference are the most common sources of contamination. These artifacts can render the recording technically inadequate, in which case the electroencephalographer has to request that the laboratory repeat recording. If the *high-frequency filter* (also referred to as the *low-pass filter* because the lower frequencies are allowed to pass) is applied, then the underlying EEG may be revealed. This can be particularly useful in the detection of seizure activity. Alternatively, high-frequency filtering (low-pass filtering) can change fast-frequency noncerebral waveforms (e.g., muscle artifact) into apparent epileptiform spikes, or slow beta or even alpha waveforms. Moreover, if the high-frequency filter or 60-Hz notch filter is used throughout the recording and the electroencephalographer leaves it on during review, the electroencephalographer will be blinded to the presence of continuous 60-Hz artifact that indicates a technically poor recording.

In the low-frequency range, body movements—including movements from respiration, eye movement, tongue movement, and changes in posture or head position; cardiobalistic movements; and scalp movements from blood vessel pulsations—are the most frequent cause of low-frequency (delta frequency range) artifact. In the event that the slow-wave activity obscuring the EEG is noncerebral, then filtering out the noncerebral slow waves may allow for a reasonable assessment of parts of the EEG. The problem with indiscriminately using the slow-wave filter (referred to as the *high-pass filter* because it allows for the passage of higher frequencies into the EEG) is that true cortical slowing will also be attenuated. Because the high-frequency (low-pass) and low-frequency (high-pass) filters can distort the EEG and lead to misinterpretation, they should only be used selectively and intermittently.

Montage Reformatting

Montage reformatting as described above allows the electroencephalographer to (a) detect abnormalities that would otherwise be missed, (b) localize the source of EEG activity, and (c) identify and troubleshoot technical problems. The following figures illustrate the importance of montage reformatting in detecting an electrographic seizure. In Figure 6-17, electrocardiographic artifact is seen, especially in the second and third channels.

However, when the same epoch of EEG recording is reformatted into a neck–chest reference montage, shown in Figure 6-18, the patient's electrographic seizure becomes apparent.

Partial cancelation between Fp1, F7, and F3 explains why the seizure is difficult to see in the longitudinal bipolar montage. However, the transverse bipolar montage shown in Figure 6-19 shows the activity even more prominently, because (a) Fz has been added; (b) the discharge is highly localized, making a bipolar montage good for detection; (c) the amplitude of the discharge is not greater than that of the intermittent alpha background, making it less easily

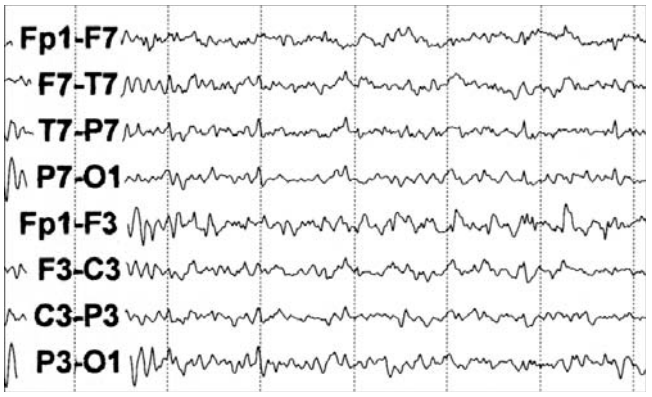

FIGURE 6-17. Longitudinal bipolar recording during a left frontal electrographic seizure. The seizure is not visible, only electrocardiogram artifact, especially in the third and fourth channels.

seen in a referential montage; and (d) the transverse bipolar derivations F7-Fp1 and F7-F3 show cancelation, but F3-Fz and Fp1-Fp2 do not.

Time Display Adjustment

Changing the timing adjustment allows the electroencephalographer to (a) compare small timing differences between channels, (b) more easily detect overall pattern changes, and (c) detect low-amplitude slow waves. Timing differences between channels are most often important when trying to decide whether EEG and simultaneous non-EEG (e.g., electromyogram or respiration) monitoring can indicate whether a scalp potential was caused by a noncerebral event.

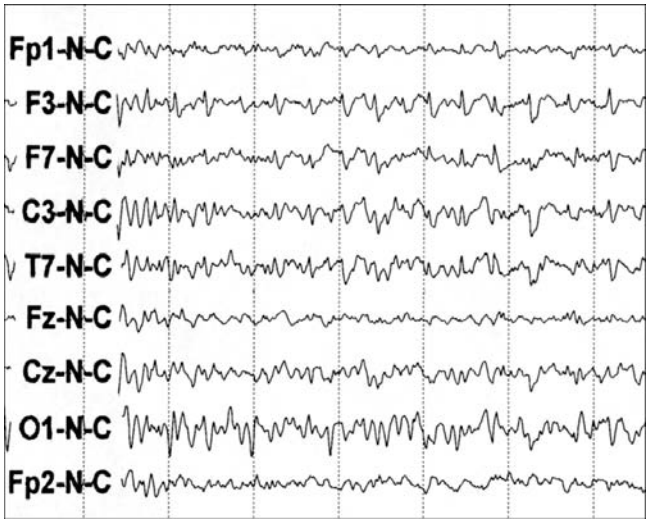

FIGURE 6-18. Neck–chest noncephalic reference montage of the same epoch of recording shown in Figure 6-17 now shows the electrographic seizure maximal in F3 with slightly less involvement of F7.

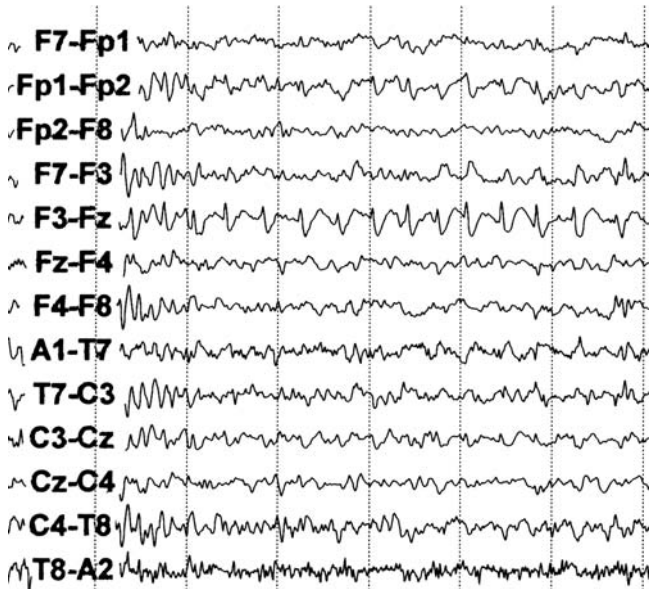

FIGURE 6-19. Transverse bipolar montage recording of the same epoch of recording shown in Figure 6-17, with Fz added, now shows prominent activity in the fifth channel caused by the steep change in voltage from F3 to Fz and partial cancelation between F3 and F7 (a low-amplitude phase reversal can be seen between the fourth and fifth channels, particularly in the last second of recording).

General pattern shifts and slow waveforms are more easily detected by slowing the paper speed (i.e., displaying a greater number of seconds of recording on the monitor screen). Therefore, burst-suppression patterns and the newborn patterns of tracé alternant and tracé discontinu are more easily seen at a slower paper speeds. In routine recordings that display 30 mm of signal per second, low-amplitude slow waves are more difficult to detect than faster waveforms because they are more spread out across the page (or monitor). By slowing the timing of the display (compressing the horizontal dimension of the display), the slow waves become more readily apparent (e.g., displaying 15 mm/second or 10 mm/second compared to 30 mm/second compresses the width of the waveforms).

CLINICAL SIGNIFICANCE

A wide variety of normal EEG patterns can be seen in different persons of the same age, and an even greater variety of normal patterns can occur in different age groups; recordings during wakefulness and drowsiness generally show more variability between subjects than do recordings performed during sleep.

Statistically unusual findings are not necessarily abnormal. For example, many of the benign pseudoepileptiform patterns occur infrequently or even rarely, but rarity of

occurrence is not the same as clinical significance. It is therefore not practical or possible to define the normal EEG by listing all possible normal patterns and their variations. Nor can the normal EEG easily be defined by requiring that specific normal components be present (e.g., the alpha rhythm is routinely evaluated, but its complete absence in an otherwise normal EEG is not clinically significant); in this regard, the EEG differs from other tests such as the electrocardiogram or evoked potentials.

The problem of defining the normal EEG is therefore better approached in a different way. There are a limited number of EEG findings that are known to be clinically significant abnormalities in each age group. The normal EEG can therefore be defined with greater specificity by the absence of abnormal components than by the presence or absence of normal patterns. An EEG is considered abnormal if it contains abnormal components regardless of whether or not it also contains normal components. The electroencephalographer therefore has to know the major features of the normal EEG at different ages, and to distinguish abnormal components from them by using a set of precise descriptors.

The clinical significance of the interictal epileptiform spike (IED) is one of the most important and most misunderstood concepts in EEG interpretation. An analysis of the IED provides an important example of how EEG interpretation is applied in clinical practice.

If you order an EEG on one of your patients, what is the likelihood that the patient will have epilepsy if the EEG records interictal epileptiform activity? IEDs can occur in people who do not have seizures, but how often?

Table 6-1 summarizes several studies of highly screened, nonhospitalized, normal individuals, most of whom are flight personnel (5,6,7,8). The subject-weighted average percentage of IEDs across all studies was less than 0.5%. In two of the studies listed above, there was follow-up to determine whether any of the subjects developed seizures. In the largest and most recent study, by Gregory and colleagues (8), only 2% went on to develop seizures. The photoparoxysmal response accounted for over 60% of normals with IEDs. In contrast, focal spikes, other than centromidtemporal spikes, are far more likely to be associated with clinical seizure disorders.

In studies asking the same question but in patients with psychiatric and/or neurological disorders, the percentage

TABLE 6-1. INTERICTAL EPILEPTIFORM ACTIVITY IN NORMAL INDIVIDUALS

	Total	Age	%IEA	Later Sz
Eeg-Olofsson et al.	743	1–15	1.9	—
Zivin & Ajmone-Marsan	142	—	0	—
Bennett	424	Adults	0.5	0
Gregory et al.	13,658	17–25	0.51	2.6%
Total:	14,967		0.47%	

TABLE 6-2. INTERICTAL EPILEPTIFORM ACTIVITY IN PATIENTS WITH VARIOUS MEDICAL DISORDERS WITHOUT A HISTORY OF SEIZURES

	Total	Age	%IEA	Later Sz
Bridgers	3,143	11–85	2.6	—
Zivin & Ajmone-Marsan	6,497	1–47	2.0	1.6
Goodin & Aminoff	948	—	4.0	—
Bennett	1,541	Adults	0.3	2.0
Total:	12,129		2.0	

frequency of interictal epileptiform activity rises somewhat, as shown in the first three studies in Table 6-2 (6,7,9,10). In contrast, in the study by Bennett of patients without neurological or psychiatric disorders (7), the percentage was about the same as that for the highly screened normal individuals. So, in regard to the problem of normal individuals also having IEDs, there is about a 99% chance that it will not happen. That makes this a remarkably specific test, and extremely so if one excludes photoparoxysmal responses and focuses only on focal epileptiform patterns that are not centromidtemporal (rolandic epilepsy) and are not benign pseudoepileptiform variants.

In 1984, Douglas Goodin and Michael Aminoff were concerned by common misconceptions about the usefulness of EEG for diagnosing seizure disorders(10). They wrote a letter to the *Lancet* making the following point. If, as we know, the EEG will show IEDs in a little over half of all individuals with epilepsy, and we conservatively assume the false positive rate to be somewhat high at 4%, then if we randomly screen 1,000 people and assume that only 0.5% have epilepsy (the true prevalence is closer to 1%), the EEG would misdiagnose 40 individuals without epilepsy as having epilepsy. Therefore, with just the EEG alone, using conservative estimates, you will correctly exclude 96% of the population from the diagnosis of a seizure disorder. However, if you begin, as you would in your clinic, with a 50% suspicion that the patient has epilepsy, and therefore consider that now the population of 1,000 has 500 with and 500 without seizures, then the EEG will only misdiagnose 20 individuals as having seizures who do not. *Stated another way, if there is a 50% probability that a patient may have had a seizure, and the EEG shows abnormal epileptiform activity, then there is a greater than 90% chance that the patient has epilepsy.* That makes this one of the more powerful laboratory tests in medicine.

Aside from its relationship to epilepsy, the clinical significance of the interictal spike is still being defined. Various studies have shown that both focal and the generalized interictal patterns can be associated with brief impairment of sensory or motor function, depending on which cortical networks are involved. For example, a single interictal spike in the frontoparietal area can produce negative myoclonus, a single interictal spike in an occipital area can produce a momentary contralateral hemianopia, and

a single temporal interictal spike may can interrupt the ultradian rhythm of female reproductive hormone secretion (11).

ARTIFACT IDENTIFICATION

EEG waveforms that appear as ongoing, sustained rhythmic activity in the upper theta and alpha frequency ranges in bipolar montages are least likely to be noncerebral in origin. One important and common exception is that rhythmic activity in the theta or alpha frequency range that is restricted to the frontopolar area is eye flutter until proven otherwise. Waveforms at the low and high frequency extremes that are intermixed with apparently normal alpha-frequency background activity are usually noncerebral in origin.

As noted earlier in the chapter, a waveform that appears with medium to high amplitude only in a single electrode despite montage reformatting should be considered artifact, until it is proven otherwise by placing an adjacent electrode that also detects the activity in question. Skull defects and recordings in neonates are situations in which it is more likely that a waveform that only appears at one electrode will turn out to be cortical in origin.

Biological artifacts (also referred to as *physiological artifacts*) are produced by electrical potentials arising from the body, or by movements produced by the body. Examples of physiological artifacts are shown in Figure 6-20. The most common are described below.

1. ECG artifact appears as a prominent R wave with positivity over the left posterior quadrant of the head and can resemble spikes. Premature ventricular contractions (PVCs) usually appear maximally over the occipital head regions and can resemble sharp waves.
2. Pulse artifact consists of delta waves produced by movement of the electrode with each pulse wave (dilatation) of the underlying blood vessels. As with other cardiac-related artifacts, the waveforms are identified by being time-locked to the ECG.
3. Eye-movement artifact consists of a positivity in nearby electrodes that appears in the direction of eye movement. Vertical eye movements appear maximally in Fp1 and Fp2, whereas horizontal eye movements appear maximally in F7 and F8.
4. Muscle artifact appears as sharply contoured (i.e., apiculate) beta activity during wakefulness or light sleep. Rarely, and usually during recordings at high gain (e.g., 2μV/mm during brain-death recordings), it may appear as beta or alpha activity.
5. Respiratory artifact is a particularly common physiological artifact in neonatal recordings. It consists of intermittent or sustained rhythmic delta activity produced by body movement that is time-locked to activity in respiratory monitors. Respiration artifact is also frequently seen in patients on ventilators. Respiratory monitoring is always helpful in such patients.
6. Glossokinetic artifact arises from tongue movement. There is a resting charge on the tongue that produces delta activity over the frontal head regions. In

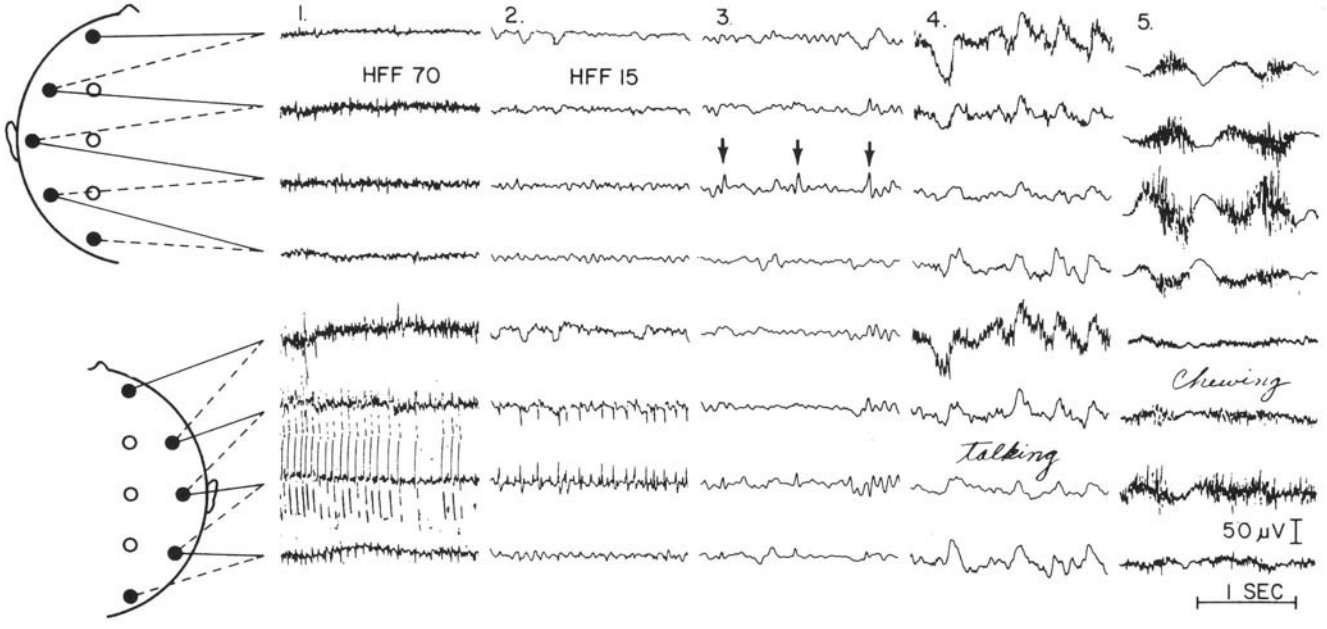

FIGURE 6-20. Physiological artifacts. 1. Muscle artifact. 2. Severely filtered muscle artifact allowing low-amplitude posterior background activity to be seen. 3. The arrows indicate electrocardiogram artifact from R waves volume conducted to the scalp. R waves are identified as left posterior head region positive potentials when the head is in the neutral position (i.e., facing straight ahead). 4. Muscle contraction and tongue movement during talking. 5. Muscle and more prominent tongue *(glossokinetic)* artifact during chewing.

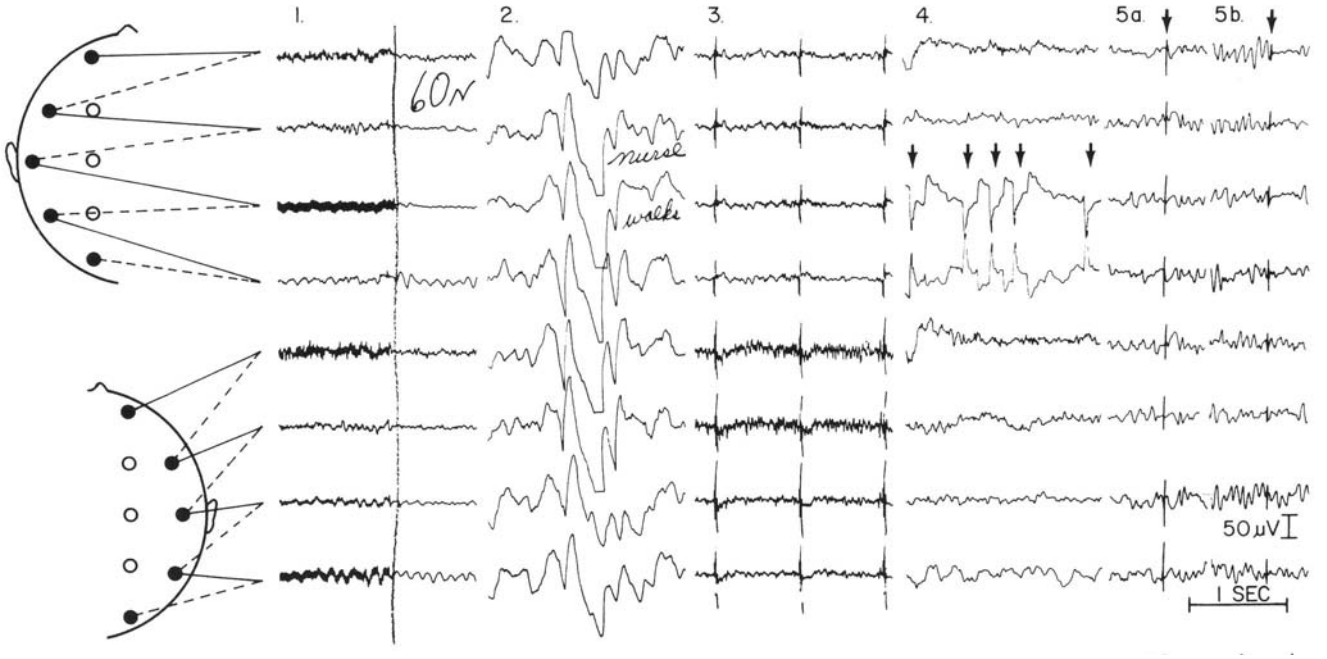

FIGURE 6-21. Nonphysiological artifacts. 1. 60-Hz electrical interference before and after the 60-Hz notch filter is applied, 2. Electrostatic artifact from a nurse walking near the patient. 3. Pacemaker artifact. 4. Electrode "pop" artifact caused by a sudden change in capacitance at the scalp–electrode interface as a result of electrode movement; notice the initial rapid deflection followed by a slower return to the baseline.

longitudinal bipolar montages, delta activity may seem to appear independently over the anterior and posterior head regions. This is best verified by placing electrodes near the mouth and seeing higher amplitudes at those electrodes compared to the scalp.

7. Tremor artifact is sinusoidal at the rate of the body tremor. A Parkinsonian tremor typically occurs at 4 to 6 Hz and may affect one or more electrodes.
8. Head movement and cardioballistic artifact produce diffuse or localized delta waves with each heart beat and subsequent head movement.

A useful body movement monitor that is always available but frequently overlooked is the electrocardiogram (ECG) channel. If there is a question of a body movement, then the gain in the ECG channel should be increased to see whether there is any evidence of body movement at the time of the scalp activity in question. If the ECG channel is to be useful as a body movement monitor, it is important that both ECG recording electrodes always be in a noncephalic location.

Whenever seizure activity is suspected, the ECG channel should be inspected for tachycardia or bradycardia. In a patient who is motionless or not engaged in physical activity, a sudden acceleration of heart rate is often a sign of seizure onset. Sinus arrhythmias may precede the onset of electrographic seizures. Neurotelemetrists (i.e., those watching the EEG and video monitors) should always be instructed to also watch for sudden unexplained changes in heart rate.

Technical (or *nonphysiological*) *artifacts* are those produced by electrical sources external to the patient's body. Common nonphysiological artifacts are shown in Figure 6-21. The most common are described below.

1. Electrical interference typically appears as 60-Hz artifact. It is more likely to occur if an electrode is not attached well to the scalp or if an electrical cable or instrument is near the electrode wires.
2. Electrostatic artifact produces either spikelike waveforms of very short duration, usually involving several electrodes, or widespread delta waves.
3. Electrode pop artifact appears either as a single triangular-shaped wave in a single electrode or as a series of waves sometimes resembling epileptiform spikes. It is caused by poor electrode contact.

Artifacts are most easily identified by monitoring their sources. In the case of constant or intermittent electrical interference, a dummy electrode in which the input 1 and 2 electrodes are connected to a resistor acts as an antenna that will display the contaminating signal. In the case of physiological artifacts, the routine or frequent use of monitors that detect common sources—such as movement of the head, tongue, extremities (e.g., tonic, clonic, or myoclonic movments), eyes, or body (e.g., tremor or respiration)—is recommended. Movement monitors should always be placed in advance over a body part in which movements are anticipated during epilepsy or ICU monitoring (e.g., a motion detector would be placed on the right hand at the beginning of the recording if seizures are believed to always begin in the right hand).

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7

COMPUTERIZED SIGNAL ANALYSIS AND EVENT DETECTION

JEAN GOTMAN

Monitoring the EEG over long periods is usually performed for the purpose of epilepsy monitoring in medical or presurgical evaluation, or for continuous noninvasive monitoring of brain function in the intensive care unit (ICU). It always results in the generation of large amounts of data. Whereas the mere storage of such data (whether on paper or on computers) used to represent a problem, in the last few years it has become a trivial matter to store large amounts of data such as multichannel EEGs and video signals of patients' behavior recorded over days or weeks. The ability to record such large amounts of data, making it simple to retain days and days of recording, has exacerbated the practical problem of what to do with all this information. It is usually not feasible for an individual to examine all the data in sufficient detail to detect all the important events, but this of course depends on what are called "important events." In epilepsy monitoring, recordings usually include 30 to more than 100 channels (with intracerebral electrodes), and it can be time-consuming to examine even a single screen that may contain 100 or more channels. However, 24 hours of EEG recording represents about 8,000 pages. Signal analysis therefore plays a critical role in assisting the human reader. The ways in which signal analysis assists can be summarized as follows:

- The selection of the sections of the EEG that are likely to include interesting events. This is primarily the realm of automatic detection of epileptic events, both ictal and interictal.
- The representation of long recordings in a concentrated format, allowing the viewing of several hours of recording on one page. This can be displayed as a trend of relevant features from the signal, such as the amount of delta activity per minute, the left/right asymmetry in alpha activity, and the burst-suppression ratio. Such displays not only concentrate the information but also may reveal subtle changes not visible by usual visual examination of the unprocessed EEG.
- Warning the patient or observer, during the monitoring session, that an important event is occurring or is about to occur. Seizure occurrence is a primary example, but the development of a background asymmetry in a patient with intracerebral hemorrhage can also be indicative of the deterioration of the patient's condition.
- Making quantitative measurements for research protocols. Examples include event-counting and quantitative measurement of the EEG signal.

The following discussion is divided between automatic event detection and trending of background characteristics. Automatic event detection has been primarily used in epilepsy monitoring, but is finding more and more application in ICU monitoring because it has been shown that many patients in the ICU experience clinically unrecognized seizures (1). Trending (displays of selected signal features over long periods of time) was primarily developed in the context of ICU monitoring to determine gradual and subtle changes in the state of the brain, but it can also be used in epilepsy monitoring for applications such as finding unusual seizures or assessing the relationships between sleep stages, wakefulness, and seizures.

Automatic Detection of Seizures and Spikes

Why Detect Epileptic Seizures?

Patients who are investigated for severe epilepsy are often subjected to long-term EEG/video monitoring, a procedure that can last from a few hours to two or three weeks. Its purpose is to record the EEG and observe behavioral manifestations during seizures in order to determine the type of seizure and thus adjust medication, or to localize the brain

area of seizure onset when surgical treatment is considered. During such a procedure, the patients are usually asked to press a button when they feel a seizure coming. If patients could always feel their seizure coming or be relied on to push an alarm button for each occurrence, there would be no need for automatic seizure detection. Unfortunately, it is more often the case that patients are unaware of their seizures or that observers are not always present or not always able to recognize a seizure. Furthermore, some seizures have very minimal clinical signs, and sometimes no visible signs at all. Finding all seizures may require the review of days and days of EEG, a process that is long and tedious—and not always effective, because short seizures can be missed (particularly if there are many channels, as in intracerebral recordings). Automatic seizure detection can be helpful in this context, because it allows marking the EEG sections that are likely to include seizure patterns. For this purpose, the detection can take place at any time during the seizure (not necessarily early) because the EEG will be reviewed *a posteriori*.

Seizure detection may also be used in real time to warn the patient or observer that a seizure has just started. In this case, the detection must occur early enough to allow the patient to take protective measures, and to allow the observers to examine the patient (to improve the understanding of clinical disability and localizing signs: can the patient follow commands, talk, remember?). Such an early seizure detection system can be used during monitoring but in the near future will also be able to be incorporated in an implantable device that could provide the patient and/or caregivers with an auditory warning.

Seizure Detection Methods

The EEG is recorded either on the scalp, on the surface of the brain (via epidural or subdural disk electrodes), or inside the brain (via intracerebral depth electrodes). Seizures consist of paroxysmal rhythmic activity generated by a large number of synchronized neurons. This activity usually evolves, with changes in spatial distribution, frequency, and amplitude. However, there are exceptions: the spike and wave bursts typical of generalized epilepsy may present little evolution. The patterns actually recorded depend both on the discharge itself and on the respective position of the electrodes relative to the neuronal signal generator. In some cases, no seizure discharge is visible because the electrodes are too far from the generator. For the same reason, the seizure discharge may appear only as a mild modification to the ongoing EEG. It is therefore important to distinguish the seizure itself from its manifestations from the vantage point of the recording electrodes. Since seizure detection is primarily performed from analyzing the EEG, only the seizures having a clear manifestation in the EEG can be detected.

In part for the reasons given above, *there is no formal definition of what a seizure consists of in the EEG*. Qualitative definitions usually include the terms "paroxysmal," "rhythmic," and "evolving," but an unambiguous definition has not been formulated. Automatic detection methods have therefore relied on trying to encode these characteristics into algorithms, and on improving the algorithms by trial and error in an effort to increase detection sensitivity and decrease the false detection rate.

The first general-purpose seizure detection method validated on a large data sample was that of Gotman (2,3). Its algorithm characterized each 2-second epoch by measures of frequency, rhythmicity, and amplitude change, as compared to a constantly updated background. A set of empirical rules then combined the findings in multiple epochs and multiple channels to reach a decision on detection. The concept of a "constantly updated background" plays an important role in the analysis of long-term data, since the background (i.e., ongoing EEG activity) changes considerably with the varying states of vigilance of the subject. It is also important that the results of detection not be dependent on the selection of a particular background epoch, which would introduce arbitrariness.

Harding (4) presented a method specifically designed for intracerebral recordings, based on the detection of a repetitive spiking pattern as well as of possible flattening at seizure onset. This method was implemented online and was subject to an extensive evaluation. Another approach was proposed by Schindler et al. (5): they simulated neuronal cells processing each EEG channel and used leaky integrators to assess increases in amplitude and slope over time. Recent wavelet-based methods have been developed separately for scalp EEG (6) and for intracerebral EEG (7), with better performance than common methods because the patterns and artifacts are quite different in scalp and intracerebral EEGs.

Artificial neural networks (ANNs) have found application in many areas of pattern recognition, including seizure detection. Jando et al. (8) demonstrated their utility to detect bursts of spike-and-wave in experimental models of epilepsy. Several methods have been presented involving various EEG features as inputs to an ANN (9–12). By being presented with a large number of training examples comprising seizure and nonseizure data, the ANN learns to differentiate seizure from nonseizure EEG patterns. A set of features characterizing the EEG needs to be specified in advance (e.g., amplitude, rhythmicity, dominant frequency, etc.), but it is not necessary to explicitly describe seizure patterns. The ANN automatically determines which combinations of features are characteristic of seizures by adapting its internal structure to reflect the training data. The performance of ANN methods depends on an appropriate set of features and on a sufficiently large training set containing a variety of seizure patterns. Large networks can handle complex classification tasks, but risk overfitting the training data and being unable to generalize to other types of seizures. It is also difficult to investigate the operation of

a large ANN; the network acts as a black box that outputs classification values depending on the features it receives as inputs. To circumvent this, Wilson et al. (13) presented an algorithm based on a set of rules, where each rule was implemented using a small ANN. With several simple rules, it became easier to analyze the operation of the system.

Performance can be improved by incorporating a wide context in detection algorithms. Rather than defining the event locally (i.e., comparing the characteristics of a 5-second epoch in one channel with the 30 preceding seconds), it is helpful to include measurements of spatial context (activity in other channels) and temporal context (state of the subject: awake, stages of sleep, previously recorded events). Qu and Gotman (14) used this philosophy to reduce false detections by allowing the method to remember the patterns that caused frequent false detections in each subject. Klatchko et al. (15) presented a method for spatial and temporal clustering of elementary detections made on individual channels and epochs, thus resulting in a global representation of seizures. This reduced false detections by only detecting a seizure with a number of elementary detections adjacent in space and time. The system of Khan and Gotman (16) was based on wavelet decomposition to detect seizures in the intracerebral EEG. Wavelet methods allow the analysis of the temporal evolution of frequencies; they are thus well suited for the identification of paroxysmal rhythmic activity. However, intracerebral EEGs also include rhythmic bursts as part of normal background activity. Therefore, Khan and Gotman's algorithm automatically adapted to the background of each patient by recognizing paroxysmal activity occurring consistently in the same channels and at the same frequencies. This resulted in an important decrease in false detections. In the study of Hopfengärtner et al. (17), the spatial context in particular was addressed: better performance was obtained when analyzing the scalp EEG with a midline reference than with a bipolar montage, which has been most commonly used in other methods.

An extension to the above concept of context is to incorporate a particular patient's seizure in the context. The method is then aimed at detecting seizures in that patient, and only seizures that look like the sample seizures incorporated in the context. The method can be labeled "patient-specific"—or more correctly "seizure-specific," given that a patient can have several types of seizure. A better performance can then be obtained (18,19).

Newborns have an incidence of seizures much higher than that of older children and adults, and when seizures occur in newborns they are also more frequent. For these reasons, it is often necessary to monitor newborns, but the monitoring does not need to be as long as that for older patients and lasts usually a few hours to a day or two. Seizure patterns are quite different in the newborn EEG than in older children and adults: the discharges are often much slower and sometimes very focal (limited to one electrode). For these reasons, methods specific to the newborn have been developed, with the particular aim of detecting the very slow discharges often present during newborn seizures (20,21). Several other methods have been developed recently: Roessgen et al. (22) proposed a neuronal model of EEG generation for seizure and of background activity. Fitting the model to the EEG indicates how much of the EEG reflects seizure activity. Celka and Colditz (23) used the minimum description length (MDL) principle to estimate the signal complexity, then used the MDL as a detection measure. Altenburg et al. (24) made use of interchannel synchronization, an approach rarely used in seizure detection. Hassanpour et al. (25) used time-frequency analysis to detect low-frequency rhythmic activity as well as high-frequency bursts of spikes. Aarabi et al. (26,27) designed a multistage system based on a large number of features, retaining only those aspects most appropriate for use in an ANN. Greene et al. (28) obtained some improvement in performance by combining EEG and electrocardiography.

Seizure Warning

The terminology is not obvious and not universally recognized, but there is a major difference between what we will call "seizure warning" and "seizure prediction." Seizure warning refers to a signal given *because a seizure has just started*. Seizure prediction refers to the ability to forecast the *future occurrence of a seizure*. The difference is major from the point of view of signal analysis, because in the first case, the issue is to detect the seizure as soon as it has started, whereas in the second case it is necessary to search for a change taking place in the EEG before a seizure—a change that has not been identified by visual analysis, and that may not always exist. An effective method of seizure warning must meet the following requirements:

- high sensitivity
- early detection (the warning is only useful if it arrives within a few seconds of onset)
- low false alarm (a warning will be ignored if it is too often erroneous).

By providing a warning only for seizures that resemble a specific template, the method of Qu and Gotman (18,28) reached a good compromise regarding these requirements. The methods of Saab and Gotman (6) and Grewal and Gotman (7) also provided a warning with good reliability, although they do not rely on a specific template. Figures 7-1 and 7-2 show examples of different types of seizures and discuss the specific issues for each. Shoeb et al. (30) designed a system for seizure warning in scalp EEGs. By training the system with wavelet features specific to each patient, they could obtain a high sensitivity and a low rate of false detections. The system of Osorio et al. (31) used a wavelet filter followed by a median filter to detect the onset of seizures in intracerebral recordings. The best performance was achieved when the system was tuned to

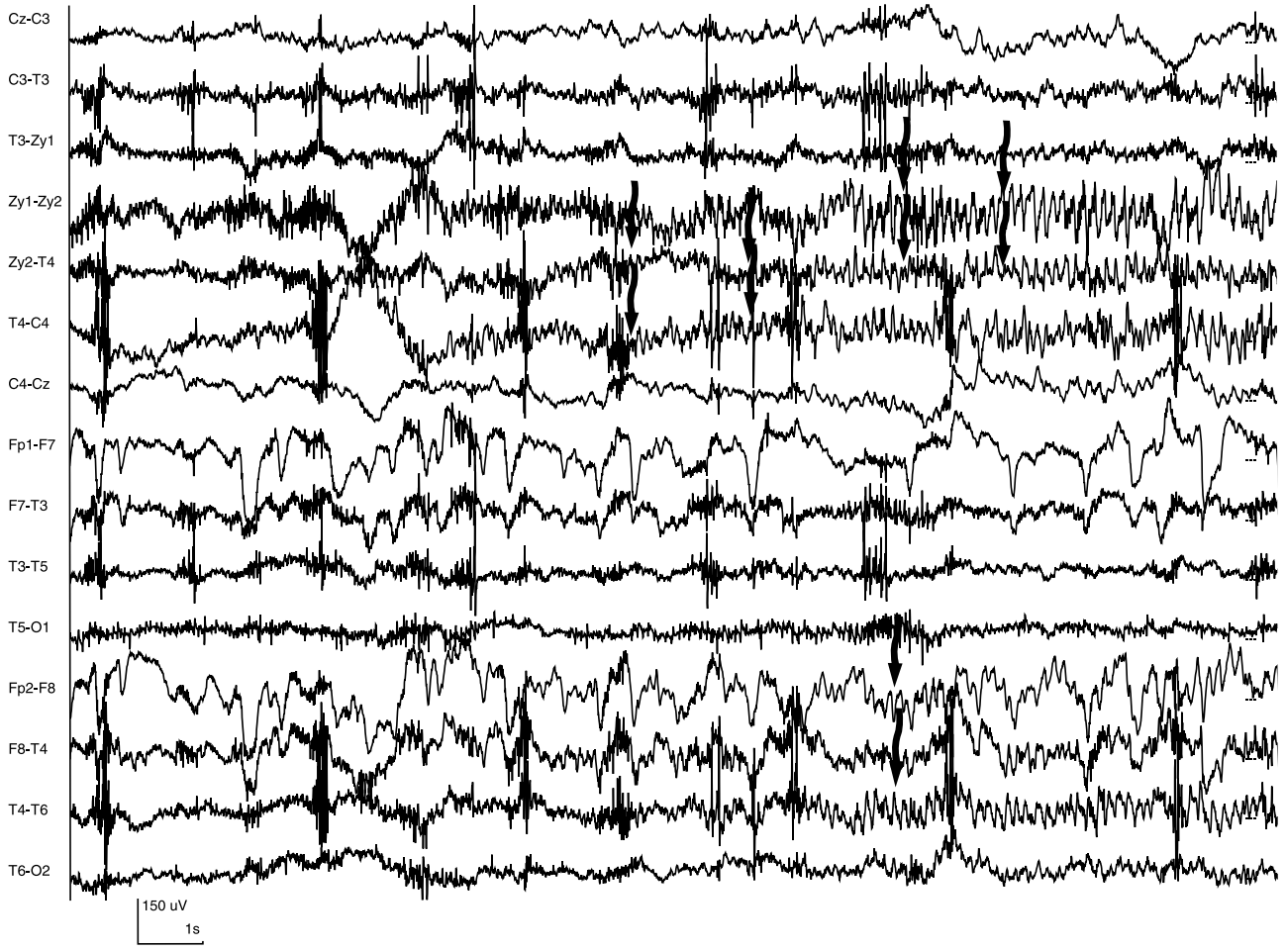

FIGURE 7-1. Examples of automatic seizure detection in scalp EEG with the method of Saab and Gotman (6). Black arrows indicate the time at which the system made detections. A. Seizure with considerable artifact from eye movement and scalp muscles. The rhythmic discharge is clear in the right temporal region and is detected as soon as it starts.

each patient, but good results were obtained without patient-specific adjustment.

The vast topic of seizure prediction will not be presented here. An excellent review is that of Mormann et al. (32).

Validation

Validation of seizure detection and seizure warning methods requires particular care if one is to obtain results that are predictive of future performance in a realistic clinical context. The method must be tested on a set of data completely independent from that on which it was developed. It is critical that the testing data be representative of the context in which the method will be used: it should include a large variety of seizures, and a much larger amount of nonseizure data than of seizure data, in order to ensure that all types of interictal data are well represented (quiet and active wakefulness, different sleep stages, different types of artifacts common during long-term monitoring). An important issue in validation is the definition of a seizure itself. Whereas there is no ambiguity with a clear seizure lasting 30 seconds or 1 minute, the question arises for short events: what is the minimum duration of a seizure? Should a seizure having clinical manifestations but no change in the EEG be counted as an event to detect? What if the EEG changes are very minor, such as a brief flattening or a short burst of slow waves? When presenting validation results, it is imperative that these issues be addressed.

Methods evaluated on extensive data sets (hundreds or thousands of hours, tens of patients) report detection sensitivities varying from 75% to 90%. Sensitivity is often lower in newborns than in adults, as some newborn seizure patterns are very subtle. The false detection rate, the most often quoted measure of failure, was around 1 to 3 per hour using earlier methods and more in the range of 0.3 to 1 per hour in more recent studies. Few studies report results in intracerebral electrodes, but these have important distinguishing characteristics: the most prominent scalp artifacts (electromyogram, movement, eye blinks) are absent, thus reducing false detections; the dynamic range

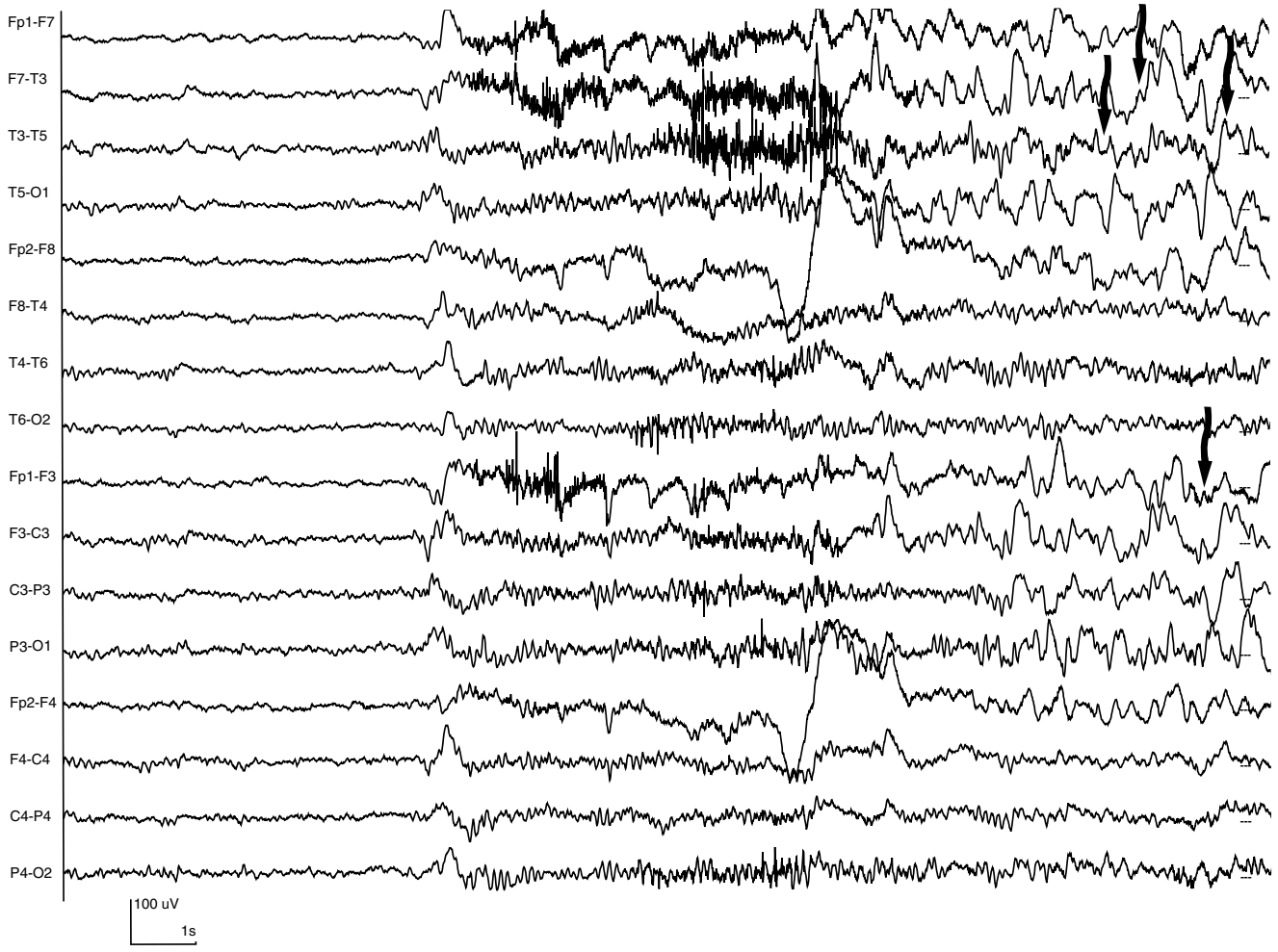

FIGURE 7-1. (CONTINUED) B. Seizure with a widespread onset occurring during sleep. The detection takes place about 10 seconds after electrographic onset. The very onset of the seizure is not detected because it resembles normal rhythmic activity.

of the spontaneous fluctuations in background is much larger in intracerebral than in scalp EEG, thus resulting in more causes for false detections; the intracerebral EEG often includes paroxysmal bursts of uncertain significance, which can also contribute to false detections; and seizure patterns are often more prominent in intracerebral EEG, thus resulting in better sensitivity.

Recording Interictal Activity

The interictal activity specific to epilepsy consists of spikes, sharp waves, and bursts of spike-and-wave. Paroxysmal interictal activity occurs unpredictably and sometimes infrequently. To obtain a full documentation of the different types of abnormalities, the traditional short EEG recording may not be sufficient. Long-term monitoring may be required, including periods of the different stages of sleep, which most often activates and modifies the interictal pattern (33). The reduction of AED doses often done during long-term monitoring to precipitate seizures also results indirectly in increased spiking (spikes are more frequent after seizures (34–37)). A complete review of recordings lasting days and nights is an awkward method to document interictal activity; automatic detection methods can be helpful.

A major difficulty of spike recognition methods is their reliance on a very incomplete definition of a spike. The definition quoted by many publications is "a sharp transient, easily distinguishable from the background, having a duration of less than 70 milliseconds for a spike and 70 to 200 milliseconds for a sharp wave" (adapted from Chatrian et al. (38)). This definition has very limited usefulness because it lacks features for differentiating transients with the same local morphology that are not spikes, such as eye blinks, vertex sharp waves, isolated alpha or spindle waves, electrode artifacts, and movement artifacts. Such transients are common during prolonged EEG recordings, when automatic spike detection is useful. Which characteristics allow a human interpreter to separate an epileptiform sharp wave from an eye blink, even though the waves themselves may have the same morphology and emerge from a similar background?

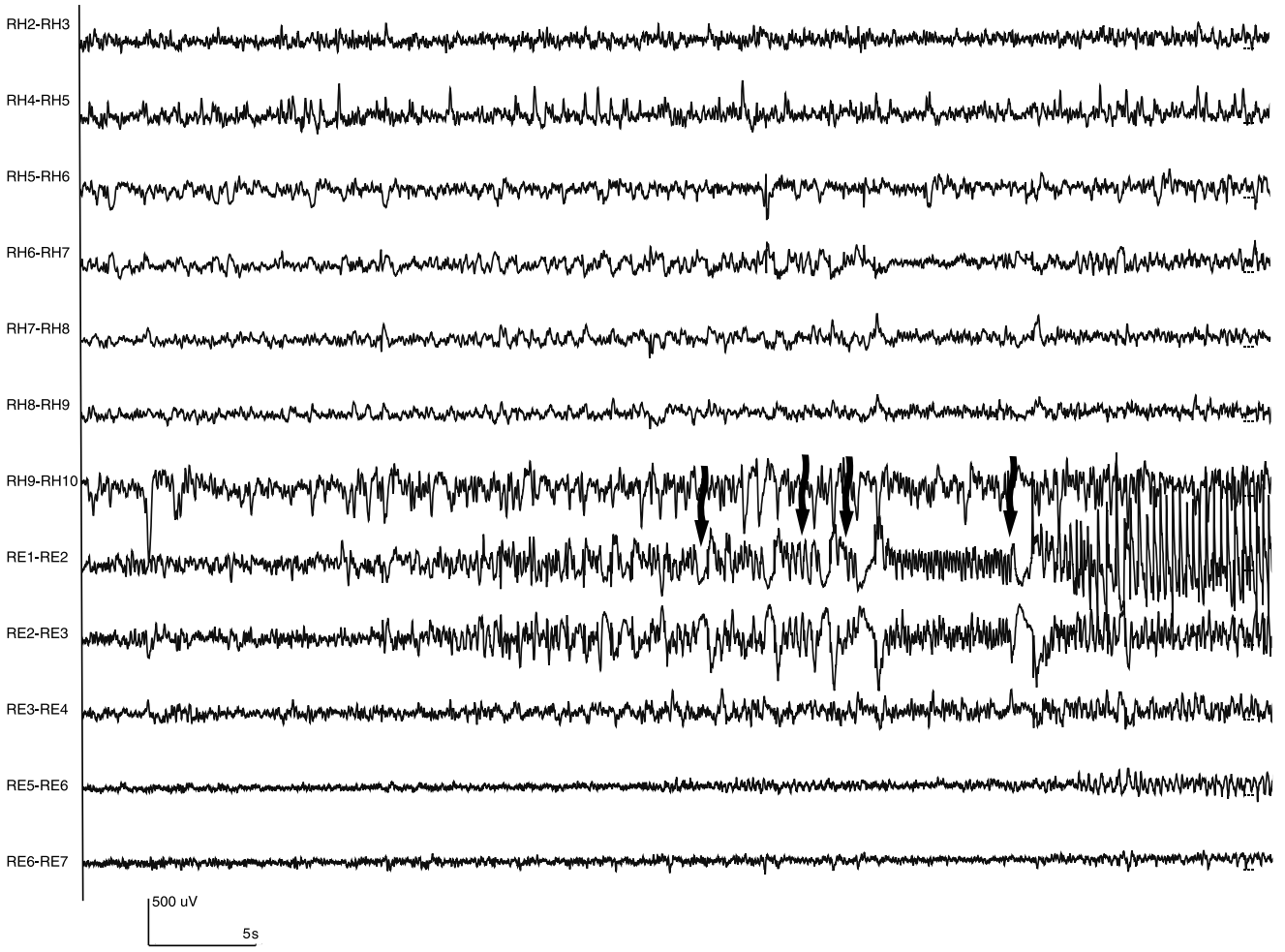

FIGURE 7-2. Example of automatic seizure detection in intracerebral EEG with the method of Grewal and Gotman (7). Note the compressed timescale. RH contacts are from an electrode implanted orthogonally to the surface of the temporal lobe, aimed at the hippocampus. Contacts 9 and 10, the most external, are in the temporal neocortex. Electrodes RE are epidural contacts on the first temporal convolution. The seizure starts in the neocortex, and is detected about 10 seconds after onset because of the irregular nature of the early part of the discharge.

The differentiating characteristics relate most importantly to the context in which the waves appear. When interpreting a wave having the morphology of a spike, the human observer takes into account events in other channels (spatial context) and in earlier and later parts of the recording (temporal context), and even non-EEG information, such as the age or clinical state of the subject. Optimism about early detection methods was based on a failure to appreciate the extent to which spike identification relies on a broad context.

The problems discussed above do not affect the ability to detect most epileptiform spikes, but they result in a large number of false-positive detections. It is thus possible to make practical use of an imperfect spike detection method, as long as it is conceived as a method to detect a high proportion of the spikes along with a possibly large number of clinically insignificant nonepileptiform transients, rather than as a method to detect only spikes. Such a practical implementation was made with the early spike detection algorithms developed at the Montreal Neurological Institute (39). Pietila and colleagues (40) presented a system that included automatic segmentation of the EEG followed by feature extraction. Compared with Gotman's system, this system showed a higher sensitivity but a lower specificity.

Automatic Spike Detection

As in seizure detection, artificial neural networks (ANNs) have also become a popular method for spike detection. The process requires a large number of sample patterns for training; the ANN then automatically adapts to the discrimination task at hand. This method was used by Gabor and Seyal (41), who obtained a good performance but evaluated their method on a very small sample. When designing an ANN method, it is crucial to select appropriate features. The short duration of spikes offers the opportunity to use the raw EEG data points as network inputs, thus foregoing the

extraction of features. Webber et al. (42), using a small data set for evaluation, compared the raw EEG to preprocessed variables in the ANN and concluded that a better performance was obtained with preprocessed parameters. Ozdamar and Kalayci (43) obtained good performance with an ANN trained on raw EEG, but Ko and Chung (44) revisited the data and suggested that the results were erroneous as a result of inappropriate data preparation.

When using raw EEG, the ANN needs to recognize all combinations of the data that can be relevant for classification. A very complex ANN will thus be required to obtain a satisfactory performance (45). To reduce the complexity of spike detectors using raw EEG as inputs, Acir and Guzelis (46) proposed a multistage approach in which the data is first reduced by identifying nonstationary transients using an autoregressive linear predictor. Only the identified transients are further examined by using the raw signal in a support vector machine. A sensitivity of 90.3%, with a 9.5% false detection rate, was reported.

The use of features instead of raw data can result in simpler classifiers. Wilson et al. (47) designed simple rules for spike detection and used small ANNs to learn each rule. It was then easier to interpret how each ANN implemented each rule. Wilson et al. also used a training set in which EEG epochs were marked with a probability value rather than a dichotomous classification as a spike or nonspike. This allowed the system to process ambiguous spikes without having to decide on a definitive classification. Hellmann (48) used cross-correlation to identify candidate spikes that resembled a given template, followed by classification using an ANN. The use of a template results in a system that is patient-specific and that can only identify one type of spike. This can be useful if the time of occurrence of known spike morphologies is desired, such as in functional imaging. Other data mining models in addition to ANNs can also automatically generate classifiers for spike detection. Valenti et al. (49) implemented C4.5 decision trees and naïve Bayesian classifiers with good results on a small data set.

There has been interest in using wavelet analysis to identify interictal EEG spikes (50,51,52,53). Wavelet features can be useful to describe the time and frequency relationships between the spike and the subsequent slow wave. These methods are well suited to the characterization of transient signals such as spikes. Another approach to improving detection performance is to make use of information from a wider context. This is complex, because the context encompasses a large amount of information, and it must be decided which specific information is relevant to spike detection. It is this selection process that human interpreters do so well. Glover et al. (54) described a context-based system aimed at reducing false detections by using a wide spatial context; information from all EEG channels, from electromyographic, electro-oculographic, and electrocardiographic channels helps assess whether a transient is likely epileptiform.

In Gotman and Wang (55,56), a wide temporal and spatial context was used to decide on the nature of a sharp event. The method is termed state-dependent spike detection because criteria for detection are dependent on the state of the EEG. Five states are defined in which spike detection should be performed differently: active wakefulness, quiet wakefulness, desynchronized EEG, phasic EEG, and slow-wave EEG. In fact, it is not so much that spike detection is done differently for these different states, but rather that false detections are handled differently. In active wakefulness, for instance, one must be particularly aware of symmetric frontal sharp waves that may be caused by eye blinks, whereas there is no such concern in the phasic EEG state, in which sharp waves maximal at the vertex are a problem. Examples of the use of this method are shown on Figures 7-3A and B. Flanagan et al. (57) suggested an improvement to this

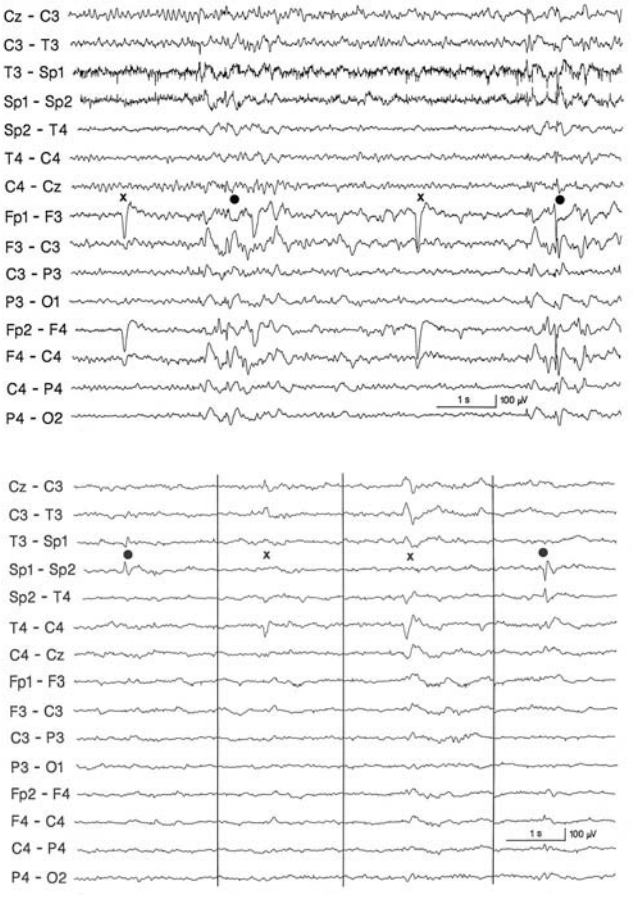

FIGURE 7-3. State-dependent spike detection allows the separation of sharp transients likely to be of epileptic origin from those originating in other phenomena. A. Transients marked by a cross are identified as eye blinks even though they occur in the same frontopolar channels as genuine epileptic transients. B. Transients marked by a cross are identified as vertex sharp waves at the same time as others in neighboring regions are identified as epileptiform. The spatial distribution, morphology, and stage of sleep or alertness help identify the eye blinks and vertex waves. From Gotman and Wang (56).

method in which an equivalent current dipole would be used to model each detection. The goodness of fit and the position of the dipole were used as features to reject artifactual transients. It was not necessary to obtain an accurate localization of the spike generator; a simple dipole model provided sufficient information to reject many false detections.

Whether neural networks or more traditional methods are used, wave morphology is insufficient to differentiate epileptiform transients from other transients. Some form of broad context sensitivity appears necessary.

EEG Monitoring in the ICU

Epileptic Seizures

Many variables are usually monitored in the ICU; an excellent overview of measures that deal particularly with brain function is provided in Wright (58). Among these different measures of neurological function, the EEG plays an increasingly important role. Whereas EEG recordings in the ICU in the past were usually of short duration and attended by an EEG technologist, it has become more and more common to perform long-term unattended monitoring of the EEG in the ICU. This has led to the discovery that many patients have unrecognized epileptic seizures while paralyzed or sedated; these seizures, particularly when they manifest as nonconvulsive status epilepticus, may be an important determinant of the patient's neurological impairment and can only be evaluated with EEG monitoring (59–61). Seizures in ICU patients often have patterns that are different from those seen in otherwise healthy epileptic patients whose EEG is recorded in an epilepsy monitoring unit (62).

Automatic seizure detection methods have not been validated in the context of ICU monitoring, and it is likely that they would not perform as well, particularly because an ictal pattern is not as unambiguously defined in ICU recordings as in "regular" EEG monitoring. In addition, there are several causes of equipment- or manipulation-related artifacts that can create rhythmic patterns in the EEG resembling seizures. To help identify such situations, video monitoring in combination with the EEG is recommended.

Trending

In addition to detecting epileptic transients, the EEG can provide useful information regarding gradual changes in background activity, which may reflect slow deterioration or improvement in the state of the brain. Such gradual changes can be represented by bar graphs that show, for instance, one bar for each minute of EEG. Given the current resolution of computer monitors, it is easy to display 1,000 such bars on one screen, thus representing about 16 hours of data. Such a representation is a very convenient way to provide a bird's-eye view of a long recording. Its validity rests on two main assumptions: (a) the user is not interested in a time resolution of much less than 1 minute (short events lasting a few seconds or a fraction of a second will not be visible or will be distorted); and (b) there is a measure that represents faithfully the characteristic of interest for that minute. It may happen that several measures are required to represent various aspects of the EEG, hence several graphs will be necessary.

One parameter that has been commonly monitored is the bispectal index of the EEG, which was originally derived primarily to help assess the depth of anesthesia (58). It has been shown to be sensitive to the level of sedation in the ICU (63), although it has also been found to be sensitive to artifacts that are common in the ICU (electromyogram and nonphysiological artifacts). Decrease over time of the variability of relative alpha activity has been used to help with the early detection of vasospasm (Figure 7-4; reference 64) and the prediction of outcome in traumatic brain injury (65). Compressed spectral arrays (CSA) and color-density spectral arrays (CDSA) are useful ways of representing the time fluctuations of the main characteristics of an EEG channel. Variables that can be trended include the activity in a frequency band (e.g., delta or alpha, in absolute value or percentage of total power), the ratio of activity between two bands (delta over alpha), the degree of asymmetry in spectral band activity (right over left delta), and the spectral edge (useful to assess the reduction in fast activity). An example is shown in Figure 7-5. Some of these methods are reviewed in Scheuer and Wilson (66). Modern computer systems allow rapid movement from a trend display to the original EEG, or the display of both simultaneously so that the actual EEG at the time of a change in the trend can easily be assessed. It is also possible to observe the EEG and the trends through network and telecommunication technology, such that the presence of the EEG specialist in the ICU itself is no longer required. The burst-suppression pattern is one that is often recorded in the ICU, but automatic detection and quantification of this pattern has not often been attempted.

The place of EEG monitoring in the ICU is growing but not yet settled. Work needs to be done to define the EEG patterns of importance in the context of critically ill patients. Once these patterns are known, it may be possible to develop automatic quantification techniques to detect and represent them. In the meantime, one can use current analysis methods and communication technology to gather more information on these patterns and to make clinical use of the changes having unambiguous significance.

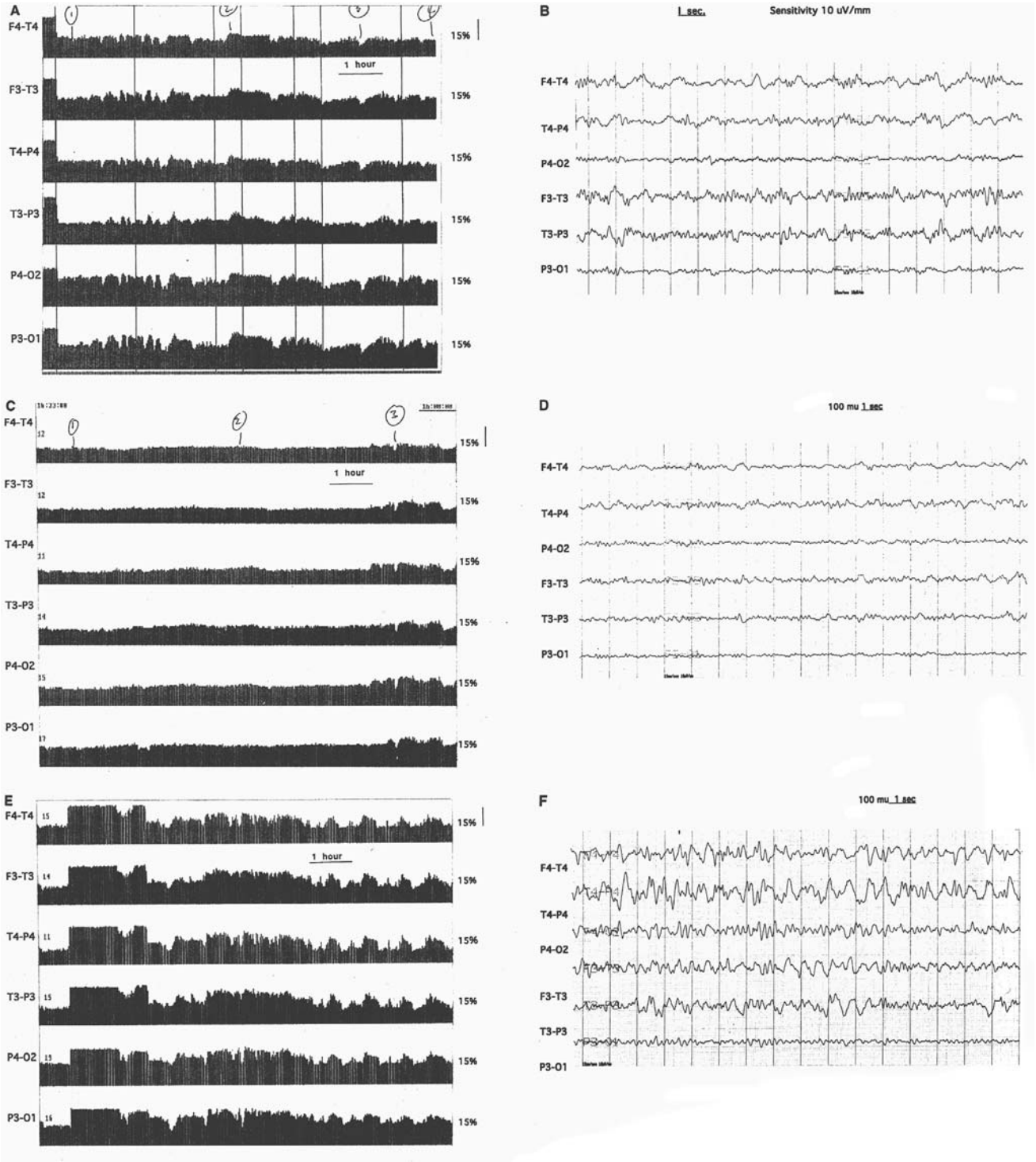

FIGURE 7-4. Histograms of relative alpha activity over 10 hours and corresponding EEG before, during, and after vasospasm for a patient who had vasospasm after a subarachnoid hemorrhage. Relative alpha variability was good before vasospasm (top), declined to very low after vasospasm (middle), and became very good with hypervolemic hypertensive therapy (bottom). The patient had a full neurological recovery. From Vespa et al. (64).

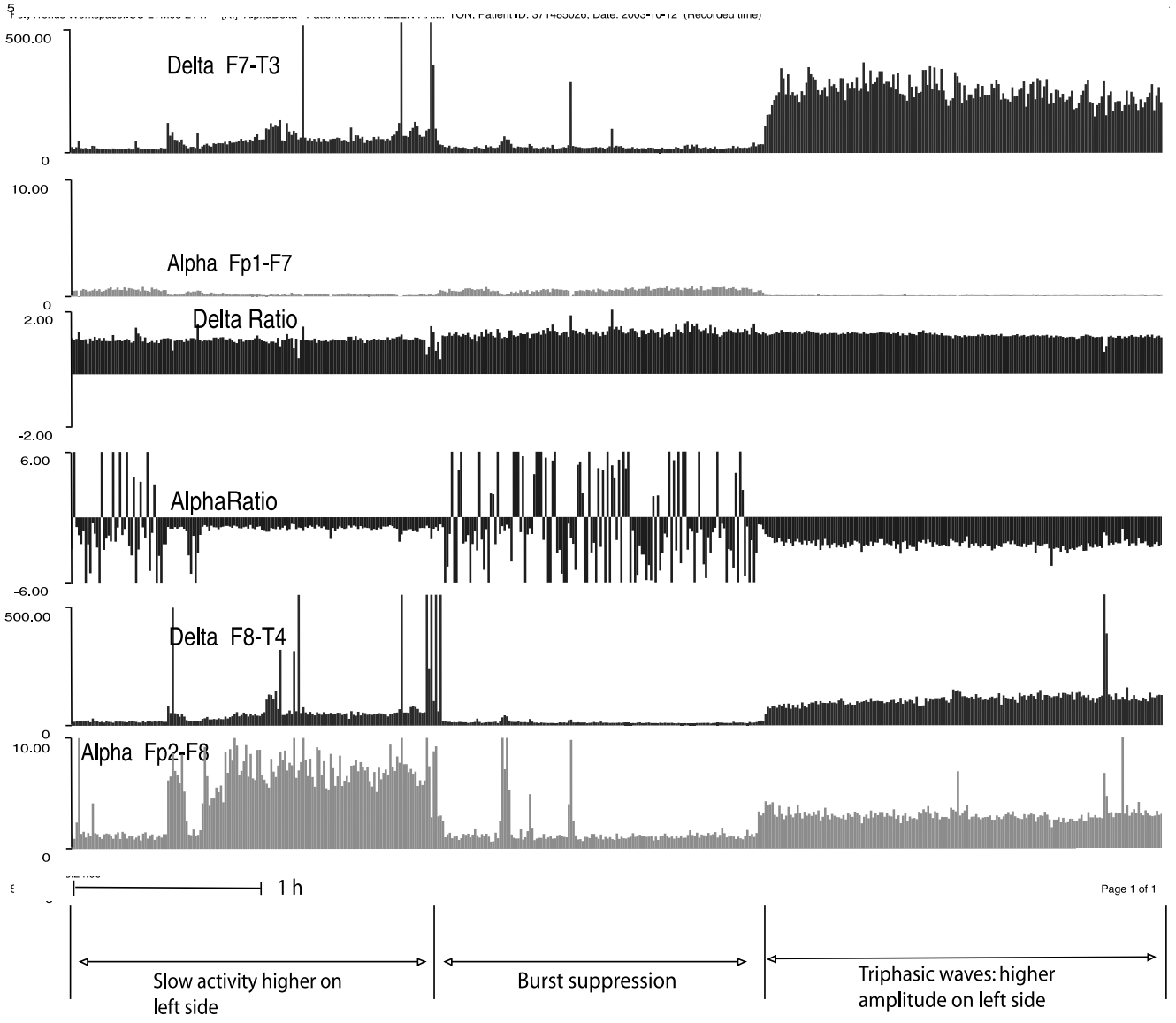

FIGURE 7-5. Trend of delta and alpha activity in two channels of the right and left hemispheres over an 8-hour period (top two and bottom two graphs). Middle two graphs represent asymmetry ratios in delta and alpha between right and left (values above baseline indicate larger power on the left side). It is remarkable that despite the important variations in background patterns, the left hemisphere shows a constant level of predominance of delta (see delta ratio graph). The alpha ratio shows erratic values at the beginning and in the middle, as a result of very low amounts of alpha in both hemispheres. When the values are not erratic, they show a predominance of alpha in the right hemisphere, particularly in the latter part of the graph. This type of graph allows the appreciation of long-term trends in several variables in a way that is difficult to appreciate by visual examination of the EEG.

CONCLUSION

Computer analysis has extended the reach of EEG examinations to the domain of long-term continuous monitoring. It has helped to extract significant information from large amounts of data. Beyond its use in epilepsy monitoring, automatic seizure detection opens the door to implanted devices that could warn a patient that a seizure has just started or attempt to abort it by active intervention, such as electrical or chemical stimulation. Long-term monitoring in the ICU, if we are able to define the parameters that predict or indicate significant changes in the state of the brain, will become as common for neurologically at-risk patients as cardiac monitoring is for patients at risk of heart problems.

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SECTION

III

EPILEPSY MONITORING: DIFFERENTIAL DIAGNOSIS

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8

SPECIAL CONSIDERATIONS IN PEDIATRIC MONITORING

KRISTEN L. PARK
DOUGLAS R. NORDLI, JR.

As any pediatrician will tell you, an infant or young child is not just a small adult. There are unique considerations in all pediatric specialties, including epilepsy. In fact, the field of pediatric epilepsy has become so broad and comprehensive that there are now experts in the interpretation of neonatal EEG, infantile seizures, and the ictal semiology of children. What follows in this chapter is a discussion of some of the key issues and distinctions that should be considered when monitoring a pediatric patient. It does not attempt to fully address the interpretation of the neonatal and pediatric EEG but does review important aspects of ictal patterns and the process of epilepsy monitoring. Related topics are discussed elsewhere in this volume; others can be found in texts of epilepsy and clinical neurophysiology (1,2).

PRACTICAL CONSIDERATIONS

Neonatal Monitoring

Monitoring of a term or preterm neonate differs dramatically from the monitoring of an older patient. It requires not only different technical considerations but also different rules of interpretation. The most obvious difference encountered is the small size of the neonatal head. For an average-term infant, the head circumference is approximately 34–34.5 cm. If a full complement of electrodes is used, the potential difference between any two adjacent electrodes is small, leading to an attenuation of the normal patterns on a bipolar montage. In addition, neonates lack activity in the extreme frontopolar regions of the head, reducing the need for electrode coverage of this area. Therefore, the system of 10–20 electrodes used in older individuals has been modified and standardized for neonates (Figure 8-1) (3). This system uses electrodes Fp3 and Fp4, which are halfway between the frontopolar and frontal electrodes. This, in turn, allows for the best visualization of background activity as well as physiologic frontal sharp waves, which are of higher amplitude in the prefrontal region (4). The remaining neonatal electrodes are C3, C4, T3, T4, O1, O2, Fz, Cz, Pz, A1, and A2. If the earlobes are too small, mastoid leads may be substituted (5). In addition to a reduced montage, neonatal head size is also accommodated by the use of smaller electrodes. Electrodes can be applied using either paste or collodion, but if the neonate is in an isolette, ventilation may be inadequate, and only paste should be used. Hypoallergenic tape should also be used during application to minimize any irritation of fragile neonatal skin. Scalp veins are often used for intravenous access when multiple sites are needed. Because this may disrupt the placement of EEG electrodes, some accommodations may be necessary. The affected electrode should be placed as close as possible to the proper location, with the contralateral electrode placed symmetric to the displaced electrode (5). Although standard electrode impedances of less than 5 kΩ can be obtained in term babies, the skin of premature neonates is so thin that significant abrasion may cause damage, and therefore higher values are tolerated. This is especially true if the monitoring is expected to continue for more than several days, in which case careful attention to the electrode sites is required to prevent breakdown and infection of the skin. At the time of electrode placement, the technologist should note the presence of any scalp edema or cephalohematoma that can attenuate the background and alter interpretation. Wrapping of the head should be gentle and should allow access to the anterior fontanel for head ultrasound, which is routinely used as a screening tool in the neonatal intensive care unit. Neonatal recording procedures are usually continued until the conceptional age (CA; see below) of 48 weeks.

In clinical practice, monitoring is usually requested for neonates who are too ill to be brought to the epilepsy

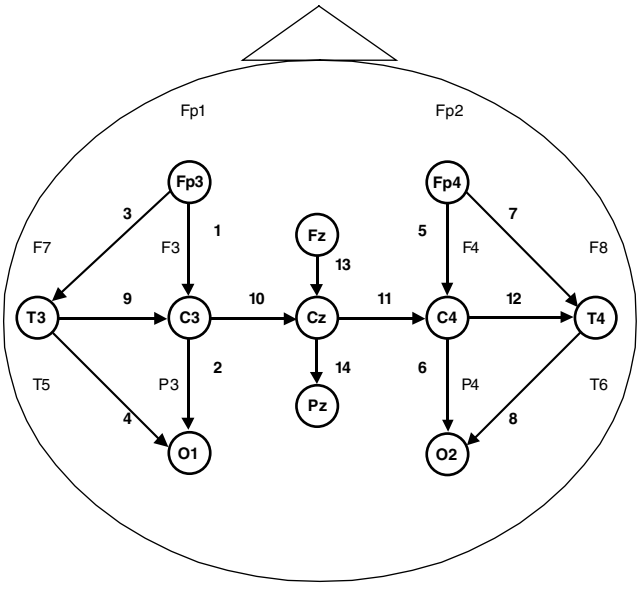

FIGURE 8-1. An example of the neonatal montage. Used electrodes from the standard 10–20 system are circled. Numbers refer to the channels, as displayed in the reading montage.

monitoring unit. Consequently, most video EEG monitoring is done in the neonatal intensive care unit (NICU) with a portable unit at the bedside. The desire to achieve a recording of technical superior quality must be balanced with the needs of the patient and of the team caring for the infant. As much as possible, the neonate should be exposed to the camera so that movements can be seen and correlated with the EEG. However, neonates in general, and especially sick or preterm newborns, have poor temperature regulation. Therefore, heat lamps or incubators may need to be employed to keep the newborn warm (6). Portable monitoring devices should be kept out of the way as much as possible so that the neonatology team can have full access to the infant. Cameras are optimally placed to allow for full visualization of the infant, with an uninterrupted line of sight during procedures and visitation. For neonates in an incubator, the wires should be tunneled out of the incubator and the head box rested on the outside of the cart—not inside, next to the patient.

Neonatal EEG is interpreted with other concurrent physiological information that requires the use of a number of extracerebral channels. These additional channels assist in the correct identification of the infant's behavioral state and often contribute to addressing the clinical event in question, such as apnea, bradycardia, or jerking movements of a limb. Many of the channels come in different varieties, and not all centers use every channel. The most common types are discussed here; a broader discussion can be found in other sources (6,5). Respiratory monitoring is done by a thermistor at the nares, an impedence pneumograph on the chest with standard EEG electrodes, or a strain gauge placed around the chest to detect motion. Alternatively, pulse oximetry and end tidal carbon dioxide may be measured. These channels allow the electroencephalographer to differentiate the regular respirations of quiet sleep from the irregular pattern seen in active sleep and wakefulness. Two eye leads are placed to detect both vertical and horizontal eye movements. One electrode is placed inferior to the outer canthus of one eye, and the other superior to the other eye. Each eye electrode can be paired with the ipsilateral ear lobe lead. Electrocardiographic (ECG) leads are placed to monitor infant heart rate. As in the adult, these can be invaluable in distinguishing artifacts from physiologic activity. Finally, two electromyography (EMG) leads are placed under the chin to monitor submental muscle tone. Optimal settings are a sensitivity of 3 mV/mm, a low frequency filter of 5 Hz, and a high frequency filter of 70 Hz. Additional EMG leads may be placed on individual limbs of interest to detect movement. These additional muscle leads can be especially helpful in determining the frequency of clonic movements or the shape of tonic contractions, thereby providing clues to their etiologies.

After the EEG and extracerebral electrodes are placed, several crucial tasks remain before the EEG can be properly interpreted by the electroencephalographer. The first is the assignment of the newborn's post-conceptional age. This is the age that is applied to the infant when interpreting the EEG, and it should be determined as accurately as possible. It is the length of the infant's gestation, based on maternal last menstrual period (LMP), plus the amount of time spent outside the womb. If maternal LMP is not known, the neonatal team may provide alternative information such as a Dubowitz score or estimated age at last ultrasound examination. As an example of conceptional age (CA), a 3-week-old, 26-week-premature infant has a CA of 29 weeks. Thus, the neonatal age range is typically considered to be up to 44 weeks CA. A working definition for infancy would be greater than 44 weeks CA but less than one year of age. A child could be considered anyone older than 1 year of age but less than 10–12 years old (depending upon the onset of puberty).

The neonatal EEG is exquisitely sensitive to external stimulation and behavioral state. Therefore, the record should be correlated as much as possible with clinical information about the neonate. This data is often found in nursing flow sheets or can be noted by the technologist or nursing staff on the record. Important events to be considered include feeding, administration of medication, and procedures. In addition to making notations about the newborn's natural state, the technologist should also stimulate the infant to allow for an assessment of reactivity. *If there are movements in question that are provoked by stimulation, they, too, should be provoked by a subsequent attempt to restrain or reposition the limb and suppress the movement.*

Two conventions of neonatal EEG interpretation are adopted before the EEG is actually read. First, *paper speed is*

set at 15 mm/sec. Viewing of the record in this compressed format assists in the visualization of slow activity, continuity, and synchrony. Second, a single bipolar montage is adopted that uses both an anterior–posterior and transverse array. This montage will include the vertex where some physiologic patterns and seizures are often confined (7). For a depiction of recommended neonatal montages with several extracerebral channels, please see the American EEG Society Guidelines (3).

Monitoring Infants and Children

Beginning two months after term, at a conceptual age of 48 weeks, the neonatal conventions for electrode placement, paper speed, and montage are replaced by the standard adult systems. In addition, the requirement for accurate age assignment to the infant lessens slightly such that an age in months is sufficient to interpret the EEG accurately. It should be noted that the voltage activity is higher in children than in adults, especially during sleep. As such, a sensitivity of 10–15 uV/mm is often adopted to make the record easier to read. A time constant of 0.3 seconds is useful for balancing the prominent delta activity seen in infants with artifact. *Automated spike and seizure detection programs are of limited utility in patients under two years of age* (8).

Activation Procedures

Activation procedures are routinely performed, particularly because they have a higher yield in the pediatric age range than later in life. They should not be performed indiscriminately, however, and several special considerations apply. Photic stimulation is not clinically useful in neonates but can be performed in older infants and children with the understanding that a photoparoxysmal response is uncommon in children less than five years of age (notable exceptions include patients with certain epileptic syndromes, such as Dravet syndrome). *Hyperventilation should be attempted in all children older than two or three years of age.* An adequate response can be obtained in these young children by asking them to use a whistle or to blow on a brightly colored pinwheel (windmill). Finally, *passive eye closure should be performed in all children over three months of age.* This will enable proper visualization of the posterior dominant rhythm, which should be well developed by this time. The technologist may accomplish this task by gently blowing on the eyelids of the young infant and then holding them closed. Older children may be able to cooperate, especially if this task is made into a game or contest.

The Pediatric Epilepsy Monitoring Unit (EMU)

After the neonatal period, most video EEG monitoring of infants and children takes place in the specialized setting of the EMU. A well-designed EMU is essential for obtaining optimal studies while caring for the patients during the stay. As is true in most pediatric hospitals, child-friendly décor goes a long way toward making children feel safe and comfortable during what can be an intimidating procedure. This is usually accomplished by bright colors, plenty of light, and prominent pictures or murals. Concealment of monitoring hardware is also important in reducing the "intimidation factor." If this is done, careful attention must be paid to giving the equipment adequate ventilation and allowing easy access for repairs. Our laboratory has found that 25-foot cables are sufficient to allow children to roam freely and do not need frequent repair. The rooms in the pediatric EMU must be large enough to accommodate parents who will need to stay with the child and indicate the events in question (6). Floors should be designed to be easily cleaned but still provide appropriate padding able to dissipate the force applied to it during a fall. Our unit has been constructed with special laminate flooring with a hardwood appearance but the resiliency necessary to provide padding. It is similar to the surfaces found on basketball courts and other indoor sports arenas. Corners of tables and workstations should be rounded to prevent injuries to wandering toddlers or other children during the course of a seizure. An additional safety concern is hot water, which can result in scalding or burns during a seizure. The EMU should have sinks that require constant pressure to produce hot water, not faucets that can be left in the running position while attention is impaired. Many units have a central playroom with camera coverage so that children can move around more freely. In addition to contributing to a friendly and welcoming environment, adequate lighting is necessary to visualize the child. Ultraviolet or infrared lighting may be needed at night to see the patient during sleep while the room is darkened.

Once the unit is constructed, it should be furnished with the pediatric patient in mind. Standard hospital cribs may need to be modified with transparent sides so that infants and children can be seen while unattended. For older children in beds, colored sheets are often effective in reducing the glare from ambient light and allowing accurate visualization of the child's face during an event. Age-appropriate activities should be available for children during their stay, either in the room or in a central playroom.

Pediatric patients can find the process of electrode placement very distressing and can be difficult to manage, especially if they are autistic or have other behavioral problems. Several strategies can be employed to deal with this issue. The technologist should have a calm and friendly demeanor. Each procedure should be explained to the child before it is performed. Employment of a child life specialist and a "distraction cart" may help to keep the child's attention engaged elsewhere during the procedure. If this is not successful, the child may need to be restrained, either by being wrapped tightly in a sheet or by the use of a papoose device. For infants, electrode placement can be performed

directly after a feeding, when an infant is usually sleeping or very relaxed.

The staff in the unit should be experienced in monitoring infants and children. This will ensure that they are attentive to the unique considerations discussed above, and that they contribute positively to the pediatric environment. Both technologists and nursing staff should be fully aware of the reason for the child's stay, as well as of any underlying diagnoses. This is necessary because they may be called upon to indicate events that occurred while parents were sleeping or absent from the bedside. The technologist or neurotelemetrist is also responsible for ensuring that the child is constantly on camera—a demanding task, as anyone who has chased a toddler can attest.

INDICATIONS AND UTILITY OF EEG MONITORING

Neonates

As stated previously, most neonatal monitoring occurs at the bedside in the NICU. In this setting, the concern for seizures (i.e. pretest probability) is high, and infants are often critically ill. The EEG in this arena has three primary uses:

1. Determine whether particular infant behaviors or clinical signs represent ictal phenomena.
2. Monitor at-risk neonates for the presence of subclinical seizures.
3. Provide prognostic information about the long-term outcome of the infant.

When performed for prognostic information, the EEG should be interpreted with caution, and by an experienced neonatal electroencephalographer. Even then, only limited information can be provided with any certainty based on available data. When monitoring is conducted in the NICU, good communication must be established between the electroencephalographer and the neonatology team. Seizures in the newborn period are rarely idiopathic and require prompt investigation for a proximal cause, as well as carefully titrated therapeutic intervention.

Infants and Children

Once outside the neonatal period, the indications for video EEG monitoring expand to reflect the increased incidence and larger variability of seizures in this population. Monitoring in this population has four primary uses, which we will discuss.

First, as in the neonate and adult, it is used to determine the nature of paroxysmal events. It is especially helpful in situations in which the interictal EEG is normal, nonepileptic events are suspected, and the interictal EEG does not match the clinical description of the event. In the vast majority of circumstances, the video EEG can be helpful in clarifying this issue, particularly if the event in question is recorded (9).

Second, video EEG monitoring may be used to quantitate the frequency of seizures or interictal epileptiform abnormalities in patients with indistinct seizure types or the inability to communicate. Communication issues may arise as the result of immaturity, encephalopathy, or specific impairments of language and communication. Infants with temporal lobe seizures may also have very subtle manifestations of their seizures (10). In many cases, there may be only a behavioral arrest and subtle eye version (11). Experienced parents will often detect this seizure, but parents new to this presentation of epilepsy in their child or with a limited ability to observe their infant first-hand may miss these seizures. Infantile spasms, although often overt and profound, may sometimes present or evolve into subtler manifestations consisting of transient upward eye deviation (sursum vergens) or slight stiffening of the back muscles (12). Atypical absence seizures can be difficult to observe clinically and may be difficult to discern from background abnormalities on EEG. In all of these circumstances, video EEG monitoring is useful in quantitating the frequency of seizures and gauging the response of seizures to treatment.

Third, video EEG can be used to identify candidates for epilepsy surgery. In older children, the determination of surgical candidacy is much the same as it is in adults. There may often be a good concordance between lateralizing features of the clinical semiology of the seizures and the ictal patterns. In infants, however, the situation is more complicated and the data often less concordant. This relates to the relative immaturity of the brain, which limits the repertoire of specific and declarative findings in both the clinical features and the EEG ictal discharges. Localized congenital or acquired lesions may manifest with generalized seizure semiology and interictal EEG background abnormalities that are generalized or poorly localized. In these situations, video EEG monitoring may afford useful information, either from the clinical features of the seizures, from the details of the ictal patterns, or from the combination of both with other clinical data. Pioneers of infantile epilepsy surgery emphasized these points and underscored the importance of ancillary information, such as that provided by PET scans (13,14). One important implication of these observations is that the video EEG monitoring of infants and young children with refractory localization-related epilepsy may not always show strong lateralizing features.

Finally, video EEG monitoring can be used to diagnose the appropriate epilepsy syndrome in children. This is most often a result of the recording of additional seizure types either not noticed by the parents or not reported in the initial history. Identification of common pediatric syndromes will be covered in another section of this book, so we will

not discuss it here. In a study of video EEG monitoring in children, 54% of the patients were assigned an epilepsy syndrome diagnosis at the end of their stay in the EMU (15). The epilepsy syndrome diagnosis provides prognostic information, contributes to the diagnostic evaluation for secondary causes of epilepsy, and helps to determine appropriate therapy.

As a result of these distinct indications, the types of patients typically found in a pediatric EMU, the length of stay, purpose of admission, and diagnosis at discharge are often quite different from those seen in adult EMUs. Our average length of stay in the pediatric EMU is in the range of 1.2–1.5 days, in contrast to perhaps the more common several-day or week-long admissions for adults. This reflects the fact that the events in question are usually happening on a frequent basis. Many units will establish protocols for observing young patients for several hours only to capture frequent events. One study has shown that even brief outpatient monitoring can lead to a change in syndrome diagnosis in up to 21% of patients (16). In this way, the length of stay can be tailored to suit the individual child, and admission may not be necessary. In a study of video EEG monitoring in children, one group found that 22% of the events recorded in its monitoring unit (out of a total of 1,000 studies reviewed) were non-epileptic (16). This percentage is consistent with the results of our unit and also with that of other groups (17). Despite quick turnaround, the pediatric epilepsy monitoring unit can be an effective tool for diagnosing paroxysmal events in infants and children.

INTERPRETATION OF THE EEG

The following is a brief discussion of abnormal background patterns in the neonate, as well as of some unique features of neonatal seizures. In addition, a brief review of the most common types of infant seizures is included. After approximately age 2, seizures in children begin to more closely resemble their adult counterparts both clinically and electrographically.

The Neonate

Abnormal Interictal Background Patterns

We have chosen to discuss the following patterns because many of them are unique to the neonatal period and offer an important framework in which to interpret neonatal seizures, which are discussed in the next section. In contrast to the normal transients and patterns seen in the neonate, the following patterns can be seen to represent varying levels of pathologic derangement along a spectrum of severity. However, prognosis based on background activity alone is difficult, for the degree of abnormality can change rapidly and is reflective of many extracerebral as well as intracerebral factors. For a full discussion of these patterns, see Clancy (5).

Isoelectric

This severely abnormal EEG pattern, consisting of a flat tracing with no discernible potentials of brain origin, can be seen in neonates after a variety of insults, including asphyxia, intracerebral hemorrhage, meningitis, encephalitis, and severe malformations of cortical development. The same technical requirements as in adults with respect to sensitivity, time constants, and interelectrode distances apply to the neonate, but this record is not synonymous with brain death. *There are no uniform criteria for the determination of brain death in this population.* This pattern does carry a grave prognosis, and most neonates with this background will have long-term neurologic sequelae.

Burst Suppression

This is also a severely abnormal background with a poor prognosis, and care must be taken to distinguish it from the normal discontinuity seen in premature infants. It is characterized by *an isoelectric background between bursts of activity that do not contain normal patterns for age.* These bursts often have rhythmic activity and prominent spikes that distinguish them from their normal counterparts. This pattern is usually not reactive to stimuli and persists invariably throughout the recording.

Excessively Discontinuous

Unlike the previous two rhythms discussed above, this abnormality represents a variation in the degree of normal rather than an abnormality unto itself. Part of the distinction lies in the fact that this pattern is reactive, has preserved state changes, and contains normal transients. The other part arises from the degree of discontinuity that in the EEG of preterm infants is expected and considered normal. The amount of discontinuity varies with gestational age and gradually decreases in the waking record as the neonate ages, finally disappearing from quiet sleep at a conceptual age of 44–46 weeks. However, excessively long periods of quiescence in the EEG have been associated with poor outcome in some studies and are therefore considered abnormal (18). There is still controversy over the normal interburst interval in infants of varying ages. *A reasonable estimate cites a maximal duration of 40 seconds in infants less than 30 weeks CA; only 6 seconds is tolerated in full-term infants* (19).

Low-Voltage Undifferentiated and Low-Voltage with Theta

These two patterns are seen most often in infants with severe neurologic insults and carry a poor prognosis when persistent into the first month of life. In the first pattern,

voltages are attenuated and range from 5 to 15 μV in wakefulness to 10 to 25 μV during sleep (20). There may be more suppression of faster frequencies. Some authors make a distinction between isolated suppression of voltage and loss of variability in the EEG. The latter pattern is described as depressed and undifferentiated because it lacks the normal frequency range and is nonreactive (5). However, the prognostic significance of this distinction is not known. A low-voltage background can be accompanied by bursts of theta activity in a focal or multifocal distribution. This pattern may be seen in the transition to an isoelectric recording. These patterns should be distinguished from the focal attenuation in voltage that can be seen with subdural hematoma or scalp fluid collections.

Diffuse Slow Activity
This severe abnormality consists of diffuse and nonreactive delta activity. The recording lacks the frequency variability and physiologic transients of the normal neonatal EEG. When persistent, it, too, seems to carry a poor prognosis but is etiologically nonspecific.

Persistent Amplitude Symmetry
The definition of this abnormality is *a difference in amplitude of greater than 50% between the two hemispheres in all behavioral states.* This pattern may be associated with focal structural abnormalities or other acquired insults, but scalp asymmetry should be ruled out first (21). If indicative of an underlying lesion, the asymmetry is often accompanied by suppression of background rhythms, slowing, or spike activity. Transient amplitude asymmetries are not as significant and may be seen after a seizure or during slow-wave quiet sleep in normal newborns.

Disturbance of Sleep States
Subtle abnormalities in the neonatal EEG are much more common but probably underreported, for some are difficult for any but the most experienced readers to detect. Abnormalities can be seen in the quantities of the various sleep stages, with mild encephalopathy characterized by an increase in the amount of transitional sleep. The quality of neonatal sleep can also be disrupted by indistinct sleep states or poor correlation between the EEG and biophysical parameters during the various stages.

Dysmaturity
An experienced neonatal electroencephalographer should be able to accurately date the conceptional age of an infant to within 2 weeks. Because of this, any lag in the maturity of a neonatal record greater than 2 weeks is considered abnormal and is noted as having been seen in chronically ill infants (22). Although some normative scales have been proposed, this abnormality is usually based on a subjective assessment of features such as continuity, synchrony, and distribution of normal transients. It should be noted that transient dysmaturity can be seen after a seizure or acute insult and is therefore not considered to be prognostically significant.

Abnormal EEG Transients

Positive Rolandic Sharp Waves
This waveform is moderately high-amplitude (50–200 μV) and surface-positive. Duration is usually 100–250 msec. Amplitude is maximal at C3–C4 with a broad field to frontal and parietal regions. These waves may be seen unilaterally or bilaterally, and singly or in runs and are often seen in association with other background abnormalities. Although frequently seen in association with intraventricular hemorrhage, they are more often a marker of indeterminate white-matter injury. *Temporal positive sharp transients do not have the same clinical connotation.*

PLEDS (Pseudoperiodic Lateralizing Epileptiform Discharges)
PLEDS are persistent, stereotyped, lateralized epileptiform discharges with a periodic or nearly periodic repetition rate, often at a frequency of about 1 Hz. These often repeat without evolution for at least 10 minutes. PLEDS have been seen in both focal and diffuse pathologies and, again, are often seen with other background abnormalities.

Ictal Patterns

The clinical semiologies of neonatal seizures are quite diverse. They include clonic, tonic, and myoclonic types. Generalized tonic–clonic seizures are rare in this age group; neonates are usually unable to sustain the type of bihemispheric synchronization necessary for this seizure. Tonic (particularly generalized) and myoclonic movements may be seen in sick neonates without a cortical electrographic correlate (23). In fact, careful studies of the video EEG features of neonatal seizures have failed to find a consistent ictal correlate for many tonic and so-called subtle seizures. Subtle seizures consist of staring or of repetitive stereotyped movements, such as bicycling of the legs or rowing of the arms (movements of progression), oral–buccal–lingual movements (tongue-thrusting, chewing), and some random eye movements (24). This has led to reconsideration of these events, more appropriately, as brainstem release phenomena. In contrast, focal clonic seizures, some asymmetric tonic seizures, and many myoclonic seizures often have an EEG ictal correlate.

Neonatal seizures manifest a wide variety of clinical forms that do not reliably correlate with the limited number of electrographic seizure types seen in neonatal recordings. In fact, many electrographic neonatal seizures may have no clinical accompaniment at all. Ictal discharges

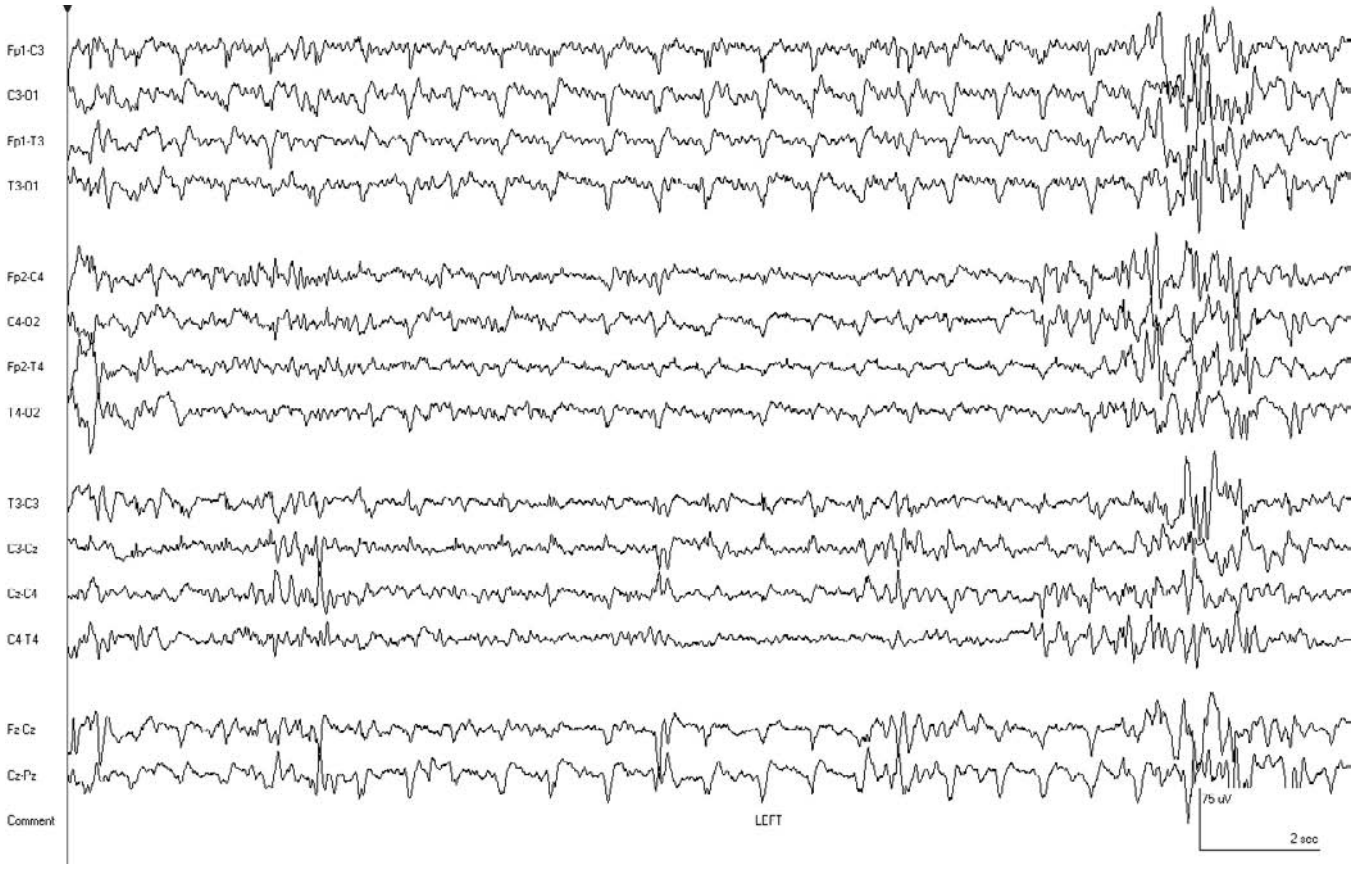

FIGURE 8-2. Monorhythmic seizure and discontinuous background associated with clonic activity of the right arm, in a 3-day-old term neonate.

may evolve in frequency, amplitude, and morphology (25). In other circumstances, however, an ictal discharge can be strikingly monomorphic and lack any clear evolution in frequency or amplitude (Figure 8-2). All frequency bandwidths are represented and the usual morphology is a simple rhythmic waveform rather than the repetitive spikes seen in adults. Occasionally, however, more complex waveforms can be seen (Figure 8-3). The majority of neonatal seizures are focal in onset and arise from a single location—most commonly the central and temporal regions. Less frequently, seizures may arise from multiple locations separately or simultaneously and independently; these are termed multifocal (Figure 8-4). Discharges commonly spread to ipsilateral regions or homotopic locations in the contralateral hemisphere, but true generalization is rare (5).

Electrographic seizures are conventionally assigned a minimum duration of 10 seconds. Shorter discharges showing evolution have been termed brief ictal rhythmic discharges (BIRDS) and are of uncertain clinical significance (26). In a study of 487 neonatal seizures, 47% lasted less than 1 minute and 18% lasted between 1 and 2 minutes (25). Remarkably, some seizures lasted up to 46 minutes. There is no accepted definition of status epilepticus in the neonate, although several have been proposed, including seizure duration greater than 30 minutes or the sum of the individual seizures totaling more than 50% of the recording (27).

The Infant and Child under 2 Years

Like neonatal seizures, infantile seizures are often quite subtle in their clinical features (28,29). This is most apparent in seizures originating from the temporal lobe, which may only be associated with behavioral arrest and occasionally mouthing movements (30). These hypomotor or behavioral arrest seizures may go unnoticed by many caregivers except for the drop in oxygen saturation seen in monitored infants. In older patients, these types of seizures are often accompanied by fine motor automatisms that are absent in infants (31).

Investigators using traditional classification schemes that attempt to categorize these and other partial seizures in infants into standard categories dependent on the presence

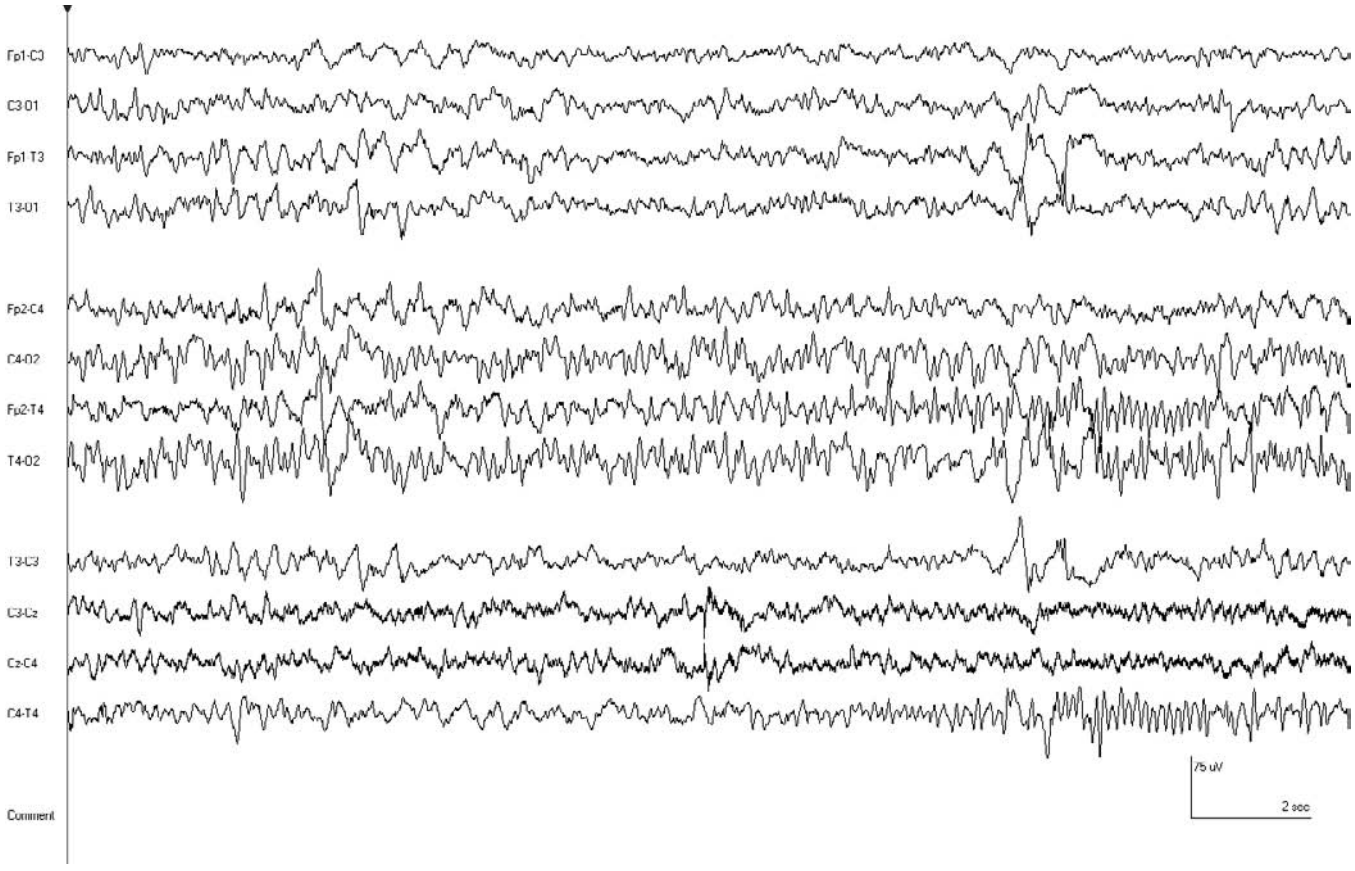

FIGURE 8-3. Complex ictal pattern seen in a term infant, with desaturation as the only clinical correlate.

or absence of normal consciousness (such as simple partial or complex partial) have found this task difficult if not impossible. Although attentiveness can be assessed by attempting to alert the infant to visual or auditory stimuli within the environment, failure to respond does not confirm an altered level of consciousness. Therefore, these terms are not very reliably used in the description of seizures in the infant and nonverbal child (32).

As we discussed in the previous section regarding surgical evaluation of the infant with intractable epilepsy, focal seizures in the infant may have clinically generalized features. Several series have reported bilateral tonic stiffening, clonic, or myoclonic movements during partial seizures in infants (33,34,32). Dravet and colleagues have also reported several children with generalized seizures (flexor spasms, atonic, or tonic seizures) that corresponded to localized ictal and interictal abnormalities (35). Therefore, ictal EEG is critical in ascertaining the localized onset of these seizures, which may be amenable to surgical intervention. However, in some cases the interictal EEG may provide the most revealing clues to localization, such as focal slowing or attenuation, and should not be overlooked.

Given the limitations discussed above, video EEG monitoring in infants and young children takes on added significance. A recent study attempted to classify infantile seizures by both their clinical and electrographic correlates after reviewing the video EEG records of 2,112 patients in this age group (11). Of the 13 distinct seizure types identified, 10 were localization-related. What follows is a summary of the most common of the seizure types identified in this study. (When broken down in this manner, numbers are small, and generalizations may therefore be limited. In addition, these observations should be confirmed by other investigators before these categories are used for any type of formal classification scheme for infantile seizures.)

Focal Clonic

The clinical semiology of this seizure type, seen in 11 patients, was unilateral or bilateral asymmetric myoclonic jerks of the limbs. The electrographic correlate was of focal onset, usually in the anterior head regions (frontal, central, or both in 8/11). Two patients had a posterior ictal focus in the parieto–temporal–occipital region, and one patient had a hemispheric onset. The remaining electrographic features (waveform, evolution, and termination) were more variable. However, the overall pattern was distinctive, characterized by a localized

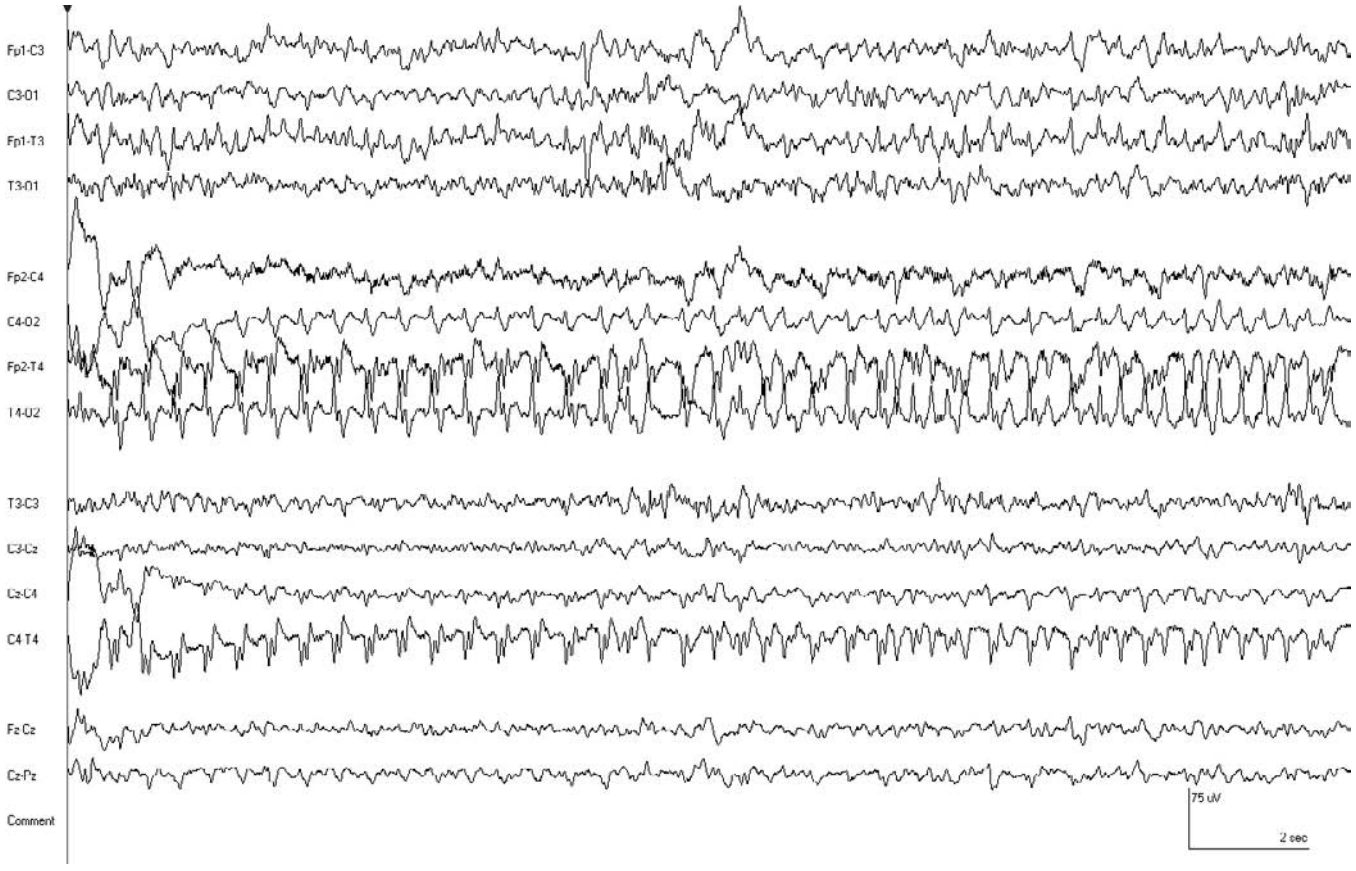

FIGURE 8-4. Multifocal seizures, seen in a term neonate. A delta frequency seizure can be seen in the right temporal region, whereas a faster, more complex seizure is occurring independently in the left frontocentral region. Clinical manifestations associated with some seizures in this infant included stiffening, asymmetric posturing, and mouthing movements.

build-up of rhythmic sharp waves in the central region followed by a diminution of ictal activity (Figure 8-5).

Focal Tonic

The clinical semiology of this seizure type, seen in 11 patients, was usually an asymmetric tonic posture. Two patients had a symmetric tonic posture associated with head or eye version. The electrographic correlate of this seizure type was more diverse, with unilateral onset seen in seven patients (63%), generalized onset in three patients (27%), and bilateral symmetric onset in one patient (9%). There was no dominant location of onset as was seen in the focal clonic seizure pattern, with seizures arising from all brain regions. Electrographic features seen in over half the patients were characterized at onset by rhythmic activity and fading termination of the ictal pattern.

Behavioral Arrest with Version

Pure behavioral arrest without any other clinical signs was seen in only 1 seizure out of the 109 events examined. Version of the head, eyes, or both as an accompaniment to behavioral arrest was more common, and was seen in 14 seizures. *Interestingly, the ictal discharge was ipsilateral to the version in 36% of the patients.* The overwhelming majority, 93% (13/14) had a unilateral focal onset, with one seizure showing bilateral but asymmetric involvement. There was no dominant location seen in this seizure type. The electrographic correlate was more uniform in that it involved rhythmic activity at onset (86%, or 12/14), but the full range of frequency bands was seen in this seizure type. Most of the seizures of this type remained confined to the ipsilateral hemisphere (71%, or 10/14), with some amount of spread to adjacent regions in half of these. The majority of seizures of this type also showed fading termination (79%, or 11/14). An example of this seizure type can be seen in Figure 8-6.

Spasms with Focal Features

This was by far the most common seizure category seen in this study, representing 28 of the 109 seizures examined. In this category, we include spasms with asymmetric features, whether clinical or electrographic, and those accompanied by distinct focal seizures. Spasms and focal seizures were

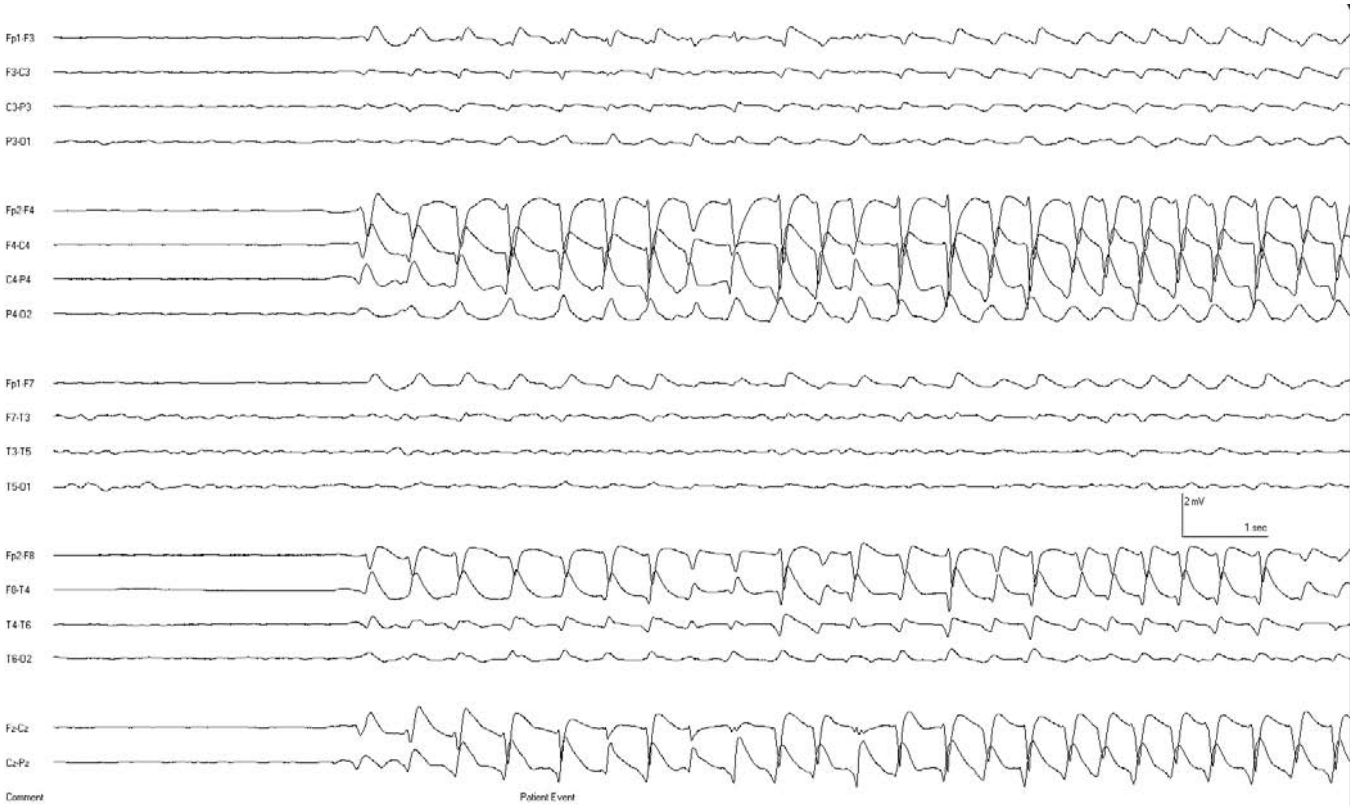

FIGURE 8-5. Ictal tracing of a focal clonic seizure involving the left upper extremity in an 11-month-old infant.

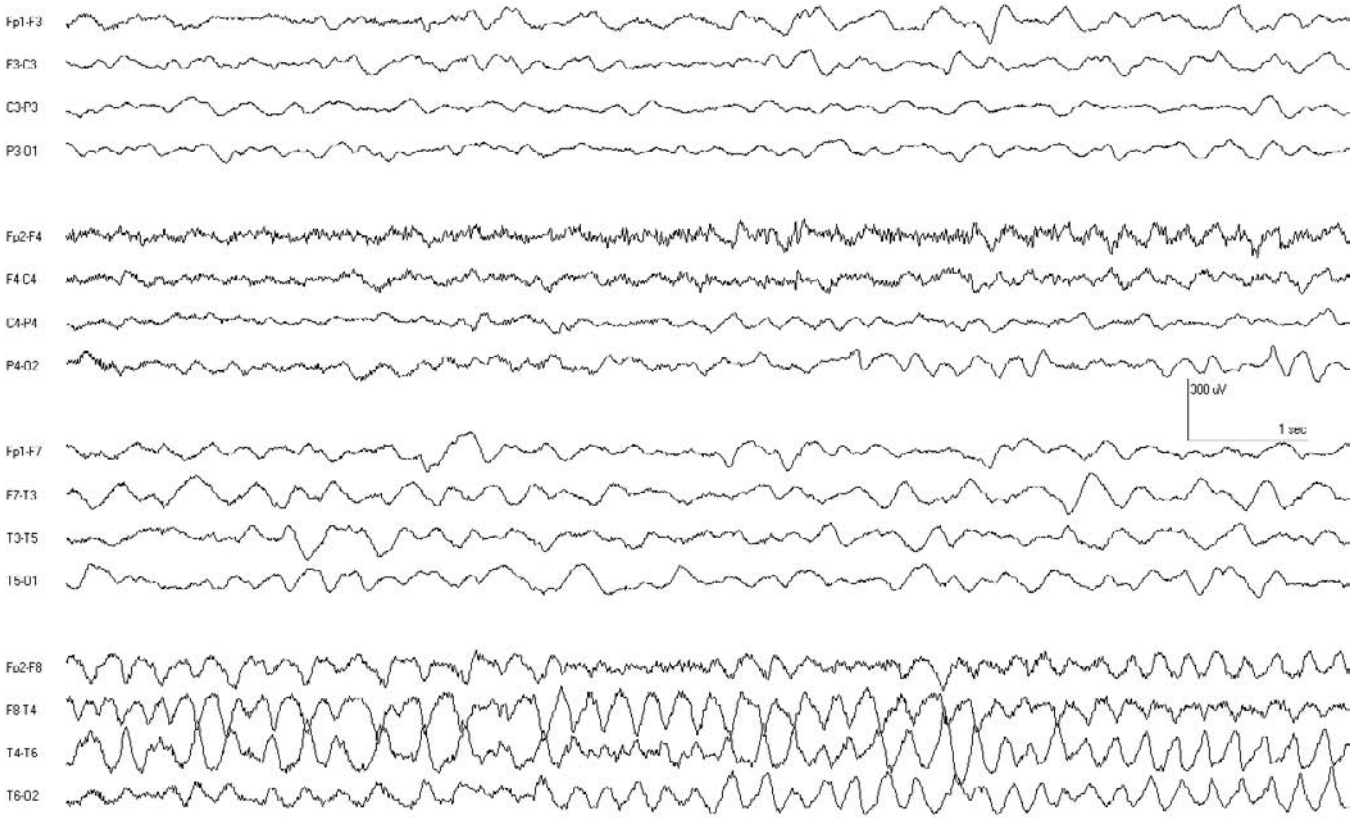

FIGURE 8-6. Example of a behavioral arrest: version seizure in a 3-month-old infant with right temporal lobe cortical dysplasia. Note the rhythmic theta alpha pattern evolving in the right posterior quadrant.

seen in 16 patients, with the most common additional seizure type being focal tonic (56%), followed by focal tonic–clonic (25%) and focal clonic (19%). In all but one case, the spasms exhibited the classic pattern of a sharp wave followed by electrodecrement. As was seen in the previous seizure type, the ictal pattern remained confined to the region of onset in the majority of cases (63%). In contrast to the previous seizure types, termination was most often stuttering (69%), although other patterns were seen.

Asymmetric spasms were seen in the remaining 12 (of 28) patients in this category. As may be inferred from the description, a bilateral but asymmetric electrographic correlate was seen most frequently in this seizure type (42%); however, a generalized onset was seen in 33% (4/12). The classic pattern of sharp wave followed by electrodecrement was seen in a lower percentage of patients (75%). All these seizures were confined to the area of ictal onset, and most had a stuttering termination (83%).

Infantile Spasms

Although discussed in the previous section as an ictal pattern accompanying other infantile focal seizures, this ictal pattern may also be seen as a generalized phenomenon. Spasms can be symptomatic of an underlying focal lesion but are also associated with Trisomy 21, lissencephaly, and certain inborn errors of metabolism, as well as with various other symptomatic encephalopathies. *West syndrome is the triad of infantile spasms, hypsarhythmia, and developmental regression.* The clinical spasm often consists of a brief myoclonic component that produces forward flexion of the trunk, head, and limbs, which are then held in a brief tonic posture before relaxation. Extensor spasms as well as mixed semiology can also be seen. As we discussed previously, spasms may also be quite subtle, with brief eye movements or contraction of axial muscles either after treatment or as the presenting manifestation. Electrographically, this seizure type is usually associated with a high-voltage slow wave with or without accompanying spikes and multifocal sharp waves, followed by a brief period of profound background attenuation. During the period of attenuation, which typically lasts several seconds, there may be admixed low-voltage fast activity, particularly in the posterior head regions. An example of the interictal and ictal patterns associated with West syndrome can be found in Figure 8-7.

Other Seizure Types

Although seen in fewer infants, several other seizure types were identified in this study. These included focal

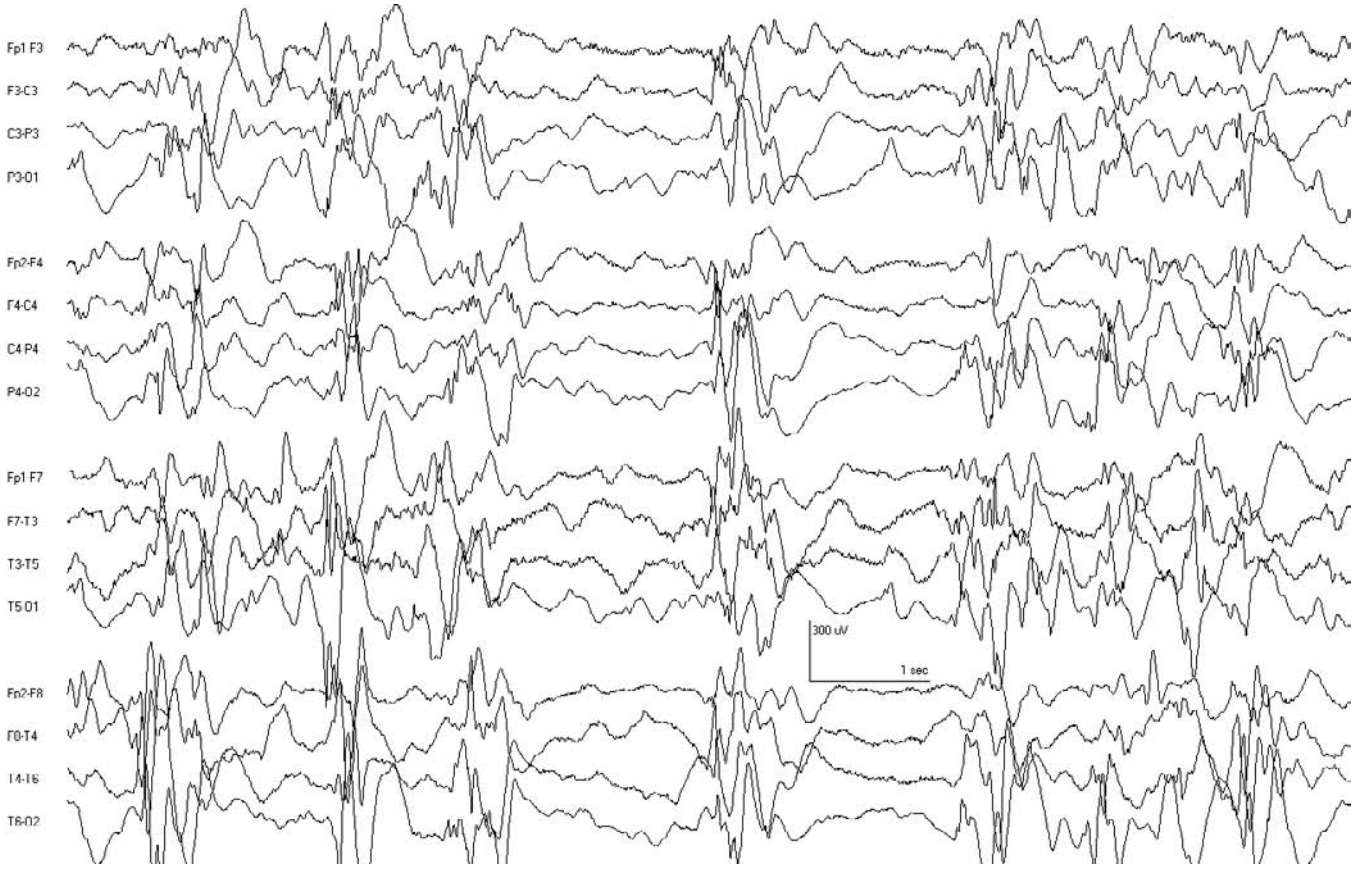

FIGURE 8-7. Interictal tracing showing hypsarhythmia followed by the classic ictal pattern of a generalized high-amplitude slow wave and electrodecrements. Note the scale; sensitivity is 20 uV/mm. The patient is an 8-month-old boy with galactosemia and infantile spasms.

tonic–clonic seizures with secondary generalization, focal tonic–clonic, pure behavioral arrest, and hypermotor seizures. Only one seizure of the last two types was seen, which limits the utility of any further comment.

The Older Child

Ictal clinical semiology changes in an orderly fashion with age. When a large group of infants and children is rigorously studied, certain trends become apparent (31). The prevalence of aura, automatisms, arm clonus, dystonic posturing, orderly secondary generalization, and unresponsiveness increase with age. In contrast, the relevance of autonomic alterations, behavioral arrest without other features, asymmetric generalized clonus, eye deviation, and symmetric tonic posturing decrease with age. It is very rare to see dystonic postures of the arm or hand, secondary generalization, distal limb automatisms, or auras in pre–school-aged children. *Children older than 6 years have many of the same clinical features seen in adults.*

Electrographic ictal patterns do not change appreciably with age, with the exception of the electrodecremental pattern, which is much more common in infants. Like spikes, ictal patterns, do, however, show an apparent anterior migration, with a greater likelihood of anterior ictal patterns as the child matures (31).

Computerized Aids to Seizure Detection

Automated spike and seizure detection paradigms have been used in adults and older children to good advantage. Their utility in infants has not been rigorously studied. In practice, we are not confident in the ability of these aids to capture interesting ictal and interictal events, particularly in the very young. As a consequence, we routinely screen the entire segment of video EEG tracing in our patients. We recognize that this may be considered an inefficient and labor-intensive practice, but the over-detection of sleep architecture as epileptiform activity and the inability to accurately identify electrodecremental patterns and diffuse abrupt periods of attenuation (often associated with myoclonic or tonic seizures) make it mandatory to screen the entire EEG. Amplitude integrated EEG and compressed spectral array analysis may help the electroencephalographer screen large segments of data, but neither is sufficiently well studied or reliable enough to substitute for complete review in infants or young children at the current time (36,37).

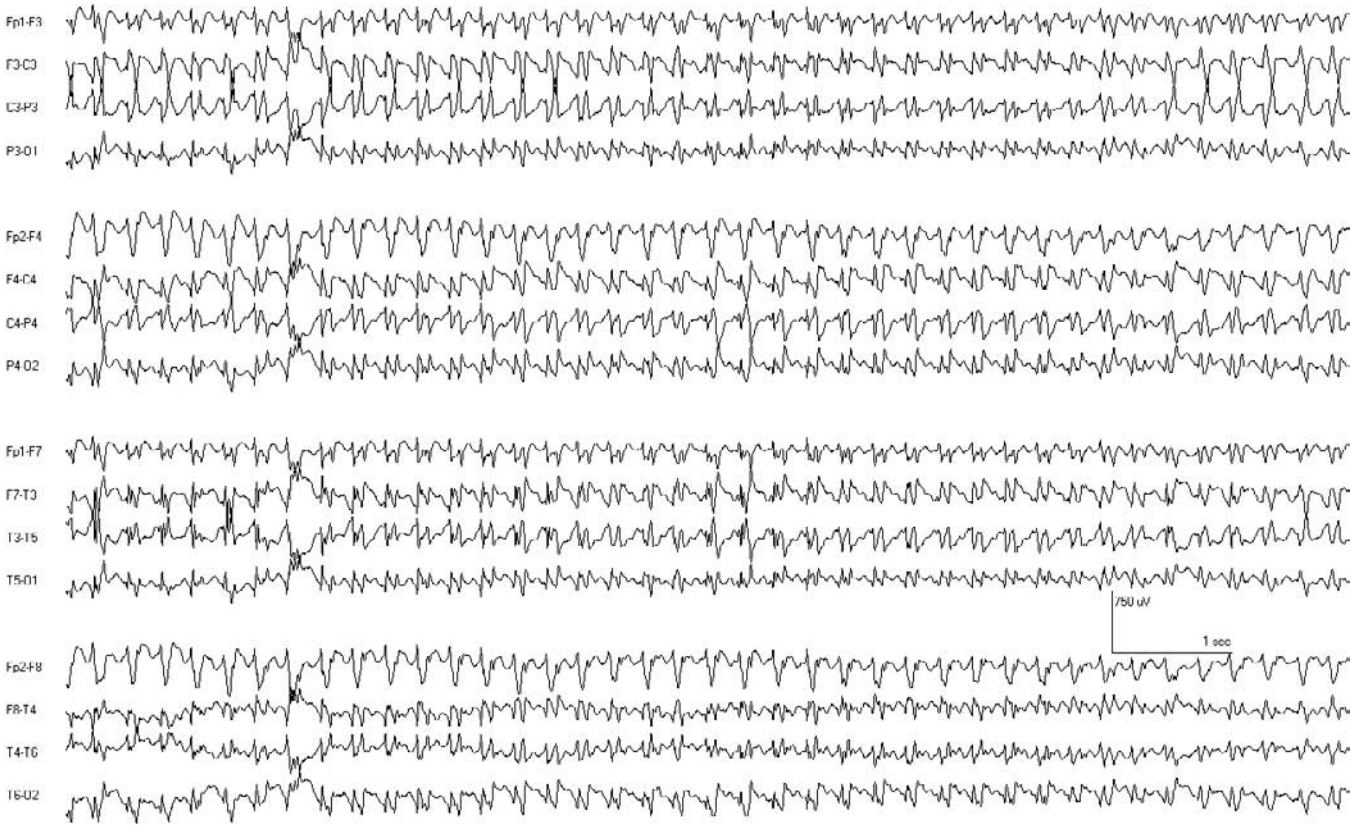

FIGURE 8-8. Artifact from chest physiotherapy in a term neonate hospitalized in the intensive care unit. Note the generalized nature, the monomorphic quality of the abnormal waveforms, and the high voltages.

Differentiation from Common Artifacts

Artifact rejection may be one of the most challenging aspects of pediatric EEG reading. A variety of artifacts are commonly seen, including pulse, EKG, rhythmic muscle and movement, patting, sobbing, chewing, and machine artifact. Careful analysis of the morphology of the waveforms might give valuable clues, and inspection of the topography of the discharges—looking for a believable electrographic field and absence of complex phase reversals—can help differentiate artifacts from cerebral electrical potentials. The use of noncerebral electrodes, such as respiratory monitors, EKG leads, and deltoid EMG leads, can facilitate recognition of cardiac, muscle, or movement artifacts. *It is extremely useful to view the concurrent video, which will often confirm the source of the artifact.* Playing the video in slow motion allows the careful study of the relationship of the movement to the cerebral activity. An example of high-frequency patting artifact during chest physiotherapy of an infant is seen in Figure 8-8.

CONCLUSIONS

We began this chapter by stating that infants and children are not just simply adults. In the video EEG monitoring of these patients, these differences become apparent from the very beginning, with attempts to attach electrodes to the neonatal scalp. With increasing use of the EEG in pediatric settings, standardization of methods has produced a systematic and effective means of adapting to the unique challenges of pediatric EEG. Practical changes include a limited montage designed to cover active areas with a high incidence of normal and abnormal patterns, the use of polygraphic recordings, and compressed display time for neonates. A child-friendly atmosphere and technologists specialized in the care of young children not only help smooth the process but also help ensure that recordings of high technical quality are obtained. In most circumstances, the clinical question can be answered in a relatively short period of time. This may require advanced planning and triaging of the patient in order to provide parents with a reasonably accurate expectation of the length of stay in the monitoring unit. But challenges in recognition and interpretation of neonatal and infantile seizures remain despite these advances. Continued research is needed to provide a more complete understanding of the full repertoire of neonatal and infantile ictal patterns.

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9

SEIZURE CLASSIFICATION IN EPILEPSY MONITORING

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THE SYMPTOMATOGENIC CORTEX IN EPILEPSY: HISTORY AND CONCEPT

> "*Epilepsy is the name for occasional sudden excessive rapid and local discharges of grey matter.*"(1)

Hughlings Jackson's conception of epilepsy as being produced by a discharging lesion of the brain highlights the beginning of modern epileptology. Jackson conceived that during a focal motor seizure there is a discharge in the gray matter of the brain, which begins at a local point and spreads, producing a march of outward phenomena (2). He named these events *epileptiform* seizures to make a distinction from the *epileptic* seizures seen in patients with "genuine" or idiopathic epilepsy (3,4). Jackson already admitted that both epileptiform and epileptic seizures were "cortical fits," starting from (hypothetically) different parts of the cortex (5). He recognized the significance of the aura in providing the most precise anatomical information about the origin of a seizure, and was the first to describe the "dreamy state" associated with a "very small patch of softening in the left uncinate gyrus" (6). He suggested that the difference between petit mal and grand mal seizures seen in genuine epilepsy may be a difference in the strength of the discharge. Localization of focal motor seizures based on Jackson's semiological concept, and confirmation through electrical cortical stimulation by David Ferrier, led to the first series of epilepsy surgeries, performed by Sir Victor Horsley in 1886. These surgeries revolutionized modern neurology and neurosurgery (7,8).

Up to today, electrical stimulation of the human cortex remains the best experimental model for reproducing the effect of cortical activation by an epileptic discharge (9). During electrical cortical stimulation, only one or two electrodes are stimulated at a time. Specific and highly localizing epileptic auras—for example, visual, auditory, or psychic sensations—can often be reproduced. Objective clinical signs can be elicited, associated either with positive (e.g., clonic, tonic, dystonic, or myoclonic motor movements) or negative phenomena that can only be demonstrated by testing (e.g., the inability to initiate movements or maintain limb posture, or interruption of speech function). The occurrence of auras, simple motor movements, or speech arrest without loss of consciousness indicates a relatively restricted cortical activation by the epileptic discharge and at the same time a modular representation of that function in the human brain. In contrast, loss of memory or awareness requires the inactivation of functional networks, and usually cannot be reproduced with circumscribed electrical cortical stimulation. Focal clinical seizures spreading out from the site of the initial epileptic discharge will invariably produce an alteration of consciousness with sufficient spatial involvement. For example, in patients with decreased level of awareness, the fact that the patient may not speak indicates only the more widespread cerebral dysfunction and extended ictal spread rather than providing localizing information of a selective inactivation of language cortex. In contrast, speech impairment in an alert person provides reliable localizing information suggesting a specific involvement of language cortex.

Seizure semiology is the result of the effect of an epileptic discharge on an eloquent area of the cortex, producing either a subjective symptom or an objective phenomenon that can be observed or elicited by testing. The area of the cortex producing symptoms when activated during an epileptic seizure is what we know as the *symptomatogenic zone*. The symptomatogenic zone is not necessarily the area responsible for the genesis of the seizures—that is, seizures may spread from the epileptogenic zone into the symptomatogenic zone. A convergence of several independent studies—seizure semiology, interictal EEG or MEG and ictal EEG findings, lesion on MRI, hypometabolism on FDG-PET—all contribute to the reliable delineation of the

epileptogenic zone, the area of cortex that is indispensable for the generation of the epileptic seizures(10).

APPROACH TO SEIZURE SEMIOLOGY

Rationale for a Semiological Approach

Video analysis during continuous EEG monitoring is able to verify the seizure description provided by the patient and witnesses. An accurate account of the various seizure types is central to answering the following cardinal questions of any diagnostic or presurgical video EEG evaluation:

- What types of seizures does the patient experience?
- Are these seizures epileptic, nonepileptic or possibly both?
- What is the best treatment? (medical, surgical)

Adequate testing during seizures is necessary (a) to determine the level of awareness (usually accomplished by evaluating verbal and nonverbal responsiveness) and (b) to evaluate memory function (see sample seizure interview included in this chapter). Testing is also mandatory to (c) explore subjective symptoms (e.g., presence and duration of an aura) and (d) to elicit objective signs (e.g., Todd's paralysis, ictal and postical speech impairment) during the seizure interview and/or immediately postictal to allow subsequent review of the recorded video EEG data and assessment. The patient should be in focus of the camera. Covering the patient with blankets or sheets should be avoided as much as possible. Sound recording should be optimized. Continuous audible narration during the seizure examination by the nurses or EEG technologists is critical to document not only subjective symptoms but also subtle clinical signs (e.g., myoclonic twitching, eye blinks or eye deviation, goose bumps) that can otherwise be missed because of insufficient video resolution.

Careful and detailed observation and analysis of the temporal correlation between clinical seizure semiology and EEG are necessary for accurate diagnosis. Prolonged alteration of awareness usually indicates widespread cortical dysfunction that is almost invariably associated with a significant alteration of the EEG background activity. The absence of surface EEG alterations and the persistence of alpha background activity in a patient with prolonged unresponsiveness during testing is usually sufficient to confidently make a diagnosis of nonepileptic seizures, whereas a normal EEG during an aura or simple motor phenomenon is not sufficient to exclude an epileptic etiology. On the other hand, preservation of responsiveness in a patient with bilateral asymmetric tonic posturing may strongly suggest an epileptic seizure from the supplementary sensorimotor cortex even in the absence of electrographic seizure activity. Therefore, EEG interpretation in isolation is not sufficient to fully assess the patient's seizure events. A good understanding of clinical semiology and its temporal correlation with EEG findings is necessary to properly classify events.

Epileptic seizures are by nature stereotyped events with variable phenotypic expression related to variation in the spread pattern and "strength" of the ictal discharge between individual seizures. The seizure description should capture the cardinal features and include all the available localizing or lateralizing information. While describing the clinical phenomena, "splitting" is necessary to describe the characteristic phases of clinical seizure evolution as well as the variability between separate events and to discriminate between seizures which may arise from multiple foci or may have different etiologies; on the other hand, "lumping" is necessary to condense the information, compare seizure types, and reach a meaningful clinical conclusion which can be easily communicated.

The semiological description of seizures requires a terminology that is simple, clearly defined, and consistent. A universal terminology and classification system is necessary to categorize seizure subtypes, to allow comparison of recorded and reported events, and to validate information with other test results (e.g., EEG findings). A classification system should facilitate clinical work and research protocols and allow communication of findings within the scientific community. In addition, the system should be applicable for various age groups and special situations (e.g., monitoring in the intensive care unit (ICU)). The International League against Epilepsy (ILAE) has published a glossary of the descriptive terminology of ictal semiology, adapted from the Semiological Seizure Classification (SSC) that has been developed in Cleveland over the last two decades (11–13). The SSC has been used in several major international epilepsy centers and provides a concise, informative classification with practical usefulness in long-term epilepsy monitoring as well as in the outpatient and general inpatient and outpatient setting (14–16).

Principles of the Semiological Seizure Classification

The semiological seizure classification (SSC) has been described in detail previously (see Table 9-1) (12,14,17,18). The SSC is based exclusively on clinical ictal manifestations, as described by witnesses and patients or documented during video monitoring. EEG findings and the results of other laboratory tests are not part of the seizure classification system and allows the independent description of the patient's symptoms without the need to make an assumption of the underlying epileptogenic zone or EEG findings.

Ictal symptoms can be sensory, motor, autonomic, or affect cognition, and are therefore divided into seizures affecting the sensorial, motor, autonomic, or cognitive sphere. Seizures affecting the sensorial sphere produce

TABLE 9-1. SEMIOLOGICAL SEIZURE CLASSIFICATION

	Type	Characteristic		Somatotopic modifier *
Epileptic Seizure	Aura	Somatosensory		Yes
		Visual		Yes
		Auditory		Yes
		Olfactory		
		Gustatory		
		Epigastric		
		Cephalic		
		Autonomic		
		Psychic		
		Unclassified		
	Autonomic Sz			Yes
	Dyscognitive Sz	Dialeptic Sz	Typical Dialeptic Sz	
		Delirious Sz		
		Aphasic Sz		
		Unclassified dyscognitive Sz		
	Motor Sz **	Simple Motor Sz	Myoclonic Sz	Yes
			Clonic Sz	Yes
			Tonic Sz	Yes
			Tonic-clonic Sz	Yes
			Versive Sz	Yes
			Epileptic Nystagmus	Yes
			Epileptic spasm	Yes
			Unclassified Simple Motor Sz	
		Complex Motor Sz	Hypermotor Sz	
			Automotor Sz	
			Gelastic Sz	
			Unclassifed Complex Motor Sz	
	Special Sz **		Atonic Sz	
			Astatic Sz	
			Hypokinetic Sz	
			Akinetic Sz	Yes
	Unclassified Epileptic Sz **			
Paroxysmal event	Non-epileptic Sz	Nonepileptic psychogenic Sz		Descriptive Comment
		Nonepileptic physiologic Sz	Syncope	
		Unclassified non-epileptic Sz		
	Epileptic Sz	*Classified as above*		

* Somatotopic Modifier: Generalized/Axial/Bilaterally asymmetric/Unilateral: left/right - eye/face/throat/arm/leg/hemibody, etc.
** Specify in brackets if loss of consciousness (LOC) present

no objective signs. These seizures are designated as *auras*, in accordance with classical terminology. Seizures with predominantly motor phenomena are classified as *motor seizures*. Seizures consisting primarily of autonomic symptoms are considered autonomic auras if the patient is aware of the autonomic disturbance but no objective signs have been documented, and are termed *autonomic seizures* when there is objective evidence of the autonomic disturbance (e.g., heart rate changes on cardiac monitoring or visible goosebumps on the skin). Seizures in which the predominant ictal manifestation is a cognitive impairment are classified as *dyscognitive seizures*. In the semiological seizure classification we distinguish three types of dyscognitive seizures: dialeptic seizures, delirious seizures and aphasic seizures. Seizures in which the patient is unresponsive during the seizure, is amnestic of the seizure and remains relatively quiet during the event are classified as "dialeptic" seizures. The word "dialeptic" is derived from the Greek *dialeipein*, meaning "to stand still," "to interrupt," or "to pass out." *Dialeptic seizures* can occur in patients with generalized

epilepsies ("absence seizures") but also in patients with focal epilepsies ("complex partial seizures"). These two types of seizures may have identical semiological characteristics and can sometimes only be differentiated by recording of an ictal EEG. The term "typical dialeptic" seizure may be used for patients where seizure duration, provocation, or a typical 3Hz eye flutter allows a clear clinical distinction as a generalized seizure type. *Delirious seizures* are also characterized by relative unresponsiveness and amnesia for the event but are associated with agitation and confusion, visual or auditory hallucinations. The term *aphasic seizure* is used for responsive patients with an isolated speech impairment during the event. These patients remember details of the ictal speech impairment. *Motor seizure* can be divided into simple and complex motor seizures. *Simple motor seizures* describe classical neurological movements seen in association with seizure, for example, clonic, tonic or myoclonic movements. *Complex motor seizures* imitate voluntary movements and can involve either proximal extremities (hypermotor seizures) or distal segments (mouth, hands) in which case they are labeled as automotor seizures. Stereotypic epileptic laughter, so-called gelastic automatisms, justifies a special classification given that they are frequently seen in patients with hypothalamic hamartomas. Seizures characterized by mainly "negative" motor signs (atonia, akinesia, hypomotor signs, and negative myoclonus) are classified as "special seizures." They are separated from motor seizures to avoid labeling an event as a motor seizure when the patient is in fact "not moving."

Seizures frequently involve clinical manifestations from two or more spheres, but in the SSC they are classified by the most prominent feature. For example, seizures with loss of awareness and prominent oral automatisms are classified as automotor seizures (a subtype of the motor seizure category); on the other hand, seizures with similar loss of awareness but only minor eye blinking are termed dialeptic seizures. The term *paroxysmal event* is reserved for episodic events that are thought to be nonepileptic based on their semiological features (such as syncope, migraine, and psychogenic nonepileptic seizures) or events that cannot be confidently classified based on the available information (e.g., limited history, no witness report, poor video quality, insufficient testing).

Seizure Semiology in Special Populations

Infants

Clinical ictal features in infants consist of a limited behavioral repertoire (19–21). Simple (clonic, tonic, myoclonic, versive, clonic-tonic) and more complex (hypermotor, epileptic spasm) positive motor phenomena are noted as well as predominant negative (atonic, hypomotor) features. Epileptic spasms and tonic, clonic, and hypomotor seizures account for more than 80% of seizures in the first 3 years of life, whereas auras, generalized tonic-clonic seizures and automotor seizures do not occur in infants. Pure autonomic seizures are very rare, similar to the adult population. That is, apnea or bradycardia in infants are in general clinically associated with tonic seizures or represent otherwise nonepileptic events (22).

Ictal semiology in infants can be classified using the general SSC extended by two terms which we introduced for this age group. *Epileptic spasms* are frequent during the first 2 years of life, but are rarely seen outside infancy (19). Sudden behavioral arrest occasionally associated with staring is a common clinical feature of seizures in adults and children. In adults, it is often associated with a loss or alteration of consciousness (dialeptic seizure). However, testing for alteration of consciousness is usually not possible in newborns, infants, or severely cognitively-impaired individuals, and the term *hypomotor seizure* is reserved for those individuals in whom testing is not feasible (17,21). In adults, appropriate testing should allow categorization of the behavioral arrest and staring as one of (a) mainly an alteration of consciousness (dialeptic seizure), (b) mainly a negative motor phenomenon with preserved consciousness (e.g., akinetic seizure), or (c) an arrest of activity due to distraction, for example, in reaction to a stunning subjective sensation (e.g., a psychic aura of fear or déjà vu).

Elderly

Seizure semiology may change with disease duration (23). In general, the overall seizure semiology in elderly patients does not differ from that seen in younger patients (24,25). Difficulties in diagnosing epilepsy in the elderly are therefore not related to an atypical semiology, but rather attributable to a variety of other factors (26,27). Patients are often unaware of the seizures, and the events may go unwitnessed for a long time. Unexplained falls may be attributed to other medical or orthopedic problems (28–30). Several conditions common in the elderly may mimic epilepsy, including cardiovascular disease, migraine, drug effects, infection, metabolic disturbances, and sleep and psychiatric disorders. Physicians seem to neglect the rising prevalence of epilepsy in this age group (31). In the past, the number of patients with epilepsy older than 60 years admitted for diagnostic video EEG monitoring has been disproportionately low, but a higher awareness of the increased incidence of epilepsy in the elderly and a number of reports demonstrating the value and relatively high yield of video EEG monitoring will likely change this situation (32–37).

Status Epilepticus

The presence of prolonged seizures has been well recognized as a life-threatening condition with a high mortality. A semiological description and classification of status

epilepticus is a useful tool for the purposes of diagnosis, research, and treatment. We recently proposed a semiological classification of status epilepticus (SCSE; see Table 9-2) (38). This classification reflects the assumption that there are as many types of status epilepticus as there are types of epileptic seizures, and relies on the same principles as the semiological seizure classification, focusing on the main clinical manifestations and the evolution of the status episode. The main categories of the classification comprise aura status, autonomic status, dyscognitive status, and motor status.

TABLE 9-2. SEMIOLOGICAL CLASSIFICATION OF STATUS EPILEPTICUS (SCSE)

Epileptic status
Aura status
Somatosensory aura status
Visual aura status
Auditory aura status
Olfactory aura status
Gustatory aura status
Autonomic aura status
Abdominal aura status
Psychic aura status
Unclassified aura status
Autonomic status
Dyscognitive status
Dialeptic status
Delirious status
Aphasic status
Dyscognitive status
Motor status
Simple motor status
Myoclonic status
Clonic status
Tonic status
Epileptic spasm status
Tonic-clonic status
Versive status
Epileptic nystagmus status
Unclassified simple motor status
Complex motor status
Automotor status
Hypermotor status
Gelastic status
Unclassified complex motor status
Special status
Atonic status
Hypomotor status
Negative myoclonic status
Astatic status
Akinetic status
Unclassified special status
Unclassified epileptic status
Paroxysmal event status
Non-epileptic status
Epileptic status (classified as above)

Each of the main categories has subgroups and an attempt should be made to be as specific as possible. For example, if the clinical history or video analysis allows, motor status should be further classified as simple motor or complex motor status, according to the semiological characteristics of the movements. Following the same method, complex motor status can be further subclassified as automotor, hypermotor, or gelastic according to semiological analysis. As mentioned above, for practical purposes, in the SCSE, we distinguish only three subtypes of dyscognitive status epilepticus according to the predominant clinical feature: (a) dialeptic, (b) delirious, and (c) aphasic status. Status episodes that cannot be clearly assigned to one of the categories below should simply be identified as "dyscognitive status." The term "dialeptic," already part of the SSC, refers to the symptomatology—that is, unresponsiveness—independent from the associated ictal EEG seizure pattern. *Delirious status* describes prolonged or repeated ictal episodes of confusion, emotional alteration, disordered thinking with psychotic connotations, and agitated behavior. *Aphasic status* refers to prolonged or repeated disturbances of speaking or understanding language, without evidence of dysfunction of primary motor or sensory pathways or consciousness; this is presumably caused by epileptic interference of cortical language areas.

The semiology of patients with dyscognitive status epilepticus is variable and an EEG is indispensable to first establish that the obtundation or confusion is produced by electrographic seizures and then to define if the underlying epilepsy is focal (so-called "complex partial status") or generalized (so-called "absence status") (39–41). A 3-Hz eye flutter has been observed on rare occasions but is usually a good indicator of an underlying generalized epilepsy (42). Aphasic status epilepticus and delirious status epilepticus with psychotic symptoms or fugue-like states may be more frequently seen in patients with focal epilepsies (43–45).

Patients with status epilepticus present with two different clinical scenarios (42,45,46). They may be admitted for overt and prolonged clinical seizure activity (motor status epilepticus). These patients represent a medical emergency, as continuous convulsive activity is known to be associated with life-threatening metabolic and cardio-respiratory complications. However, a significant number of patients present with nonepileptic convulsive "pseudostatus" and are often prematurely intubated and sedated before a correct clinical diagnosis is made. The diagnosis of nonepileptic psychogenic status requires a detailed history with an accurate seizure description (preferably from direct observation by a physician). Unfortunately, the wrong diagnosis of epilepsy in a patient with "pseudostatus" is often difficult to be undone and may require subsequent video EEG recording of the typical events once the patient recovered from sedation and muscle relaxation.

The second scenario includes patients with so-called nonconvulsive or "subtle" status epilepticus. Patients may

present to the outpatient clinic or emergency room with "dialeptic status" consisting of relative unresponsiveness combined with amnesia for ictal events and often decreased motility due to continuous seizure activity. Patients in the emergency room or ICU who initially presented with motor status epilepticus are at highest risk to develop subsequent electrographic status epilepticus (47). Recent reports claim that the percentage of patients with electrographic seizures without associated motor phenomena may be as high as 90% (48–51). In some patients, subtle clinical events (clonic twitching of the tongue, face, eyes, or extremities), which are highly indicative of clinical seizure activity, are detectable during bedside inspection or optimally focused, high resolution video recording (51).

Patients with no history of motor status but evidence of an underlying condition that is able to produce coma or stupor by itself may show electrographic seizure activity on EEG. Typical etiologies include diffuse brain anoxia, severe head trauma, intracerebral or subarachnoic hemorrhage. It is often difficult to decide if the stupor or coma is due to the underlying brain insult, the intoxication from aggressive antiepileptic drug management, the electrographic seizure activity or a mixture of these conditions. A variety of clinical events in the ICU that are of concern for the primary service turn out to be non-epileptic. Video recording combined with continuous EEG may be able to capture these events and prevent unnecessary interventions.

Non-epileptic Seizures

In the SSC, seizure-like events which cannot be defined by the physician if they are epileptic or not, are classified as paroxysmal events. These paroxysmal events can be further subclassified into epileptic seizures or non-epileptic paroxysmal events when more information becomes available (witness report, video monitoring). Non-epileptic paroxysmal events are classified into non-epileptic psychogenic seizures and non-epileptic physiologic seizures (e.g., syncope) (52–55). The characteristics of these events can be described in detail in the body of the video EEG report.

The SSC does not provide a terminology to subclassify paroxysmal events, but it is practical to add a comment after classifying seizures as paroxysmal events. The comment can indicate either the main differential consideration (e.g., syncope) or the predominant feature of the psychogenic NES. This can be done using the patient's own terminology or by summarizing the cardinal features.

Patients with non-epileptic psychogenic seizures often have multiple seizure types. It is useful to group the patient's reported events into broad categories for two reasons: (a) it assures that coexisting epileptic seizures are not overlooked, and (b) it provides a road map for subsequent video EEG monitoring. Three major subtypes of psychogenic NES have been described based on cluster analysis: (a) catatonic behavior, (b) minor motor movements, and (c) major motor movements (53–55). Semiological features inconsistent with cortical epileptic phenomena or other features characteristic of psychogenic NES (e.g., ictal weeping) should be mentioned in the video EEG analysis (54–58). Behaviors inconsistent or rarely seen with epileptic seizures, but frequently encountered during non-epileptic seizures include the following:

1. Tremor
2. Pelvic thrusting
3. Bilateral, often alternating clonic (but not tonic) movements of the extremities despite preserved consciousness
4. Forced eye closure
5. Ictal stuttering
6. Motor activity interrupted by distraction or passive movement

SEMIOLOGICAL SEIZURE CLASSIFICATION

Evolution of Clinical Symptoms

Most seizures consist of symptoms that evolve as the seizure discharge spreads to adjacent cortical areas. In the SSC, this evolution is indicated by considering each one of the seizure types described above also as a individual component of a seizure. Any given seizure can consist of one or more of these components, which are listed in order of appearance and are linked by arrows (18), as in the following examples:

- Left hemifield visual aura → left hand clonic seizure → generalized tonic-clonic seizure
- Abdominal aura → automotor seizure → left hemibody clonic seizure
- Generalized myoclonic seizure → generalized tonic-clonic seizure
- Typical dialeptic seizure → generalized tonic-clonic seizure

Seizure Components

Aura

Auras consist exclusively of subjective symptoms and usually occur at the beginning of a seizure. In general, they are brief, lasting seconds, and only rarely may persist for minutes. They may occur in isolation from any other ictal symptoms, and, if so, tend to last slightly longer. The epileptic nature of aura-like symptoms can be documented objectively only if the aura evolves into a dialeptic or motor seizure or if EEG monitoring demonstrates an EEG seizure pattern during the aura.

In the SSC, auras are subdivided into the following subgroups:

Somatosensory auras consist of abnormal somatic sensations. The term should be limited for sensations involving clearly defined somatosensory regions of the body that are unilaterally represented in the primary sensory cortex or bilateral during activation of the secondary sensory areas or the supplementary sensorimotor area. This term is not meant to encompass vague, poorly localized sensations.

Visual auras consist of visual hallucinations or illusions as the predominant feature of the aura. The images consist of simple sparks of light of different colors that are moving or stationary in one or more quadrants of the visual field. Not infrequently, the patient sees the flashing lights in the middle of the visual field with no clear lateralization. Complex visual symptoms can be part of a multisensorial experience with an overwhelming sense of familiarity or another strong emotional component; in this case, they should be classified as psychic auras (see below). This category also does not include poorly defined alterations of vision, such as "blurred" vision.

Auditory auras are isolated simple auditory hallucinations or illusions, like simple sounds or alteration of sounds. The patient often finds the sounds difficult to localize in his or her surrounding. If auditory symptoms are complex (hearing music or somebody talking) and accompanied by multisensorial hallucinations or illusions, they should be classified as auditory auras only if the auditory symptoms are relatively simple and clearly the predominant feature of the aura. Otherwise, the symptoms are classified as psychic auras.

Olfactory auras and *gustatory auras* are abnormal sensations of smell or taste, respectively. As with visual and auditory auras, they may be accompanied by other complex alterations of perception; such complex experiential auras should be classified as psychic auras unless the olfactory or gustatory component is clearly the predominant feature. The smells are often perceived as unpleasant and described as "rubbery" or burning.

Autonomic auras are sensations such as palpitations, sweating, and hot flashes, for which no objective evidence of an actual autonomic alteration has been documented.

Psychic auras consist of complex multisensorial hallucinations and illusions involving alterations in the perception of familiarity with a situation, such as sensations of déjà vu or jamais vu, or alterations of emotion, such as the isolated sensation of fear. Psychic auras frequently involve complex visual, auditory, olfactory, and gustatory sensations. These auras have been originally labeled as experiential auras by Penfield.

Abdominal auras are isolated abnormal abdominal sensations, commonly observed in seizures of temporal lobe onset. The sensation is often described as "rising" and may be accompanied by nausea or by "flipping" of the stomach. These abdominal auras may be the result of either increased abdominal peristalsis—an autonomic ictal sign—or activation of sensory cortical areas representing the abdominal viscera. Regardless of the exact pathogenesis, abdominal auras are frequently associated with temporal lobe epilepsy, and therefore deserve to be classified independently from autonomic auras.

Autonomic Seizures

Autonomic seizures consist of alterations of autonomic function elicited by activation of autonomic cortical areas. To classify a spell as an autonomic seizure, there must be documentation of autonomic signs using appropriate monitoring of blood pressure, heart rate, and so on, and/or direct observation. These seizures are rare because autonomic changes (e.g., ictal tachycardia) accompanying epileptic seizures are usually overshadowed by other signs and symptoms and are not classified. In addition, documented episodes of autonomic dysfunction may be clinically silent (i.e., the event associated with an electrographic seizure pattern may only be detected by a monitor, without the patient experiencing any symptoms).

Dyscognitive Seizures

Seizures in which impairment of cognition is the predominant ictal manifestation are classified as *dyscognitive seizures*. In the semiological seizure classification we distinguish three types of dyscognitive seizures: dialeptic seizures, delirious seizures, and aphasic seizures.

Dialeptic seizures are characterized predominantly by alteration of responsiveness, amnesia for the ictal events, and relative decrease of motility. Dialeptic seizures occur in patients with both generalized and focal epilepsy. An example of the latter is the motionless, unresponsive stare in patients with temporal lobe epilepsy. We use the term *typical dialeptic seizure* for events consisting of brief (>5–20 seconds) episodes of altered responsiveness and "blank staring" that begin and end abruptly, and are most frequently seen in patients with absence epilepsy. These seizures may be associated with 3-Hz eye blinking.

Delirious seizures are also characterized by relative unresponsiveness and amnesia for the event, but combined with agitation and confusion, and visual or auditory hallucinations.

Aphasic seizures are characterized by an inability to speak and/or understand written or spoken language with preserved memory at least for part of the aphasia and preserved non-verbal responsiveness during the ictus. They are generated by inactivation of cortical language areas by the epileptiform discharge with a high localizing value and should not be confused with the arrest of speech in dialeptic seizures often indicating a diffuse cortical dysfunction.

Motor Seizures

Motor seizures are divided into simple and complex seizure types. *Simple motor seizures* involve movements

that are relatively "simple," unnatural, and similar to movements elicited by cortical stimulation of the primary motor areas (Brodmann areas 4 and 6). *Complex motor seizures* involve movements that are more elaborate or relatively "complex" and simulate natural movements, though inappropriate for the situation. Unlike the ILAE classification system that subdivides partial seizures into simple and complex partial seizures depending whether consciousness is preserved or not during the event, in the SSC, the terms simple or complex do not refer to preservation or alteration of consciousness.

SIMPLE MOTOR SEIZURES

Simple motor seizures are further subdivided into the following subgroups:

Myoclonic seizures consist of brief, isolated muscle contractions usually lasting less than 200 milliseconds. When they occur repetitively, they are nonrhythmical and/or affect different muscle groups independently (multiregional myoclonus). Myoclonic seizures result from activation of the primary motor area, although generalized myoclonic seizures may result from activation of subcortical brainstem reticular activation systems.

Tonic seizures consist of sustained muscle contractions, usually lasting more than 3 seconds. They are primarily generated by activation of Brodmann area 6 and particularly its mesial frontal region, namely the supplementary sensorimotor area. Generalized tonic seizures may also be generated by direct stimulation of brainstem reticular activation systems.

Epileptic spasms consist of sustained muscle contractions of axial muscles, frequently occurring in clusters. The duration of the epileptic spasms is variable and in a given cluster it is not unusual to observe a mixture of short, myoclonic movements and longer, more sustained tonic epileptic spasms. They typically involve flexion of the trunk and abduction and elevation of both arms ("salaam" position).

Clonic seizures affect specific body parts and result from cortical activation of the primary motor cortex. Any part of the motor strip can be affected, but it is most common to see involvement of the hands and face, reflecting the larger representation of those regions in the motor homunculus.

Tonic-clonic seizures are characterized by an initial tonic posturing of upper and lower extremities, with adduction and extension of the elbows and knees and ankles. The wrists are in flexion. Infrequently flexion at the elbows may also be observed. Tonic-clonic seizures are either generalized or bilateral asymmetric. The tonic posturing evolves gradually into a clonic phase with flexion of both elbows and rhythmic brief jerks of increasing amplitude and decreasing frequency.

Versive seizures are characterized by sustained and extreme deviation of the eyes and head to one side. The lateral movement of the eyes frequently consists of small ("stepwise") saccades superimposed on a smooth tonic lateral deviation of the eyes to an extreme position. Version of the body similarly consists of small clonic lateral movements superimposed on a forced, smooth lateral movement of the head or body. During head version, the chin frequently moves laterally and upward. In extreme cases of version, the body may complete a 360-degree turn. Versive movements should be differentiated from nonsustained lateral eye and head turning, which often is misinterpreted as lateralizing information. True versive seizures, in contrast, are a valuable localizing sign, particularly when they occur immediately prior to a generalized tonic-clonic seizure. The symptomatogenic zone for head and eye version is the frontal eye field, located in the primary motor area at the junction of the precentral and superior frontal sulci.

Epileptic nystagmus consist of lateral eye movements with a slow movement to the side followed by a fast movement to the opposite side that brings the eye back towards its original position. This movement repeats many times ("nystagmus"). The term epileptic nystagmus is used when no version of the head or body is present.

COMPLEX MOTOR SEIZURES

Complex motor seizures are subdivided into the following categories:

Automotor seizures consist of automatisms involving the distal segments of the body, particularly the hands, fingers, feet, mouth, and tongue. These seizures are usually associated with diminished responsiveness and amnesia for the event. However, in seizures originating from the nondominant hemisphere, responsiveness may be partially or completely preserved. These seizures are most frequently seen in association with temporal lobe epilepsies. The symptomatogenic zone for automatisms is not clearly defined.

Hypermotor seizures consist of elaborate movements sometimes accompanied by loud vocalizations that involve the proximal limbs and trunk, and at times appear violent. These complex movements resemble natural movements but are inappropriate for the situation and serve no purpose. The movements are often repetitive, (for exemple, bicycling motion) and may represent automatisms (coordinated, adapted, and involuntary movements). During hypermotor seizures, responsiveness is usually altered and the patients are amnestic of the episodes. These seizures most frequently are produced by stimulation of frontal or cingulate cortex.

Gelastic seizures consist of laughing as the essential ictal manifestation. The laughing tends to be stereotyped, unnatural or mechanical, and inappropriate for the situation. These seizures are classified separately because of the common association of gelastic seizures with hypothalamic

hamartomas, although they can be also seen in patients with frontal and temporal lobe epilepsy.

SPECIAL SEIZURES

Seizures characterized by mainly "negative" motor signs (atonia, akinesia, hypomotor signs, and negative myoclonus) are classified as "special seizures."

Negative myoclonic seizures consist of brief episodes of muscle atonia, often resulting in a brief, sudden movement resembling a myoclonic jerk. Unlike myoclonic jerks, however, this movement is caused by a brief interruption of tonic muscle activity if recorded with an EMG electrode, and not by the burst of muscle potentials characteristic of myoclonic seizures. Negative myoclonic seizures only manifest clinically when the patient is contracting, in a sustained fashion, the specific muscles involved in the intermittent atonia. These seizures are most likely the result of involvement of the primary sensorimotor area.

Hypomotor seizures are characterized by a decrease in or total absence of motor activity (behavioral arrest). This category is reserved for those patients in whom it is not possible to test consciousness during or after the seizure, such as newborns, infants, or severely cognitively impaired individuals.

Akinetic seizures are characterized by the inability to perform voluntary movements in the setting of preserved consciousness. Typically, the distal muscles are implicated, with little involvement of more proximal muscle tone. These seizures result from activation of the negative motor areas in the mesial and inferior frontal gyri.

Atonic seizures cause a loss of postural tone, often resulting in a fall if the patient is standing. Atonic seizures generally occur in patients with generalized epilepsy.

Astatic seizures are characterized by an epileptic fall for which the exact mechanism producing the fall is undetermined. Epileptic falls can be caused by tonic seizures, atonic seizures, and myoclonic jerks. In patients in whom it is impossible to determine clinically the exact etiology for a fall, "astatic" is a useful category. In many patients with diffuse brain damage and seizure related falls, an initial myoclonic jerk causes loss of balance and is followed immediately by a generalized atonia that suppresses any reflex movements, which in other seizure types may help to prevent injury from the fall. Patients with this sequence should be classified as generalized myoclonic seizure followed by a generalized atonic seizure.

Many of the seizure types listed above have a clearly defined somatotopic distribution of the corresponding signs or symptoms. The SSC uses somatotopic modifiers to characterize the seizures better and to define their origin more precisely (see Table 9-1)—for example, "left hand clonic seizure," "throat somatosensory aura," "left foot tonic seizure."

The SSC lists the seizure components in a sequential way and specifies the seizure component during which consciousness is lost by inserting the expression "LOC" in parenthesis. However, there is no need to insert the expression LOC if consciousness is by definition lost for that specific seizure type. For example, in dialeptic seizures and generalized tonic-clonic seizures, consciousness is always impaired.

Localizing and Lateralizing Signs

Most of the semiological features that have lateralizing and localizing value will occur at the onset of a seizure at a time when consciousness is still intact (e.g., auras, unilateral simple motor seizure). In the case of simple motor seizures, as the ictal discharge spreads (often in association with altered awareness), localizing value vanishes but lateralizing significance may still be present. The majority of localizing and lateralizing semiological features are part of the SSC and its somatotopic modifiers. For example, left hand somatosensory aura, left hemifield visual aura, autonomic aura (e.g., urinary urge), autonomic seizure (e.g., ipsilateral piloerection), or left head versive seizure.

Lateralizing signs not included in the SSC as part of a seizure component are listed in Table 9-3, and include the figure-of-four (or fencing) sign, unilateral dystonic posturing, automatisms with preserved responsiveness, ictal spitting or vomiting, asymmetric ending of the clonic phase of secondarily generalized tonic-clonic seizures, unilateral eye blinking, and ictal speech. There are also postictal lateralizing features, such as postictal aphasia, Todd's palsy, postictal hemianopia, and nose wiping that are not included in the SSC proper, but should be listed after classifying the ictal semiology (59).

Consider the following example: A patient has a psychic aura consisting of sudden fear, followed by an automotor seizure. During the automotor seizure, the patient has loss

TABLE 9-3. LATERALIZING SIGNS

Lateralizing signs	Lateralizes to the hemisphere
Motor	
Figure-of-four sign	Contralateral to the extended arm
Unilateral dystonic posturing	Contralateral to the posturing limb
Automatisms with preserved responsiveness	Nondominant
Last clonic jerk	Ipsilateral
Unilateral eye blinking	Ipsilateral
Language	
Ictal speech	Nondominant
Postictal features	
Postictal "palsy" (e.g., Todd's palsy, hemianopia)	Contralateral
Postictal nose wiping	Ipsilateral to the wiping limb

of consciousness and dystonic posturing of the right hand. This is followed by postictal aphasia. This seizure would be classified as follows:

Psychic aura → Automotor seizure (LOC)
Lateralizing signs: right arm dystonia, postictal aphasia

Localizing and lateralizing features are extremely useful in predicting the hemisphere and seizure-onset zone involved in the epileptic discharge. In this example, right hand dystonia lateralizes the seizure to the left hemisphere, and post ictal aphasia similarly suggests seizure onset in the dominant hemisphere (usually the left hemisphere).

EPILEPSY CLASSIFICATION

The classification of epilepsies into generalized and focal ("partial") dates back to the first ILAE epilepsy classification from 1970 (60, 61). Revisions of the ILAE classification have emphasized the presentation of epileptic seizures as "electroclinical complexes" that closely relate to or define "epileptic syndromes." The importance of semiological information (particularly in regard to focal seizures) was greatly diminished in the 1981 ILAE classification of epileptic seizures, but a description of ictal phenomenology has now been reintroduced in the 2001 proposal for a classification of epileptic syndromes. In this classification, the terms "simple" and "complex" partial seizures, referring to partial seizures with respectively preserved and altered consciousness, are no longer recommended (11,62–64). Unfortunately for the clinical practitioner, the classification of epileptic syndromes was more intended to represent a taxonomy of "the state of knowledge in a scientific field in a systematic order," rather than a diagnostic tool applicable for direct use in individual cases (65). In clinical practice this has led to considerable overlap, redundancy, and confusion (12,64,66–68).

A clinically useful approach to seizure and epilepsy classification primarily emphasizes seizures as an expression of cortical pathology of various etiologies affecting different locations of the brain (66). A detailed description of the ictal semiology is essential in any epilepsy classification because the ictal semiology is the cardinal symptomatology of the disorder, epilepsy, and is the main focus of our management of a patient with epilepsy. Besides, the semiological seizure type and the subdivision of the epileptogenic zone into focal or generalized are the main factors guiding us in our medication selection. A comprehensive, patient-oriented epilepsy classification following the approach outlined above has recently been proposed. This classification consists of five dimensions that present a concise summary of the essential information:

1. Lesion localization (based on the results of all available information, e.g., semiology, EEG, MRI, PET, genetic testing, etc.)
2. Clinical symptoms (according to the SSC)
3. Etiology
4. Seizure frequency
5. Related medical condition (if applicable)

The last (fifth) dimension allows information on important complementary findings in the history—for example, "head trauma with loss of consciousness 1996," "febrile convulsions," "family history of epilepsy," physical examination (e.g., "left hemiparesis"), and additional diagnostic tests the results of which are not already an integral part of the classification (e.g., "right centrotemporal, benign focal epileptiform discharges on EEG" in a patient with left temporal lobe epilepsy and left temporal sharp waves).

In the context of epilepsy, "lesion localization" represents not only the location but also the extent of the epileptogenic cortex capable of triggering epileptic seizures, which we define as the *epileptogenic zone*. With currently available technology, we can usually estimate the location and extend even if the exact epileptogenic zone can only be determined with certainty by epilepsy surgery when resection results in a seizure-free outcome (10). As mentioned above, the epileptogenic zone together with the seizure semiology is essential to determine which antiepileptic medication may be most effective but is also paramount to determine if the epilepsy may be amenable to surgical resection.

As an example case, consider a 33-year old patient with right temporal lobe epilepsy with a history of generalized tonic-clonic status epilepticus at the age of 1.5 years, followed by habitual seizures starting the same year. The patient describes an aura of a butterfly sensation in his stomach followed by loss of awareness. His mother reports that he becomes unresponsive and starts fumbling with both hands. This can last 1–2 minutes, and occasionally progresses into twitching of the left side of his face and body and sustained left-sided head- and eye-turning followed by stiffening of the arms and legs and then bilateral rhythmic jerking. The patient failed several antiepileptic drugs over the last three decades and continues to have two to four seizures a month. He developed bilateral gynecomastia as a side effect of carbamazepine and is considering cosmetic surgery.

The above description would produce the following patient-oriented epilepsy classification:

1. Epileptogenic zone: right temporal
2. Semiology: abdominal aura → automotor seizure (LOC) → left versive seizure → generalized tonic-clonic seizure
3. Etiology: unknown
4. Frequency: persistent (two to four per month)
5. Related medical information: status epilepticus as an infant; bilateral gynecomastia from carbamazepine

Subsequent testing revealed an MRI of the brain with right hippocampal atrophy on T1-weighted images and hyperintensity on fluid-attenuated inversion recovery

(FLAIR) sequences consistent with hippocampal sclerosis. Routine EEG showed right temporal sharp waves, and video EEG monitoring demonstrated right temporal EEG seizures associated with the patient's habitual clinical seizure semiology. During video review, four events were recorded, none of them preceded by an aura or push-button. The remainder of the semiology history was confirmed. Tonic extension of the left arm with flexion of the right arm (figure-of- sign) was seen following left head version before the generalized tonic-clonic convulsion. During testing, the patient was less responsive, but able to repeat the word "house" and identify objects (e.g., a pen). After the seizure ended, he did not remember the color given to him, or recognize the fact that he had a seizure.

This additional information would be incorporated into the epilepsy classification as follows:

1. Epileptogenic zone: right temporal
2. Semiology: (abdominal aura →) automotor seizure → left versive seizure → generalized tonic-clonic seizure. Lateralizing signs: Ictal speech, figure-of-4-sign
3. Etiology: right hippocampal sclerosis
4. Frequency: persistent (two to four per month)
5. Related medical information: status epilepticus as an infant; bilateral gynecomastia from carbamazepine

The five-dimensional, patient-oriented epilepsy classification approach shifts the emphasis from an epilepsy syndrome classification to a standard, neurological, patient-oriented approach, using independent criteria in each dimension. This is helpful in particular because ILAE syndromes are rare when applied in clinical practice, and can be identified in less than 20% of patients even at a tertiary epilepsy center (72,73). However, for those patients with an identifiable epilepsy syndrome, the information can be added to the classification.

The classification for a patient with juvenile absence epilepsy might appear as follows:

1. Epileptogenic zone: generalized (juvenile absence epilepsy)
2. Semiology: typical dialeptic seizure
3. Etiology: unknown (idiopathic)
4. Frequency: persistent
5. Related medical information: family history of epilepsy

The principle advantages of this approach have been outlined in detail: minimal redundant information, applicability to all patients, inclusion of all essential information, and independence from specific contemporary diagnostic tools (66,71).

SUMMARY

The use of video EEG monitoring has revolutionized modern epileptology. Video EEG monitoring now allows accurate seizure description using a semiological classification. A practical and patient-oriented epilepsy classification can reduce many of the ambiguities seen with prior classification systems, and supports clinical decision making by creating an accurate, complete representation of clinical information.

SEIZURE INTERVIEW

1. Give Patient a color: red or yellow or blue, etc.
2. Have Patient follow commands: raise your right arm, stick your tongue out, point to the door
3. Tell Patient: "Say the word HOUSE"
4. Show and have Patient name:
   What is this? What do you do with it? (Pen, watch, cup, telephone, etc.)
5. Ask: "What is your name?"
6. If Patient can talk, ask: "Can you describe what you are feeling?"; "Is it still going on?"; "Is it over?"
7. Describe what you observe—for example, clonic movements, head or eye deviation, posturing, or any other clinical signs

Do not obstruct the camera during the interview!

POSTSEIZURE QUESTIONS

1. When was your last seizure?
2. What just happened?
3. *If Patient admits he/she just had a seizure:* What makes you think you just had a seizure?
4. Did you feel anything particular before you had the seizure?
5. Do you remember the color given? *If "No," give three choices*
6. *Show objects and have Patient name each object and its function*
7. Is the seizure over?
8. Are you OK?
9. Where are you?
10. What day is it?
11. *Test for Todd's Paralysis—ask Patient to smile, hold up arms.*

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10

EPILEPSY SYNDROMES*

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Epilepsy syndromes are based on the nonrandom clustering of electroclinical findings in individuals with epilepsy. In contrast to diseases, epilepsy syndromes do not have a single well-defined etiology. In the epilepsy monitoring unit all epilepsy patients should receive a preliminary epilepsy syndrome diagnosis based on age at the onset of epilepsy, seizure types, neurological condition, family history, and other clinical data. Routine electroencephalography (EEG) is extremely helpful in syndrome classification, but video EEG monitoring is often necessary to reach a definitive syndrome diagnosis. Selecting an appropriate epilepsy syndrome will narrow down the choice of etiologies and guide the selection of special tests to confirm or exclude specific epileptic diseases. It will also usually allow the neurologist to predict the course of the disease and to estimate the probability of remission or seizure control with antiepileptic drugs. But even when a specific etiology has already been demonstrated, it is not prudent to omit a syndrome diagnosis. A good match between syndrome and etiology will put the diagnosis on solid ground, whereas a mismatch will prompt a review of the evaluation to explain the discrepancy. Syndrome diagnosis will also prevent the uncritical acceptance of an etiology based on radiological findings when, in fact, those findings and the patient's seizures are not causally related.

EPILEPSY SYNDROMES: AN OVERVIEW

Table 10-1 is a summary of adult and pediatric epilepsy syndromes that are currently recognized by the International League against Epilepsy (ILAE) and catalogued in the ILAE website: http://www.ilae-epilepsy.org/ctf/syn_frame.html (1–37). The list does not include epilepsy syndromes that are not yet recognized by the ILAE (38). It also excludes benign nonfamilial neonatal seizures, febrile seizures, and other disorders classified by the ILAE as "conditions with epileptic seizures that do not require a diagnosis of epilepsy" (39,40). We have retained the official ILAE name of most of the syndromes and adopted some of the names in the recent proposal of the ILAE Task Force on Classification (41). We have also assigned each syndrome a unique abbreviation, which we will use throughout the chapter instead of the full syndrome name. Thus, the reader might need to refer to this table from time to time. In keeping with the recommendations of the ILAE Task Force on Classification, we will treat LKS as a subtype of ECSWS, not as a separate syndrome (41). The other differences between the ILAE list and our list are mainly the result of our more liberal notion of a syndrome. Thus, we listed MTLE, LTLE, FLE, OLE, and PLE as separate syndromes even if these entities were listed by the ILAE as "MTLE with hippocampal sclerosis," "MTLE defined by specific etiologies," and "neocortical epilepsies: other types defined by location and etiology." Although common names are still used for BFNS, ADNFLE, FTLE, and FFEVF, these syndromes will probably be expanded and renamed in the future to accommodate nonfamilial and sporadic forms in the same way that "benign familial infantile seizures" was renamed to BFNIS. We are aware of the endless controversy of syndrome classification, but some organization is necessary in discussing epilepsy syndromes (42). Therefore, we divided the syndromes into five groups: encephalopathic epilepsies, idiopathic generalized epilepsies, idiopathic focal epilepsies, symptomatic focal epilepsies, and reflex epilepsies.

There are already many publications that describe each epilepsy syndrome in detail, and it is not our intention to discuss them individually. For a detailed discus-

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TABLE 10-1. EPILEPSY SYNDROMES. The syndromes are classified into six groups. The official ILAE name is retained for most syndromes, but modified for some. Each epilepsy syndrome is assigned a unique abbreviation (column next to syndrome). These abbreviations are used instead of the full syndrome names throughout this chapter. The reference number corresponds to the main reference for the syndrome (see reference list).

Encephalopathic Epilepsies		
Early myoclonic encephalopathy	EME	Ref. 1
Ohtahara syndrome	OS	Ref. 2
West syndrome	WS	Ref. 3
Lennox-Gastaut syndrome	LGS	Ref. 4
Epilepsy with continuous spike-waves during sleep[a]	ECSWS	Refs. 5, 6
Migrating focal seizures of infancy[b,e]	MFSI	Ref. 7
Dravet syndrome[c]	DS	Ref. 8
Myoclonic encephalopathy in nonprogressive disorders[d,e]	MEND	Ref. 9
Progressive myoclonus epilepsies	PME	Ref. 10
Idiopathic Generalized Epilepsies		
Benign myoclonic epilepsy of infancy	BMEI	Ref. 11
Childhood absence epilepsy	CAE	Ref. 12
Juvenile absence epilepsy	JAE	Ref. 13
Juvenile myoclonic epilepsy	JME	Ref. 14
Epilepsy with generalized tonic-clonic seizures only[f]	EGTCS	Ref. 15
Generalized epilepsy with febrile seizures plus	GEFS+	Ref. 16
Epilepsy with myoclonic absences	EMA	Ref. 17
Epilepsy with myoclonic astatic seizures[g]	EMAS	Ref. 18
Idiopathic Focal Epilepsies		
Benign familial neonatal seizures	BFNS	Ref. 19
Benign familial and nonfamilial infantile seizures	BFNIS	Ref. 20
Benign childhood epilepsy with centrotemporal spikes	BCECTS	Ref. 21
Benign childhood epilepsy with occipital spikes—Panayiotopoulos type	BCEOS-1	Ref. 22
Benign childhood epilepsy with occipital spikes—Gastaut type	BCEOS-2	Ref. 23
Autosomal-dominant nocturnal frontal lobe epilepsy	ADNFLE	Ref. 24
Familial temporal lobe epilepsies[h]	FTLE	Ref. 25
Familial focal epilepsy with variable foci	FFEVF	Ref. 26
Symptomatic Focal Epilepsies		
Mesial temporal lobe epilepsy[i]	MTLE	Ref. 27
Lateral temporal lobe epilepsies[i]	LTLE	Ref. 28
Frontal lobe epilepsies[i]	FLE	Ref. 29
Parietal lobe epilepsies[i]	PLE	Ref. 30
Occipital lobe epilepsies[i]	OLE	Ref. 31
Hemiconvulsion hemiplegia and epilepsy syndrome	HHE	Ref. 32
Rasmussen syndrome	RS	Ref. 33
Reflex Epilepsies		
Idiopathic photosensitive occipital lobe epilepsy	IPOLE	Ref. 34
Visual pattern–sensitive epilepsy	VPSE	Ref. 35
Primary reading epilepsy	PRE	Ref. 36
Epilepsy with startle-induced seizures	ESIS	Ref. 37

a. ECSWS includes Landau-Kleffner syndrome (LKS) and the non-LKS type of ECSWS.
b. MFSI is used here instead of "migrating partial seizures of infancy" (MPSI).
c. DS was originally known as "severe myoclonic epilepsy of infancy" (SMEI).
d. MEND is used here instead of "myoclonic status in nonprogressive disorders" (MSNE).
e. MFSI and MEND are considered as "syndromes in development" by the ILAE.
f. EGTCS includes the syndrome of "grand mal on awakening" (GMA).
g. EMAS is also known as "myoclonic-astatic epilepsy" (MAE) or "Doose syndrome."
h. The two types of FTLE, mesial FTLE and lateral FTLE, are most likely separate syndromes.
i. These syndromes are listed by the ILAE as "MTLE with hippocampal sclerosis," "MTLE defined by specific etiologies," and "neocortical epilepsies: other types defined by location and etiology."

sion of epilepsy syndromes, we recommend the ILAE Web site: http://www.ilae-epilepsy.org/Visitors/Centre/ctf/syndromes.cfm (1–37), and the following textbooks: *Epilepsy: A Comprehensive Textbook,* second edition (2007), by Engel, Pedley, Aicardi, Dichter, and Moshé; and *The Treatment of Epilepsy: Principles and Practice*, fourth edition (2006), by Wyllie, Gupta, and Lachhwani. The appendix at the end of this chapter gives an outline of the most important features of the epilepsy syndromes. The following features are listed for each syndrome: seizure types; ictal and interictal

EEG features; activating effects of sleep, photic stimulation, hyperventilation, and other factors; course and evolution; and common etiological factors. The appendix is intended to complement the text, so the reader might find it useful to glance through it from time to time.

The next section deals with the *clinical diagnosis* of epilepsy syndromes based on age at presentation, seizure types, and other clinical features. With these clinical data, the physician can formulate a preliminary syndrome diagnosis. The third section is the most important section of the chapter. Here, we will discuss the *electroclinical diagnosis* of epilepsy syndromes using data obtained from electrophysiological studies, especially video EEG monitoring. The emphasis is on distinguishing epilepsy syndromes based on their typical ictal and interictal EEG findings. The effects of sleep and other activating factors on these electroclinical features are also described. The fourth section briefly describes the different *etiological factors or diseases* that are associated with the epilepsy syndromes. Some are clearly the cause or substrate of the epilepsy; in other cases, a causal relationship between the disease and epilepsy is difficult to ascertain. A detailed discussion of individual diseases is beyond the scope of this chapter; the reader should refer to the appendix for a summary of the most commonly encountered diseases in each syndrome. The chapter is concluded with a brief comment about the place of epilepsy syndrome diagnosis in the overall scheme of *epilepsy health care*.

CLINICAL DIAGNOSIS OF THE EPILEPSY SYNDROME

Epilepsy is a condition of chronic, recurrent seizures. All patients with epilepsy should initially receive a preliminary epilepsy syndrome diagnosis based on age at the onset of epilepsy, seizure types, and other clinical data. Electroencephalography (EEG), especially video EEG monitoring, is necessary for a definitive diagnosis of an epilepsy syndrome (see next section).

Age at Initial Presentation

Table 10-2 classifies the epilepsy syndromes according to the typical age period at presentation. In *age-dependent* syndromes, the onset of seizures is relatively restricted to the neonatal period, infancy, childhood, or adolescence.

Three epilepsy syndromes begin in the *neonatal period* (up to the age of 3 months): OS, EME, and BFNS (1,2,19). OS and EME are encephalopathic epilepsies that must be distinguished from each other and from other causes of neonatal seizures (43). BFNS should be distinguished from benign nonfamilial neonatal seizures (fifth-day fits), which is now listed by the ILAE under "conditions with epileptic seizures that do not require a diagnosis of epilepsy" (39,44).

TABLE 10-2. AGE PERIOD AT PRESENTATION OF EPILEPSY SYNDROMES. Age-dependent syndromes are classified according to period of typical onset: neonatal period, infancy, childhood, or adolescence. Syndromes that are less age-dependent are listed last.

Neonatal Period
Ohtahara syndrome (OS)
Early myoclonic encephalopathy (EME)
Benign familial neonatal seizures (BFNS)
Infancy
West syndrome (WS)
Migrating partial seizures of infancy (MFSI)
Dravet syndrome (DS)
Myoclonic encephalopathy in nonprogressive disorders (MEND)
Benign myoclonic epilepsy of infancy (BMEI)
Benign familial and non-familial infantile seizures (BFNIS)
Childhood
Lennox-Gastaut syndrome (LGS)
Epilepsy with continuous spike-and-wave during sleep (ECSWS)
Hemiconvulsion hemiplegia and epilepsy syndrome (HHE)
Benign childhood epilepsy with centrotemporal spikes (BCECTS)
Benign childhood epilepsy with occipital spikes—Panayiotopoulos type (BCEOS-1)
Benign childhood epilepsy with occipital spikes—Gastaut type (BCEOS-2)
Childhood absence epilepsy (CAE)
Epilepsy with myoclonic absences (EMA)
Epilepsy with myoclonic astatic seizures (EMAS)
Adolescence
Juvenile absence epilepsy (JAE)
Juvenile myoclonic epilepsy (JME)
Epilepsy with generalized tonic-clonic seizures only (EGTCS)
Epilepsy with febrile seizures plus (GEFS+)
Less Specific Age Relationship
Autosomal-dominant nocturnal frontal lobe epilepsy (ADNFLE)
Familial temporal lobe epilepsies (FTLE)
Familial focal epilepsy with variable foci (FFEVF)
Mesial temporal lobe epilepsy (MTLE)
Neocortical epilepsies (LTLE, FLE, OLE, PLE)
Rasmussen syndrome (RS)
Reflex epilepsies (IPOLE, VPSE, PRE, ESIS)
Progressive myoclonus epilepsies (PME)

Epilepsy with onset in *infancy and toddlerhood* (excluding the first 3 months) should raise the suspicion of an encephalopathic epilepsy (45). West Syndrome (WS) is the most common encephalopathic epilepsy during infancy; it can develop in infants with obvious brain disorder (some have OS) or in those who are apparently healthy (3). WS must be distinguished from the less common encephalopathic epilepsies of infancy including MFSI, DS, MEND, and early-onset LGS (7–9,46). ECSWS, PME, HHE, and RS may also begin in infancy (6,10,32,33). BMEI and BFNIS are the only ILAE-recognized benign idiopathic epilepsy syndromes of infancy (16,20). The remaining infantile epilepsies are symptomatic of malformative, destructive, or degenerative diseases of the brain.

Childhood is notable for the propensity of idiopathic focal and generalized epilepsies (47,48). Of the idiopathic

focal epilepsies, BCECTS is the most common, followed by BCEOS-1; BCEOS-2 is relatively uncommon (21–23,47). The familial focal idiopathic epilepsies ADNFLE, FTLE, and FFEVF rarely begin in childhood, and their incidence is far less compared to BCECTS and BCEOS-1. The most prevalent idiopathic generalized epilepsy in children is CAE (12). Occasionally, JAE, JME, or EGTCS may begin in childhood (13–15,48). EMA and EMAS may have a less favorable course and should be distinguished from LGS (17,18). LGS is the most common childhood encephalopathic epilepsy; it may emerge *de novo* or develop in a child with antecedent WS (4). Other childhood epilepsy syndromes with a significant risk of neurological sequelae include ECSWS, HHE, and RS (5,6,32,33). Some neurodegenerative diseases are initially expressed in childhood as PME (10).

It is common for idiopathic generalized epilepsies to begin in *adolescence* (49). Included in this group are JAE, JME, EGTCS, and GEFS+ (13–16,49). PME that is initially expressed in this age period must be distinguished from JME (10). The familial idiopathic focal epilepsies ADNFLE, FTLE, and FFEVF may present in adolescence (24–26). These syndromes must be distinguished from the symptomatic focal epilepsies, which are not much different from those with onset in adulthood (49). The most common is MTLE with hippocampal sclerosis (27). LTLE, FLE, PLE, OLE and other neocortical epilepsies caused by malformative, vascular, and neoplastic lesions are also common (28–31). Rasmussen Syndrome (RS) is the most devastating focal epilepsy syndrome in this age group (33). Some reflex epilepsies initially become manifest at adolescence (34–36).

Most *adult-onset* epilepsy syndromes are not age-dependent and may also begin in adolescence or childhood. Epilepsies that are initially expressed in adult life are usually focal and symptomatic. A large number of patients with MTLE and hippocampal sclerosis begin having seizures in adolescence (27). Symptomatic epilepsy caused by extratemporal lesions also becomes increasingly important with increasing age (28–31). A wide array of diseases and lesions have been associated with adult-onset symptomatic epilepsy. Some reflex epilepsies begin in adult life (34–36). Although most idiopathic generalized epilepsies encountered in adults started in adolescence (e.g., JAE, JME, EGTCS) (13–15), it is not uncommon for an idiopathic generalized epilepsy to begin in adult life (e.g., JME, EGTCS) (50).

Seizure Types

The different seizure types are listed in Table 10-3. The scheme used is a modification of the classification scheme recently proposed by the ILAE Classification Core Group (41). A detailed discussion of each seizure type is available on the ILAE Web site (see references 51–71).

TABLE 10-3. SEIZURE TYPES. The list is a modification of the ILAE Classification Core Group proposal. Alternative or original names and other comments are in parenthesis.

Bilateral-onset seizures
typical absences (typical absence seizures)
atypical absences (atypical absence seizures)
myoclonic absences (myoclonic absence seizures)
tonic-clonic seizures (primary generalized tonic-clonic seizures)
clonic seizures
tonic seizures
epileptic spasms (infantile spasms)
bilateral epileptic myoclonus (including massive bilateral myoclonus)
eyelid myoclonia
myoclonic-atonic seizures (myoclonic-astatic seizures)
atonic seizures
Focal-onset seizures
focal clonic seizures
jacksonian seizures (jacksonian march)
focal atonic seizures (inhibitory motor seizures)
asymmetric tonic seizures (supplementary motor area (SMA) seizures)
focal myoclonus (including multifocal myoclonus and erratic myoclonus)
focal sensory seizures (with elementary or complex symptoms)
aphasic seizures
rolandic seizures
hippocampal-amygdaloid seizures
hemiclonic seizures
hyperkinetic seizures
dyscognitive seizures (complex partial seizures)
autonomic seizures
focal seizures with secondary generalized tonic-clonic seizures
focal seizures with secondary generalized absence seizures
Status epilepticus seizures
epilepsia partialis continua
hemiclonic status
supplementary motor area status
aura continua
limbic status (complex partial status epilepticus)
autonomic status
absence status (typical or atypical)
myoclonic-absence status
myoclonic status
tonic status
tonic-clonic status
subtle status

The *seizure types* that are expressed in each of the epilepsy syndromes are listed in the appendix. Except for the rare spontaneous or provoked seizure in the clinic, good history-taking is initially the only means to identify a patient's seizure types. On purely clinical grounds, the physician can broadly characterize the seizures as absence seizures, seizures with brief symmetric bilateral movements, epileptic falls, focal epileptic myoclonus, focal-onset seizures, tonic-clonic seizures, reflex seizures, or status epilepticus. Video EEG

monitoring is often necessary to accurately diagnose specific seizure types (see Electroclinical Diagnosis).

Absence seizures are usually experienced by children and adolescents with idiopathic generalized or encephalopathic epilepsy, and some of these patients continue having absences as adults (48,49). As a rule, absences do not occur in infancy and are rare before the age of 4 years. *Typical absences* are expressed by all patients with CAE and JAE, by 10%–30% of patients with JME, and by a few patients with EGTCS and GEFS+ (51). Some authors consider typical absences as the only seizure type in CAE (tonic-clonic seizures may occur but only after childhood) (12). In addition to absences, tonic-clonic seizures, myoclonus, or both are often present in JAE. However, early-onset JAE with absences only can masquerade as CAE. In general, absences are very frequent in CAE (>10 per day) and moderately frequent in JAE (1–5 per day). The EEG may also help differentiate childhood-onset JAE from CAE (see Electroclinical Diagnosis). *Atypical absences* are common in LGS, ECSWS, and other encephalopathic epilepsies, often in combination with other seizure types (52). *Myoclonic absences* are absence seizures with axial hypertonia and prominent rhythmic (~3-Hz) jerking of the shoulders and arms (53). This is the principal seizure type of patients with EMA (17).

Seizures with brief symmetric or nearly symmetric bilateral movements include epileptic spasms, tonic seizures, atonic seizures, and bilateral epileptic myoclonus. *Epileptic spasms*, once called infantile spasms and thought to be specific for WS, have been described in other syndromes (OS, LGS) and in older children and adults (54). Nevertheless, epileptic spasms that begin in infancy and occur in clusters indicate WS. *Tonic seizures* are the hallmark of LGS, but also occur in OS, WS, EMA, and EMAS (55). Patients with EMA or EMAS do not exhibit tonic seizures early, but those who later do usually experience a less benign course (17,18). Because tonic seizures are brief and occur mainly (sometimes exclusively) in sleep, they are easily overlooked. Video EEG monitoring is necessary to detect or exclude tonic seizures in order to distinguish LGS from ECSWS, MEND, MFSI, DS, and early EMAS. *Atonic seizures* are expressed as pure ictal atonia or as atonia mixed with other ictal elements in LGS and other epilepsy syndromes (56). Atypical absences with prominent atonia suggest ECSWS (5,6). *Bilateral epileptic myoclonus* is the main seizure type in JME and BMEI (57). It can also occur as a minor seizure type in JAE and GEFS+. It is often expressed as *myoclonic-atonic seizures* in EMAS (58) and as *myoclonic absences* in EMA (17). Bilateral myoclonus is also common in EME, DS, MEND, and PME (1,8–10). Whether bilateral or focal, myoclonus is caused either by activation (positive myoclonus) or by interruption of muscle activity (negative myoclonus) (59,60).

Epileptic falls can be precipitated by seizures with sudden bilateral movements or atonia (54–58). An ambulant child with WS may fall as a result of *epileptic spasms* (3). Most falls and injuries in children with LGS are caused by *tonic seizures*, but *atonic seizures* and *atypical absences* account for some of them (4). In EMAS, *myoclonic-atonic seizures* are responsible for most falls; some are caused by pure atonic or myoclonic seizures (18). Attacks of *massive bilateral myoclonus* can precipitate falls in BMEI, DS, PME, and rarely in JME (57). Some falling episodes in ECSWS result from *atypical absences with atonia* or from *negative myoclonus* (22,23). In ESIS, *startle-induced seizures* can lead to falls (37). *Focal atonic seizures*, *focal negative myoclonus*, or *asymmetric tonic seizures* can rarely cause falls in FLE (29). *Tonic-clonic seizures* are perhaps the most important cause of epileptic falls and injury overall. Video EEG monitoring with additional placement of electromyographic surface electrodes will often explain why the patient falls.

Focal epileptic myoclonus can be confined to a small group of muscles or affect multiple noncontiguous muscles in different parts of the body (multifocal myoclonus) (59). Myoclonic jerks can also appear in one body part, disappear, and appear again in another part (erratic myoclonus). *Multifocal myoclonus* is prominent in EME, DS, MEND and PME (1,8–10). It helps distinguish these syndromes from OS, WS, and LGS. Children with DS manifest myoclonus late or not at all; hence "severe myoclonic epilepsy of infancy" is not a good name for this syndrome (8). It remains uncertain whether *LGS with prominent myoclonus* is an LGS variant, a separate syndrome, or a phenotypic overlap of syndromes. Nonetheless, before diagnosing LGS in a child with prominent myoclonus, epilepsy syndromes that mimic LGS (e.g., EMAS) must be excluded first.

Focal-onset seizures are usually symptomatic but may be idiopathic, particularly when there are no bilateral-onset seizures. *Mesial temporal seizures* with typical aura, cognitive dysfunction, and automatisms are highly (but not absolutely) specific for MTLE (61). *Lateral temporal seizures* are not always heralded by a vestibular, auditory, or visual aura (62). Intratemporal ictal spread is common, making the clinical distinction between MTLE and LTLE difficult. The two FTLE phenotypes, mesial-FTLE and lateral-FTLE, are clinically equivalent to MTLE and LTLE (25). *Frontal lobe seizures* in patients with FLE are manifested as focal clonic, asymmetric tonic, or complex motor phenomena, without or with mild cognitive dysfunction; they are brief and often occur in clusters during sleep (54). In ADNFLE, ictal semiology (paroxysmal arousal, nocturnal paroxysmal dystonia, or episodic nocturnal wandering) often leads to an incorrect diagnosis of parasomnia (24). *Rolandic seizures* (oral paresthesia, hypersalivation, dysarthria, drooling) indicative of BCECTS are sometimes seen in BCEOS-1 (21,22). *Parietal lobe seizures* in PLE may or may not begin with a somatosensory aura (64). *Occipital lobe seizures* are often experienced as visual phenomena in OLE or BCEOS-2; headache is common and the diagnosis is often migraine (64,23). *Autonomic seizures* with nausea

and emesis predominate in BCEOS-1 (21). Focal-onset seizures are also prominent in BFNS, BFNIS, FFEVF, HHE, RS, and IPOLE (19,20,26,32–34). Patients with LGS, ECSWS, MFSI, DS, and PME may exhibit focal seizures (other than focal myoclonus) (4–8,10).

Tonic-clonic seizures can be expressed by patients with focal or generalized epilepsy, except neonates and young infants (65). Focal-onset seizures (whether clinically evident or not) can evolve into secondarily generalized tonic-clonic seizures; this is more likely in FLE, OLE, and PLE (29–31). *Most of the so-called "primarily generalized" tonic-clonic seizures in JME and other idiopathic generalized epilepsies are preceded by repetitive and rhythmic myoclonus (clonic jerking)* (65).

Status epilepticus and short-duration seizures are fundamentally related (Table 10-3). The most common status overall is *tonic-clonic status*. The status in idiopathic generalized epilepsy is often an *absence status* with myoclonic elements and a terminal tonic-clonic seizure (66). In LGS, atypical absence seizure status contains tonic elements, begins and ends gradually (no tonic-clonic seizure), lasts longer, and tends to occur more frequently. Adults with a remote history of absences or with no prior epilepsy can manifest *de novo absence status* during an acute brain insult. FLE or MTLE can be complicated by *limbic status* (67). Rarely, *aura continua* is encountered in MTLE or other focal epilepsies (68). Patients with DS, MEND, EMAS, or PME may exhibit *myoclonic status;* this is rare in JME (69). About half of patients with RS manifest *epilepsia partialis continua* (70). Protracted autonomic seizures (>30 minutes) are common in BCEOS-1; otherwise, *autonomic status* is rare (22).

Reflex seizures are evoked by specific stimuli and expressed as tonic-clonic, myoclonic, absence, tonic, or focal seizures (71). *Photosensitive seizures* may occur in BMEI, JME, EMAS, DS, and PME but, unlike reflex epilepsies, spontaneous seizures predominate in these syndromes (11,14,18,8,10). IPOLE, VPSE, and PRE are idiopathic reflex epilepsies; reflex seizures are evoked by *flicker* in IPOLE, by *visual pattern* in VPSE, and by *reading* in PRE (34–36). *Startle-induced seizures* are the sine qua non of ESIS; the majority of patients with ESIS also have spontaneous seizures (37).

Other Clinical Data

Clinical course is the product of epilepsy evolution, disease progression, and brain maturation. These processes are intricately intertwined and difficult to separate. From a practical standpoint, the course of epilepsy is described in terms of the cognitive and behavioral abnormalities that develop with time, the evolution of seizure characteristics with age, and the probability of future seizure remission or pharmacological resistance (72–74). These features are summarized for each epilepsy syndrome in the appendix (see "course" entries).

Neurological deficits are more common in some epilepsy syndromes than in others. Long-lasting deficits are caused directly by the underlying disease or develop because of frequent epileptic activity. It is difficult, and often impossible, to determine how much of the deficits are caused by the disease and how much are the result of epileptic activity (75). The actively developing brain is vulnerable to the adverse effects of status epilepticus, seizures, or interictal epileptic activity (76,77). Any of these forms of epileptic activity can exacerbate pre-existing neurological deficits or result in *de novo* mental retardation or focal deficits.

Mental retardation or *developmental delay* in a patient with epilepsy should not automatically be attributed to an encephalopathic epilepsy (78). For example, a child with static encephalopathy can have MTLE and focal seizures. Focal seizures are not uncommon in encephalopathic epilepsies, but bilateral-onset seizures usually predominate. In the early stages of ECSWS, DS, and MFSI, cognitive function is often intact and focal seizures may be the only seizure type (5–8). Cognitive impairment has been incorporated in the classic diagnostic criteria of encephalopathic epilepsies. *Epileptic spasms, hypsarrhythmia, and developmental delay constitute the classic triad of WS* (3). *LGS is diagnosed in children with tonic seizures, EEG slow spike-waves, and mental retardation* (4). The non-LKS type of ECSWS is often associated with cognitive and behavioral changes (6). Cognitive impairment is the rule in MFSI, DS, and MEND (7,8). Occasionally, patients with intact neurological function will manifest electroclinical features consistent with an encephalopathic epilepsy. In such cases, the emergence of a full-fledged encephalopathic epilepsy must be anticipated, and a tentative syndrome diagnosis should guide treatment and the search for an etiology. EMA and EMAS differ from other idiopathic epilepsies in having a relatively high incidence of neurological sequelae (17,18). All patients with epilepsy and mental retardation should be investigated with routine EEG. In many patients, video EEG monitoring is necessary to detect or exclude an encephalopathic epilepsy and to identify the specific epilepsy syndrome. It is also important to distinguish mental retardation from the cognitive effects of antiepileptic drugs and from subclinical status epilepticus or frequent subclinical seizures.

Focal neurological deficits should not be confused with the transient focal manifestations of seizures or the postictal state. Focal neurological deficits are common in the encephalopathic epilepsies and some symptomatic focal epilepsies, but unlikely in the more benign idiopathic generalized and focal epilepsies. Rarely, patients with BCECTS develop cognitive or behavioral abnormalities as the syndrome evolves into a state similar to ECSWS (21,5). The clinical diagnosis of LTLE, FLE, OLE, or PLE is more secure when the focal deficits are consistent with the seizure types (28–31). The hemiplegia in HHE is initially a postictal phenomenon, but becomes a fixed deficit in a matter of days or weeks (32). In RS, focal deficits are initially absent but invariably

develop in the course of epilepsy (33). In encephalopathic epilepsy, focal deficits are not always caused by structural lesions. Aphasia and sleep-activated bitemporal spike-waves are required to diagnose the LKS form of ECSWS (5). Symptomatic focal epilepsies with aphasia are distinguished from LKS by means of polysomnography or long-term monitoring.

The evolution of seizure types and neurological deficits reflects the time-dependent maturational, pathological, and adaptive changes in brain structure and function. Age-dependent syndromes evolve in more or less predictable ways, and knowing common paths of evolution can guide diagnosis and prognosis (73). *A well-known sequence is OS → WS → LGS*. Infants with OS or EME develop psychomotor retardation, and about 50% die in infancy or childhood (1,2). EME survivors may go into a persistent vegetative state, continue manifesting myoclonus, or develop severe multifocal epilepsy (1). OS survivors develop WS or focal epilepsy (2). In WS, epileptic spasms usually disappear before the age of 3 years; other seizure types emerge (>50% of cases) and in some (~25% of cases) the seizures are typical of LGS (3). Rarely, epileptic spasms persist into adulthood. Most adults with a history of WS exhibit learning disabilities or mental retardation (72). In LGS, any seizure type can persist, but tonic seizures increase in prominence as cognition declines (73). Seizure remission and normal cognition is uncommon. In PME, myoclonic and tonic-clonic seizures persist until death supervenes in early adulthood (10). Spontaneous remission is the rule in some idiopathic epilepsies (BMEI, CAE, BCECTS, BCEOS); in others (JME, JAE, ADNFLE, FTLE, FFEVF), remission is effectively sustained with antiepileptic drugs (74). Of the idiopathic generalized epilepsy syndromes, EMA and EMAS are exceptional in that the probability of unfavorable outcome is relatively high (~50% of cases) (17,18).

BRIEF COMMENT ON THE BENIGN-SEVERE CLASSIFICATION OF EPILEPSY SYNDROMES

The benign-severe dichotomy is useful but cannot be consistently applied (79,80). In EMAS and EMA, the probability of a favorable or poor outcome is virtually 50–50 (17,18). Some cases of WS, LGS, and ECSWS are known to resolve with minimal or no sequelae (80). In most encephalopathic epilepsies, prognosis also depends on etiology and treatment. Some children with BCECTS and BCEOS-1 have subtle cognitive and behavioral abnormalities, and there are some reports of BCECTS evolving to ECSWS (81). BFNS cases complicated by psychomotor retardation, intractable epilepsy, or both have been recognized recently (82). Prognosis is generally favorable in BMEI, but the incidence of mental retardation in this syndrome is significantly higher than in the general population (83). Learning disorder is common in CAE despite seizure and spike-wave remission (80). Seizure control is hard to achieve in some patients with JAE, JME, and BCEOS-2 (13,14,23). Intractable MTLE is common but is neither "benign" nor "severe" (27). These examples demonstrate the shortcomings of describing an epilepsy syndrome as benign or severe, and emphasize the importance of an individualized prognosis in the different epilepsy syndromes.

Family history is useful in epilepsy diagnosis, but it can be easily misused by somebody who is not familiar with epilepsy genetics. A *negative family history* (no relatives with epilepsy) is not unexpected in patients with symptomatic epilepsy (usually caused by an acquired disease). However, most patients with idiopathic epilepsy also have a negative family history (84). Most of the nonfamilial or sporadic forms of idiopathic epilepsy have been attributed to *de novo gene mutation* (85). Recently, the syndrome of benign familial infantile seizures (BFIS) was expanded and renamed to BFNIS to accommodate sporadic forms. BFNS, ADFLE, FTLE, and other syndromes should probably also be expanded and renamed to include both familial and sporadic forms (86,87). It is evident that most cases of DS are caused by *de novo* mutation (88). *A minority of all patients with idiopathic epilepsy have a positive family history.* The majority of these familial cases exhibit *complex inheritance* (89). The mechanism of complex inheritance in epilepsy is poorly understood. Multiple susceptibility genes presumably interact, or their individual subthreshold effects sum up to produce the epilepsy phenotype. Although infrequent, *simple Mendelian inheritance* is always possible in patients with idiopathic epilepsy. The currently known epilepsy genes were mostly identified from families with many affected individuals and an autosomal dominant segregation pattern (90). Most genetic diseases with a PME phenotype follow an autosomal recessive pattern. The etiological bases of PME and other genetic epilepsies are discussed later (see "Etiological Diagnosis").

ELECTROCLINICAL DIAGNOSIS OF THE EPILEPSY SYNDROME

EEG is required to diagnose the epilepsy syndrome, which, by definition, is an electroclinical syndrome. *Routine EEG* is indicated in patients with possible or definite epilepsy; repeating the study once or twice may increase the diagnostic yield of routine EEG in some of these patients (91). *Long-term EEG monitoring* is also indicated if the goal is to reach a definitive epilepsy syndrome diagnosis (92). Noninvasive video EEG monitoring is usually preferred over ambulatory EEG (93). *Other physiological events* (e.g.,

muscle potentials, limb movements, eye movements) can also be monitored during the course of long-term monitoring (94). *Other neurophysiological tests* (e.g. evoked potentials, polysomnography) can provide information that is not readily obtained with video EEG monitoring. *Neuroimaging* can reveal a lesion and corroborate a particular syndrome, but it can also lead one away from the correct syndrome diagnosis. The appendix lists the salient electroclinical features of each epilepsy syndrome (see "interictal EEG" and "ictal EEG" entries).

BRIEF COMMENT ON THE USE OF THE TERM "GENERALIZED" TO DESCRIBE EPILEPTIC PHENOMENA

There is a large body of experimental evidence (including recently published quantitative EEG, functional imaging, and animal studies) telling us to stop describing seizures and interictal activity as "generalized" (95–101). These studies have correlated "generalized" ictal or interictal activity with activation of specific cortical regions (often bifrontal), discrete cortical areas, or specific thalamocortical networks (a large portion of the cortex and thalamus is spared), but not with diffuse, homogeneous, or widespread cortical activation (which is implied by the term "generalized") (95–101). The fact that 3-Hz spike-waves may be expressed as fragments or focal discharges also suggests that the extent of cortical activation can fluctuate and be more circumscribed. The word "bisynchronous" may be more appropriate in that it does not imply the extent of activation, only that both hemispheres are activated simultaneously. However, computerized EEG analysis of some so-called "bisynchronous" ictal or interictal discharges have shown that activation does not really occur in synchrony (primary bilateral synchrony). Instead, part of one hemisphere is activated first, followed by activation of the contralateral area (secondary bilateral synchrony) (102). Meticulous measurements have revealed timing differences of up to 20 milliseconds in the epileptiform discharges of each hemisphere, with discharges in one hemisphere leading the discharges in other. Despite these difficulties, it is still appropriate to describe bilateral activity as "bisynchronous" if the discharges appear simultaneous on visual inspection of the EEG; otherwise, the word "bilateral" can be used. However, the use of the term "generalized" is hard to justify.

BRIEF COMMENT ON THE VALUE OF THE INTERICTAL EEG IN EPILEPSY SYNDROME DIAGNOSIS

Long-term monitoring is performed primarily to record seizures and their EEG correlates. In general, the ictal EEG is more useful than the interictal EEG for diagnosing seizure types and syndromes. However, the interictal epileptiform discharge is quite distinctive in some epilepsy syndromes (e.g., BCECTS, CAE, MTLE), and failure to demonstrate it with proper technique can cast doubt on the diagnosis (91,103). Among the epilepsy syndromes, ECSWS is unique in requiring an interictal epileptiform pattern (CSWS) for diagnosis (5,6). The interictal background activity of some syndromes (e.g., EME, OS, WS, LGS) is highly suggestive of the syndrome (1–4). Even if the diagnostic value of the interictal EEG varies among syndromes, combined interictal EEG and seizure analysis is likely to be more informative than seizure analysis alone. The search for interictal epileptiform discharges and background changes must be guided by the preliminary syndrome diagnosis. A large number of interictal changes are state-dependent, and some occur only with certain types of activation. The search must focus on high-yield epochs, but different sleep-wake stages should also be sampled.

Absences and Spike-Waves

The type of absence seizure expressed depends on the epilepsy syndrome (104). Patients with idiopathic generalized epilepsy (except SMEI and EMAS) manifest typical absence seizures (41), and those with LGS, ECSWS, or EMAS manifest atypical absence seizures (42). The early stage of LGS or the active phase of ECSWS can be confused with a benign epilepsy syndrome if atypical absence is the only seizure type and neurological function is still intact.

Typical absences are the hallmark of CAE and JAE (12,13). Patients with JME, EGTCS, or GEFS+ also have absence seizures, but not as the main seizure type (14–16). Two subtypes of typical absence have been delineated based on whether the "blank stare" is the only change (simple absence) or is accompanied by a motor component such as myoclonus, change in tone, or automatism (complex absence) (92). Some authors consider typical absence as the only seizure type in CAE; tonic-clonic seizures can occur later but never in childhood (105). This view is not shared by other authors (106). Typical absences are also prominent in JAE, often in combination with tonic-clonic and myoclonic seizures. JME patients may manifest typical absences, but these are overshadowed by myoclonic or tonic-clonic seizures (106). "CAE evolving to JME" has more in common with JME than with CAE (including prognosis) (104). It is not easy to distinguish CAE from childhood-onset JAE with typical absences and no other seizure type. As a rule, typical absences occur more frequently in CAE than in JAE (106). The impairment of consciousness is profound in CAE, moderate in JAE, and minimal in JME (12–14). The EEG can also help differentiate JAE from CAE.

Typical or *3-Hz spike-and-wave* and interruption of consciousness indicate typical absence seizure (Figure 10-1) (51). Shorter duration 3-Hz spike-waves are also common

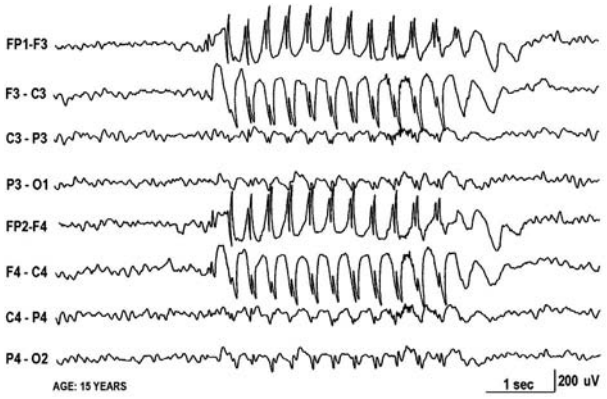

FIGURE 10-1. 3-Hz spike-waves during typical absence seizure. The patient failed to respond to auditory stimuli (clicks) during this brief discharge. Note the bifrontal (F3, F4) voltage peak of the spikes and slow waves. *Source:* Adapted from Noachtar S, Wyllie E (232):192.

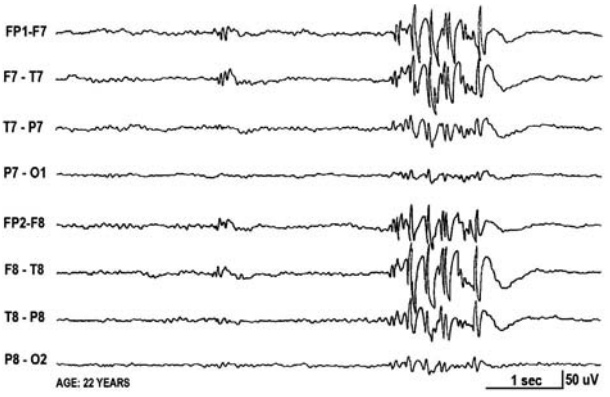

FIGURE 10-3. Atypical spike-waves in the interictal EEG. These discharges are common in juvenile myoclonic epilepsy and usually appear as repetitive 4–6 Hz polyspike-waves without any associated myoclonus. *Source:* Adapted from Fisch BJ (107):289.

(Figure 10-2). Typical 3-Hz spike-and-wave patterns appear as bisynchronous rhythmic 2.5- to 4–Hz spike-wave complexes that begin and end abruptly (12,51). The probability of detecting cognitive dysfunction or motor arrest is proportional to the duration of the discharge and the sensitivity of the detection method; simple observation is unlikely to detect any clinical change if the discharge is brief (≤3 seconds). Most 3-Hz spike-wave activity lasts about 10 seconds (>30 seconds is unusual). The discharge is initially 3.5–4 Hz, but slows down to 2.5–3 Hz (12). Each spike-wave complex contains one or two (or rarely three) spikes and a slow wave. The discharge is typically symmetric with a frontal voltage maximum. Postictal changes do not occur, and the background resumes as soon as the seizure stops. The ictal 3-Hz spike-waves of JAE are in many respects similar to those of CAE, except for a slightly higher discharge rate (3.5–4.5 Hz),

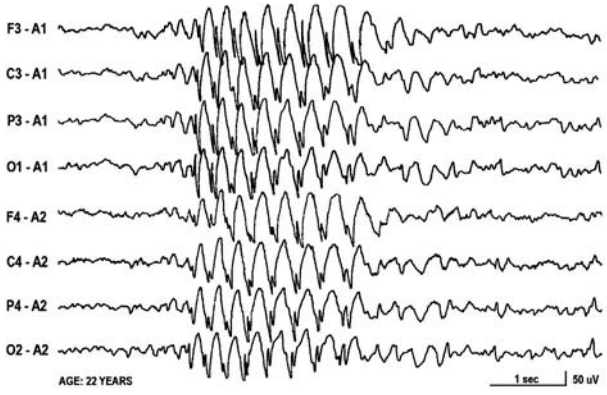

FIGURE 10-2. 3-Hz spike-waves in the interictal EEG. A test word presented during this brief discharge was recalled later by the patient. The apparent broad distribution of this discharge is in part an effect of the referential montage (compare with Figure 10-1 above). *Source:* Adapted from Fisch BJ (107):288.

the presence of discontinuities, a larger number of spikes, and longer duration (despite less impairment in consciousness) (13). The fragmentation of 3-Hz spike-waves in sleep or with treatment can mislead the inexperienced electroencephalographer (see "Activation of Seizures . . ." below).

Atypical generalized spike-and-wave patterns appear either as an irregular complex of multiple spike-and-wave activity or as bifrontal, rhythmic, 4- to 6-Hz spike-and-wave in the interictal EEG of patients with JME, JAE, PME, and other syndromes (Figure 10-3) (107). Sleep modifies the 4- to 6-Hz pattern in the same way as it affects 3-Hz spike-waves, resulting in increasingly irregular admixtures of spikes and slow waves. Atypical spike-waves repeating at a rate of 6 Hz should not be confused with the normal EEG variant known as *6-Hz phantom spike-waves* (107).

Myoclonic absences are absence seizures with prominent rhythmic typical 3-Hz spike-and-wave (range is 2.5–4.5 Hz) accompanied by bilateral myoclonic jerks of the shoulders, arms, and legs (rarely face) (53). This seizure phenotype is expressed in EMA, often in conjunction with pure absences (17). *Eyelid myoclonia with absences* are the hallmark of Jeavon's syndrome, a form of photosensitive idiopathic epilepsy (104,108). *Perioral myoclonia with absences* has also been described as a seizure phenotype in idiopathic epilepsy (38). Because all three seizure types have the same EEG correlate (3-Hz spike-wave), only the motor events distinguish these mixed seizures from typical absence and from each other.

Atypical absence seizures are usually associated with the generalized slow spike-and-wave pattern, and are not as specific as nocturnal tonic seizures for identifying LGS, but they are much easier to recognize (52). Atypical absences usually have a gradual onset and termination (typical absences start and end abruptly), longer duration (typical absences usually last 10 seconds), milder impairment of consciousness (patients tend to continue their activity),

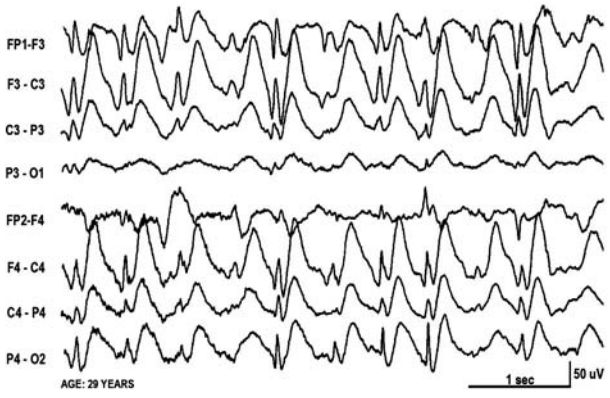

FIGURE 10-4. Slow spike-waves during atypical absence. The interictal version is shown in Figure 10-5 below. Other than the slightly more regular appearance of the ictal discharge, the ictal and interictal versions are not easy to distinguish. *Source:* Adapted from Pedley TA, Mendiratta A, Walczak TS (122):550.

more prominent postictal confusion (postictal recovery of consciousness in typical absences is rapid), and associated motor manifestations (eyelid or perioral myoclonia, loss of postural tone, neck-stiffening, head-nodding, etc) (52). The active phase of ECSWS is frequently associated with atypical absences (in some this is the only seizure type) and cognitive dysfunction, thus mimicking LGS (5,6). Tonic seizures are common in LGS but essentially absent in ECSWS (4–6). Focal motor seizures often occur in ECSWS but are rare in LGS (4). Regardless, EEG is often the only means to distinguish these syndromes (see CSWS pattern). Atypical absences are also common in EMAS (18). *Tonic absences* have been detected by video EEG recording in some patients with encephalopathic epilepsies (109).

The *generalized slow spike-and-wave pattern* is usually present in the EEG during atypical absence seizures (Figure 10-4) (52), but is more commonly seen as an apparently interictal pattern (Figure 10-5). Whether ictal or interictal, the slow spike-and-wave pattern consists of 1- to 2.5-Hz bisynchronous sharp- and slow-wave complexes. It also differs from 3-Hz spike-waves in having a more irregular morphology, a variable discharge rate, and a less uniform appearance. A bifrontal or bitemporal voltage maximum is present in almost all cases; voltage asymmetry with shifting laterality is also common. Slow spike-waves often coexist with multifocal spikes in the EEG of patients with LGS (4). Sleep modifies the appearance of slow spike-waves and multifocal spikes; in LGS, the slow spike-waves may become more continuous and mimic the CSWS pattern of ECSWS or create a discontinuous pattern sometimes resembling burst-suppression (4).

Continuous spike-waves in slow-wave sleep (CSWS) is the sine qua non of ECSWS, a unique "epilepsy syndrome" that can be diagnosed in the absence of clinical seizures (110). Also known as electrical status epilepticus in sleep (ESES), CSWS is a clinically interictal EEG pattern consisting of bilateral slow (2- to 2.5-Hz) spike-waves that are activated in slow-wave sleep and are present in 85%–100% of stage 3 and 4 sleep epochs (Figure 10-6) (110). Polysomnography, all-night EEG, or video EEG monitoring is necessary to detect CSWS. Similar slow spike-waves (which are not CSWS per se) appear sporadically or in short bursts in the waking EEG of patients with ECSWS. In the *non-Landau-Kleffner syndrome form of ECSWS,* the spike-waves are maximal over the frontal head regions and associated with cognitive and behavioral disturbances (6). In *ECSWS due to Landau-Kleffner syndrome* (LKS), the spike-waves arise from the posterior temporal area and are associated with aphasia (Figure 10-25) (5). LKS is likely when the EEG of a child with acquired aphasia shows bitemporal spikes and/or CSWS; the resolution of aphasia with antiepileptic therapy is confirmatory (110). Most (but not all) patients with LKS manifest clinical seizures before or after the onset of aphasia (5). Patients with LKS or non-LKS ECSWS often exhibit focal seizures (temporal lobe seizures in LKS, frontal lobe seizures in non-LKS) and atypical absences (5,6). Both types of ECSWS also have a nonactive and active phase

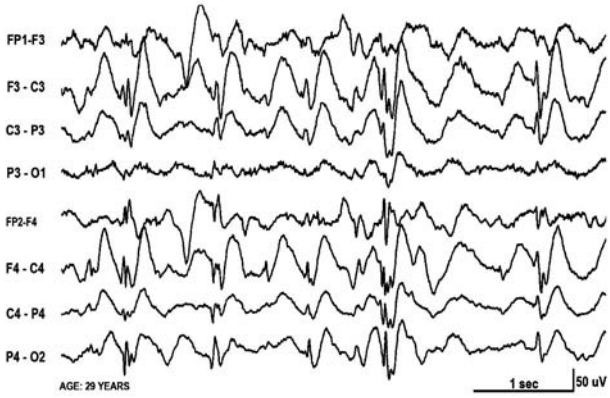

FIGURE 10-5. Slow spike-waves in the interictal EEG. Despite the long duration of the discharge, there is no clinical evidence of an alteration of consciousness. *Source:* Adapted from Pedley TA, Mendiratta A, Walczak TS (122):549.

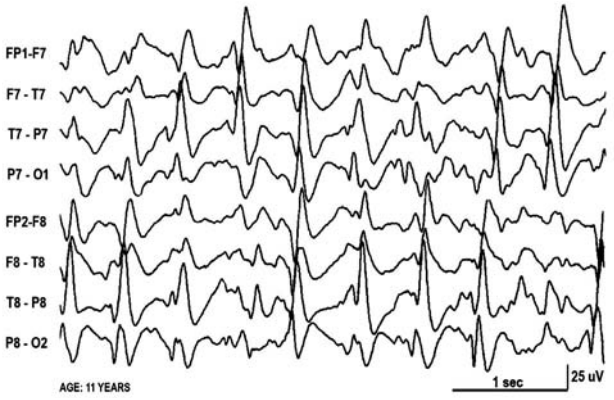

FIGURE 10-6. Continuous spike-waves in slow-wave sleep (CSWS). To qualify as CSWS, bilateral slow (2–2.5 Hz) spike-waves must be present in 85–100% of stage 3 and 4 NREM sleep epochs. *Source:* Adapted from Pedley TA, Mendiratta A, Walczak TS (122):558.

(5–6,110). In the *nonactive phase,* focal seizures occur infrequently; the wake EEG shows focal slow waves, spikes, or spike-waves (temporoparietal in LKS, frontal in non-LKS), and infrequent bursts of bilateral slow spike-waves (absent in many LKS and some non-LKS); and the sleep EEG shows more slow spike-waves (although present in <85% of slow-wave sleep epochs) and attenuated or absent sleep spindles in the non-LKS type. In the *active phase,* focal seizures are more frequent, and atypical absences and atonic seizures occur (with or without ictal EEG correlates); the wake EEG changes of the nonactive phase are enhanced; and the sleep EEG shows definite CSWS (slow spike-waves in ≥85% of slow-wave sleep epochs) (5–6,110).

Seizures with Brief Symmetric Bilateral Movements

Seizures that manifest as sudden brief symmetric or nearly symmetric bilateral body movements include epileptic spasms, tonic seizures, atonic seizures, and bilateral epileptic myoclonus (54–57). Epileptic spasms are usually more sustained (0.5–3 seconds) than myoclonus (<0.2 seconds), but not as sustained as tonic or atonic seizures (>5 seconds) (111,112). Video EEG with surface electromyography is often necessary to accurately diagnose these seizures and identify the epilepsy syndrome (94,112).

Epileptic spasm (formerly "infantile spasm") is a specific seizure type seen in infants with WS (54,113). It is now clear that epileptic spasms can occur in other age groups or syndromes (e.g., OS, LGS) (114–116). The spasm is a sudden, brief, bilateral axial muscular contraction. The type of muscles (flexors, extensors, mixed) and their location (neck, chest, shoulders, proximal limbs, or combinations thereof) determine the clinical appearance of the spasm (54,113). Classical forms of epileptic spasm include jackknife seizures (contraction of abdominal flexors bending the trunk at the waist), salaam seizures (jackknife seizures plus abduction or adduction of the arms), head-nodding, and shoulder-shrugging (54). Spasms can also manifest as subtle behavioral arrest, ocular deviations, or changes in respiration or heart rate. The frequency of spasms varies from a few times a day to several hundreds a day, and spasms usually occur in clusters (usually 10–20 spasms) (54). The jerks are usually symmetric; asymmetric spasms suggest cortical brain injury and structural lesions (113).

A *high-voltage slow wave followed by electrodecrement* is the most common EEG correlate of epileptic spasms (Figure 10-7) (54). The slow wave correlates with the spasm, and the electrodecrement may be a postictal phenomenon. Recording a diamond-shaped burst of electromyogram (EMG) activity (0.5–3.0 seconds in duration) during the spasm increases confidence in the diagnosis (112). This can be achieved in most patients by recording deltoid EMG with surface electrodes during EEG acquisition (EEG-EMG polygraphy). Another ictal EEG correlate of epileptic spasm is *low-voltage fast activity*. The tendency of epileptic spasms to occur in *clusters* can also help distinguish them from other causes of brief bilateral symmetric jerks (54). In some patients, *focal spikes* are present before, during, or after a cluster of spasms; in others, *focal seizures* lead the cluster of spasms (117,118). Therefore, in a subset of patients, focal interictal or ictal activity is involved in driving the spasms or in initiating the cluster of spasms (113,117,118).

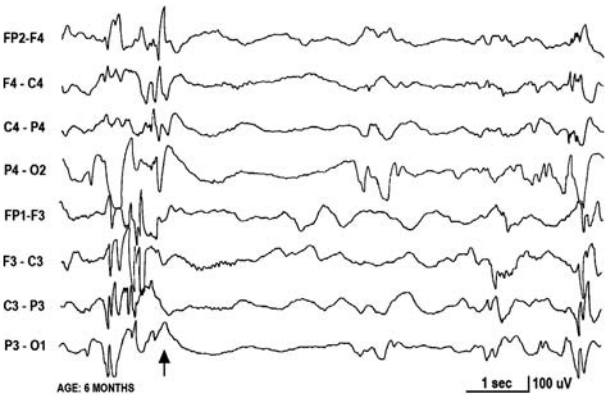

FIGURE 10-7. High-voltage slow wave during an epileptic spasm. The slow wave correlates with the spasm (arrow). In this particular case, the slow wave is followed by electrodecrement. *Source:* Adapted from Fisch BJ (107):315.

Hypsarrhythmia is a distinctive, high-voltage, interictal EEG pattern that is seen in infants with WS (Figure 10-8) (3). Although classic for WS, it is not present in the EEG of some infants with epileptic spasm (119). In hypsarrhythmia, the EEG background activity is completely replaced by a disorganized pattern of irregular high-voltage spike, theta, and delta activity (54). The discharges are usually bilateral and can be symmetric or asymmetric; pronounced asymmetry suggests a gross cortical malformation (e.g., hemimegalencephaly). *Modified hypsarrhythmia* pertains to the variants of hypsarrhythmia, including hypsarrhythmia

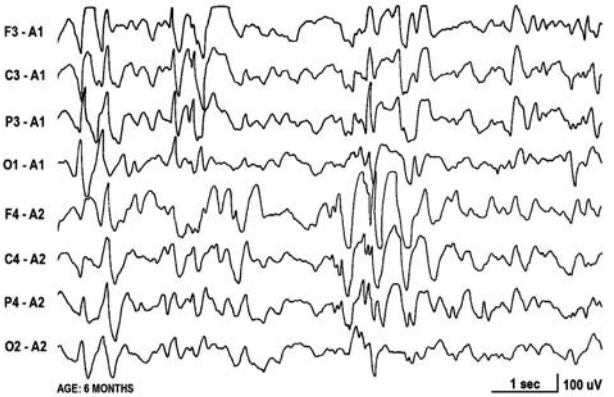

FIGURE 10-8. Hypsarrhythmia in the interictal EEG. The normal background features are lost and are replaced by a disorganized pattern of irregular high-voltage spike, theta, and delta activity. *Source:* Adapted from Fisch BJ (107):313.

with increased interhemispheric synchrony (which may be a result of maturation of transcallosal pathways), asymmetric hypsarrhythmia (persistent voltage asymmetry), rapid hypsarrhythmia variant (which may be a harbinger of paroxysmal fast activity), and hypsarrhythmia with intermittent attenuation (recurrent episodes of generalized, regional, or focal attenuation lasting 2–10 seconds) (54). The last variant, which is analogous to the burst-suppression of OS (see below), is often associated with cerebral malformations (e.g., schizencephaly, Aicardi syndrome, hemimegalencephaly) (113). Sleep modifies the appearance of hypsarrhythmia (see "Activation . . .") (113).

A burst-suppression pattern and seizures in the first 3 months of life suggest EME or OS (Figure 10-9) (1,2). As a rule, this EEG pattern is encountered during sleep in EME and during all states in OS. Tonic seizures predominate in OS, and myoclonus is the main seizure type in EME. However, these two syndromes share many common features and the boundary between them is not always clear (120).

Tonic seizures are the most characteristic seizures in LGS (55,121). Patients with WS and OS can also manifest tonic seizures (55,120). The appearance of tonic seizures in the course of EMA or EMAS has been considered a poor prognostic sign (17,18). The lack of tonic seizures in ECSWS, MFSI, DS, and MEND helps distinguish these syndromes from LGS (5–9,4). Tonic seizures consist of sustained (5- to 20-second) bilateral (often symmetric) contractions of axial and proximal limb muscles resulting in face, jaw, or neck rigidity, shoulder elevation, or back stiffening (55,121). Hip flexor spasm may precipitate a fall and laryngeal spasm may produce a high-pitched cry. Tachycardia, mydriasis, flushing, and other autonomic changes also occur. Brief (0.5- to 0.8-second) tonic seizures, called axial spasms, are difficult to distinguish from epileptic spasms (55). Tonic seizures that are subtle (e.g., eye deviation) or that occur only in sleep are easily overlooked. Video EEG monitoring is often necessary to diagnose tonic seizures (55,92).

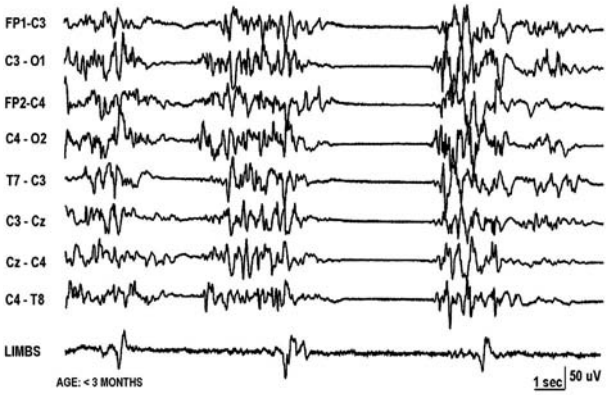

FIGURE 10-9. Burst-suppression pattern in a neonate with early myoclonic encephalopathy. The bursts are associated with myoclonic jerks which are evident in the electromyogram channel (see channel labeled "limbs"). *Source:* Adapted from Clancy RR, Mizrahi EM (233):505.

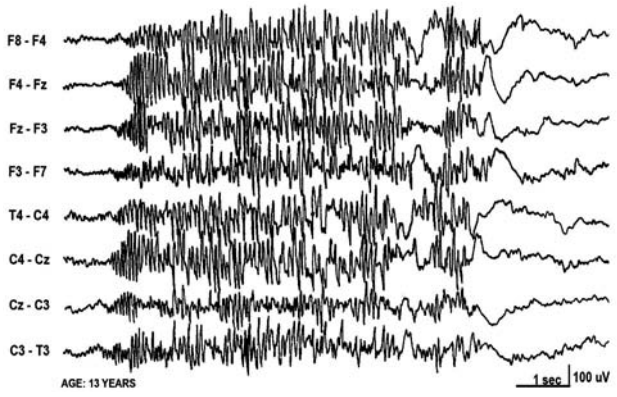

FIGURE 10-10. Paroxysmal fast activity during a tonic seizure. This is a burst of 10–25 Hz activity (15 Hz in this case). Note the initial rapid buildup with the discharge reaching a peak within the first second. *Source:* Adapted from Tatum WO, Farrell K (124):322.

Paroxysmal fast activity (PFA) is the most common ictal correlate of tonic seizures (Figure 10-10). This is a burst of bisynchronous, 10- to 25-Hz, low- to medium-amplitude activity with a bifrontal or central and parasagittal voltage maximum (121,122). The PFA amplitude reaches a peak within 1 second of onset and fluctuates thereafter. *Slow spike-waves* may lead or trail the PFA. *Diffuse attenuation* with or without PFA may also occur during tonic seizures (121–123). Tonic seizures are usually associated with an electromyographic interference pattern in the EEG recording, as are voluntary muscle contractions (123). Postictally, bilateral slowing may be present for a few seconds. *Interictal PFA* is more common than ictal PFA; nearly all patients with LGS have interictal PFA in sleep (Figure 10-11). Studies have shown that tonic muscle activity is common but subtle (e.g., brief eye movements, paraspinal EMG bursts) during so-called "interictal" PFA (123).

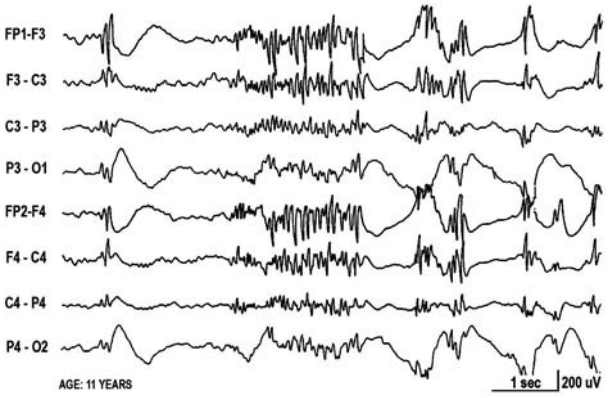

FIGURE 10-11. Paroxysmal fast activity in the interictal EEG. This is common in Lennox-Gastaut syndrome during sleep. It may be associated with subtle tonic muscle activity, such as eye deviation or electromyogram bursts in the paraspinal muscles. *Source:* Adapted from Noachtar S, Wyllie E (232):196.

Atonic seizures occur in LGS and other syndromes as pure atonia or as atonia with other ictal phenomena (e.g., myoclonic-atonic seizure in EMAS; atypical absence with atonia in ECSWS) (124). The abrupt loss of postural tone in the neck, trunk, or limbs is manifested as a head nod, a slump, or a fall (124,125). Bradycardia, apnea, and other autonomic changes also occur (124). Brief (1- to 2-second) atonic seizures allow the patient to stand up immediately after a fall. Prolonged (1- to 10-minute) atonia is associated with impairment of consciousness and a longer recovery period (124,125).

Bisynchronous spike-waves or polyspike-waves are often present in the EEG at the onset of atonic seizures (Figure 10-12) (123,124). Atonia is evident as an *EMG silent period* that is time-locked to the slow-wave component of the EEG discharge. The spike-wave complex may or may not be followed by *diffuse voltage attenuation* or *low-voltage fast activity* (124). Other ictal EEG patterns have been described including *slow spike-waves* and *bilateral slow waves* with peak voltage at the vertex or central regions (123–125).

Falling seizures include seizures with sudden bilateral movements or atonia and other seizure types of which falling is a cardinal manifestation (124,125). *Epileptic spasms* in WS can precipitate a fall in the ambulant child (3). *Tonic seizures* propel the patient forward or backward, causing falls and injuries in children with LGS (124,125). *Atonic seizures* cause straight-down falls; the buttocks hit the ground first, so injury is rare (124,125). *Myoclonic-atonic seizures* are responsible for most of the falls in EMAS; some falls are caused by pure atonic or myoclonic seizures (58). *Massive bilateral myoclonus* causes falls in BMEI, DS, PME, and, rarely, JME (see next section). *Atypical absences with prominent atonia* and *negative myoclonus* are responsible for some falls in ECSWS (5,6). *Startle-induced seizures* may precipitate falls in patients with ESIS (37). *Tonic-clonic seizures* (usually not considered as falling seizures) are the most important cause of epileptic falls and injury from a general perspective. Falling seizures are not prominent in focal epilepsy syndromes; when present, they are usually *asymmetric tonic seizures, negative focal myoclonus,* or *focal seizures with prominent atonia* in patients with FLE (124,125). Video EEG monitoring is necessary to accurately diagnose the type of falling seizure (125).

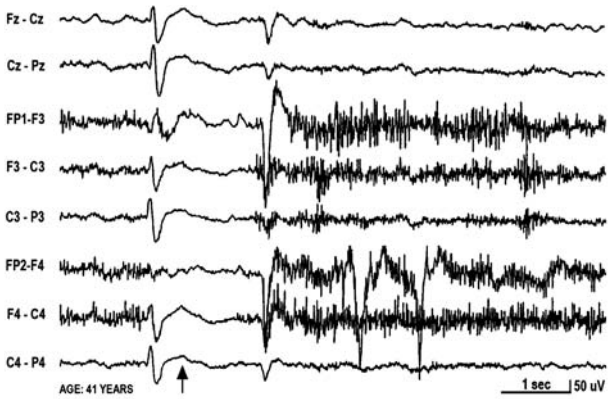

FIGURE 10-12. Spike and slow wave during an atonic seizure. The slow wave correlates with the muscle atonia (arrow). In this particular case, the slow wave is followed by diffuse voltage attenuation. *Source:* Adapted from Noachtar S, Wyllie E (232):197.

Epileptic Myoclonus

Myoclonus is a brief (<0.2-second) movement that occurs when motor neurons are involuntarily activated (positive myoclonus) or inhibited (negative myoclonus) because of cortical or corticothalamic hyperexcitability (epileptic myoclonus) or extrapyramidal, brainstem, or spinal cord dysfunction (non-epileptic myoclonus) (59,60). It can occur spontaneously or it can be triggered by movement (action myoclonus) or touch (reflex myoclonus). EMG-EEG polygraphy is the best way to distinguish non-epileptic from epileptic myoclonus: a ballistic or tonic EMG pattern (50- to 300-millisecond agonist burst, asynchronous/synchronous antagonist burst) and absence of an EEG correlate indicates *nonepileptic myoclonus;* a reflex EMG pattern (10-to 100-millisecond agonist burst, synchronous antagonist burst/silent period) and a cortical spike detected by routine EEG or burst-locked back-averaging indicates *epileptic myoclonus* (126,127). Non-epileptic myoclonus is beyond the scope of this chapter. Epileptic myoclonus or a *myoclonic seizure* can be bilateral or focal.

Bilateral epileptic myoclonus (bilateral and often symmetric myoclonic jerk) implies bilateral activation of homologous parts of the sensorimotor cortex by thalamic or brainstem inputs. The jerk can be mild (e.g., head nod) or it can be massive and lead to a fall. The latter is known as *massive bilateral myoclonus* (57). As a rule, consciousness remains intact during a single jerk, but it can be impaired with repetitive and frequent jerking (124). Bilateral myoclonus is the main seizure type in JME and BMEI and it is commonly expressed as *myoclonic absences* in EMA and as *myoclonic-atonic seizures* in EMAS (128). It may also occur as a minor seizure type in JAE and GEFS+. The bilateral myoclonus in idiopathic epilepsy is most likely *thalamocortical myoclonus* (primary bilateral myoclonus) (129). Bilateral myoclonus is also common in EME, DS, MEND, and PME (1,8–10). However, this may be the result of focal cortical discharges activating the thalamocortical apparatus or rapidly spreading to the contralateral cortex (secondary bilateral myoclonus). Large numbers of cortical foci firing in near synchrony can also masquerade as bilateral myoclonus. *Reflex bilateral myoclonus* is common in VPSE, PRE, and ESIS, but rare or absent in IPOLE (34–37).

Polyspike-waves, or *multiple spike-and-wave complexes,* are often seen in the EEG during bilateral myoclonus (Figure 10-13). The brief (<0.2-second) *myoclonic EMG burst* is time-locked to the spike component of the EEG discharge (57). Likewise, the repetitive jerks in *myoclonic absences* coincide with the spike component of the 3-Hz

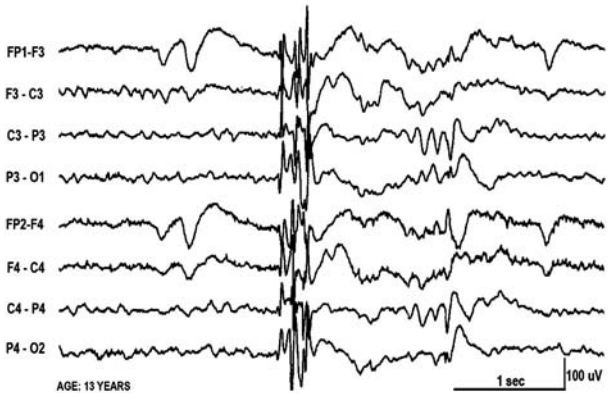

FIGURE 10-13. Polyspikes-waves during bilateral myoclonus. The spike component correlates with the myoclonic jerk. This was recorded from a patient with juvenile myoclonic epilepsy. Similar polyspike-waves also occur interictally. *Source:* Adapted from Pedley TA, Mendiratta A, Walczak TS (122):539.

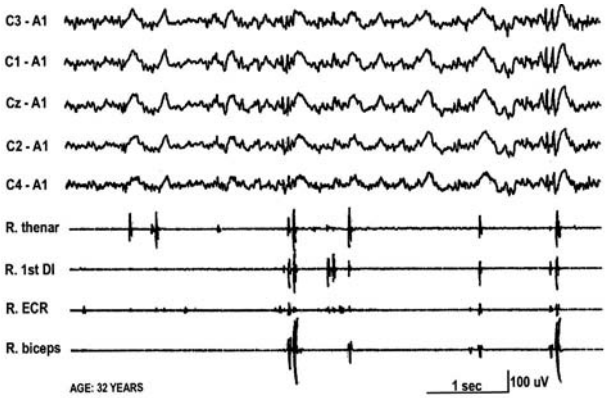

FIGURE 10-14. Focal EEG spikes and focal myoclonus. This is an EEG-electromyogram record of a patient with progressive myoclonus epilepsy and myoclonic jerks of the distal upper extremities. An EEG spike correlates with most (but not all) of the right thenar, first dorsal interosseus (first DI), extensor carpi radialis (ECR), and biceps muscle jerks. *Source:* Adapted from Shibasaki H, Hallett M (132):161.

spike-waves (53). Other EEG correlates of bilateral myoclonus are known, including *polyspikes* and *atypical spike-waves* (123,124).

Focal epileptic myoclonus is usually a *cortical reflex myoclonus;* this "epileptic" phenomenon is also viewed as an exaggerated response of the sensorimotor cortex (or a part of it) to normal sensory inputs (130). The distal extremity or facial muscles are preferentially involved in focal myoclonus, but any muscle of the body is potentially at risk. The jerks are usually random and isolated, but repetitive or periodic jerking can also occur (e.g., "cortical tremor," epilepsia partialis continua) (70). *Multifocal myoclonus* and *erratic myoclonus* are pathophysiologically related to focal, not bilateral, myoclonus. The focal myoclonus in EME, DS, MEND, and PME is usually a cortical reflex myoclonus (1,8–10,57). Children with EME, DS, and MEND usually exhibit *erratic myoclonus* and *myoclonic status epilepticus* (1,8,9). Many children with myoclonus who are diagnosed with LGS actually have EMAS (18). In LGS, myoclonus is most likely "focal" or "secondary bilateral," but, in EMAS, myoclonus is most likely "primary bilateral" (131).

Focal spikes are occasionally seen in the EEG of patients with focal myoclonus; however, they are not always time-locked with the *myoclonic EMG bursts* (Figure 10-14) (132). The demonstration of *premyoclonic EEG potentials* using jerk-locked back-averaging proves that the jerk is a cortical myoclonus (Figure 10-15) (59,132). Several tests are also available (e.g., evoked potentials, C-reflex) to determine whether cortical hyperexcitability is present in patients with myoclonus (see "Activation . . .") (132).

Focal-Onset Seizures Excluding Focal Myoclonus

Mesial temporal seizures (MTS) with typical auras, moderate cognitive dysfunction, and manual or oral automatisms indicate MTLE (61,27). MTS can also manifest as pure aura or as pure cognitive dysfunction. The classic aura is an epigastric rising sensation, but fear, déjà vu, and other auras also occur (133). As a rule, the seizure focus is ipsilateral to the automatism and contralateral to the dystonic hand (134). Postictal confusion is common and aphasia may occur with dominant temporal lobe seizures. *Lateral temporal seizures* (LTS) may start with a vestibular, auditory, visual, or psychic aura (62). Because of frequent intratemporal seizure spread, the distinction between MTLE and LTLE can be difficult without video EEG monitoring (135). The scalp EEG usually shows rhythmic theta or alpha activity in one or both temporal regions within 30 seconds of the clinical onset in MTS (Figure 10-16) and slightly later in LTS (62). At times, the initial change is voltage attenuation

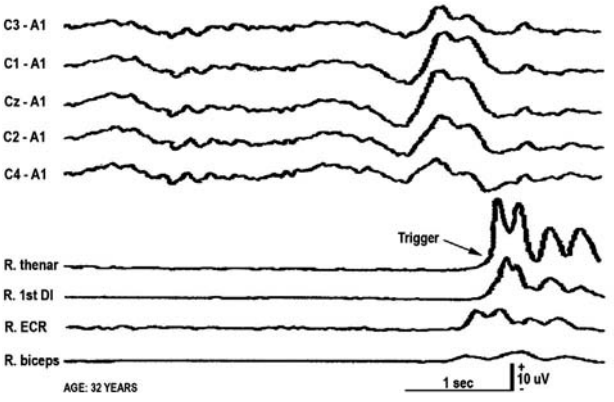

FIGURE 10-15. Focal EEG spike preceding a myoclonic jerk revealed by back-averaging. The onset of the myoclonic jerk in the thenar muscle (arrow) is used to trigger the data sampling process. The tracing shown is the average of 50 data samples acquired from the same patient in Figure 10-14 (abbreviations are also the same). *Source:* Adapted from Shibasaki H, Hallett M (132):162.

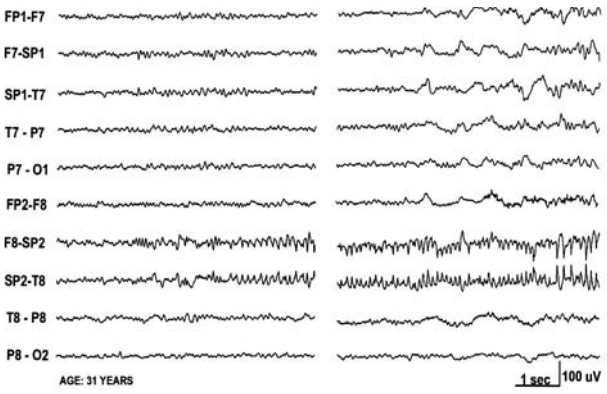

FIGURE 10-16. Mesial temporal lobe seizure onset. Rhythmic alpha activity is detected in the right sphenoidal electrode (SP2) 14 seconds before clinical onset (left tracing). Bilateral rhythmic delta activity appears in the scalp electrodes around the time of clinical onset (right tracing). *Source:* Adapted from Noachtar S, Wyllie E (232):203.

or low-voltage fast activity. Slower (2- to 5-Hz), more polymorphic, bilateral or diffuse patterns, and the absence of an EEG correlate, are more common in LTS than in MTS (133). Secondary generalization in MTLE and LTLE is less frequent than in FLE. The two FTLE phenotypes, mesial-FTLE and lateral-FTLE, share the electroclinical features of MTLE and LTLE, respectively (25).

Frontal lobe seizures are heterogeneous, but, in most FLE patients, the seizures are focal clonic, asymmetric tonic, or complex motor with or without mild cognitive dysfunction; they are usually brief and occur in clusters during sleep (29). Secondary generalization is common and occurs early. The scalp EEG can be diagnostic, normal, nonlocalizing, or obscured by artifact (29). Focal clonic seizures may be accompanied by a frontal low-voltage fast or rhythmic spike-wave activity (Figure 10-17) (29). The asymmetric posture in supplementary motor area (SMA) seizures may coincide with low-voltage fast activity or attenuation near the vertex (133). In mesial frontal seizures with complex automatisms, bifrontal voltage attenuation is often followed by rhythmic theta or delta activity (133). Bifrontal attenuation also occurs in orbitofrontal seizures, but frontopolar rhythmic alpha or beta activity is more common (133). The semiology of ADNFLE seizures (paroxysmal arousal, paroxysmal nocturnal dystonia, episodic nocturnal wanderings) suggests a mesial frontal or orbitofrontal focus, but this is seldom confirmed by EEG (136).

Occipital lobe seizures manifest as positive or negative visual phenomena in patients with OLE (64). Recording an occipital ictal discharge is confirmatory (Figure 10-18), but a falsely localizing EEG is not uncommon (133). In patients with PLE, *parietal lobe seizures* often begin as a somatosensory aura with no EEG correlate; any subsequent discharge is the result of seizure spread (64). Occipital and parietal lobe seizures can spread to the mesial temporal region, to the SMA, or to other parts of the frontal lobe. Secondary generalization is relatively frequent.

Rolandic seizures consist of paresthesia of the oral mucosa, hypersalivation, and contractions of face, tongue, and pharyngeal muscles resulting in dysarthria, dysphagia, and drooling (21). Focal centrotemporal attenuation or low-voltage fast activity occurs at the onset of seizure (137). Seizure spread results in contralateral jerking of the arm (rarely with the leg). Rolandic seizures indicate BCECTS, and rolandic spikes confirm the diagnosis (21). *Autonomic seizures* (nausea, vomiting, etc.) and eye deviation in children suggest BCEOS-1, and *visual seizures* suggest BCEOS-2 (22,23). The ictal EEG shows occipital and posterior temporal rhythmic theta or delta in BCEOS-1 and fast spike discharge in BCEOS-2 (137). Temporal or frontal seizure spread may occur. Focal seizures are also prominent in FFEVF and IPOLE (26,34). A number of idiopathic focal epilepsy syndromes have been

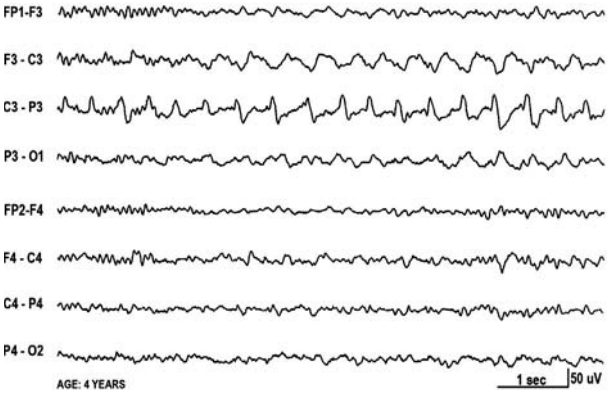

FIGURE 10-17. Frontal lobe seizure onset. A focal discharge with peak negativity at C3 is present during right shoulder jerking. This is followed by rightward head version and jacksonian spread of clonic motor activity to the right arm and right leg. Consciousness is not affected. *Source:* Adapted from Noachtar S, Wyllie E (232):209.

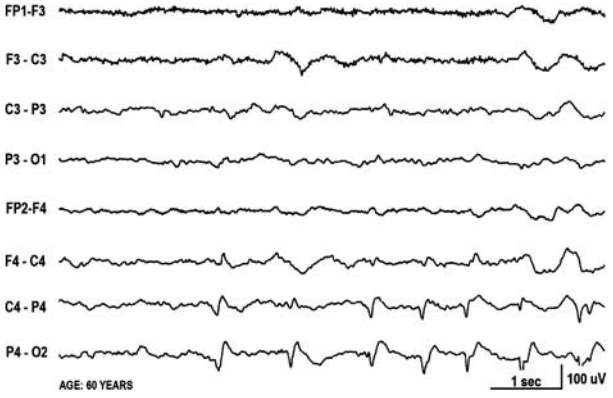

FIGURE 10-18. Occipital lobe seizure onset. The initial activity is a focal discharge with peak negativity at O2. Clinically, the patient experiences a visual aura (flashing lights) followed by leftward version of the eyes. Spread of seizure to the frontal lobe (not shown) results in left face and arm jerking. *Source:* Adapted from Noachtar S, Wyllie E (232):207.

described in infancy, but only BFNS and BFNIS are currently recognized by the ILAE (138–140).

Focal-onset seizures (other than focal myoclonus) are common in some encephalopathic epilepsy syndromes (MFSI, DS, ECSWS), and are also encountered in some of the "generalized" epilepsy syndromes (e.g., LGS, PME).

Focal Interictal Epileptiform Discharges

Focal interictal epileptiform discharges (IED) include sharp waves and slow waves, spike-waves, and spikes; we will refer to all of these variations as "spikes." Periodic lateralized epileptiform discharges (PLEDs) and temporal intermittent rhythmic delta activity (TIRDA) also have a significant correlation with epilepsy (141,142).

Temporal lobe spikes are common in symptomatic MTLE and LTLE; some are detected only after sequential or long-term EEG recording. Although no features of temporal spikes are absolutely specific for MTLE or LTLE, some caveats help distinguish the two syndromes: temporal spikes with a maximal *anterobasal temporal* (T1/FT9, T2/FT10, or sphenoidal electrode) negativity and a broad vertex positivity indicate MTLE (Figure 10-19); most LTLE spikes have a *broad temporal negativity* and no vertex positivity (122). Midtemporal and posterior temporal spikes are consistent with LTLE, but do not rule out MTLE (133). Temporal spikes are occasionally detected in mesial-FTLE, lateral-FTLE, and ADFLE, but the EEG is often normal; family history is key to recognize these syndromes (143). *Independent bitemporal spikes* are prevalent in MTLE and LTLE. In some patients with LTLE or MTLE, the scalp EEG is normal or only shows slow waves or mild asymmetries, suggesting an epileptogenic focus in the sulcal neocortex (LTLE) or hippocampal-limbic cortex (MTLE) in the absence of superficial neocortical hyperexcitability.

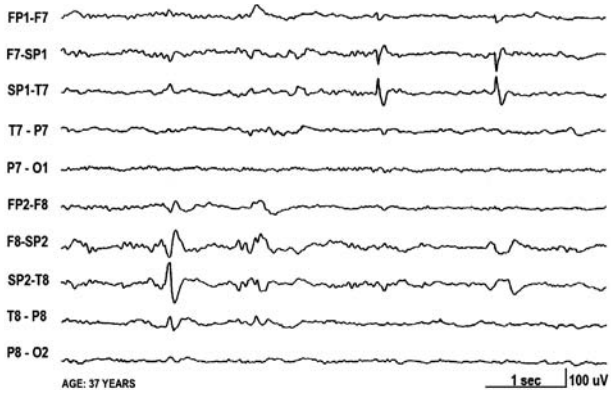

FIGURE 10-19. Anterior temporal spikes in the interictal EEG. In this particular case of mesial temporal lobe epilepsy, the interictal EEG demonstrates independent bitemporal spikes with peak negativity in the sphenoidal leads (SP1, SP2). However, all of the recorded seizures were right mesial temporal in onset. *Source:* Adapted from Noachtar S, Wyllie E (232):202.

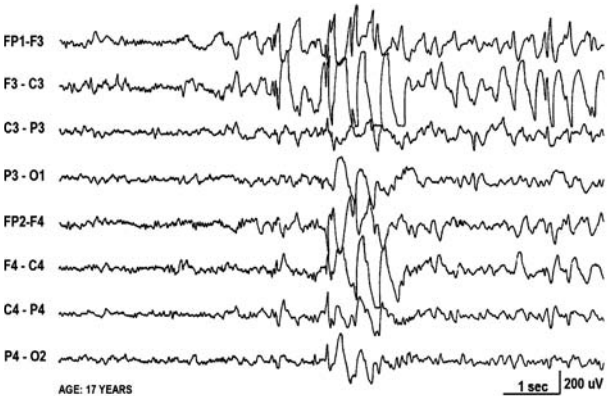

FIGURE 10-20. Frontal spikes and secondary bilateral synchrony. The patient has symptomatic frontal lobe epilepsy, a left frontal encephalomalacia, and a history of head injury. The spikes have a negative voltage peak at F3 and are often followed by secondary bilateral synchrony. *Source:* Adapted from Noachtar S, Wyllie E (232):205.

Extratemporal spikes are much more likely to be absent or nonlocalizing than temporal spikes (144). Although prevalence estimates vary, a localizing or lateralizing IED is detected in only about half of patients with symptomatic FLE, PLE, or OLE. The rest have normal EEGs, nonepileptiform EEG patterns, or nonlateralizing or nonlocalizing IEDs (133). *Secondary bilateral synchrony* occurs in PLE, OLE, and TLE, but is more common in FLE where the cause is often mesial-FLE (Figure 10-20) (133). *Midline spikes* (peak voltage at or near Fz, Cz, or Pz) also suggest a mesial frontal focus; when present only in sleep, they are difficult to distinguish from vertex waves (145). The scalp EEG can also be normal, nondiagnostic, or falsely localizing in mesial FLE. *Frontal intermittent delta waves* from an orbitofrontal focus are usually sharply-contoured and lateralized to the side of the focus (133). A frontal IED is detected in only about a third of ADFLE cases; some ADNFLE patients have a temporal IED, but most have a normal EEG (136). *Occipital spikes* with stereotyped features are the hallmark of BCEOS (see below); in contrast, a wide array of IEDs is found in symptomatic OLE, including occipital or bioccipital spikes, widely distributed IEDs, and falsely localizing IEDs (e.g., temporal or frontal spikes) (133). *Parietal spikes* are also elusive; patients with symptomatic PLE often manifest nonlocalizing or falsely localizing temporal or frontal IED (133).

Rolandic spikes are recognized by their stereotyped morphology, prominent central (C3/C4) or midtemporal (T7/T8) negative peak (a subtle frontal positive peak is also present), and dramatic accentuation by drowsiness and non-REM (NREM) sleep (Figure 10-21) (146). In a child with rolandic seizures, these spikes are virtually diagnostic of BCECTS; recording similar spikes in the child's asymptomatic siblings confirms the diagnosis. *Occipital spikes* with morphology similar to that of rolandic spikes indicate BCEOS-1 or BCEOS-2 (147,148). Many children

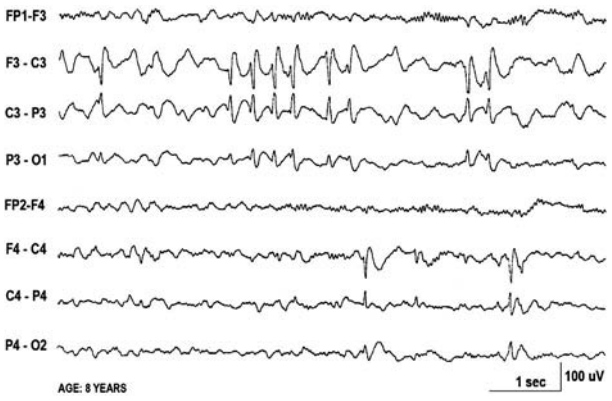

FIGURE 10-21. Rolandic spikes in the interictal EEG. In this child with rare nocturnal tonic-clonic seizures, the rolandic spikes are bilaterally independent, have a negative voltage peak at C3/C4, appear stereotyped, and occur mainly in non-REM sleep. These findings indicate benign childhood epilepsy with centrotemporal spikes (BCECTS). *Source:* Adapted from Noachtar S, Wyllie E (232):200.

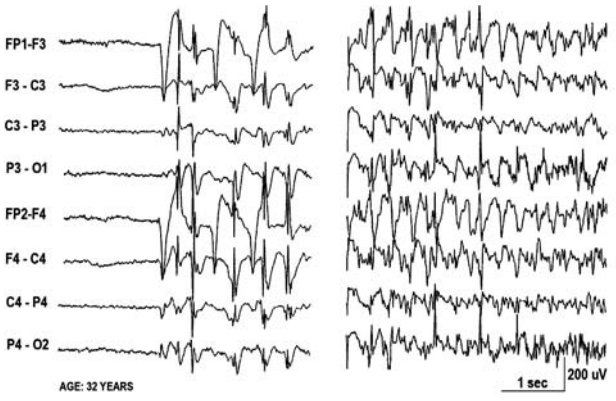

FIGURE 10-22. Tonic-clonic seizure, pretonic phase. Left tracing: onset of bilateral spike-waves and repeated myoclonic (clonic) jerks. Right tracing: discharge acquires a polyspike-wave appearance and rhythmic fast activity appears (onset of tonic phase). *Source:* Adapted from Noachtar S, Wyllie E (232):194.

with typical BCEOS-1 features have occipital and extraoccipital spikes, and some have extraoccipital spikes only, prompting suggestions to rename BCEOS-1 to Panayiotopoulos syndrome (147). Symptomatic OLE (e.g., celiac disease) should be excluded before diagnosing BCEOS-1 or BCEOS-2. The interictal EEG is normal in BFIS; *theta pointu alternant* is common but not specific for this syndrome (149).

Multifocal spikes are found (in order of decreasing probability) in the temporal, occipital, central, frontal, and parietal areas (150). In LGS, WS, DS, MFSI, and PME, multifocal spikes coexist with background slowing, slow spike-waves, hypsarrhythmia, or other abnormalities. The multifocal spikes in BCEOS-1 have a distinctive morphology and resemble rolandic spikes (147).

Tonic-Clonic and Related Seizures

Tonic-clonic seizure (TCS) is officially referred to as generalized tonic-clonic seizure (GTCS), but, like other "generalized" seizures, there is evidence that cortical activation is not generalized in TCS (see brief comment on the term "generalized") (151). As a rule, infants do not express TCS (152). Beyond the age of 2 years, TCS can occur in any epilepsy syndrome, although CAE might be an exception (see "Clinical Diagnosis . . ." above) (15). TCS progresses through a sequence of phases (65). The *pretonic phase* is heralded by forceful head or eye version, vocalization, or facial contraction. In the *tonic phase,* sustained muscle contractions give rise to stiff postures and an interference pattern in the EEG. The *vibratory phase* reflects the emergence of clonic activity, which is initially low in amplitude and irregular. In the *clonic phase,* tonic contractions are replaced by an alternating pattern of muscle jerking and relaxation. The *immediate postictal state* starts after the last jerk and is associated with an isoelectric EEG. *Postictal recovery* of consciousness takes about 30 minutes, but mild degrees of slowing can persist in the EEG for 24 hours or longer (153).

A nomenclature that incorporates the "initiating event" of TCS is better than one that only describes TCS as "primary" or "secondary generalized." Examples using this scheme are myoclonic-TCS, absence-TCS, and focal seizure → TCS. Note that a hyphen is used if the onset of the initiating event is bilateral and an arrow is used if it is focal. If there is no apparent initiating event, the TCS is simply called "TCS." TCS with subclinical focal onset can be represented as focal onset → TCS. The names can be refined as more data is obtained (e.g., frontal lobe seizure → TCS, P3 onset → TCS). In idiopathic generalized epilepsy, "primarily generalized TCS" can be *myoclonic-TCS, absence-TCS, tonic-TCS,* or other forms of TCS. In JME, TCS is often myoclonic-TCS or clonic-TCS (Figure 10-22). Features of *focal seizure → TCS* that help lateralize the seizure focus include asymmetric facial contraction or limb postures, forced head or eye version in the late pretonic or early tonic phase, asymmetric seizure termination, and asymmetric postictal changes. Ironically, these lateralizing signs have also been detected in "primarily generalized TCS" (154,155).

Status Epilepticus

Certain types of status epilepticus are likely to occur in some epilepsy syndromes than in others. *Tonic-clonic* status, the most common and most familiar form of status, is hardly expressed by patients with idiopathic epilepsy (156). *Tonic status* is rare and almost always caused by LGS; it is often associated with low-voltage fast activity in the EEG (157). *Atonic status* affects infants mainly, and often shows bisynchronous spike-waves in the EEG (157). *Absence status* consists of protracted (>30 minutes) confusion and waxing-waning bisynchronous 1- to 4-Hz spike-waves in the EEG

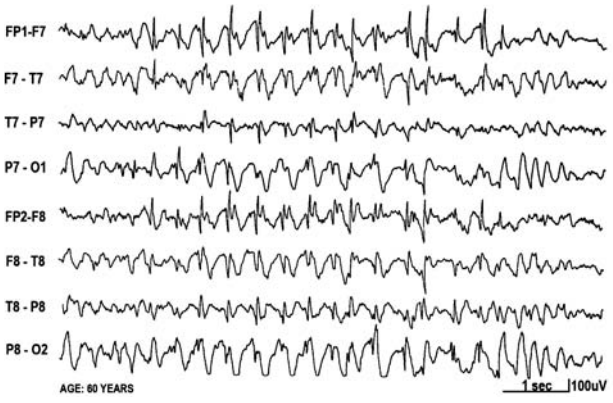

FIGURE 10-23. Spike-waves during absence status epilepticus. This EEG was recorded from a 60-year-old woman with tonic-clonic seizures since childhood (but without any history of absence seizures.) The status epilepticus started two days prior to this study. *Source:* Adapted from Fisch BJ (107):292.

(46,156). The absence status in idiopathic generalized epilepsy is often accompanied by myoclonus and ends in a tonic-clonic seizure (156). In contrast, the absence status in LGS occurs more frequently, lasts longer, begins and ends gradually, manifests tonic events, and never ends in a tonic-clonic seizure; the spike-wave discharge rate and amplitude are also more irregular (156). Absence status complicating an acute brain disorder in adults with or without a history of absence seizures is referred to as *de novo absence status* (Figure 10-23) (157). *Limbic status* (complex partial status), a rare complication of FLE and TLE, manifests as waxing-waning cognitive or behavioral symptoms and diffuse, bilateral, or focal rhythmic theta or delta activity (67). *Myoclonic status* is common in DS, MEND, EMAS, PME, and rare in JME (69). *Epilepsia partialis continua* is classic, but not specific, for RS; it can occur in destructive, neoplastic, and degenerative brain disorders (Figure 10-24) (70,158). *Autonomic status* is common in BCEOS-1, but it can also occur in children with symptomatic epilepsy and, exceptionally, in adults (159). The notion of *electrographic status* has been applied to the CSWS pattern in ECSWS and to the hypsarrhythmia in WS (160).

Activation of Seizures and Interictal Epileptiform Discharges in the Epilepsy Monitoring Unit

It is well established that sleep and sleep-wake transitions, sleep deprivation, hyperventilation, photic stimulation, and other stimuli can activate seizures or interictal epileptiform discharges (IEDs). These factors can increase the diagnostic yield of EEG during routine and long-term studies (161,162). While each of these factors may lower the seizure threshold, it remains poorly understood why some factors are more activating than others toward a particular seizure type or epilepsy syndrome.

Sleep-wake processes affect the expression of epilepsy, and different epilepsy syndromes vary in their susceptibility to sleep activation (163,164). As a rule, light NREM sleep favors seizures, light and deep NREM sleep enhances interictal epileptiform discharges, and REM sleep suppresses both (163,164). In ECSWS, bilateral slow (2- to 2.5-Hz) spike-waves are activated in slow-wave sleep. When spike-waves occur frequently and occupy ≥85% of slow-wave sleep, the pattern is called *continuous spike-waves in slow-wave sleep* or CSWS (Figure 10-25) (5,6). In the LKS form of ECSWS, the spike-waves have a temporal or parietal maximum and persist as more circumscribed discharges in REM sleep (5). Similar spike-waves occur in wakefulness, but in short bursts. In the non-LKS form of ECSWS, the spike-waves have a frontal maximum and disappear in REM sleep (6). The most dramatic effect of

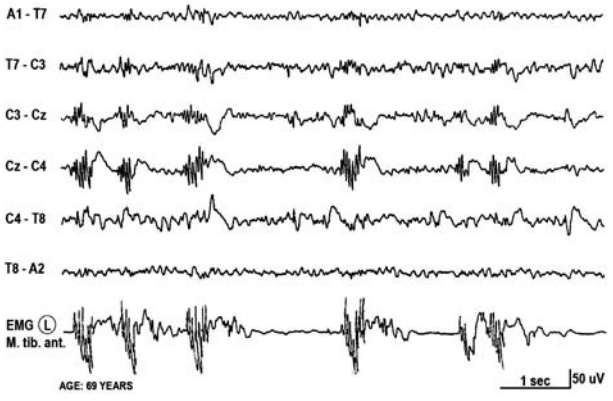

FIGURE 10-24. Polyspike-waves in epilepsia partialis continua. The polyspike-waves are periodic and focal (peak voltage left of the vertex is paradoxical), and correlate with the myoclonic jerks in the left tibialis anterior (electromyogram tracing). This was recorded in a patient with continuous jerking of the left foot and leg. *Source:* Adapted from Noachtar S, Wyllie E (232):211.

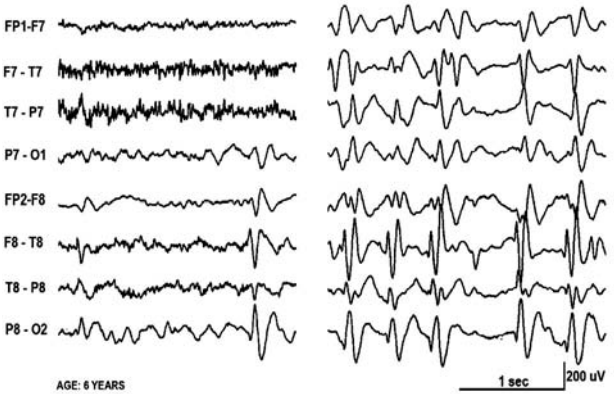

FIGURE 10-25. Interictal spike-waves in the LKS subtype of ECSWS. Left tracing: in wake, temporal spikes occur infrequently and tend to be focal (T8, P8 in the example shown). Right tracing: in slow-wave sleep, bilateral slow spike-waves occupy ≥85% of slow-wave sleep epochs (see also Figure 10-6). *Source:* Adapted from Pedley TA, Mendiratta A, Walczak TS (122): 555–556.

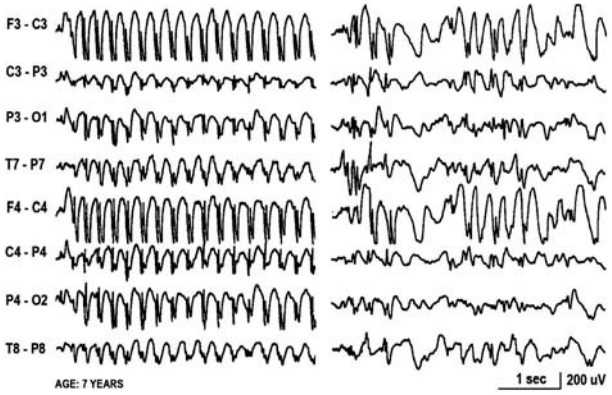

FIGURE 10-26. 3-Hz spike-waves and sleep-wake effects. Left tracing: in wake, they are more regular and uniform in appearance. Right tracing: in non-REM sleep, they appear fragmented and more irregular; sometimes they are asymmetric or focal and are misread as focal epileptiform discharges. *Source:* Adapted from Pedley TA, Mendiratta A, Walczak TS (122):523.

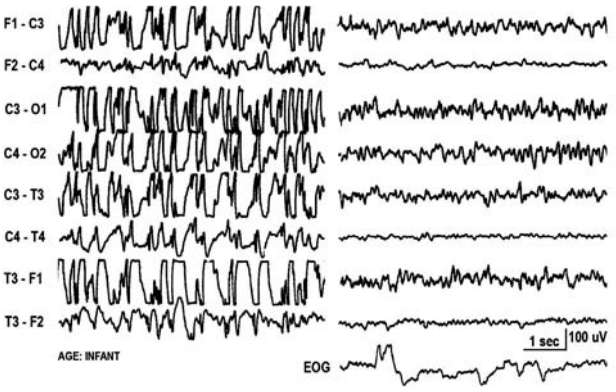

FIGURE 10-27. Hypsarrhythmia and sleep-wake effects. Left tracing: hypsarrhythmia is continuous in wake (also see Figure 10-8). It tends to fragment in non-REM sleep (not shown). Right tracing: hypsarrhythmia is suppressed during REM sleep (electro-oculogram tracing shows deflections consistent with eye movements in REM sleep). *Source:* Adapted from Hrachovy RA, Frost JD Jr. (123):414.

sleep on interictal spikes is seen in BCECTS, BCEOS-1, and BCEOS-2 (163,164). In BCECTS, *rolandic spikes* appear in large numbers as soon as the child falls asleep; *rolandic seizures* usually occur with nocturnal sleep and occasionally with daytime naps (21). In ADNFLE, *frontal lobe seizures* occur in clusters shortly after falling asleep or before awakening (24). Sleep activates *focal spikes* in MTLE, LTLE, and other symptomatic focal epilepsies (27–31). The activating effect of sleep on *focal seizures* is strong in FLE, modest in TLE, and minimal or lacking in OLE and PLE (165). The propensity of seizures to occur soon after awakening is a cardinal feature of JME, JAE, and EGTCS (13–15). In JME, *polyspike-waves* are accentuated by sleep onset, but *myoclonus* and *tonic-clonic seizures* usually occur after awakening from a full-night sleep or from a nap (13). Knowing that *3-Hz spike-waves* can appear irregular and fragmented in sleep helps to avoid misreading these waveforms as focal epileptiform discharges (Figure 10-26) (163). In LGS, sleep activates *paroxysmal fast activity* and *tonic seizures; slow spike-waves* are also accentuated, become more synchronous, and acquire a polyspike-wave appearance (4). In WS, *epileptic spasms* occur in clusters during sleep-wake or wake-sleep transition; *hypsarrhythmia* is more sustained in wakefulness, fragmented in NREM sleep, and suppressed in REM sleep (Figure 10-27) (3). Sleep also activates *multifocal spikes* and enhances their synchrony. The synchronizing effects of sleep can lead to recurring cycles of polyspike-waves and low-voltage intervals in WS or LGS, analogous to the burst-suppression pattern that is constantly present in OS and detected during sleep in EME.

Sleep deprivation is an effective means of activating *interictal epileptiform discharges* by helping to induce sleep in the patient (161). The majority of evidence suggests that there may be an additional activating effect of sleep deprivation that is independent of the effect of sleep (162). Some patients with previously normal EEGs who are sleep-deprived the night prior to the study will manifest interictal epileptiform discharges whether or not they fall asleep during the study. The efficacy of sleep deprivation in activating seizures is less well established. In one study, the rate of seizure activation from sleep deprivation was found to be nearly the same (~25%) in idiopathic generalized and temporal lobe epilepsy (166). However, it is difficult to separate the effect of sleep deprivation on cortical hyperexcitability from the effects of physical or emotional stress, drugs or substances, sleep disorders, and other factors that often coexist with or cause sleep deprivation (166). *In a recent study, sleep deprivation did not significantly change the seizure frequency of patients with focal epilepsy when performed in an inpatient setting that was relatively free of the stresses of everyday life* (167). The mechanism by which sleep deprivation activates epileptic activity is poorly understood. A recent study showed that sleep deprivation exerts its effects on interneurons that regulate the excitability of corticospinal neurons (168). Some syndrome specificity in the effect of sleep deprivation was also noted, but further studies are needed to clarify this finding (168).

Hyperventilation activates bisynchronous slow waves in the EEG of children, adolescents, and some adults; this effect is accentuated in some patients with epilepsy (162). In CAE, JAE, and other untreated idiopathic epilepsies, *typical spike-waves* and *absences* are easily activated with hyperventilation (Figure 10-28) (12,13). Given the variability in the ability of LGS patients to perform hyperventilation, the activation rate of *slow spike-waves* or *atypical absence* with hyperventilation is less certain (estimated as ≤50% in patients capable of performing hyperventilation) (161). The effectiveness of hyperventilation in activating

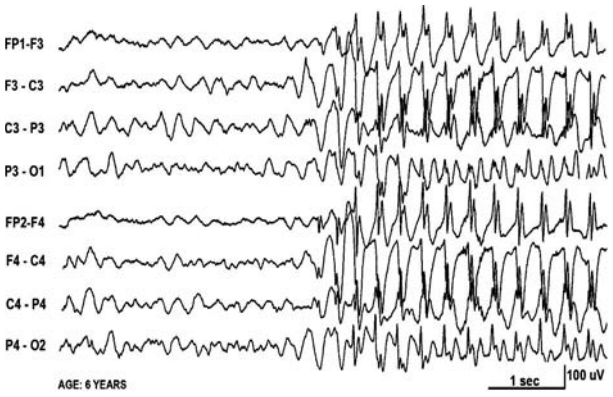

FIGURE 10-28. Hyperventilation-induced 3-Hz spike-waves and typical absence seizure. The seizure occurred after about 2 minutes of hyperventilation. Note the posteriorly-dominant bisynchronous slow waves induced by hyperventilation prior to the onset of the seizure. *Source:* Adapted from Pedley TA, Mendiratta A, Walczak TS (122):520.

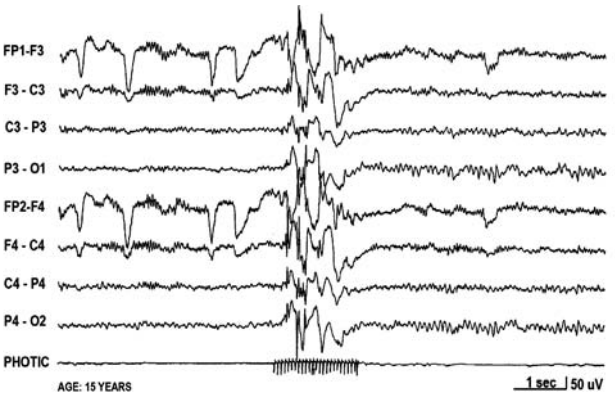

FIGURE 10-29. Photoparoxysmal response (PPR) and myoclonus. In this particular case of juvenile myoclonic epilepsy, intermittent photic stimulation at 16 Hz triggered a PPR (in the form of polyspike-waves) and a seizure (bilateral myoclonus). The brief PPR did not outlast the stimulus. *Source:* Adapted from Noachtar S, Wyllie E (232):194.

focal spikes or *focal seizures* has not been fully established. In one study, focal spikes or seizures were activated with hyperventilation in 11% of patients with complex partial seizures (169). However, a recent study of the effects of hyperventilation during routine outpatient EEG showed much lower activation rates for focal spikes (3.4%) and focal seizures (0.52%) in patients with focal epilepsy on their usual antiepileptic regimen (170). On the other hand, repeated hyperventilation during video EEG monitoring was found to be quite effective in activating seizures in patients with TLE whose antiepileptic drugs had been reduced or omitted (171). The effect of hyperventilation in patients with FLE and other focal epilepsies remains uncertain.

Photic stimulation can provoke a photoparoxysmal response or, rarely, a seizure in subjects who are photosensitive, some without epilepsy (161). The seizures triggered usually consist of tonic-clonic seizures, eyelid myoclonia, myoclonic arm jerks, or absence, but tonic seizures or occipital lobe seizures can also occur (172,173). The *photoparoxysmal response* consists of bisynchronous spikes, spike-waves, or slow waves with a broad scalp EEG potential (Figure 10-29) (172). It is considered the hallmark of photosensitivity and should be distinguished from photic-induced *occipital spikes, prominent photic driving,* and *photomyogenic (myoclonic) response*. The latter consists of eyelid or forehead electromyographic potentials that appear when the eyelid reflex latency is shorter than the flash interval (172). The prevalence of *photosensitivity* is: (a) high (30%–90%) in JME, DS, eyelid myoclonia with absences, and facial myoclonia with absences; (b) modest (10%–30%) in BMEI, JAE, CAE, EGTCS, EMA, EMAS, BCEOS-2, and the reflex epilepsies; and (c) very low in BCECTS and BCEOS-1 (174). Photosensitivity is also common in PME caused by Lafora disease, Unverricht-Lundborg disease, and late infantile and adult forms of neuronal ceroid lipofuscinosis (173). In both forms of neuronal ceroid lipofuscinosis, photic stimulation at low flash rates can elicit a *high-voltage photic driving spike response* (173). Photic-induced *occipital lobe seizures* suggest IPOLE, BCEOS-2, or symptomatic OLE. *Visual stimulation with geometric patterns* (e.g., stripes) can provoke a seizure or a photoparoxysmal response in subjects who are pattern-sensitive (most are also photosensitive) (175). The cause of *pattern-sensitivity* is usually one of the common photosensitive epilepsy syndromes; only rarely is it caused by "pure" VPSE. *Eye closure and elimination of central vision* activates occipital spikes in some patients with BCEOS-2, BCEOS-1, or symptomatic OLE; this phenomenon is known as *fixation-off sensitivity* or *scotosensitivity* (176).

Specific modes of activation other than visual stimulation can be revealing in selected patients (177,178). Seizure activation by *language-related tasks* (e.g., reading, talking) has been described in JME, PRE, and focal epilepsies (177). In PRE, reading triggers myoclonic jaw jerks, aphasia, absences, or tonic-clonic seizures. Seizures are also triggered by *nonverbal cognitive tasks* (e.g., calculation, praxis) in JME and reflex epilepsies. An *unexpected stimulus* (e.g., noise, touch) can provoke startle and myoclonus in BMEI or ESIS; the former is idiopathic and the latter is associated with cerebral palsy and mental retardation (178). Various *reflex focal seizures* have been encountered in patients with symptomatic epilepsy, including those triggered by somatosensory (e.g., touch, rubbing, tooth-brushing), proprioceptive (e.g., movements), thermal (e.g., hot water), and auditory (e.g., musicogenic) stimuli (177).

Evoked potentials can be informative in some epilepsy patients. Pattern-shift visual stimulation evokes *giant visual cortical potentials* (high-voltage P100) in some

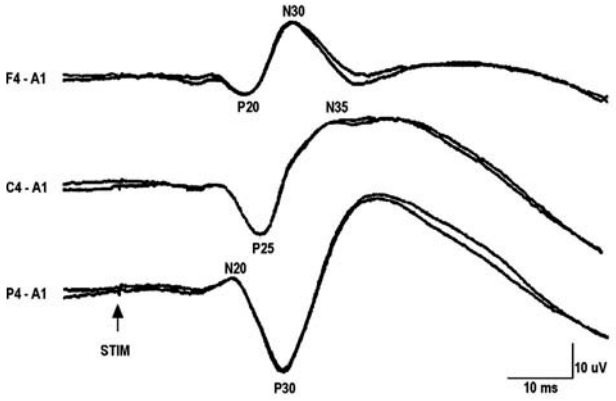

FIGURE 10-30. Giant somatosensory evoked potentials. P25, N30/P30, and N35 amplitudes are increased significantly (>(mean + 3SD)) but N20/P20 is not affected. Each tracing in the pair is the average of 200–400 data samples acquired after left median nerve stimulation (STIM) in a patient with progressive myoclonus epilepsy due to Lafora disease (see reference for other technical details). *Source:* Adapted from Ikeda A et al. (180):302

subjects who are photosensitive (179). Median nerve stimulation often triggers *giant somatosensory cortical potentials* (high-voltage P25, N30/P30, and N35; but N20/P20 is often normal) in PME and other diseases with focal cortical reflex myoclonus (e.g., postanoxic; see Figure 10-30) (180). This is unusual in JME and other epilepsy syndromes for which the main seizure type is bilateral thalamocortical myoclonus.

ETIOLOGICAL DIAGNOSIS

Epileptic disease is defined by the ILAE as a pathological condition with a single, specific, well-defined etiology (40). The search for an *etiology* should be guided by the epilepsy syndrome, and not by some vague concept or ambiguous terminology.

BRIEF COMMENT ON THE USE OF THE TERMS IDIOPATHIC, CRYPTOGENIC, AND SYMPTOMATIC

As defined by the ILAE, "symptomatic" epilepsy has one or more identifiable pathological disturbances in brain structure or metabolism, whereas "idiopathic" epilepsy has no such disturbance and the primary etiology is most likely genetic. Epilepsy that is probably symptomatic but without demonstrable pathology was previously referred to as "cryptogenic." Because the term "cryptogenic" is actually in and of itself cryptic, its use is no longer recommended (40).

Epilepsy Genes and Their Products

Idiopathic epilepsy syndromes are presumed to be caused by abnormal genes *(epilepsy genes)* and their products that disturb the brain's physiology without disrupting its structural integrity (181). Table 10-4 is a list of epilepsy genes that have been mapped or cloned in families with idiopathic epilepsy. Most are *Mendelian genes* encoding components of ion channels or their ligands (182). The same phenotype (e.g., CAE, JME, ADFLE, FEVS+, BFNC) can be produced by different genes, and the same gene (e.g., CLCN2, SCN1A, GABRG2) can give rise to different phenotypes. Moreover, the same genes producing well-defined ILAE syndromes can give rise to phenotypes that slightly deviate from the ILAE syndromes. Only a few epilepsy *susceptibility genes* are currently known (183). The three susceptibility genes that have been identified in JME are included in Table 10-4. The fact that complex inheritance is the rule in idiopathic epilepsy underscores our need to find more susceptibility genes and to determine how they interact to produce different epilepsy phenotypes (184). The importance of *de novo gene mutation* as a pathogenetic mechanism of idiopathic epilepsy is also becoming evident (185). This mechanism accounts for most sporadic forms of DS, ADFLE, and FTLE (186).

Chromosome Lesions with Significant Risk of Epilepsy

Table 10-5 is a list of chromosomal disorders with a significant risk of epilepsy. The risk of epilepsy is high in the Miller-Dieker (MDS), Wolf-Hirschhorn (WHS), and Angelman (AMS) syndromes, the ring-chromosome syndromes (r17 and r20), and the 15q inv-dup syndrome (187–190). The probability of a chromosomal disorder in a patient with mental retardation and epilepsy is about 6%, but this increases to 50% when multiple congenital abnormalities are present (188). Because of lack of specificity of the epilepsy syndromes, chromosomal disorders are recognized based on more distinctive features such as the "Greek helmet" appearance in WHS; the presence of lissencephaly in MDS; the craniofacial features, lack of speech, and distal myoclonus in AMS; and the retinal abnormalities in r14 (188). WHS and AMS also have characteristic EEG findings (191,192). The absence of dysmorphism and overt cognitive deficits makes r20 difficult to recognize (188).

Malformative and Neoplastic Brain Lesions

Cortical malformations are common pathological substrates of encephalopathic epilepsies and intractable focal epilepsies (193). Table 10-6 is a list of developmental

TABLE 10-4. EPILEPSY GENES. The following are shown from left to right: chromosome locus, abnormal gene (including candidate genes), protein encoded by the gene, and the resulting epilepsy phenotypes or syndromes. Three genes are regarded as susceptibility genes (SG); the rest are Mendelian genes. Abbreviations are used instead of full names (see Table 10-1 and footnote*). GABA = γ-aminobutyric acid.

Locus	Gene	Protein	Epilepsy Phenotypes
2q24	SCN1A	voltage-gated sodium channel, α1-subunit	GEFS+, DS, ICEGTCS*
2q24	SCN2A	voltage-gated sodium channel, α2-subunit	GEFS+, BFNIS*, FSAS*, EMAS•
19q13	SCN1B	voltage-gated sodium channel, β1-subunit	GEFS+, EMAS•
20q13	KCNQ2	voltage-gated potassium channel, α-subunit	BFNS, BFNS with myokymia*
8q24	KCNQ3	voltage-gated potassium channel, α-subunit	BFNS
2q22	CACNB4	voltage-gated calcium channel, β4-subunit	JME
3q27	CLCN2	voltage-gated chloride channel	JME, CAE, JAE, EGTCS
8q24	candidate	unknown	CAE, adult form of JME*
5q34	GABRA1	GABA-A receptor, α1-subunit	JME
5q31	GABRG2	GABA-A receptor, γ2-subunit	GEFS+, CAE , CAE-FS*
20q13	CHRNA4	nicotinic acetylcholine receptor, α4-subunit	ADNFLE
1q21	CHRNB2	nicotinic acetylcholine receptor, β2-subunit	ADNFLE
15q24	candidate	unknown	ADNFLE
10q24	LGI1	leucine-rich glioma inactivated protein	FTLE-lateral type
4q13	candidate	unknown	FTLE-mesial type
22q11	candidate	unknown	FFEVF
15q14	candidate	unknown	BCECTS
Xp22	ARX	Aristaless-related homeobox protein	X-linked WS
Xp22	STK9	serine-threonine kinase 9	X-linked WS
6p12	EFHC1[SG]	unknown	JME
6p21	BRD2[SG]	none; gene is a transcription regulator	JME
15q14	candidate[SG]	? nicotinic acetylcholine receptor, α7-subunit	JME

* These may represent phenotypic overlaps or variants of ILAE syndromes: benign familial neonatal-infantile seizures (BFNIS), intractable childhood epilepsy with frequent generalized tonic-clonic seizures (ICEGTCS), febrile seizures with afebrile seizures (FSAS), BFNS with myokymia, CAE and febrile seizures (CAE-FS), and the adult form of JME.
• SCN1B and SCN2A mutations were reported in a few patients with EMAS within large families with GEFS+.

malformations found in patients with encephalopathic epilepsy. Malformations (including neurocutaneous syndromes) are common in OS, WS, and LGS, and have been detected in some patients with EME, MEND, or ECSWS (193,194). The list of malformations attributed to gene mutation continues to grow (195). Table 10-7 is a partial list of cortical malformations for which a causative gene has been mapped or cloned. Classification schemes, genetic terms, and other details are available elsewhere (195,196). As a rule, children with *tuberous sclerosis*

TABLE 10-5. CHROMOSOME DISORDERS ASSOCIATED WITH A SIGNIFICANT RISK OF EPILEPSY. The risk of epilepsy (Risk) is an estimate based on reviews. Abbreviations are used for the epilepsy syndromes (see Table 10-1).

Disease/Syndrome	Lesion and Locus	Risk	Epilepsy Phenotypes or Syndromes
Wolf-Hirschhorn syndrome	del 4p16-ter	50–100%	WS, LGS, MEND, focal epilepsy
Miller-Dieker syndrome[1]	del 17p13-ter	~100%	WS, LGS, myoclonic epilepsy, focal epilepsy
Angelman syndrome[2]	del 15q11-13 mat	~90%	MEND, EMA, WS, LGS
15q inversion-duplication	inv-dup 15q11-13	~90%	LGS, WS, myoclonic epilepsy, ECSWS
1p terminal deletion	del 1p36-ter	50–75%	myoclonic epilepsy, focal epilepsy, WS
1q terminal deletion	del 1q42-ter	~50%	focal epilepsy, myoclonic epilepsy, WS
Ring chromosome 14	r14	~100%	FLE, other focal epilepsy, myoclonic epilepsy
Ring chromosome 20	r20	~100%	nonconvulsive status, FLE, TLE, LGS
Fragile-X syndrome[3]	del Xq27	20–40%	focal epilepsy, WS, LGS, rolandic-like spikes
Klinefelter syndrome	XXY	2–10%	focal epilepsy, absences epilepsy
Down syndrome	trisomy 21q	5–10%	focal epilepsy, WS, LGS, reflex epilepsy
Trisomy 12p[4]	trisomy 12p	?	EMA, other myoclonic epilepsy

[1] Caused by microdeletion or mutation of the LIS1 gene (LIS = lissencephaly) at the 17p13 locus.
[2] Usually caused by deletion of maternally derived 15q11-13 segment; occasionally caused by gene mutation.
[3] Usually caused by CGG expansion in the FMR1 gene at the Xq27 locus; point mutation and deletion are rare.
[4] More cases are needed to estimate the risk of epilepsy.

TABLE 10-6. DEVELOPMENTAL MALFORMATIONS IN THE ENCEPHALOPATHIC EPILEPSIES. Ohtahara Syndrome (OS), West Syndrome (WS), and Lennox-Gastaut Syndrome (LGS) are commonly associated with malformations, including those that manifest as neurocutaneous syndromes. Less commonly, malformations are detected in ECSWS and EME. However, there is a lack of evidence of a developmental malformation as the etiological basis of Dravet Syndrome or MFSI.

OS	hemimegalencephaly, agenesis of the corpus callosum, Aicardi syndrome, dentato-olivary dysplasia, diffuse cortical migrational disorders
WS	tuberous sclerosis, hemimegalencephaly, lissencephaly, agenesis of the corpus callosum, Aicardi syndrome, focal cortical dysplasia, septal dysplasia, Sturge-Weber syndrome, neurofibromatosis-1, incontinentia pigmenti, hypomelanosis of Ito
LGS	tuberous sclerosis, focal cortical dysplasia, subcortical band heterotopia, hemimegancephaly, dysembryoplastic neuroepithelial tumor, porencephaly, Sturge-Weber syndrome
ECSWS	focal cortical dysplasia, unilateral or bilateral perisylvian polymicrogyria, schizencephaly, arachnoid cyst, tumors
MEND*	bilateral polymicrogyria, partial agenesis of the corpus callosum, microcephaly with vermis hypoplasia

* All malformations associated with MEND listed above are based on a recent series of 29 patients (190).

manifest focal epilepsy or WS; the severity of the epilepsy correlates with the number and size of hamartomas (194,197). Most children with developmental delay and *lissencephaly* manifest epileptic spasms; hypsarrhythmia is not always present, but evolution toward LGS is common (194). The degree of neurological impairment in *subcortical band heterotopia* depends on the band thickness and amount of pachygyria, but almost all patients develop focal or encephalopathic epilepsy, particularly LGS (194). The risk of epilepsy is likewise high (~90%) in *periventricular heterotopia,* and intractability is common. About 80% of patients with *schizencephaly* have focal epilepsy; those with bilateral clefts usually have mental retardation and intractable epilepsy. The variable extent of *polymicrogyria* results in a wide range of clinical manifestations; bifrontal polymicrogyria and bilateral perisylvian polymicrogyria are often associated with mental retardation and focal epilepsy or LGS (194). Some children with bilateral or unilateral perisylvian polymicrogyria develop ECSWS (194). High-resolution MRI will often show a *focal cortical dysplasia* in patients with FLE, LTLE, MTLE, or other focal epilepsies (198). Further studies are needed to determine the role of *heterotopias* and *microdysgenesis* in epileptogenesis (199).

Vascular malformations manifest as cerebral hemorrhage, seizures, or intractable focal epilepsy (200). Seizures are more likely to occur in *arteriovenous malformation* with posterior frontal or temporal location, large size (>3 cm), or early presentation (age ≤20 years) (200,201). More than half of patients with *cavernous angioma* manifest seizures (200,202). Most of these patients experience the first seizure in middle age and develop focal epilepsy with no other symptoms. Because the risk of epilepsy is low in *venous angioma* and *capillary telangiectasia*, detecting these lesions should not deter the search for a more tenable etiology of the epilepsy syndrome. The *leptomeningeal angioma* in Sturge-Weber syndrome is often associated with focal epilepsy, WS, or LGS (196). Other neurocutaneous syndromes, moyamoya disease, and vein of Galen aneurysm can also present as early-onset focal epilepsy.

Neoplastic lesions of the brain account for 5% of epilepsies and 15% of adult-onset epilepsy (200). Most tumors causing epilepsy are low-grade or slow-growing and involve the superficial cortex, particularly the central, temporal, and parietal regions (200). The most common tumor detected in adults with epilepsy is *low-grade astrocytoma* (50%–70% of tumors in such patients). It is usually betrayed by seizures in the third and fourth decades of life, and it carries a high risk of epilepsy (70%). The risk of epilepsy is higher (92%) in *oligodendroglioma*. This tumor appears in the fourth or fifth decades of life or during childhood. Calcification is common (up to 90%). The incidence of seizures has been reported as 29%–60% in meningiomas, 29%–49% in glioblastoma multiforme, 20%–35% in brain metastasis, 10%–15% in leptomeningeal tumors, and 10% in primary central nervous system lymphoma (203). In some published surgical series for intractable focal epilepsy, *gangliogliomas* or *dysembryoplastic neuroepithelial tumor* (DNET) is the pathological diagnosis in as many as 50% of the resections (204,205). Both tumors have a predilection for the temporal and frontal lobes and are often associated with cortical dysplasias; some authors have classified them as cortical malformations (see Table 10-7) (195). *High-grade gliomas* are rarely found in epilepsy surgery patients (204,205).

Metabolic and Degenerative Diseases of the Brain

Inherited metabolic disorders can cause neurodegeneration, abnormal development, and epilepsy (206,207). Table 10-8 is a list of inherited metabolic diseases that can give rise to encephalopathic epilepsy or other epilepsy phenotypes. It is unlikely that this list is complete, but it illustrates the wide range of inherited metabolic diseases that are expressed as EME, OS, WS, LGS, or PME and the relative lack of evidence of similar diseases in DS, MEND, MFSI, and ECSWS (206,207). Although the range of metabolic

TABLE 10-7. CORTICAL MALFORMATIONS CAUSED BY GENE MUTATIONS. The list includes selected disorders of neuronal or glial proliferation or apoptosis (top), neuronal migration (middle), and cortical organization (bottom). Space constraints prevent us from listing the causes of cobblestone lissencephaly and other cortical malformations and from explaining the genetic terms used. The reader is encouraged to consult Online Mendelian Inheritance in Man, review articles, or textbooks for a more complete understanding of the classification and genetics of developmental malformations.

Disease	Locus	Gene	Protein
Tuberous sclerosis	9q32	TSC1	hamartin
Tuberous sclerosis	16p13.3	TSC2	tuberin
Microcephaly	9q34	CDK5RAP2	CDK5RAP2
Microcephaly	13q12.2	CENPJ	centromeric protein J
Microcephaly-periventricular heterotopia	1q31	ASPM	spindle-like
Microcephaly-periventricular heterotopia	8p23	MCPH1	microcephalin
Microcephaly-periventricular heterotopia	20q13.13	ARFGEF2	ARFGEF2
Microcelissencephaly (Seckel syndrome)	3q22-q24	ATR	AT-Rad3 related protein
Lissencephaly (Miller–Dieker syndrome)	17p13.3	LIS1, etc.	PAFAH1B1,14-3-3ε, etc
Lissencephaly	17p13.3	LIS1	PAFAH1B1
Lissencephaly	Xq22.3-q23	DCX	DCX
Lissencephaly (with abnormal genitalia)	Xp22.13	ARX	Aristaless-related protein
Lissencephaly (with cerebellar hypoplasia)	7q22	RELN	Reelin
Subcortical band heterotopia	Xq22.3-q23	DCX	DCX
Subcortical band heterotopia	17p13.3	LIS1	PAFAH1B1
Periventricular nodular heterotopia	Xq28	FLNA	Filamin-A
Periventricular nodular heterotopia	5p15	Unknown	Unknown
Bilateral frontoparietal polymicrogyria	16q13	GPR56	Unknown
Bilateral perisylvian polymicrogyria	Xq28	Unknown	Unknown

diseases in OS, WS, and LGS is wide, these diseases are far less common than malformative or destructive lesions (2–4). Table 10-9 is a list of common PME diseases, including the different forms of *neuronal ceroid lipofuscinosis* (208,209). Epilepsy phenotypes other than PME have been observed in some of the "PME diseases," (e.g., LGS in NCL, Lafora body disease, and sialidosis; WS in the juvenile form of neuronal ceroid lipofuscinosis ; see Table 10-8) (206,207). The risk of epilepsy in *juvenile Huntington disease* is notably high (30–90%), and 74% of patients with this condition have epileptiform discharges in the EEG (210).

Adult-onset neurodegenerative diseases generally carry a lower risk of epilepsy. While it is generally accepted that 10% of patients with Alzheimer disease manifest seizures, the incidence of epilepsy in this disease has not yet been established (211). The risk of epilepsy is mildly elevated in Wilson disease, Hallevorden-Spatz disease, and neuroacanthocytosis, but not in Parkinson and related diseases, with the possible exception of progressive supranuclear palsy (212).

Ischemic, Traumatic, and Other Destructive Brain Lesions

Destructive brain lesions caused by ischemic, traumatic, anoxic, and other forms of injury result in loss of neurons, encephalomalacia, cystic changes, gliosis, or atrophy (213). Static encephalopathy after *perinatal brain injury* is manifested as cerebral palsy, mental retardation, or both (214,215). Large vessel infarction with porencephaly and spastic hemiplegia may be complicated by focal epilepsy, WS, LGS, or ECSWS (214). Perinatal hypoxia-ischemia producing tetraplegia and mental retardation is frequently associated with encephalopathic epilepsy (214,215). The risk of epilepsy is also elevated in dystonic cerebral palsy

TABLE 10-8. INHERITED METABOLIC DISORDERS THAT MANIFEST AS ENCEPHALOPATHIC EPILEPSY, PME, OR OTHER SYNDROMES. PME is the epilepsy syndrome most consistently associated with an inherited metabolic disorder (see Table 10-9 below). EME is also typically associated with inherited metabolic disorders. Although OS, WS, and LGS are usually due to malformative or destructive lesions, a wide range of metabolic disorders have been described in these syndromes.

EME	nonketotic hyperglycinemia, pyridoxine-dependency, methylmalonic academia, propionic acidemia, D-glyceric acidemia, molybdenum cofactor deficiency
OS	nonketotic hyperglycinemia, pyridoxine dependency, carnitine palmitoyltransferase deficiency, cytochrome-c oxidase deficiency, Leigh disease
WS	phenylketonuria, pyruvate dehydrogenase deficiency, pyruvate carboxylase deficiency, leucine-sensitive hypoglycemia, hyperornithemia, isovaleric acidemia, pyridoxine-dependence, GM2 gangliosidosis, tetrahydrobiopterine deficiency, Rett syndrome, mitochondrial cytopathy, Menkes disease, PEHO syndrome, juvenile neuronal ceroid lipofuscinosis
LGS	phenylketonuria, homocysteinuria, maple syrup urine disease, metachromatic leukodystrophy, neuronal ceroid lipofuscinosis, Lafora body disease, sialidoses
PME	neuronal ceroid lipofuscinosis, Unverricht-Lundborg disease, Lafora disease, sialidoses, galactosialidoses, Gaucher disease, dentatorubral-pallidoluysian atrophy, myoclonic epilepsy with ragged-red fibers, neuroaxonal dystrophy, β-galactosidase deficiency, GM2 gangliosidosis, juvenile Huntington disease
MEND[1]	Rett syndrome
EMAS	glucose transporter-1 deficiency, late-infantile neuronal ceroid lipofuscinosis
Others[2]	GM1 and GM2 gangliosidoses, infantile neuroaxonal dystrophy, glut-1-deficiency, tyrosinemia type1, arginase deficiency, multiple carboxylase deficiency, tetrahydrobiopterin deficiency, methylene tetrahydrofolate reductase deficiency

[1] based on a recently published study of 29 cases (see Reference #190)

[2] epilepsy phenotypes that do not conform with ILAE-recognized syndromes or that are poorly characterized

as a result of basal ganglia injury (e.g., kernicterus) and in spastic diplegia as a result of prematurity-related periventricular necrosis (214). The overall risk of *post-traumatic epilepsy* is about 4%, but the risk is much higher (>50%) in injuries with depressed skull fracture, dural penetration, cortical damage, parenchymal hemorrhage, or retained foreign material (216). The risk of *post-stroke epilepsy* is almost the same (2.5%) for ischemic and hemorrhagic strokes (217). The most commonly identified etiology of epilepsy in the elderly is stroke (218). Myoclonus can occur soon after *anoxic brain injury* or several days later. Early postanoxic myoclonus can be focal, multifocal, or bilateral; the latter is associated with the worst prognosis (219). Delayed postanoxic myoclonus (Lance-Adams syndrome) is caused by interruption of voluntary movements by positive jerks or brief atonias, and is probably of subcortical origin (219).

Hippocampal sclerosis (HS) is characterized by neuronal cell loss, gliosis, and atrophy (similar to other destructive brain lesions) in parts of the hippocampus, with CA1 as the most vulnerable area (220). Extrahippocampal changes, such as amygdalar sclerosis and white-matter infiltrates, are common. In MTLE, HS is usually bilateral, but one side is usually more sclerotic. Some patients with mesial-FTLE (familial MTLE) also have evidence of HS on MRI (220). HS is also increasingly being detected in epilepsies with *dual pathology;* the other lesion is often a cortical malformation, but vascular malformations, tumors, and other lesions have also been detected (221,222). The association of HS with another lesion is more than coincidental: the associated lesion and HS may have a common developmental source, or the associated lesion may have caused HS through kindling (223). A more plausible theory is that the *associated lesion* predisposed the patient to *febrile seizures* or *status epilepticus* (or subclinical epileptic events) that damaged the hippocampus during a period of rapid growth (before the age of 5 years) in a child with genetic susceptibility (specific factors unknown) (221,224).

Inflammatory and Infectious Diseases of the Brain

CNS infections, such as *cysticercosis* and *tuberculomas,* remain important causes of epilepsy in some parts of the world (200). The risk of epilepsy is 10%–22% in *viral encephalitis* and 2%–13% in *bacterial meningitis;* the risk is not increased in uncomplicated viral meningitis (225). Encephalopathic epilepsies (e.g., WS) may occur in infants with *congenital infections* from toxoplasma, cytomegalovirus, or other organisms. Human herpesvirus 6B has recently been implicated as a cause of MTLE (226). It has been estimated that 6% of patients with *HIV infection* manifest seizures or epilepsy caused by HIV encephalitis, toxoplasmosis, progressive multifocal leukoencephalopathy, and other lesions (227). *Subacute sclerosing panencephalitis* (SSPE) should be suspected when children with a history of measles develop progressive dementia and myoclonus. The EEG is diagnostic if periodic high-voltage sharp- and slow-wave complexes appear every 3–8 seconds on an attenuated background (Figure 10-31) (228). *Creutzfeld–Jakob disease* (CJD) is suggested by the triad of rapidly progressive dementia, myoclonus, and periodic sharp-wave complexes (Figure 10-32) (229). *Rasmussen encephalitis*, the pathological substrate of RS, is a chronic inflammatory process of unknown cause

TABLE 10-9. ETIOLOGY OF PROGRESSIVE MYOCLONUS EPILEPSY. The different forms of neuronal ceroid lipofuscinosis (NCL) are listed first followed by other diseases causing PME. The inheritance pattern is autosomal recessive in all diseases except some adult NCL and DRPLA (autosomal dominant) and MERRF (maternal inheritance).

Disease	Locus	Gene	Product
Infantile NCL (Santavuori-Haltia)[1]	1p32	CLN1	palmitoyl-protein thioesterase-1
Late infantile NCL (Jansky-Bielschowsky)	11p15.5	CLN2	lysosomal peptidase
Juvenile NCL (Batten or Spielmeyer-Vogt)	16p12.1	CLN3	probable lysosomal protein
Adult NCL (Kuf)	unknown	CLN4	unknown
Finnish variant of late infantile NCL	13q21	CLN5	unknown
Early juvenile variant of late infantile NCL	15q21	CLN6	unknown
Turkish variant of late infantile NCL	unknown	CLN7	unknown
Northern epilepsy variant of juvenile NCL	8p22	CLN8	putative transmembrane protein
Unverricht-Lundborg disease	21q22.3	CSTB	cystatin B
Lafora disease A	6q24	EPM2A	laforin
Lafora disease B	6p22.3	EPM2B	malin
Sialidosis type 1 (cherry-red spot myoclonus)	6p21.3	NEU	lysosomal neuraminidase
Galactosialidosis	20q13	PPCA	cathepsin A
Gaucher disease type 3	1q21	GBA	acid β-glucosidase
DRPLA[2]	12p13.31	DRPLA	putative cytoplasmic protein
MERRF[3]	MtDNA	$tRNA^{lys}$	lysine-tRNA

[1] Excluded from the group of progressive myoclonus epilepsies by some authors.
[2] Dentatorubral-pallidoluysian atrophy; caused by expansion of the trinucleotide CAG in the DRPLA gene.
[3] Myoclonic epilepsy and ragged-red fibers; caused by mutation in the mitochondrial (MtDNA) $tRNA^{lys}$ gene.

that predominantly affects one hemisphere and results in epilepsia partialis continua, intractable epilepsy, and progressive neurological deficits (230). Various *noninfectious inflammatory processes* can manifest as chronic meningitis, encephalitis, or vasculitis and cause recurrent seizures as a result of immune-mediated tissue injury, cerebral infarction, or other destructive effects. The risk of epilepsy in *multiple sclerosis* is three to six times higher than the adult population; seizures can be the presenting symptom, or they can be associated with relapses (231).

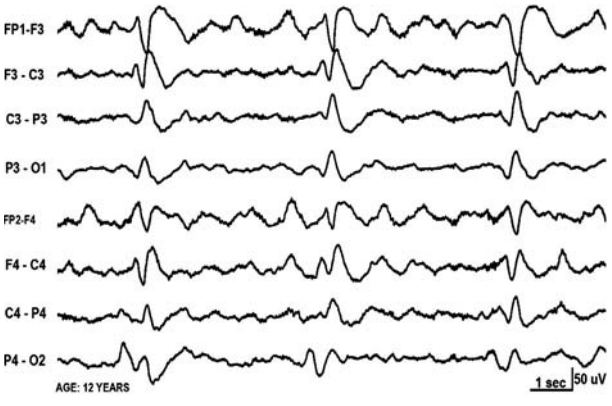

FIGURE 10-31. Periodic epileptiform discharges in subacute sclerosing panencephalitis (SSPE). High-voltage bilateral sharp waves appear periodically every 3–8 seconds and stand out against an attenuated background activity. *Source:* Adapted from Klass DW, Westmoreland BF (234):102, with permission of Mayo Foundation for Medical Education and Research.

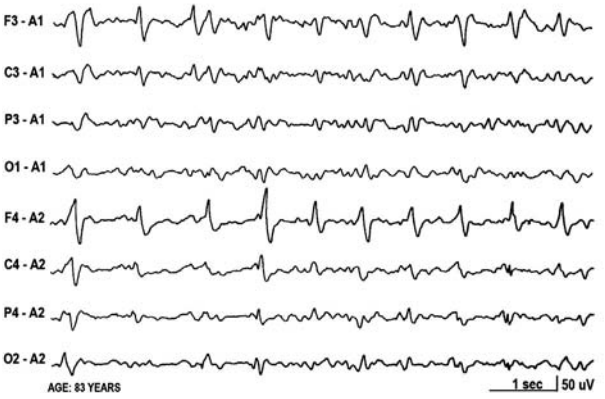

FIGURE 10-32. Periodic epileptiform discharges in Creutzfeldt-Jacob disease (CJD). The sharp waves are bifrontal and repeat approximately every 1 second. The background activity is often slow and attenuated. *Source:* Adapted from Fisch BJ (107):324.

CONCLUSION

Having described how an *epilepsy syndrome* is identified based on age, electroclinical features, and other data, we wish to conclude this chapter with a brief comment on the role of epilepsy syndrome diagnosis in the general context of epilepsy diagnosis and epilepsy health care.

The place of epilepsy syndrome diagnosis in the larger scheme of *epilepsy diagnosis* can be understood in terms of the general methods of neurology. The evaluation of a neurological problem begins with data acquisition and proceeds toward a sequence of "diagnoses" in which the symptoms, the syndrome, the anatomical defect and physiological disturbance, and the disease or etiology are determined. The diagnoses are then arranged into priority levels or "*axes*." This multiaxial approach, which was formally implemented in psychiatry (in the Diagnostic and Statistical Manual of Mental Disorders), is suitable for any complex and multifaceted medical disorder such as epilepsy. The choice of axes and the order of priority are arbitrary. In epilepsy diagnosis, the axes may be arranged in this order: Axis I: epilepsy syndrome; Axis II: epileptic disease; Axis III: seizure types; and Axis IV: seizures focus. The scheme may also be expanded as needed to include other pertinent data (e.g., Axis V: other medical disorders, and Axis VI: psychosocial problems/quality of life).

Epilepsy syndrome diagnosis is only one of the tasks in the grand scheme of *epilepsy health care*. The manner in which diagnostic and therapeutic tasks are implemented by the epilepsy health care team is shown in Figure 10-33. The general method of neurology (interpretation of attacks → localization → seizure diagnosis → syndrome diagnosis → disease diagnosis) is used as a "backbone" (thicker boxes), but the emphasis on linearity and unidirectionality is reduced to allow for flexibility and bidirectionality. In other words, the evaluation process proceeds according to the fundamental sequence, but, whenever necessary, the physician should always be prepared to leave a task with only a presumptive diagnosis, complete the next task in sequence, and return to the unfinished task when data are already sufficient for a definitive diagnosis.

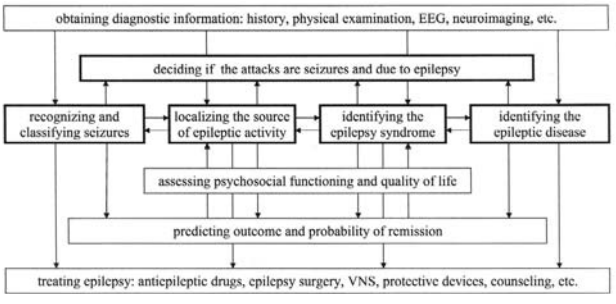

FIGURE 10-33. The care of patients with epilepsy involves performing specific tasks (one of which is identifying the epilepsy syndrome). The general method of neurology is used as "backbone" (thicker boxes), and the flow chart arrows indicate greater flexibility in moving from one task to another.

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11

NEUROLOGIC AND CARDIOVASCULAR DISORDERS THAT RESEMBLE SEIZURES

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While some clinical presentations of seizures are quite characteristic and easily classified, many symptoms can be difficult to differentiate from those of other neurological syndromes or from neurological symptoms caused by systemic diseases. This chapter reviews both neurological and syncopal events that mimic seizures, including specific etiologies in adult and pediatric patients. Etiologies covered include systemic disturbances, movement disorders, cerebrovascular disorders, migraines, and syncope (additional information can be found in Chapter 12, Sleep Disorders That Resemble Seizures).

ADULT DISORDERS

Metabolic Disorders

Most metabolic disorders produce systemic effects with nonspecific neurological symptoms, such as altered mental status or lethargy. The signs and symptoms of metabolic disturbances are usually most marked when associated with rapid and severe changes from the homeostatic state. Some metabolic derangements result in focal neurological signs and symptoms. In addition, many of these abnormalities lower the seizure threshold, further increasing the difficulty of the etiological diagnosis. As the etiologies may be diverse and include electrolyte, metabolic, and endocrine abnormalities, these will be reviewed separately.

Disorders of sodium balance, in particular, are most severe when rapid and drastic changes in sodium levels occur. Hyponatremic symptoms may be suggestive of complex partial seizures or nonconvulsive status epilepticus, as patients frequently present with confusion and lethargy. Patients may also note headache, restlessness, generalized weakness, and nausea (1–3). Rarely, focal neurological signs may be present, suggesting a postictal paralysis (monoparesis or hemiparesis) or aphasia (2). Similarly, hypernatremia may also present with altered mental status that can be mistaken for complex partial seizures or nonconvulsive status epilepticus.

Hypocalcemia and hypomagnesemia present in similar fashion, with confusion, agitation, hallucinations, delusions, and, rarely, movement disorders of chorea and parkinsonism (2), again suggesting complex partial seizures or nonconvulsive status epilepticus. The initial presentation may include perioral and distal numbness, which may suggest a partial sensory seizure, followed by tetany in a similar distribution (4). Less frequently, hypercalcemia may be seen with increasing weakness, fatigue, lethargy, and confusion, which may again be suggestive of nonconvulsive status epilepticus (4). These syndromes may also occur with either hypoparathyroidism or hyperparathyroidism, respectively (5).

Hyperglycemia and hypoglycemia may produce focal transient neurological deficits that can resemble postictal aphasia or hemiparesis or produce movement disorders that can be mistaken for focal motor seizures. Shaw (6) described a patient with paroxysms of chorea and ataxia associated with hypoglycemia caused by an insulinoma. Others (7–9) described patients with diabetes who presented with nocturnal episodes of hemiparesis, hemianopsia, or aphasia, frequently with demonstrated hypoglycemia. Unfortunately, correction of the low blood sugar does not always ameliorate symptoms. With nonketotic hyperglycemia, patients may similarly have focal weakness or movement disorders, which resolve with the reintroduction of a normoglycemic state (10,11).

The systemic effects of uremia, hepatic failure, and sepsis may all produce an encephalopathic state that may be indistinguishable from confusion, lethargy, and word-finding difficulties seen in nonconvulsive status epilepticus patients (12). Both conditions, uremia and nonconvulsive status epilepticus, may have associated myoclonus or asterixis that can resemble focal motor seizures or myoclonic seizures.

Similarly, the systemic effects of Hashimoto's thyrotoxicosis may also result in an encephalopathic state or in stroke-like episodes (13,14). The vasculitic variant of this disease is associated with intermittent episodes of confusion and focal neurological deficits, which may appear as a complex partial seizure, nonconvulsive status epilepticus, or postictal state. The diffuse progressive variant of the disease is less frequently confused with seizures, as it presents with a more slowly progressive confusion, lethargy, and psychosis. In either variant, patients may experience tremors or myoclonus, which may suggest focal motor or myoclonic seizures. However, most patients have elevated antithyroid antibodies and respond well to treatment with immunosuppressants, which certainly helps differentiate this syndrome from epilepsy.

Finally, mitochondrial diseases have immensely variable presentations, with primarily neurological symptoms. While mitochondrial diseases are frequently associated with seizures in and of themselves, the other associated symptoms may also be confused with seizures. Specifically, mitochondrial encephalopathy with lactic acidosis (MELAS) often presents with stroke-like episodes, particularly including visual hallucinations and distortions that may be difficult to differentiate from occipital seizures without EEG guidance (15). Many of the mitochondrial diseases may present with intermittent paroxysms of focal or generalized weakness or movements disorders, which may suggest postictal paralysis, atonic seizures, or focal motor seizures.

Thus, numerous systemic electrolyte, endocrine, and metabolic disorders may be misinterpreted as various forms of epilepsy. Assessment of other medical conditions, medication use, associated symptoms, and simple laboratory tests may help identify these conditions. Finally, these abnormalities contribute to a lowered seizure threshold, which may further complicate the differentiation between metabolic mimics and true seizures.

Movement Disorders That Mimic Seizures

Many movement disorders—specifically, hyperkinesias—can mimic partial motor seizures. The history and phenomenology of the abnormal movements are extremely useful in helping to differentiate the two conditions. Triggers for the movements, and movements that vary, are more characteristic of a movement disorder than of epilepsy. In general, seizures involve fast, rhythmic movements, whereas movement disorders involve slower and regular rhythms such as tremor, or more erratic jerks such as dystonia, myoclonus, or ballismus. Chorea, athetosis, and ballismus are considered to be on the same continuum of hyperkinetic disorders.

The term *chorea*—derived from the Greek word *choreia,* meaning "a dance"—refers to a hyperkinetic disorder characterized by brief, jerky, nonrhythmic movements that shift randomly from one body part to another. Typically, bilateral involvement is seen. Chorea may be seen in a wide variety of conditions affecting the basal ganglia, but it is most often associated with Huntington's disease, Sydenham's chorea after streptococcal infections, or stroke. It is also associated with various systemic disorders such as hyperthyroidism, systemic lupus erythematosus, primary antiphospholipid antibody syndrome, or paraneoplastic syndromes. Hormonal changes associated with oral contraceptive use or pregnancy are also recognized causes of chorea. In contrast, focal motor seizures tend to be stereotyped rhythmic movements affecting one part of the body with or without spread. If progressive involvement is seen, it typically follows the pattern of the motor homunculus and this pattern of progression is known as the "Jacksonian march." Thus, obtaining the relevant history and the clinical phenomenology will help to distinguish the two conditions.

Athetosis consists of slow, continuous writhing movements affecting the limbs, trunk, head, face, or tongue. The limbs can be affected unilaterally or bilaterally. It is often seen with lesions affecting the basal ganglia resulting from a variety of causes, such as stroke, tumor, demyelination, or infection, or it may be drug-induced. It typically occurs in association with chorea, and is then referred to as *choreoathetosis*. In the pediatric population, athetosis is associated with perinatal injury to the basal ganglia and thalamus. The phenomenology of the movements is distinct from that of focal motor seizures.

The term *ballismus* or ballism is derived from the Greek word meaning "to throw." Ballismus is another hyperkinetic disorder characterized by rapid, violent, flinging or flailing, high-amplitude movements of the limbs, predominantly affecting the proximal muscles. These movements typically affect one side of the body, and this phenomenon is known as hemiballismus. In contrast, focal seizures are stereotyped, rhythmic, and predictable movements. Ballism can be caused by a variety of conditions that affect the striatum or subthalamic nucleus, including structural lesions such as infarction and tumor, or systemic disorders such as hyperglycemia (16,17). Medications such as phenytoin, levodopa, and oral contraceptives have also been known to cause ballismus.

Dystonia is characterized by paroxysmal sustained muscle co-contractions of the agonist and antagonist, which can result in twisting, repetitive movements or abnormal postures of a body part (18). The movements are usually slow but can also be quick and jerky, and have some rhythmic component; they often affect the limbs, but facial muscles can also be involved. The movements may be confused with those seen in partial seizures. Triggers for these movements include anxiety or stress. Some patients have "sensory tricks" that consist of various maneuvers or positions that decrease the dystonia. Dystonia is caused by abnormal basal ganglia function, and has been associated with dysfunction of the brainstem and spinal cord inhibitory interneuronal circuits and with altered thalamic control of cortical motor

planning and execution (19). It can be idiopathic or secondary to a variety of causes, including strokes, tumors, neurodegenerative processes, medications, and various toxic substances.

Myoclonus is characterized by sudden, shock-like, brief involuntary movements that are caused by muscle contraction (positive myoclonus) or inhibition of muscle contraction (negative myoclonus). It can be restricted to certain muscle groups, or it can involve certain body segments, or the entire body. There are numerous causes of myoclonus, and it is typically divided into four major groups:

1. Physiological (e.g., hiccups)
2. Essential (also known as hereditary or idiopathic)
3. Symptomatic, with an underlying abnormality (toxic, metabolic, infectious, anoxic causes)
4. Epileptic, with myoclonus as part of an epileptic syndrome such as juvenile myoclonic epilepsy

Benign essential myoclonus is a hereditary disorder with an autosomal dominant pattern of inheritance. Symptoms typically consist of myoclonic jerks in the arms or trunk, which may be seen in association with dystonia. Symptomatic myoclonus is typically associated with an underlying systemic disturbance, such as infectious, toxic, or metabolic disturbances. Symptomatic myoclonus may be a manifestation of neurodegenerative disorders, stroke, or injury to the spinal cord (spinal myoclonus). As mentioned earlier, myoclonus may be a feature of an underlying epilepsy syndrome, such as juvenile myoclonic epilepsy. EEG is an essential tool to distinguish between epileptic and non-epileptic myoclonus, since non-epileptic myoclonus does not have any EEG correlate. Occasionally, electromyography may be helpful in that the electromyographic burst seen in epileptic myoclonus is usually short, lasting less than 50 milliseconds, whereas that seen in non-epileptic myoclonus lasts 200–300 ms (20). The presence of a cortical EEG onset potential can also be established in some cases using back-averaging (i.e., recording and averaging the EEG during the time period immediately preceding the onset of the electromyogram potential caused by myoclonus).

Tics are an extremely heterogeneous group of disorders. They consist of brief, intermittent, involuntary movements (motor tics) or sounds (phonic tics) that may be suppressed briefly. They have a variety of etiologies, including structural lesions, genetic abnormalities, psychiatric disorders, and streptococcal infections (21,22), or they may be seen in normal individuals. Patients typically describe an urge that builds and is relieved by the tic. Tics commonly begin in childhood and peak in adolescence. Complex motor tics such as eye blinking may occasionally be confused with absence seizures; however, patients do not have any alteration of awareness. Other complex motor tics such as head shaking, jumping, and obscene gestures are less likely to be confused with seizures, because they are usually not stereotyped and can be briefly suppressed by suppressing the urge to tic.

Hemifacial spasm is a disorder that may be mistaken for focal motor seizures. It is characterized by irregular contractions of the facial muscles, typically on one side of the face, though bilateral involvement has also been reported (23). It is caused by spontaneous firing of the facial nerve, typically resulting from vascular compression after the nerve exits from the brainstem, or it may occur sporadically; rarely, demyelination in the brainstem caused by multiple sclerosis plaques may be the cause. In the case of vascular compression, surgical decompression may be an effective treatment. Occasionally, there is an association with a past history of Bell's palsy or injury to the facial nerve. Additionally, synkinesis after Bell's palsy, characterized by co-contraction of the facial muscles related to aberrant regeneration of the facial nerve, may sometimes mimic focal motor seizures. The history and EEG will help to differentiate the two conditions.

Paroxysmal kinesiogenic dyskinesia is a hyperkinetic disorder characterized by recurrent attacks of brief movements that may include any combination of dystonic postures, chorea, athetosis, and ballism (24). These movements may be unilateral or bilateral, and are typically brief, lasting seconds, and always less than 5 minutes. Triggers for these movements include sudden movements, hyperventilation, or startle. The primary form carries both an autosomal dominant and a recessive inheritance pattern (25), whereas the secondary forms may result from other disorders such as multiple sclerosis (26). Paroxysmal nonkinesiogenic dyskinesia is similar, but it is not triggered by motion, but rather by a number of substances, including coffee or alcohol. It may also be a manifestation of psychiatric disease. The movements typically last longer, on the order of minutes to hours.

Tardive dyskinesia and *tardive dystonia* are typically associated with dopamine antagonist medications, such as antipsychotics, antiemetics, and even antidepressants. Tardive dyskinesia consists of choreiform movements of the mouth, tongue, head and neck, and arms and legs. Tardive dystonia consists of dystonic posturing or twisting caused by sustained muscle contractions (27). Symptoms most often improve when the offending medication is discontinued; however, sometimes, additional pharmacological treatment is needed. Again, the history, the appearance of the movements, and EEG findings will help to distinguish these disorders from epilepsy.

Hyperekplexia, also known as startle disease, is an autosomal dominant disorder with variable penetrance that should be distinguished from startle epilepsy and frontal lobe epilepsy. The hallmark features of this condition include excessive and persistent startle in response to sudden auditory, visual, or sensory stimuli (28,29). It typically begins in infancy, and sudden stimuli can evoke leg or body stiffening causing stiff baby syndrome—sometimes severe enough to interfere with breathing and cause apnea (30). Affected babies demonstrate the McCarthy reflex, in

which gentle tapping of the nose or forehead causes excessive startle. In children, attacks can result from sudden stimuli or strong emotions such as excitement or fear, causing sudden falls without loss of consciousness. In addition to startle, patients may have spontaneous clonus in lower extremities, lasting up to minutes at night (28,29). A family history of this disorder is often present and examination of the parents is important in the diagnostic process. EEGs in these patients during the spells do not show epileptic activity; however, this may be difficult to distinguish from frontal lobe epilepsy, in which scalp EEG may also be normal. Treatments using clonazepam and valproate have been shown to be effective for symptomatic relief (28,31).

Startle disease must be distinguished from startle epilepsy, which is characterized by seizures induced by unexpected auditory or tactile stimuli, usually a sudden sound (32). The seizures are typically brief, lasting less than 30 seconds, and consist of a startle response followed by tonic phase which is usually asymmetric. Patients may fall and may have clonic jerks. Such patients typically have a neurological deficit such as hemiparesis, quadriparesis, or diffuse encephalopathy. The abnormality usually involves the supplementary motor area. The EEG in this disorder can show frontal, central, or frontocentral spikes (32).

Excessive startle is a key feature of a syndrome known as the jumping French men of Maine, initially described by Beard in a group of loggers in Maine (33). These patients had characteristic features of excessive startle, echolalia, and echopraxia, which are thought to represent multiple tics. The underlying molecular basis is still unknown.

In summary, the differentiation of epilepsy and movement disorders is complex and relies upon not only a careful history, but direct observation of the movements, will greatly facilitate the diagnosis process such that the correct conclusion can be made.

Cerebrovascular Imitators of Epilepsy

Cerebrovascular conditions such as ischemic stroke or transient ischemic attack may manifest as paroxysmal events that can be easily mistaken for epileptic activity. Spontaneous movements of the limbs caused by an acute stroke, such as tonic posturing and twitching of the limbs, may be difficult to differentiate from seizures (34). Different descriptions have been reported, including tonic-clonic, jerking, shaking, fasciculation-like, and shivering movements, which may involve the upper and lower extremities, unilaterally or in a multifocal fashion. The movements are often sudden in onset, with wide variations in their nature, amplitude, and frequency. Saposnick and Caplan described a patient with an acute infarction of the basis pontis and tegmentum who presented with impaired consciousness and stereotyped brief clonic contractions of the upper limbs bilaterally (34). The EEG did not show any epileptiform discharges. Ischemia rather than infarction can produce similarly confusing presentations, particularly if it involves the posterior circulation. Basilar ischemia may cause tremulousness and decerebrate posturing prior to quadriplegia. Ropper described eight patients with basilar occlusions who had convulsive-like movements in the limbs (35). In these patients, other accompanying symptoms may serve as clues, such as bilateral leg weakness, ataxia, vertigo, and, in particular, eye movement abnormalities—such as internuclear ophthalmoplegia, one-and-a-half syndrome, and vertical nystagmus, which are all indicators of brainstem involvement (36). It is postulated that the involuntary movements are related to ischemia of the corticospinal tracts in the brainstem, rather than being true convulsions with a brainstem nuclear origin (34).

Transient ischemic attacks (TIAs) occasionally cause a phenomenon known as "limb-shaking TIAs," and they can also represent a diagnostic challenge. Patients have repetitive rhythmic or arrhythmic shaking of the hand, arm, or leg, related to severe carotid occlusive disease contralaterally (37). As expected, the Jacksonian march pattern that is typically associated with focal motor seizures is not observed in these patients. Another important distinguishing feature of limb-shaking TIA is that symptoms are provoked by maneuvers that compromise cerebral perfusion, such as standing, and resolve with re-establishment of blood flow when the patient sits or lies down (38). Occasionally, jerking may be seen in both arms, asymmetrically. Another probable distinguishing feature, other than the retention of normal consciousness, is the sparing of facial muscles. In most patients, evidence of ischemia or infarction in the affected frontal lobe can be seen on neuroimaging studies. The hypoperfusion theory was confirmed in one patient with severe bilateral carotid artery stenosis presenting with limb-shaking TIAs of the left arm upon standing (39). Regional blood-flow studies and carotid and transcranial dopplers demonstrated decreased perfusion, in the watershed regions but maximally in the right dorsofrontal and upper rolandic regions (39). In that patient, simultaneous EEG recording during attacks demonstrated intermittent rhythmic focal theta activity maximal at F4 that was not felt to represent an epileptiform abnormality (personal communication with Bruce Fisch, editor). EEG studies in nine other patients with limb-shaking TIAs showed diffuse delta slowing or temporal delta slowing, but no epileptiform activity (40). Management of these patients is aimed at improving cerebral blood flow through careful control of blood pressure and surgical revascularization.

TIAs may also manifest as repetitive stereotyped sensorimotor symptoms contralaterally caused by occlusion of small penetrating arteries, but they typically occur over 1 to 3 days (41). TIAs from occlusion of larger vessels may also present with repeated attacks, but they rarely persist for longer than 6 months because patients either have a stroke or develop collateral circulation to compensate for the ischemia. Seizures, on the other hand, are stereotyped events that will persist for years if left untreated (42).

Convulsive movements also may be seen in patients with ischemia or hemorrhage in the basal ganglia. Some patients may demonstrate paroxysmal choreoathetoid movements, with or without weakness. Hemorrhages involving the putamen have produced abnormal jerking or tremulous movements in the limbs ipsilaterally before patients develop contralateral weakness, while thalamic hemorrhages may cause these movements contralaterally (36).

Visual disturbances related to TIA or infarction of the occipital region may result in positive and negative symptoms that resemble epilepsy. Anton's syndrome—cortical blindness caused by destruction or infarction of the occipital cortex bilaterally with denial of blindness by the patient—leads to elaborate hallucinations that are sometimes referred to as release phenomena.

Structural lesions in the brainstem other than ischemia have also been reported to cause limb jerking. Convulsion-like episodes were reported in 32 (26%) of 122 patients with acute brainstem lesions, most of them secondary to tumors (43). The underlying mechanism is unclear.

In summary, a number of abnormal movements may accompany cerebrovascular disorders, challenging the diagnostic process. However, careful recording of patient history, detailed examination, and concomitant video EEG monitoring will help the clinician in arriving at the correct diagnosis.

Migraine

Migraine is a common condition that causes episodic neurological symptoms, sometimes mimicking epilepsy. Migraine and epilepsy both present as paroxysmal events and often coexist in individuals. A study by Ottoman demonstrated that migraine and epilepsy may have a shared genetic susceptibility given that the prevalence of migraine in patients with epilepsy ranges from 8% to 23% and the prevalence of migraine is 15% to 26% for the family members of these patients (44). In comparison, in the general population of the United States, an estimated 18% of women and 6% of men are diagnosed with migraine (45). The clinical symptoms and treatment of these two conditions have significant overlap, making it sometimes difficult to differentiate one from the other.

Approximately 20%–30% of patients with migraine have auras consisting of focal neurological symptoms, such as visual, sensory, or motor symptoms, which can sometimes be confused with seizures. Visual symptoms are by far the most common complaint, and typically progress over 5–30 minutes. They may consist of a mix of positive features, such as scintillations, fortification spectra, colorless geometric shapes (lines, curves, circles), photopsia, or colors, or negative features such as scotomas, all of which are suggestive of migraine. In particular, the outward migration of scintillating lights or fortification spectra from the point of fixation in one visual field is most characteristic of the migraine aura. Disturbances of visual perception—such as micropsia, macropsia, and metamorphosia, sometimes referred as the "Alice in Wonderland" syndrome—have also been described by migraineurs. In contrast, visual symptoms of epileptic origin are predominantly multicolored flashing lights or spots with a spherical pattern, and typically are not well-formed images (46). Epileptic visual images evolve at the typical rate of seizures and may move more rapidly across the visual field than their migraine equivalents. The migraine aura usually lasts between 5 to 20 minutes, whereas visual symptoms in epilepsy typically are shorter, on the order of seconds to five minutes. Other associated features—such as automatisms, positive motor features such as jerking or shaking, and alteration of consciousness—favor an epileptic aura, although confusional migraine (a rare phenomenon) may be misinterpreted as a complex partial seizure triggered by migraine in some patients. Language disturbances can also occur, with lesser frequency, in patients with migraine, and can occur as an isolated symptom, although they are often associated with a visual aura.

In differentiating between sensory symptoms resulting from migraine and those caused by epilepsy, it is notable that numbness or paraesthesia related to migraine typically progress slowly over the course of 10–15 minutes, starting from the hand and slowly migrating across the hand or moving into the arm, face, and tongue. Indeed, the relatively slow migration of positive somatosensory symptoms also differentiates the migraine aura from evolving TIA or stroke. The sensory symptoms of epileptic origin may be described as a burning, cramping, stinging, aching, electric, or throbbing sensation, and are typically much briefer in duration, lasting seconds to minutes.

Motor disturbances in patients with migraine are typically negative symptoms such as weakness—whereas in patients with epilepsy, the motor disturbance consists of positive symptoms such as jerking, shaking, and dystonic posturing during the seizure, and postically, patients may have focal weakness known as Todd's paresis. Migraine and epilepsy may coexist in patients with a defect in the P/Q-type voltage-gated calcium channel gene on chromosome 19 in familial hemiplegic migraine.

The migraine aura is thought to be related to cortical spreading depression, a wave of depolarization moving across the cerebral cortex at a rate of 3.5 millimeters per minute, preceded by a brief excitatory phase followed by nerve cell depression (47).

EEGs recorded during a migraine aura are often normal. Acutely, a decrease in the amplitude of normal rhythms such as alpha activity may occur together with focal delta and theta activity; spike discharges may be seen in 8% of patients (48). Patients with hemiplegic or aphasic migraine have unilateral delta or theta activity acutely, with minor hemispheric abnormalities persisting subsequently (49). Thus, in patients for whom the diagnoses of headache and

epilepsy are not clear, EEG recording during the event can help to differentiate between the migraine aura and epileptic aura.

One does have to keep in mind that in a small number of patients, seizures are preceded by migraine, as in the case with patients with benign occipital epilepsy of childhood with occipital paroxysms (BOEP). Seizures, on the other hand, can also trigger migraine. Patients with mitochondrial disorders may present with multiple central nervous system abnormalities, including both migraine and seizures.

Familial hemiplegic migraine can be distinguished from epilepsy based on the usual accompaniment of headache and a family history of the disorder. Hemiparesis can occasionally occur during the prodrome of the migraine, and often resolves within 20–30 minutes, followed by a contralateral headache. Some patients with more severe symptoms develop hemiplegia, affecting the same side or the opposite side of the headache, which may persist for days or weeks after the headache resolves. The disorder carries an autosomal-dominant pattern of inheritance, based in a mutation within the CACNLIA4 gene on chromosome 19, which encodes for a P/Q type calcium channel unit, while other mutations in the gene cause episodic ataxia type 250.

Alternating hemiplegia of childhood is an autosomal dominant disorder characterized by flaccid hemiplegia or quadriplegia lasting minutes to days (51,52). It typically begins in the first 18 months of life (52). Symptoms begin with nystagmus and strabismus before 6 months of age, along with intermittent tonic and dystonic posturing movements, which may be mistaken for tonic seizures. In many patients, the periods of flaccid hemiplegia can be mistaken for postictal paralysis. Patients also have choreathetoid movements in between attacks of hemiplegia, and all patients have cognitive impairment as well. It is important to note that a small number of patients also have concomitant epilepsy (52).

Transient Global Amnesia

This is an entity with an unclear etiology, with various studies suggesting a migrainous or an ischemic etiology. Imaging studies of transient global amnesia (TGA) have demonstrated cortical spreading depression. During positron emission tomography (PET) imaging of a patient experiencing TGA, Eustache and colleagues found decreased metabolism in the left frontotemporal region and lentiform nuclei with preserved cerebral blood flow. In contrast, metabolism was preserved in the hippocampal gyrus and occipital cortex and cerebral blood flow was reduced in the occipital region. This pattern of findings is similar to cortical spreading depression, characterized by an initial decrease in metabolism with hyperemia followed by oligemia while metabolism normalized, with the typical pattern of progression from the occipital cortex to the frontal cortex (53). In support of the ischemic theory, diffusion-weighted imaging signal abnormalities were noted in seven patients with TGA in the left mesial temporal lobe (54). The exact mechanism still needs to be elucidated.

PEDIATRIC DISORDERS

Paroxysmal Disturbances in Infants and Children Resembling Seizures

Apnea and Breath-Holding Spells

Apnea in infants and children may raise concern for seizure activity; however, it can be related to a variety of causes, including obstruction or hypoventilation with a central cause. It is frequently encountered in premature infants and is associated with bradycardia, likely related to brainstem immaturity. Apnea in the absence of any other symptom is rarely, if ever, caused by seizures, particularly if it is prolonged, lasting more than 15 seconds. However, when it is accompanied by symptoms such as eye deviation, papillary dilatation, tachycardia, or hypertension, careful evaluation for seizures should be sought (55). Apnea may also be encountered in other neurological conditions such as hypoxic ischemic encephalopathy, intraventricular hemorrhage, infection, medication effects, or hypoglycemia.

Breath-holding spells, also known as cyanotic syncope, can frequently be mistaken for seizures in infants, toddlers, and children. The key feature is that they are provoked by emotional upset or minor injury that triggers a vasovagal response. Most of the spells start with crying, followed by apnea, cyanosis, and then loss of consciousness and tone. Occasionally, clonic jerking or tonic stiffening may be seen and this may be mistaken for seizure activity. These spells typically resolve by 3 to 4 years of age (56).

Pallid syncope is similar to breath-holding spells in that it too is provoked by minor injury or emotional upset. However, the child becomes pale and loses consciousness without crying or cyanosis. There may be associated tonic stiffening if the event is prolonged. The underlying mechanism is thought to be bradycardia or asystole causing decreased cerebral perfusion. Again the history of emotional upset or minor injury as a trigger is the key to diagnosis (56).

Syncope is the most common condition that is confused with tonic-clonic seizures since it can be associated with anoxic convulsions or tonic posturing. The prodromes of lightheadedness, gradual dimming of vision, diaphoresis, and pallor are important indicators of syncope rather than seizure. Cardiac syncope may be caused by structural defects such as valvular stenosis or arrhythmias. Neurocardiogenic syncope is caused by alterations in blood pressure and heart rate in the setting of prolonged standing, pain, or fear.

Jitteriness

Jitteriness is commonly seen in newborns and is characterized by quick oscillations in the limbs; it should not be

confused with clonic or myoclonic seizures. It may be precipitated by touch or loud noise and suppressed by calming the child or relaxing the limb. The neonate remains awake, and no other associated symptoms such as tachycardia or hypertension are seen (57). Jitteriness can be seen in a number of conditions, including drug withdrawal, hypoglycemia, hypoxic-ischemic encephalopathy, and hypocalcemia.

Benign Neonatal Myoclonus of Sleep

Benign neonatal sleep myoclonus is a well-recognized and benign phenomenon that is typically seen in the first few weeks of life and resolves by 2 to 3 months. It occurs solely during sleep, and the movements resolve when the child is awakened. There are no other associated features such as tachycardia or change in blood pressure, and the child is otherwise normal neurologically and developmentally. The EEG during these jerks is normal (58).

Benign Myoclonus of Infancy

Benign myoclonus of early infancy, also known as benign non-epileptic infantile spasms, is a condition in which the child has clinical events, consisting of flexion or extension of the extremities, that resemble infantile spasms, but the ictal and interictal EEG are normal (59). The child is developmentally normal and neurologically intact, and imaging with brain MRI is also normal. The condition usually begins between 3 and 8 months of age and resolves spontaneously by 2–3 years of age.

Shuddering

Shuddering attacks are characterized by a brief, fast tremor of the head, shoulder, or trunk, lasting seconds, often associated with eating. The condition typically starts in infancy or childhood and resolves spontaneously in the teens. The child is developmentally normal, neurologically intact, and the EEG is normal during these attacks. There seems to be an association with a family history of essential tremor (60).

Hyperekplexia

Hyperekplexia, also known as startle disease or stiff baby syndrome, is an autosomal dominant disorder involving an abnormal gene on chromosome 5q for the subunit of the glycine receptor (61). Characteristic features are excessive startle and stiffness of the baby in response to sudden expected auditory or tactile stimuli. In neonates, the episodes of stiffening can be severe and cause apnea and anoxic brain injury.

Opisthotonus

Opisthotonus is a manifestation of gastroesophageal reflux disease also referred to as Sandifer syndrome, which causes intermittent generalized stiffening or extension posturing of the body. The episodes may also be associated with apnea, staring, and minimal jerking of the extremities, but a history of the spells occurring with feedings, typically within 30 minutes of a feed, is a good clue to the condition. The EEG during these events is normal.

Stereotypies

Stereotypies consist of various repetitive and stereotypic movements, such as head-banging, body rocking, or hand flapping, that can be seen in normal children, but are also commonly encountered in patients with neurological disturbances, such as mental retardation and autism. The behaviors may be seen while the child is awake or falling asleep, and are thought to be "self-stimulating" behaviors that may be relaxing.

Spasmus Nutans

Spasmus nutans consists of a triad of clinical symptoms: monocular nystagmus, head nodding, and head tilt. These symptoms are recurrent throughout the day and may be mistaken for seizures. The typical age of onset is 4 months and the symptoms typically resolve within a few years. The exact underlying cause is still unknown.

Disorders of the Sleep–Wake Cycle

Sleep disorders frequently mimic seizures, particularly nocturnal frontal lobe seizures. Night terrors represent a form of confusional arousal from stage 4 sleep, in which children wake up looking frightened and agitated and do not respond appropriately. These episodes typically occur within 1–2 hours of falling sleep and may be prolonged, lasting 10–15 minutes, but usually occur only once per night. Characteristically, the more the parent tries to calm the child, the worse the symptoms of crying and screaming become. Children are typically amnestic for these events. Figure 11-1 demonstrates the EEG of slow-wave sleep during a night terror. Frontal lobe seizures, on the other hand, are usually shorter in duration, tend to occur in clusters, and may occur at any stage of the sleep cycle during the night.

Nightmares are another entity that may mimic seizures, but occur in REM sleep, and children will usually wake up quickly and have memory of the dream. By contrast, nocturnal seizures rarely occur in REM sleep, and patients are amnestic for them. Children with narcolepsy-cataplexy present with sudden loss of tone, usually provoked by emotion such as excitement or laughter. Patients who have the rare condition of isolated cataplexy will have preserved consciousness, whereas children with narcolepsy will often proceed to REM sleep. Other symptoms associated with narcolepsy include sleep paralysis, hypnogogic or hypno-

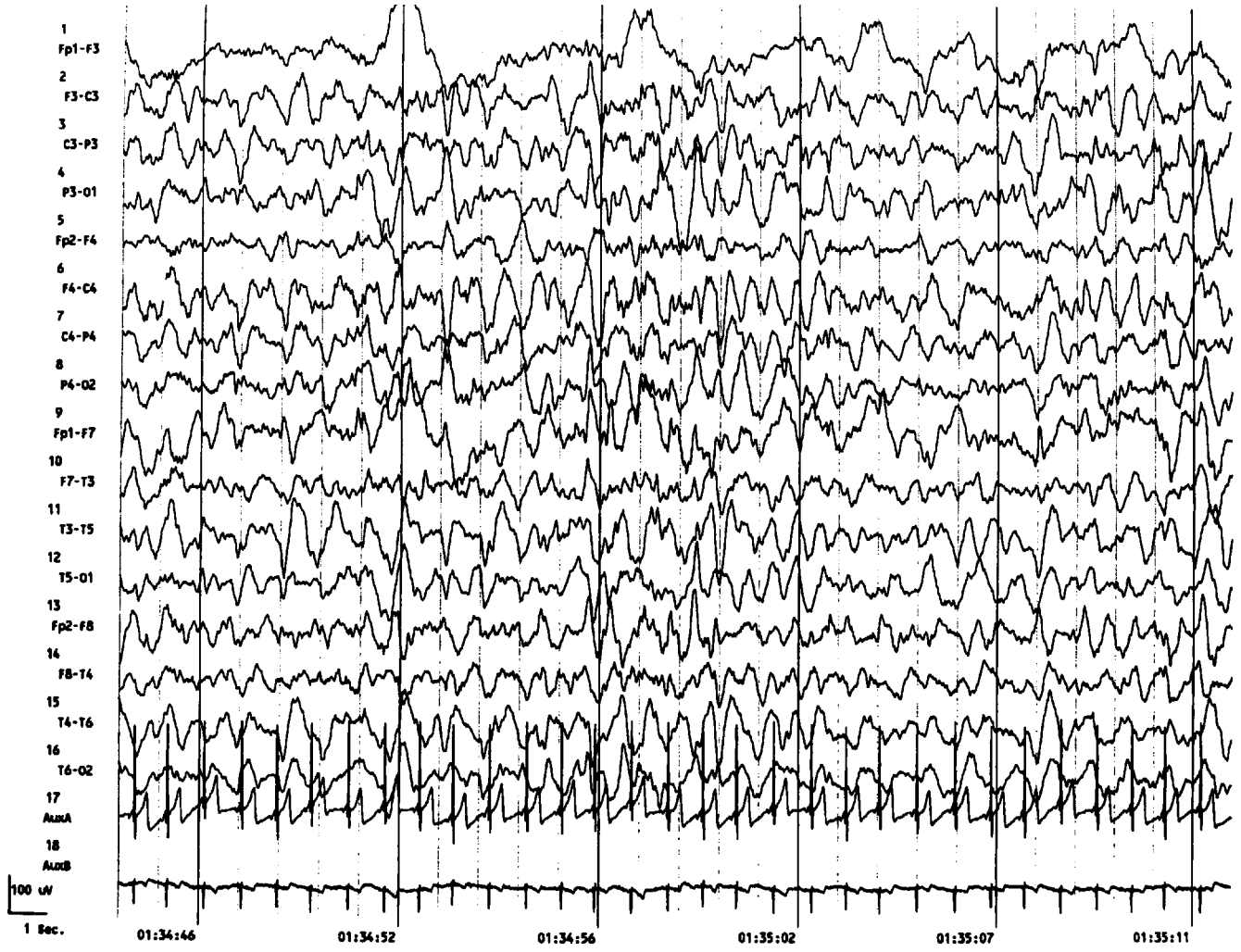

FIGURE 11-1. This is a 5-year-old girl with the recent onset of nighttime events marked by suddenly screaming in terror, crying inconsolably, and sitting upright in bed rocking back and forth. Each event would last for several minutes and the child had no awareness of the event the following morning. Telemetry during the night captured one of these events as noted. The child was in stage 4 sleep throughout the event, characteristic of night terrors. No evidence for epilepsy was found.

pompic hallucinations, and excessive daytime sleepiness. Symptoms of this disorder typically begin before age 16 (62). The diagnosis is made by history and multiple sleep latency testing.

Daydreaming

Daydreaming is a common phenomenon in children and may be mistaken for absence or complex partial seizures. However, unlike seizures, children can respond to questions appropriately when their attention is redirected. There are no postictal symptoms, in contrast to children with complex partial seizures.

Non-epileptic Seizures

Non-epileptic seizures in the pediatric population can usually be readily recognized, given their atypical clinical features, without any EEG correlate to the events. It is important to diagnose these attacks as soon as possible such that appropriate treatment can be started early. It is also important to explore the underlying etiology—for example, post-traumatic stress disorder, and especially physical and sexual abuse, which are extremely common and often require intervention by social services.

In summary, the differential diagnosis of epilepsy in children is broad and complex. A careful history from a variety of sources from school and at home plays a paramount role in the complex diagnostic process.

Syncope

Syncope is frequently defined as a self-limited abrupt loss of consciousness and postural tone resulting from decreased cerebral perfusion. Syncope represents a frequent diagnostic

dilemma, as it comprises up to 3% of emergency room evaluations and 6% of hospital admissions per year in the United States (l). The abrupt loss of consciousness seen with syncope is frequently misinterpreted as a seizure, particularly when accompanied by tonic spasms and myoclonic jerks. Furthermore, the potential etiologies range from the benign to the grave, necessitating a thorough understanding of the symptoms that differentiate seizures from syncope and of the symptoms that differentiate between different syncopal etiologies.

Symptomatic Descriptions

Classically, syncope begins with prodromal symptoms, including constriction of visual fields with tunnel vision, decreased hearing, diaphoresis, warmth, nausea, and generalized weakness, followed by loss of consciousness and fall, with resumption of consciousness shortly thereafter. However, if cerebral perfusion remains lacking for a prolonged period of time, abnormal movements may be seen. In healthy volunteers who self-induced syncope, Lempert and colleagues (63) witnessed myoclonus in 90% of subjects, frequently described as arrhythmic multifocal or multifocal and generalized myoclonus. Furthermore, many subjects also had lateral head turning, lip-smacking, chewing, and fumbling movements (79%), vocalizations (40%), or righting movements (76%). Grubb and colleagues (64) observed abnormal movements in 14 of 15 patients undergoing tilt-table testing for unexplained syncope. Convulsions began with a rigid, flexed posture, followed by upward eye rolling and head extension, with 30% of patients subsequently experiencing bilateral myoclonic rhythmic jerks and 27% experiencing urinary incontinence. When witnessed by untrained observers, these movements may be mistaken for a seizure, with generalized shaking, moans, and possibly movements suggestive of complex partial seizures.

Sheldon and colleagues (65) distributed questionnaires to 671 patients with either known epilepsy or syncope and evaluated the responses to determine which symptoms helped best differentiate between seizure and syncope. *A loss of consciousness was more likely epileptic if there were frequent episodes, often precipitated by stress, with head turning and unresponsiveness during the episode. Conversely, a loss of consciousness was more likely syncopal if the event occurred after prolonged sitting or standing or was accompanied by diaphoresis before or after the event.*

Of note, physicians must also remember the rare condition of ictal bradycardia, commonly seen in men with temporal lobe seizures. An EEG recording of ictal bradycardia is shown in Figure 11-2. In these patients, a seizure from the temporal lobe results in clinical symptoms, including bradycardia. The slowed heart rate leads to decreased cardiac output, syncope, and possibly convulsions associated with the anoxic event. Rossetti and colleagues (4) were able to capture such an event with depth electrode video EEG and simultaneous electrocardiogram recordings. In their patient, the spread of electrical activity from the left to the right hippocampus was associated with asystole, followed

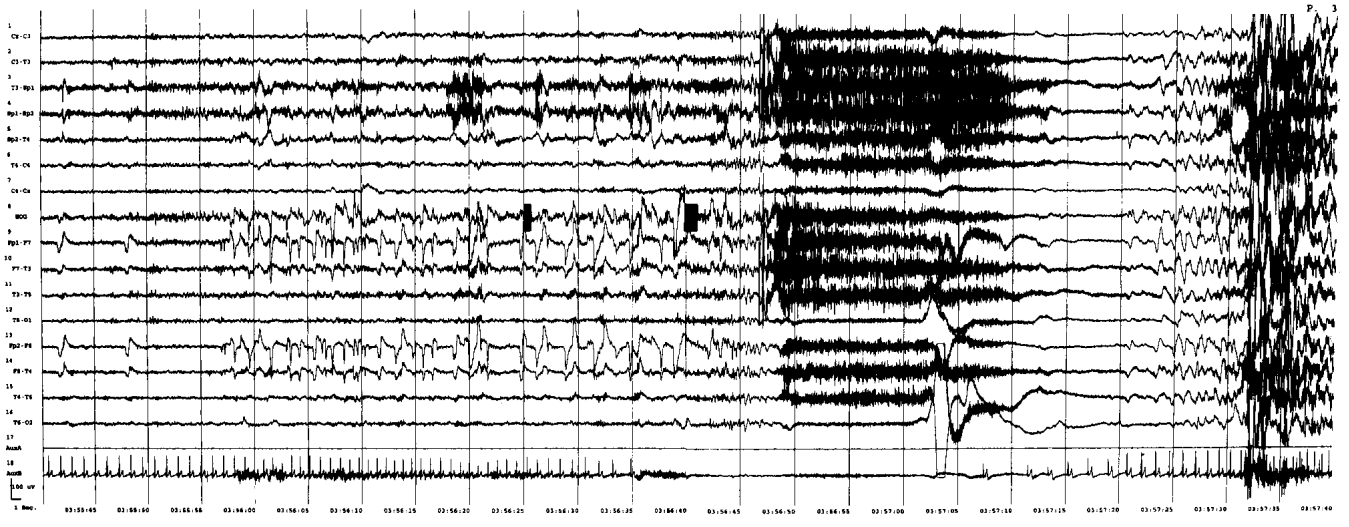

FIGURE 11-2. A 35-year-old man with a long-standing history of partial seizures felt to be under good control. He gradually developed increasingly frequent nighttime events in which he appeared to have lateralized body stiffening followed by generalized flailing of all four extremities and difficultly arousing post-event. The EEG, shown at a slow playback speed to demonstrate the entire event, shows some temporal fast activity that was shown at normal playback speeds on video review to be a brief left temporal electrographic seizure during a minor arousal. The patient then went on to have a prolonged cardiac asystole lasting 30 seconds, during which time he developed the generalized flailing. We felt that he had a seizure-driven cardiac bradycardia (severe) with anoxic behavioral activity. This was treated with medication changes and a cardiac pacemaker for protection against these prolonged asystoles. Thanks to Dr. B. Krishnamurthy for sharing this case with us.

by convulsive syncope. Treatment included both pacemaker insertion and anticonvulsant therapy.

Etiologies

Syncope may result from any decrease in cerebral perfusion, whether through neurally mediated etiologies, orthostasis, cardiac arrhythmias, or cardiac outflow obstructions. Neurally mediated syncope occurs because of an inappropriate bradycardia and hypotension resulting in loss of consciousness and postural tone. Neurally mediated syncope may occur with vasovagal faints, carotid sinus hypersensitivity, and situational faints, such as those induced by physical pain, micturition, defecation, or cough. Cough syncope may be triggered by certain foods, particularly alcohol, with the patient developing apnea during inhalation followed by automatisms as consciousness is lost. Carotid sinus hypersensitivity is triggered by pressure on the carotid sinus, resulting in an increase in vagal nerve tone that causes bradycardia, hypotension, or both. Orthostasis may result from autonomic dysfunction seen with either systemic diseases such as diabetes, alcoholism, and amyloidosis, or with neurological disorders with autonomic dysfunction, such as Parkinson's disease, Shy-Drager syndrome, or postural orthostatic syndrome. Alternatively, a decrease in blood volume with dehydration or blood loss may result in orthostasis, as may medications that cause peripheral vasodilation (e.g., nitroglycerin, beta-blockers).

Cardiac arrhythmias that disrupt cardiac output may similarly decrease cerebral perfusion and cause syncope (Figure 11-3). These may include bradyarrhythmias such as

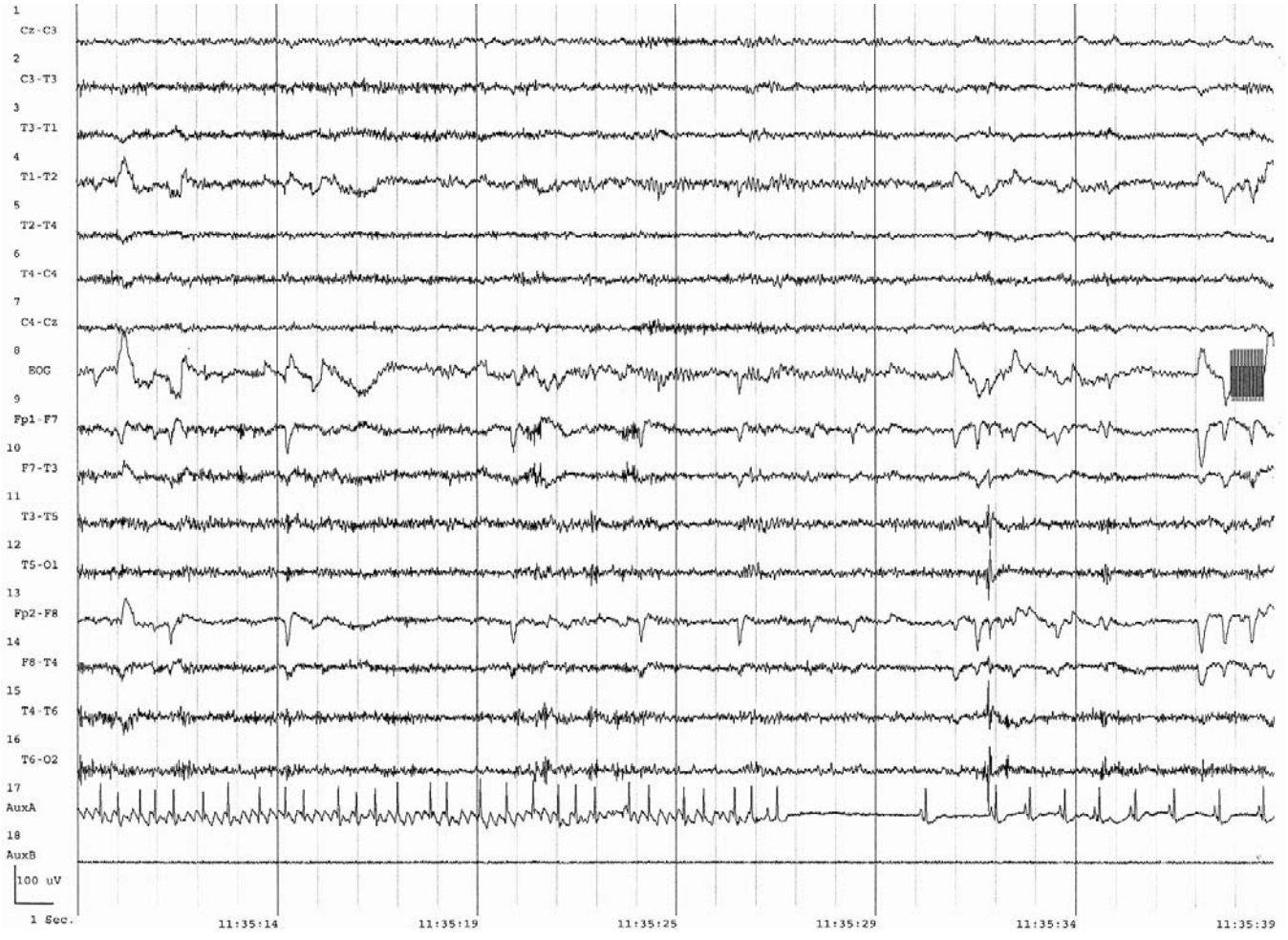

FIGURE 11-3. A 55-year-old man with a recent onset history of experiencing new "short duration periods of feeling as if he was not present." He also was recently diagnosed with atrial fibrillation, felt to be under control with medication. The time between the darker time lines is 5 seconds, and the time between the lighter colored lines is 1 second. The patient was aware that something had happened at the point where the record is overridden by a 60 Hz (marker on channel 8). Prior to 11:35:27, he was in atrial fibrillation with a ventricular rate of 96; see channel #17. He then had a 5–7 second cardiac pause, during which time he experienced his usual feelings that caused him to push the marker. He regained either a normal sinus or junctional rhythm with a rate of 60 beats per minute.

atrial fibrillation with slowed ventricular response, atrioventricular block, or long QTc syndrome, or tachyarrhythmias such as supraventricular tachycardia, ventricular tachycardia, or torsades de pointes. Decreased cardiac output may arise from obstructive cardiac disease, such as hypertrophic obstructive cardiomyopathy and aortic stenosis, or from poor cardiac output caused by low ejection fraction from prior myocardial infarctions. Thus, a patient presenting with a syncopal event needs to be evaluated for a variety of potential etiologies.

Sheldon (65) performed historical symptomatic questionnaires with patients who had confirmed either vasovagal or cardiac syncope, and attempted to discern which symptoms best differentiated between these causes. Historical features suggestive of vasovagal syncope included onset in with pain or a medical procedure, diaphoresis or warmth prior to event, onset with prolonged sitting or standing, and an absence of cardiac abnormalities. Cardiac syncope was more likely present if the history included advanced age, known bifasicular block, asystole, supraventricular tachycardia, diabetes, or symptoms including cyanosis and recollection of the event. Alboni and colleagues (66) similarly found that neurally mediated syncope was associated with prodromes lasting more than 10 seconds in patients without heart disease, and associated with nausea or recurrent episodes of syncope or presyncope over more than 4 years in patients with known cardiac illness. However, a cardiac cause of syncope was more likely in patients with cardiac disease if the symptoms were present for less than 4 years, with onset in the supine position and with associated blurred vision. *Thus, neurally mediated causes of syncope are more frequently associated with precipitants, diaphoresis, and lack of cardiac history, while cardiac arrhythmias and outflow obstructions are more frequently associated with a known cardiac history, diabetes, older age, and recall of the episode.*

Evaluation

Beyond historical features that may help differentiate seizure from syncope and its possible etiologies, many routine and more extensive investigations may help to discern the cause of the event. Most authors advocate completion of a detailed history, physical examination, orthostatic blood pressure testing, and electrocardiogram as an initial first step. Historical symptoms as described above should be elicited, as well as any indication of autonomic dysfunction, such as anhidrosis, impotence, urinary retention or incontinence, constipation, or altered vision (67). If no definitive etiology can thus be determined, more focused evaluations may then ensue. If neurally mediated vasovagal syncope is suspected, further evaluation with tilt-table testing and carotid sinus massage is indicated. If a cardiac etiology is presumed, further testing with prolonged monitoring and echocardiography, and possibly electrophysiology testing or cardiac catheterizations, may be indicated. Nonetheless, a known etiological diagnosis is not established in up to 24%–40% of patients (1,68,69).

Neurally mediated syncope is frequently associated with hypotension, bradycardia, or both during tilt-table testing or carotid sinus massage. Grubb and colleagues (64) induced convulsive syncope during positive tilt-table testing in patients with recurrent unexplained loss of consciousness that had previously been refractory to anticonvulsant therapy. Passman and colleagues (70) confirmed the diagnosis of neurally mediated syncope with a positive tilt-table test in 32% of all patients evaluated for etiological diagnosis of syncope. They found that patients with either convulsive movements or neurological deficits (e.g., aphasia or focal extremity movements) induced by tilt-table testing had a significantly lower heart rate than those who simply lost consciousness with testing. Humm and colleagues (71) evaluated patients with unexplained syncope using carotid sinus massage and autonomic testing. They found that 13.7% of patients demonstrated bradycardia, hypotension, or both during carotid sinus massage; however, all of these patients were over 50 years old, and the incidence increased with each advanced decade. Thus, neurally mediated syncope may detected in up to 32% of patients with tilt-table testing and to a lesser degree with carotid sinus massage, which should be limited to patients more than 50 years old.

Cardiac syncope may be evaluated with numerous testing procedures. Cardiac factors are a particularly concerning etiology for syncope, as some anticonvulsants that affect ion channels may worsen cardiac arrhythmias and lead to an increased number of syncopal events (72). An initially abnormal electrocardiogram is strongly suggestive of a cardiac etiology. In patients with a normal electrocardiogram and no known cardiac history, the echocardiogram revealed either normal or irrelevant findings; however, those with either an abnormal electrocardiogram or a history of cardiac dysfunction demonstrated low ejection fractions, which was associated with cardiac arrhythmias in 50% of patients (68). Prolonged monitoring for cardiac arrhythmias may be performed with Holter monitors or with implantable loop recorders. Krahn and colleagues (73) found that patients with recurrent unexplained syncope or syncope associated with injury were more likely to establish a diagnostic etiology using an implantable loop recorder for 12 months than with conventional monitoring, including tilt-table testing, use of an external loop recorder for 2–4 weeks, and electrophysiological testing.

These results suggest that an earlier use of loop recorders may help determine a diagnosis with greater accuracy and less expense. Implantable loop recorders also helped to diagnose neurally mediated syncope in patients who had had negative tilt-table tests previously,

because, during the loss of consciousness sinus bradycardia or arrest was recorded (74). Most authors advocate electrophysiological testing upon recommendations of a cardiology consultant. Overall, the initial electrocardiogram and prolonged cardiac monitoring are recommended, with echocardiography reserved for patients with a known cardiac history or abnormal electrocardiogram and electrophysiological testing upon the suggestion of a cardiologist.

If a neurally mediated or cardiac etiology are not proven with the above testing and suspicion remains for seizures, an EEG during the event may help clarify the diagnosis. Numerous EEG studies of syncope have revealed generalized high-amplitude theta and then delta slowing occurring concomitantly with the loss of consciousness. If the loss of consciousness is prolonged (>15 seconds), the EEG may reveal electrocerebral flattening. As syncope resolves, a reverse sequence of the initial EEG changes occurs. The patient may experience myoclonic jerks, with no corresponding epileptiform discharges (75,76). Conversely, epileptic loss of consciousness may reveal epileptiform discharges consistent with the seizure type.

Risks

Upon initial evaluation in the emergency room, patients should be stratified according to presumed etiology and risk for recurrent syncope, injury, and death. Patients presenting with signs and symptoms suggestive of neurally mediated syncope have a 1 year mortality rate of 0% and may be safely discharged from the emergency room with outpatient evaluation and follow-up (77,78). Conversely, patients with an abnormal electrocardiogram, a history of congestive heart failure, age greater than 45 years, and no prior history of syncope have a significantly increased risk of death at 1 year (69). Specifically, Crane (77) stratified patients according to the American College of Physicians guidelines into three prognostic groups, with high-risk patients having a 36% mortality rate at one year. Thus, *patients who are at high risk, including those with symptoms and signs discussed above, should be hospitalized for acute evaluation*, while those with suspected neurally mediated syncope may be safely discharged.

The differentiation between seizure and syncope, and the many potential causes of syncope, may often be difficult to determine. A thorough history and physical examination, followed by orthostatic blood pressure checks and an electrocardiogram, should be included in the initial evaluation. Further diagnostic testing should be performed based on the suspected etiology of the loss of consciousness, on cardiac risk factors, and on the risk for injury with recurrent loss of consciousness.

CONCLUSION

Seizures may present with a myriad of symptoms depending on the cortical region involved, and may include sensory disturbances, motor manifestations, or loss of consciousness. As a result, seizures are frequently misidentified and the symptoms may instead represent neurological manifestations of other systemic disturbances or neurological syndromes, including movement disorders, cerebrovascular disease, and migraines, as summarized in Table 11-1. Children may present with many age-specific symptoms that mimic seizures, as noted in Table 11-2. A careful review of history, observation of the event, and further appropriate diagnostic testing will help differentiate a true seizure from a seizure mimic.

TABLE 11-1. SEIZURE MIMICS ACCORDING TO ILAE SEIZURE CLASSIFICATION: EPILEPSY MIMICS ACCORDING TO TYPE OF SEIZURE. Table 11-1 reviews the differential diagnosis of seizure mimics according to ILAE seizure classification. Please see the accompanying text for further details on these syndromes.

- Simple partial seizure
  - Sensory
    - Metabolic (hypocalcemia, hypomagnesemia)
    - Hyperventilation syndrome
    - Migraine
  - Motor
    - Movement disorders
    - Cerebrovascular disorders
    - Familial hemiplegic migraine
    - Alternating hemiplegia of childhood
    - Metabolic (hypo/hyperglycemia, hypocalcemia, mitochondrial)
    - Sleep disorders
    - Non-epileptic
  - Autonomic
- Complex partial seizure
  - Metabolic disturbances
  - Transient global amnesia
  - Stereotypies in children
- Primary generalized seizure
  - Atonic, tonic, myoclonic, generalized tonic-clonic
    - Convulsive syncope
    - Apnea and breath holding spells
    - Jitteriness in infants
    - Benign myoclonus of sleep
    - Benign myoclonus of infancy
    - Shuddering
    - Hyperekplexia/startle disease
    - Opisthotonus
    - Spasmus nutans
    - Nonepileptic myoclonus
    - Cerebrovascular disorders (basilar artery insufficiencies)
  - Absence, nonconvulsive status epilepticus
    - Metabolic disturbances
    - Tics

TABLE 11-2. SEIZURE MIMICS ACCORDING TO AGE. Table 11-2 reviews the differential diagnosis of seizure mimics according to age group. Please see the accompanying text for further details on these syndromes.

Infant
Apnea
Benign myoclonus of sleep
Benign myoclonus of infancy
Hyperekplexia
Jitteriness
Metabolic disorders
Opisthotonus/Sandifer syndrome
Spasmus nutans
Shuddering
Preschool
Alternating hemiplegia of childhood
Breath-holding spells
Pallid syncope
Syncope
Staring spells
Stereotypies
School-age
Attentional difficulties (e.g., ADHD)
Daydreaming
Sleep disorders (e.g., night terrors, somnambulism)
Tics and other movement disorders
Adolescent
Psychogenic
Sleep disorders (e.g.. narcolepsy)
Medication-induced
Convulsive syncope
Migraine equivalents
Movement disorders
Adult
Psychogenic
Sleep disorders
Convulsive syncope
Migraine equivalents
Movement disorders
Elderly
Psychogenic
Sleep disorders (e.g., REM sleep behavior disorder)
Cerebrovascular disease (e.g., TIA)
Metabolic disorders
Hallucination syndromes
Medication induced
Movement disorders
Transient global amnesia

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12

SLEEP DISORDERS THAT RESEMBLE SEIZURES

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Sleep disorders may present as paroxysmal events. Disorder of arousal such as sleep walking, sleep terrors, and REM sleep behavior disorder are classical events occurring during the typical sleep period, and may be confused with epileptic events (1). Although most clinicians readily consider sleep issues in nocturnal events, other sleep-related symptoms may occur at any time, including during the transitions from wake to sleep or sleep to wake, or even during wakefulness. Events such as rhythmic movement disorder, hypnogogic hallucinations, sleep paralysis, or exploding head syndrome typically occur near the transition between sleep and awake. Some patients have difficulty describing irresistible daytime sleep bouts or sleep attacks, and clinicians may be misled by the facial jerking associated with typical cataplexy. The ardent clinician will carefully discern that nighttime and daytime nonepileptic events are a rich mixture of disorders, including symptoms of sleep-related events. Similarly, the array of sleep disorders portrayed as paroxysmal disorders may be difficult to distinguish for seasoned clinicians.

In this chapter, we will review the sleep symptoms and disorders that may present as paroxysmal events, and discuss potential differentiating features that may aid the clinician in discerning these categories. Clinicians should focus on key features such as time of the event, memory for the event, characteristic behavior witnessed, length and frequency, triggers, family history, and other associated symptoms. The use of these key features may guide the clinician; however, the most powerful tool for the clinician is still a detailed history.

SLEEP EVENTS PRESENTING IN WAKE

Excessive Daytime Sleepiness and Sleep Attacks

We spend approximately one-third of our lives asleep. Our current societal demand for more hours of time awake continues to challenge our biological need for sleep. As a result, many individuals are sleep-deprived and suffer from excessive daytime sleepiness. Recent national surveys show that 26% of people feel sleepy on 3 or more days per week (2). For all of our experience with sleepiness, some patients have difficulty in recognizing or describing the experience of being sleepy. Patients who have bouts of irresistible sleep may describe the experience as waves of closing in or as a strange sensation. Others may note the inability to communicate or a clouding of thought. In our own cohort, patients with excessive sleepiness have described the sensations as symptoms of eye fatigue, double vision, and a feeling of sinking or warmth. Others have described a transition into a dream-like state. These individuals may be witnessed to have decreased responsiveness to stimuli, and some have even suffered traumatic accidents. On the basis of the decreased responsiveness, these sleep attacks can be confused with other paroxysmal disorders.

Sleep attacks have been described in a variety of sleep disorders and with use of particular medications. Although the classical irresistible sleep attack is associated with narcolepsy, these bouts may also present in severe sleep deprivation, sleep apnea, idiopathic hypersomnia, or Parkinson's disease, or following head trauma or encephalitis (1,3). These events may follow lesions of the midbrain and hypothalamus or bilateral thalamic lesions. Not surprisingly, hypnotic agents may also cause sudden sleep onset, but this has also been seen with the use of dopamine agonists.

Although more frequent in the very early morning and afternoon periods, sleep attacks commonly occur during the periods when the circadian rhythm is more conducive to sleep onset. Sleep attacks may occur quickly and with little warning; patients may be in the midst of activities such as driving and may not recognize that these are episodes of sleep. Patients on dopamine agonists must be warned of the danger of these sleep attacks, since case reports have documented incidents of patients falling asleep

while driving (3). Events may last minutes, and have been documented on occasion to last nearly an hour. Patients with idiopathic hypersomnia may have periods of sleep drunkenness and may be very difficult to arouse, such that they appear encephalopathic (1). More commonly, patients will notice that time has passed, and they may have no memory for the event. Patients are typically sedentary or semisedentary during an event.

Patients undergoing long-term monitoring may suffer sleep attacks while on monitoring. On electroencephalographic recording, the attack starts as quick entrance of sleep figures, typically features of non–rapid eye movement (NREM) sleep. Patients with narcolepsy may directly enter rapid eye movement (REM) sleep, but other causes of sleep onset REM are sudden withdrawal of REM-suppressing medications, severe REM sleep deprivation, affective disorders, and circadian rhythm issues.

The clinicians should ask about features that may make sleepiness more likely to occur. Questions regarding bed time and wake time may give clues to potential sleep deprivation. The patient should also be questioned regarding symptoms of snoring or gasping at night, indicating sleep apnea, or excessive movements, suggesting periodic limb movements in sleep. Other clues in the history may include excessive caffeine or stimulant use, and a review of medications and supplements is necessary. Subjective daytime sleepiness may be quantified using the Epworth Sleepiness Scale. Objective testing such as the Maintenance of Wakefulness Test may indicate the patient's ability to stay awake. However, the Multiple Sleep Latency Test should be used to quantify sleepiness and to look for sleep-onset REM sleep as a marker for narcolepsy (4). Prior to this daytime testing, the patient should undergo an overnight polysomnogram to evaluate for sleep disturbance. Additional information regarding the amount of time dedicated to sleep may be obtained from a sleep diary or, in some patients, from actigraphy.

Cataplexy

Cataplexy is typically a daytime sleep-related event, and is characterized by abrupt loss of muscle tone (5). The events are triggered by strong emotional stimuli or physical exercise, and occur most commonly with laughing or surprise and, rarely, with anger, fear, or athletic endeavors. Individual experiences vary from a mild feeling of weakness or jaw dropping to sudden falls. Some patients may describe a swooning feeling, or the need to lean up against an object for support. The attacks are generally brief, lasting less than less than 5 minutes. Patients then regain their muscle control without postictal confusion or deficits. Patients are aware of their surroundings and have clear memory of the complete events. Longer events may terminate with the patient entering sleep and then awakening. Patients eventually learn to minimize the cataplexy by not to allowing themselves to experience emotion.

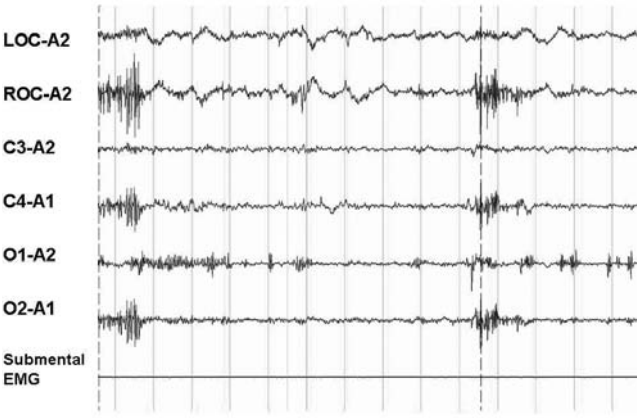

FIGURE 12-1. This figure demonstrates the polysomnographic features of cataplexy. Note the phasic muscle burst in the first portion of the record. The recording window is 30 seconds in length.

Cataplexy is the result of inappropriate expression of the REM sleep atonia in wakefulness (Figure 12-1). The combination of excessive daytime sleepiness and cataplexy is nearly always related to narcolepsy. Cataplexy can, rarely, be seen as an isolated symptom suggesting an underlying neurological disorder.

If a clinician has an opportunity to examine a patient during the event, areflexia is the key feature on examination. Patients have paralysis with diffuse hypotonia, diminished corneal reflexes, preserved pupillary responses, and phasic muscle twitching. Phasic twitching is most commonly seen in the face and occurs as single jerks or repetitive twitches.

TABLE 12-1. SLEEP-RELATED EVENTS THAT OCCUR IN THE DAYTIME

Disorder	Predominant Symptom	Time of Occurrence	Triggers	Memory	Physical Findings	EEG Finding	Stereotypic
Sleep Attacks	Irresistible sleep, feeling foggy, lapse of time	Any time	Inactivity	Partial	Appear drowsy and hard to awaken	Normal sleep figures	Potentially
Cataplexy	Weakness, paralysis with retention of consciousness	Any time	Laughter, surprise, sudden emotion, exertion	Yes	Areflexia, occasional facial twitching	Awake	Yes

Patients maintain consciousness and memory, which differentiates these events from most seizures and syncope. The presence of a clear emotional or exertional trigger differentiates cataplexy from atonic seizures, vertebral basilar insufficiency, or neuromuscular disorders producing periodic paralysis. Selective serotonin reuptake inhibitors, desipramine, protriptyline, and venlafaxine are mainstays of treatment. Intractable cases may respond to gamma hydroxyl butyrate.

SLEEP EVENTS PRESENTING IN THE TRANSITION FROM WAKE TO SLEEP

Rhythmic Movement Disorder

Patients with rhythmic movement disorder are noted to have rocking or head-banging movements occurring prior to sleep onset (6–9). Movements are stereotyped; involve large muscles, usually of the head and neck; and are sustained into light sleep. These repetitive behaviors may include head banging (jactatio capitis nocturna), body rocking, leg rolling, humming, and chanting, and may be more prevalent during periods of emotional stress. The movements are typically more disturbing to the witness than to the patient, but the events can occasionally lead to injury including skull factures and subdural hematomas. Some patients are unaware of the movements, while others describe the movements as calming. Older patients may experience the movements as a compulsion needed to bring on sleep. These behaviors are observed in nearly half of infants and 10% of 4-year-olds. The prevalence of the behavior declines with age, but it remains more prevalent in males. Typical episodes on polysomnography involve rhythmical movements preceding sleep onset and during NREM stage 1 sleep.

The key feature of rhythmic movement disorder is the stereotypic/repetitive nature of the behaviors occurring near sleep onset (Figure 12-2). These behaviors may last for minutes to hours and the patient retains consciousness or regains it very rapidly when stimulated from sleep. The length of the event and the persistent metronomic feature helps differentiate this disorder from seizure activity.

Hypnic Foot Tremor

Hypnic foot tremor is a relatively brief repetitive movement involving one extremity, typically the foot (6,8,9). The movement is characterized by a low-amplitude 0.3- to 4-Hz tremor-like action lasting seconds. The events typically occur near the onset of sleep, and may recur throughout the night as the patient transitions from wake to sleep. Most patients are unaware of the movement, but bed partners may take notice. The tremor is not associated with any pathology and does not require treatment.

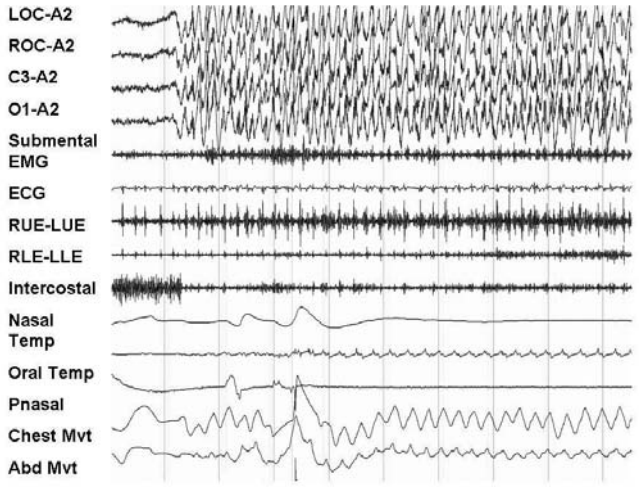

FIGURE 12-2. A recording of head banging prior to sleep onset. Note the rhythmical artifact in the cephalic and respiratory channels.

Alternating Leg Movement Activation

This movement is also characterized by brief repetitive limb movement similar to that of the hypnic foot tremor, but involves alternating limb movement (6,8,9). This feature also differentiates it from the hypnic tremor. The movement occurs at 0.5 to 3.0 Hz, lasting at least for a set of four movements near sleep onset. These events are benign and do not require treatment. The movements have elements similar to the bicycling motion seen in frontal lobe seizures. However, unlike seizures—which are typically associated with arousal—alternating leg movement activation events occur as a transition to sleep.

Excessive Fragmentary Myoclonus

These single, quick jerks or electromyographic discharges, occurring in NREM sleep, have a maximal duration of 150 milliseconds and typically have a frequency of more than 5 per hour (6,8,9). The movements may not be seen, but can cause twitch-like movements across small joints. Rarely, large joints may be involved. Similar small phasic movements in REM sleep may cause movements across fingers or of facial muscles, and are normal. Excessive fragmentary myoclonus is usually benign and may be differentiated from epileptic myoclonus by the lack of epileptiform discharge on EEG.

Bruxism

Sleep bruxism is the repetitive or rhythmic clenching of the jaw during the transition to sleep (10). These movements may produce load snaps or grinding sounds. Studies suggest that as much as 85% of the population grind their teeth to some degree. These events typically begin in adolescence, and a family history is common. Most patients are

TABLE 12-2. SLEEP EVENTS THAT OCCUR AT THE TRANSITION BETWEEN SLEEP AND WAKE

Disorder	Predominant Symptom	Duration of Event	Memory	Physical Findings	Polysomnographic Findings	Stereotypic
Rhythmic movement disorder	Rocking, head banging	Minutes to hours	Yes	May have callus on exposed surface	Rhythmic movement artifact during wake and light sleep	Yes
Hypnic foot tremor	Foot shaking	Seconds	No	None	Brief repetitive foot movements, minimum of four movements at 0.3–4 Hz	Yes
Alternating leg movement activation	Leg movement	Seconds	No	None	Brief alternating limb movement at 0.5–3 Hz with a minimum of four movements	Yes
Sleep bruxism	Teeth grinding	Seconds	No	Worn crowns of teeth, buccal mucosal bite marks	Repetitive EMG activity in the temporalis and chin EMG channels	Yes
Catathrenia	Nocturnal moaning	Minutes to hours	No	None	Prolonged expiratory moans and groans with slowed respiratory rate	Yes
Hypnic jerks	Single jerks	Less than a second	Yes	None	Drop in EMG tone just before the jerk	Yes
Exploding head syndrome	Loud painless sound of explosion inside the head	Seconds	Yes	None	Near the onset of Sleep	Yes
Sleep paralysis	Feeling of awakening paralyzed; may have accompanying fear and hallucinations	Seconds to minutes	Yes	None	Arousals and awakening from REM sleep	Yes
Hypnogogic hallucinations	Visual, auditory, or somatosensory hallucinations	Seconds	Yes	None	At sleep onset, mixed features of sleep and awake	No
Automatic behaviors	Nonsensical or semipurposeful actions after awakening	Minutes	Partial	None	Continuation of background slowing in wakefulness	No

asymptomatic, but some experience jaw pain, headache, facial pain, or tooth pain. Dentists may note secondary excessive wear of the teeth. Patients may have a few to hundreds of events per night. The polysomnogram demonstrates repetitive bouts of increased temporalis muscle activity prior to sleep onset and continuing through NREM stage 2 sleep. On the video recording, an audible click sound may be associated with the movement. The lack of epileptiform activity just prior to the movement, and the onset just at sleep onset, helps differentiate sleep bruxism from epileptic-related bruxism.

Catathrenia (Nocturnal Groaning Syndrome)

Catathrenia is characterized by light to loud prolonged expiratory monotonous vocalizations (11). These sounds typically are more prominent in the second half of the night

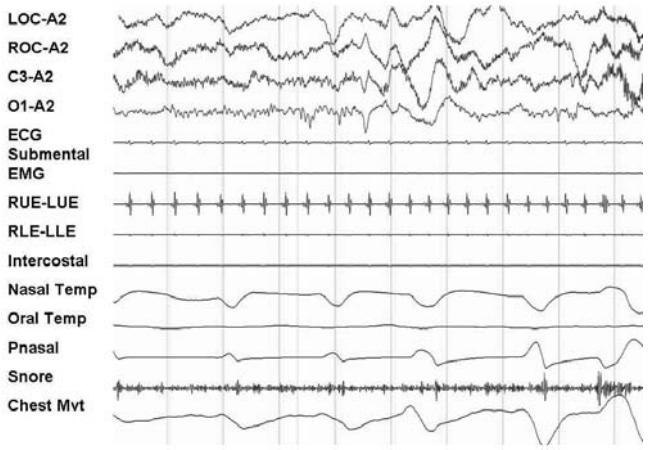

FIGURE 12-3. Catahrenia is characterized by prolonged expiratory vocalization.

about 2–6 hours after sleep onset. The vocalizations typically occur in the lighter stages of NREM sleep and REM sleep, and last hours. The patient may display a troubled expression, but is usually unaware of the vocalization. Evaluation should include polysomnography to exclude obstructive sleep apnea or sleep-related laryngospasm. Polysomnography reveals vocalization occurring during a slow expiratory phase, occasionally in clusters ending with a sigh or snort (Figure 12-3). Patients have been reported to respond to continuous positive airway pressure. The repetitive nature of the vocalization and the length of the events in the face of no clear electroencephalographic correlate differentiate these vocalizations from seizures.

Hypnic Jerks or Sleep Starts

Hypnic jerks or sleep starts or are quick, brief, sudden movements occurring at sleep onset. These movements may involve any part or all of the body. Virtually everyone may experience these movements, especially when falling asleep in a strange position or after sleep deprivation or emotional stress, and they are frequently seen in the epilepsy monitoring unit (6,12). Some patients experience brief sensory phenomena during the event, such as a roaring or buzz sound, brief visual scene, sense of floating, or pain. (A variation of the hypnic jerk is the "exploding head syndrome," in which the patient typically experiences a loud, painless, explosion-like sound.) Occasionally the subject may note a jerk or stab of pain together with a sound. Hypnic jerks typically occur at the onset of sleep, rather than at the offset. The lack of a preceding spike discharge helps differentiate hypnic jerks from epileptic myoclonus, and the presence only at sleep onset differentiates hypnic jerks from propriospinal myoclonus, which can occur at any time. Hypnic jerks do not require further evaluation or treatment unless the patient snores or displays symptoms of other sleep disorders.

Exploding Head Syndrome

This syndrome encompasses a variety of sensory events that occur just at the onset of sleep (13). Typically, the patient describes a painless loud bang or explosion inside of the head. More subtle sounds may occur just as the patient is falling asleep. These sound events are more common in individuals who are sleep-deprived or under personal stress. Occasionally the subject may note a jerk or stab of pain with the sound. As a pure sensory event, the actual timing of the occurrence is dependent upon the patient report. Occurrence of the events during monitoring is rare, and the few that have been captured show the patient awakening from light sleep.

Sleep Paralysis

Sleep paralysis is an inability to move during the transition into or out of sleep. As with cataplexy, the events are associated with the inappropriate intrusion of REM sleep atonia into wakefulness, but the association with intentional sleep distinguishes these events from cataplexy. Patients describe partial or complete awareness of their surroundings with an inability to move even their fingers or speak. Some describe a feeling of suffocation and attempts to scream that only produce a whisper. Patients may feel the presence of a sinister being or have the sense of impending doom or eminent danger. Other tactile or auditory hallucinations may accompany the episode. These events can be emotionally charged, leaving a lasting memory patients vividly recall years later. Most episodes last a few minutes, ending after the patient is touched; if the event is allowed to persist, the patient usually reenters sleep and awakens later. These events are experienced by many individuals after severe sleep deprivation, schedule disruption, or ingestion of alcohol, and are frequently observed in patients with depression or narcolepsy (14).

Sleep paralysis events are rare in the sleep laboratory and monitoring unit. The key feature on the recording is the patient appears to be alternating between REM sleep and wakefulness (Figure 12-4). The lack of other electroencephalographic findings differentiates these events from atonic seizures, and the presence of hallucinations also differentiates sleep paralysis from vertebral basilar insufficiency.

Hypnagogic and Hypnopompic Hallucinations

Auditory, visual, or tactile hallucinations can occur with sleep onset (hypnagogic) or at the end of sleep (hypnopompic). They may include several components and usually last seconds. These events occur at the transition between wake and sleep, incorporating some dream-like features. The events can be pleasant or terrifying. For some patients the events may be difficult to distinguish from reality. Visual hallucinations may involve poorly-formed colors or shapes, well-formed images of people, or images of animals that vary in expression. Patients have reported seeing people or animals, and have even called

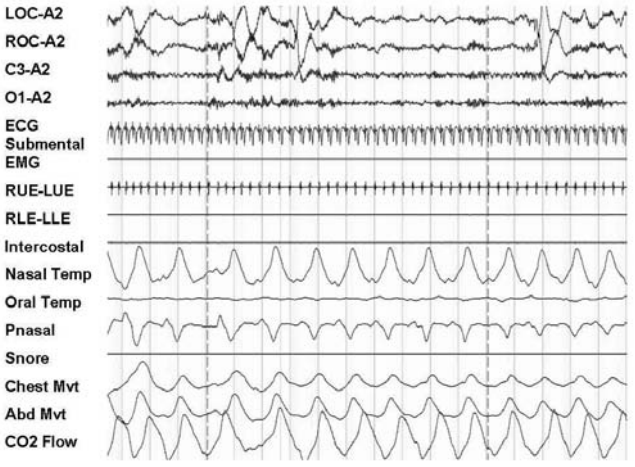

FIGURE 12-4. This polysomnographic recording of sleep paralysis demonstrates the mixture of features of REM sleep and wakefulness. The patient awoke to relay the sense of complete paralysis. This event was accompanied with the visual and somatosensory hallucination of a person sitting on the patient's head.

police to look for intruders. Auditory hallucinations may involve simple sounds or even voices. Some patients may note weightlessness, falling, flying, or out of body–like experiences that sometimes terminate with a sudden jerk (hypnic jerk). The events are aborted once the patient awakens. Change in sleep schedule, sleep deprivation, alcohol ingestion, or withdrawal of REM sleep–suppressing medications may provoke events. These events are not usually stereotypic, but may be repetitive. The lack of stereotypy distinguishes them from seizures. The hallucinations occur near sleep, which distinguishes them from hallucinations that occur with psychosis or dementia. These events may represent an inappropriate intrusion of features of REM sleep. Therefore, patients with excessive daytime sleepiness and these events should be evaluated for narcolepsy (5). The cornerstone of treatment includes reassurance and explanation of the underlying process. Some patients with recurring hypnogogic hallucinations may benefit from a selective serotonin reuptake inhibitor.

Automatic Behaviors

During the final awakening from the sleep period, individuals may experience components of sleep lingering on. This is a time period when some individuals may experience semipurposeful inappropriate activities lasting minutes to hours. Patients relay stories of putting milk containers in the dryer, putting cereal bowls in the refrigerator, or putting on clothes backwards. Patients are usually partially or totally amnestic for the event, and witnesses relate that the patient appeared drowsy or groggy during the episode. Automatic behaviors are most common in individuals with idiopathic hypersomnia or narcolepsy, but are also observed in patients with delayed sleep phase syndrome or sleep deprivation. Most events are associated with NREM sleep.

These events are not stereotypic, which distinguishes them from the automatisms associated with seizures. Patients with sleep-related automatic behavior can be appropriately alerted, differentiating it from postictal confusion or an encephalopathic process. Patients should be evaluated for sleep deprivation, disorders disturbing sleep quality, and issues of controlling sleep onset or offset such as idiopathic hypersomnia or narcolepsy.

SLEEP EVENTS OCCURRING DURING SLEEP

Disorders of Arousal

Although we portray wakefulness, NREM sleep, and REM sleep as distinct states, nature provides us examples of how these states may overlap. We currently define these states based upon physiological measurements including the electroencephalogram, eye movements, and muscle tone. Yet a wide array of physiological parameters, including respiration, thermoregulation, blood pressure, and variability in heart rate, are altered by sleep stage (15,16). In monitoring of these parameters, the determinants of the states can appear in a mixture in which behaviors that normally accompany one state intrude into another (17). The mixture of wakefulness into NREM sleep can be seen in the classical disorders of arousal (sleep walking, sleep terrors, and confusional arousals). These disorders are not distinct, but actually represent a continuum of behaviors that may occur in sleep. They share common key features of occurring from sleep, occurring more commonly in the first third of the sleep period, leaving patients totally or partially amnestic for the events, typically lasting seconds to minutes, and involving a variety of nonstereotyped behaviors. Some patients experience spells at atypical times and/or report a memory of visual imagery and auditory hallucinations. Events are more common in children (seen in approximately 30%), but 1% to 5% of adults have sleepwalking or sleep terror events. Family members note the patient's eye may be open but have a glassy appearance. Patients often report a positive family history of nocturnal events (18). Disorders of arousal from NREM sleep are defined by incomplete arousal from NREM stage 2 or NREM stages 3 and 4 (slow-wave) sleep, resulting in wakeful behaviors while asleep. Events are relatively rare to capture in a monitoring unit. Electroencephalographic recording during events shows that patients awaken from slow-wave sleep and may have continued slowing on a background of alpha frequency activity during the event. Tachycardia may start slightly before the arousal. The partial waking state of the hypothalamus and limbic structures explains the flurry of autonomic responses observed in these events, particularly sleep terrors.

Disturbed sleep or frequent arousals precipitate all of these disorders of arousal. Therefore, physicians should search for arousing phenomena such as other sleep or environmental disturbances. Clinicians should consider

factors that may perpetuate parasomnias, such as poor sleep hygiene, sleep deprivation, circadian rhythm abnormalities, fever or other illnesses, emotional stress, medication use, and ingestion of alcohol or sedatives before sleep onset. Sleep disorders that cause frequent arousals, such as obstructive sleep apnea, narcolepsy, or periodic limb movements, may also exacerbate the events (19). Additionally, medical disorders such as arthritis, congestive heart failure, asthma, chronic obstructive pulmonary disease, gastroesophageal reflux, and renal failure—or their treatment—can increase events. Neurological insults and seizures need to be considered as possible factors perpetuating the arousal disorder. The lack of stereotypical features at event onset suggests that the events are not related to a seizure disorder. Monitoring shows the events to arise from NREM sleep, and to lack any epileptiform activity (20). Some patients demonstrate the classical slow-wave sleep arousals on polysomnography (21). This pattern of hypersynchronous delta waves begins prior to the arousal and is not observed in all patients. Continuation of slowing into the arousal is a more consistent and diagnostically helpful finding.

Overnight polysomnography (PSG) is necessary if the history is atypical, sleepiness is significant, other sleep disorders are suspected, or the patient risks harming him- or herself or others (Table 12-3). Patients with classical features of disorders of arousal do not require monitoring (22).

TABLE 12-3. SLEEP-RELATED EVENTS THAT OCCUR IN SLEEP

Disorder	Symptoms	Time of Night	Duration Findings	Frequency	Stereotypic	Memory	Polysomnographic
Sleep-walking	Slow, deliberate, complex behaviors	First half of sleep period	Seconds to minutes	Less than one per night to fewer	No	No or partial vague memory	Arousal from slow-wave sleep
Sleep terrors	Piercing scream, followed by fright and flight response	First half	Seconds to minutes	Less than one per night or fewer	No	No or partial vague memory	Arousal from slow-wave sleep
Confusional arousals	Variety of unusual behaviors upon sudden awakening	Any time	Seconds to minutes	Less than one per night or fewer	No	No or partial vague memory	Arousal from slow-wave sleep
Sleep-related eating	Eating of high-calorie or strange foods in a messy manor	First half	Minutes	May occur nightly	No	No or partial vague memory	Arousal from NREM sleep
Sleep talking	Vocalization or verbalization	Any time	Seconds to minutes	Variable	No	No	Occurs in any stage of sleep
Enuresis	Uncontrolled urination in sleep	Any time	Minutes	May occur nightly	No	No or partial vague memory	Occurs more commonly from NREM sleep but can occur in REM sleep
Periodic limb movements	Movement of legs or arms in a periodic fashion	More common in first half of night	Intermittently throughout the night	Nightly	Yes	No	Periodic limb movements in NREM sleep
REM sleep behavior disorder	Dream enactment; may be violent	Latter half	Seconds	Nightly or multiple times per night	No	Yes	Loss of REM sleep atonia
Nightmares	Frightening dreams associated with anxiety	Latter half	Seconds to minutes	Variable	No but may have a common theme	Yes	Occur in REM sleep

Sleepwalking

Sleepwalking encompasses a wide range of behaviors that can be subdued or elaborate, including behaviors such as dressing, unlocking locks, cleaning, cooking, driving, and even operating firearms (17,23). Events typically occur out of slow-wave sleep during the first third of the sleep period, and usually last seconds to minutes. Patients observed while sleepwalking do not fully react to their environment, and speech is often slow and less animated than is normal. Patients usually have no memory for the event, but may describe vague feelings, impressions, or event-related imagery. These patients are normal neurologically, but should be questioned for symptoms of other sleep disorders. One report of an ictal single photon emission computerized tomography (SPECT) scan during a sleepwalking event showed increase blood flow in the posterior cingulate region, indicating activation of the limbic system (24).

Sleep Terrors

Sleep terrors (night terrors, pavor nocturnes) begin with a piercing scream, and the patient has a look of intense fear (17). Witnesses rarely forget these striking events, but patients typically have no memory of them. At onset of the event, patients exhibit features of high sympathetic outflow, including tachycardia, tachypnea, flushing, diaphoresis, and mydriasis. Patients are confused and disoriented, and attempts to intercede can be dangerous. Some patients may become violent, resulting in injury to the patient or to the person interceding. Episodes typically occur in the first third of the night and are single events. Rarely, patients may have multiple events in one night. Adults often recall vague feelings or portions of the episodes. Activities such as shift work, alcohol use, stress, or recovery from sleep deprivation, which accentuate the chance of arousals or slow-wave sleep, may increase the chance of the events. Patients typically have a normal diurnal neurological exam. As with sleepwalking, patients should be questioned for the presence of other sleep disorders.

The lack of stereotypia is key in differentiating these events from seizures. Some patients may be difficult to arouse, but once awakened they should not be confused. EEG features similarly may demonstrate hypersynchronous delta activity just prior to the event, and continued slowing into the behavioral event (21).

Confusional Arousals

These partial awakenings from NREM sleep display the classical features of NREM sleep events, such as difficulty with memory, and may be provoked from sleep (17). Characterized by disorientation, slow speech, and inappropriate behavior upon wakening, confusional arousals may be brief or last as long as 40 minutes. Events are usually shorter in adults. The frequency of the events decreases with age, although some individuals have events in adulthood. Many patients endorse a positive family history. As with the other disorders of arousal, sleep deprivation, shift work, alcohol use, psychological stressors, and affective disorders may precipitate events.

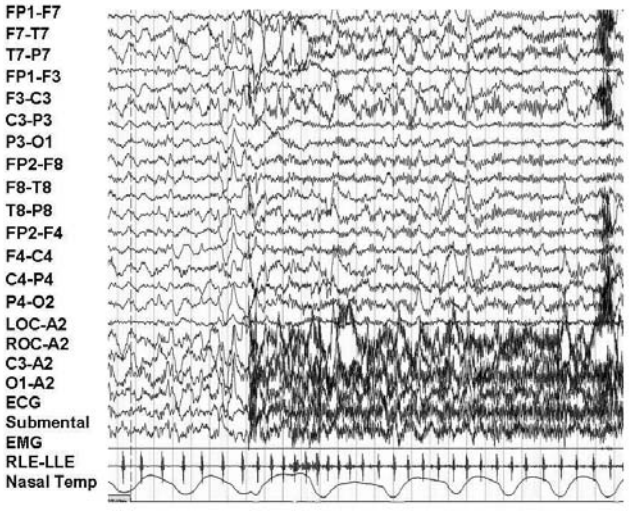

FIGURE 12-5. During this recording, the patient suddenly awakes confused. Note the slow-wave sleep prior to the arousal and continuation of the slowing into the awakening.

A milder form of confusional arousal known as "sleep drunkenness" represents an inability to attain full alertness upon awakening from sleep. Patients are drowsy, disoriented, and poorly coordinated. Concentration is difficult and automatic behavior may occur. Sleep drunkenness represents dysfunction of the arousal system and is associated with idiopathic hypersomnolence. Medications such as hypnotics, antidepressants, and tranquilizers can precipitate events. These events do not consist of stereotypic behavior, which differentiates them from seizures. Electrographically, patients awaken from typically NREM sleep and have some persistent background slowing (Figure 12-5).

Treatment and Management

Physicians should consider the degree of functional impairment and the risk level of the events before choosing from the treatment options (17). Events that have no potential for injury of the patient or bed partner may not require medical therapy. Clinicians should advise all patients and families of the underlying disorder, potential provocative factors, and related safety issues. Family and bed partners should be instructed that during events, patients should be kept safe and calmly guided back to bed. Confrontation during events may escalate into violence.

The mainstay of treatment is to limit potential arousals. Extraneous sound or light should also be minimized,

and patients should be advised to avoid sleep deprivation, alcohol, and exercise in the evening. Other sleep disorders should be diagnosed and treated, because they may provoke events (19). The sleep environment should be made safe by removing dangerous objects, placing mattresses on the floor, covering windows and glass doors with thick drapes, and locking doors. When necessary, medical treatment may consist of low-dose benzodiazepine therapy or imipramine, desipramine, or paroxetine. Behavioral therapy, stress management, and hypnosis are helpful in patients with underlying psychological issues. Anticipatory arousal therapy is effective in children who have a consistent time of occurrence for their events (25).

Sleep-Related Eating Disorder

This disorder involves involuntary eating episodes occurring as a partial arousal from sleep. The disorder is identified as a distinct entity in the International Classification of Sleep Disorders (second edition), but has many features that overlap with confusional arousals and sleepwalking (1). Patients have little to no memory of the events. Patients may eat high-calorie foods such as raw meats, candies, boxes of cookies, cake mix, or coffee grounds, usually in a messy manner. Patients may have a feeling of being full in the morning and unexplained weight gain. These events can occur multiple times per night, from all stages of sleep. Some patients endorse having a history of sleepwalking as a child, whereas others may not. Individuals with diurnal eating disorders have a higher prevalence of sleep-related eating disorder than the general population. More recently, some short-acting hypnotic drugs have been implicated in provoking new-onset sleep-related eating events (26). Patients with sleep-related eating disorder should be evaluated for other potential sleep disorders provoking the arousals. Some patients respond to individualized therapies such as dopaminergic medications or topiramate (27).

Sleep Talking

Brief utterances or longer soliloquies in sleep can occur during any stage of sleep. Although more common in the first half of the night, sleep talking may occur at any time during the sleep period. Events are more likely to occur during time periods of acute medical illness or emotional stress, or upon starting new medications. The lack of a stereotypical nature to the events differentiates these events from epileptic seizures. However, the clinician should query the patient and bed partner about more elaborate events to evaluate the possibility of sleepwalking and REM sleep behavior disorder. Simple sleep talking does not require evaluation or treatment unless another sleep disorder is suspected. Reduction of exacerbating factors and avoidance of alcohol and sedatives may reduce the events.

Nocturnal Enuresis (Sleep-Related Enuresis)

Normal at certain ages, enuresis is only considered significant after the age of five and with a minimum of two events per week. Maturation allows for greater control over voiding during sleep. Patients are classified as having primary or secondary enuresis based upon enuresis-free period. Primary enuresis is considered in those without a 6-month enuresis-free period, whereas secondary is considered in patients with a 6-month free period. Primary enuresis results when children do not arouse from sleep in response to bladder sensations. Secondary sleep-related enuresis may be related to psychological stressors, as well as the inability to concentrate urine, increased urine production, neurological pathology, seizures, and obstructive sleep apnea. Evaluation focusing on urological function and assessment of neurological function, especially of the lower extremities, may provide etiological clues (28). Rarely, patients may undergo electroencephalographic monitoring for the enuresis. Other stereotypical behavior would be a significant feature to indicate the need for monitoring. Monitoring may show an electrographic seizure several minutes prior to the recognition of the enuresis event. No matter what the underlying etiology, reassurance and trust are the foundation of treatment, and children should be given positive reinforcement for attaining even small goals. Treatments should be directed toward the underlying cause, and may include limitation of nighttime liquid, urination before going to bed, bed alarms, or even medication in rare patients.

Periodic Limb Movements of Sleep and Restless Legs Syndrome

Periodic limb movements of sleep are repetitive stereotyped movements, usually of the lower extremities, and typically consisting of extension of the great toe with dorsiflexion of the ankle and flexion of the knee and hip (29). Some movements may have more of a rotation motion, and movements can involve the arms and axial muscles. The individual movements are brief, lasting 0.5 to 5 seconds, and occur at 10- to 90-second intervals (Figure 12-6). Movements must occur in a set of at least four to be scored as periodic limb movements. Patients are typically unaware of the movements, but bed partners may complain. Movements may seem random, but are demonstrated to be periodic on polysomnographic recording. Only a minority of patients with periodic movements of sleep will have periodic limb movement disorder (PLMD), which includes sequelae such as excessive daytime sleepiness or insomnia. In contrast with periodic limb movements, a sensory component is expressed in restless legs syndrome. Patients note a discomfort with a strong urge to move that is worse during rest, is made better with movement, and occurs more frequently in the evening (30). A majority, but not all, individuals

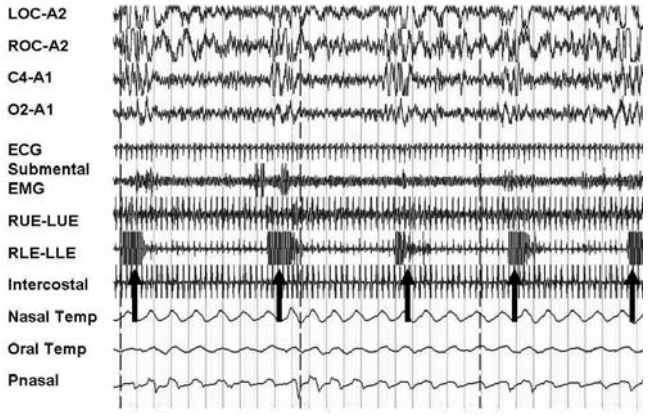

FIGURE 12-6. Limb movements, denoted by the arrows, occur in a periodic fashion during NREM sleep. This is a 90-second window.

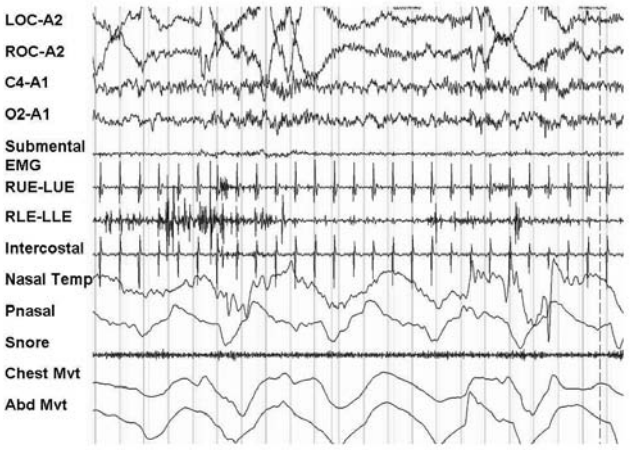

FIGURE 12-7. The excessive muscle activity in REM sleep is accompanied by dream enactment in this patient with multiple system atrophy and REM sleep behavior disorder. Note the low electromyographic activity in the submental electromyogram.

with restless legs syndrome have periodic limb movements of sleep. These movements are easily distinguished from epileptic phenomena on the basis of their periodic nature and lack of an electroencephalographic correlate.

REM Sleep Behavior Disorder

REM sleep is characterized by low-amplitude fast electroencephalographic activity, rapid movements of the eyes, and paralysis of the somatic muscles (31). REM sleep behavior disorder (RBD) is characterized by loss of REM sleep, electromyographic atonia, and elaborate motor activity associated with dream mentation (Table 12-3). This potentially violent disorder was originally described by Jouvet in 1965 when he lesioned specific pontine tegmental regions in cats, causing the animals to lose the REM sleep–induced atonia (32). The human correlate was not described until 1986 by Schenck and Mahowald (33). Patients with this disorder display dream enactment that may include punching, kicking, leaping, running, talking, yelling, or other acts. Most movements are relatively brief, lasting seconds, and patients rarely leave the bedroom. Despite the brevity of each movement, bed partners and patients are frequently injured. In contrast to NREM parasomnias, bed partners may note that the patient's eyes were closed. Most patients have vivid recall of dreams that correlate with the witnessed behavior, but dream recall is not uniformly noted. Events can occur at any time that the patient enters REM sleep, and are more common in the latter half of the night. Most cases begin in late adulthood, and males are more likely to exhibit the disorder. The polysomnogram demonstrates excessive electromyographic tone in the chin or excessive twitching of the chin or limb leads during REM sleep (Figure 12-7). Additionally, there should be videotape documentation of excessive limb or body jerks, complex movements, or vigorous movements during REM sleep. The report of dream memory can be supportive evidence.

Acute RBD can be induced by REM-suppressing medications such as tricyclic antidepressants, monoamine oxidase inhibitors, and serotonin reuptake inhibitors, or can occur during alcohol and benzodiazepine withdrawal. Patients with chronic RBD may experience behaviors for years prior to presenting for medical evaluation. In over one-third of individuals, idiopathic RBD appears to precede the development of Parkinson's Disease, Multiple System Atrophy, or Lewy Body Dementia (34). Other case reports identify lesions caused by strokes, posterior fossa tumors, demyelination, or degenerative disorders as the cause for loss of REM sleep atonia. An epileptic version of RBD has been identified. In this case, the dreams and the dream enactment are stereotypic, differentiating them from idiopathic RBD.

Patients and their families should understand that these events can be violent, and the bed partner should sleep in a separate room. Only once the events are controlled should the bed partner consider moving back into the same room for sleeping. We recommend sleeping in separate beds for safety. Firearms and other dangerous weapons should be locked away. Most patients respond well to clonazepam or temazepam, and melatonin, donepezil, and dopamine agonists have been used as second-line therapies with varying success.

Nightmares

Nightmares or distressing dreams involve clear visual imagery and auditory perception, associated with the patient suddenly awakening with a sense of fear or anxiety. Subjects may recount the dream with plot-like clarity. Significant autonomic outlay may follow the event, but memory remains intact and consciousness is preserved upon awakening. These events usually occur out of REM sleep. Nightmares diminish in frequency with age, but may increase with emotional stress or antihypertensive or antidepressant medications (35).

Recurring nightmares may result from personal trauma or underlying psychological issues. Common diagnoses include post-traumatic stress disorder, affective disorders, or other psychological pathology. These patients suffer frequent recurring dreams, or dreams of the same theme, but are not exactly the same dream each time. Recurrent dreams have been reported as a symptom of epileptic seizures. In these patients the recurrent dreams were stereotypic, and resolved with anticonvulsant therapy. Imagery rehearsal is helpful for many patients with typical recurrent nightmares, but patients who continue to have recurring nightmares should undergo more intensive medical therapy or psychotherapy (36).

CONCLUSIONS

Sleep-related events may present as paroxysmal symptoms that may be difficult to distinguish from epileptic seizures. A detailed history and clear description from the patient and witness may aid in establishing clues about the underlying etiology. However, clinicians must remain mindful that these events may present an excellent prospect to go beyond the classical nonepileptic label and find underlying neurological and sleep-related pathology that benefits from treatment. These events provide a window to physiological pathways and neuronal networks that are otherwise silent during our typical neurological examination, and should not be ignored.

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13

PSYCHIATRIC DISORDERS THAT RESEMBLE SEIZURES

STEVEN C. SCHACHTER

The diagnosis of epilepsy is usually made on clinical grounds, supported by neuroimaging and interictal electrophysiological studies, and empirically confirmed by a partial or complete clinical response to antiepileptic drugs (AEDs). Patients with unusual seizure semiology, or those whose presumed epileptic seizures do not respond as expected to AEDs, may have nonepileptic seizures.

A significant proportion of patients referred to comprehensive epilepsy centers with a diagnosis of intractable seizures have nonepileptic seizures, and most of these have no identifiable organic etiology. Among this latter group of patients, episodes resembling epileptic seizures associated with underlying psychopathology are generally called psychogenic nonepileptic seizures (PNES). This chapter reviews the epidemiology, diagnosis, psychopathology, treatment, and long-term outcomes of patients with PNES, and suggests areas for further research. Comprehensive discussions of the diagnosis and treatment of specific psychiatric syndromes associated with recurrent and transient behavioral changes, such as depression, anxiety, panic disorders, somatoform and dissociative disorders, catatonia, intermittent explosive disorder (episodic dyscontrol), Tourette syndrome, agitated psychosis, and fugue states are beyond the scope of this chapter (see 1–4). Likewise, factitious seizures and malingering are not covered.

DEFINITION AND TERMS

Nonepileptic seizures are sudden alterations in movements, sensations, or conscious experiences that mimic those seen in patients with epileptic seizures but without the characteristic neurophysiological features of epileptic seizures (5–7). Physiological causes include syncope and anoxic seizures, parasomnias, paroxysmal movement disorders, migraine, and drug and alcohol withdrawal states (8). Nonepileptic seizures with a presumed underlying psychopathological etiology are generally called psychogenic nonepileptic seizures (PNES) or nonepileptic attacks (9). Other terms, such as hysteroepilepsy, hysterical pseudoseizures, hysterical seizures, pseudoepileptic seizures, and pseudoseizures, are found in the older literature and are generally considered pejorative by today's standards compared to the term PNES (10).

PNES are characterized by physical symptoms and complaints that have no identifiable underlying organic etiology. Consequently, PNES meet the criteria for a conversion disorder, which previously was known as hysteria. Conversion disorders are listed under somatoform disorders in the *Diagnostic and Statistical Manual of Mental Disorders* (fourth edition, revised (11)) and under dissociative disorders in the International Statistical Classification of Diseases and Related Health Problems (ICD-10) (12), though Brown argues that dissociation is a fundamental aspect of PNES (13) and Sackellares and Kalogjera-Sackellares maintain that PNES do not fit within the current diagnostic framework of the somatoform disorders (14). Besides conversion and other somatoform and dissociative disorders, psychiatric conditions associated with PNES include posttraumatic stress disorder, depression, anxiety, and a variety of personality disorders (15–17). Therefore, as pointed out by Gates, "using 'hysterical seizures' interchangeably" with PNES is "inaccurate, much like referring to all complex partial seizures as 'temporal lobe seizures'" (18).

EPIDEMIOLOGY

Incidence and Prevalence

Because the diagnosis of PNES generally involves video EEG monitoring, many epidemiological studies of PNES are conducted at comprehensive epilepsy centers and their associated

tertiary hospitals, which may cause underestimation of the incidence and prevalence of PNES because of incomplete ascertainment.

A retrospective review of all video EEG telemetry recordings performed over a 5-year period at an Irish tertiary referral center identified 50 patients with PNES, indicating an estimated annual incidence in the surrounding general population of 0.91/100,000 (19)—somewhat lower than an estimated annual incidence of 1.4/100,000 from an Icelandic study (20) and considerably lower than the maximum annual incidence of 4.6/100,000 found in a study conducted in the Midwestern United States (21). The prevalence of PNES may be as high as 33/100,000 (22).

In a study of Dutch patients presenting to an emergency room, primary care physician, or neurologist with their first episode of loss of consciousness, 18% were eventually found to have PNES (23). Similarly, a significant proportion of patients referred to comprehensive epilepsy centers for evaluation of medically refractory seizures are subsequently diagnosed with PNES, including approximately one in five patients evaluated as possible candidates for epilepsy surgery and up to half of patients with medically refractory status epilepticus (22,24). Patients with an emergency admission to the hospital for status epilepticus following a short illness history, at least one episode per week, normal interictal EEGs, and use of fewer than three AEDs in the past may be particularly likely to be diagnosed with psychogenic status epilepticus (25).

Though most published studies of PNES primarily concern young to middle-aged adult patients, PNES is not uncommon in children or the elderly (26). In children, behavioral manifestations vary by age and typically consist of episodic quiet unresponsiveness or head and limb movements (27,28). Panic symptoms may be seen in adolescents (29). Nonepileptic seizures of presumed psychological origin may also be seen in patients with developmental learning disabilities (30).

Risk Factors and Associations

In addition to the psychiatric disorders listed above, other risk factors for PNES described in the literature include head injury (31–34), female gender (16,19), and sexual and physical abuse (16,35,36). Personal history of depression, family history of epilepsy and psychiatric illness, and an inadequate family environment appear to be risk factors in children and adolescents (37). Among patients with learning disabilities, a past history of sexual abuse is less often seen compared to patients without learning disabilities, whereas a previous history of psychogenic status epilepticus and situational or emotional triggers for events is more likely (38).

Chronic, medically unexplained (somatoform) pain occurs in 13%–43% of patients with PNES, and when present has a high predictive value for the diagnosis of PNES (19,34,39). Patients with PNES may be up to four times more likely than patients with epilepsy to take narcotics for pain, as well as other classes of medications such as antihypertensives, inhalers, antireflux medications, and benzodiazepines (40).

Epilepsy is a major risk factor, occurring in 10%–60% of patients with PNES, depending on the study (19,41–45). PNES may be more frequently associated with epilepsy among patients with learning disabilities than in those without (38). Interestingly, *de novo* PNES began 6 weeks to 6 years after cranial surgery for epilepsy in 3.5% of patients in one surgical series (46).

DIAGNOSIS

Rationale

The diagnosis of PNES is often delayed for years after the onset of symptoms (45,47), and the majority of patients eventually diagnosed with PNES are treated with AEDs, often for years, on the presumption that they have epilepsy. Therefore, the diagnosis of PNES should be pursued when clinically suspected to avoid the iatrogenic complications of unnecessary AED therapy and medical procedures (48). Neurotoxic and potentially fatal, though rare, idiosyncratic side effects of AEDs are not outweighed by any possible benefits in patients with well-documented PNES without concurrent epilepsy, assuming that the AEDs are prescribed to prevent epileptic seizures. Likewise, the morbidity and possible mortality associated with medical procedures employed in the emergency room or the intensive care unit for the treatment of psychogenic status epilepticus in children and adults is significant (49–51).

The economic costs associated with unnecessary epilepsy treatment and the psychosocial, stigmatizing consequences of a diagnosis of epilepsy are considerable. In addition, the incorrect diagnosis of epilepsy in patients with PNES usually delays the start of appropriate PNES treatment, worsening the prognosis and unnecessarily exposing the patient to the morbidity and possible mortality (i.e., suicide) associated with their underlying psychiatric disorder(s) (52,53).

Clinical Features

The diagnosis of PNES should be considered when (a) presumed epileptic seizures do not respond as expected to AEDs, leading to frequent changes in AEDs; (b) description of the behaviors experienced or seen during the episodes by the patient or observers, respectively, is atypical for epileptic seizures; or (c) patients are admitted for recurrent status epilepticus. Hantke et al. reviewed medication records of 348 consecutive adults who were diagnosed with either epilepsy or PNES, but not both, and found that the ratio of the total number of AEDs tried by the patient to the duration of illness was significantly higher in those with PNES (mean 4.8) than in those with epilepsy (mean 0.5) (40).

In 1985, Gates and colleagues differentiated the clinical features of PNES from those of status epilepticus, emphasizing the former's side-to-side head movements, out-of-phase arm and leg movements, high-amplitude forward pelvic thrusting, lack of rigidity, and vocalization at the start of the event (54).

Further studies with video EEG monitoring showed that some of the behaviors identified by Gates et al. could be seen with frontal-onset seizures, and other authors subsequently noted a variety of distinct behavioral patterns in patients with PNES involving unusual movements of the limbs, trunk, and head; stiffening or loss of tone; decreased movements; or a dramatic cry, shriek, or weeping in the middle of the event or at the end (55). The observations of these authors collectively suggest that the historical and clinical features particularly supportive of the clinical diagnosis of PNES, when they occur, include psychological conflicts, stressful precipitating factors such as a death or divorce, major emotional trauma such as sexual or physical abuse in childhood, occurrence of the events in the presence of others, and the behaviors listed in Figure 13-1 (44,49,54,56–63). It should be noted that the behaviors associated with PNES vary considerably from patient to patient, and may be inconsistent from episode to episode in the same patient.

Conversely, certain clinical features favor the diagnosis of epilepsy, such as postictal confusion or a seizure arising from sleep, while other features are nonspecific, including bodily injury, incontinence, tongue biting, and impaired consciousness or memory of the event.

Patients with panic disorder experience recurrent attacks of panic, typically but not always in the setting of a stressful or frightening situation (3). The events usually last minutes (compared with seconds for seizure-associated panic) and are often followed by fatigue and, less often, headache. Diagnostic confusion arises when the events are coupled with confusion or focal neurological symptoms, or when antipanic therapies are ineffective (64,65).

Classification schemes for PNES on the basis of semiology have been proposed on the presumption that classified groups may respond differently to specific treatment strategies or have different underlying psychopathologies and prognoses (66–69). For example, PNES may be classified by their behavioral similarities to generalized tonic-clonic or complex partial epileptic seizures (70), or by whether they consist of motor features (positive or negative) or sensations (62). Abubakr et al. showed that patients with motor manifestations were more likely to have a history of sexual and physical abuse than patients with limp and unresponsive presentations (71).

Selwa and colleagues distinguished six categories of PNES—catatonic, thrashing, automatisms, tremor, intermittent, and subjective—and showed that patients with catatonic episodes had a higher likelihood of remission than those whose episodes consisted of thrashing behaviors (68). Griffith et al. modified these categories and evaluated their relationships with Minnesota Multiphasic Personality Inventory (MMPI-2) profiles (72). They found significant differences in MMPI-2 clinical scales and Harris-Lingoes subscales across PNES subtypes, such as less severe psychopathology associated with the catatonic PNES subtype, suggesting a possible underlying connection between particular PNES behaviors and specific psychopathologies.

Postictal behaviors have been investigated for their ability to distinguish PNES from epileptic seizures. Chabolla and Shih conducted a retrospective review of 100 consecutive patients undergoing video EEG monitoring for evaluation of medically refractory seizures or clinically indeterminate episodes (73). During the postictal period, 75% of patients with PNES answered questions by EEG technicians or nursing staff in a whispering voice using telegraphic speech or "baby talk," and responded to commands, such as a request to hold arms up, with partial motor responses. By contrast, no patients with EEG-confirmed epilepsy exhibited these behaviors in the postictal period.

There are no historical or clinical features that have been shown in multiple studies to be 100% specific to or sensitive for PNES. Consequently, expert observation of a patient's typical episode, including the opportunity to examine the patient during the event and afterwards, coupled with interictal studies, may not be as reliable as video EEG monitoring for confirming the diagnosis of PNES (24).

History and Interictal Diagnostic Tests

The diagnostic process starts with the history. Obtaining information from both the patient and eyewitnesses is important. Key elements of the history include accurate descriptions of the episodes and the preceding/precipitating stressors and circumstances, prior or concurrent history of psychiatric illness or physical/sexual/psychological abuse or trauma, previous or present diagnosis of epilepsy and descriptions of typical seizures, social history, exposure to other persons with epilepsy or family history of epilepsy,

- Variable, nonstereotypic, out-of-phase movements that wax and wane or have gradual onset and discontinuation
- Pelvic thrusting
- Forcefully closed eyes during tonic-clonic seizure-like events or while the patient is spoken to or examined
- A protracted time course for the event including full recovery
- Full alertness after the movements cease

FIGURE 13-1. Clinical features of episodic behaviors supportive of the clinical diagnosis of PNES

overall cognitive strengths and level of functioning, ability to cope with stress, and previous and current medications.

Imaging studies, interictal EEG, and neuropsychological tests are often abnormal in patients with PNES, suggesting a biological substrate or vulnerability for PNES. For example, Reuber and colleagues found that 22% of patients with PNES only (no coexisting epilepsy) had interictal epileptiform EEG abnormalities (9%), structural abnormalities on brain MRI (10%), or neuropsychological deficits (10%) (74). In another study, the same researchers showed that patients with PNES were nearly twice as likely to have EEG abnormalities as age-matched healthy controls (75). However, in clinical practice, some "epileptiform" abnormalities described on EEGs obtained outside of comprehensive epilepsy centers may represent normal variants (76).

Psychopathology

A comprehensive psychiatric evaluation is an essential part of the diagnostic process for patients with suspected or video EEG–confirmed PNES. The importance of communication of findings and treatment plans between treating psychiatrists and neurologists cannot be overemphasized.

Assessment of personality and underlying psychopathology with the MMPI/MMPI-2 has been favored in the literature as a means of supporting the diagnosis of PNES and identifying possible psychotherapeutic targets (77–80). Scores for the MMPI-2 clinical scales 1 (hysteria) and 3 (hypochondriasis) are typically elevated in patients with PNES compared to patients with epilepsy (17,63,81,82).

Associated psychopathologies may be different between patients with only PNES and those with both PNES and epilepsy. Kuyk et al. noted that somatoform disorders are more prevalent in patients with PNES only, whereas personality disorders are more often seen in patients with PNES and concomitant epilepsy (83).

Hixson et al. hypothesized that patients with PNES have an elevated internal "setpoint" for gauging their emotional experiences, especially in the domain of fear, and administered the Modified Fear Survey Schedule to patients with PNES (17). Compared to patients with epilepsy and to healthy volunteers, the PNES group exhibited a statistically significant higher level of fear sensitivity, which was independent of other comorbid psychological factors or psychiatric conditions.

Video EEG Monitoring

The advent of video EEG monitoring was a major advance in the recognition of the entity of PNES and its diagnosis (54,56,58,84–88). Video EEG monitoring is most helpful diagnostically when (a) all of a patient's events of interest occur during the recording and the simultaneous EEG appears unequivocally unchanged from the patient's interevent waking baseline even in the presence of movement or muscle artifacts, (b) the behavior of the patient can be adequately observed on video, and (c) the recorded events are typical of those experienced by the patient as confirmed by the patient and/or eyewitnesses. When the EEG is obscured by artifacts, other simultaneous physiological changes such as oxygen desaturation and heart-rate acceleration at or just before seizure onset favor the diagnosis of epileptic seizures (89–92). Likewise, EEG patterns occurring during and immediately after episodes that have the typical morphologies associated with epileptic seizures, as discussed elsewhere in this volume, are inconsistent with the conclusion that the associated episodes represent PNES. The converse is not necessarily true, however, as described below, and neither the presence nor the absence of elevated postictal serum prolactin concentrations is diagnostic of epileptic or psychogenic seizures, respectively.

The majority of patients undergoing inpatient or outpatient video EEG monitoring for presumed PNES will have spontaneous events consistent with their habitual episodes while being monitored, usually within the first 2 days of testing and often within several hours or between midnight and 6 a.m. (56,93–97). While outpatient monitoring is more cost-effective, tapering AEDs when necessary to precipitate seizures should be reserved for the hospital setting to mitigate the risks of status epilepticus. For patients who do not have spontaneous occurrence of their habitual episodes while on video EEG monitoring, a variety of provocative methods have been described and employed to increase the likelihood that they will occur and be recorded (97–99). These techniques include application of a tuning fork to the forehead, hypnosis, application of a soaked pad to the skin, application of a colored alcohol pad, anhydrous ammonia, suggestion, photic stimulation, hyperventilation, and saline infusion (99). While controversial and rarely the trigger of an epileptic seizure, these techniques may facilitate the diagnosis of PNES and institution of appropriate therapy, as well as the discontinuation of potentially harmful AEDs if there is no additional evidence of epileptic seizures (10,100).

Some patients—24% in one study (56)—are left without a definitive diagnosis at the conclusion of video EEG monitoring, and others are not candidates for video EEG monitoring because their episodes occur too infrequently. The absence of ictal or postictal EEG abnormalities does not conclusively support the diagnosis of PNES in patients whose seizure semiology suggests partial-onset seizures, since some partial seizures have no accompanying ictal features when recorded with scalp electrodes, especially simple partial seizures and those limited to the mesial frontal lobes. Further, in the author's experience, the presence of AEDs may lesson the likelihood that concomitant ictal EEG abnormalities will be seen during partial-onset seizures, and a complete AED taper should be considered when feasible

in these patients. Patients with simple partial seizures manifesting as ictal depression, anxiety, or panic are particularly challenging to evaluate because of the purely affective clinical presentation (65). Selection of a recording montage that uses sphenoidal electrodes may improve the likelihood of recording ictal patterns in patients with temporal lobe epilepsy (101,102). Patients whose events are consistently accompanied by a time-locked but nonepileptiform change on surface EEG may require intracranial recordings for a definitive diagnosis. Whether to proceed to invasive monitoring or continue AEDs in patients without a definitive diagnosis is a difficult decision that must be individualized and revisited periodically.

As noted earlier, the diagnosis of PNES based on appropriate neurophysiological monitoring should prompt a thorough psychiatric evaluation, unless already completed, to identify underlying psychopathology and potential targets for psychotherapy. Throughout this process, it is often beneficial to involve other specialists, such as a psychologist, social worker, nurse specialist, and neuropsychologist (103).

TREATMENT

Treatment begins with informing the patient of the diagnosis. It is critical to communicate the findings to the patient in an individualized, nonjudgmental manner that is understandable and will motivate him or her to accept the diagnosis and engage in recommended psychotherapy, in which case the long-term outlook is more favorable (104,105). It is preferable that the physician conveying the diagnosis be one whom the patient already trusts, and that the findings be presented as good news because they suggest that AEDs are unnecessary (unless the patient also has epileptic seizures) and that more appropriate treatment can be offered. Interestingly, some patients may promptly respond to the news of the diagnosis with an apparent remission (106), only to resume having PNES some time later (107).

Patients who have carried the diagnosis of epilepsy for years may have particular difficulty accepting the diagnosis and the recommendation to discontinue AEDs, as well as the accompanying implication of underlying psychopathology. Patients with both PNES and concomitant epilepsy, and their caregivers, need guidance to help them understand that there could be a distinctly different cause for some of the seizures, and to help them differentiate epileptic seizures from PNES so they can be tracked separately over time.

Various methods for communicating the diagnosis have been suggested (104), but even under the most favorable circumstances nearly half or more of patients may not follow through with recommended psychotherapy (19,108). Not surprisingly, therefore, one study found that two in five patients with only PNES were still prescribed AEDs 4 years after the diagnosis was made (109), highlighting the need for the neurologist to discuss the diagnosis and treatment plan with the patient's primary care provider, who may not agree with the diagnosis or understand it—even in the face of video EEG findings—and who may not accept the rationale for psychological therapy (110).

A variety of psychotherapeutic modalities have been recommended for the treatment of patients with PNES (111). In general, the selection of a particular approach is based on individual factors, including the psychiatric formulation. Cognitive behavioral therapy is often used, both individually and in groups (112,113). No controlled trials comparing different treatment approaches have yet been published.

Psychotropic medications may be recommended for patients with depression, anxiety, or post-traumatic stress disorder. Drugs that appear safe to use in patients with epilepsy should be selected, when possible, especially in patients with both PNES and epileptic seizures. In patients who continue on AEDs, neurotoxic doses should be avoided if possible, since several case series suggest that excessive AED treatment may increase the frequency of PNES (114–116).

OUTCOME

While the outcome of patients diagnosed with PNES is improved by early diagnosis and psychotherapeutic intervention, the overall long-term medical and psychosocial prognosis is discouraging and similar to that of patients with other somatoform disorders, with at least one-third of patients continuing to have PNES (117–121). O'Sullivan et al. found that only 24% of their patients had a seizure reduction of at least 50%, and less than 1 in 5 were seizure-free at a median follow-up of 21 months following diagnosis (19). Additionally, the overall unemployment rate in patients 18–65 years old with PNES was increased twofold above the rate in the general population. Likewise, Reuber and colleagues collected 1- to 10-year follow-up data on 164 patients with PNES and found that two-thirds continued having seizures and that the majority depended on the government for financial support (109). Improvement or freedom from episodes does not necessarily resolve disability or bring improved quality of life (121,122), and the presence of major depression and dissociative or personality disorders portends a poor prognosis (109,123,124), as does a lack of understanding by the patient (105).

There are fewer studies of prognosis in children, but the outcome appears more favorable than in adults. For example, Wyllie et al. found that 81% of pediatric patients were event-free by 3 years after video EEG diagnosis (27).

NEEDED RESEARCH

Virtually every aspect of the diagnosis and management of PNES requires further study to improve the understanding of these disorders and the care of affected patients. In recognition of the absence of biological models, clinically relevant classification schemes, and proven therapies, a PNES workshop was held in 2005, sponsored by the National Institute of Neurological Disorders and Stroke, the National Institute of Mental Health, and the American Epilepsy Society.

The international, interdisciplinary group of researchers who attended the workshop reviewed the PNES literature, identified the major research questions pertaining to PNES treatments, and discussed specific, treatment-related research strategies in a number of areas, including pediatric PNES, methods for presenting the diagnosis of PNES, outcome measures, classification of PNES subtypes, and design of trials of pharmacological and psychotherapeutic treatments (125). Potential studies discussed by the participants included:

- a retrospective review of histories of children diagnosed with PNES, combined with a prospective collection of information on behavior, cognitive testing, school performance, and psychosocial environment;
- a multisite interrater reliability study to evaluate the reliability of diagnosis using video EEG monitoring;
- a multicenter observational study to identify which approach to presenting the PNES diagnosis is most likely to result in treatment compliance;
- a survey of comprehensive epilepsy centers to determine whether there is a therapeutic standard of care;
- a three-armed, randomized clinical trial to test the efficacy of current treatments.

SUMMARY

Patients with atypical or medically refractory seizures may have nonepileptic seizures. Psychogenic nonepileptic seizures (PNES) mimic epileptic seizures but do not have the characteristic neurophysiological features or an identifiable underlying "medical" etiology, and are thought to result from underlying psychopathology.

PNES commonly occur in patients presenting with their first episode of loss of consciousness, or in those referred to comprehensive epilepsy centers for evaluation of medically refractory seizures or recurrent, medically refractory status epilepticus. Risk factors include epilepsy and a family history of epilepsy, post-traumatic stress disorder, depression, anxiety, personality disorders, medically unexplained pain, family history of psychiatric illness, and an inadequate family environment in children and adolescents.

The diagnosis should be pursued when clinically suspected to avoid unnecessary AED therapy and medical procedures and a delay of appropriate PNES treatment. While no historical or clinical features are diagnostic in the absence of video EEG confirmation, suggestive historical and clinical features include psychological conflicts; stressful life events; sexual or physical abuse in childhood; variable, nonstereotypic, out-of-phase movements that wax and wane or have gradual onset and discontinuation; pelvic thrusting; and full alertness after the movements cease.

Comprehensive psychiatric evaluation and video EEG monitoring are essential components of the diagnostic process. Most patients undergoing monitoring will have spontaneous events consistent with their habitual episodes, and others will have episodes when subjected to provocative methods. Nonetheless, a definitive diagnosis cannot be reached in some patients, and the decision to continue AEDs or proceed to invasive EEG monitoring should be individualized in those cases.

Communicating the diagnosis to the patient begins the treatment and should help the patient understand and accept the diagnosis as well as the rationale for psychotherapy. Cognitive behavioral therapy is the usual psychotherapeutic approach, often augmented by psychotropic medications. The outcome is improved by early diagnosis and adherence to psychotherapeutic intervention, but the overall long-term medical and psychosocial prognosis remains unfavorable. Therefore, further research is needed to improve the identification and treatment of patients with PNES.

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SECTION

IV

EPILEPSY MONITORING: DIAGNOSTIC AND PRESURGICAL EVALUATIONS

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14

DIAGNOSTIC AND LOCALIZING BEHAVIORAL FEATURES OF EPILEPTIC SEIZURES

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Behavioral features of ictal events can be helpful for differential diagnosis when psychogenic nonepileptic seizures are suspected. Although there are no semiological features that are pathognomonic of psychogenic nonepileptic seizures, there are a few that are sufficiently more common with these events than with epileptic seizures that they are useful in confirming the electrophysiological diagnosis (1–4). Behavioral features of epileptic seizures are also used to localize the epileptogenic region for surgical resection, although even in this situation the behavior often indicates a site of projection (the symptomatogenic zone) and not the primary area necessary and sufficient for spontaneous seizure generation (the epileptogenic zone) (5).

The behavioral semiology of focal epileptic seizures was described by the ancients in India (6) and Mesopotamia (7), and in Greece, where Hippocrates already knew that the right hemisphere of the brain controlled the left side of the body (8). For centuries afterward in the West, however, only generalized tonic-clonic seizures were recognized as epilepsy until the early eighteen hundreds. Although Bravais (9) in France and Todd (10) in England described focal ictal and postictal events, it was John Hughlings Jackson, at the National Hospital in London, who most carefully used ictal semiology, in concert with postmortem identification of cerebral pathology, to determine localization of function in the human brain (11). David Ferrier (12), a colleague of Hughlings Jackson, carried out cortical stimulation in monkeys to reproduce ictal semiology that confirmed clinical observations. This work made it possible to localize "invisible" epileptogenic lesions in the brain based on initial patterns of focal ictal behavior, leading to surgical resection as an effective treatment for epilepsy (13). Characteristic behavioral patterns of "hysterical" seizures were also described during this time in France by Charcot (14).

Behavioral semiology of spontaneous seizures, often reproduced by direct cortical stimulation, constituted the most important localizing information for surgical treatment of epilepsy for decades until the advent of EEG (15). Even after demonstration that a focal epileptogenic lesion can often be identified by interictal EEG recordings (16), investigations continued into the anatomical substrates of specific ictal behaviors. Led by Wilder Penfield, Herbert Jasper (17), and other members of the Montreal group, careful documentation of ictal signs and symptoms, coupled with observations of effects of intraoperative stimulation, were used to describe localization of function in the normal human brain; this information was then used for localizing abnormal epileptogenic lesions in patients who were potential candidates for surgical treatment.

Behavioral features of epileptic seizures have played a progressively smaller role in surgical localization, with the predominance first of interictal and ictal EEG monitoring and, more recently, of structural and functional neuroimaging. Nevertheless, many workers have stressed the importance of careful descriptions of ictal signs and symptoms in the evaluation of epileptic seizures, particularly during presurgical evaluation. Electroclinical correlations have been greatly facilitated by the development of video EEG monitoring, and the remainder of this chapter summarizes the results of such studies over many decades. The behavioral signs and symptoms of ictal discharges in specific cerebral areas have been carefully described by many workers; however, it is important to know that while these clinical behaviors help to localize the "symptomatogenic zone," they do not necessarily indicate the location of the "epileptogenic zone." The latter is defined as the brain area necessary and sufficient for generating spontaneous seizures, the boundaries of which can only be approximated indirectly though a variety of structural and functional studies (5); the former is the area responsible for the clinical manifestation of seizures, which *can* include the epileptogenic zone, but which often reflects propagation from a distant "silent" brain area where

seizures are initiated. Ictal semiology, therefore, must always be treated as a supplemental, and never the sole, criterion for localization, but this information can be helpful when other criteria are inconsistent, and conflicting behavioral localization should always be taken seriously. This chapter will also discuss ictal and postictal behaviors that are useful for lateralizing the epileptogenic zone for surgery, and patterns of seizure occurrence that have some localizing value. The International League against Epilepsy has published a glossary of terminology that is recommended for use when describing ictal semiology (18).

BEHAVIORAL SIGNS AND SYMPTOMS THAT HELP IN THE DIFFERENTIAL DIAGNOSIS OF PSYCHOGENIC NONEPILEPTIC SEIZURES

At most epilepsy centers, approximately one-third of patients are admitted to the video-telemetry monitoring unit for differential diagnosis of nonepileptic seizures (NES). Behavioral features of the ictal events are an important part of the diagnostic evaluation, and may be the only basis for diagnosis when ictal EEG is equivocal. No ictal semiology, however, is pathognomonic for NES. Indeed, experienced epileptologists viewing videotaped ictal events can be wrong in their diagnosis 30% of the time (19).

NES are discussed in Chapter 13, Psychiatric Disorders That Resemble Seizures, so this section will only briefly review important behavioral aspects of NES. Much has already been written about this elsewhere (1–4,20). Ictal semiology is more reliable for the differential diagnosis of convulsive ictal events than for the differential diagnosis of focal seizures; this is particularly problematic when there is no impairment of consciousness, in which case the ictal EEG is normal or shows only nonspecific changes. The majority of patients transferred to video-telemetry monitoring units for status epilepticus turn out to have NES, reflecting the fact that status epilepticus is usually easily recognized and treated in community hospitals. NES often tend to be more prolonged than epileptic seizures, so a state resembling epileptic status is not uncommon. Accurate diagnosis is essential to avoid unnecessary iatrogenic morbidity and mortality due to inappropriate aggressive pharmacotherapy and intubation. The behavioral features characterizing nonepileptic status epilepticus consist of the same ictal semiology seen with individual NES.

Ictal thrashing with alternating asynchronous limb and side-to-side head movements is commonly encountered during psychogenic nonepileptic convulsive-like ictal events; other movements, such as opisthotonic posturing and pelvic thrusting, can also be part of the typical semiology. All of these behaviors, however, can also be seen occasionally with epileptic seizures originating from frontal lobe and other neocortical areas. Retained consciousness during bilateral motor seizures, including ability to respond to the environment and lack of amnesia for the ictal event, strongly suggest NES, but can also occur with prolonged myoclonic seizures (so-called myoclonic storms), and with unilateral clonic seizures where the movements are so severe that the contralateral side appears to be involved. Vocalization during NES is more likely to consist of understandable speech than vocalization during epileptic convulsive seizures. Bilateral movements of the body without involvement of the face, and tightly closed eyes, may be a more reliable indication of NES, particularly when the patient forcefully resists attempts to pry open the eyelids.

With respect to focal seizures, there are no additional features that clearly distinguish psychogenic nonepileptic from epileptic ictal events, except that NES are likely to last longer, be nonstereotyped, lack a smooth evolution (e.g., movements and other behaviors that stop and start), demonstrate inconsistent findings during ictal examination, and have no postictal disturbances. Brief frontal lobe seizures with bizarre behaviors and little or no postictal confusion are commonly misdiagnosed as NES. The presence of a postictal cough and/or nose wipe, often seen on video monitoring, is a fairly good indication that the event was a complex partial epileptic seizure. Whereas weeping is considered to suggest NES, dacrystic (crying) epileptic seizures also occur, for instance with hypothalamic hamartomas. It is untrue that patients are not incontinent and do not injure themselves during NES. NES can consist of drop attacks with resultant injury. Nonepileptic drop attacks are much more likely to be followed by a prolonged period of unresponsiveness than epileptic drop attacks. Mouth injury from biting tends to involve the side of the tongue and cheeks during epileptic seizures, and the tip of the tongue and lips during NES. For these reasons, patients with NES should also be instructed to follow routine seizure precautions until attacks are resolved. NES do not arise out of sleep; although they may appear to do so, EEG recordings will show that the patient actually arouses for a few seconds or more prior to onset of the ictal event.

BEHAVIORAL SIGNS AND SYMPTOMS OF ICTAL DISCHARGES IN SPECIFIC CEREBRAL AREAS

Temporal

Temporal lobe epilepsy is the most common form of medically refractory epilepsy (21), and has a very characteristic appearance. Seizures are typically bland, beginning with behavioral arrest and staring. Comprehension is usually impaired (22), although the patient may continue to interact with the environment and answer questions. Speech arrest is common, which is due to involvement of the basal temporal regions, specifically in the case of left temporal onset (23).

Automatisms are a hallmark of temporal lobe epilepsy, and are typically manual or oroalimentary. The manual automatisms are complex motor behaviors, usually of the searching and exploring type, including picking, grasping, dressing, and undressing. Oral automatisms, such as chewing, swallowing, and lip smacking, occur in approximately 10% of patients with temporal lobe epilepsy (24). These automatisms are contrasted with simple motor activity such as facial twitching or arm twitching, which is much less common, occurring in less than 4% of patients with temporal lobe epilepsy (24). Typically the patient is amnestic of this phase of the seizure, but when consciousness is retained during the automatisms, this is highly suggestive of right temporal onset (25).

Contralateral upper extremity motionlessness is common in temporal lobe epilepsy, and often involves a dystonic posturing of the hand and arm. This posture is usually a flexed posture at the elbow and wrist, with extension and adduction of the thumb. The fingers are typically extended as well, but are frequently also seen in a cupped posture. This dystonic posturing is a very strong lateralizing sign to the contrateral hemisphere (26,27).

Stronger motor manifestations may occur later in the seizure, with clonic, tonic, and versive movements. Clonic movements in temporal lobe epilepsy occur after the onset of behavior arrest and automatisms, and involve body regions in proportion to the size of their cortical representation. The face is the most commonly involved, approximately 30%–50% of the time, followed by the hand (20%) and less often the leg (7%) (28–30).

When evaluating patients with epilepsy, features that are suggestive of temporal lobe onset are amnesia of the event, reactive automatisms, duration of the seizure for longer than one minute, and prolonged postictal confusion. Reactive automatisms are seemingly purposeful behaviors, in which the patient interacts with objects or people in the environment. Usually, these are tasks that the patient was performing prior to the seizure, such as continuing to turn pages in a book, scribbling on paper, eating, or rearranging items. If spoken to, the patient may have reactive verbal responses, such as answering "yes" or "no" to questions.

There may also be experiential phenomena described by the patient that suggest temporal onset. Auras are very common, and often occur in isolation. The auras are typically autonomic and psychic simple partial seizures. In mesial temporal lobe epilepsy, the more common symptoms are nausea and a rising epigastric sensation. Patients may also experience borborygmi, belching, pallor, flushing of the face, pupillary dilation, and respiratory arrest. The most common psychic phenomena with mesial onset seizures are panic and fear.

In contrast to mesial onset, lateral temporal lobe seizures have more pronounced psychic phenomena. Patients will often describe the sense of being in a dreamy state. Visual perceptual changes may occur, in which objects appear larger or smaller, or out of place in perspective. Visual illusions are also possible, in which objects take on different characteristics, or appear entirely different. Multimodal hallucinations with visual, auditory, olfactory, and sensory components may also occur.

Other features that suggest a lateral temporal onset are vertigo and early clonic movements. Clonic activity early in the course of a seizure is rarely seen with mesial temporal onset (31).

Frontal

Seizures arising from the frontal lobes are characterized by movement, typically simple motor behaviors. The type of movement depends on the area of the frontal lobe involved. Because the primary motor cortex is better classified with the perirolandic area, this region is discussed later in this chapter.

Perhaps the most dramatic and stereotypical motor manifestation is the fencer's posturing of the supplementary motor area. This was described by Penfield and Jasper early on as "the arm being raised and the head and eyes turned as though to look at the hand" (17). Ajmone-Marsan and Ralston, who named this the M2e seizure, expanded on this concept, and noted that the head may look at either the extended or the flexed arm (32). Although the most dramatic aspect to the posture is the extended arm and the hand, which is typically in a pointing posture, Penfield and Jasper believed that the head turn was the lateralizing characteristic, implicating the contralateral supplementary motor area (17). However, Ajmone-Marsan and Ralston and others discovered that the head turn is not always reliable, and that it may be ipsilateral to seizure onset (32,33). In contrast to temporal lobe epilepsy, patients typically do not lose consciousness during these seizures.

The supplementary motor area typically produces a tonic seizure, with tonic posturing lasting for more than 5 to 10 seconds (17,34–36). This tonic posturing involves the proximal segments of the limbs (37), giving rise to large movements of the entire limb. These movements can be reproduced with studies of direct stimulation of the cortex (34,38). Stimulation produces tonic posturing, and only rarely clonic movements (35,39). Bilateral asymmetric posturing usually results, although Fried et al. found that ipsilateral and bilateral posturing can be elicited from the right supplementary motor area (SMA) (39). Others have since shown that this can occur from activation of the left SMA as well (35). When activating the superior frontal gyrus, all four extremities are usually involved, but asymmetrically (34,36,40). Even with involvement of all four extremities, consciousness is preserved.

Although tonic, static posturing is the most common manifestation, SMA seizures can cause violent and bizarre movements, predominantly of the trunk and proximal extremities (34,40,41). Stimulation of the mesial superior frontal gyrus on either hemisphere results in repetitive

vocalizations (42–44). Rarely these are words, but the majority of the vocalizations in SMA seizures are barking and yelping sounds.

The most violent motor manifestations arise from seizures originating in the orbital frontal cortex. They involve bizarre thrashing and kicking movements (45), and are often organized complex motor behaviors that occur in the absence of tonic, clonic, or dystonic movements. Complex motor behaviors arising from the orbital frontal region usually appear as automatisms, and include gripping something or someone, tapping on the table, slapping the thigh, stamping one foot, kicking, and rubbing of the legs and genitals. These differ from the automatisms seen in temporal lobe epilepsy (TLE) in that they are more animated, and typically involve faster movements than the searching behavior seen with TLE.

Complex behaviors are also seen with activation of the anterior cingulate gyrus. Seizures arising in this region typically involve touching, rubbing, and sucking, which is also seen experimentally with direct cortical stimulation (46). The automatisms produced are often distal, with more complex motor behavior of the fingers and wrist (46), and they may be coordinated into complete gestures. This is helpful in distinguishing them from the automatisms of the orbital frontal region, which typically have more proximal than distal involvement. Ictal laughter is attributed to the anterior cingulate, and when this is present early in the seizure it is a potentially localizing sign (47,48). In addition to laughter, the patient may also experience changes in mood or vegetative symptoms during the seizure. Seizures arising from the anterior cingulate may also produce violent behaviors mimicking the orbital frontal region (45,46).

Lack of movement, or the arrest of movement, is also seen with frontal lobe seizures. This arises from the negative supplementary motor area, immediately adjacent and anterior to the supplementary motor area (49). Stimulation of this area produces behavior arrest, and inhibition of movement can be elicited with direct stimulation (35,36,40). Negative motor effects are seen with stimulation of the inferior frontal gyrus (50,51) or with stimulation of the mesial portion of the superior frontal gyrus (35), which produces contralateral more than ipsilateral loss of motion. The most dramatic form of this is the atonic seizure, in which there is loss of postural muscle tone resulting in a drop attack.

Akinetic seizures can also occur from the negative supplementary motor area (51–53). These seizures are characterized by the inability of the patient to perform voluntary movements, with preserved consciousness (51,52,54). They will often activate nearby motor areas, so it is not uncommon to have an akinetic seizure of the hand, with clonic movements of the face and tongue (both contralateral to seizure onset). These differ from atonic seizures in that there is no loss of motor tone and distal muscles are more often affected. When only one limb is affected in an akinetic seizure, it is contralateral to the side of seizure onset.

Speech arrest is common in frontal lobe seizures, and may occur from motor inhibition or from aphasia (55). Motor inhibition of speech can be produced from the negative supplementary motor area, or through tonic contracture of the muscles necessary for speech from the supplementary motor or primary motor areas. Seizure activity in Broca's area can produce a profound expressive aphasia, which is typically more severe than the speech arrest produced by involvement of the basal temporal area as seen in temporal lobe epilepsy (23).

The most prevailing signs of frontal lobe seizures are prominent motor activity at onset. This may take several forms, depending on where in the frontal region the seizure begins, including posturing, focal tonic activity, and elaborate gestures. Unilateral or bilateral tonic limb posturing, and bicycling movements are highly suggestive of frontal onset (56–58). Atonic seizures are very characteristic of frontal origin, and implicate the supplementary negative motor area. Speech arrest is often profound when it occurs, but may be difficult to distinguish from speech arrest and aphasias from other localizations. However, vocalizations, in particular barking and nonverbal vocalizations, are very suggestive of frontal onset. Frontal lobe seizures are often brief, lasting under 1 minute, and typically less than 30 seconds, with little to no postictal phase (56–58). They tend to occur with higher frequency, often have a nocturnal predilection (45,59,60), and are usually preceded by an arousal a few seconds prior to the seizure (60). In comparison to other seizure types, they are more apt to secondarily generalize. When psychic symptoms do occur, they tend to be mood and affect changes, producing vegetative signs and symptoms. The hallucinations of frontal lobe seizures are olfactory in nature rather than auditory or visual.

Parietal

Seizures arising from the parietal lobe have predominantly experiential characteristics, with minimal outward clinical findings (61). Most of the features associated with parietal seizures are somatosensory phenomena described by the patient. When primary sensory cortex is involved, the patient may rarely describe a sensation of numbness or pain. The pain is usually a burning paresthesia, although vague episodic pain is also a common complaint (62,63). Although this pain may be diffuse, a unilateral onset of pain has been shown to occur with seizures arising from the contralateral parietal region (64,65). Patients will also often describe an intra-abdominal sinking sensation, and if the inferior and lateral parietal lobe is involved, nausea. A sensation of choking may also be felt.

The sensation of the absence of a body part can be produced by parietal lobe seizures. This is in contrast to a hemineglect phenomenon, which can also occur with nondominant parietal lobe seizures, in that the patient is aware of the deficit.

Patients will sometimes describe a vertiginous sensation, but when pressed, they confirm that it is not of a spinning nature. It is more often a disorientation of space, in which the patient will not have a good grasp on how he or she is positioned or on how he or she is moving in relation to other objects.

When clear manifestations do occur to an observer, they are often in the realm of language, with the production of an aphasia. Receptive aphasia occurs with involvement of Wernicke's area. When the seizure occurs near Wernicke's area, a conduction-type aphasia is produced. When motor symptoms are present, they are often rotatory and postural movements. When other signs occur, such as tonic posturing or automatisms, this is usually a result of the spread of the seizure to frontal lobe. When seizures arise in "silent" areas of the parietal lobe and propagate anteriorly, they can be confused with frontal lobe seizures.

Occipital

Patients with occipital epilepsy frequently describe visual phenomena at the onset of the seizure. The visual changes occur in the hemifield contralateral to the side of ictal onset, and are often fleeting perceptions (66,67). The visual perceptions may be of either positive or negative phenomena. When the phenomena are negative, patients will often describe a visual scotoma, which in some cases may be as large to be a complete hemianopsia. Positive phenomena are more common, and include sparks of light, flashes, and phosphenes.

During an occipital seizure, patients can also experience a sense of movement, in which they have the perception of swaying movements of their eyes and vision. In addition to this ocular oscillation, patients can have the sensation of involvement of the whole body in the oscillation. Patients often have headache associated with occipital epilepsy, and with the visual phenomena this may mimic migraine.

Subtle motor signs including palpebral jerks, more severe forced eyelid closure, tonic or clonic version of the eyes and head with the version being contralateral to the side of onset, and nystagmoid movements can also occur in an occipital seizure. This may also be limited to isolated oculoclonic or oculogyric deviation. Ictal onset above the calcarine fissure tends to propagate to give rise to frontal lobe seizures (66,67), while onsets below the calcarine fissure propagate to cause mesial temporal complex partial seizures (68).

Multilobar

Perirolandic

Seizures arising in the perirolandic area involve the primary motor and sensory cortex. Because these two regions are tightly connected, seizures beginning in this area often contain features of both modalities.

Primary motor cortex stimulation results in clonic or tonic contraction of the muscles controlled by the underlying cortex (17,69). Most often, stimulation in this area produces clonic activity that is distal (37). Seizures arising from this area typically have focal clonic activity as the initial manifestation, as opposed to the tonic activity seen predominantly throughout the remainder of the frontal lobe. This clonic activity at onset has a highly significant association with the frontal region (57). However, because clonic activity can be seen as a manifestation of seizures arising throughout the frontal lobe, it is not a reliable localizing sign within the frontal lobes (70).

The clonic movements are typically unilateral, and usually involve the hand and face; Involvement of the leg and trunk is much less frequent (71,72). This is due to the relative size of the cortical representations of these muscle groups. In addition, when seizures present with marching motor activity beginning in the face and then arms, it is highly suggestive that they originate in the perirolandic area.

If the clonic movements are an early manifestation of the seizure, then consciousness is often preserved during the clonic phase. If clonic movements appear later in the seizure, consciousness is often impaired (73). Therefore, if the patient recalls the clonic movements during the seizure, it is suggestive of a perirolandic onset.

Tonic posturing from the perirolandic area is more focal than that arising from the remainder of the frontal lobe—affecting only one limb—and tends to be unilateral only (74). Other motor seizure types are also seen in the perirolandic area. Myoclonic seizures consisting of brief nonrhythmical contractions lasting less than 200 milliseconds occur with activation of Brodmann area 4 and 6. Versive seizures are also observed; these begin with smooth or saccadic version of the eyes, followed by turning of the head after the eyes reach full lateral gaze, and then by turning of the body (75,76).

Speech arrest in the perirolandic area is produced by stimulation of the primary motor cortex, which causes contraction of tongue and lips. Postictally, there is often a Todd's paralysis involving the limb that was most involved during the seizure.

Sensory phenomena arising from seizures in the perirolandic area involve body parts based on their cortical representation. Thus, as in the motor areas, the face, tongue, hand, and arm are most commonly involved (61,77). Patients will often describe a tingling or electrical paresthesia, which may march through their body as the seizure spreads (77). Painful paresthesias may also be elicited with seizure activation of the contralateral postcentral gyrus (63), and are typically unilateral from this location. In addition, the patient may have a strong sense of akesthesia, or may have the perception that a body part is moving when it is actually stationary.

Seizures beginning in the lower perirolandic region often involve speech arrest, although, conversely, vocalizations may occur. When able to speak, the patient is often dysphasic and

may complain of sensations of stiffness, coldness, or crawling within the tongue. This can also be associated with similar sensations in the face. The patient can have repetitive swallowing, and contralateral facial movements.

When seizures arise in the middle perirolandic region, patients can experience similar features, often with contralateral upper extremity movements. If the paracentral lobule is the site of onset, these movements are usually isolated to the lower extremity. When tonic foot movements occur, they are usually ipsilateral to the side of seizure onset. With the paracentral lobule, the patient can also have sensations in the lower extremities, as well as lateralized genital sensations.

Frontal-Temporal-Parietal Operculum

The opercular region tightly connects three lobes and involves the insula, so seizures in this area can mimic those with other localizations, particularly the temporal lobe. There are some unique features that suggest opercular onset, with spread to other regions. Seizures arising from this area often begin with masticatory movements and repetitive swallowing. The seizure may be limited to a simple partial seizure with clonic facial movements. Excessive salivation can also be seen with opercular seizures. By itself, excessive salivation is not a pure localizing feature, and has also been described with seizures of mesial temporal, orbital frontal, and cingulate gyrus onset.

At the onset of the seizure, patients can have psychic and sensory phenomena. Numbness, particularly of the hands, is common from this region. Patients can also have laryngeal symptoms, with the feeling of something in their throat. They can experience an epigastric sensation associated with fear or vegetative symptoms, similar to that seen in temporal lobe epilepsy.

When the insula is involved, the patient can display spitting or vomiting. With stimulation studies, other symptoms attributable to the insula have been confirmed, including salivation, chewing, swallowing, and respiratory inhibition. Vomiting and belching are produced with stimulation of the posterior portion of the insula.

Temporal-Parietal-Occipital Junction

Seizures beginning at the temporal-parietal-occipital junction can have a variety of characteristics depending on their exact location of onset. As this area contains much association cortex and projects to multimodality sensory areas, the symptoms tend to be more complex than other areas (78). The visual perception changes that occur in this region are both visual illusions and hallucinations. Patients can experience changes in object size, reporting micropsia or macropsia. They can also have an altered sense of distance perception, in which objects appear to be closer or farther away; inclination changes; or distortion of the visual environment and metamorphopsia, with changes in the shape of objects. The latter occurs more commonly with nondominant hemisphere onsets.

When hallucinations are present, they are often complex scenes, and frequently involve multiple modalities including visual, auditory, and gustatory perception. Patients also describe autoscopy, in which they feel as though they are watching themselves from an external location.

Since the temporal-parietal-occipital junction contains Wernicke's area, language is often affected when seizures arise from the dominant hemisphere. This can include speech arrest, but also neologisms, paraphasic errors, and comprehension difficulties. Patients can also complain of vertigo.

When seizures arise from the parietal-occipital junction, the patient can have blinking and eye deviation (66). Seizures arising from this location tend to spread to the frontal regions, and thus tonic or clonic activity often follows (66,67).

Occipital-temporal seizures typically contain more formed hallucinations, and spread to the temporal regions, producing a mesial temporal complex partial seizure semiology. In a study by Palmini et al., no clonic movements were seen in occipital-temporal seizure onsets (68) as opposed to the parietal-occipital region, in which clonic and tonic movements are common.

Hypothalamic

Seizures arising from hypothalamic hamartomas produce complex partial seizures, in which mirthless laughter (gelastic seizures) is a classical feature, but crying (dacrystic seizures) can also occur (79,80). This classical feature is highly suggestive of the presence of a hypothalamic hamartoma, and studies have shown that the seizure is generated in the hamartoma itself (47,79–85).

LATERALIZING SIGNS AND SYMPTOMS

Certain features occurring during a seizure can give clues to the hemisphere of ictal onset. Language is often affected during seizures. Speech arrest and aphasias early in the seizure suggest language-dominant (almost always left) hemispheric onset. Alternatively, the patient may retain clearly intelligible speech during the seizure, which occurs more frequently with nondominant (almost always right) lateralization of seizure onset (86).

Although automatisms themselves are not lateralizing (87), when they occur with retained consciousness they are highly suggestive of lateralization to the right hemisphere (25). It should be noted that the converse, impaired consciousness with the onset of automatisms does not lateralize to the left hemisphere. Seizures with preserved consciousness account for only approximately 5% of seizures with automatisms (25).

Preservation or impairment of consciousness at seizure onset can have lateralizing significance. With complex partial seizures, impairment of consciousness at the onset of the seizure implies a left hemispheric onset, whereas preservation of consciousness at the onset of the seizure implies a right hemisphere lateralization.

Posturing during a seizure can provide lateralizing information in multiple ways. Unilateral dystonic posturing is usually distal, affecting the hand and fingers, with a torsional component. This is thought to occur from activation of the contralateral basal ganglia, and is thus a reliable lateralizing sign to the contralateral hemisphere (27,88). Unilateral tonic posturing frequently occurs; it is seen in up to 55% of patients with frontal lobe epilepsy (89), which is strongly lateralizing to the contralateral hemisphere (90).

Asymmetric tonic posturing with secondary generalization can contain lateralizing features. Often there is extension of one arm with flexion of the other, which has been called the "sign of four" posture due to the appearance of the number four given by the arms. This sign lateralizes to the contralateral side of the extended arm (91). In addition, asymmetrical termination of a secondarily generalized seizure suggests an ipsilateral onset of the seizure (92,93).

Forced movements, especially of the head and eyes, carry lateralizing value. Hughlings Jackson first noted that consistent head turning to one side suggests contralateral onset (94). Foerster and Penfield refined this observation to be more specific to forced turning movements of the head and eyes, which they called adversive (95). Gastaut coined the term versive, with turning of the eyes, then the head, then sometimes the body (96). Mouth deviation and arm clonic movements within 5 seconds of the onset of version provide additional lateralizing value (97). Forceful version and unilateral clonic movements lateralize contralateral to seizure onset (97–102).

Head version is often seen prior to progression to secondary generalization, and is a reliable lateralizing sign (97,103,104). Just prior to generalization, strong head version implies seizure onset contralateral to the direction of version (105). This is more significant with concomitant upward face tilting (106) and neck extension (107). In addition, head turning at the end of secondary generalization is a weakly lateralizing sign ipsilateral to the side of head turning (108).

Head turning by itself is somewhat controversial as a lateralizing sign. In most instances, it is not reliably lateralizing. However, in temporal lobe epilepsy, early head turning within the first 30 seconds of seizure onset has been shown to be ipsilateral to seizure onset in 94% of patients (105). This is more reliable when head turning ends before secondary generalization (105).

There are other reliable lateralizing signs during secondary generalization, along with the sign of four posture and head version. Eye deviation and unilateral facial twitching at the onset of secondary generalization are contralateral lateralizing signs. Unilateral clonic activity is also an excellent contralateral lateralizing sign.

During most seizures, the patient's eyes remain open. Many seizures may have associated blinking. Rarely, seizures may have forced eye closure; this most often involves both eyes, which has no lateralizing value. Unilateral repetitive ictal blinking without other facial clonic movements is overwhelmingly (83% to 90%) associated with ipsilateral seizure onset when seizures arise from the temporal regions (109–111), and is contralateral to occipital onset of seizure.

Ictal vomiting—vomiting during the amnestic phase of the seizure—is lateralized to the right hemisphere with rare exceptions (112). The physiology and mechanism of this is unknown, but has been postulated to be from activation of the insula. This has also been shown for ictal spitting (113,114) and coughing (115), which also relay a right hemisphere lateralization (116).

Ictal urinary urge was described early on by Freindel and Penfield (117), although at the time its lateralizing significance was not known. Recently, studies have shown that urinary urgency during a seizure localizes to the nondominant hemisphere (118,119). The mechanism of this is thought to involve activation of the mesial frontal region or the operculum.

During the postictal phase of a seizure, the patient may have unilateral weakness, known as a postictal Todd's paralysis (9,120,121). This feature lateralizes to the contralateral hemisphere. In relation to this, postictal nose wiping has been shown to be an ipsilateral lateralizing feature (122–124), and this observation has been expanded to show that other postictal manual tasks are also ipsilateral. The mechanism behind this has been postulated to be a relative paralysis of the contralateral upper extremity, causing the behavior to be performed by the ipsilateral hand.

Following a seizure, aphasia sometimes persists prominently in the postictal phase. Although contraction of the muscles of speech may produce an ictal aphasia, paralysis of these muscles postictally is not known to occur. Thus the aphasias produced postictally are typically from language areas, which lateralize to the dominant hemisphere (86,88,125).

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15

DIAGNOSTIC AND LOCALIZING EXTRACRANIAL EEG FEATURES OF EPILEPTIC SEIZURES

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LAURA A. STROM

The acquisition of a continuous video electroencephalogram in an epilepsy monitoring unit (EMU) is usually done with one of two main goals in mind: the diagnosis of a recurrent paroxysmal behavioral disorder or the presurgical localization of the epileptogenic zone. Although the majority of patients admitted to the EMU have epileptic seizures, the differential diagnosis of paroxysmal events is time-consuming. Other entities that present as paroxysmal events include narcolepsy, fugue states, night terrors, transient ischemic attacks, movement disorder, syncope, nonepileptic seizures (NES), and complicated migraines, to name those most commonly encountered. Of these, NES are the most frequently diagnosed. In the United States, fully 30% of admissions receive a diagnosis of NES (1).

The primary test for the diagnosis of a paroxysmal event is a good medical history. History is obtained from the patient, describing in detail what is experienced in plain language with a precise timeline of events. Because patients usually cannot accurately describe the behavioral events taking place during the seizure, observations from witnesses are extremely important and should be aggressively sought. Elements of the history will strongly suggest the diagnosis in many cases. However, if the diagnosis remains unclear or the patient is not responding to medication, an EMU admission is warranted. It is important to capture the patient's typical events. Ultimately one can be most confident of the diagnosis when an episode is captured, a technically adequate electrophysiological recording is made, and the event can be verified as typical by someone who has witnessed the patient's attacks.

The scope of this chapter is the value and strength of ictal scalp EEG. The scalp EEG yields recognizable changes useful for both characterizing epilepsy and localizing seizure onset; the latter is particularly useful for patients being considered for ablative surgery. For presurgical patients, the results of EEG monitoring are essential, but final decisions regarding surgery are made from a variety of tests. These data include a detailed neurological history and physical exam, MRI scans, neuropsychological evaluation, intracarotid amytal testing, positron emission tomography and single photon emission computed tomography scans, magnetoencephalography, and interictal scalp electroencephalography. There is variable opinion between epilepsy centers about the need for all or some of these tests, and variation also exists based upon the exact nature of each case.

In the straightforward case, epilepsy monitoring clearly identifies a single epileptogenic zone according to EEG and localizing behavioral changes. However, more often the information obtained requires presurgical planning with a higher level of complexity. In some cases it will be unclear whether all of the patient's typical events have been captured and identified as epileptic seizures (e.g., in a small but significant percent of patients both epileptic and nonepileptic seizures will exist). The seizures must be identified not only as localization-related but also as potentially amenable to an ablative procedure (i.e., surgery in the relevant area would not result in serious functional deficits). The scalp EEG can demonstrate the characteristic pattern of primary generalized epilepsy, for which current ablative procedures are not helpful. The ictal recording may reveal that there are seizure foci in more than one area, which may or may not preclude a surgical intervention. The epileptologists must determine whether the information obtained adequately defines the ictal onset and is sufficient for surgical decision making, and if not whether proceeding to invasive recording is likely to be of benefit to the patient. When invasive recording is required, then scalp ictal and interictal EEG is used to direct the placement of invasive electrodes.

LIMITATIONS OF SCALP ICTAL EEG

Ictal EEG changes can be subtle and in some cases undetectable. There are a variety of reasons for which an epileptic seizure will not be localizable or visualized on the scalp recording. Measurement of electrical seizure activity on scalp EEG relies upon distance between the recording electrode and the neuronal generator as well as on the absolute volume of cortex involved in the ictus, the electrical orientation of the firing neurons, and the synchrony of the firing cells (2).

There are large areas of the cerebral cortex that are too distant from the standard placement of scalp electrodes to be recorded with scalp EEG. Electrical changes that are generated in deep cortical structures including interhemispheric, basal frontal, occipital, and inferior and medial temporal regions often fail to project to the recording electrodes. The consequence is that the standard scalp EEG recordings fail to record activity from at least two-thirds of the cortex. Even in those areas of cortex that can be detected by routine scalp electrodes, the signal of the electrographic recording needs to be strong enough (i.e., encompass enough volume) and oriented toward the recording electrodes to be detected. Simple partial seizures usually have a restricted field, often with low-amplitude fast patterns that produce lower voltage activity than the ongoing background and therefore commonly fail to appear on the scalp EEG (2–4). The pattern of electrical noise due to muscle activity, movement, and other artifacts that occur during seizures frequently obscures localizing EEG patterns. This sometimes prevents a firm conclusion as to localization, but can yield other useful information about the patient's epilepsy. For example, postictal focal or lateralized EEG slowing has localizing value. Although the goal of presurgical epilepsy monitoring is to define the epileptic zone correlating with the area where the seizure begins, the electrographic seizure often first appears in the scalp EEG at some distance from the actual area of seizure onset. In such cases, the pattern of EEG spread combined with localizing behavioral changes may allow inference of the site of seizure onset.

The Ictal EEG

Although there is no absolute definition of the ictal electrographic pattern in terms of morphology or duration, the ictal EEG usually persists for more than several seconds. Features of the EEG before and after seizure activity, as well as the ictal onset and spread, are all elements of the recording that are used for interpretation and localization of seizure onset. *The hallmark of the ictal EEG is rhythmic activity unrelated to the patient's usual background patterns that begins abruptly and then evolves.* The features of the interictal EEG depend upon the underlying etiology and localization of seizure onset. The interictal EEG may infrequently be normal, or may more typically contain epileptiform activity in the form of spike discharges or sharp waves (5). The ictal EEG can consist of spikes, but can also demonstrate rhythmic sinusoidal waves without any sharply contoured components. The key feature is rhythmicity that begins abruptly and evolves.

The evolution of ictal patterns involves four dimensions: (a) frequency, (b) amplitude, (c) anatomic distribution, and (d) accompanying changes in the EEG background pattern. Frequency and amplitude can evolve in a variety of ways, but most often waveforms near the beginning of the seizure are faster in frequency and then evolve to slower frequencies. Occasionally there is waxing and waning of the frequency of the ictal pattern during a seizure. The amplitude of the waveforms typically increases as the seizure evolves. Anatomic spread of seizure activity often conforms to the underlying anatomy with the potential of migrating into adjacent cortex or moving via white-matter pathways. Usually the spread is regional prior to spreading between hemispheres. Less specific EEG changes can also be noted prior to the onset of any rhythmic activity. Attenuation of ongoing background activity may occur, most often seconds prior to the obvious onset of rhythmic discharge. These changes can be localized or regional, or can involve the entire EEG. Exceptionally, seizures are heralded by an increase or decrease in the interictal spike frequency.

Each seizure should be examined for postictal changes. Postictal localizing changes consist of slowing and/or attenuation or absence of alpha and beta activity, and usually have the same anatomic distribution as the ictal onset (Figure 15-1). Postictal focal EEG changes are more common after partial seizures in mesial temporal lobe epilepsy than after partial seizures that originate extratemporally (6,7).

EEG ictal changes in scalp recordings may be very subtle and consist only of a mild focal attenuation in amplitude or of another nonspecific change in the EEG baseline. In some patients, these subtle EEG alterations are the only electrographic indication of an ictal event. It is therefore essential, in these subtle cases, to continue recording long enough to observe multiple events so that stereotypical clinical and electrophysiological features can be confirmed. In this way, as with signal averaging in evoked potential recording, it can be demonstrated in many patients that a consistent EEG event occurs with the patient's seizures that is not otherwise typical of the patient's spontaneous baseline changes or artifact.

Nomenclature of the Anatomical Distribution of Electrographic Seizure Onset

Seizure onset may be described as focal, regional, hemispheric, or nonlateralized. Focal onset is confined to one or two scalp electrodes and implies a highly restricted area of seizure onset (Figure 15-2). Detection of a regional onset may be seen in specific lobes of the brain. The term "lateralized" is reserved for seizures wherein the ictal discharge can be assigned to one hemisphere at onset, but has a broadly distributed electrical

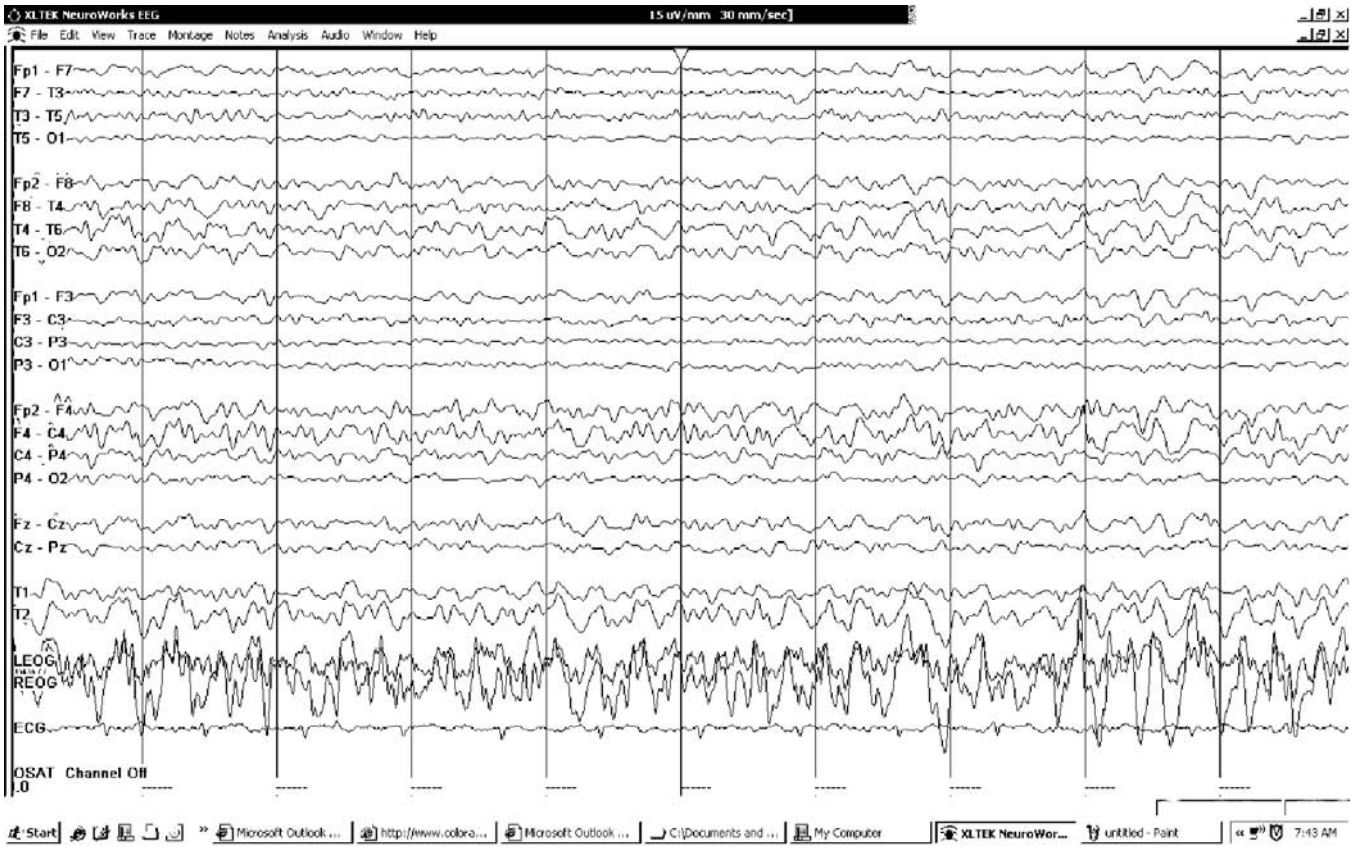

FIGURE 15-1. Focal onset seizure. The onset is localized to the anterior temporal area (F7). However, the actual area of onset (epileptogenic zone) was localized to the region of Heschl's gyrus using intracranial monitoring.

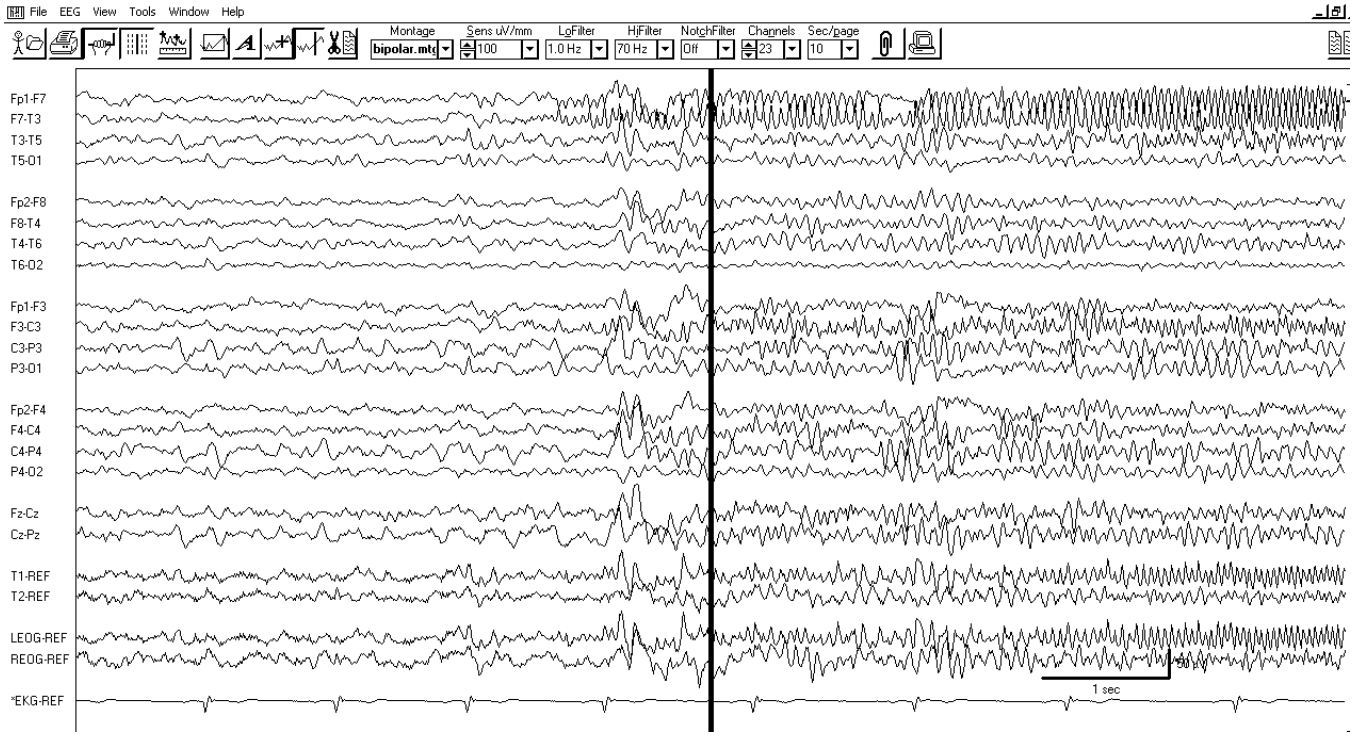

FIGURE 15-2. Postictal right-sided slowing in a patient with right mesial temporal lobe epilepsy; this was not present on the patient's baseline EEG prior to seizure onset.

field, making more precise localization impossible. A nonlateralized seizure is one in which the ictal charges appear simultaneously in both hemispheres.

Specific Epilepsy Types and Their Scalp EEG Ictal Correlate

Mesial Temporal Lobe Onset

There is no pathognomonic surface pattern for mesial temporal onset. However, a common sequence of EEG changes is often encountered. The first EEG change is often widespread attenuation of background activity just prior to the onset of rhythmic seizure activity. In some instances, interictal spikes that characterize the baseline background of some EEGs stop just prior to the rhythmic evolution of the seizure. Typically, the next change is onset of rhythmic frequencies. These may demonstrate a distinct lateralized pattern or focal features at the outset, which helps to localize the seizure onset.

Recall that *seizures beginning in the mesial temporal structures are inaccessible to direct recording with surface electrodes*. Scalp EEG changes must be explained, therefore, as the result of ictal trans-synaptic propagation and the development of a large field of volume conduction by the ictal generating neurons. Given the limitations of surface recordings described above, it may seem surprising that the scalp EEG can provide accurate localization information. The stereotypical propagation of seizures originating in the mesial temporal lobe, however, provides assurances. Most commonly, the initial propagation is from the mesial temporal structures to the ipsilateral temporal neocortex (7,8). Alternatively, initial propagation may be to the contralateral hippocampus. A third pattern of propagation results in nearly simultaneous spread to the ipsilateral neocortex and contralateral hippocampus. In contrast, in studies of temporal lobe–onset seizure propagation, seizures of unilateral mesial temporal origin do *not* propagate first to contralateral neocortex (7,8). However, false lateralization of temporal lobe seizures has been reported (9). In these cases, the ictal onset is in a temporal lobe that has a large structural lesion or severe unilateral mesial temporal sclerosis. Presumably, the false lateralization occurs because the diseased temporal lobe cannot produce a detectable electrical scalp signal prior to spread to the healthier contralateral cortex that *can* generate a visible EEG change. From available data, the onset of lateralized seizure activity with rhythmic temporal activity on a scalp EEG is likely mesial temporal and ipsilateral to the side of electrical onset. This is probably the result, in part, of the fact that the large majority of individuals with temporal lobe epilepsy have seizure onset in the mesial temporal lobe (Figure 15-3).

Neocortical Temporal Lobe Epilepsy

Neocortical temporal lobe epilepsy is not as common as mesial temporal lobe epilepsy. Some authors feel that the failure to recognize neocortical lobe onset as a separate entity from mesial temporal onset correlates with less satisfactory outcomes following ablative temporal lobe surgery (10,11). From an ictal standpoint, the activity at onset is more widely distributed and often hemispheric, in contrast with the focal discharges found in mesial temporal lobe epilepsy. Ictal frequencies are generally slower, with less stability of frequencies and amplitude. Ipsilateral or contralateral spread to the parasagittal region is seen more in neocortical temporal lobe epilepsy. According to Ebersole, scalp EEG from a seizure focus in the temporal neocortex often shows irregular, polymorphic, 2- to 5-Hz lateralized activity, sometimes followed by theta rhythms or preceded by sharp waves (10). The most common ictal finding in seizures of temporal neocortical onset was found in this same study to be the lack of a clear lateralized EEG discharge. The absence of scalp ictal discharge is also more common in neocortical epilepsy than in mesial temporal epilepsy. However, the overlap in EEG findings between these two entities precludes distinction by ictal EEG alone (10–14).

The interpretation of temporal lobe epilepsy should also include consideration of the "temporal lobe plus" entity specifically (15). Barba and colleagues found that 83% of their patients had hippocampal sclerosis, probably representing a secondary lesion. These patients had poorer surgical outcomes with respect to seizure control as compared to cases with a working diagnosis of mesial temporal epilepsy alone. The clinical semiology, ictal spikes, and ictal EEG onset show differences compared to pure mesial temporal lobe epilepsy. The scalp EEG in these cases may be useful in directing further invasive recordings prior to an ablative procedure. Temporal-plus subjects were more likely to have the first EEG changes localized over the anterior and prefrontal region (FP2–F4 and/or FP1–F3), the posterior-temporal/parietal region (T5–P3, T6–P4), or frontal central regions (F4–C4 and F3–C3) compared to the pure mesial temporal lobe group (15). Unfortunately, these features alone do not allow definitive discrimination between mesial temporal seizures and cases of temporal-plus seizures.

Reliability of Scalp EEG

Given the various limitations of scalp EEG determined by volume of seizure activity, proximity to recording electrodes, subtle changes on EEG, and artifact produced by seizure activity, it is evident that localization of seizure origin cannot always be accomplished with noninvasive monitoring. Walzack (1992) defined formal criteria for the lateralization of temporal lobe epilepsy. His gold standard for localization was seizure freedom following resection (16). He defined inter-rater reliability by asking questions about the activity at seizure onset. Seizure onset was defined as attenuation of spikes and sharp waves or focal attenuation of the background. The onset of rhythmic activity and accuracy of lateralization was high for temporal lobe

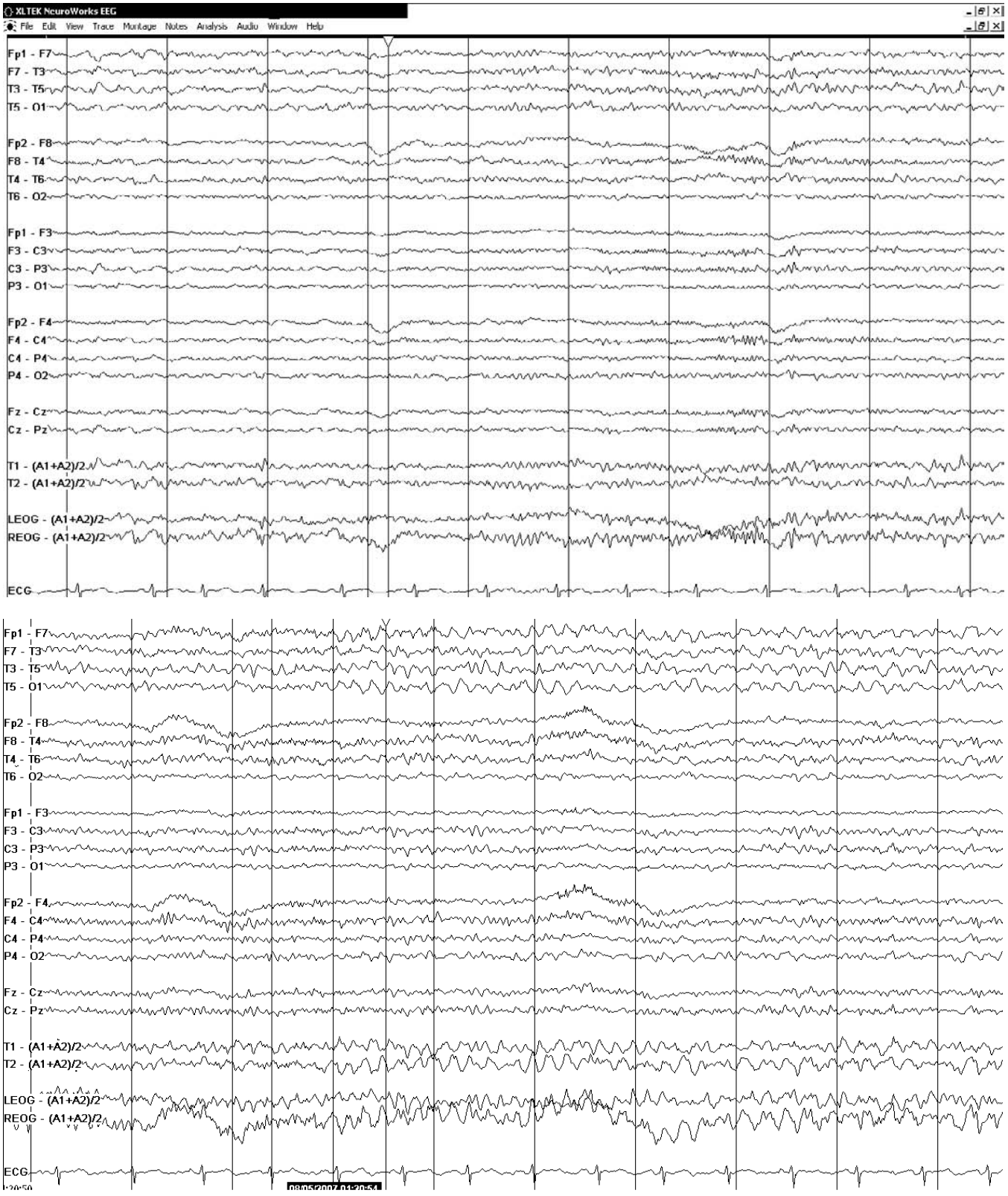

FIGURE 15-3. Patient with left mesial temporal lobe epilepsy. Note seizure onset with focal left slowing progressing to rhythmic theta.

onset seizures if all three electroencephalographers agreed with confidence on the lateralizing capacity of the ictal recording. The reliability of scalp localization was correct in 97%–99% of the cases when all three reviewers confidently lateralized the side of seizure onset. Extra–temporal lobe onset did not produce the same level of inter-rater reliability or accuracy of lateralization of seizure onset.

In Blume's study of temporal lobe cases, the ictal EEG correctly lateralized to the ipsilateral side of resection in 55% of cases, was neutral (nonlateralizing) in 27%, and was contralateral in 18% of cases (17). In this study, the measure of correct lateralization was seizure freedom two years post-surgically or at least 90% improvement of seizure activity. Spencer's study in *Neurology* compared accuracy of scalp localization with ictal EEG to that with depth electrodes as a gold standard (18). The scalp EEG disagreed with the depth electrode findings in 3%–17% of cases. Spencer's study also assessed inter-rater reliability. She found 2%–4% disagreement in the lateralization between electroencephalographers. The most common disagreement was whether or not the reader felt confident with the localization and lateralization. In this study 46%–49% of the disagreements were in lateralization and 21%–38% were in lobe localization. The most common error was not false lateralization but rather the finding of a focal temporal scalp ictal pattern when none was observed with invasive recordings (19). This probably represented a spread phenomenon into the temporal lobe. Foldvary and colleagues found that ictal lateralization was correct in 92% of their patients with mesial temporal lobe epilepsy, incorrectly localized in 4%, and obscured in 4% (20). Foldvary's gold standard for lateralization was an Engel class I outcome at 1-year follow up. In summary, scalp recording localization in temporal lobe epilepsy in the best of circumstances is subject to some degree of error. Figure 15-1 illustrates this point showing ectopic localization of seizure onset to the anterior temporal region in a patient whose seizures actually arose from the area of Heschl's gyrus.

Frontal Lobe Epilepsies

Frontal lobe epilepsy may represent the most difficult seizure type to evaluate and localize with scalp EEG. *The EEG in frontal lobe epilepsy is nonlocalizing in the majority of patients* (21–24).There is often no electrographic correlate seen in the scalp recording. As a general rule, frontal lobe epilepsies spread very quickly in contrast to temporal lobe epilepsy, making localization and lateralization difficult. At ictal onset, frontal lobe epilepsies may appear generalized (Figure 15-4). This pattern is often ictus in evolution and represents secondary bilateral synchrony (i.e., the rapid

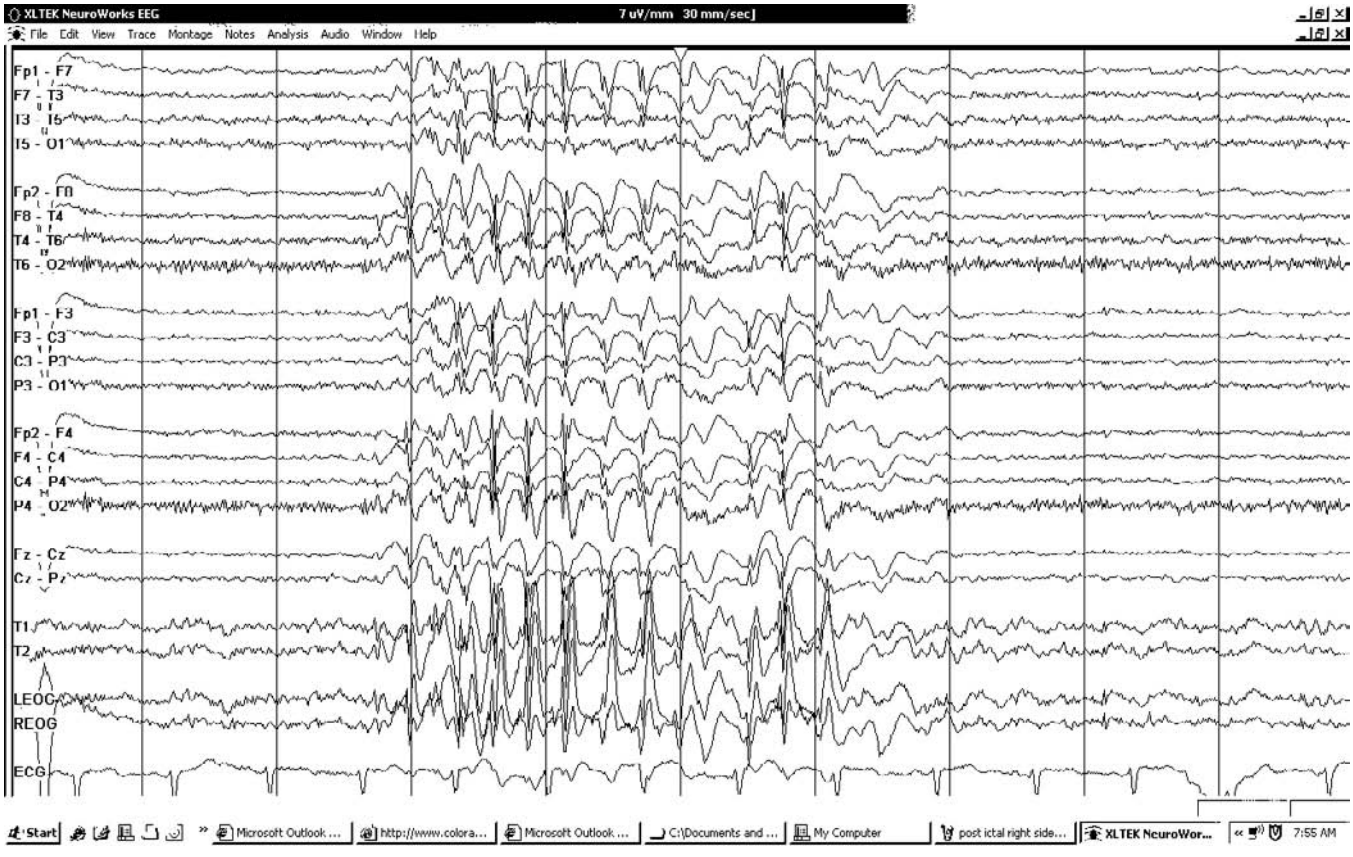

FIGURE 15-4. Secondary bilateral synchrony in a patient later shown by intracranial recording to have a mesial frontal lobe focus. Seizure onset occurred with bilateral spike and wave complexes shown here.

interhemispheric spread of a unilateral epileptogenic zone that gives the appearance of a generalized seizure onset). Swartz reviewed this topic, demonstrating a preponderance of this diffuse generalized pattern with ictal onset in the frontal lobe epilepsies compared to temporal lobe loci (25). False localization of frontal lobe epilepsy to the temporal lobe reflects prominent interconnections between those two structures. The clinical behavior of a seizure originating in the frontal lobe often consists of early and prominent motor activity. This usually creates movement and muscle artifact that obscures EEG activity.

The various anatomic regions of the frontal lobe produce seizures that may be distinct from one another electrically. Seizures of dorsal lateral frontal origin are usually associated with a localizing ictal discharge. In one study, 80% of patients with dorsal lateral frontal lobe seizures demonstrated this pattern (25). Seizures originating in the orbitofrontal region may produce frontal rhythmic alpha or beta activity in the frontal polar electrodes (26,27). Diffuse, bilateral voltage attenuation is another common pattern described with orbitofrontal onset. The supplementary motor area seizure can be associated with a focal rhythmic discharge localized near the vertex (28). However, voltage attenuation, seen diffusely distributed in the bilateral frontal region, and followed by diffuse rhythmic theta or delta, is more commonly described (29–32).The frontal suprasylvian area is intimately connected with temporal regions via the uncinate fasciculus and cingulum. These likely account for the very rapid ictal spread between these two areas of cortex, which makes determining ictal onset a challenge. Swartz also compared frontal onset with temporal onset seizures (25). Temporal lobe seizures more commonly begin focally, with 26% in the temporal lobe group beginning with this pattern versus 12% in the frontal group. A pattern of regional onset was seen more commonly in the frontal group at 24%, versus the 10% of temporal cases with regional onset. Regional and focal onset seizures had better surgical outcomes than those with bilateral or diffuse attenuation at onset.

Diffuse patterns are felt to represent a spread phenomenon implying inadequate determination of the true epileptogenic zone. In a series of 16 patients with frontal lobe epilepsies and anatomically heterogeneous frontal lobe lesions, only 5 had localized frontal onset (33). These were correctly localized in three of the patients. Errors in localization included one seizure that was contralateral to the scalp recording and one patient with bilateral independent onset seizures. Williamson's series of 10 patients with frontal lobe complex partial seizures found 7 without appreciable ictal electrical activity other than artifact, and 5 with patterns suggestive of temporal lobe abnormalities (the study did not clearly define these as ictal or interictal) (30). In Foldvary's study, lateral frontal lobe epilepsy was correctly localized in 60% of cases, and medial frontal lobe epilepsy was localized in only 25% (20). Salanova found that only 42% of a series of 19 patients with frontal lobe epilepsy had localization to one frontal lobe. One of this series with localized scalp onset at F8 was shown with subdural electrodes to have an extensive epileptic zone (23).

Parietal Lobe Epilepsy

The parietal lobe encompasses a relatively small geographical region that may be resolved on scalp EEG. Additionally, much of the parietal lobe is eloquent cortex subserving higher-level cognitive function, which is difficult to map. As a result, the potential for surgical ablation is complicated by the difficulties of source localization to eloquent cortex and the surgical limitations this imposes. In spite of this, in a series of 40 parietal lobe cases, 22 of 26 selected for focal cortectomy had a favorable outcome defined as seizure freedom (follow-up >1 year except in one case) (34). Correct localization in parietal lobe epilepsy with scalp electrodes is a challenge. In Foldvary's study, five of seven cases were correctly localized (20). Williamson reported a series of 11 cases found to have parietal lesions on imaging (35). Three had the correct lateralization with a buildup of rhythmic slower sharp waves in the ipsilateral hemisphere, but only one of these cases correctly localized to the parietal lobe. The remaining eight cases had bilateral abnormalities with no clear lateralization. False localization to the ipsilateral temporal lobe is also seen in ictal patterns originating in the parietal lobe (35,36).

Occipital Lobe Epilepsy

Occipital lobe epilepsy is relatively rare. In part this reflects some of the difficulties in diagnosing this focal epilepsy. Occipital lobe epilepsy is not usually well defined by scalp EEG. Although rare, clearly defined ictal onset patterns have been reported in the occipital region (Figure 15-5). In two separate studies with patients who had occipital lobe onset confirmed by subdural grids, only 15%–20% of patients demonstrated occipital ictal onset with scalp electrodes (23,25). Foldvary's series described six occipital lobe epilepsies; of these, three were correctly localized with scalp EEG, one was falsely localized, and two appeared generalized (20). A seizure may spread quickly from its occipital origin into motor areas and result in rapid secondary generalization. Alternatively, the seizure activity may spread via the arcuate fasciculus into the ipsitlateral mesial temporal lobe and mimic the semiology and electrical ictal behavior of a mesial temporal lobe seizure. Lee et al. reported a series of 26 occipital lobe epilepsy cases; several patients had more than one pattern of ictal spread (37).

Often the characteristic clinical features of visual hallucinations at the beginning of the seizure, or a structural abnormality on imaging studies, help localize the occipital onset of these partial seizures. Although visual hallucinations are considered the hallmark feature, this symptom

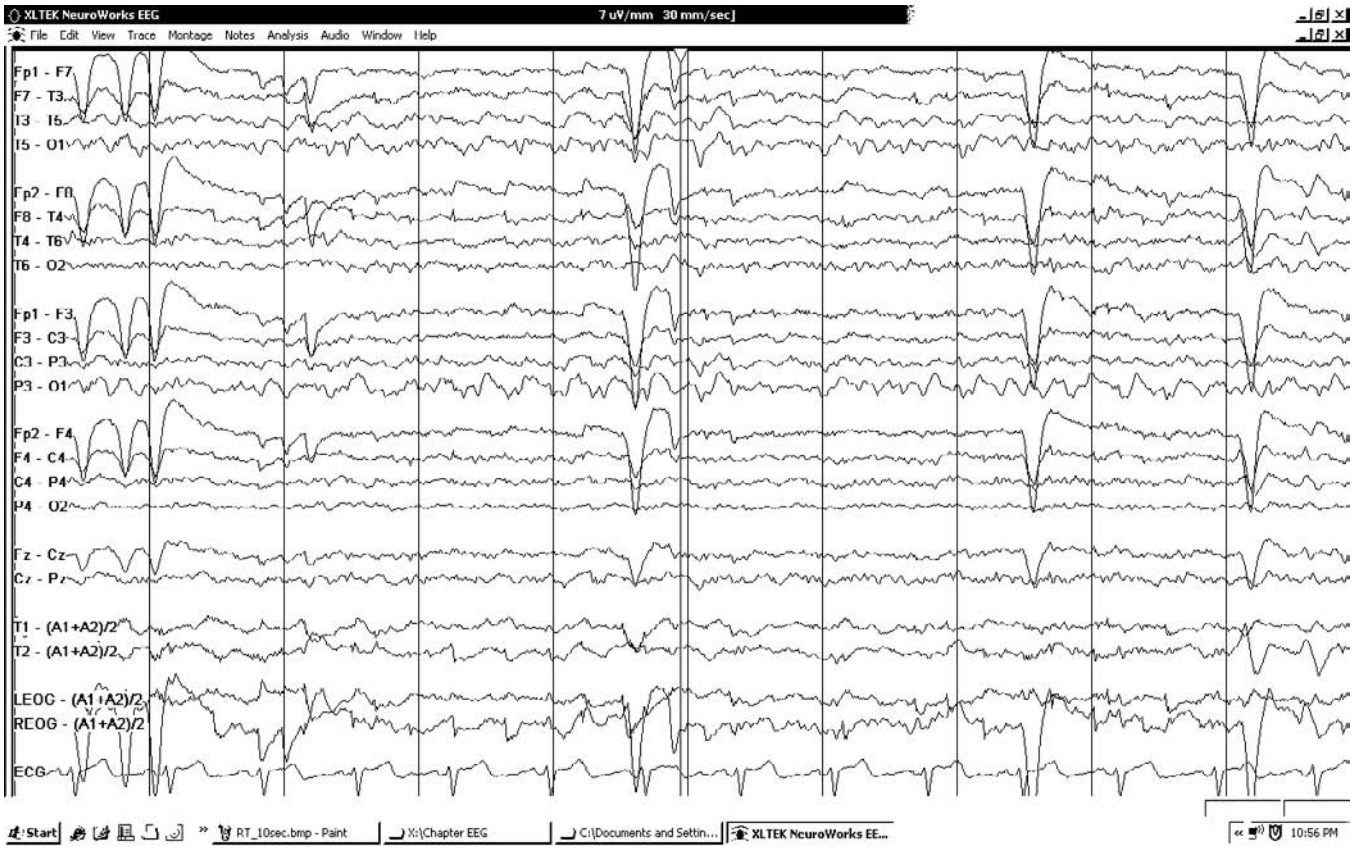

FIGURE 15-5. Occipital lobe epilepsy. A patient with occipital lobe epilepsy with focal onset in the left posterior quadrant on scalp EEG.

can be difficult to elicit and in some cases is unhelpful (37). At times, epileptic visual hallucinations are confused with the more common visual disturbances of migraine and are therefore misdiagnosed. Most case series report that obtaining concordant data from other presurgical testing is necessary in order to correctly localize occipital lobe epilepsy.

Pitfalls

The hallmark of the scalp ictal electroencephalogram is activity that begins suddenly with rhythmic characteristics. There are normal patterns that are not ictal that share these features; these are referred to as pseudoepileptiform patterns. These patterns include 14- and 6-Hz positive bursts, rhythmic midtemporal discharges, paroxysmal hypnogogic hypersynchrony, and subclinical rhythmic EEG discharge of adults (SREDA) (38). The reader should be aware of these patterns, their morphologic characteristics, and their benign significance.

SUMMARY

In summary, scalp ictal EEG is a very useful tool in the identification and at times the localization of epileptic seizures. The defining features of partial seizures on scalp EEG include an identifiable change from the background at seizure onset, a clear evolution in the amplitude and frequency of rhythmic activities, an identifiable electrical termination, and, finally, postictal slowing. Anatomic spread may or may not be seen. Mesial temporal lobe epilepsy appears to have the most consistently identifiable ictal pattern, and is most amenable to the use of scalp EEG to localize seizure onset.

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16

DIAGNOSTIC AND LOCALIZING INTRACRANIAL EEG FEATURES OF EPILEPTIC SEIZURES

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MICHAEL DUCHOWNY
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Although the EEG is easily recorded from scalp electrodes, recording the EEG directly from the cerebral cortex sometimes provides critical information that cannot be obtained any other way (1). Chronic intracranial EEG recording from cortex is primarily used for two reasons: for planning epilepsy surgery and to assess the brain's electrical activity during cortical mapping sessions. Once placed, electrodes can also be used to map cortical function during stimulation. While the proportion of surgical patients who require this technique has steadily decreased as noninvasive evaluation methods have improved, intracranial EEG is still required in patients with ambiguous noninvasive studies. During electrical stimulation of the brain, cortical EEG recording is also used to verify that the stimulus remains local and that afterdischarges are not provoked.

This chapter will review the methods of recording EEG from cortex and the intracranial EEG. In many respects, intracranial EEG resembles the extracranial EEG. Some difficulties presented by extracranial EEG are eliminated with cortical recording, though new difficulties are introduced. The usual waveforms are readily visible, only more so. The intracranial EEG is not filtered by the scalp and skull and, consequently, ordinary rhythms look different. Normal rhythms sometimes appear sharper and less benign, and waveforms that are not seen in the scalp EEG are sometimes discerned. Epileptiform discharges look different in the intracranial EEG, and it is possible to study seizures and the interictal EEG in much greater detail than with scalp EEG.

WHEN IS INTRACRANIAL EEG USED?

The intracranial EEG may be recorded for a brief time during a neurosurgical procedure, or for a longer time in a monitoring suite after electrode insertion in the operating room. Acute intraoperative EEG recording can be done quickly with a minimum of inconvenience and risk. Chronic recording is more complex, expensive, and riskier, and requires greater justification.

Chronic Intracranial EEG Recording

Two requirements must be satisfied to use chronically indwelling intracranial electrodes when evaluating someone for epilepsy surgery. First, it should not be possible to define an area for resection through safer noninvasive means or with acute intraoperative recording during a neurosurgical procedure. The major objective of the presurgical evaluation process is to establish whether a single epileptogenic structural lesion exists that can be safely removed or transected. When magnetic resonance imaging (MRI) and other ancillary techniques, including positron emission tomography, single photon emission computed tomography, and magnetoencephalography, are used alongside the clinical history and examination, most patients are able to have surgery without intracranial electrodes. Only when these noninvasive methods yield conflicting data or are insufficiently localizing should intracranial electrodes be employed (1–4). Second, before placing intracranial electrodes, one must have a reasonable hypothesis regarding the location of the epileptogenic zone; intracranial electrodes should not be placed in the absence of a clear idea of where seizures most likely originate, and there should be reasonable evidence that seizures emanate from a single source.

The rationale for recording intracranial EEG in epilepsy can be concisely summarized. Intracranial EEG helps establish whether there are one or more well-localized epileptogenic zones, helps demarcate the boundaries of a single zone, and establishes the function of the tissue within and adjacent to that zone. In practice, this means (a) determining the laterality of the focus, (b) localizing the focus to a specific lobe or lobes, and (c) defining the boundaries of

the epileptogenic zone. It is also necessary to (a) determine whether there are multiple epileptogenic areas, which might dissuade one from recommending surgery; (b) confirm that seizures are focal rather than generalized (occasionally, a frontal focus may appear as a generalized spike and wave discharge in the scalp EEG); and, (c) confirm the diagnosis of epilepsy and define a focus for excision when the scalp EEG is negative (a rare indication).

Rarely, chronic indwelling intracranial electrodes are placed for the sole purpose of mapping cortical function. This is generally done in complex cases in which the mapping procedure is expected to last so long that it would not be safe or tolerable to do it in the operating room. For example, most children and some adults cannot remain awake during surgery, so electrodes are inserted and electrical stimulation is performed over the next day or two outside the operating room (5,6). The electrodes are removed after cortical mapping is completed.

Acute Intraoperative Recording

Intraoperative electrocorticography is used for identical purposes, to reveal abnormal discharges and to monitor the EEG if electrical stimulation is performed (7–11). However, physicians must have identified the area for excision with reasonable certainty prior to surgery, and the intraoperative EEG then helps the surgeon to refine the excision margins about a known lesion. Since the recording time is limited, decisions must be made quickly.

The same electrodes, recording techniques, montage design, and methods of interpretation apply in the operating room as in chronic recording. The only differences are in the duration of recording, the types of artifacts, and the potential confounding effects of anesthetic agents during the two types of recording session. Operating suites contain electronic and mechanical equipment that may introduce artifact in the EEG. Several measures can be taken to eliminate or reduce the extraneous artifact, ranging from disconnecting some equipment to conducting a thorough evaluation of the building's grounding cables. Since some anesthetics can either provoke or suppress interictal spikes, these agents are best avoided during intraoperative electrocorticography. Most neurophysiologists prefer to rely upon a combination of narcotic medication, such as fentanyl, and nitrous oxide if general anesthesia is used. Local anesthesia provides pain control without affecting the EEG, but it is not suitable for all patients.

INTRACRANIAL ELECTRODES

Different types of electrodes can be used to record the intracranial EEG (Table 16-1), including depth electrodes, subdural electrodes, epidural electrodes, and foramen ovale electrodes (Figure 16-1). Each has unique advantages and disadvantages, and their use depends upon the question being posed in an intracranial evaluation. Often, multiple electrode types are used simultaneously to maximize the yield of an intracranial EEG recording session.

TABLE 16-1. INTRACRANIAL ELECTRODES

Electrode Type	Recording Characteristics
Depth electrodes	Record from buried cortex (e.g., amygdala, hippocampus) although may be used for superficial or basal cortex (limited neocortical sampling)
Subdural electrodes	Record from superficial, interhemispheric, or basal cortex, ideal for broad sampling, used for stimulation to map cortical function
Epidural electrodes	Record from superficial or basal cortex, have dura interposed between electrode and cortex, less useful for mapping cortical function
Foramen ovale electrodes	Record from mesial temporal cortex, extradural location

Depth Electrodes

Depth electrodes are wires or catheters that pierce the substance of the brain (1,12). Contacts are placed at regular intervals along the electrode at any desired interval, typically every 5 mm. Since depth electrodes penetrate the brain, their contacts can rest within the cortex, in contrast to the other types of intracranial electrodes that record from the pial or dural surface. They are ideally suited to record from buried, otherwise inaccessible nuclei such as the amygdala and hippocampus. They may also be used to record from cingulate and orbitofrontal cortex, although these areas can be easily reached with subdural electrodes. Limited numbers of these electrodes are used in any one patient to reduce the risk of hemorrhage; consequently, sampling is limited.

Subdural Electrodes

Subdural electrodes are thin plastic (silastic) sheets with embedded electrode contacts. The contacts can be arranged in any pattern and spaced at any interval, though contact spacing typically ranges from 5 mm to 10 mm. The most common electrode types are referred to as strips and grids. Subdural strips have a single or double row of contacts placed in a straight line. Subdural grids are rectangular or square arrays of contacts spaced at regular intervals. Subdural electrodes are placed directly on the pia mater and are not inserted into the brain. They record from the gyral surface and can be placed over cortex to sample widely from one

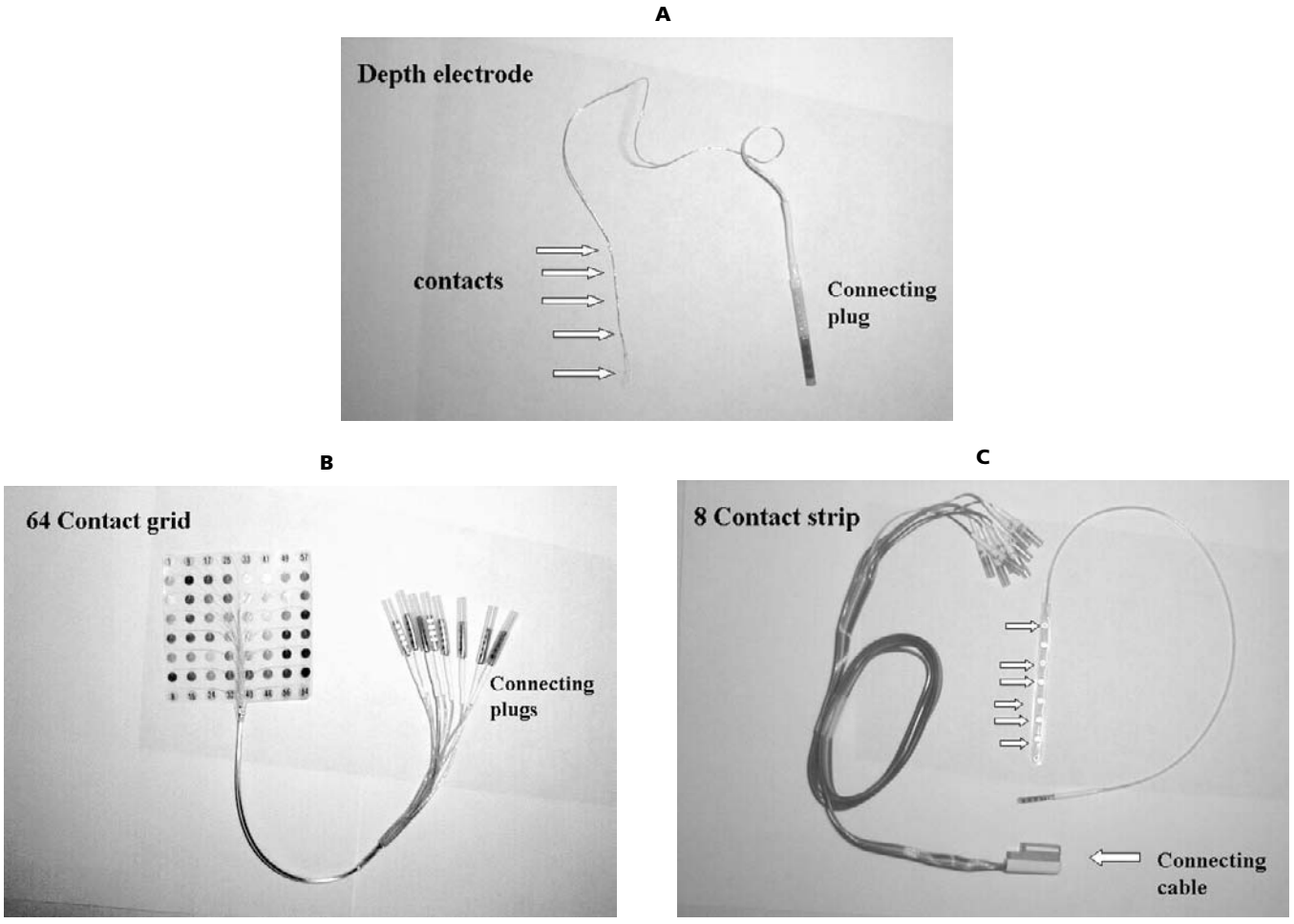


FIGURE 16-1. Illustrations of depth electrode (a) and subdural electrodes (b,c).

or more lobes (13,14). When epidural recording is desired, the same electrodes may be used as in subdural recording, though other types have been designed. Accurate subdural electrode placement is the first and one of the most critical steps to optimize data capture and localize seizure origin. Put simply, if subdural electrodes are not placed accurately, the likelihood of achieving complete resection and seizure freedom is extremely low. To this end, noninvasive data provide the basic framework for correct anatomic placement of subdural electrodes: placement requires a careful multimodal review of scalp EEG, anatomic, and functional imaging data. Unfortunately, despite these maneuvers, the ictal onset zone involves the edge of subdural electrode coverage in approximately half of patients (15).

Arrays of subdural electrodes are placed over the neocortical surface to adequately cover the hypothesized epileptogenic region(s). Larger grids are generally directed over the cortical convexity, whereas strips are preferable for smaller or less accessible regions on the hemispheric base or interhemispheric surfaces. When the suspected target lies in proximity to eloquent cortex, larger grids are usually required to both record seizures and map functionality.

Subdural grids should not be folded over two cortical surfaces. Such placement can seriously compromise venous drainage of the hemisphere into major sinuses and lead to significant venous infarction. For this reason, grid placement should be limited to a single neocortical surface. Larger draining veins such as Labbé and Trolard are particularly vulnerable to subdural grid compression.

Foramen Ovale Electrodes

Foramen ovale electrodes consist of wires with multiple contacts and are similar to depth electrodes (16–17). They are inserted via the cheek through the foramen ovale to rest in the epidural space adjacent to the mesial temporal lobe. They were developed as a substitute for depth electrodes. It is not clear that they carry a lower morbidity, though the insertion technique is simpler and less expensive. They will not be discussed further in this chapter.

ADVANTAGES AND DISADVANTAGES OF INTRACRANIAL ELECTRODES

Intracranial electrodes have several advantages over scalp electrodes (18). They are close to the cortex, so EEG signal is neither attenuated nor altered by overlying skull or scalp. The scalp and skull act as a filter, and preferentially pass lower frequencies more readily than higher frequencies (1). Practically speaking, this means that beta and gamma frequencies are attenuated more than delta or theta frequencies, and that the fast components of interictal and ictal spikes are more attenuated. In addition, the intracranial EEG signal cannot be obscured by electromyographic artifact; this is often a problem with scalp recording. Intracranial electrodes record signals from small pools of neurons that do not generate a sufficiently strong signal for scalp electrode detection. Consequently, intracranial electrodes detect seizures earlier and more often than scalp or sphenoidal electrodes, and hippocampal seizures are usually detected earlier with depth electrodes than with subdural electrodes (19,20). Interictal spikes are detected in greater number and in more locations with intracranial electrodes than with scalp electrodes. Focal disruptions of normal rhythms are more readily apparent with intracranial electrodes as well, because the spatial averaging properties of the scalp are eliminated.

However, these advantages are accompanied by disadvantages. Only a limited amount of cortex can be sampled by intracranial electrodes, and clinically important signals that are generated at a distance from the electrode may not be detected (1). Since the amplitude of any EEG signal is proportional to the solid angle of the dipole, potentials with a tangential orientation might not be detected, although this limitation applies to scalp EEG as well. Signals that emanate from cortical sulci are usually not recorded by intracranial electrodes. Finally, because the skull and/or dura must be breached to place intracranial electrodes, patients are exposed to risk and significant discomfort. While the risk of a major complication such as hemorrhage, infection, or herniation is small, it is not negligible.

Intracranial EEG Acquisition and Playback

The methods used to record and review intracranial EEG are the same as those used for scalp EEG, with a few minor exceptions. The same amplifiers are used for scalp and intracranial EEG. Signals are usually digitized by commercial equipment at a rate of 200–400 Hz, which allows for adequate display of virtually all clinically relevant EEG signals. Some commercial equipment permits higher sampling rates; these are necessary to record signals greater than 200 Hz, and these higher-frequency signals may be of importance. The number of channels required depends upon the number of electrode contacts used. Most commercial equipment generally allows the simultaneous recording of at least 128 channels. The same filter settings are commonly used for clinical intracranial EEG as scalp EEG (low frequency filter: 1 Hz; high frequency filter: 70 Hz), though high frequency cut-off limitations do not necessarily apply. Indeed, very high frequency activity up to 500 Hz has been recorded in the intracranial EEG with depth electrodes using appropriate sampling rates (22,23). Because signal amplitudes are considerably higher, typically three- to eight-fold, in the cortical EEG than in scalp EEG, amplifier gains must be adjusted accordingly.

Intracranial EEG montages are designed using the same principles as are employed in scalp EEG, although the specifics vary depending upon the number of electrodes used and their location. Referential or bipolar montages can be created, and there are often advantages to reviewing data in more than one montage because of in-phase cancellation or an active reference. EEG channels are generally best displayed in a logical framework, with linear sequences (e.g., anterior to posterior, superior to inferior, etc.), and channels should be grouped by location. For example, deep temporal lobe contacts may be grouped together in a series of channels, followed then by grouping lateral neocortical temporal contacts in the next series of channels, and so forth. This is shown in the EEG illustrations in this chapter. If a referential montage is used, either an extracranial or an intracranial contact can be used. It is important to choose a reference contact that has as little artifact as possible and is uninvolved in the discharge of interest. Interpretation of intracranial EEG is often made difficult by the large number of channels that are needed to display information from all contacts. It is not uncommon to collect between 64 and 128 channels of data, which must then be simultaneously reviewed.

ELECTRODE LOCATION

Many patients who come for surgical evaluation have mesial temporal lobe epilepsy (24), which is characterized by seizures originating in the hippocampus or, less often, in the amygdala. Depth electrodes are ideally suited to study patients with this condition, since they directly record the EEG from limbic structures. In contrast, subdural, epidural, and foramen ovale electrodes are placed at a distance from the hippocampus and amygdala, which limits their sensitivity. Temporal lobe depth electrodes are most often inserted via a lateral approach from the middle temporal gyrus to the desired mesial temporal targets, which include the amygdala, hippocampus, and parahippocampal gyrus. This is a relatively avascular route that minimizes the risk of producing an intracerebral hematoma. Adequate sampling of mesial temporal structures requires placement of between three and six electrodes when a lateral approach is used. An alternative strategy, used less often, targets the hippocampus from a posterior approach through the occipital lobe. This

technique permits placement of multiple contacts within mesial temporal structures with one electrode. The posterior approach puts the electrode through more brain tissue than the lateral approach, and objections have been raised because this method skewers the hippocampus, theoretically posing greater risk. In practice, however, no clinically significant problems have been reported using the posterior approach. Depth electrodes are generally placed in both mesial temporal lobes, both because of the possibility of bilateral independent seizure onsets and to measure the interhemispheric propagation time (25). Unfortunately, temporal lobe neocortex is not well sampled by depth electrodes, so a combination of temporal lobe subdural strips and depth electrodes is often preferred to allow for detection of both limbic and neocortical temporal lobe seizure origin (19,20,26–28).

Subdural electrodes are best suited to record from cortex outside mesial temporal limbic structures, although depth electrodes have been used as well. Subdural electrodes provide broad sampling of virtually all other neocortical regions. Consequently, depth electrodes are now used sparingly outside the temporal lobe in most institutions, and are reserved for situations in which technical considerations prevent adequate sampling with subdural electrodes. Finally, depth electrodes have been used in some patients with epilepsy and movement disorders to record and stimulate subcortical nuclei such as the thalamus and basal ganglia (29).

RISKS

Placement of intracranial electrodes occasionally causes complications, but these are rarely permanent. Chronic intracranial EEG recording has a morbidity ranging between 1% and 4% (30–33), and this morbidity is mainly transient. Technical advances in electrode fabrication and modern neurosurgical techniques have made intracranial electrode implantation reasonably safe, and there appears to be no safety advantage of one electrode type over another—morbidity and mortality rates appear similar. Even foramen ovale electrodes, introduced as a theoretically safer method, appear to pose risks similar to those associated with subdural or depth electrodes. Acute intraoperative recording with subdural or epidural electrodes has virtually no added risk other than that imposed by the added time needed for general anesthesia. If depth electrodes are used for acute intraoperative recording, the main risk is hemorrhage.

Hemorrhage is the most feared complication of intracranial electrode placement—mainly intracerebral hematoma with depth electrodes, subdural hematoma with subdural electrodes, and epidural hemorrhage with epidural electrodes. The incidence of life-threatening hemorrhage has been reduced by using preoperative angiography to define vascular anatomy, by directly visualizing cortex through use of a craniectomy rather than a burr hole for insertion, and by using relatively avascular routes of electrode insertion in the case of depth electrode placement. In the authors' experience, major hemorrhages requiring therapy are rare and occur in less than 0.3% of patients. The chance of hemorrhage can be reduced by preoperative evaluation of coagulation and clotting parameters, and by counseling patients to avoid drugs that inhibit platelet function in the week before surgery. Limiting the number of intracranial electrodes to a necessary minimum also reduces risk.

The other major risk is infection. In addition to the ordinary perioperative risks of any neurosurgical procedure, there is an ongoing risk of developing infection while the electrodes reside in the brain. The wires leading from the intracerebral contacts to the jackbox provide a route for organisms to gain entry to the brain and meninges. The risk of infection is minimized by use of a technique whereby the wire is tunneled under scalp tissue for several centimeters before exiting the scalp through a separate stab wound. Tissues can then form a reasonably tight seal around the wire to block infection. Administering antibiotics during the perioperative period also helps prevent infection. Infections usually cause symptoms of meningitis with fever, headache, photophobia, and stiff neck, and have always cleared with antibiotic use in the authors' experience. The vast majority of patients with meningeal symptoms have chemical meningitis rather than a bacterial infection, but examination and culture of cerebrospinal fluid is needed to clarify the diagnosis. In these circumstances, it is appropriate to treat with broad spectrum antibiotics until cerebrospinal fluid culture results are known. In our experience, infections readily respond to treatment. Antibiotic therapy should treat routine skin flora that may be inadvertently introduced during surgery or afterwards. While we have not observed brain abscesses following depth electrode placement, these are possible.

The last major risk is posed by using subdural grid electrodes. On rare occasions, particularly with older, thicker electrode designs, brain swelling and edema could occur beneath the grid. Herniation has been reported, usually in the first few days after electrode placement, though the incidence of this complication is well under 1% with modern electrodes. Because of this potential complication, careful neurological assessments are required, and emergent grid removal may become necessary.

On balance, the decision to use an invasive EEG technique must be made weighing the anticipated benefits against the risks. There are two expected benefits: (a) to gain sufficient knowledge so that a therapeutic procedure can be performed that otherwise could not be done, or done as safely; or (b) to avoid a procedure that would not help—for example, by learning that seizures are multifocal and that surgery should not be performed. Because the use of intracranial electrodes carries some risk, the benefits to be gained should substantially outweigh the risks.

EEG DATA

The intracranial EEG must be cautiously interpreted. Since recording is from a limited part of the brain, there is a risk of recording from cortex that is irrelevant or only marginally relevant to the epileptic process. The electrodes might be in the wrong place, perhaps even in the wrong hemisphere, and all data could be misleading. Only potentials that are near the electrode contacts are detected, and these potentials might consist of propagated activity that has spread from a distant primary epileptogenic zone. The significance of interictal spikes and nonparoxysmal discharges is not fully understood. How to interpret seizures is also a subject of debate, and how different seizure types should be weighed is not certain.

Most chronic intracranial EEG recording sessions aim to record and evaluate interictal and ictal data. The interictal abnormalities may be epileptiform or nonepileptiform. The ictal onset zone, where seizures begin, should be delineated. The remainder of this chapter will review interictal and ictal EEG findings recorded with intracranial electrodes.

Interictal EEG: Normal Findings

All of the EEG rhythms seen in the scalp EEG can be seen in the intracranial EEG. Provided that electrodes are placed over the appropriate lobe of the cortical area, any rhythm can be detected. For example, one can record the alpha rhythm, beta activity, mu rhythm, sleep spindles, and any other activity, according to the location of the electrodes.

EEG: Nonepileptiform Abnormalities

The interictal EEG can show a variety of focal nonepileptiform abnormalities. It is worth reemphasizing that in contrast to what is the case with scalp recordings, faster frequencies are no longer attenuated by scalp and skull; therefore, the electroencephalographer must avoid overinterpreting sharply contoured waveforms in the intracranial EEG. Many normal rhythms, such as normal beta activity, rhythmic temporal theta of drowsiness, wicket rhythms, the mu rhythm, lambda waves, positive sharp transients of sleep, and even the alpha rhythm may look quite spiky in the intracranial EEG. These should not be misinterpreted as pathologic spikes or sharp waves.

Focal disturbances in the EEG background correlate with the presence of either hippocampal atrophy or neocortical gliosis (34). The following types of nonepileptiform interictal abnormalities have been described:

Focal Slowing

Focal slow waves may appear in the delta or theta frequency bands in one or more cortical regions. Since many kinds of artifact can masquerade as focal slowing, diagnosing focal slowing requires that one compare the frequencies in the suspect area with rhythms in homologous contralateral cortex, with rhythms from surrounding cortex in the same lobe, and with the EEG recorded from the same region in other individuals. Transient slowing of frequencies from electrode placement immediately following electrode insertion is usually not of clinical consequence, and artifactual sources, such as pulsation of blood vessels, must be considered (35). Focal slowing may indicate that a structural lesion is present, but it is reliable only when other abnormalities are present in the same area, as described below. Although focal slowing may indicate the presence of a structural lesion, it does not suggest that the lesion is epileptogenic, and seizures may start in a different area. Slowing typically varies over time and with behavioral state, and occasionally results from compression of the brain by the overlying subdural grid matrix. Excessive and widespread polymorphic slowing in conjunction with attenuated waveforms should raise concern about cerebral edema beneath a grid surface. Should this occur, urgent grid removal may be indicated.

Focal Attenuation of Alpha or Beta Frequencies

A localized attenuation of fast frequencies suggests underlying cortical gliosis. When seen in combination with focal slowing of background frequencies, focal loss of faster frequencies strongly suggests the presence of an underlying structural lesion, such as gliosis or tumor.

Focal Attenuation of Normal Sleep Rhythms

Normal sleep rhythms seen in the scalp EEG are also seen in the intracranial EEG. During slow-wave sleep, sleep spindles can appear in frontal, parietal, and temporal cortex. Spindles may even appear in the hippocampus. A focal attenuation of sleep spindles suggests that a lesion is present (for example, one caused by gliosis).

Focal Burst-Suppression

A focal burst-suppression pattern may appear in the intracranial EEG, usually in sleep, suggesting the presence of gliosis.

Lack of Full Beta Induction with Pharmacologic Activation

Intravenous injection of thiopental or diazepam increases the amount and amplitude of beta activity in the scalp and intracranial EEG (36). Lack of or reduction in beta induction in one region suggests the presence of gliosis or a tumor. Similarly, development of a focal burst-suppression pattern after thiopental injection suggests gliosis (37).

Interictal EEG: Epileptiform Abnormalities

Interictal spikes appear different in the intracranial EEG than in the scalp EEG because of the lack of filtering by scalp and skull. They are shorter in duration and higher in amplitude, and may be either positive or negative, or more often polyphasic (Figure 16-2). Some intracranial spikes have a highly restricted field and appear in a single electrode contact. Other spikes may be quite widespread, involving part of all of a single lobe or more than one lobe in a hemisphere, or may be generalized and synchronous in both hemispheres.

Dipoles are more often evident in the intracranial EEG than in scalp EEG, and both positive and negative phase reversals might be seen along the course of a multicontact depth electrode or a row of subdural contacts. However, the usual cautions apply when interpreting spikes. Potential fields must make anatomic and physiologic sense. Since spikes are sharper in the intracranial EEG, caution should be exercised when interpreting sharp waves. These may represent distant, temporally spread potentials that have propagated from a distant site, or they may simply be normal sharply contoured activity. One should exercise great caution in interpreting sharp waves in the intracranial EEG as indicative of immediately underlying pathology.

In temporal lobe epilepsy, all patients have interictal spikes with intracranial EEG recording (Figure 16-1). Spikes commonly appear bilaterally and independently in the hippocampus, amygdala, parahippocampal gyrus, and temporal lobe neocortex. Negative spikes recorded in the hippocampus are not detected by sphenoidal or scalp electrodes (38–40). Scalp, nasopharyngeal, and sphenoidal

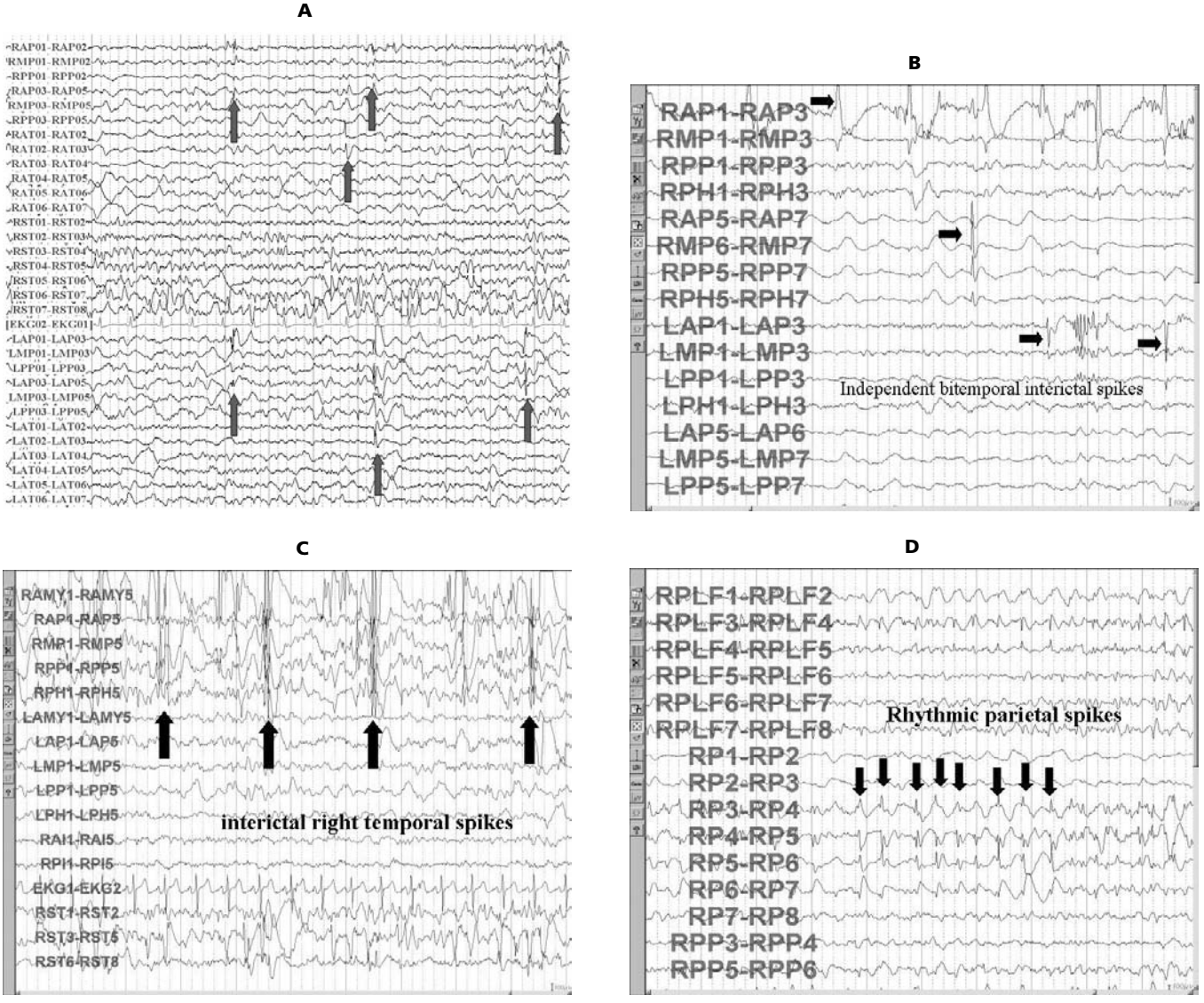


FIGURE 16-2. Illustrations of interictal spikes recorded with depth and subdural electrodes.

electrodes record from basal temporal neocortex, not hippocampus. When a negative spike is seen in the surface EEG, hippocampal electrodes may show no activity, or may show a simultaneous negative or positive component. In the amygdala, a characteristic broad triangular positive spike is often seen; this is not common in the hippocampus (40). Left and right hippocampal spikes are nearly always asynchronous in mesial temporal lobe epilepsy. The occurrence of synchronous hippocampal spikes is associated with a poor prognosis after temporal lobectomy and suggests a strong possibility of a distant focus (41). In mesial temporal lobe epilepsy, multifocal spikes occur within the hippocampus and amygdala; independent spikes are commonly observed in the amygdala, anterior hippocampus, and posterior hippocampus, along with other widespread "regional" spikes that involve all mesial temporal limbic structures in one hemisphere. In addition, it is common to see interictal spikes occurring independently in other lobes of the brain in patients with temporal lobe epilepsy, especially in orbitofrontal and cingulate cortex.

Interictal spikes nearly always occur in patients with frontal, parietal, and occipital epilepsies as well. Both positive and negative spikes and polyspikes can be seen, and their distribution varies from one patient to the next. Multifocal patterns are common, and even though a structural epileptogenic lesion may be present in one lobe, interictal spikes can be widespread in one or both hemispheres. Interictal spikes are commonly activated by slow-wave sleep, and have a reduced rate of occurrence in REM sleep and wakefulness.

Since spikes recorded with intracranial EEG may emanate from a minuscule amount of cortex, a general consensus is lacking with regard to their clinical relevance. It is unclear which types of spike signify the presence of pathologic tissue that should be excised. For example, many investigators believe that PLED-like (pseudoperiodic lateralized epileptiform discharges) spikes and spike burst-suppression correlate more strongly with the presence of underlying pathologic cortex and an epileptogenic zone than do other types of spikes, but the literature contains conflicting data (42–48). Fiol and colleagues (43) noted more spikes in the postexcision electrocorticogram for temporal lobectomy patients with recurrent seizures than for those whose seizures stopped. In contrast, Tran et al. (42) and Schwartz et al. (48) found no relation between the presence of residual spikes and surgical success. However, no investigators have categorized spikes in a way that might distinguish between different types of discharges (e.g., PLED-like spikes, isolated rare spikes, etc.). Lieb et al. (41,49) suggested that some characteristics of hippocampal spikes predict outcome. Spikes with greater autonomy—that is, with less dependence on sleep state and less interspike interval variability—more often indicated the epileptogenic zone than spikes that were less autonomous. The frequency with which spikes occur is a poor predictor of the site of seizure origin or of surgical outcome. Lange et al. (49) noted alterations in the spatial organization of limbic spikes shortly before seizures begin, but no interictal spike patterns are yet proven to reliably identify when seizures might occur or their source of origin.

Focal fast frequencies are an interictal paroxysmal disturbance, and are sometimes reliable markers of the epileptogenic region, particularly if they are consistent. Widdess-Walsh et al. (15) found that paroxysmal fast activity and slow runs of repetitive spikes correlated with the ictal onset zone in three-quarters of areas with these patterns. Incomplete resection was highly correlated with seizure recurrence. Asano et al. (46) noted a significant association between quantitative assessments of focal spike frequency and the zone of ictal onset. Focally dysplastic cortex was associated with runs of repetitive spikes and trains of high-frequency discharges on both scalp and intracranial EEG recordings. Although continuous epileptiform discharges were initially believed to be specific for focal cortical dysplasia, further examination suggests that they are a nonspecific marker of tissue histopathology (50).

Consequently, most authorities are reluctant to rely on interictal spikes alone for planning surgery. For example, multifocal spikes may be present in patients with well-localized mesial temporal lobe epilepsy who respond to surgery, and interictal spikes may not be present in a location from which seizures arise (51). Hence, interictal spikes are probably most useful when considered in conjunction with ictal EEG findings. If most interictal spikes and paroxysmal fast bursts arise from the same area as seizures and other interictal nonepileptiform disturbances, this is *probably* a favorable prognostic sign.

Seizures: Ictal EEG

The ictal onset zone is the single most definitive localizing feature of the epileptogenic region. For this reason, it is important to identify all intracranial electrodes involved in seizure onset. As for scalp EEG analysis, the earliest features of intracranial electrographic seizure onset should be correlated with clinical seizure semiology. Once behavioral changes are detected on video, intracranial recordings are reviewed for evidence of prior electrographic involvement. EEG evidence of seizure onset should precede behavioral onset, or they should occur simultaneously. The appearance of clinical seizures prior to electrographic seizure onset strongly suggests seizure origin at a site distant from implanted electrodes.

Differentiating ictal onset from interictal discharges may be challenging, and multiple seizures may need to be reviewed. Significant patterns of ictal seizure onset include low-voltage fast frequencies, repetitive spikes or sharp waves, high-amplitude discharges that may be highly restricted or widespread, and decremental (attenuation of amplitude of all activity) patterns. Partial seizures may

begin at any frequency (delta, theta, alpha, beta, gamma), sometimes preceded by an increase or decrease in interictal spike rate or spike autonomy. Focal fast-frequency discharges are highly correlated with the ictal onset zone. Sequences of multiple morphological features are common, with a characteristic evolution of frequencies and spatial distribution. For example, a burst of high-amplitude discharges may be followed by an electrodecrement and a subsequent run of repetitive spikes and sharp waves. A typical sequence may consist of low-amplitude fast-frequency discharges that become higher in amplitude and rhythmic before developing into sharp theta activity with spread to surrounding cortex. Conversely, rhythmic theta activity at electrographic seizure onset signals that true seizure onset may be occurring at a distant unrecorded site (52). The typical EEG pattern is one of varying ictal frequency that evolves during the course of the seizure, subtle or prominent lateralized amplitude maxima during different portions of the seizure, and postictal slowing or suppression of background frequencies. At times, the beginning or end of the seizure is not clearly delineated, because subtle changes may develop in the EEG over several seconds or more. Sometimes, seizures appear to start and then stop seconds later, only to resume a few seconds afterward in the same region or elsewhere.

Lee et al. (53) found that seizure-onset frequency was significantly related to spatial distribution and anatomic localization. Extratemporal and regional onsets were more commonly noted in the gamma frequency range, whereas temporal- and focal-onset seizures were more often in the beta range or slower. A wide frequency bandwidth is therefore decidedly advantageous to achieve accurate cortical localization of electrographic seizure onset.

Patterns of electrographic ictal onset may be complex and difficult to interpret on subdural recording. Seizures recorded from the hippocampus may begin focally in just the anterior hippocampus, or regionally within the entire hippocampus and amygdala. (1,3,12,25,36,40,51,54). Seizure onset may remain circumscribed at a single subdural electrode or may immediately involve multiple electrodes. Multielectrode ictal onset usually occurs at adjacent electrodes, but near-simultaneous seizure onset at distant electrodes is not uncommon on subdural recording. Although the precise mechanism is poorly understood, this phenomenon likely represents rapid cortico-cortical propagation, given that transmission via fascicular pathways seems unlikely. Widespread electrodecremental seizure onset has been recorded subdurally, predominantly in the frontal lobes (55). This pattern has little localizing value and is associated with reduced likelihood of seizure freedom. The distribution of onset is dependent upon recording methods, and even patterns of spread and seizure duration depend upon these (56).

While many focal seizures have an obvious focal onset in the intracranial EEG, this is not a constant feature. Some seizures spread so rapidly when they start that conventional EEG recording methods cannot reliably detect the localized ictal onset; alternatively, seizures may arise in widely distributed cortical areas. In these cases, the earliest-observed ictal changes may appear in more than one lobe of the brain or in both hemispheres.

Seizures may spread to other regions of the brain, and the extent of propagation determines the clinical behavior exhibited during a seizure. Some seizures remain restricted to the cortex (neocortex, parahippocampal, or hippocampal) in which they start, and produce no symptoms (57). Others may spread within a single lobe or hemisphere. With unilateral spread or spread confined to a single lobe, consciousness is generally preserved. When seizures propagate to the contralateral hemisphere, consciousness is nearly always impaired; the rare exception consists of mesial frontal or parietal seizures that remain restricted to mesial cortex. Secondary generalization occurs as a consequence not only of widespread activation of cortex in both hemispheres, but also of substantial subcortical activation.

Seizure propagation patterns in the intracranial EEG relate to prognosis (58,59). Most mesial temporal lobe seizures first propagate to ipsilateral temporal or orbitofrontal cortex, and then to the contralateral hemisphere, presumably via the corpus callosum. Other hippocampal seizures spread to the opposite hemisphere through the hippocampal commissures. When studied with depth electrodes, long interhemispheric propagation times predict a better prognosis after anterior temporal lobectomy, whereas short interhemispheric propagation times, particularly those less than 5 seconds, are associated with postoperative seizure recurrence (25,60,61).

The EEG patterns of seizure termination are of interest, but there is no consensus whether they correlate with prognosis after surgery (62,63). Independent electrographic seizures at neighboring sites may occur late in the ictal sequence after well-localized seizure onset. These "intra-ictally" activated neocortical zones may be capable of independent epileptogenesis, and may need to be resected along with the primary onset zone (64).

Depth electrodes sometimes offer advantages for recording hippocampal seizures. They detect seizure onset earlier than do subdural or foramen ovale electrodes. Hippocampal electrodes detected seizure onset 30 seconds earlier on average than subdural electrodes in patients with mesial temporal lobe epilepsy (19,20). Since some seizures propagate rapidly throughout both hemispheres once they leave the hippocampus, depth electrodes are sometimes essential to detect the focal onset of these seizures (19,20,65,66). The (rarely) observed spread of ictal activity from one hippocampus to contralateral temporal lobe neocortex led to the conclusion that seizure onset might be incorrectly localized by subdural electrodes alone (19,20). However, it should be noted that subdural and depth electrodes usually lead to the same diagnosis in patients with mesial temporal lobe epilepsy. Nevertheless, because of the potential for

inaccurate localization of mesial temporal lobe epilepsy when only using subdural electrodes, the literature supports investigating temporal lobe epilepsy suspects with both depth and subdural electrodes to maximize the chances of making a correct diagnosis. This also allows accurate characterization of both limbic and neocortical seizure foci.

When planning the intracranial EEG study of patients with suspected neocortical epilepsy, subdural electrodes offer more comprehensive and versatile recording characteristics than depth electrodes. Depth electrodes have more limited sampling capabilities, and hence may be less likely to detect ictal onset. Subdural electrodes are also more suited for mapping of cortical function with electrical stimulation, which is sometimes required prior to resection.

INTRACRANIAL EEG INTERPRETATION

Intracranial EEG recording is worthwhile for two reasons. First, it reveals epileptogenic cortex that is not apparent from any other testing, permitting surgery that otherwise could not be offered. Second, information gathered during an intracranial EEG recording session can spare unnecessary resection of brain tissue in some individuals.

How should intracranial EEG be used to make a surgical decision? Ideally, the intracranial EEG shows seizures that consistently arise from one location and display concordant interictal EEG disturbances. If seizures cannot be localized or if they are multifocal, then surgery might be inadvisable. However, an ambiguous intracranial EEG evaluation sometimes still leads to a good surgical result. For example, some patients with bitemporal seizures stop having seizures after temporal lobectomy, and excising a structural lesion appears to be the major factor that predicts success (67).

However, much remains to be learned about effective use of intracranial EEG. What constitutes an adequate sample of seizures? How should the different aspects of the interictal and ictal EEG be weighed? How should the intracranial EEG findings be reconciled with the remainder of the clinical evaluation? Human intuition and insight have often yielded success in spite of these deficiencies, but the above questions need answers.

To properly assess the usefulness of a technique, one must also assess its yield. Unfortunately, the yield of intracranial EEG is difficult to determine. This depends largely on patient selection, physician judgment and experience, and the availability of noninvasive testing methods. Nonetheless, the need for intracranial EEG introduces bias. Intracranial EEG is used only in complex cases that, by definition, have a lower chance of successfully identifying the epileptogenic zone and a reduced probability of a good outcome. Despite this bias, most intracranial EEG evaluations lead to a therapeutic procedure; success rates, however, are usually lower than when surgery could have been offered relying on noninvasive testing alone (68).

The most important remaining challenge is to integrate the intracranial EEG data with other clinical information. Interictal and ictal EEG findings must be interpreted in light of the history, clinical symptoms, structural lesions, and functional deficits. The intracranial EEG usually does not provide better information than noninvasive techniques; it merely offers additional information that can be better utilized.

CASE STUDIES

The following cases illustrate examples of intracranial EEG recording. Interictal and ictal findings are shown, along with diagrams and imaging studies where appropriate.

Case 1

A 35-year-old man developed medically refractory seizures at age 22. They began with a sense of difficulty speaking and comprehending speech, followed by unresponsiveness, lip smacking, and, occasionally, convulsive movements. The patient had no risk factors for epilepsy and he failed to respond to multiple medications. The neurological examination was normal. The interictal scalp EEG showed left midtemporal spikes, and ictal onset was unclear. MRI and PET scans were normal. The patient underwent intracranial EEG recording, with depth electrodes placed in the left hippocampus and subdural electrodes placed over lateral temporal and frontal cortex, since his epileptogenic zone was suspected to be near primary language cortex.

Figure 16-3 parts a–c show the map, X-ray, and MRI of electrode placement. Figure 16-3 parts d–i show ictal onset focally in the left anterior hippocampal electrode (LAP), with rhythmic spiking, then a transition to fast activity that evolves, a gradual spread to temporal neocortex, and finally seizure termination. Electrode labels are shown in Figure 3a.

Hippocampal seizure onset was unexpected in this patient, and video correlation showed symptoms beginning only when seizures spread to lateral temporal and frontal lobe neocortex.

Case 2

A 27-year-old right-handed woman had medically refractory complex partial seizures beginning at age 12. She usually had an aura of an ill-described feeling for several seconds and then had a lapse in awareness with automatisms. She had a simple febrile convulsion at age 20 months and had developed normally, though school performance was mediocre. The remainder of the history was remarkable only for complaints of memory difficulty, and the neurological examination was notable only for impaired memory. The interictal EEG showed left and right anterior temporal sharp waves. Six complex partial seizures were recorded that appeared to originate in the left anterior temporal region. MRI showed bilateral

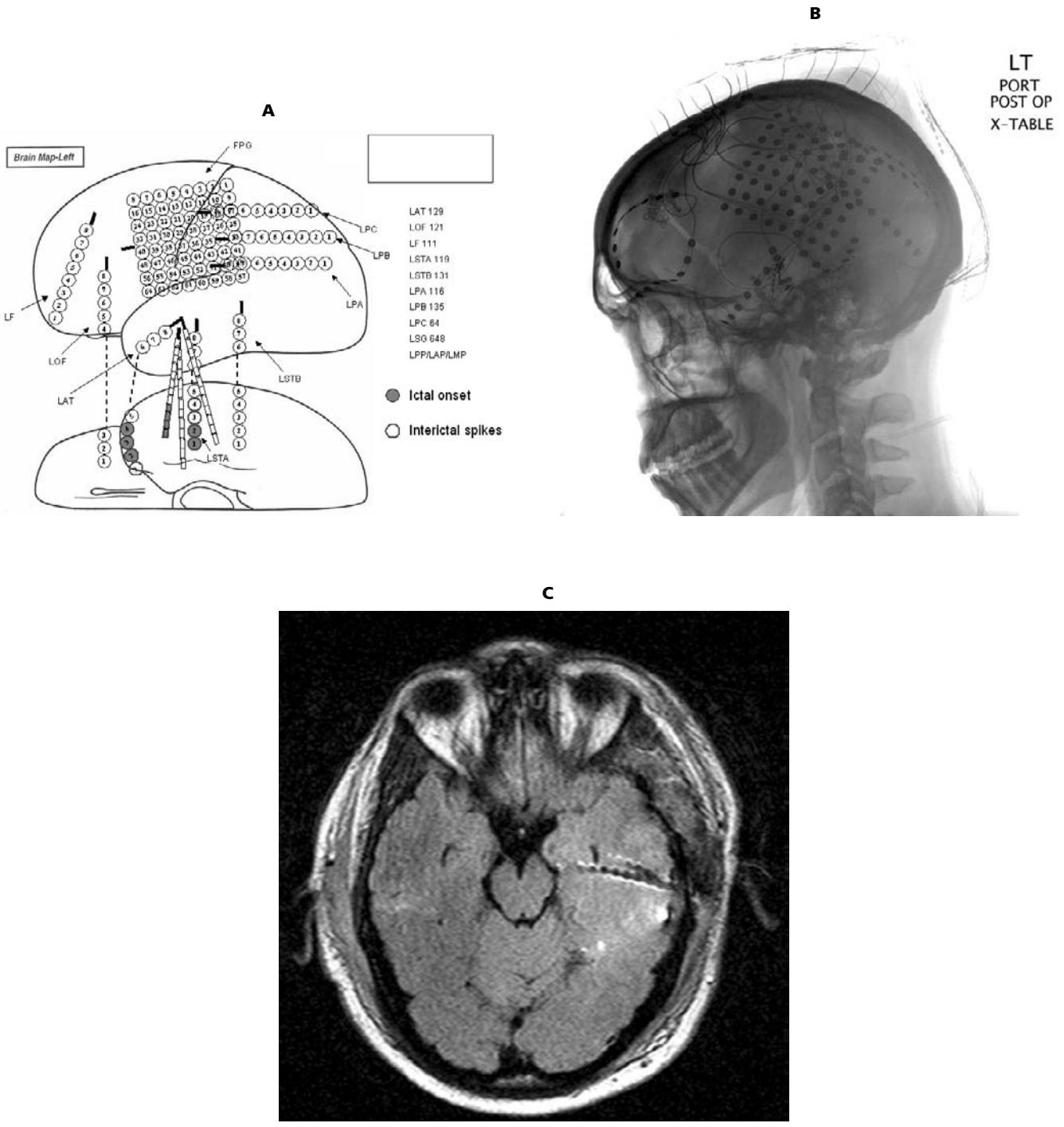


FIGURE 16-3. (A) Map, (B) x-ray, and (C) MRI showing placement of electrodes for intracranial EEG recording.

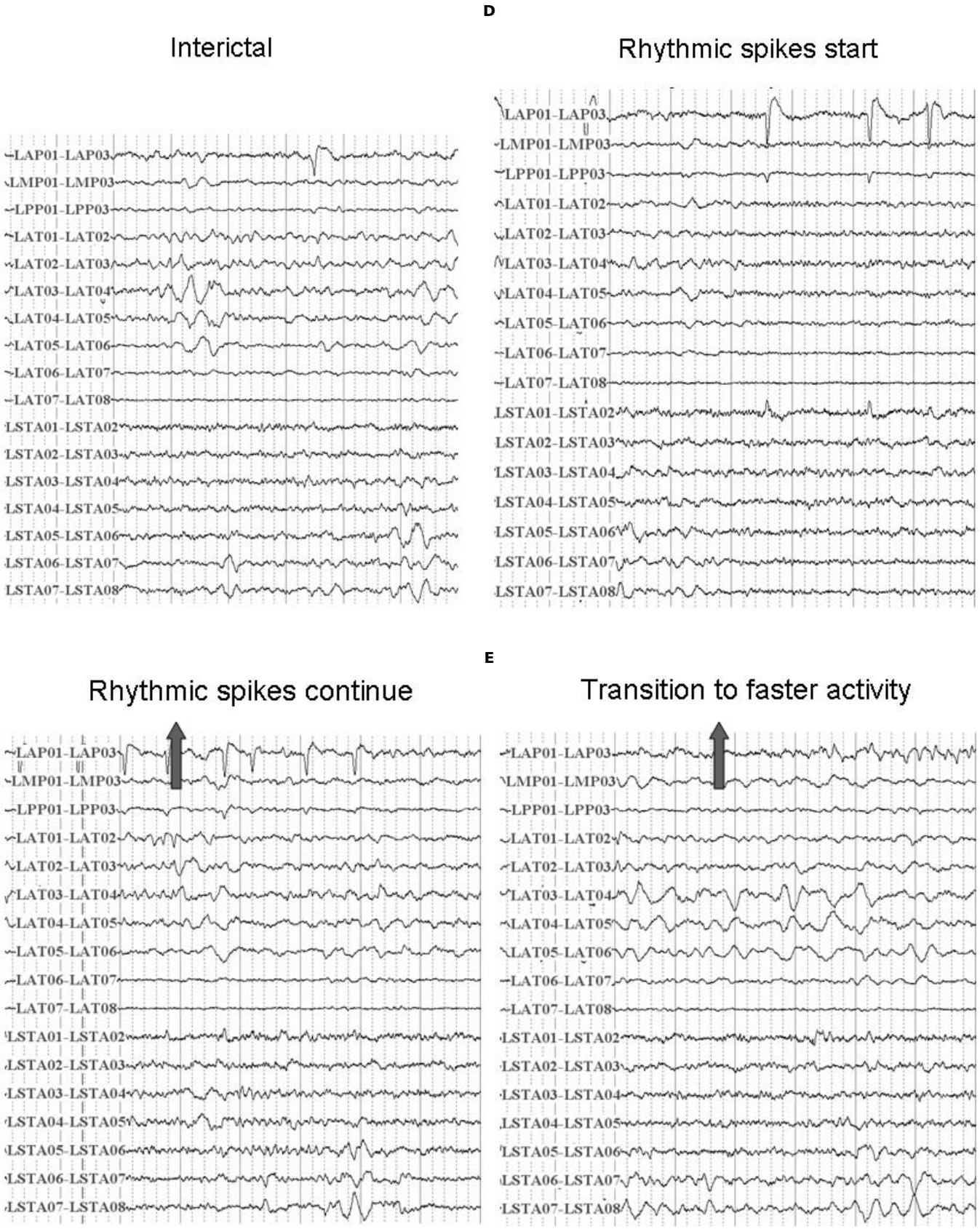


FIGURE 16-3. d. The interictal EEG shows a spike in the left anterior hippocampal electrode (LAP) (left segment). Then rhythmic spiking begins in the left anterior hippocampal electrode (LAP), increasing in frequency towards the end of the page as the ictal transformation occurs (right segment). e. The spiking continues in the LAP electrode in the segment on the left (arrow). As the seizure develops (right segment), faster frequency activity appears and the spikes disappear (arrow).

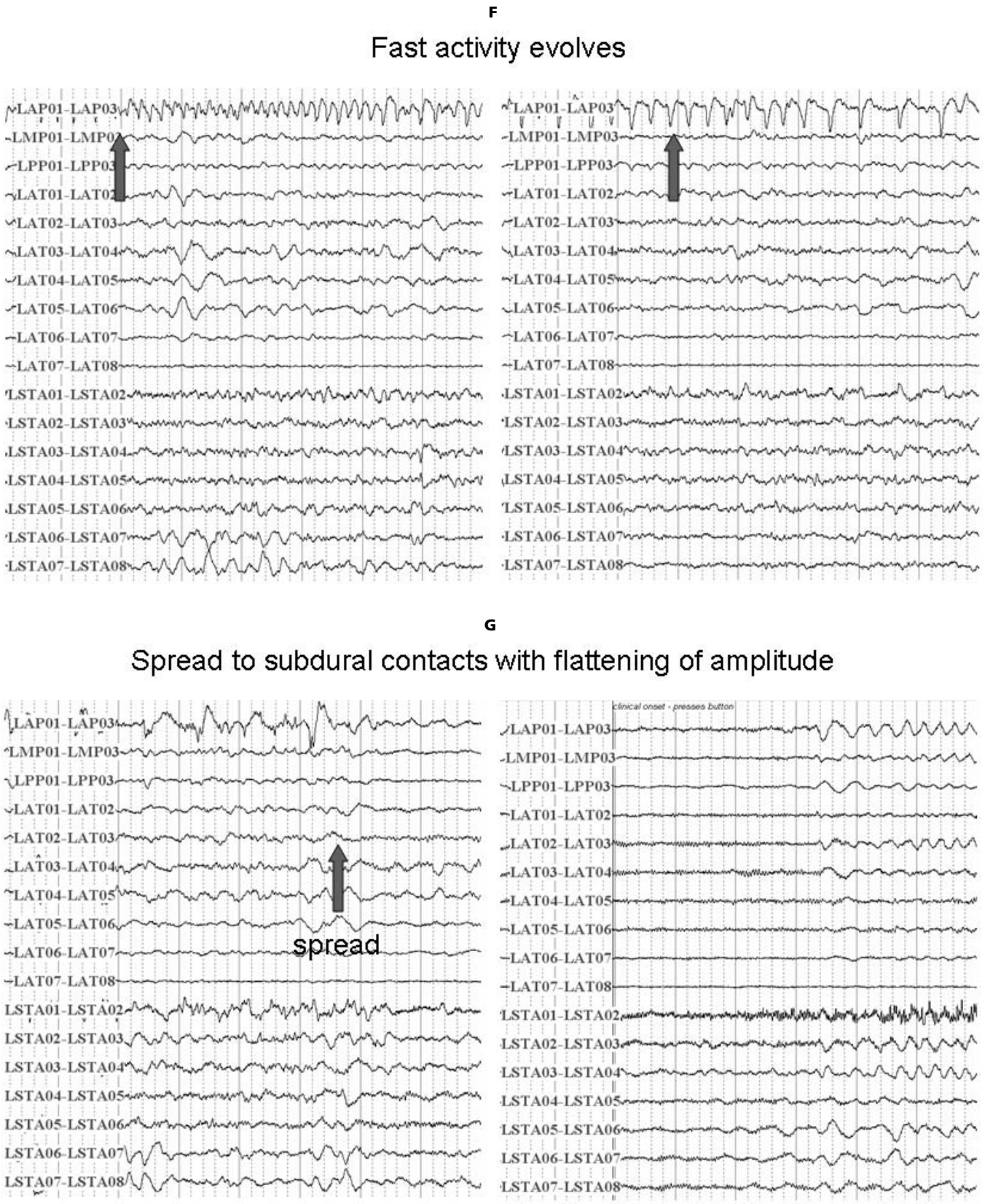


FIGURE 16-3. *(Continued)* f. Rhythmic fast activity appears most prominently in the left hippocampal electrode (LAP), evolving in frequency. This activity spreads to adjacent hippocampal electrodes as the seizure progresses (arrows). Note that the seizure remains confined to the hippocampus, with no evidence for spread in other electrodes. g. At six seconds (left segment), a flattening with fast activity appears, with evidence of spread to the overlying left anterior temporal subdural electrode (LAT). In the second segment, more widespread ictal invasion is noted, with flattening and fast activity spreading to involve additional subdural contacts in the left subtemporal electrode (LST).

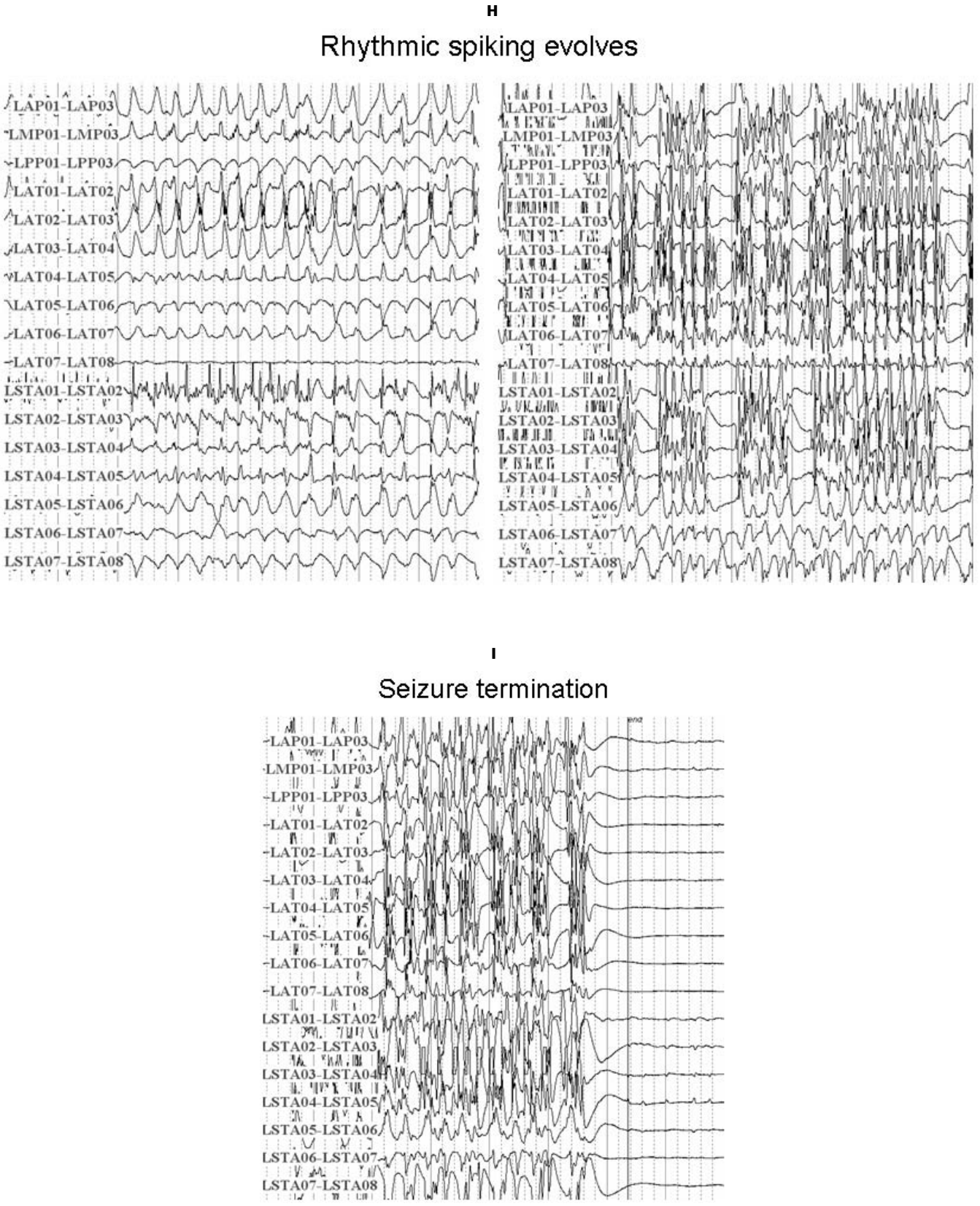


FIGURE 16-3. *(Continued)* h. The seizure continues, with slower frequency spiking in the left segment, and a later portion of the seizure showing higher frequency spiking interrupted by brief suppressions, which are a manifestation of inhibition. i. The seizure ends abruptly with suppression of all electrographic activity in the left temporal lobe.

hippocampal atrophy, slightly worse on the left side, and PET showed bilateral temporal lobe hypometabolism. Functional MRI showed left hemisphere dominance for language.

Because of the possibility of bitemporal disease, the patient had intracranial EEG recording using depth and subdural electrodes sampling from both temporal lobes. Figure 16-4a shows a map of electrode placement. Figure 16-4b shows regional seizure onset in the left hippocampus. Figure 16-4c shows regional seizure onset of a different seizure in the right temporal lobe neocortex with early involvement of the right hippocampus. Spread of the ictal discharge to the left side occurs 18 seconds after start of the seizure, as shown in Figure 16-4d. Figure 16-4e shows asymmetric seizure termination approximately 1 minute later, the seizure stopping first in the left temporal lobe and then the right.

Because the intracranial EEG confirmed the presence of independent bitemporal seizures and other evidence for bitemporal disease, the patient was not offered surgery.

Case 3

A 2-year-old boy developed medically refractory infantile spasms starting at the age of 9 months. This was preceded by concerns of slow development starting at age 6 months. Figure 16-5a shows a lateral skull X-ray revealing subdural electrodes consisting of a 48-contact grid over right frontoparietal cortex, a 16-contact grid over right temporal cortex (orange), and two 8-contact strips over the interhemispheric region (red) and occipitotemporal cortex (blue). In Figure 16-5b, subdural EEG recording reveals seizure onset consisting of a burst of high-amplitude paroxysmal discharges in the right temporal region (arrow, surrounded by purple line), followed by widespread suppression of background activity throughout the convexity (green). The focal seizure onset provides evidence for localized pathology in what is often considered a generalized or multifocal condition.

Case 4

An 18-year-old boy developed secondarily generalized seizures that began in the right arm at age 5 years. Scalp ictal EEG changes were masked by artifacts and were nonlateralizing. Figure 16-6a shows an ictal SPECT demonstrating a region of intense hyperperfusion in the left frontal and insular cortex. Figure 16-6b is a

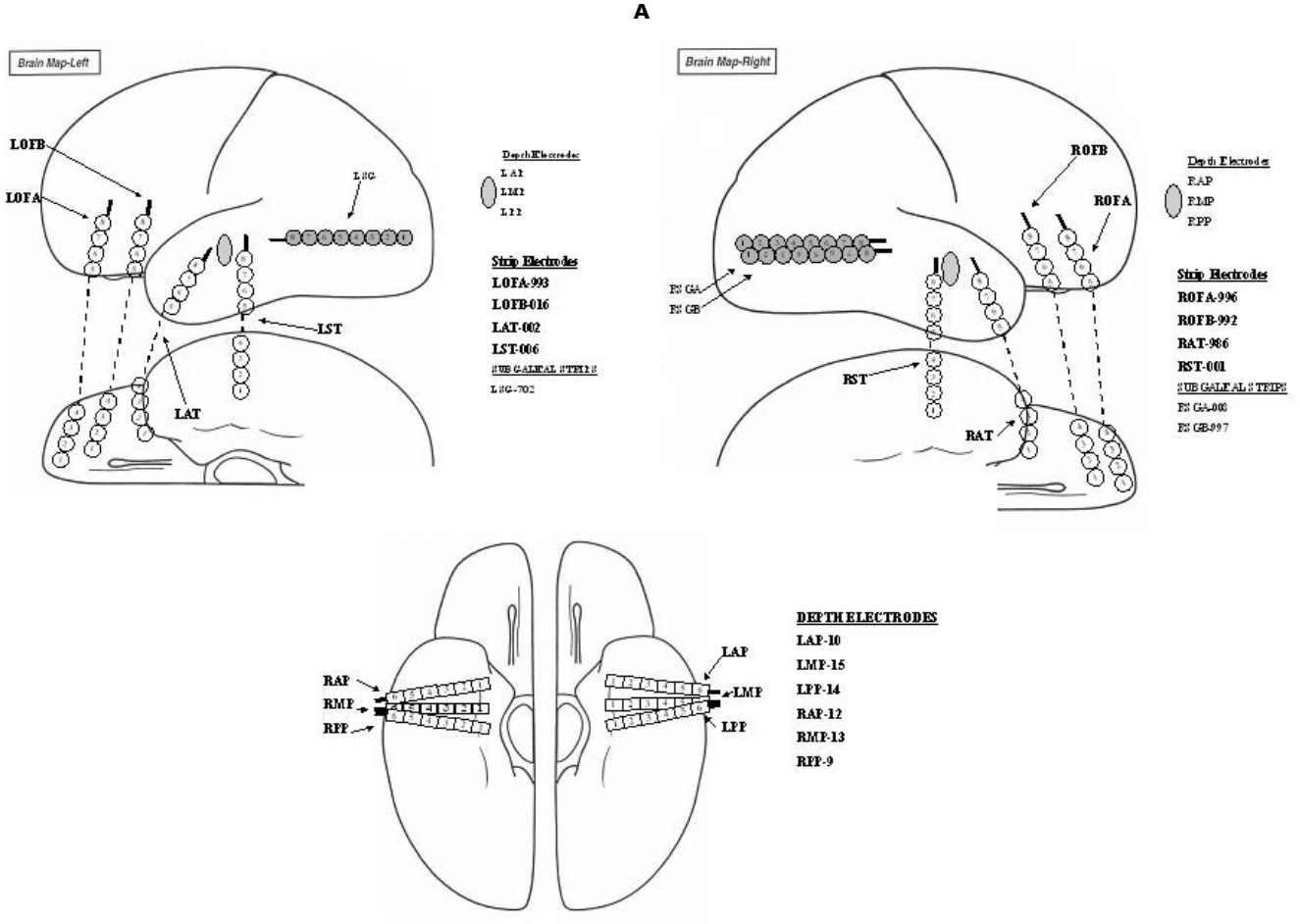


FIGURE 16-4. a. Seizure 1: Regional onset of ictal activity is seen in the left hippocampal depth electrodes (LAP, LMP, LPP) beginning with rhythmic spiking that transforms to ictal fast activity. The subdural electrodes overlying the left temporal lobe, LAT and LST, do not show ictal activity, nor do the right sided electrodes, which are shown in the channels above the EKG.

B

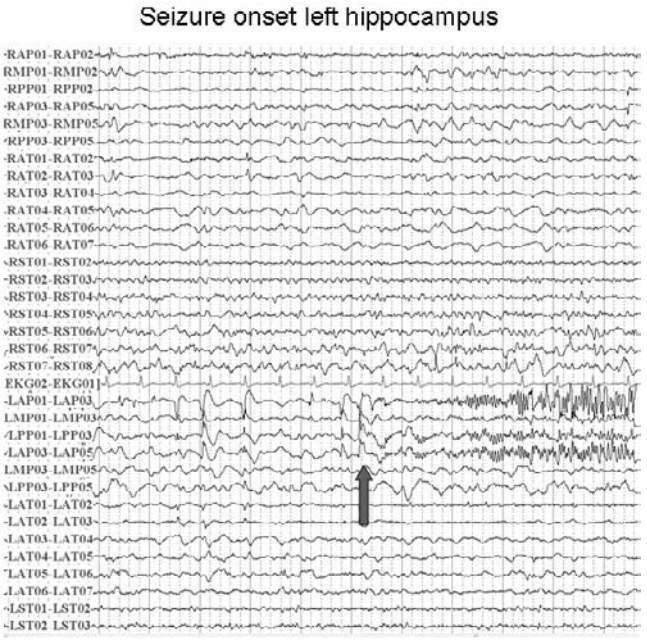


FIGURE 16-4. *(Continued)* b. Seizure 2: Ictal onset is observed in the right temporal lobe in this EEG. The left arrow shows ictal flattening and fast activity in the right anterior temporal subdural electrode (left arrow) and near simultaneous fast activity in the right depth electrodes (RAP, RMP, RPP) (left arrow)

C

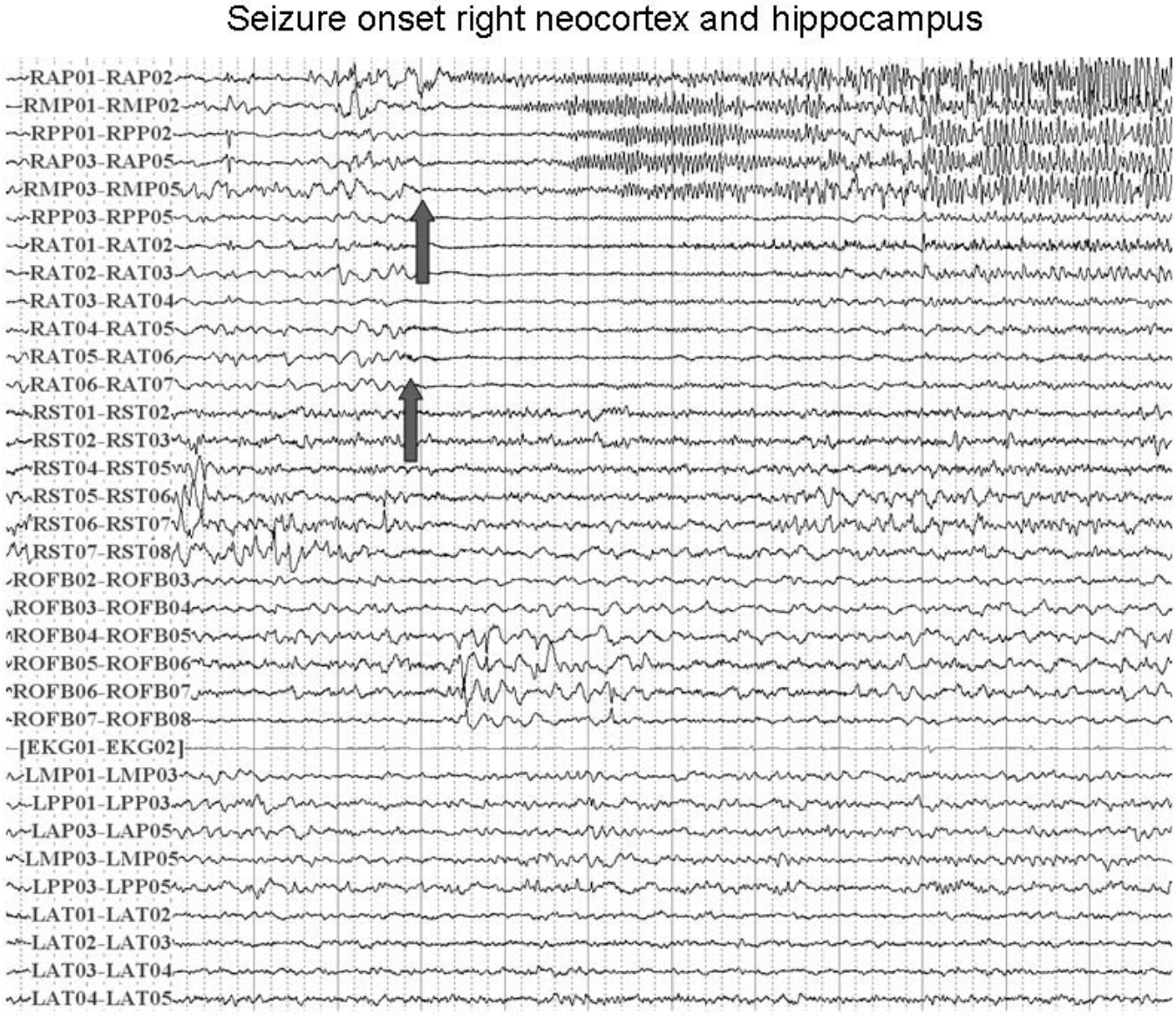


FIGURE 16-4. *(Continued)* c. This is a continuation of the seizure that began in 16-4b. The ictal activity is present in right sided electrodes at the start of this page, and ictal activity then appears in the left temporal electrodes (arrow) in the middle of this page.

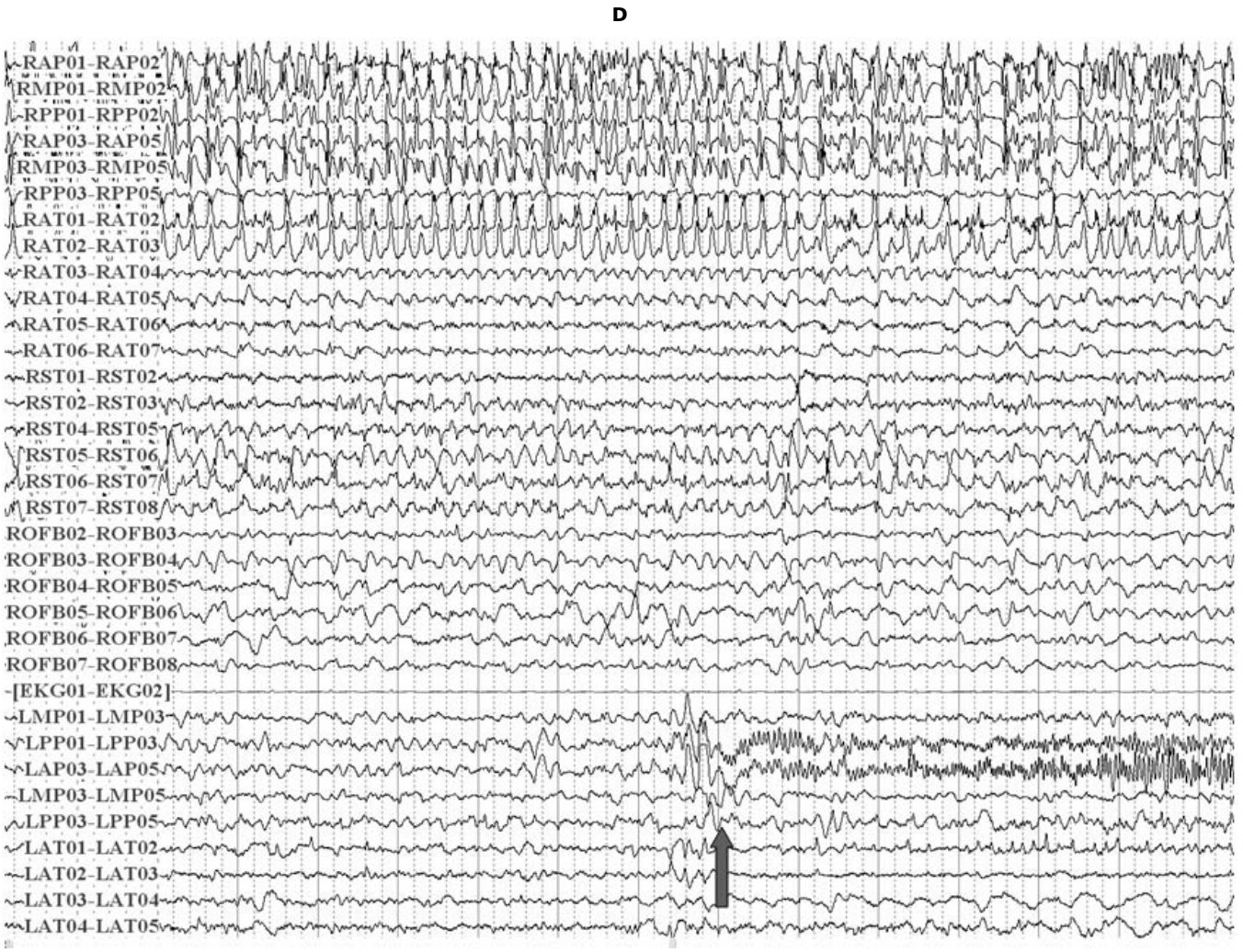


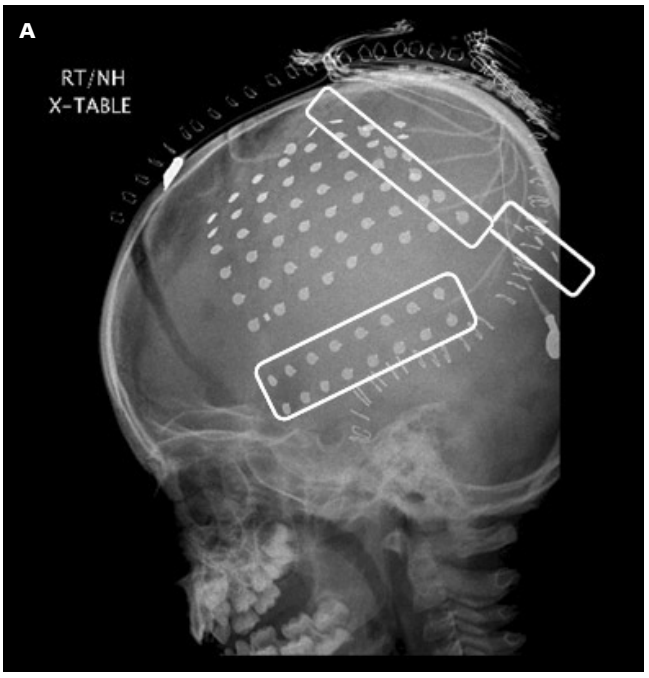
FIGURE 16-4. *(Continued)* d. The seizure terminates on this page, first in the left hippocampus (left arrow) and later in the right hippocampus (left arrow). Asymmetric seizure termination is common.

diagram of subdural EEG electrode placement, showing a 48-electrode grid over the left central convexity and an interhemispheric strip of 8 electrodes. In Figure 16-6c, subdural EEG recording reveals a burst of high-amplitude paroxysmal discharges (arrows on left), seen maximally at grid electrodes 15 and 28 and interhemispheric strip electrodes 3–8. After a 4-second burst of high-frequency discharges, a region of localized and sustained seizure activity (arrow on right side of page) is noted at electrode 15, confirming a zone of electrographic seizure onset.

Case 5

A 37-year-old man developed medically refractory seizures at age 32. He would be awakened from sleep by a sense of choking and inability to breathe without loss of awareness. He made audible choking sounds, and the seizures lasted for 10–15 seconds. They occurred four times per night and significantly disrupted his sleep. The remainder of the history was negative and his neurological examination was normal. The interictal EEG was normal. Ictal video EEG recording showed arousal from sleep during the seizures with no ictal patterns in the EEG. MRI, PET scan, and neuropsychological testing were normal. Ictal SPECT scanning showed left supplementary motor hyperperfusion.

The patient underwent investigation with intracranial electrodes. His first electrode insertion consisted of bilateral subdural strip placement over the frontal lobes and insula. This suggested a right frontal opercular ictal onset, and a second operation was performed to place a subdural grid over the dorsolateral frontal lobe in the right hemisphere and to place a subdural electrode strip in the sylvian fissure. Figure 16-7a shows a diagram representing electrode placement, with the contacts highlighted in red indicating where



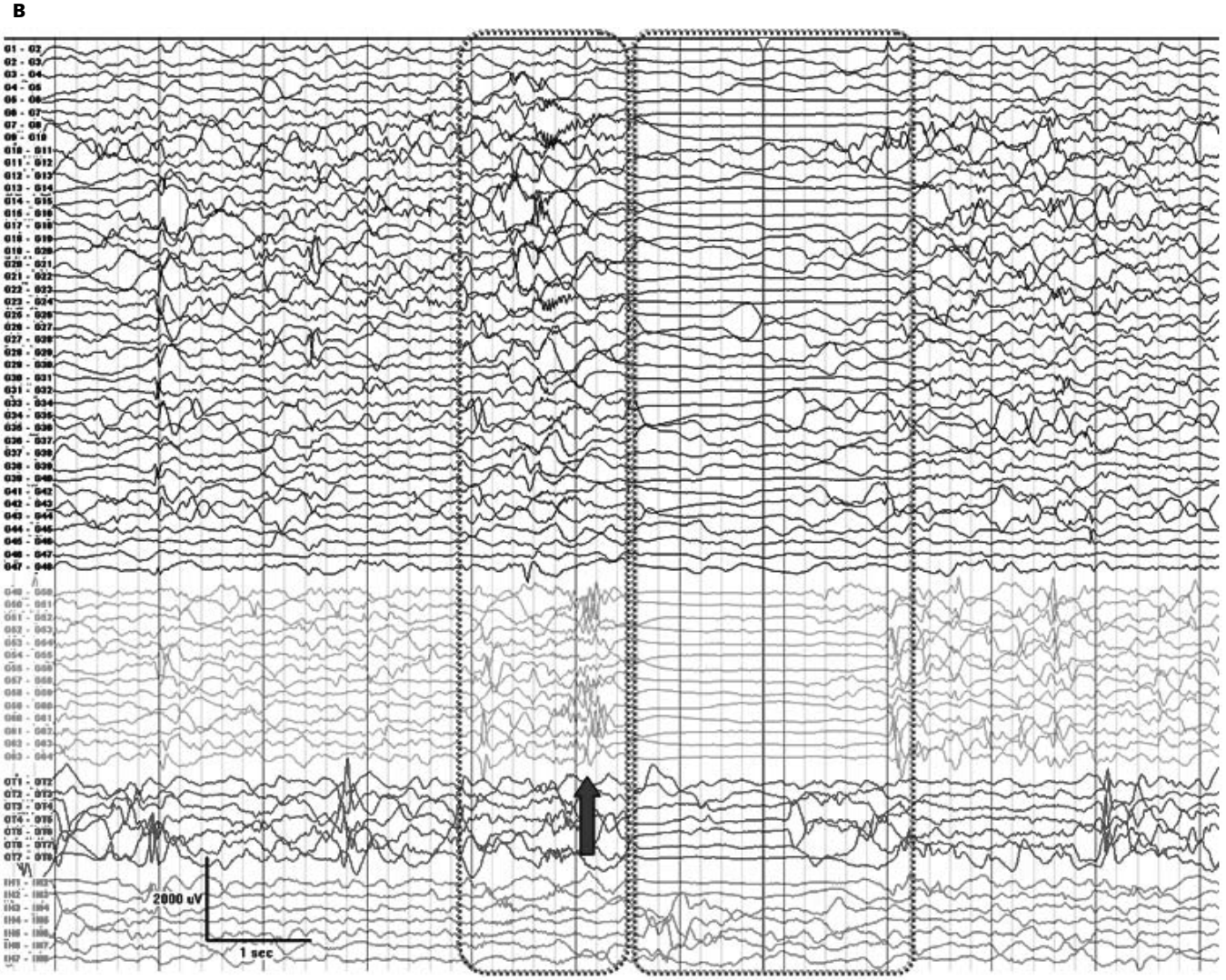


FIGURE 16-5. a. Lateral skull x-ray revealing subdural electrodes consisting of a 48-contact grid over right frontoparietal cortex, a 16-contact grid over right temporal cortex (orange), and two 8-contact strips over the interhemispheric region (red) and occipitotemporal cortex (blue). b. EEG showing seizure onset with a burst of high-amplitude paroxysmal discharges in the right temporal region (arrow, surrounded by purple line), followed by widespread suppression of background activity throughout the convexity (green). (*See color insert*).

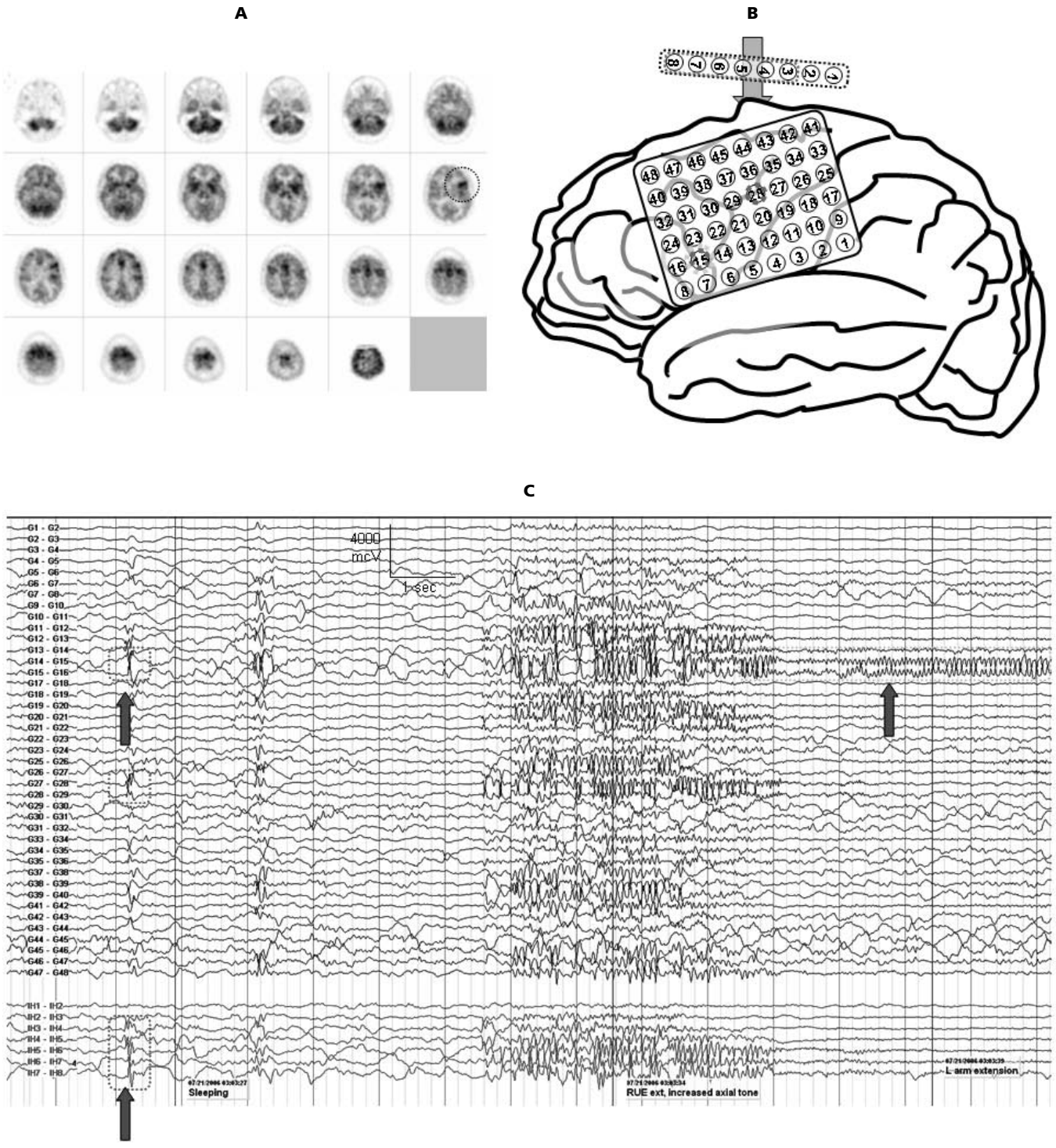


FIGURE 16-6. a. Ictal SPECT demonstrating a region of intense hyperperfusion in the left frontal and insular cortex. b. Diagram of subdural EEG electrode placement, showing an 48 contact subdural grid over the left central convexity and an interhemispheric strip containing 8 contacts. c. Subdural EEG recording showing a burst of high-amplitude paroxysmal discharges (left arrows) maximal at grid electrodes 15, 28, and interhemispheric strip electrodes 3-8. After a 4-second burst of high-frequency discharges, localized and sustained seizure activity (arrow on right side of page) is noted at electrode 15, confirming the zone of seizure onset.

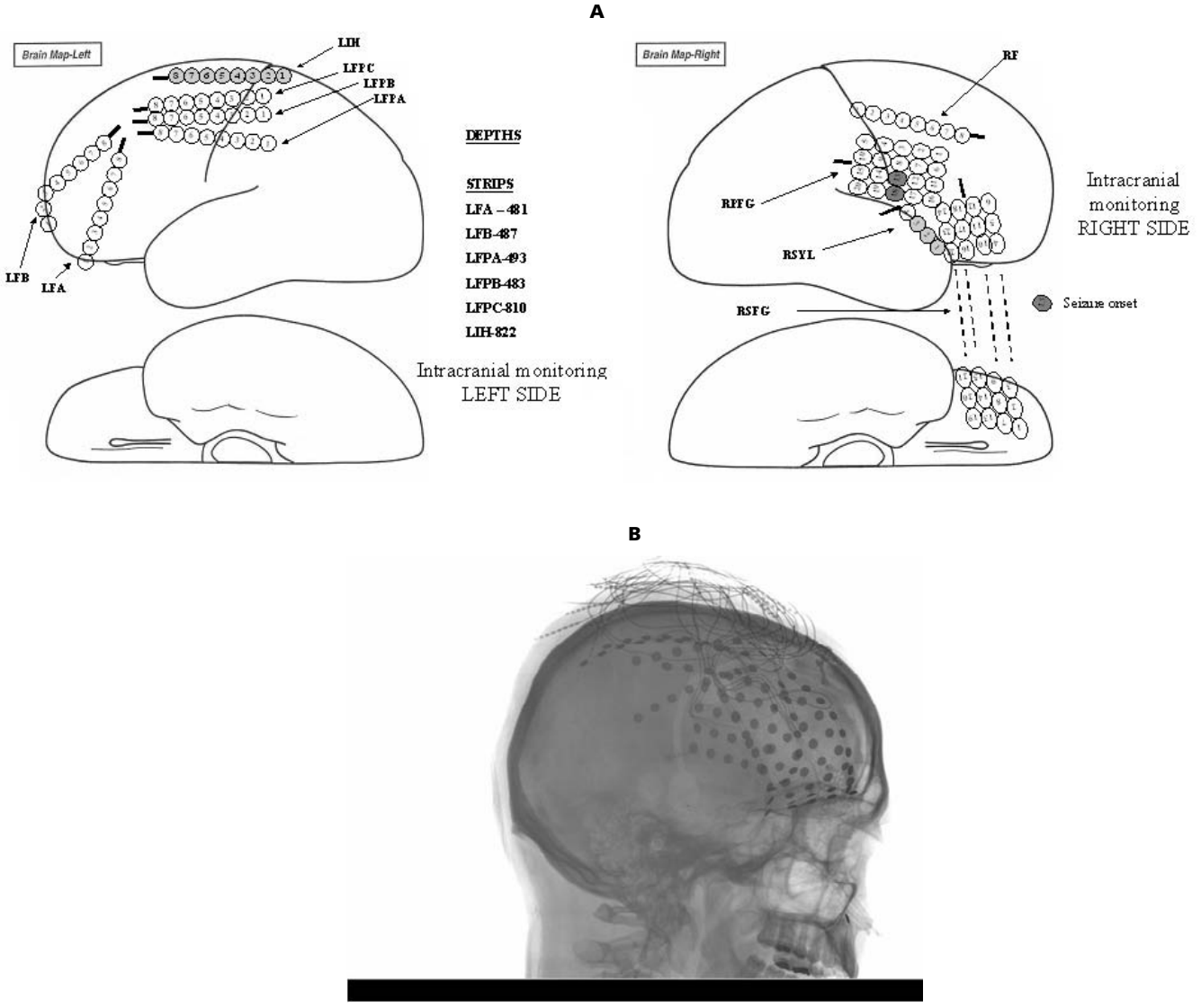


FIGURE 16-7. a. Diagram showing electrode placement, with the contacts highlighted in red indicating where ictal activity was first seen. b. Lateral skull x-ray showing electrode contacts over right frontal lobe.

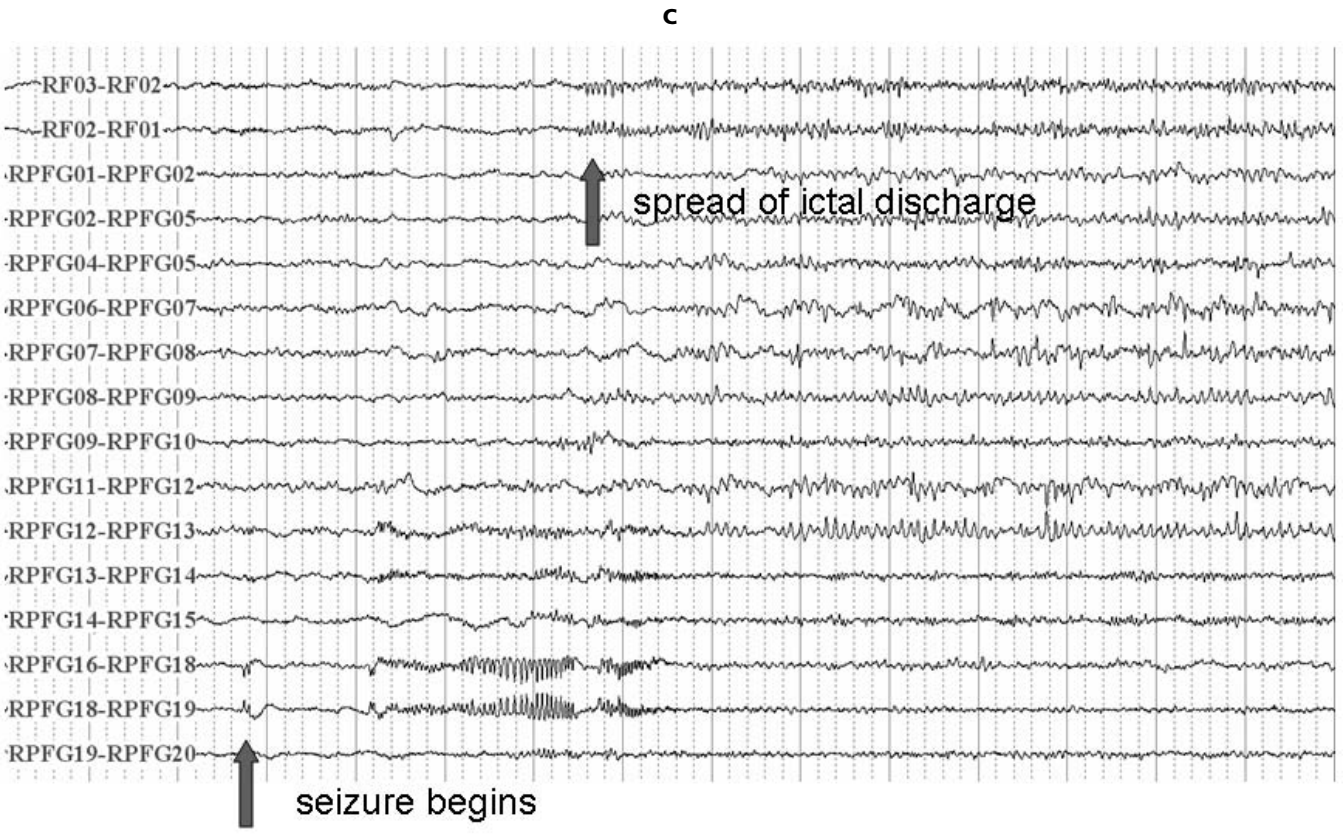


FIGURE 16-7. *(Continued)* c. Intracranial EEG showing ictal onset beginning focally in contact 18 (and perhaps contact 13) of the subdural grid (left arrow). This later spreads to adjacent contacts in the subdural electrode.

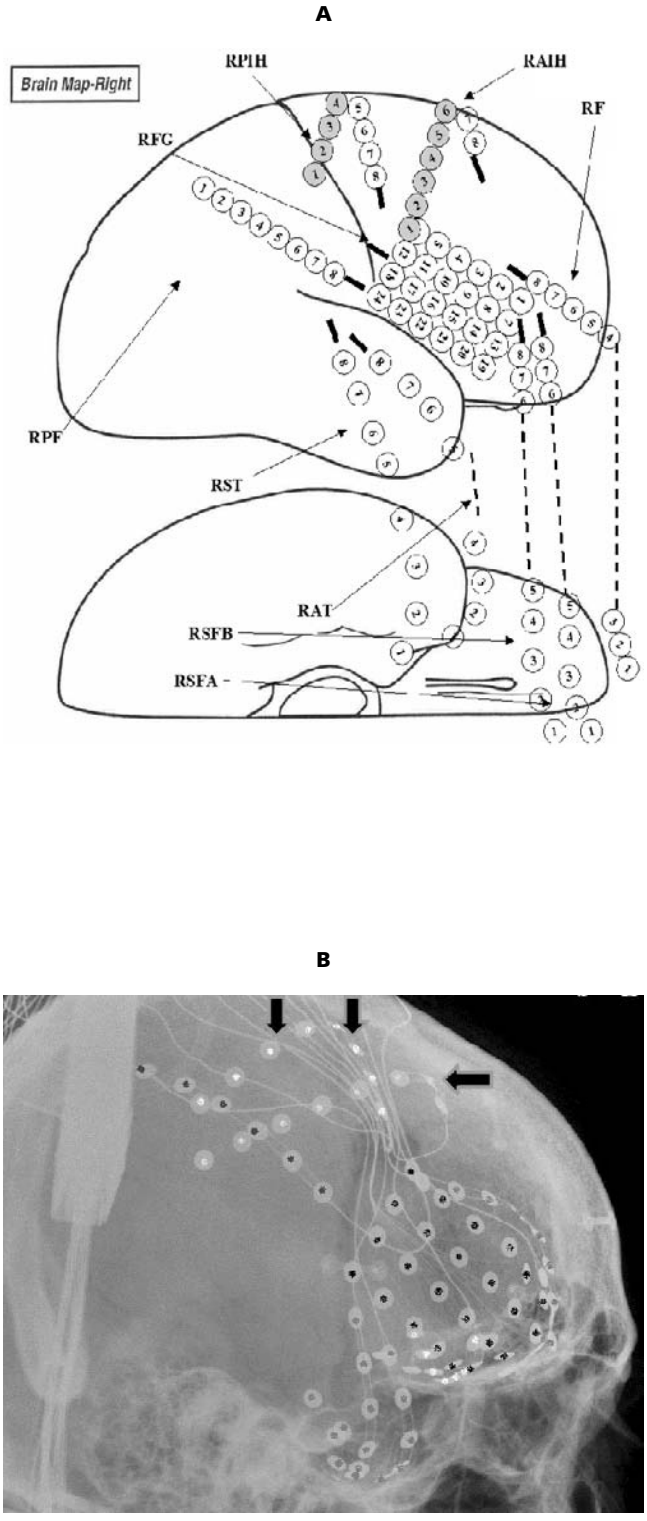


FIGURE 16-8. a. Diagram illustrating subdural electrode placement over right frontal, temporal, and parietal lobes. BSubtemporal, subfrontal, and interhemispheric cortex was sampled by the electrodes. b. Skull x-ray showing the electrodes in the previous diagram. The electrodes marked in yellow and green course over the frontal lobe to the interhemispheric fissure. The electrodes in red are placed over the temporal lobe.

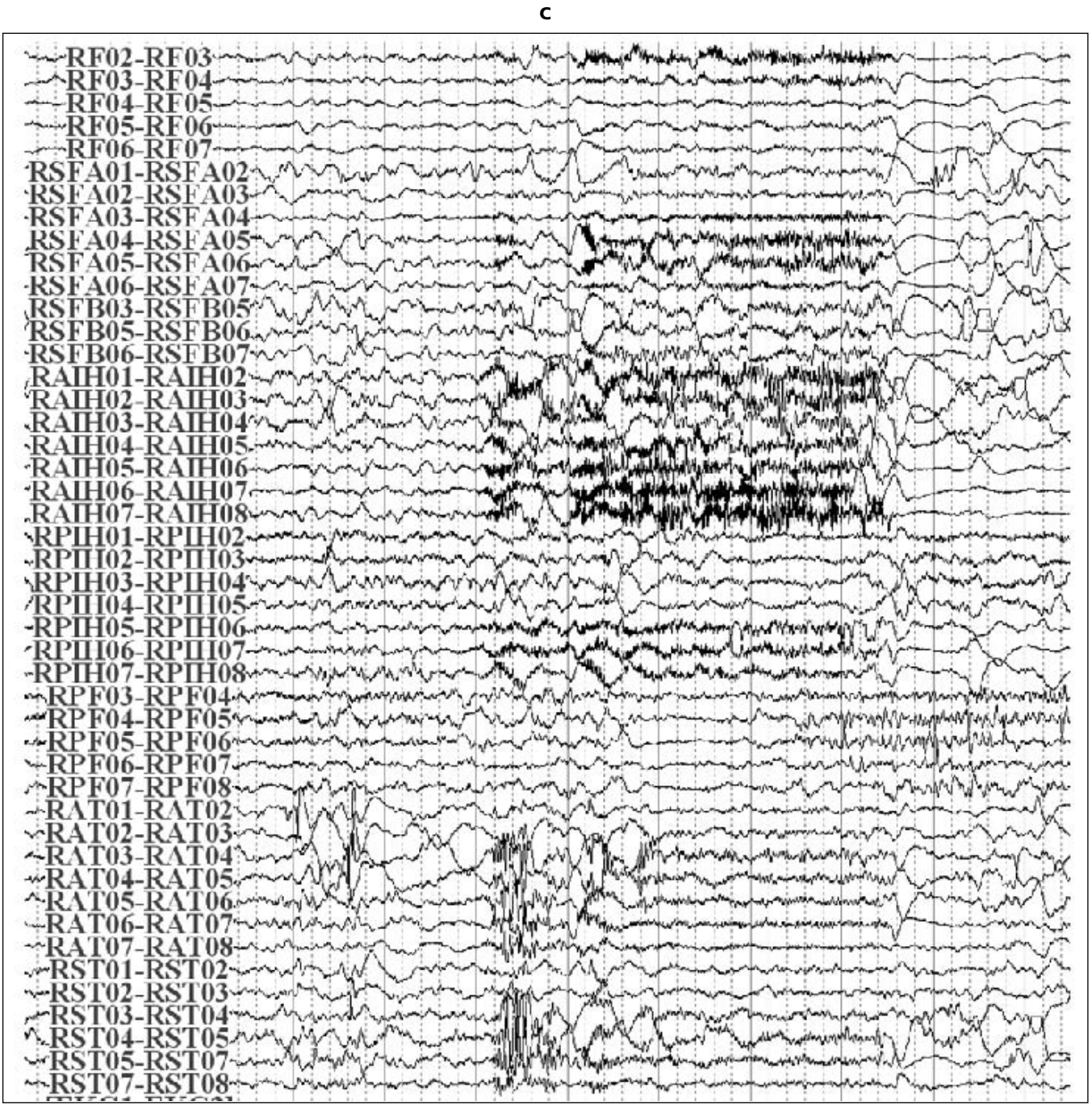


FIGURE 16-8. *(Continued)* c. EEG showing ictal onset with fast activity in contacts sampling cortex from interhemispheric fissure (RAIH, RPIH), temporal lobe (RAT, RST), and even dorsolateral frontal cortex (RF, RSFA). Although amplitude and frequencies are highest in the interhemispheric electrode contacts, the extensive field at the start of the seizure and the lack of sustained ictal rhythm in these contacts do not lead to confidence that a well-localized seizure has been recorded.

ictal activity was first seen. Figure 16-7b shows the lateral skull X-ray. Figure 16-7c shows ictal onset, with the seizure beginning focally in contact 18 (and perhaps contact 13) of the subdural grid (left arrow) with later spread to adjacent contacts. No interictal spikes were seen.

The cortex underlying the ictal onset zone was excised and seizures stopped.

Case 6

A 16-year-old girl had uncontrolled seizures since age 13. She had no warning of seizures, and would suddenly lose consciousness, stiffen the left arm, grunt, and fall to the ground. She had a learning disability and repeated third grade. Neurological examination showed evidence of

posturing of the right hand with stress gait. The interictal scalp EEG showed right midtemporal sharp waves, and the ictal scalp EEG was not well-localized and largely obscured by muscle artifact. MRI was normal.

Intracranial electrodes were placed over right frontal and temporal lobes as shown in Figure 16-8a. Subdural strips were placed in the interhemispheric fissure as well as the dorsolateral surface of the frontal lobe. Figure 16-8b shows the skull X-ray, with the electrodes marked in yellow and green coursing (arrow) to the interhemispheric fissure. Figure 16-8c shows ictal onset, which is not terribly clear. Ictal fast activity is seen in contacts sampling cortex from the interhemispheric fissure (RAIH, RPIH), temporal lobe (RAT, RST), and even dorsolateral frontal cortex (RF, RSFA). The ictal build-up continues most prominently in frontal contacts, but the area involved was quite extensive and surgery was not advised.

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17

INTRACRANIAL STIMULATION

TARA SKARPASS
MARTHA MORRELL

Over a half-century ago, intracranial stimulation was first used for the identification of functional cortical regions and, more controversially, epileptogenic zones (1). Today, intracranial stimulation is still a key technique used to identify eloquent cortex, and mapping studies can be conducted either intraoperatively or extraoperatively as part of phase 2 monitoring. Information obtained from these studies is critical for the planning of successful epilepsy surgeries, particularly when the epileptogenic region is suspected to be near functional areas. In addition to the role in mapping, both focal and nonfocal intracranial stimulation are now being evaluated in clinical trials as novel treatment strategies for patients with medically intractable epilepsy. This chapter will discuss the use of intracranial stimulation in epilepsy.

Epilepsy surgery is an important therapeutic option for some patients (2). The success of the surgery, defined as maximal seizure control without incurring neurological deficits, is dependent on precise localization of the epileptogenic focus, as well as a precise understanding of the function of the cortex to be resected. It is essential to accurately identify both the functional regions to be spared and the epileptogenic zone to be resected. Since the 1930s, intracranial stimulation of the cortex has been used to identify brain regions essential for motor, sensory, and language functions. Despite advances in functional neuroimaging (3–5), *direct electrocortical stimulation is still considered the gold standard for predicting postoperative impairment*. Recently, techniques based on the analysis of electrocorticographic (ECoG) activity in the frequency domain have shown promise (6,7). However, further studies need to be conducted to determine how well these methods predict functional impairment before cortical stimulation can be replaced.

The initial mapping studies using intracranial stimulation noted that electrocortical stimulation could produce electrographic afterdischarges, auras, and clinical and electrographic seizures. It was hypothesized that these responses might be used to localize the epileptogenic zone, defined as the region necessary and sufficient to produce seizures (1). Subsequent intraoperative and extraoperative cortical stimulation studies have suggested that the localizing value of electrically evoked afterdischarges and auras is at best unclear (8). Moreover, resections based on electrically evoked seizures have a substantially higher failure rate than resections based on the recording of spontaneous seizures (9). In general, it is now thought that localization of epileptogenic zones requires a multimodal approach that may include a combination of video EEG monitoring, neuroimaging (MRI, PET, interictal and ictal SPECT), neuropsychological evaluation, and sometimes intracranial electrocorticographic monitoring. Many of these techniques will be discussed in greater detail throughout this book.

Even after a careful evaluation to locate the epileptogenic focus, one-year seizure remission following resection has been reported in only 56% of patients with extratemporal neocortical epilepsy and 65%–77% of patients with epilepsy of mesial temporal lobe origin (10). In addition, many patients are not candidates for cortical resective surgery because the epileptogenic region involves functional cortex and the risks of postoperative neurological deficits are too high. Thus alternative treatment strategies are needed. In the 1950s, Penfield and Jasper reported that focal and nonfocal electrocortical stimulation could result in a flattening of epileptiform and background electrographic activity. Building on these observations, research studies beginning in the 1970s have tested the ability of intracranial stimulation to inhibit epileptiform activity and ultimately prevent or terminate clinical seizures. Clinical trials are currently testing the safety and efficacy of implantable devices that deliver intracranial stimulation to patients with intractable epilepsy.

This chapter will provide a review of the use of intracranial stimulation in mapping functional and epileptogenic regions, as well as a discussion of the current understanding of intracranial stimulation as a therapeutic option for medically intractable epilepsy patients. Although we will discuss results from longer-term clinical trials, this section will largely center on the results from acute studies conducted during intraoperative and extraoperative monitoring and mapping. Original work by Penfield and Jasper (1) as well as comprehensive reviews by Ojemann (11,12) and Oommen (13) are suggested as sources of considerable additional information.

FUNCTIONAL MAPPING

In general, resective surgery in patients with neocortical epilepsy is an option only when the epileptogenic region does not involve eloquent cortex. This can be determined to some extent according to specific anatomic landmarks. However, there is considerable inter-individual variability in the functional anatomy of the cortex, particularly with respect to language (11,14,15) and motor regions (14). Therefore, functional mapping with electrical stimulation is used to confirm functional anatomy and to optimize surgical outcome by allowing for the resection of the largest epileptogenic zone without disrupting function. Most commonly, mapping is performed after seizure recording and localization, at which point the patient's antiepileptic medications can be resumed to prevent the occurrence of seizures during mapping. In some cases, additional treatment with lorazepam may also be needed to prevent seizures.

Electrical stimulation of the cortex can elicit both positive and negative responses. Positive responses are usually associated with stimulation of sensory and motor cortex, including the supplementary motor area. These responses can be composed of localized movements, localized sensations, flashes from primary visual cortex, and buzzing from auditory cortex. In contrast, negative responses typically follow stimulation of association cortex, and include disruption of language functions including object naming and reading. There is also evidence for disruption of motor activities following stimulation of certain motor areas (16,17). These negative motor regions are thought to play a role in the planning of voluntary motor movements. As noted above, the results of mapping usually follow anticipated anatomical boundaries, so significant variations can occur. It is therefore important to note that cortical regions that do not produce a response to the electrical stimulus *can only be assumed to be nonessential if regions essential for the functions being tested are also identified* (e.g., the primary motor area is mapped, as is the area that produces no motor response).

It may seem intuitive that the intensity of electrical stimulation that interrupts function would be less than or equal to that which triggers an afterdischarge (i.e., a response lasting > 1 second that resembles and ictal discharge). Unfortunately, this is not always the case, particularly in children, so that *the absence of a clinical response during an afterdischarge does not guarantee that the stimulated cortex lacks functional significance* (e.g., the stimulation intensity of functional interruption in very young children often exceeds the threshold for afterdischarges; less often in adults). Moreover, afterdischarges can activate functional regions that are distant from the region being stimulated, and may not provide an accurate functional map. A practical challenge is that the afterdischarge threshold often changes from one stimulation trial to the next, even in the same location.

Functional mapping using direct cortical stimulation can be conducted intraoperatively or extraoperatively using chronically implanted intracranial electrodes. There is some controversy regarding the appropriate indications for intraoperative versus extraoperative mapping (12). In general, intraoperative mapping requires that the patient be awake under local anesthesia and able to stay in the same position for 1–2 hours. *Therefore, intraoperative mapping is not recommended in young children.* Extraoperative mapping requires two surgical procedures, one to place electrodes and one to remove the electrodes and perform any desired resection. Thus it has been argued that extraoperative mapping exposes the patient to a greater risk of infection and results in greater health care costs. This method is typically used when intracranial ictal recording is also required or when the patients are not anticipated to be able to cooperate with mapping procedures during surgery under local anesthesia. In addition, extraoperative mapping is often chosen when comprehensive language and motor region maps are required. As noted above, extraoperative mapping is typically performed after seizures have been recorded and anticonvulsant medications can be administered to reduce the likelihood of triggering afterdischarges or actual seizures. Most sites now use both methods.

Although the specific stimulation parameters may differ slightly among institutions, the majority of mapping studies use a stimulation strategy similar to that originally used by Penfield. *Most often, a high-frequency (50-Hz) biphasic square wave stimulus with a pulse duration of 0.3 msec delivered continuously for 3 to 5 seconds.* Longer stimulus durations may be used to test more complex functions. Although there is no convincing evidence for cortical injury or kindling using these stimulation parameters over the relatively short period of time needed to map cortical function, the consensus opinion is that only the minimal amount of stimulation necessary to complete the goals of testing should be used. Stimulation may be delivered as either monopolar (with one electrode over the cortical area of interest and a distant reference in a functionally silent cortical or noncortical area) or more commonly, bipolar (the stimulating current is passed between adjacent subdural cortical electrodes). Stimulation generally starts at 1 mA. The current level can then be adjusted in 0.5–1-mA increments until a response

is elicited, the afterdischarge threshold or the maximum current of 15–17.5 mA is reached. Recording of motor evoked potentials in response to single-pulse stimulation has been suggested as a method to identify primary motor cortex vs supplementary motor cortex, as well as a way of mapping motor cortex without risk of seizure induction or prolonged afterdischarges (afterdischarges may sometimes last minutes to, rarely, hours). An alternative stimulation strategy for intraoperative mapping of motor cortex during general anesthesia consists of using 5–6 pulses of a monopolar 500-Hz stimulus (12,18).

IDENTIFICATION OF EPILEPTOGENIC ZONES

In contrast to functional mapping, the effectiveness of using cortical stimulation to identify the epileptogenic region is somewhat controversial. As mentioned above, one consequence of stimulation can be the production of cortical electrical afterdischarges. While afterdischarges are not the same as spontaneous epileptiform activity, they are similar in morphology to spontaneous discharges and can evolve into clinical seizures. In the 1950s, Penfield and Jasper hypothesized that the areas most susceptible to afterdischarges with stimulation, especially if the discharges were associated with an aura or onset of a clinical seizure, could indicate hyperirritable cortex and the seizure focus. However, intraoperative and extraoperative studies have shown that the stimulation threshold and duration required to elicit an afterdischarge varies across cortical regions, and even within the same area from day to day and from one electric stimulation to the next. For example, the afterdischarge threshold can be elevated following stimulation (19) and in areas with structural abnormalities (20,21). Equally confusing, the afterdischarge threshold may be relatively higher at the site of electrograpic seizure onset than at adjacent locations. Afterdischarges can also be prominent in locations not demonstrating interictal spikes (22) and have not been consistently related to the site of spontaneous ictal onset (20). There are even conflicting opinions about the localizing significance of stimulation-induced auras typically experienced by the patient during spontaneous seizures, because the aura may reflect the spread of the stimulation to a distant location. Furthermore, Fish et al. (8) demonstrated that the same clinical response could be elicited from stimulation of multiple, sometimes noncontiguous, regions in the same hemisphere or both hemispheres. This suggests that electrically elicited auras might also lack reliable localizing value.

Recently, Valentin and colleagues have evaluated the use of single-pulse electrical stimulation to identify epileptogenic cortex (23,24). They have described abnormal cortical responses to single-pulse intracranial stimulation, and established that regions showing the onset of spontaneous seizures are associated with these late responses. For example, in patients with epilepsy of temporal lobe origin undergoing extraoperative monitoring, a single stimulation produced an early and a delayed response. The early sharp deflections were found after all stimuli and were not indicative of hyperexcitable cortex. In contrast, there was a significant association between the location of delayed responses (spikes or spike-and-slow-wave complexes >100 milliseconds and <1 second after stimulus) and the seizure onset region (Figure 17-1a). In addition, repetitive responses (bursts of high-amplitude slow waves) were observed immediately following single-pulse stimulation of epileptogenic cortex (Figure 17-1b). The repetitive responses could be observed at several locations, and thus their presence in a particular location was not localizing. However, they only occurred following stimulation of the epileptogenic region. Thus, when the repetitive responses were observed, this indicated that stimulation had been in a region of interest. Of course, one of the main goals of localizing the seizure onset region is a successful outcome following resective surgery. In a subsequent study, postsurgical seizure control and the results of single-pulse electrical stimulation were correlated in 115 patients for at least 12 months after epilepsy surgery (24). Patients with abnormal responses exclusively in the resected region were more likely to have a favorable outcome (21 of 22) than were patients with abnormal responses in both resected and nonresected regions (5 of 7) and patients with abnormal responses exclusively outside the resected region (0 of 3). Neuropathological examination of the resected tissue showed structural abnormalities in the area identified as abnormal by the single-pulse stimulation in 26 out of 29 patients that had this tissue resected. These studies suggest that abnormal response to single-pulse electrical stimulation may be a functional marker of epileptogenic structural abnormalities, can identify hyperexcitable cortex, and may predict surgical outcome. Single-pulse electrical stimulation may provide a valuable technique for identifying epileptogenic regions during intraoperative testing.

INTRACRANIAL STIMULATION FOR TREATING EPILEPSY

Acute Clinical Studies

One of the earliest reports of intracranial stimulation disrupting epileptiform activity came from Penfield and Jasper in 1954 (1). In their functional mapping studies, Penfield and Jasper documented two interesting phenomena. The first phenomenon, extinction, was observed at the primary electrodes immediately after delivery of a stimulation, after an afterdischarge, or a after a spontaneous epileptic discharge. Extinction was defined as a postexcitatory depression in activity and excitability, and was thought to be a result of exhaustion of local cortical neurons following

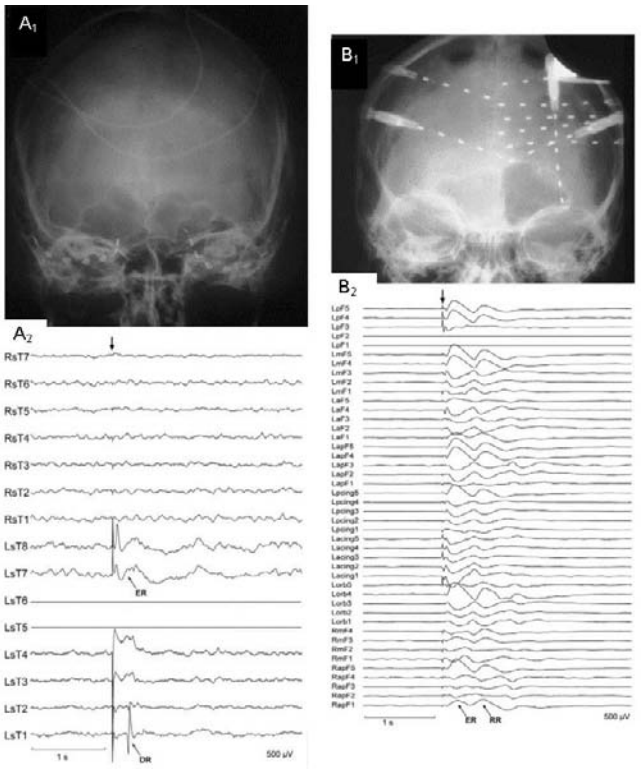

FIGURE 17-1. Delayed and repetitive responses to single-pulse electrical stimulation (SPES). A1: Frontal radiograph showing implanted subdural subtemporal strips in a patient with temporal lobe epilepsy. A2: Early and delayed responses to SPES in patient SP-40. Delayed responses were evident at contact 1 of left subtemporal strip (LsT1) when stimulating through contacts 5 and 6 of same strip (LsT5 and LsT6). Early responses were mainly at contacts 3, 4, 7, and 8 of same strip. Contact 1 was the most distal electrode to the insertion burr hole and closest to mesial temporal structures. B1: Frontal radiograph showing implanted intracerebral (depth) electrode bundles. B2: Early and repetitive responses to SPES in patient SP-30. Repetitive responses were evident when stimulating through contacts 1 and 2 of the left posterior frontal electrode bundle (LpF1 and LpF2). Recording displayed in common reference to Pz. Arrow=electrical stimulation; ER=early response; DR=delayed response; RR=repetitive response; RsT=right subtemporal strip; LsT=left subtemporal strip; RapF=right anterior polar frontal; RmF=right midfrontal; LmF=left midfrontal; LpF=left posterior frontal; LaF=left anterior frontal; Lorb=left orbitofrontal; Lpcing=left posterior cingulate; Lacing=left anterior cingulate. Figure reprinted from Valentín MA, Alarcón G, García Seoane JJ, Selway R, Binnie CD, Polkey CE, Responses to single pulse electrical stimulation identify epileptogenesis in the human brain in vivo, Brain 2002;125(8):1709–1718.

excessive activity. The second phenomenon, suppression, was observed at sites distant from the stimulating electrode. Specifically, Penfield and Jasper noted an immediate flattening of normal and spontaneous epileptiform activity following electrical stimulation. Suppression differed from extinction in that it occurred over large areas and at a distance from the stimulation site. Also, unlike extinction, suppression occurred after stimulation of specific cortical regions, whereas extinction could be observed at any cortical region stimulated. The mechanism of suppression was postulated to result from the activation of inhibitory pathways. The observation of extinction and suppression suggested that both focal stimulation at the seizure focus and nonfocal stimulation of inhibitory regions outside the focus could be used to inhibit epileptiform activity.

Subsequently, a number of acute studies of both focal and nonfocal intracranial stimulation have been conducted following implantation of electrodes for invasive monitoring. Additionally, several long-term studies have also reported acute results acquired during monitoring. In these studies, two main approaches to the timing of stimulus delivery have been explored, namely open-loop and closed-loop stimulation. Open-loop stimulation was the first approach tested and is similar to the approach used in deep brain stimulation for treatment of Parkinson's disease and in vagus nerve stimulation for treatment of epilepsy. An open-loop approach delivers stimulation on a scheduled basis and the stimulation is not contingent on the presence of epileptiform activity. In contrast, the goal of closed-loop or responsive stimulation is to provide brief stimulation only when abnormal (ictal or interictal) discharges are detected. The efficacy of both of these approaches has been evaluated in patients with intractable epilepsy undergoing invasive evaluation for possible surgery.

Kinoshita et al. (25,26) tested the effect of focal open-loop cortical stimulation on interictal activity and electrocorticogram (ECoG) power spectra during extraoperative monitoring and functional mapping in a total of five patients with epilepsy of frontal lobe or mesial temporal lobe origin. The spike frequency and ECoG power spectra before and after high (50 Hz) and low (0.9 Hz) frequency stimulation were compared. There was a significant reduction in the number of interictal spikes poststimulation compared to a prestimulation baseline. In addition, high-frequency stimulation significantly decreased the power of low-voltage fast activity. Thus, these studies demonstrated that open-loop focal cortical stimulation could inhibit interictal epileptiform activity. Similarly, other groups have demonstrated a significant reduction in interictal spiking following open-loop stimulation of the hippocampus (27,28) and motor cortex (29).

Kinoshita et al. (26) also examined the effect on epileptiform activity of 50-Hz stimulation provided by cortical electrodes distant from the seizure focus (i.e., nonfocal). This nonfocal stimulation did not inhibit spiking and did not alter the power of high-frequency activity. However, the regions stimulated in this study were different from nonfocal regions previously reported to have a suppressive effect on epileptic discharges. For example, Zumsteg et al. (30) demonstrated that open-loop stimulation of the anterior thalamic nucleus produced inhibition in the hippocampus. Moreover, several studies have reported an effect of nonfocal stimulation on epileptiform activity and clinical seizures

following stimulation of regions thought to be associated with the activation of inhibitory networks including the cerebellum (31), caudate nucleus (32), and several thalamic nuclei (33).

A number of studies have also examined the effect of focal and nonfocal closed-loop stimulation on epileptiform activity in patients that have had subdural electrodes placed for presurgical evaluation. Lesser et al. (34) reported one of the first studies testing focal closed-loop stimulation in this setting. They examined the effect of cortical stimulation in 17 patients undergoing functional mapping for language, motor, and sensory regions. They found that afterdischarges produced by a localizing stimulus during the mapping could be aborted by a brief burst of stimulation delivered via the same electrodes used to elicit the afterdischarge. These results were extended by Motamedi et al. (35), who demonstrated that the success of a brief burst in aborting an afterdischarge was enhanced if the stimulus was applied early, to the primary electrodes, and at a specific phase of the afterdischarge.

In order to provide closed-loop stimulation to spontaneous epileptiform activity, an integrated system that performs real-time electrographic analyses and automatically delivers stimulation to detected events is required. Acute clinical trials of two systems have been conducted using nonimplantable bedside prototypes tested in patients undergoing evaluation with intracranial electrodes as part of an epilepsy surgery evaluation. Peters et al. (36) described the first of these systems. The system included subdural electrodes for recording and stimulating, an ECoG acquisition system, two computers, and Grass S12 stimulators. The first computer was used to store and process ECoGs, and the data was then transferred to the second computer for advanced analysis and control of stimulation delivery through the Grass S12 stimulators.

Osorio et al. (37) reported the effect of closed-loop stimulation on spontaneous seizures in eight patients using this system. If the seizures were determined to be originating from a discrete location, the patient was assigned to the focal closed-loop stimulation group and received stimulation to the seizure onset zone. In contrast, patients with seizures originating from multiple independent foci were assigned to the remote (nonfocal) closed-loop stimulation group, and stimulating electrodes were then implanted into the anterior thalamic nucleus. All patients received high-frequency (100–500 Hz) biphasic stimulation. Closed-loop stimulation reduced the seizure rate by 55.5% in the focal group and 40.8% in the nonfocal group. This study demonstrated that automated closed-loop high-frequency stimulation could be delivered in close temporal proximity to the seizure onset. Moreover, the data suggested that closed-loop stimulation might produce a significant reduction in clinical seizures.

Results from a small subset of patients enrolled in a large multicenter acute study of a second bedside prototype also suggested that closed-loop stimulation could alter or block electrographic seizures (38). The external responsive neurostimulator (eRNS) is a battery-operated device that processes digital data in real-time and has three different detection tools that can be programmed to identify a patient's electrographic seizure onset. The detectors used consist of a half-wave, line length, and area tool. The half-wave tool is a computationally efficient method of detecting a specific onset frequency; the line length and area tools detect increases in complexity or energy from background trends. These tools were used individually or in combination as needed to detect epileptiform activity as identified by the physician for a given patient (25,26,38). The authors reported that responsive stimulation terminated some electrographic seizures. Figure 17-2 shows examples of electrographic seizures in one patient without (A) and with (C) closed-loop stimulation. Note the return to baseline electrographic activity following stimulation in Figure 17-2(C).

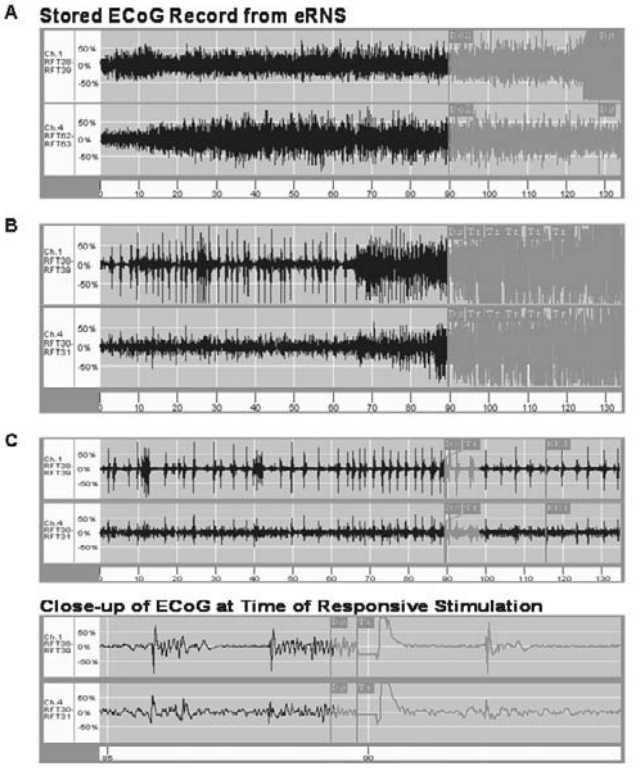

FIGURE 17-2. Electrocorticographic (ECoG) recordings of electrographic seizures from the same patient. A: Seizure recorded without stimulation. The electrographic activity correlated with a clinically reported seizure. Detection, denoted by light gray, had not been tuned for the seizure onset and was late. B: Seizure recorded with focal high-frequency stimulation delivered by the eRNS late after the seizure onset. Stimulation is denoted by Tr. Again detection had not been tuned for the seizure onset, and as a result detection and stimulation were late and the seizure progressed. C: Early detection of electrographic seizure onset pattern and early focal responsive high-frequency stimulation delivered to the seizure onset by the eRNS.

These acute studies suggest that both focal and nonfocal stimulation can acutely inhibit epileptiform activity. In addition, they demonstrate that both open-loop and closed-loop stimulation can be effective. However, the acute studies do not address the effect of stimulation on clinical seizures, nor do they address the efficacy or safety of long-term intracranial stimulation.

Chronic Clinical Studies and Implantable Devices

The first long-term clinical studies of chronic brain stimulation were conducted by Cooper and colleagues in the 1970s, and tested the effect of cerebellar stimulation on clinical and electrographic seizures. This group reported a significant reduction in seizures following open-loop stimulation of the cerebellum. However, results from follow-up randomized trials have been mixed (13). Cooper and colleagues were also the first group to demonstrate that stimulating the anterior nucleus of the thalamus could inhibit clinical seizures (33). Since then, clinical studies using implantable devices have shown a reduction in seizure frequency following stimulation of regions outside the seizure focus, including several thalamic nuclei, subthalamic nucleus, caudate, mammillary bodies, locus coeruleus, and basal ganglia. The majority of these studies employed continuous open-loop stimulation. Although there is limited evidence that stimulation of the anterior nucleus of the thalamus may inhibit complex partial seizure events (39), most results indicate that indirect stimulation can more successfully inhibit secondarily generalized seizures.

To date, a number of small clinical studies have tested the efficacy of implantable devices that deliver stimulation to the seizure onset zone. Many of these studies have focused on continuous open-loop stimulation to mesial temporal structures and have shown promising results. For example, Velasco et al. (28) studied the effect of high-frequency biphasic stimulation in patients implanted with hippocampal depth leads via an occipital approach. They demonstrated that 130 Hz, 200–400 μA stimulation could block clinical seizures and significantly reduce interictal spikes at the focus; this stimulation produced no histopathological tissue damage and no negative effect on short-term memory. In addition, they noted that stimulation therapy was most effective when the electrodes extended to the anterior pes hippocampus near the amygdala. A subsequent study followed patients for 5–21 months after implantation of amygdalo-hippocampal depth leads and a pulse generator (40). They noted a >50% reduction in seizure frequency in four out of seven patients, one of whom was seizure-free for 1.5 years. In addition, two of the patients could be tapered off of one antiepileptic drug. No side effects were reported. Although one randomized trial of hippocampal stimulation demonstrated a smaller nonsignificant seizure reduction (41), a recent double-blind trial in nine patients demonstrated a significant reduction of seizure frequency in response to hippocampal stimulation (42). Importantly, there were no adverse effects reported in either study, and the stimulation did not have any detrimental effects on cognitive and memory functions.

Outside the hippocampus, a recent case report has demonstrated the efficacy and safety of stimulating the primary motor cortex (29). The patient was initially studied during extraoperative cortical mapping that identified the seizure onset zone as the primary motor hand region. During the mapping study it was noted that direct 50-Hz stimulation for 3 minutes at 2 mV significantly suppressed interictal spiking for 10 minutes. The spiking then gradually returned but could be suppressed upon subsequent stimulation. Because the onset region was primary motor cortex, the patient was not a candidate for resection. Instead, the patient was implanted with a permanently indwelling electrode array at the seizure focus, and a pulse generator was placed in the subclavicular area. The patient received continuous cyclical open-loop stimulation (biphasic 50 Hz, 2.1 mV, 3 minutes on and 10 minutes off) for 5 years without evidence of injury. Moreover, the stimulation reduced the seizure frequency by more than 90%.

These studies suggest that open-loop stimulation of both neocortical and mesial temporal seizure foci can be efficacious in the treatment of medically intractable epilepsy patients.

The first implantable responsive neurostimulator for epilepsy, the NeuroPace RNS System, is currently being evaluated for safety and efficacy in clinical trials. A schematic of the implanted device appears in Figure 17-3. The implantable components include a cranially implanted

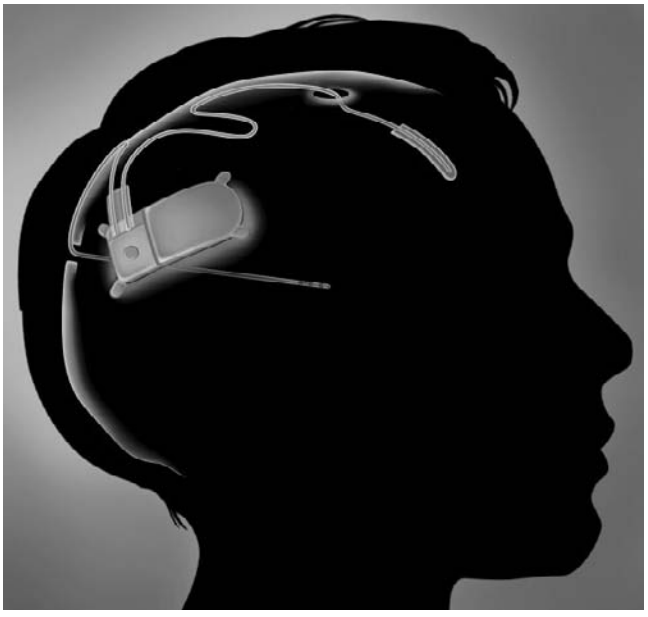

FIGURE 17-3. Schematic of the NeuroPace RNS™ neurostimulator, depth and strip leads.

pulse generator and depth and strip leads containing four electrodes each. Up to two leads can be connected to the neurostimulator. The system also includes an external programmer used to program detection and stimulation parameters and retrieve stored electrographic activity, and a wand that allows wireless communication between the stimulator and the programmer. A data transmitter is provided to the patient to allow uploading and remote monitoring of device data between clinic visits. The RNS System continually analyzes the patient's electrographic activity, and automatically delivers electrical stimulation to the seizure focus when the patient's characteristic epileptiform activity is detected. An initial single center report demonstrated a 45% decrease in seizures in seven of eight patients with a mean follow-up of 9 months (43). A randomized, double-blind, sham-controlled clinical trial is currently being conducted to demonstrate the safety and efficacy of the RNS System.

Optimizing Therapeutic Stimulus Parameters

A variety of parameters may influence the response to both open- and closed-loop stimulation. These parameters include dose or number of stimulations, stimulus frequency, current intensity, stimulus duration, stimulus waveform, and the location. Both high and low frequencies have been shown to inhibit epileptiform activity and seizures. There is some suggestion in the literature that the optimal stimulus frequency may be dependent on the region being stimulated (32). In addition, the efficacy of responsive stimulation may be influenced by how early the electrographic seizure can be detected. For example, stimulations delivered later in a seizure failed to terminate the electrographic event, while stimulations delivered early resulted in a return to baseline activity (Figure 17-4). Therefore, adjusting detection parameters to detect at the earliest sign of an electrographic event may also be important in optimizing responsive stimulation.

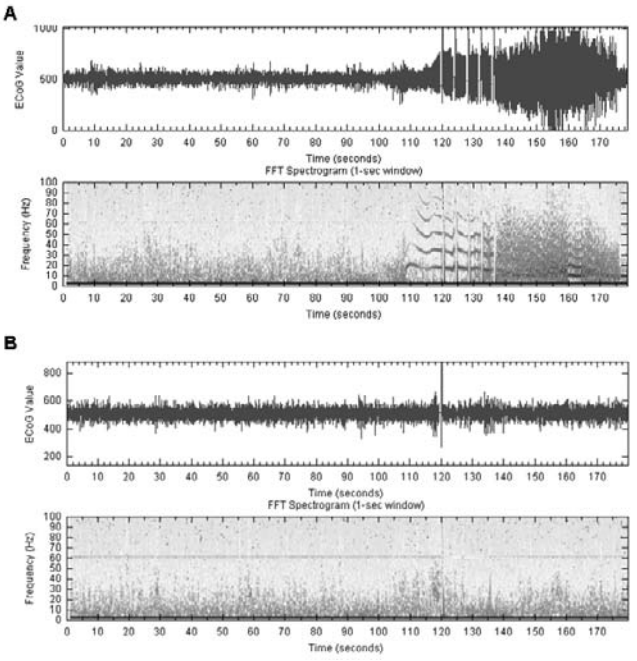

FIGURE 17-4. Time series and spectrograms of electrographic seizures receiving late (A) and early (B) stimulation relative to the seizure onset, using the implantable RNS System. Note that the seizure continues to evolve when focal stimulation is delivered several seconds after the onset of the seizure (A), whereas the electrographic activity does not evolve when focal stimulation is delivered earlier (B). *(See color insert).*

SAFETY OF INTRACRANIAL STIMULATION

No damage has been observed in human cortex exposed to intermittent stimulation used to perform functional mapping as long as the charge delivered remains below 50–60 μC/cm^2/phase (44,45). However, there is a safety concern that chronic subthreshold stimulation, like that used by implantable devices for the treatment of epilepsy, may induce neural injury. Experience with deep brain stimulation for Parkinson's disease suggests that long-term intracranial stimulation can be delivered safely (46). Animal studies have suggested that tissue damage resulting from stimulation is correlated with charge density per phase and the total charge per phase, as well as with cumulative exposure of tissue to stimulation (47). From these studies it appears that damage induced by continuous stimulation may be more severe than that induced by intermittent stimulation. Therefore, responsive or closed-loop stimulation may limit the amount of tissue damage from chronic intracranial stimulation. However, further studies are required to determine whether either open-loop or closed-loop stimulation produce damage to tissue following long-term use.

Surgically implanting devices to deliver intracranial stimulation for the treatment of epilepsy may be associated with some additional risks. Reports from the implantation of deep brain stimulators for Parkinson's disease include pain and hearing loss, and suggest that the procedure is associated with a 5% risk of infection and a 5%–7.5% risk of intracerebral hemorrhage (39). Surgical risks may vary depending on the site of implantation, the size of the device, and the general health of the patient population.

SUMMARY

Intracranial stimulation has long been used for presurgical evaluation of patients with medically intractable epilepsy. These studies have provided substantial information regarding the functional organization of the human cortex. However, considerable inter-individual variability in functional brain anatomy has demonstrated the continued need for functional mapping in preoperative planning of resections.

Implantable neurostimulation devices may provide new diagnostic and therapeutic alternatives for patients with medically intractable epilepsy. As patient reports of their own seizure frequencies are often highly unreliable, implanted devices may allow clinicians, for the first time in medical history, to accurately assess the occurrence of seizures and actual effects of medications over long periods of time. An important advantage of intracranial stimulation for the treatment of epilepsy is that the therapy is largely reversible. In addition, stimulation therapy can be delivered to a specific onset region or inhibitory network and can be adjusted for individual patients. Thus intracranial stimulation may offer more specificity than antiepileptic drugs. Ongoing clinical trials of intracranial stimulation may reveal that that there is more than one approach to brain stimulation that is safe and effective. Further studies will be required to identify patients who might benefit from stimulation, to identify safe and effective stimulation targets, and to ascertain the optimal stimulation parameters for individual patients or groups of patients.

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SECTION

V

ICU MONITORING: MEDICAL AND SURGICAL NEUROLOGICAL DISORDERS

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18

EVENTS THAT MIMIC SEIZURES DURING ICU MONITORING

NISHI RAMPAL
LAWRENCE J. HIRSCH

The intensive care unit (ICU) presents a unique challenge to the clinician and electroencephalographer with respect to the diagnosis of seizures. Patients are often comatose, pharmacologically sedated, or paralyzed, obscuring typical clinical signs. Furthermore, ICU patients have a conglomerate of complex medical issues that can in and of themselves present with a vast array of signs and symptoms. It is the challenge of the ICU team to separate epileptic seizures from the myriad of seizure mimics, from mental status changes to myoclonus. Making the situation even more daunting is the fact that seizures, even status epilepticus, often have no apparent clinical signs in critically ill patients (nonconvulsive seizures or nonconvulsive status epilepticus (NCSE)) (1,2). It is this clinical uncertainty in the critically ill that underscores our dependence on EEG and on its accurate interpretation in the diagnosis of seizures. On the diagnostic side of the equation, with the increased use of continuous EEG monitoring (cEEG), longer recordings are being performed (3). These longer recordings increase our ability to capture seizures, both clinical and subclinical. Yet at the same time, confusing nonepileptic clinical and electrographic events can occur (4,5), and these may be mistaken for epileptic activity and misdirect clinical care (see examples in Figure 18-1). For example, in one large, single-institution study, up to 10% of patients undergoing cEEG in the neurological–neurosurgical intensive care unit were shown to have "nonepileptic behavioral spells" on cEEG (6). The identification of such events is crucial for the avoidance of unnecessary and potentially detrimental medications.

BEHAVIORAL EVENTS THAT MIMIC SEIZURES

The clinical features of seizures in the critically ill differ greatly from those in a healthier patient population. Identifiers such as subtle or brief changes in consciousness, behavioral arrest, and patient-reported experiences are often lost. When present, movements may be subtle and less rhythmic, reflecting poor electrical synchronization and propagation. Stereotypic events should raise suspicion of seizures, but with wide fluctuation in medical parameters this hallmark may also be absent. In addition, a large proportion of ICU patients have underlying neurological illness, but not all abnormal neurological signs, rhythmic, stereotyped or otherwise, are seizures. Any unexplained depressed level of consciousness should provoke consideration of nonconvulsive seizures or NCSE.

Some of the clinical events that can mimic seizure activity are summarized in Table 18-1. Several medical

TABLE 18-1. CLINICAL EVENTS THAT CAN MIMIC SEIZURES IN ICU PATIENTS

Movement Disorders
Myoclonus (including negative myoclonus, or asterixis)
Tremors
Tardive dyskinesia
Psychogenic seizures
Delirium/Encephalopathy
Eye Movement Abnormalities
Nystagmus
Eye deviation
Autonomic dysfunction
Paroxysmal tachycardia or hypertension
Apnea
Posturing (decerebrate, decorticate, pain-related, during hypoperfusion)
"Convulsive" syncope (myoclonus or posturing during hypoperfusion)
Tendon-reflex clonus
Chewing
ICU psychosis
Alterations in consciousness from medications
Voluntary movements in weak limbs
Hiccups
Hallucinations
Rigors

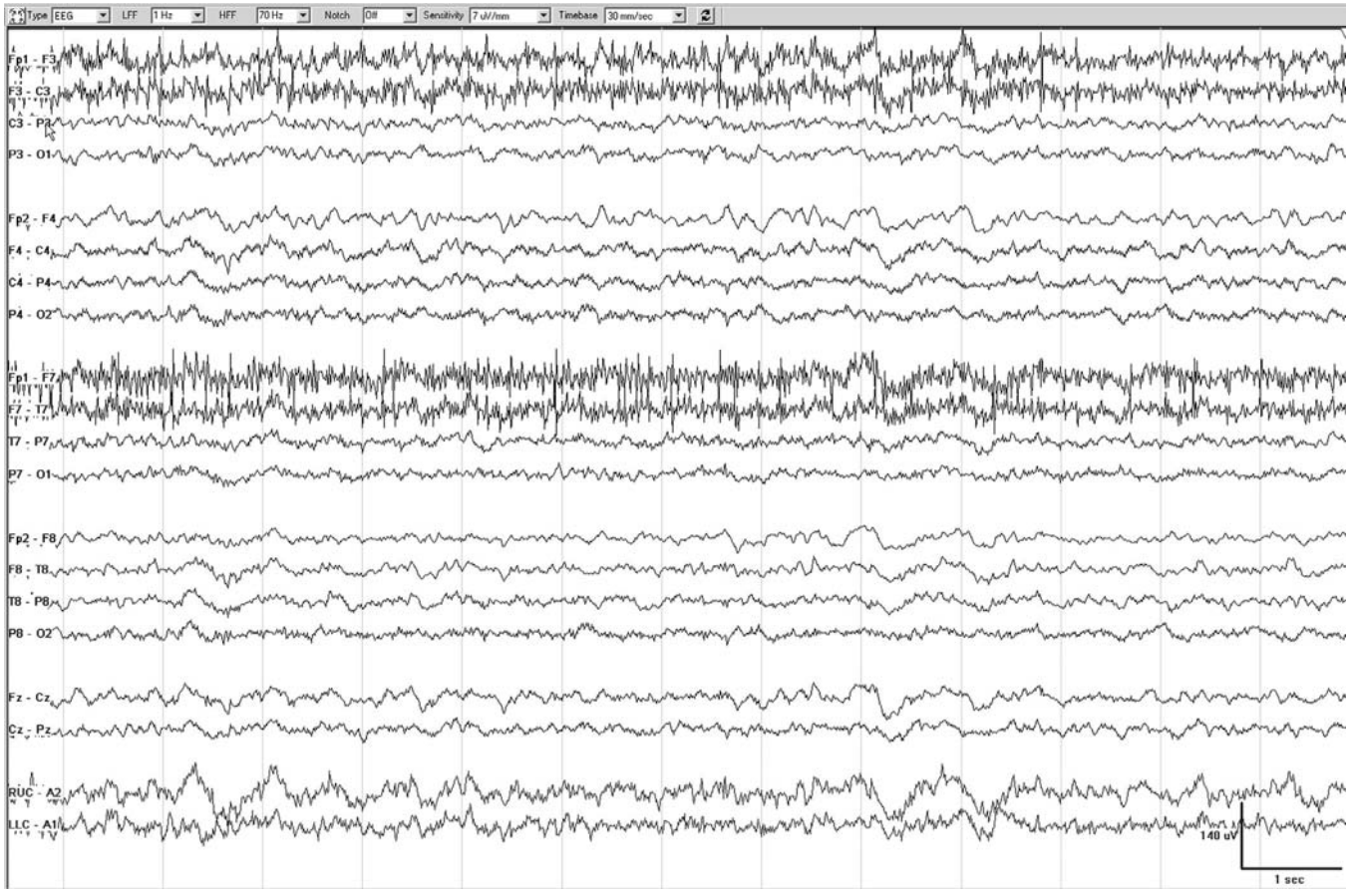

FIGURE 18-1. Physiologic nonepileptic spell (also known as ICU "pseudoseizure"): posturing and tendon-reflex clonus. EEG in bipolar montage with eye channels in a comatose Neurological ICU patient during a spell of possible seizure activity. The EEG demonstrates diffuse slowing and left frontal muscle artifact without an alpha rhythm. No epileptiform activity is seen on EEG during the spell (shown in the figure), and no seizures were found on prolonged monitoring.

conditions can produce clinical features that overlap with epileptic events, while at the same time predisposing patients to an increased risk of seizures. For example, withdrawal syndromes (from ethanol, barbiturates, or benzodiazepines) can produce tremors, autonomic instability, bizarre behaviors, hallucinations, psychosis, and fluctuation in mental status, all of which can mimic seizures (7).

Another challenging group of seizure imitators is movement disorders (8). Movement disorders are often repetitive, stereotyped, and episodic. New-onset movement disorders caused by acute subcortical injury may manifest with complex movements. It can be helpful if the clinician can discern whether the movement occurs at rest, with action, or during maintained posture, because seizures are only rarely consistently related to these factors. If the movement can be suppressed either voluntarily or with change in position, seizure is an unlikely etiology. Movement disorders usually resolve during sleep. Conversely, seizures can be seen in any state, with transition periods and sleep being common states for epileptic events. cEEG during movement disorders will demonstrate a lack of epileptiform activity (Figure 18-2).

Specific disorders of movement such as myoclonus (often presenting after cardiac arrest), tremors, tardive dyskinesia (from neuroleptic drug usage), and other paroxysmal basal ganglia–related movements can all demonstrate repetitive, involuntary, purposeless movements ranging from rapid movements of the limbs to lip smacking and eye blinking. Nonepileptic myoclonus is commonly seen in ICU patients and can be caused by a range of disorders including stroke, kidney or liver failure, and chemical or drug exposure. It can be difficult to discern between epileptic myoclonus (of cortical origin, usually with an EEG correlate, and with a strict relationship between cortical discharge and subsequent jerk on formal testing) and nonepileptic myoclonus (usually of brainstem origin, often without an EEG correlate, and with variable time relationship between EEG discharge when present and jerk) (see Figure 18-3) (9–11). In the postanoxic setting, both types can coexist. Although not well studied, focal cortical (epileptic) myoclonus tends to involve body parts with greater cortical representation, such

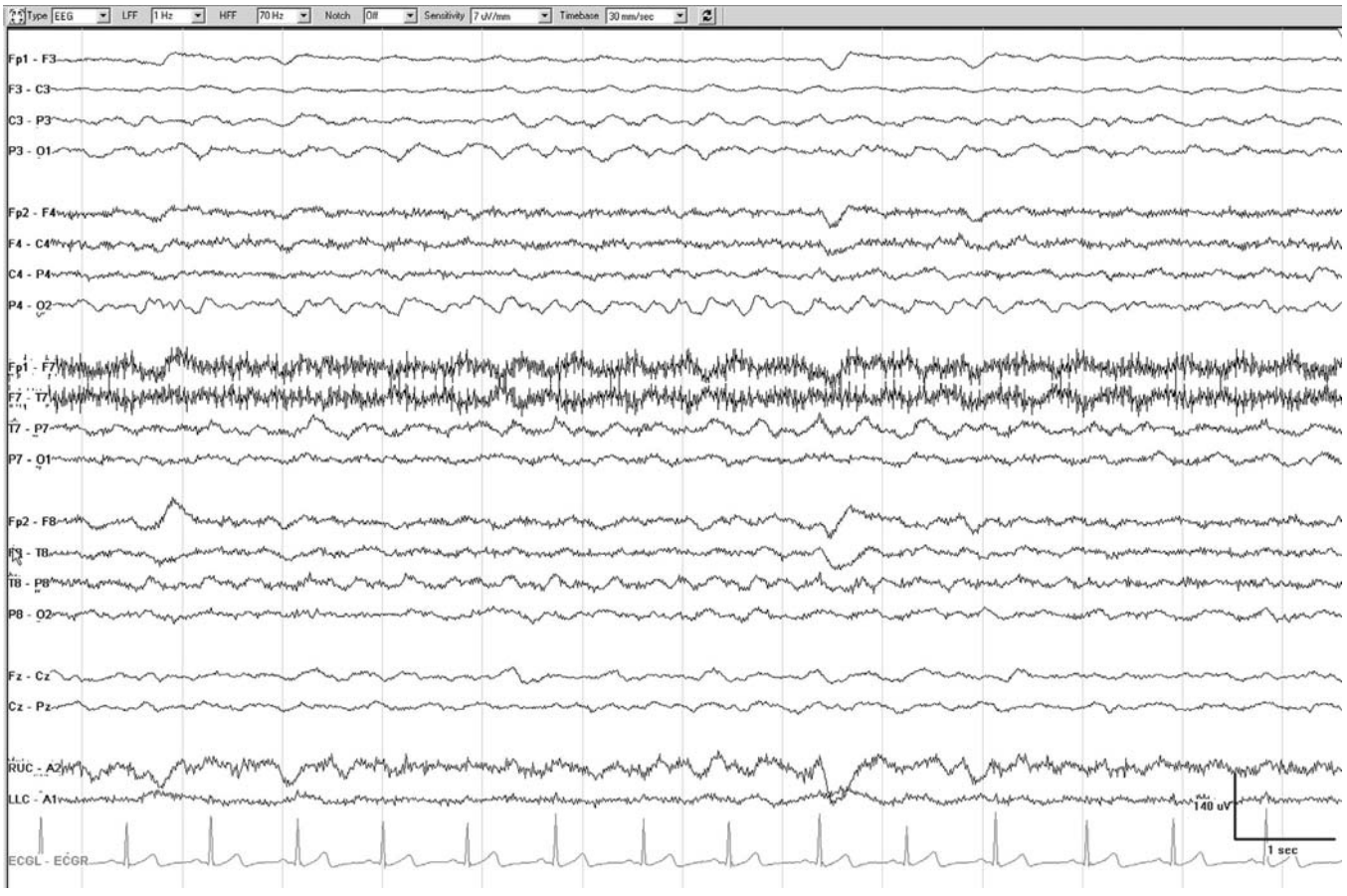

FIGURE 18-2. Physiologic nonepileptic spell (also known as ICU "pseudoseizure"): unusual truncal movements. EEG in bipolar montage with eye channels and electrocardiogram (EKG) lead in a comatose NICU patient reveals diffuse slowing with no alpha rhythm. EKG is in normal sinus rhythm. This EEG corresponds to a period during which the patient was demonstrating abnormal, side-to-side rhythmic movements of the head and torso with eye opening and deviation thought by ICU staff to be seizure. The cEEG demonstrated that the movements were unlikely to be either seizure (given the lack of change in EEG) or volitional movements (given the severity of the EEG background slowing).

as the hand or face, whereas nonepileptic myoclonus tends to involve midline or truncal muscle groups, including neck muscles. Multifocal myoclonus after status epilepticus may originate from multiple cortical sites, and may not have clear findings on surface EEG; it is quite difficult to be certain of the epileptic or nonepileptic nature of such movements. The teaching that synchronous jerks of multiple body parts is more likely cortical and epileptic than asynchronous jerks may be true to some degree, but is often misleading or variable in our experience, particularly in critically ill patients; asynchronous jerks are not unusual in epileptic seizures.

Psychiatric disorders can be particularly difficult to distinguish from epileptic seizures. Further complicating the clinical picture is the fact that both can improve with benzodiazepines. Psychogenic nonepileptic seizures (PNES) deserve specific mention because of the occasional coexistence of nonepileptic and epileptic events in the same individual, and the potentially severe iatrogenic harm of treating psychogenic status epilepticus as epilepsy. In the critical care setting where time is not afforded, each event should be individually assessed and treated accordingly. Psychogenic status epilepticus has been reported in up to 20% of patients admitted to ICUs with a diagnosis of status epilepticus, and its misdiagnosis can lead to unnecessary, expensive, and dangerous treatments (12–16). Psychogenic status can present with a multitude of signs, including face twitching, head shaking, unilateral or bilateral limb shaking, speech arrest, apparent loss of consciousness, cyanosis, and autonomic signs. In one study comparing 13 psychogenic status patients to 13 epileptic status patients, patients in psychogenic status often displayed retained consciousness, bilateral motor activity with vocalizations, resistance to examination, and rapid recovery. Both groups had tongue biting, incontinence, and cyanosis, and among the psychogenic status patients nearly half of the interictal EEGs had epileptiform features (17). One patient was reported to have had 27 venous cut-downs for intravenous access because of frequent presentations of psychogenic status

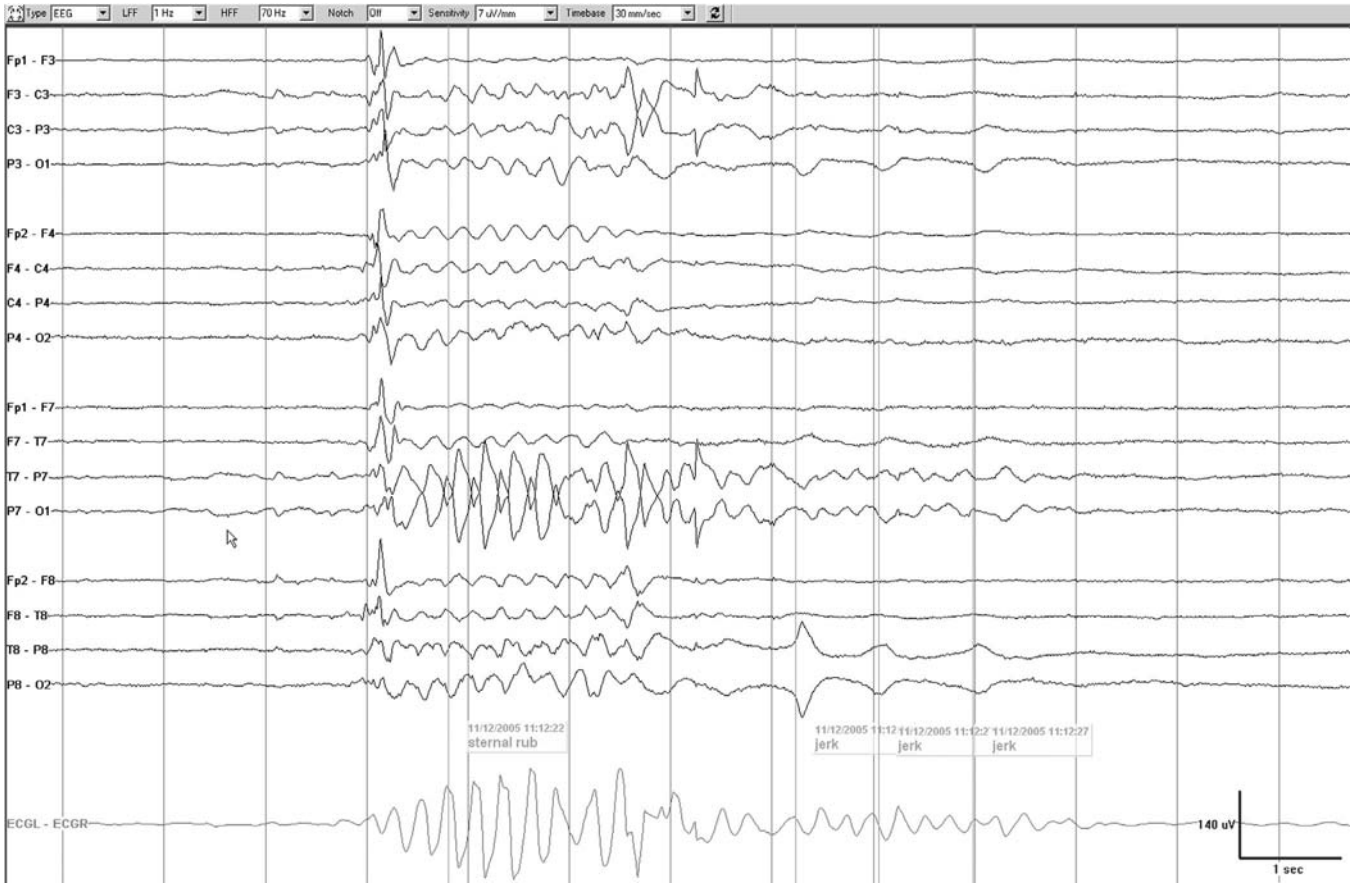

FIGURE 18-3 Nonepileptic myoclonus. EEG in bipolar montage with EKG lead in a comatose medical ICU patient demonstrates diffuse slowing and attenuation, as well as artifact, most prominent in the EKG leads, that corresponds to sternal rubbing lasting 3 seconds. This elicited three myoclonic jerks (see labels on EEG) with no EEG correlate (occipital delta wave can be seen caused by slight head movement), most consistent with nonepileptic myoclonus.

(14; unclear why rectal, nasal or buccal medication could not be used, as all are effective means of delivery of benzodiazepines), and many patients with misdiagnosed psychogenic seizures will receive large doses of sedatives and anticonvulsants. Continuous EEG plays an important role in preventing this iatrogenicity.

It should be recalled that EEG can be negative during epileptic seizures, especially with large extra-axial collections, highly focal seizure foci, or seizures from the medial or inferior frontal lobe. In general, a surface EEG correlate will not be present unless at least 10 cm^2 of cortex is discharging synchronously (18). Thus, lack of an EEG correlate should not dissuade one from diagnosing focal seizure activity if the clinical picture is convincing.

Abnormalities of eye movements, including nystagmus, repetitive blinking, opsoclonus, and eye deviation, can potentially mimic seizure. On the other hand, these ocular movement abnormalities (including hippus) are associated with a greater risk of NCSE in patients undergoing cEEG (50% versus 14% in one series, $p < 0.05$ (19)).

Hepatic and renal insufficiency and failure along with acid–base disturbances are commonly present in the ICU population. Along with depressed consciousness, these disorders commonly cause aberrant movements, including myoclonus and asterixis. Toxins, whether ingested accidentally or intentionally, can produce a similar clinical picture, and should be aggressively investigated—especially if encountered in a previously healthy individual. Similar findings can be seen in endocrine disorders, particularly thyroid, vitamin, and heavy metal disorders.

EEG FINDINGS THAT MIMIC SEIZURES

The ICU setting poses a unique challenge to the electroencephalographer with respect to artifacts. Because the behavioral events that occur can be misdiagnosed as seizures and because there is no clinical correlate to the majority of seizures in the critically ill, the clinician has no option but to rely heavily upon the EEG. The treatment for seizures in the ICU begins with conventional intravenous medications, but often progresses to more aggressive combinations of medications. These medications are often poorly tolerated and their side effects can be

life-threatening in the critically ill, reinforcing the necessity for accurate diagnosis.

There are numerous sources of artifacts that can mimic seizures on the EEG. These include environmental, patient care–related, and procedure-related sources, complex therapeutics, and artifacts seen with prolonged EEG recordings (Table 18-2). In-room bedside monitors may display activity that resembles seizures and in the absence of skilled interpretation may mislead clinical care. Remote access capability for timely expert review and the addition of audio and video components to the EEG recordings are crucial components of cEEG effectiveness.

Environmental artifacts can be created by external and even internal sources. The most common artifact captured on EEG is 60-Hz artifact from main power lines (or 50 Hz in Europe). While this artifact is not specific to the ICU, it is very frequently encountered in this setting of prolonged recordings in a noisy environment. Notch filters can be used to remove this artifact; however, routine use of a notch filter must be avoided, because this may lead to misinterpretation of EEG findings, and to delayed recognition of electrodes that have poor contact and therefore unreliable signals.

A patient may have a unique internal environment that can create marked EEG artifact, limiting interpretation. This is being seen with increasing frequency as a result of implanted devices like deep brain stimulators (DBS) for diseases including movement disorders. Often briefly disabling the device is the only way to obtain a high-quality recording.

The majority of ICU patients are dependent upon mechanical devices. Ventilators can produce an EEG artifact that is coupled to the respiratory rate and can mimic periodic discharges. Though this can be distinguished by the experienced neurophysiologist fairly easily, video or respiratory leads make the distinction easier. Fluid in the ventilator circuit can create an EEG artifact as the pooling liquid moves and generates signals with each respiratory cycle (see Figure 18-4). Other common events that can cause EEG findings that may resemble seizures in the ICU include oral hygiene and pulmonary toileting (automatic bed oscillations or manual chest percussion by respiratory therapy) (20–22). Chest percussion/patting is one of the most commonly encountered seizure mimics in the ICU; it mimics seizures because it starts and stops abruptly with rhythmicity, at times even appearing to evolve (see Figures 18-5a and b). The pattern commonly has a physiologic field, because the artifact is maximal in the electrodes contacting the bed, usually on one side as they are turned on their side during chest percussion.

TABLE 18-2. EEG EVENTS THAT CAN MIMIC SEIZURES OR PERIODIC DISCHARGES IN THE ICU

Ventilator artifact
Mechanical ventilation/head movement
Fluid in ventilator circuit
Mechanical Bed Vibrations (e.g., for automatic pulmonary toileting)
Pulmonary toileting (e.g., chest percussion by respiratory therapists)
Infusion pumps
Patting patients (especially in infants)
Mouth swabbing/oral care
Glossokinetic/chewing artifact
ECG and pacemaker artifact
Rhythmic body movements, voluntary or involuntary (see Table 18-1 for examples)

Electrode artifact and electrode failure are significant sources of artifacts on an EEG recording. Poor electrode contact, and failure from sweat or skin breakdown, improper grounding or shielding, or impedance errors, can all lead to artifacts that, in certain contexts, may resemble seizures. Collodion adhesive is the more commonly used applicant with EEG scalp disk electrodes, but with long-term monitoring, most adhesives will break down. Some advocate the use of subdermal wire electrodes for long-term monitoring to eliminate the need for regular electrode maintenance (23). Even after leads are detached from a patient, random environmental noise can produce electrical patterns that may appear as cerebral activity if the EEG recording is inadvertently continued. These events highlight the importance of experienced technicians and clinicians for thorough troubleshooting.

In encephalopathic patients for whom NCSE is suspected, periodic discharges are often seen on EEG. Triphasic waves (TWs) are a subtype of generalized discharges that are broadly distributed, typically with an AP lag (anterior to posterior time gradient, best appreciated on bipolar recordings); recur at 1–2 Hz; and have a characteristic morphology. TWs present a conundrum to the clinician because the EEG features alone are not adequate to distinguish them from NCSE. Both are likely to respond to benzodiazepines; thus, this EEG response is not helpful for making the distinction (24). Patients in whom the EEG *and clinical state* improve immediately after benzodiazepines can be considered to have been seizing, regardless of the underlying EEG pattern. However, because periodic discharges of all types, including TWs, will improve on EEG (i.e., will demonstrate suppression) with benzodiazepine administration, an EEG improvement without clinical improvement leaves the diagnostic issue unresolved; unfortunately, this is a common result of diagnostic benzodiazepine trials (25). TWs of metabolic etiology will occasionally resolve or suppress when the patient is aroused, helping to differentiate between seizure and other causes. The converse—an increase in discharges with stimulation—is not helpful diagnostically, because alerting stimuli commonly induce epileptiform EEG patterns, including seizures, in encephalopathic patients (26, 27).

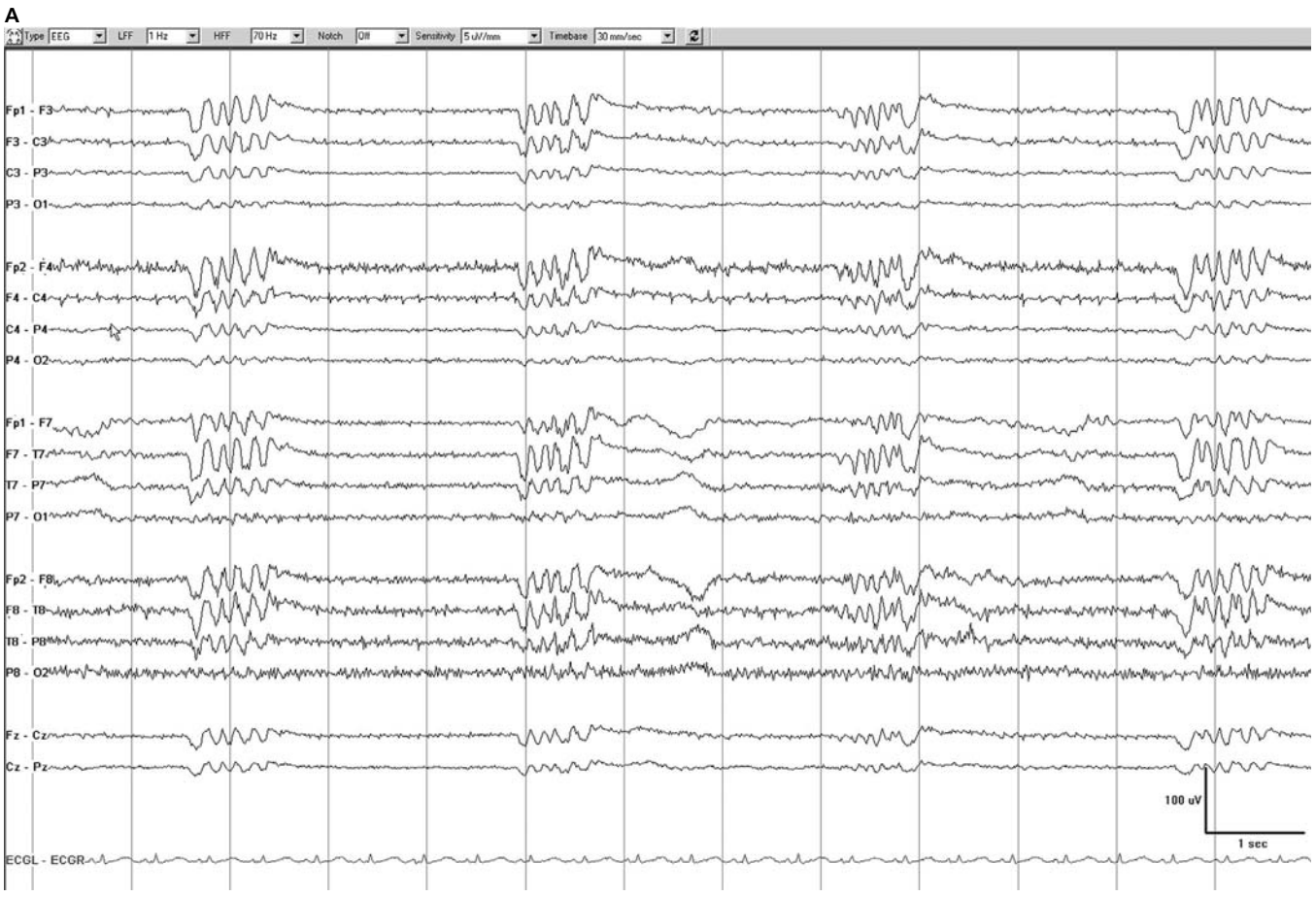

FIGURE 18-4 EEG artifact from ventilator circuit fluid. (a) EEG in bipolar montage and EKG lead in a comatose Neurological ICU patient reveals periodic 1-second bursts of rhythmic theta activity occurring every 3 seconds with intervening marked attenuation, potentially mimicking burst-suppression or generalized periodic discharges. This periodic pattern correlated with fluid oscillations in the ventilatory circuit. EKG is in normal sinus rhythm.

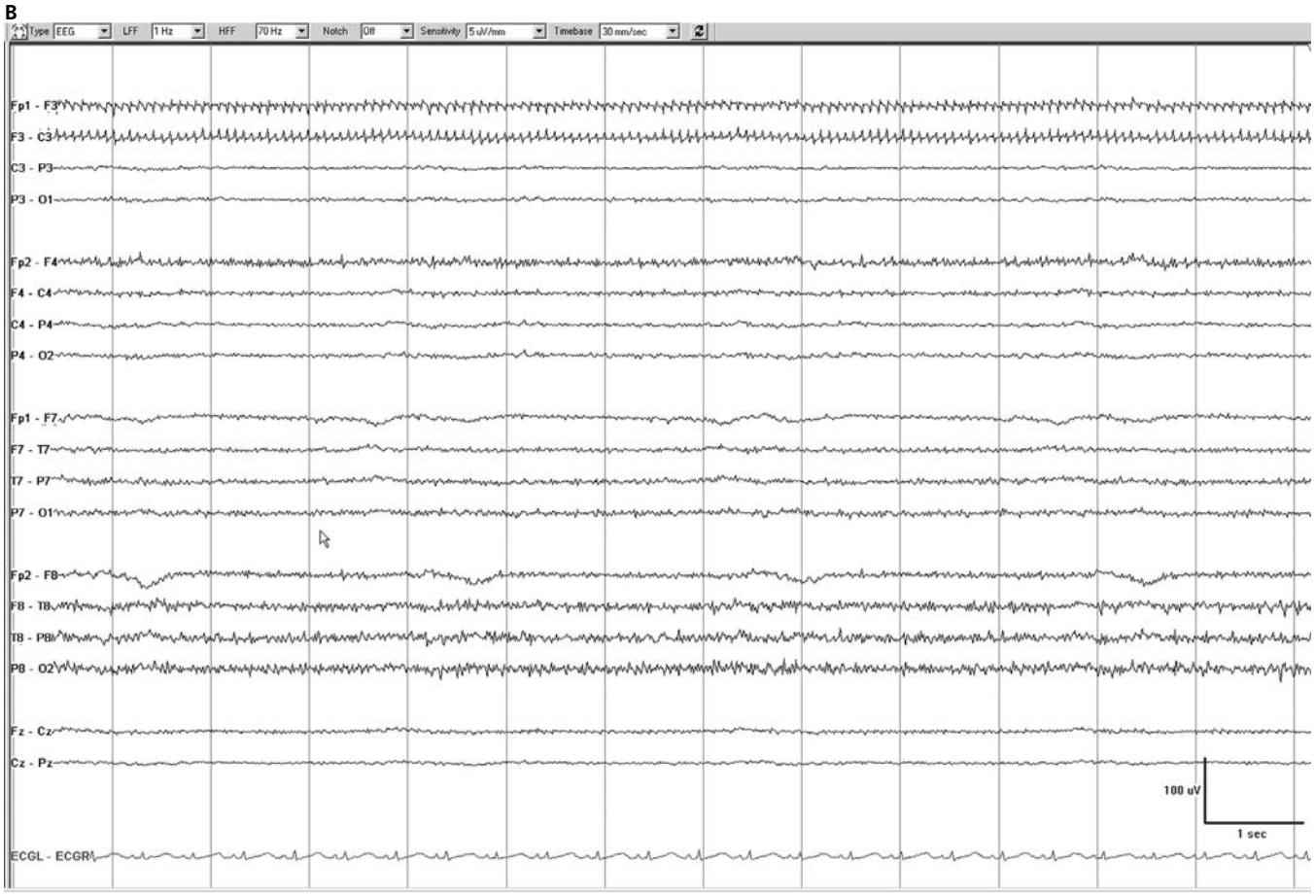

FIGURE 18-4 (b) After suctioning of the fluid in the same patient (a), theta bursts are no longer present. Marked attenuation of cerebral activity (background) persists. EKG is in normal sinus rhythm.

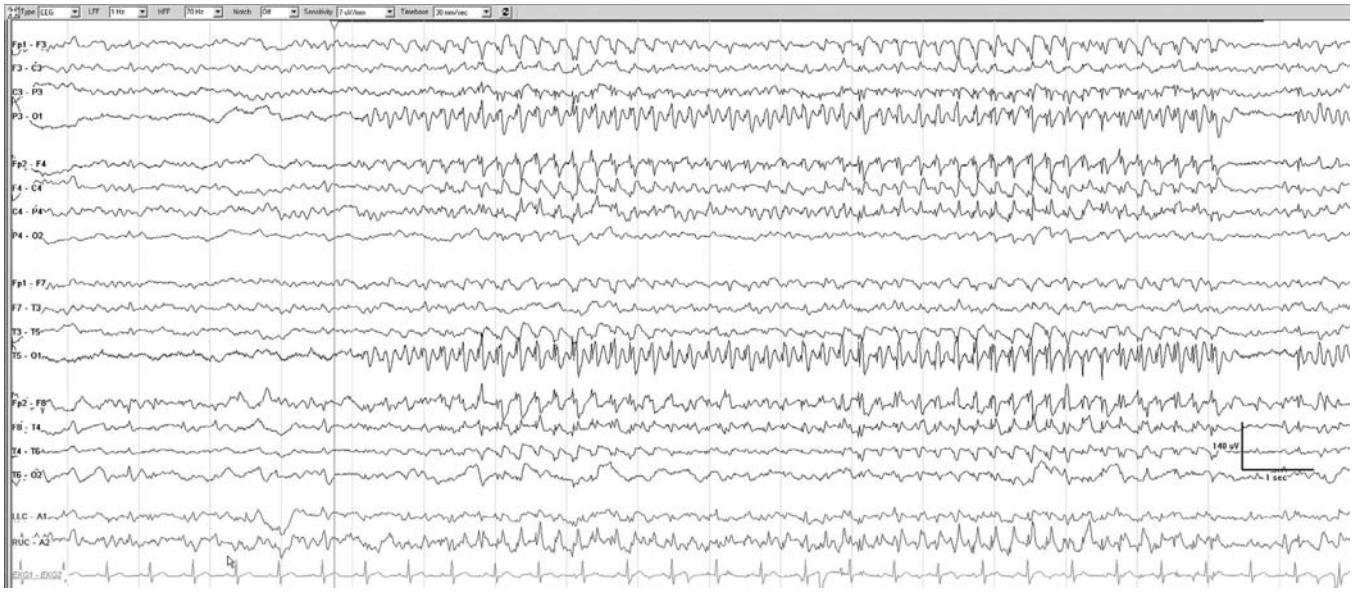

FIGURE 18-5 Chest percussion artifact that mimics electrographic seizure. (a) EEG in bipolar montage with eye channels and EKG lead in a comatose adult Neurological ICU patient demonstrates rhythmic high-amplitude activity with spike-and-wave morphology most prominent over the left posterior quadrant, but "spreading" to the right and evolving, with sudden onset and offset, effectively mimicking a seizure. EKG is normal sinus rhythm without artifact.

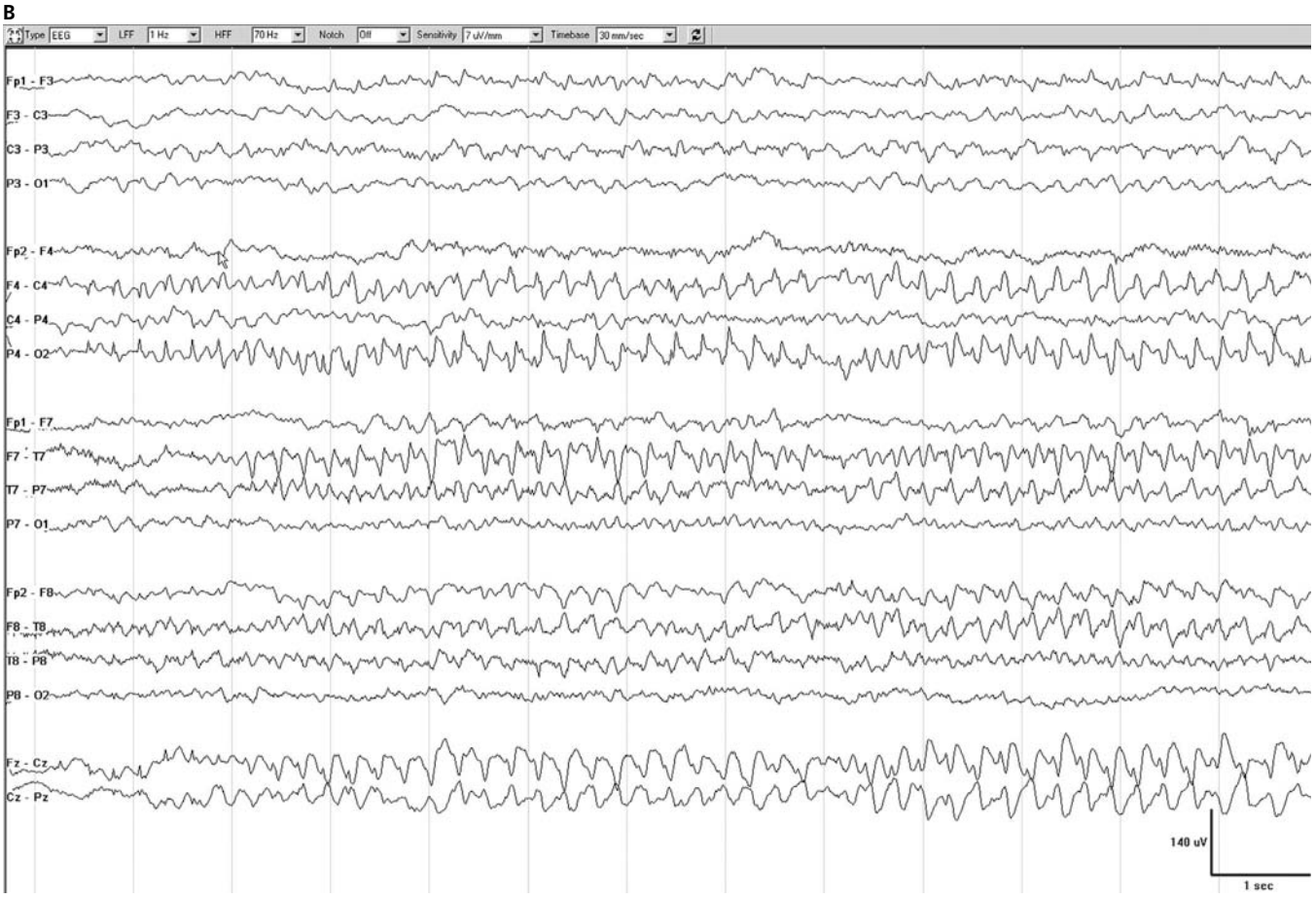

FIGURE 18-5 (b) EEG in bipolar montage in an infant in the pediatric ICU demonstrates a spike-and-wave pattern initially seen over the right centroparietal region, with some evolution and spread, mimicking seizure.

CONCLUSIONS

The multiplicity of behavioral and EEG findings that can mimic seizure illustrates the importance of accurate EEG interpretation in the ICU. An understanding of the clinical and electrographic pitfalls is essential. These pitfalls can be avoided or minimized through proper training of ICU and neurophysiology staff, proper electrode application and maintenance, and thorough documentation of ICU events, preferably via the use of video and audio with remote viewing capability. Although cEEG has immense potential for improving patient care and outcomes, its complexity and potential misinterpretation are important caveats that must be recognized and addressed.

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19

CONVULSIVE SEIZURES AND STATUS EPILEPTICUS

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ROBERT S. FISHER*

Any type of seizure can become prolonged or rapidly recurrent and enduring, thus meeting the definition of status epilepticus (SE). This chapter focuses on SE with motor symptoms in adults. Generalized motor, partial motor, and myoclonic SE should be distinguished as different entities with different etiologies, morbidities, mortalities, corresponding EEG patterns, and treatments. In this chapter, each category of seizures with motor manifestations will separately be considered.

GENERALIZED CONVULSIVE STATUS EPILEPTICUS

Generalized convulsive status epilepticus (GCSE) has been defined in a variety of ways. One influential definition considers GCSE to be a tonic-clonic seizure lasting at least 30 minutes or a cluster of seizures without return to baseline (1,2). However, true tonic-clonic seizures rarely last 30 minutes, and the emergency nature of such seizures mandates treatment before 30 minutes.

GCSE can be operationally defined as any or all of the following:

1. A single generalized motor seizure or cluster of seizures lasting long enough to cause, by virtue of the prolonged nature of the event, either brain injury, other end-organ injury, or ventilatory insufficiency with imminent risk of diffuse hypoxemic compromise (requiring intubation)
2. A generalized motor seizure that shows no signs of remitting once the usual tonic-clonic seizure duration has been reached (3–5)
3. A generalized motor seizure or cluster that appears to be making the transition from convulsive to nonconvulsive without clinical improvement in the patient's global neurological status over minutes

Epidemiology of GCSE

The incidence of GCSE ranges from 10 to 41 per 100,000 persons per year, and for many patients it is their first seizure (6–10). The mortality rate associated with GCSE ranges from 10% to 33%, although wider ranges have been published (8). Much of this mortality is caused by the primary illness that provokes SE, rather than by SE itself. Associated mortality comes from secondary medical consequences of seizures as well as their therapies. Risks and causes of GCSE differ by age, gender, and geographic location (11,12), although such discussion is beyond the scope of this chapter.

The common causes of GCSE are stroke, head trauma, intracranial hemorrhage, central nervous system infection, neoplasia, raised intracranial pressure, severe metabolic derangement, and other structural or inflammatory lesions (11,12). In people with pre-existing epilepsy, rapid withdrawal from antiseizure medication is a common precipitant. Many of these etiologies are focal or lateralized, so GCSE commonly begins with partial seizures and then transitions into GCSE (11). Uncontrolled, pre-existing epilepsy in properly treated patients is a relatively rare cause. SE can be classified in many ways; one broad dichotomy exists between reactive SE and cryptogenic or idiopathic SE. Consistent with the notion that mortality from SE often relates to the underlying provoking medical illness, idiopathic SE has a uniquely good prognosis (8). Conversely, with diffuse hypoxemic brain injury (a frequent cause of generalized and myoclonic SE), overall prognosis depends on the extent of ischemic injury rather than on seizure control. Aggressive treatment of seizures in the context of any profound, devastating brain injury raises complex clinical, ethical, and social questions.

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Self-Sustaining Seizures and Physiologic Changes during GCSE

The concept of "self-sustaining status epilepticus" has been proposed by several important workers in the field (11). Prolonged seizures can develop "pharmacoresistance" (11), such that antiseizure medications will be less and less effective over minutes of a progressing seizure (13). As seizures continue, hippocampal and extrahippocampal GABAergic inhibition fails, and response to benzodiazepines and barbiturates attenuates (13). Early diagnosis and treatment of SE helps to prevent refractory SE and the need for more aggressive later interventions (14). Glutamate-mediated excitotoxic neuronal injury, necrosis, apoptosis, brain and cerebrospinal fluid (CSF) lactate elevation, and receptor dysfunction all appear within minutes of generalized SE (11,15). Hippocampal pyramidal cell loss has been confirmed histopathologically (16). Brain edema as revealed by magnetic resonance imaging can occur within minutes as well. Laboratory markers of brain injury or stress, such as CSF pleocytosis, elevated CSF protein, or elevated neuron-specific enolase are relatively insensitive and etiologically nonspecific. CSF pleocytosis from prolonged seizures rarely exceeds 80 cells/mm3, and often is minimal or absent (12).

Systemic, noncerebral sequelae of GCSE include acidosis (with resultant changes in protein conformation and function), rhabdomyolysis (with subsequent renal insufficiency), pulmonary edema, aspiration, fever, elevations in catecholamine levels, leukocytosis, and traumatic injuries to the tongue, teeth, head, cervical spine, and long bones (12,17). Ventilatory insufficiency can be a consequence of generalized motor seizures, medications used to stop them, or both.

Clinical Care of Patients with Possible GCSE

The list below summarizes the steps involved in evaluating a patient with possible GCSE. The first steps, as with any medical emergency, are to assess and secure the airway, breathing, and circulation (ABCs), and to initiate basic laboratory studies. The second major step involves making an assessment as to whether the motor activity is a result of seizure or of one of its "imitators" (18). If the initial impression is one of SE, then the third step is rapid seizure control. The next usual step is investigation of etiology, once the patient is clinically stable. Since many interventions need to happen simultaneously, a team approach and a prior plan or protocol are essential.

TABLE 19-1. STEPS IN INITIAL MANAGEMENT OF GCSE

1. Assess and secure ABCs, begin initial serum assays
2. Assess whether the event is seizure or one of the "imitators"
3. If the event is a probable seizure, obtain immediate seizure control
4. Determine the type of status epilepticus
5. Investigate etiology

1. ABCs

Evaluating a patient's airway during a convulsive seizure can be challenging. During generalized tonic-clonic seizures, patients often are apneic and cyanotic. If the onset of the seizure is witnessed and tonic or clonic movements stop before approximately 2 minutes have elapsed, the patient will likely begin spontaneous vigorous ventilation. If the duration of apnea is unclear or if it appears to last several minutes, manual bag-mask ventilation or intubation should be considered. Generalized seizures present a risk of aspiration. If the patient does not begin ventilating after the motor component of a seizure has ended, airway obstruction from aspiration should be considered. Although circulatory collapse from seizures is rare, intravenous access should be obtained immediately. Cardiac dysrhythmia from seizure is common. Ictal cardiac rhythms range from sinus tachycardia to complete asystole (19). Cardiac monitoring should begin during the initial clinical survey. Administration of oxygen and control of hyperthermia are believed useful to limit neuronal injury during SE, although, to our knowledge, no controlled studies have been in done in humans to document this seemingly obvious assertion.

Since a common cause of seizures is either hypoglycemia or hyperglycemia, finger-stick blood glucose should be obtained. If no sample can be gathered, intravenous dextrose (and thiamine) should be given assuming possible hypoglycemia. Initial laboratory investigations should include a complete blood count (CBC), a comprehensive metabolic panel including creatine kinase (CK), aspartate aminotransferase (AST), alanine aminotransferase (ALT) and magnesium, prothrombin time (PT) and international normalized ratio (INR), partial thromboplastin time (PTT), arterial blood-gas analysis, a toxicology screen, and medication levels for commonly used antiseizure medications.

2. Assess Whether the Witnessed Event Is a Seizure

The differential diagnosis of GCSE includes so-called "psychogenic nonepileptic seizure" or "PNES-status" (which is conversion disorder with prolonged seizure semiology), multifocal myoclonus, malignant hyperthermia, rigors, and the misnamed entity "cerebellar fits" reflecting intermittent decerebrate rigidity (20–23). Rigors are common with fever, sepsis, and therapeutic hypothermia, now commonplace in neurological intensive care settings. Patients with malignant hyperthermia and brainstem or cerebellar pathology need specific interventions that have no relationship to seizure treatment. Patients with rigors often require muscle relaxants to prevent physical discomfort and rhabdomyolysis, sometimes including dantrolene, meperidine, and dexmedetomidine.

A convulsing patient can present a diagnostic challenge at the bedside. All of the imitators of convulsive seizures can sometimes coexist with seizures, substantially complicating clinical assessment. Clues that the patient is having a seizure

include (but are not limited to) an initial ictal cry; a clear tonic phase followed by a clonic phase; complete loss of consciousness during convulsions; synchronous, rapid, high-amplitude motor phenomena; true obtundation during and immediately following a generalized motor seizure; lateral tongue or cheek bites; urinary incontinence; and serious injuries sustained during the seizure. The term convulsion, although likely to eventually be removed from the lexicon of epileptology, currently connotes medium- or high-amplitude, clonic or rhythmic limb jerking; a seizure with typical tonic-clonic semiology; or diffuse, often robust flexion-contraction movements. Such movements should be distinguished from dystonia, ballism, chorea, and potentially volitional behavior. Tonic-clonic seizures have often been equated with convulsion, although convulsive seizures often fail to progress from the tonic to the clonic phase in an orderly two-step sequence, especially during SE. Either the tonic or clonic phase can be absent or prolonged, or recur in a complex sequence (24).

Semiologic clues favoring diagnosis of a purely psychogenic event include irregular, asynchronous, fluctuating motor manifestations; rapid side-to-side head turning; rolling in bed; arm-flailing; pelvic thrusting; forced eye closure; gaze aversion; ability to follow commands, attend, or speak during bilateral motor manifestations; and nearly immediate return to attentiveness after the event (25,26). Exceptions abound, especially with regard to frontal lobe seizures, and if there is uncertainty on physical exam, the examiner should assume, for purposes of emergency stabilization, that the patient is having seizures.

Decerebrate or decorticate posturing can be caused by seizures, but such posturing also can be confused with seizures. Posturing suggests increased pressure on deep CNS structures and should be immediately evaluated with neuroimaging. Rigors are tremors that are diffuse, rhythmic, typically low-amplitude, and non-evolving or complex. Rigors can be associated with an identifiable metabolic derangement, changes in core temperature, or medication toxicity. Multifocal myoclonus appears as scattered, shock-like jerks of limbs, trunk, or head. Myoclonus often is stimulus-induced.

EEG recordings can be critically important in distinguishing among these etiologies. Patients with a conversion

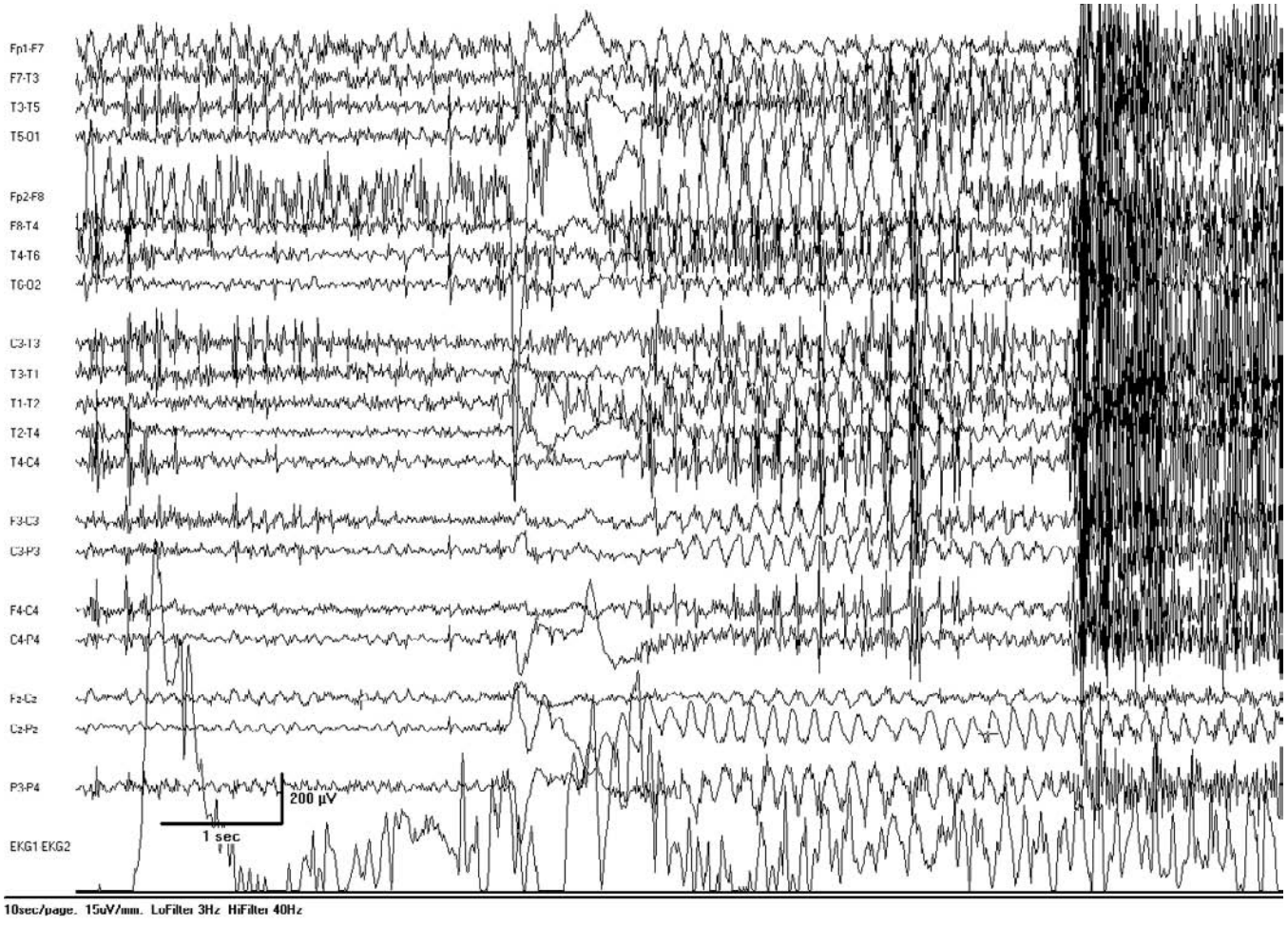

FIGURE 19-1. Example of "PNES-status." Rhythmic movements generate electromyographic artifacts that can mimic electrographic seizure. (This figure and all others were generated using a Nicolet digital EEG machine, the standard International 10–20 System of Electrode Placement, and software version 3.6).

disorder manifesting as convulsive episodes are at risk of iatrogenic injury, including complications of endotrachial intubation, exposure to coma-inducing antiseizure medications, prolonged hospital stays, and delays in treatment directed at the primary psychiatric illness. After exposure to coma-inducing medications, the EEG typically portrays a variety of nonspecific abnormalities, which further obscures the psychiatric etiology.

3. Initial Treatment of the Convulsing Patient

Although treatment may begin during the early phases of clinical assessment and intervention, the discussion of common treatment options for GCSE is presented at the end of this section.

4. Determine Type of Status Epilepticus

Initial assessment should distinguish among focal status, complex partial status, and generalized motor SE. If the patient has impaired mentation, EEG can serve as a useful tool in differentiating among ongoing complex partial seizures, nonconvulsive SE, postictal obtundation, and other causes of delirium or diffuse encephalopathy.

5. Determine Etiology

A clinician treating a patient with SE will determine etiology in two stages. Initial screens are done for those conditions that themselves require immediate treatment, including hypoglycemia, hypoxia, hyponatremia, hypocalcemia, hypomagnesemia, thyroid crises, antithyroid antibody–mediated Hashimoto disease, drug intoxication, and sepsis. Treatment should not be delayed while waiting for return of laboratory studies. A second stage of etiologic studies is performed after immediate motor seizure control. These studies usually include a detailed clinical history, physical examination, blood tests for less-urgent conditions such as renal or hepatic failure, brain imaging, CSF examination, and possibly even testing for mitochondrial or genetic conditions. As a practical issue, imaging a patient is difficult or impossible during tonic-clonic seizures, and therefore control of motor manifestations before imaging is encouraged.

EEG Patterns of GCSE

The EEG patterns of GCSE are diverse and often complicated by the presence of rhythmic muscle and movement artifact. A common EEG pattern of diffuse or generalized, evolving, rhythmic spiking is shown below.

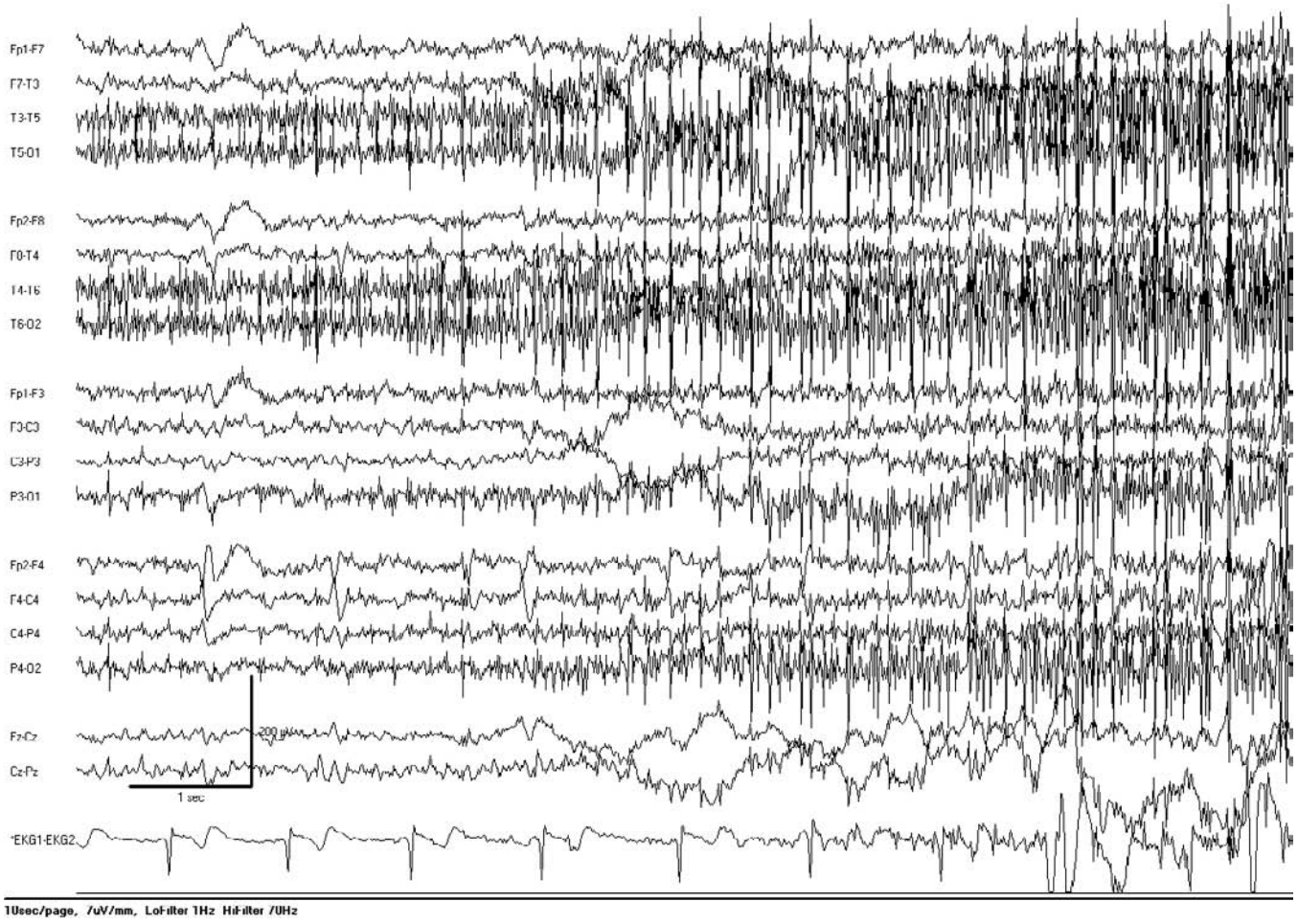

FIGURE 19-2. EEG of a patient with severe multifocal myoclonus.

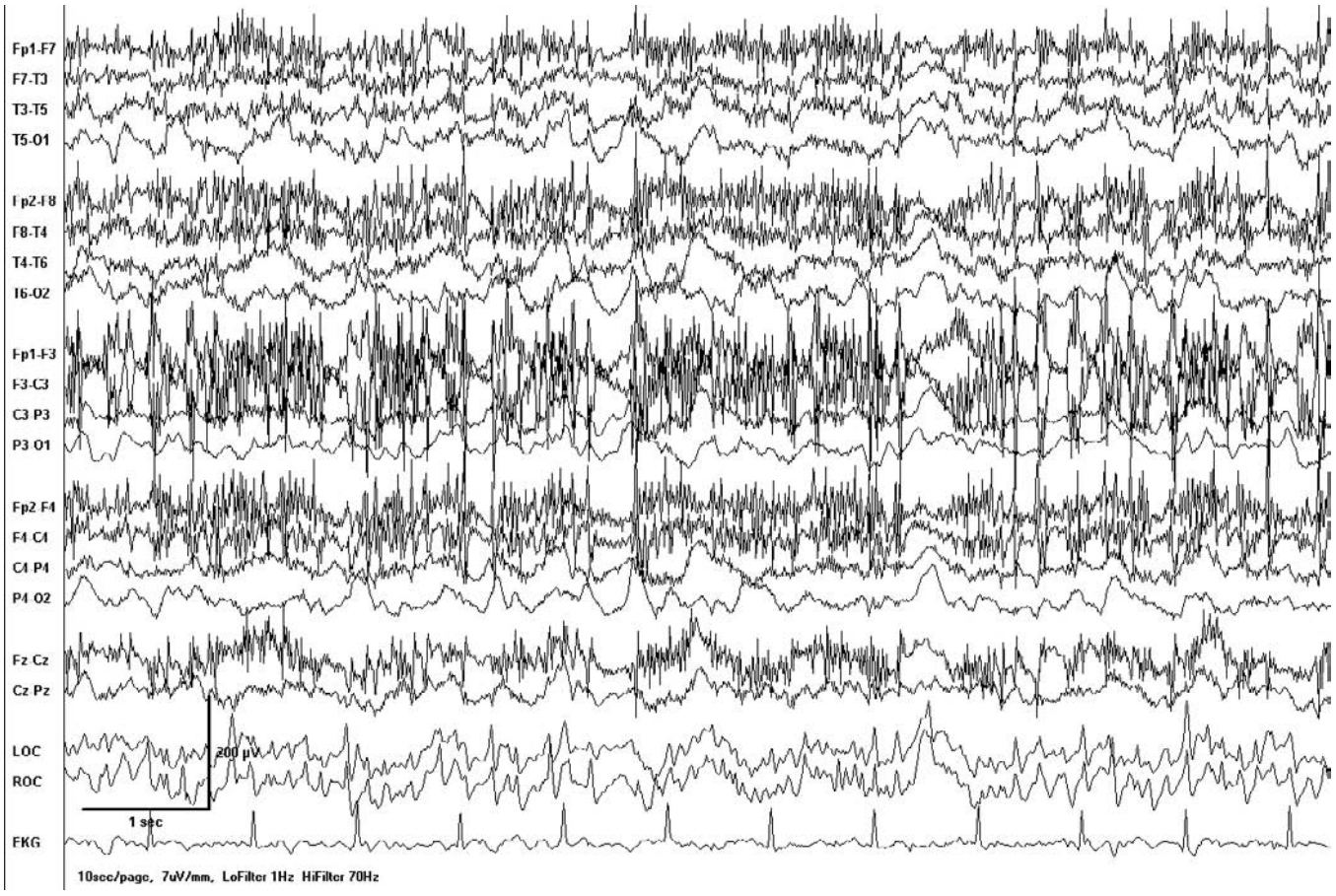

FIGURE 19-3. EEG of a patient with severe rigor without epileptiform activity.

Another common pattern is entrenched, diffuse rhythmic spiking, as seen below.

EEG Stages of SE and Patterns of Evolution

Most cases of GCSE begin either with partial seizures or partial SE (24). In early stages of SE, the EEG frequently discloses discrete electrographic seizures. The EEG then progresses to waxing and waning epileptiform activity with less-clear transitions between ictal and interictal periods. As SE continues, the ictal EEG rhythms become less obvious. Spikes become slower and less sharp, ictal rhythms become slow, and evolving, discrete seizures convert into more amorphous, blunted electrographic patterns. The example below is from a patient who was in presumed motor SE for days before EEG diagnosis. The morphological EEG criteria for diagnosing SE (and nonconvulsive SE) should be broadened as time into the illness progresses, since typical seizure morphology dissipates over time.

Tonic SE

The EEG of tonic SE is similar to that of isolated tonic seizures. During each seizure there is a rapid evolution of diffuse, low-voltage, fast-frequency activity, which is either generalized from onset or associated with rapid secondary-generalization. The EEG example below is from a patient who had up to 100 tonic seizures per day. Between motor seizures, he remained lethargic.

Subtle Motor SE

Overt GCSE can convert over minutes to hours to subtle motor SE (24). As brain energy stores are depleted (especially if brain hypoxia appears), ictal brain activity attenuates as well. Partial seizure control secondary to antiseizure therapies can also encourage the transition from overt GCSE to subtle motor SE. Subtle convulsive movements can be low-amplitude twitches or rhythmic movements of the eyes, face, jaw, lips, trunk or limbs (27). The figure below is from a patient who initially had overt, frequent, convulsive seizures (without intervening return to neurological baseline) and who, after days, developed intermittent rhythmic axial and neck tremor. EEG confirmed subtle convulsive SE. As subtle convulsive SE can be a transitional stage between GCSE and nonconvulsive SE (NCSE), the abatement of motor manifestations does not preclude the correct diagnosis of ongoing seizure.

Stimulus-Induced Subtle Convulsive SE

SIRPIDs (stimulus-induced rhythmic, periodic, or ictal discharges) can accompany motor SE (28). The two examples below are from a patient with encephalitis. The first example was recorded with the patient at rest; the second after vigorous, manual tactile stimulation. After stimulation, an evolving run of generalized epileptiform discharges appears. The clinical correlates were rhythmic eye movements and axial rhythmic jerking.

Before stimulation, the EEG discloses diffuse, polymorphic theta and delta. After robust tactile stimulation, rhythmic delta with embedded spikes appears:

The clinical significance of SIRPIDs is an area of active research. Clinical seizures induced by stimulation are treated with antiepileptic medications and minimization of stimulation. The optimal treatment for SIRPIDs visible only by EEG remains uncertain, but treatment is commonly attempted.

Treatment of the Convulsing Patient

Generalized convulsive status epilepticus should be treated using an orderly clinical protocol. Comparisons of several initial medication regimens favor intravenous lorazepam, unless contraindicated for individual cases (30). If seizures do not stop within minutes, a longer-acting antiseizure medication should be administered. Current parenteral options include fosphenytoin, intravenous phenytoin, phenobarbital, valproic acid, or levetiracetam, and "anesthetic" agents considered below. Clinical data on the use of levetiracetam and valproic acid for SE are limited, although preliminary information is encouraging (30). Cardiac and blood-pressure monitoring should accompany all pharmacologic interventions. If motor manifestations persist after benzodiazepines and an intravenous loading of a long-acting agent, intubation and continuous infusion of propofol, midazolam, or pentobarbital can be employed. Blood pressure support via pressor therapy should accompany the initiation of each of these agents. Significant complications, including hemodynamic insufficiency, metabolic disturbances, and prolonged coma, can result from such interventions, so continuous intravenous therapy should only be employed when such risks are justified. Other sources can be consulted for details of treating SE with propofol, midazolam, or pentobarbital, including efficacy and complications (12). The table below summarizes dosages of common medications used for convulsive status epilepticus in average-sized adults (31). Neuromuscular blockers mask behavioral manifestations of seizures, but do not eliminate risk for cerebral or pulmonary edema, cardiac arrhythmias, and potentially lethal complications of the seizures.

Fosphenytoin, valproic acid, and propofol all have safe upper limits for dose. Vigilant monitoring for the propofol "infusion" syndrome, with metabolic acidosis, rhabdomyolysis, hyperlipidemia, and myocardial failure, should accompany its use, especially with longer durations of infusion or in children. Barbiturates and benzodiazepines have no upper dosing boundary as long the patient's cardiovascular stability is maintained. However, it should be kept in mind that the half-life of pentobarbital increases with increasing duration of administration, and that with all general anesthetic agents the risk of complication increases with the duration of administration.

Nonpharmacologic treatments for refractory GCSE have included electroconvulsive therapy (ECT), vagus nerve stimulation (VNS), and urgent resective epilepsy surgery. Data regarding the first two options is anecdotal and should not currently be considered standard of care (32). Urgent epilepsy surgery is rarely used. It should be employed only on a case-by-case basis in a tertiary-care center by experienced epileptologists and epilepsy surgeons.

PARTIAL MOTOR SE

Background

Definition of Partial Motor SE

Partial motor SE can be operationally defined as:

1. A single partial motor seizure or cluster of partial seizures lasting long enough to cause, by virtue of the prolonged nature of the event, potential brain injury
2. A partial motor seizure that shows no signs of remitting once the usual seizure duration has been reached
3. A single partial motor seizure or cluster of seizures that appears to be making a transition from motor to nonmotor without clinical improvement in the patient's neurological status over minutes

As with other seizure types, 30 minutes of seizing or recurrent seizures for at least 30 minutes without intervening return of normal function can be taken as an operational definition of partial motor status. However, 10 minutes may actually be a more conservative criterion, because the vast majority of partial motor seizures last less than 10 minutes. *Partial SE with hemiconvulsion, rhythmic focal motor, or hemiclonic clinical correlates (without secondary generalization) is not associated with the same morbidity and mortality as GCSE, and its treatment should depend on the ictal functional status of the patient, the risk of generalization of the seizure, the underlying etiology, and the focality of the electrographic epileptiform pattern.* For example, patients with epilepsia partialis continua (EPC) should not typically be exposed to artificial ventilation or coma-inducing antiseizure medications.

Etiology and Epidemiology of Partial SE

The epidemiology and etiology of partial, convulsive SE are similar to those of GCSE. Partial SE often converts to

TABLE 19-2. COMMON ANTISEIZURE MEDICATIONS USED TO TREAT GCSE

Agent	Loading Dose (IV)	Maintenance Dose
Lorazepam	2–8 mg	None
Fosphenytoin	20 mg (phenytoin equivalents)/kg	Approximately 100 mg q 8 hrs or enough to achieve serum level of 20–30 or free phe nytoin level of 2–3 mcg/mL
Depacon™	25 mg/kg	Approximately 250–1000 mg q 8 hrs or enough to achieve serum level of 75–125 mg/L
Phenobarbital	15–20 mg/kg	2–8 mg/kg/day IV (titrate to EEG)
Propofol	Initial bolus of 1 mg/kg	1–15 mg/kg/hr (titrate to EEG)
Midazolam	0.2 mg/kg	0.05 to 1–4 mg/kg/hr (titrate to EEG)
Pentobarbital	5–10 mg/kg	0.5–5 mg/kg/hr (titrate to EEG)

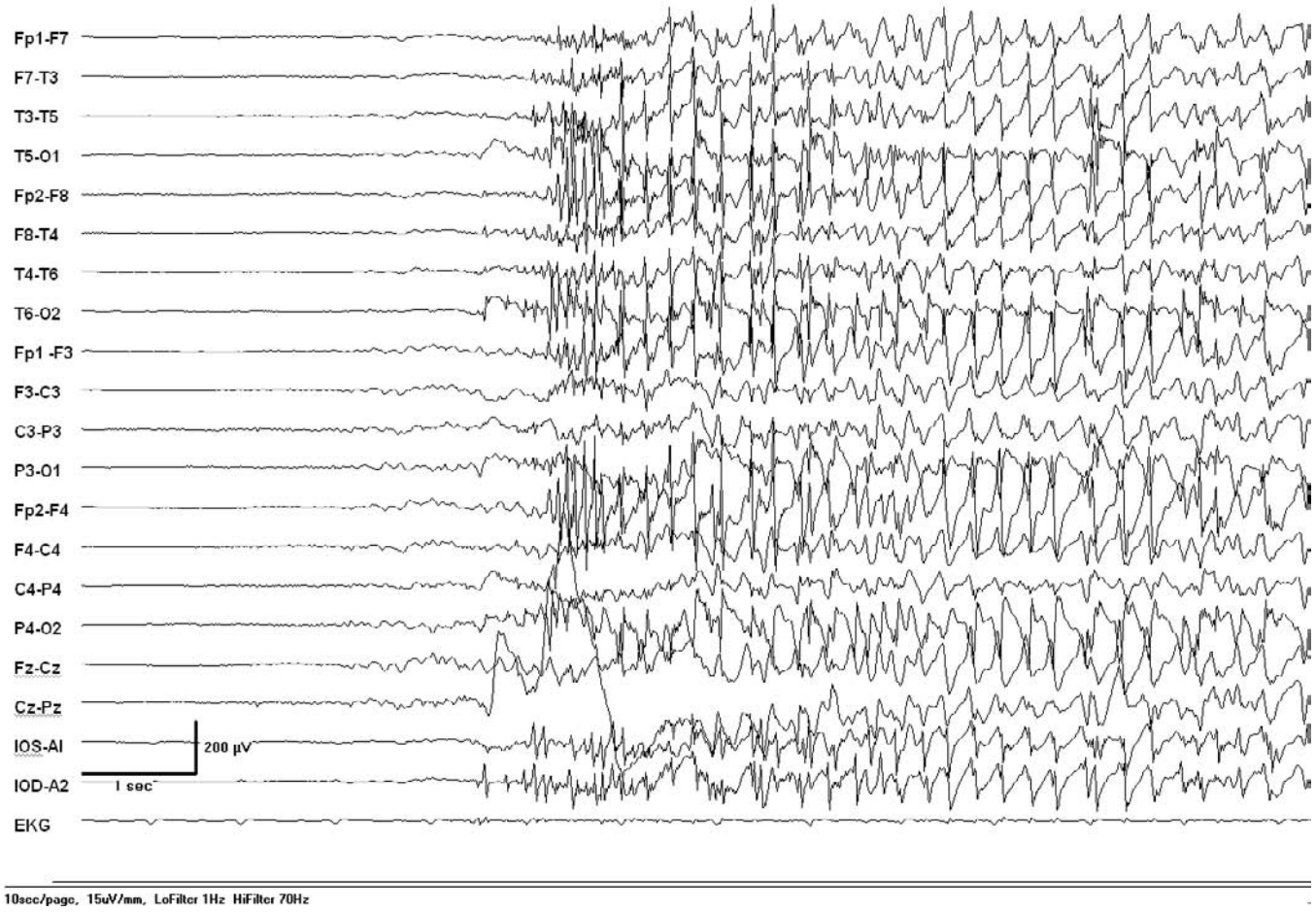

FIGURE 19-4. Generalized, evolving, rhythmic spiking.

generalized motor SE, and vice-versa. Most cases of GCSE actually start as partial-onset seizures, given the usual causes in the form of lateralized brain lesions or injuries.

A quintessential form of focal motor SE is epilepsia partialis continua (EPC or Kojewnikoff syndrome). Initially described 1895, it later became associated with Rasmussen encephalitis or Rasmussen syndrome (33). More often seen in children, Rasmussen syndrome does occur in adults approximately 10% of the time (34). Invariant features include intractable localization-related epilepsy and progressive hemiparesis. Etiology is unknown, and there may be several different causes. The common form of the disease is presumably autoimmune, and there have been associations with autoantibodies against the ionotropic glutamate receptor Glu-R3, but associations with other epitopes are also recognized, including, recently, the voltage-gated potassium channel (35).

Differential Diagnosis of Partial Motor SE

The differential diagnosis of partial convulsive SE includes partial seizures, subtle generalized convulsive SE in which the motor manifestations have become lateralized (for example as a result of hemiparesis), dystonia, chorea, tics, hemiballismus, lateralized brainstem myoclonus, segmental myoclonus, focal jerking or neuromyotonia from peripheral nerve hyperexcitability states, and conversion disorder (36).

The motor manifestations of partial motor SE range from violent hemiclonic jerking to subtle twitching. The most focal forms may involve just a small portion of a limb, of the trunk, or of the face. The clinical semiology of partial motor SE is truly varied, and there is no substitute for clinical experience in assessing afflicted patients. Other clinical correlates of partial motor SE include nystagmus, palatal tremor, and asterixis (or negative myoclonus) (37). Patients in complex partial status epilepticus, in addition to having alteration in cognition, may display automatisms, hyperorality, lip smacking, picking, and other typical behaviors associated with discrete complex partial or temporal lobe seizures. Focal seizures located occipitally often induce abnormal eye movements.

EEG Features of Partial Motor SE

A variety of scalp EEG patterns may be seen in patients with partial motor SE. The following examples display some of the commonly seen EEG patterns. Below is an EEG from a patient with intermittent focal and hemiclonic jerking. Left-sided, delta-range, rhythmic spiking is present. Right-sided EMG artifact is also captured.

Tonic SE can present with partial-onset seizures or tonic seizures with lateralized semiology. The following example is from a patient with tonic SE who had very asymmetric posturing during seizures. It reveals low-voltage fast-frequency activity in the right paracentral region that evolves to slower frequencies and propagates spatially over seconds.

Hemiclonic SE

Patients with lateralized brain abnormalities often will have prolonged or continuous partial seizures with contralateral, hemiclonic jerking. The example below is from a 29-year-old with Rasmussen syndrome. Rhythmic and periodic spiking can be seen near the vertex and leftward. The patient experienced focal and hemiclonic seizures lasting hours to days. These rarely generalized.

The preceding example also represents a form of periodic lateralized epileptiform discharges (PLEDs). PLEDs often accompany partial motor SE. Some experts disagree whether PLEDs should be considered an interictal, ictal, or transitional pattern (38). In reality, PLEDs can occur in each of these contexts. Some suggest subcategorization of PLEDs depending upon the nature of the EEG between the discharges (39). Chatrian and colleagues were among the first to characterize PLEDs (40). In terms of strictly defining their electrographic features, Daly recommended allowing no more than 20% variation in periodicity (41). Discharges with more than 20% variability have been termed "pseudoperiodic." Discharges with even more variability have carried the awkward designation "pseudo-pseudoperiodic." Periodic epileptiform discharges (PEDs) present as several variants, including bilateral independent periodic lateralized epileptiform discharges (BIPLEDs) and generalized periodic epileptiform discharges (GPEDs). No controlled study exists to guide us in the importance of eradicating PLEDs, so most clinicians rely upon the clinical context. Vigorous treatment to reduce or eradicate PLEDs is only supported in the case of intense or frequent clinical seizures, plausible correlation of the location of the PLEDs with clinical symptoms, and association of the PLEDs with other more clearly ictal epileptiform activity. PLEDs that occur in an otherwise stable patient, without an associated deficit, may not always require aggressive treatment. At the very least, periodic epileptiform activity increases the risk of clinical seizures, and thus antiseizure prophylaxis is often indicated.

The example below is from another patient with hemiclonic jerking and PLEDs. Left paracentral spikes and sharp waves are present.

Periodic discharges can coexist with discrete temporally evolving or spatially propagating electrographic seizures. The examples below are recordings of a patient in focal motor SE. His baseline EEG reveals left posterior quadrant PLEDs, correlated at baseline with subtle focal motor twitching of the right face, arm, and leg and mild motor aphasia. Periods of clear global aphasia were marked on the EEG by loss of PLEDs and evolving focal runs of rhythmic theta and delta in the same region as his periodic discharges.

The tracing above is from the patient at baseline revealing static PLEDs. The tracing below is from a time when the patient

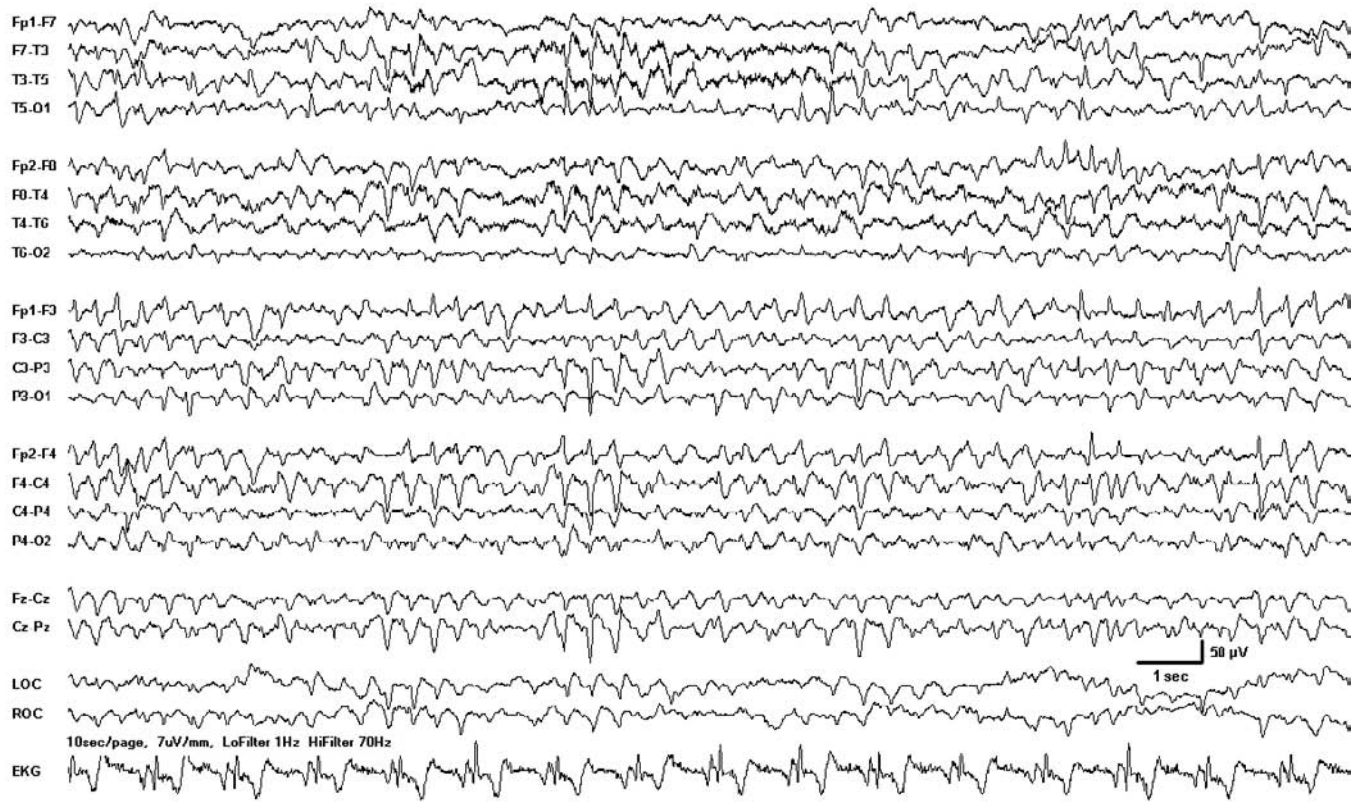

FIGURE 19-5. Static, diffuse, rhythmic spiking.

was aphasic. An evolving run of rhythmic theta and delta with embedded sharp waves is present. This electrographic seizure lasted approximately 60 seconds. Other frequent stereotyped seizures were captured and these confirmed the patient's ictal language deficits. Thus, the loss of static periodic epileptiform discharges may herald the onset of a discrete seizure.

Very Focal Motor Manifestations and Focal EEG Patterns

Despite the utility of EEG, there remains the possibility that an ictal rhythm will appear in only one electrode or can escape the resolution of scalp EEG entirely. The amount of cortex involved in a seizure or epileptiform discharge needed to generate a pathological change on scalp EEG ranges from 6 to 20 cubic centimeters (42,43). A normal EEG with very focal motor movements does not rule out a focal seizure, but merely fails to identify such a seizure electrographically. Most clinicians regard epileptiform activity confined to a single electrode as potential artifact, given that there is no visual confirmation of a plausible "cerebral field." Despite this, rare instances occur during which a very focal ictal rhythm can be recorded by only a single electrode. Most often this situation arises as a result of facilitated volume conduction to the scalp surface caused by either (a) a skull defect (in which case a breech rhythm can also be seen), or (b) neonatal recordings (in which highly focal seizures combine with the reduced resistance of the neonatal skull). The example below is from an adult patient with unrelenting focal frontal lobe seizures who experienced ictal, rightward conjugate eye deviation and head turning. It is likely that the frontal eye fields were involved in the seizures. The capture of the electrographic seizure near F3 was likely aided by a distant prior craniotomy in the same region.

When epileptiform activity appears in only one electrode, additional electrodes can be added in the region of interest to exclude the possibility of artifact.

On a final note, although epileptiform activity in patients with partial motor SE is virtually always contralateral to the side of clinical motor change, there are rare exceptions. Patient with lesions very close to the midline can have ipsilateral EEG and motor phenomena (44).

Clinical Management of Patients with Partial Motor SE

Most patients with partial seizures protect their airways and do not require endotrachial intubation, but this is not true for all. Initial assessment should still include evaluation of the airway, breathing, and circulation, with attention to measures required to avoid aspiration pneumonia and injury. The same medications effective for partial seizures are potentially effective for partial SE. Phenytoin, fosphenytoin, phenobarbital, lorazepam, diazepam, midazolam, valproic acid, and leveti-

racetam can be administered intravenously. There is a natural reluctance to use anesthetic agents to stop partial motor status in awake, alert patients, but it may be considered if the motor seizures are very severe. In less severe cases of partial motor status, non–coma-inducing antiseizure medications can be employed. On occasion, oral administration suffices; gabapentin, pregabalin, topirimate, zonisamide, and less commonly used seizure medications are candidate therapies. If medications are administered via a feeding tube, the clinician should be aware of potential poor absorption in the presence of ileus or medication adherence to the feeding tube itself.

MYOCLONIC SE

Background

A myoclonic jerk is a rapid shock-like movement. Myoclonus can be generated cortically, subcortically, from brainstem structures, from the spinal cord, or even peripherally (45). When myoclonus occurs from an abnormal cortical, hypersynchronous neuronal population discharge, it is a myoclonic seizure. Subcortical, palatal, and spinal segmental myoclonus usually is categorized as a movement disorder. The dichotomy between seizure and nonseizure, based on caudal distance from the cortex and on myoclonus with or without scalp EEG correlate, is somewhat artificial. There may be a spectrum between obvious cortical myoclonic seizure and other forms of subcortical myoclonus in terms of how well each type conforms to our traditional notion of seizure.

Intermittent myoclonic seizures can be a component of various idiopathic or symptomatic generalized epilepsy syndromes, or can be an acute symptomatic response to a major central nervous system insult. Myoclonic SE, or frequent, sustained, or unrelenting myoclonus, can occur in patients with pre-existing myoclonic epilepsy, or can accompany encephalitis, neurodegenerative and spongiform encephalopathies, or diffuse hypoxic encephalopathy, most commonly after cardiac arrest (46). After severe, diffuse ischemic brain injury, treatments are directed at seizure control if prognosis is fair, or at supportive care if prognosis is poor.

Myoclonus is a symptom. It can be distinguished from asterixis, in which muscles show sudden loss of tone (sometimes called "negative myoclonus"), tremor, tics, and normal hypnic jerks. Myoclonic SE is a descriptor for frequent, unrelenting myoclonic seizures. As there is overlap between causes of myoclonic SE and other forms of motor SE, a single patient can have myoclonic seizures in addition to other types of SE.

EEG Patterns of Myoclonic SE

A typical EEG pattern of generalized myoclonic SE is generalized spikes with subsequent slow-waves, usually periodic (as seen in generalized periodic epileptiform discharges or GPEDs), and often with superimposed electromyographic artifact during each myoclonic jerk. The example below is from a patient recovering from cardiac arrest and diffuse hypoxic-ischemic encephalopathy.

As the origin of prolonged generalized myoclonus can be subcortical or even spinal, it need not have a cerebral scalp EEG correlate. The EEG example below is from a patient with idiopathic encephalitis who had violent, stimulus-induced myoclonus that did not have an epileptiform scalp EEG correlate, although the diagnosis was that of myoclonic seizures. The myoclonic electromyographic artifact is evident, although epileptiform discharges are obscured.

Lack of an EEG epileptiform scalp correlate to myoclonic events does not exclude myoclonic seizures. If the patient's primary neurological problem is located cortically and myoclonic seizures seem plausible, treatment directed at cortical myoclonic seizures can be initiated. Typical agents directed at myoclonic seizures include valproate, levetiracetam, benzodiazepines, and (if given enterally) zonisamide and topiramate.

Focal Myoclonic SE

When focal epileptiform discharges are associated with time-locked, clinical myoclonus, each event should be interpreted as a myoclonic seizure. The example below is from an awake, interactive patient with pseudoperiodic, focal vertex epileptiform discharges who often had axial and lateralized myoclonic jerks time-locked with each discharge. After treatment with therapies targeted to myoclonic seizures (valproic acid, clonazepam, and levetiracetam), his EEG improved and myoclonus abated.

Techniques for Proper EEG Interpretation of Myoclonus

When muscle artifacts on the EEG preclude clear interpretation of cerebral potentials, two main techniques can help to clarify the relationship between clinical jerks and EEG deflections. If the cerebral potentials cannot be discriminated from nearly simultaneous electromyographic artifact, and the patient is artificially ventilated, a short-acting neuromuscular blockade can be used to abolish muscle activity.

The examples below are from a patient with diffuse hypoxemic brain injury from cardiac arrest. On examination, irregular limb-jerks raised the possibility of myoclonic SE. The initial EEG was not interpretable due to severe muscle artifact. After administration of cis-atracurium (neuromuscular blockade), there is a clean cerebral recording and generalized epileptiform activity is revealed.

The figure above is an EEG of a patient with diffuse multifocal myoclonus; the EEG is difficult to interpret because of severe muscle artifact.

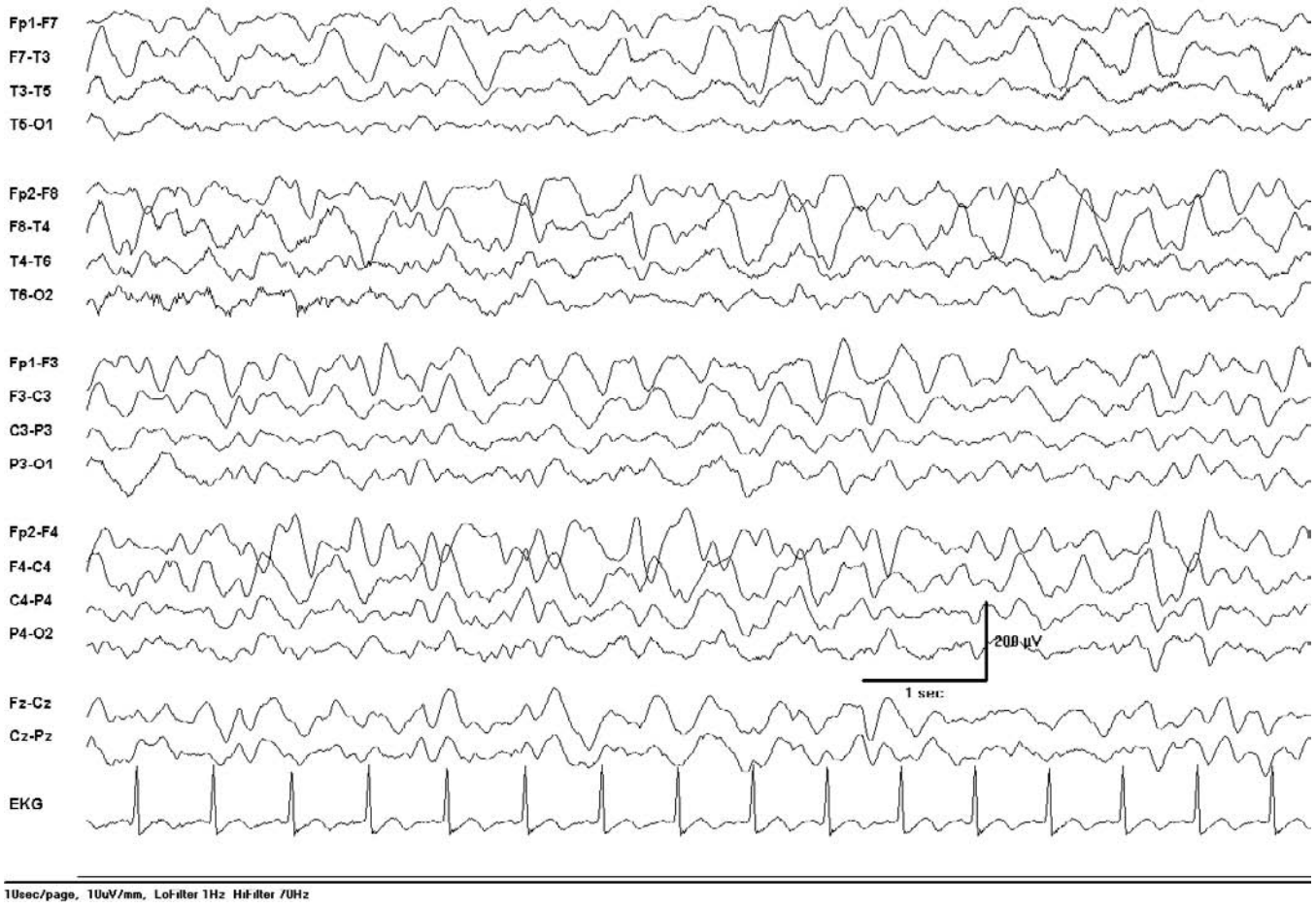

FIGURE 19-6. Blunted, slowed, generalized, rhythmic epileptiform activity.

The figure above is the same patient's EEG one minute after administration of a short-acting neuromuscular blocker (cis-atracurium); there are generalized periodic epileptiform discharges.

When a myoclonic electromyographic artifact obscures cerebral EEG potentials, another available technique is "back-averaging" several captured EEG potentials and correlating their temporal relationship with peripheral movements (47). Most current EEG systems will allow add-in software to perform such analysis.

SUMMARY

Convulsive status epilepticus is a medical emergency affecting the brain and other organ systems. Although generalized convulsive status epilepticus may be obvious at the bedside, there remains a differential diagnosis. Motor manifestations of status epilepticus may become subtle, and as generalized convulsive status epilepticus may quickly transition to nonconvulsive status epilepticus, EEG is a vital diagnostic tool even in the early phase of the illness.

Convulsions rarely remain generalized for extended periods of time. Persisting generalized convulsions often transform into more lateralized or focal motor patterns. Although prolonged partial motor seizures do not carry the same morbidity as GCSE, the mechanisms by which seizures become self-perpetuating are likely similar, and intensive management is required. EEG is an essential tool for determining the amount of cortical involvement in partial motor seizures and for monitoring response to therapy, even after overt motor manifestations have abated.

Myoclonic status epilepticus shares some etiological, clinical, and EEG features with GCSE. Partial motor SE and myoclonic SE may accompany other forms of SE. When there is uncertainty regarding the anatomic origin of myoclonus, scalp EEG or back-averaging may disclose the answer. Discriminating among the various forms of myoclonus has important diagnostic and therapeutic ramifications.

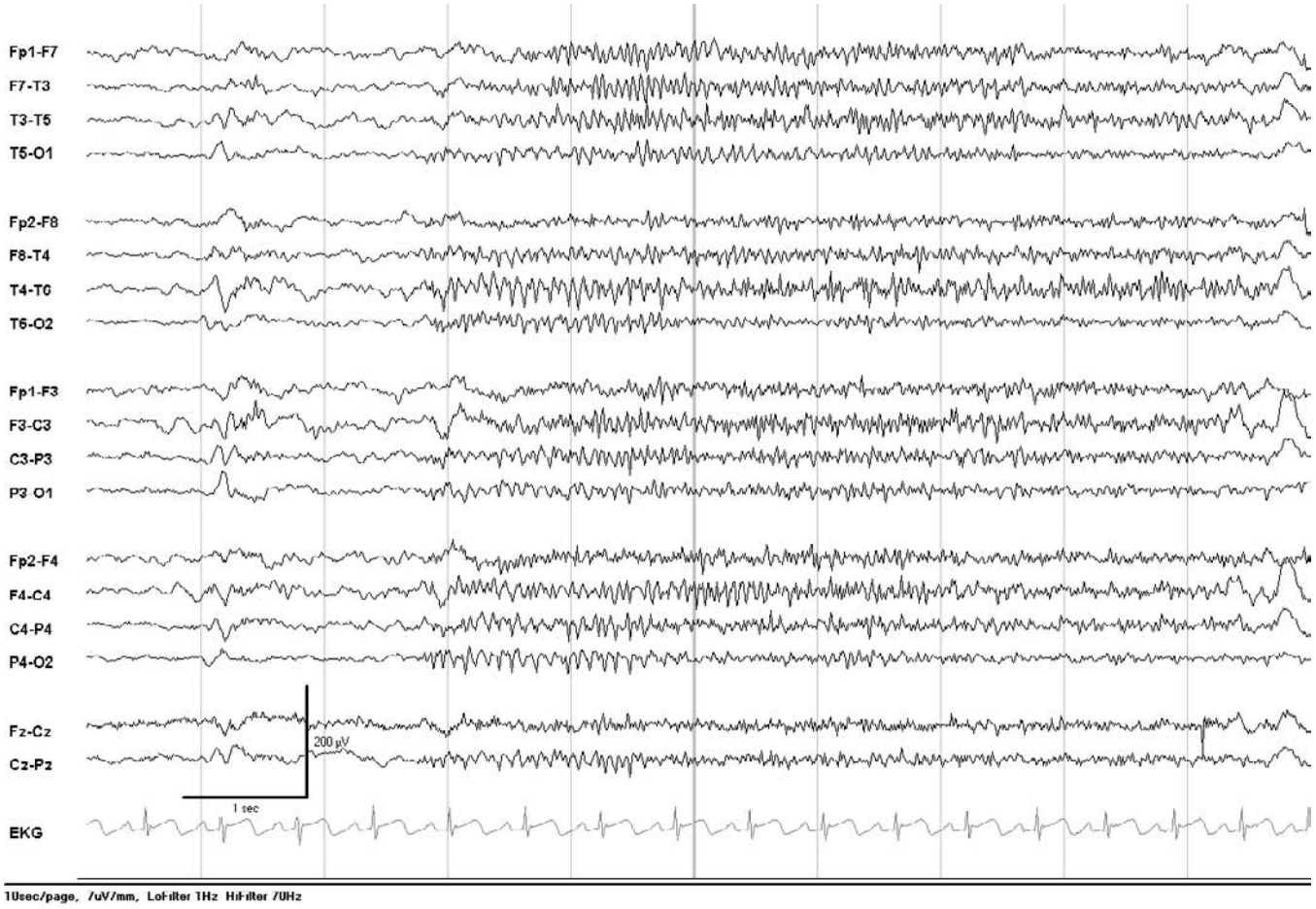

FIGURE 19-7. Generalized-onset tonic seizure.

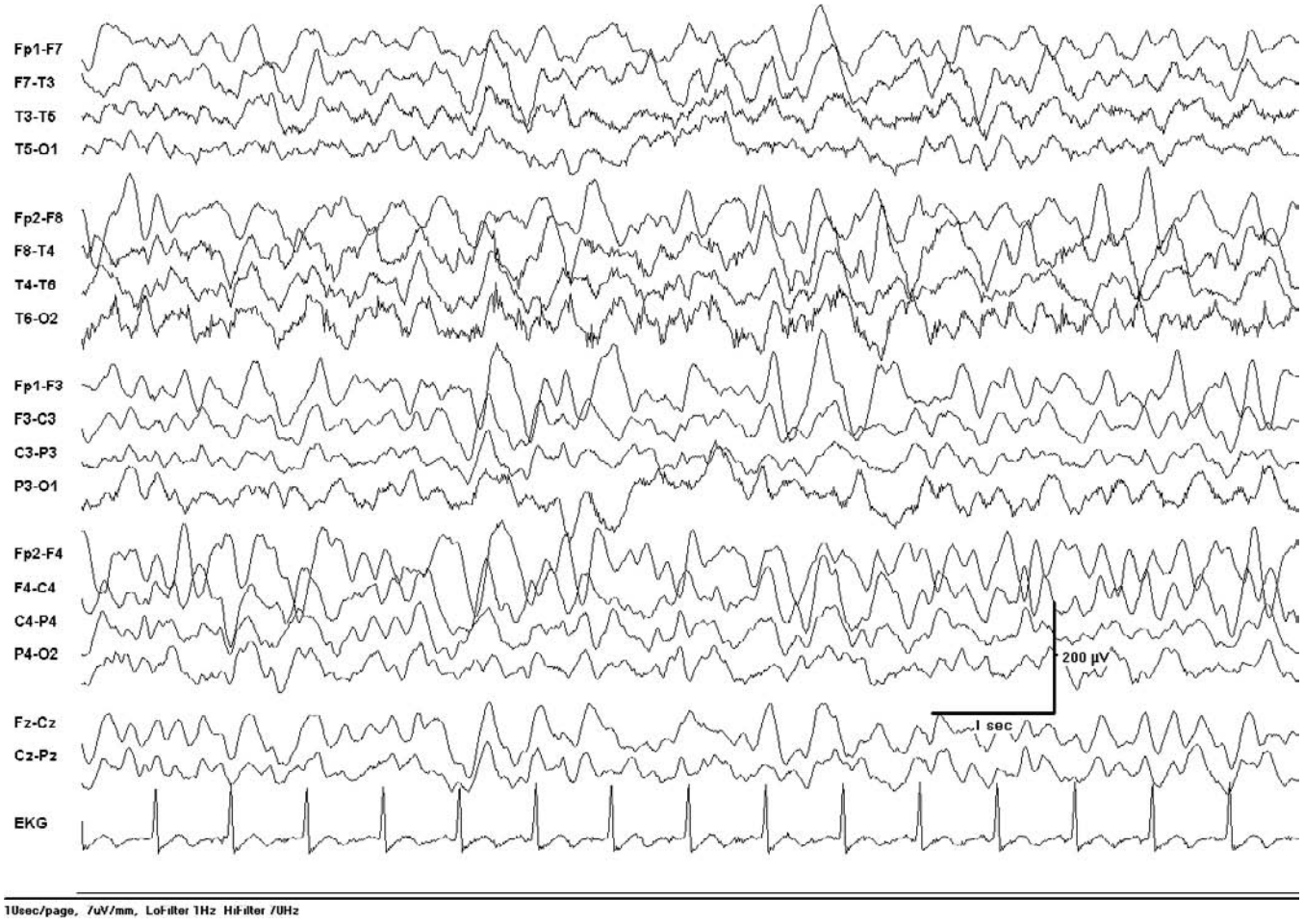

FIGURE19-8. Subtle convulsive SE.

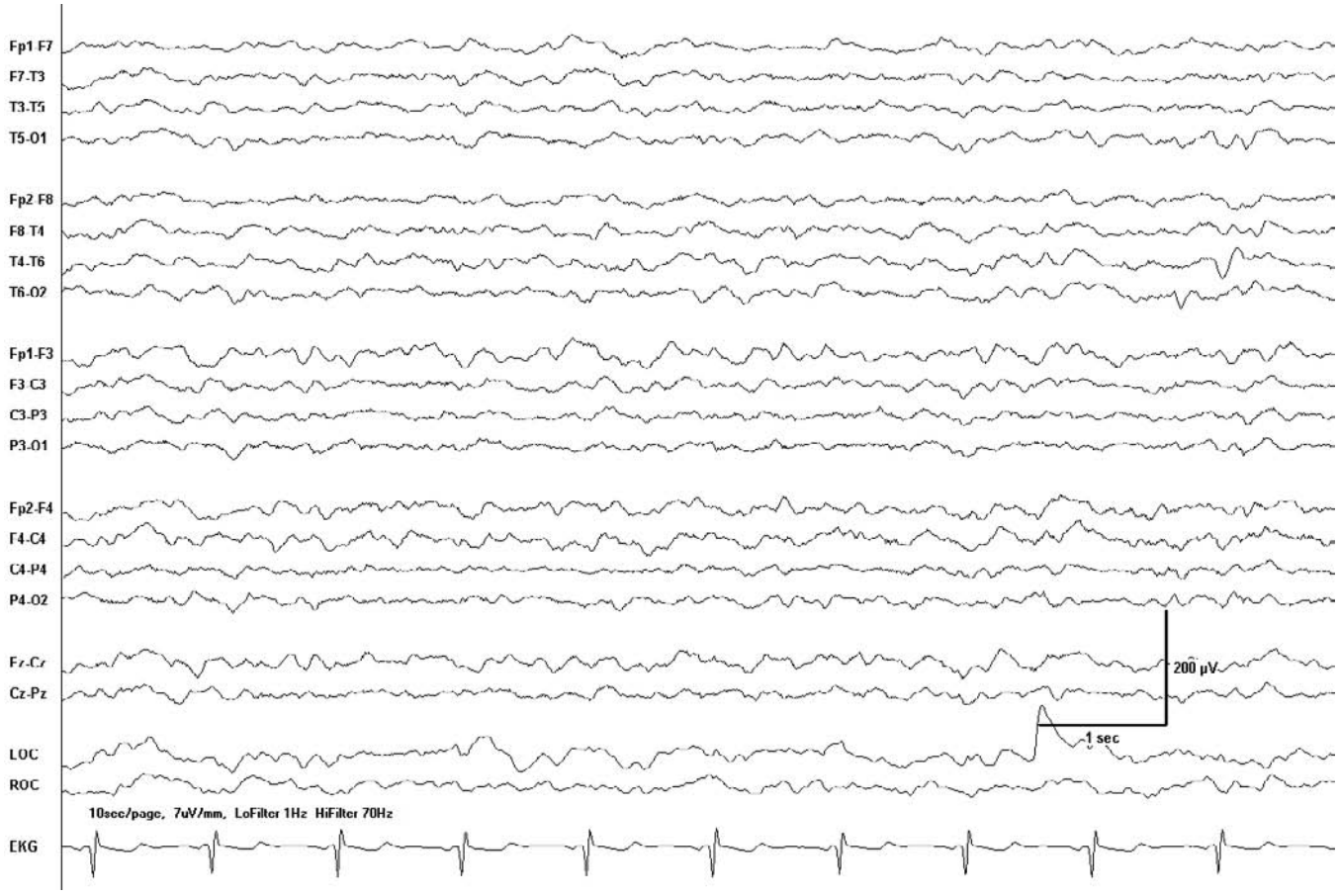

FIGURE 19-9. EEG before Stimulation in a Patient Prone to SIRPIDs.

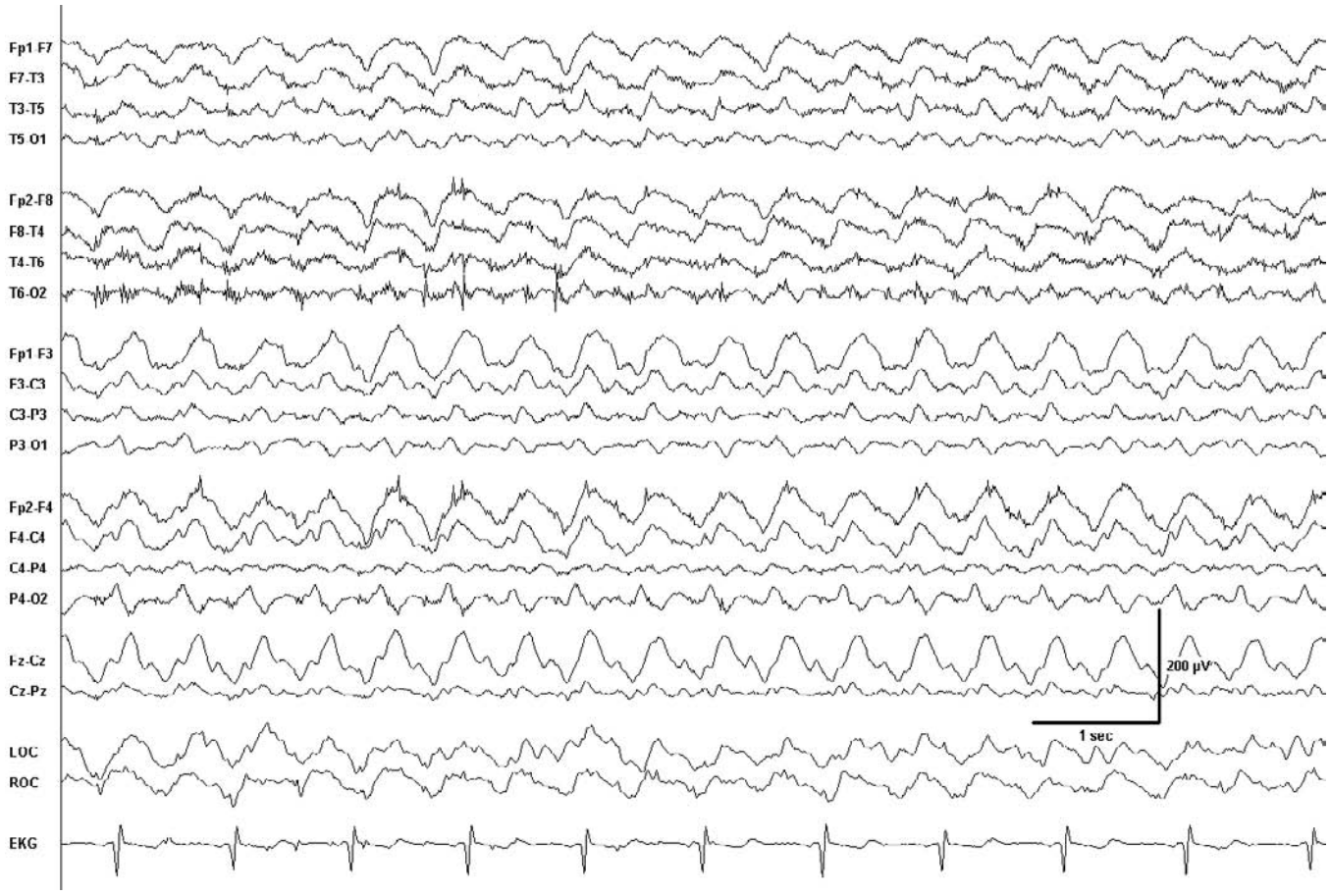

FIGURE 19-10. EEG after stimulation in a patient prone to SIRPIDs (7 mV/mm, low filter 1 Hz, high filter 70 Hz).

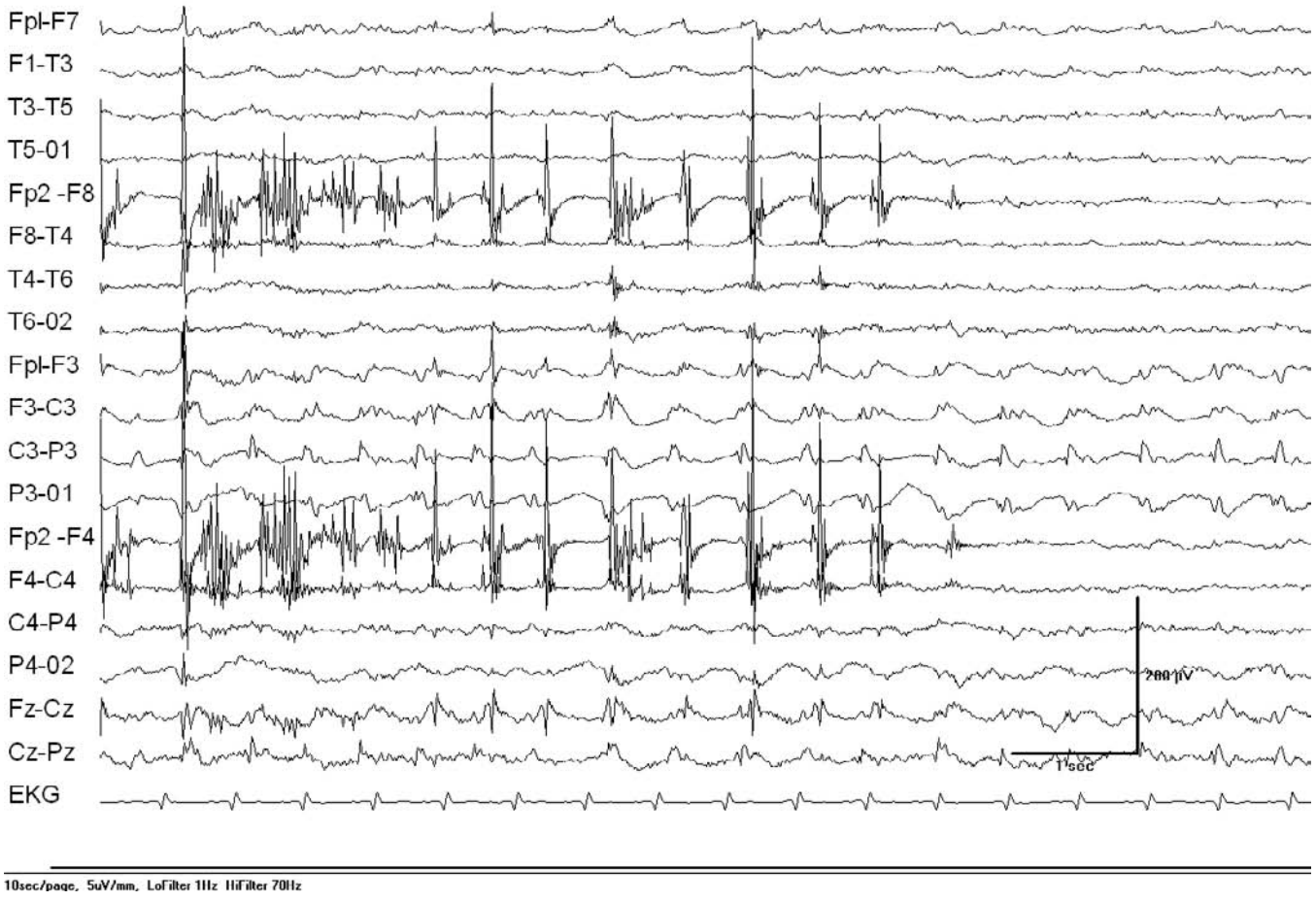

FIGURE 19-11. Lateralized rhythmic spiking.

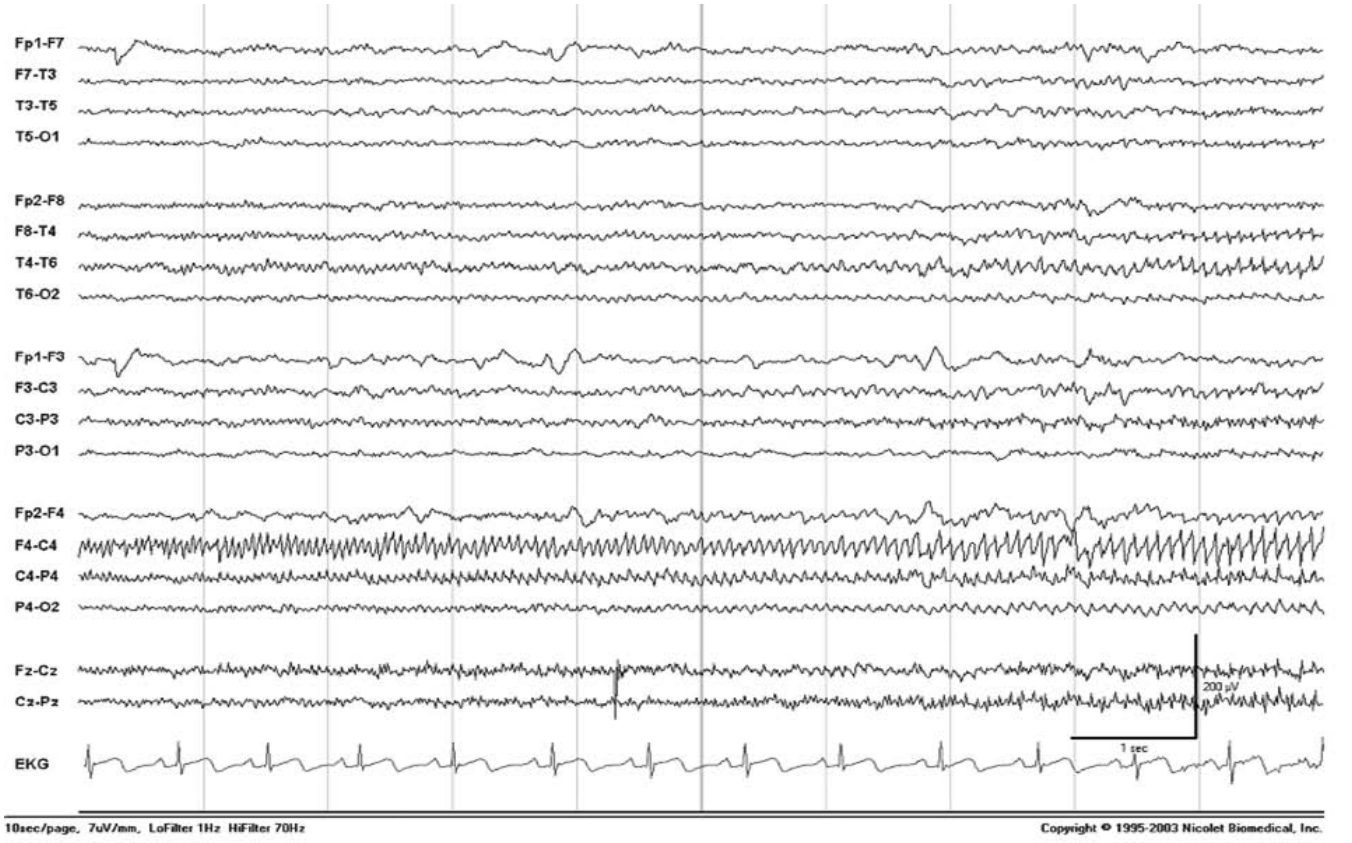

FIGURE 19-12. Partial-onset tonic seizure.

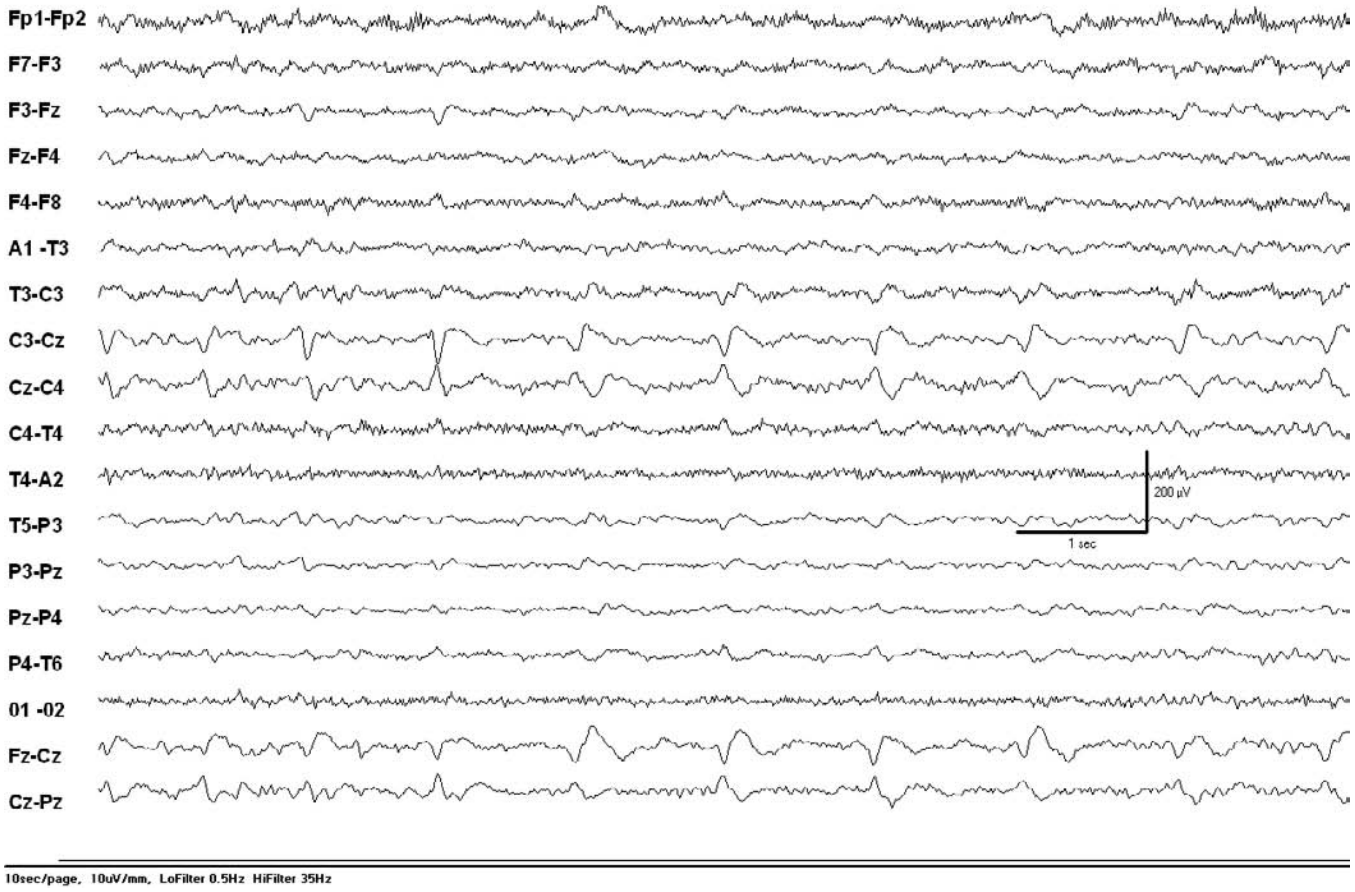

FIGURE 19-13. Focal periodic discharges associated with hemiclonic jerking.

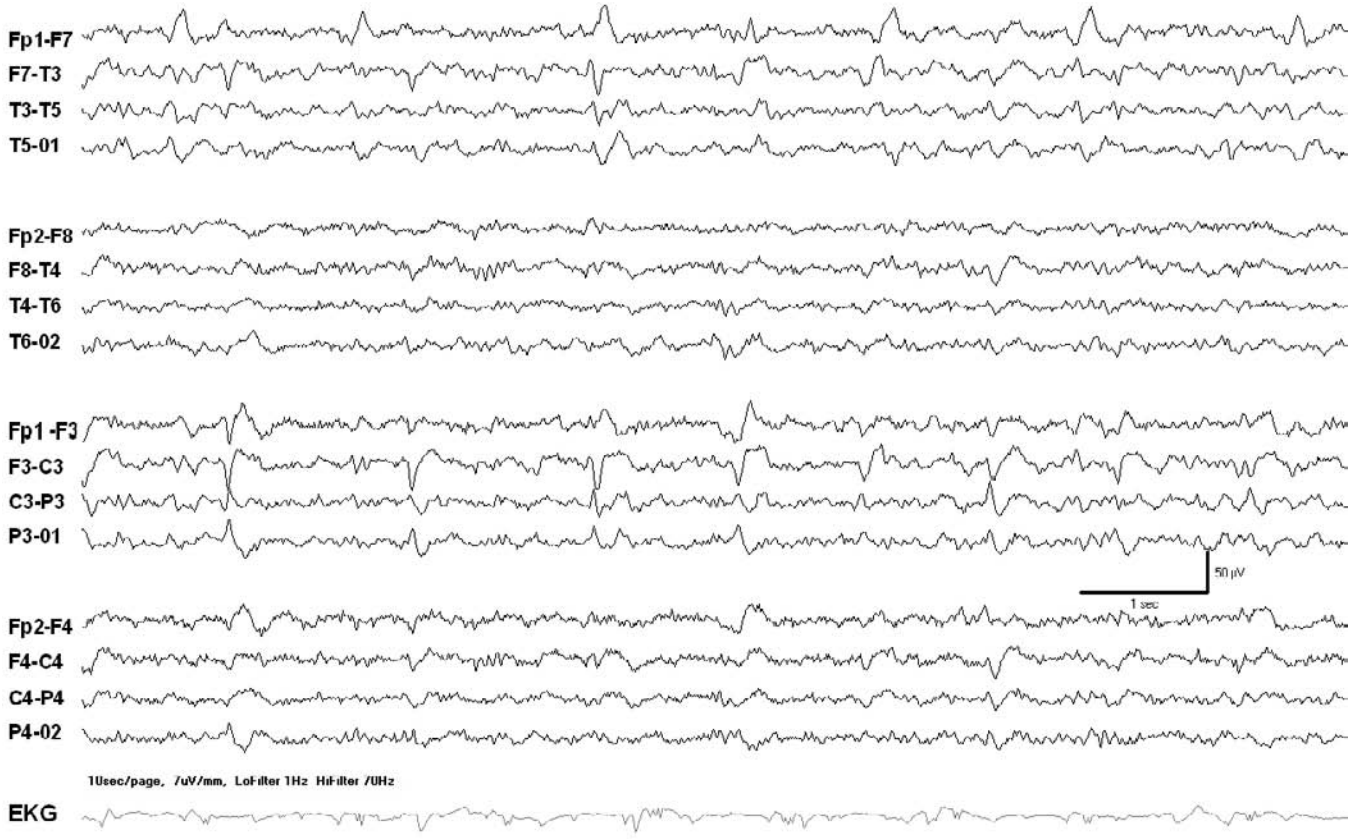

FIGURE 19-14. Another example of focal periodic discharges associated with clonic jerking.

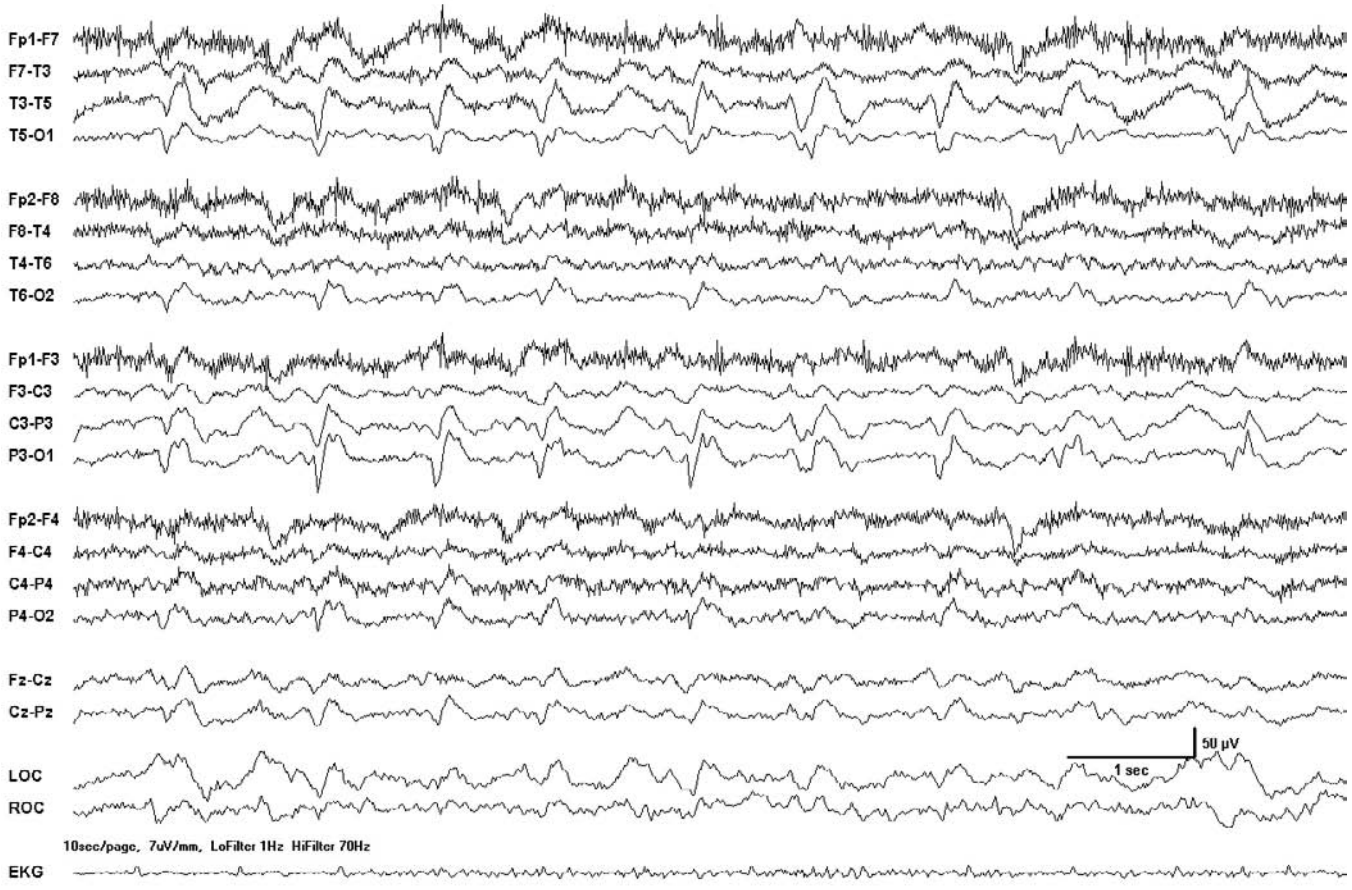

FIGURE 19-15. Interictal PLEDs.

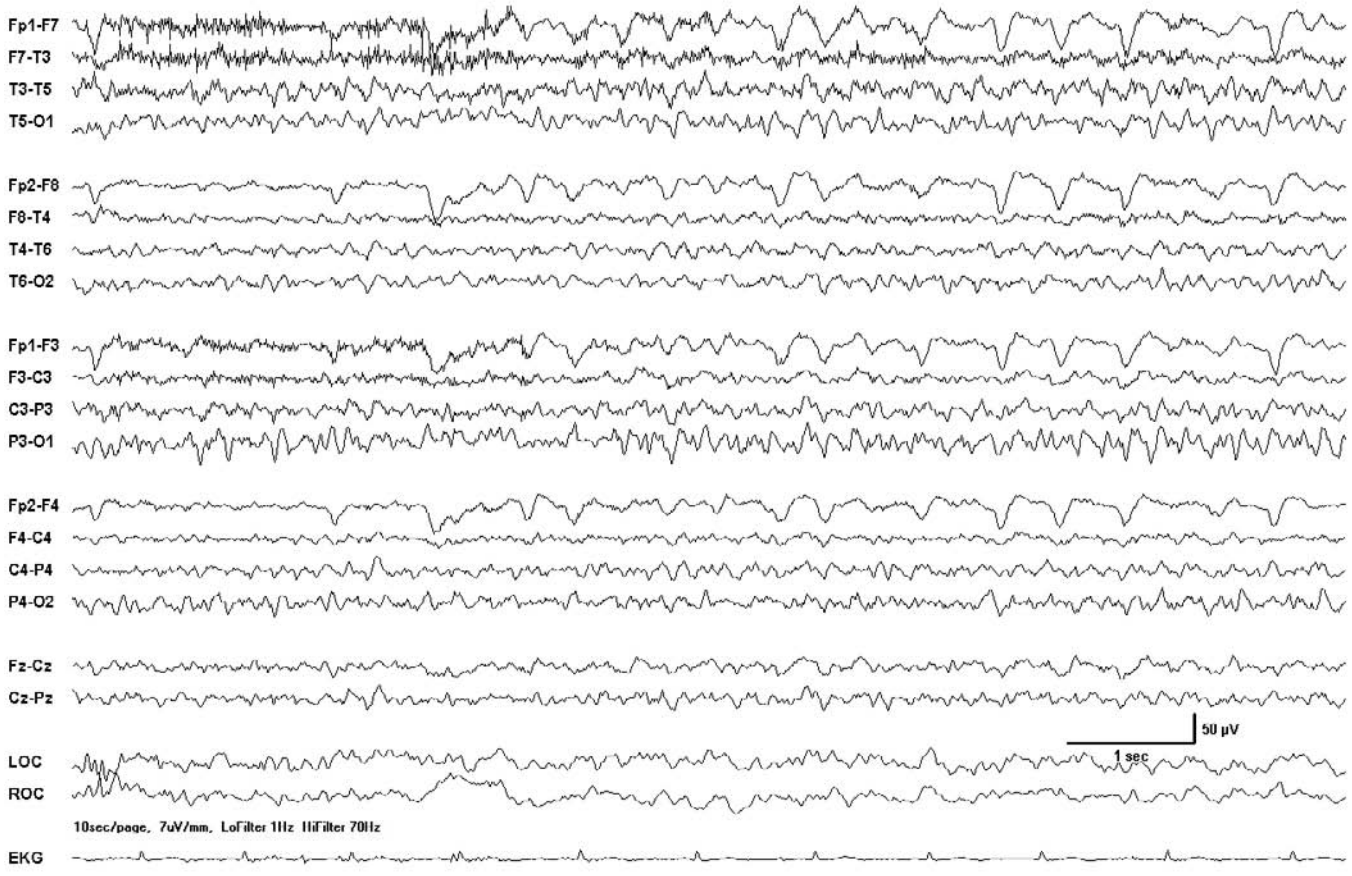

FIGURE 19-16. Loss of interictal PLEDs and the onset of a focal electrographic seizure in the left posterior quadrant in the same patient as above.

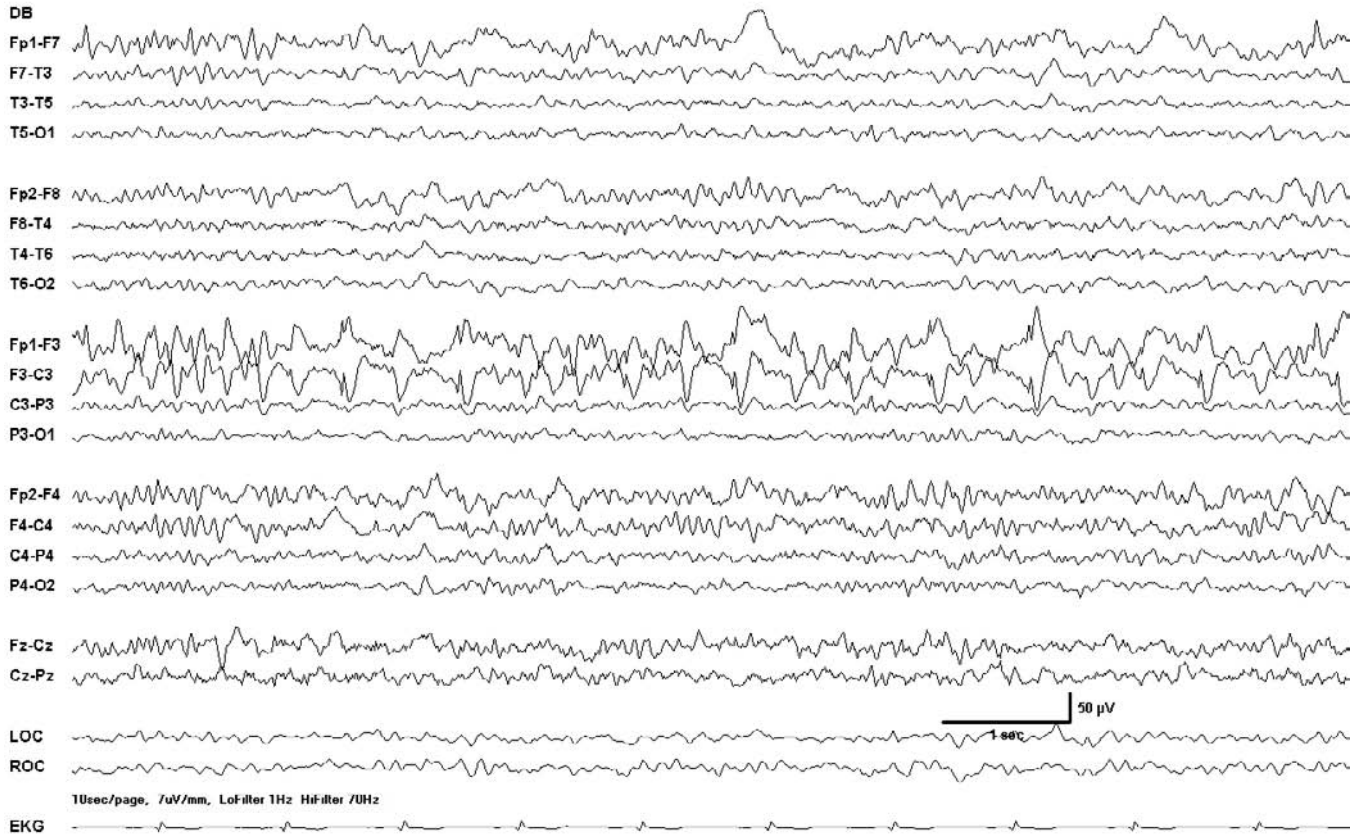

FIGURE 19-17. Irregular, evolving epileptiform activity limited to the region around F3.

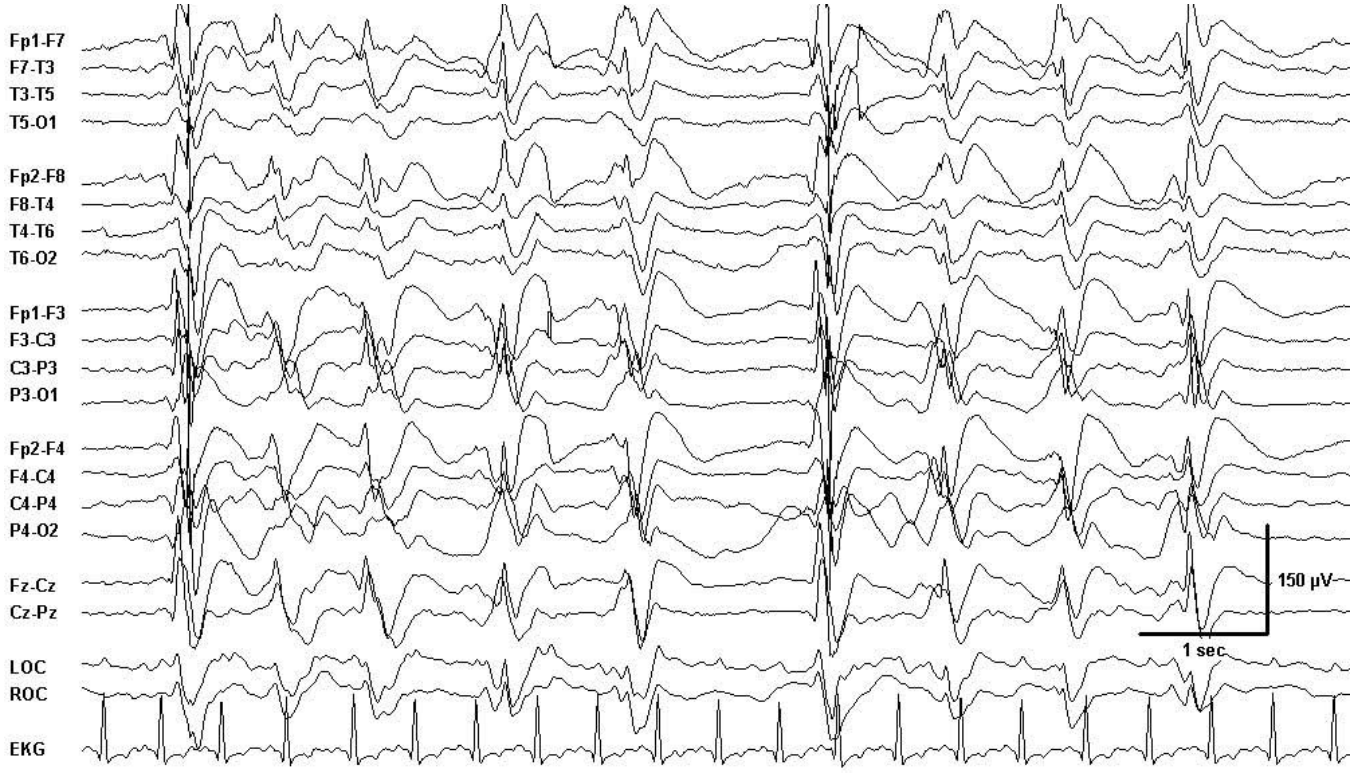

FIGURE 19-18. Generalized, pseudoperiodic spike-wave discharges in a patient with myoclonic SE.

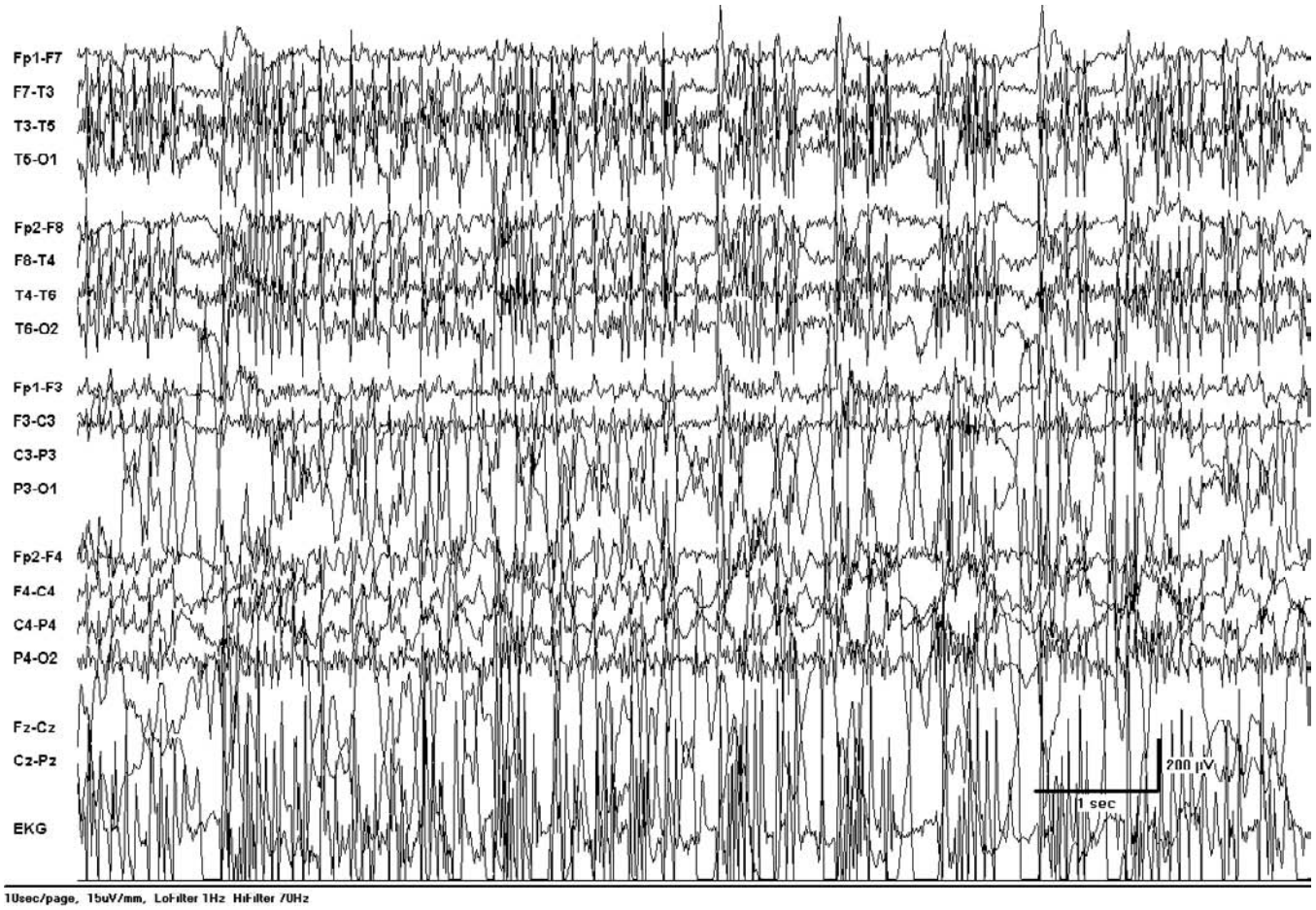

FIGURE 19-19. EEG from a patient with severe myoclonus (likely cortically-based), without pathological EEG correlate.

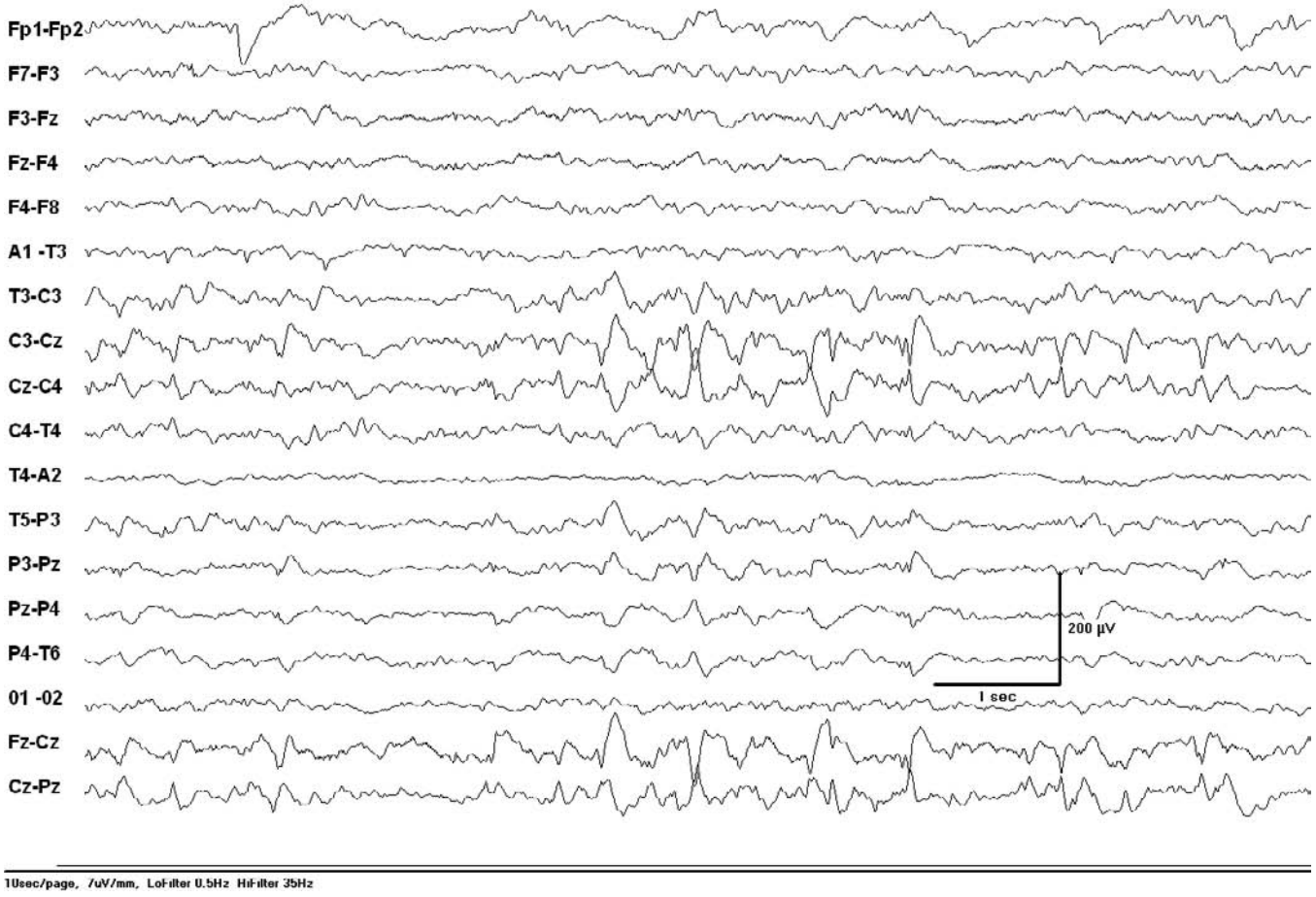

FIGURE 19-20. Focal epileptiform potentials, each associated with a myoclonic jerk.

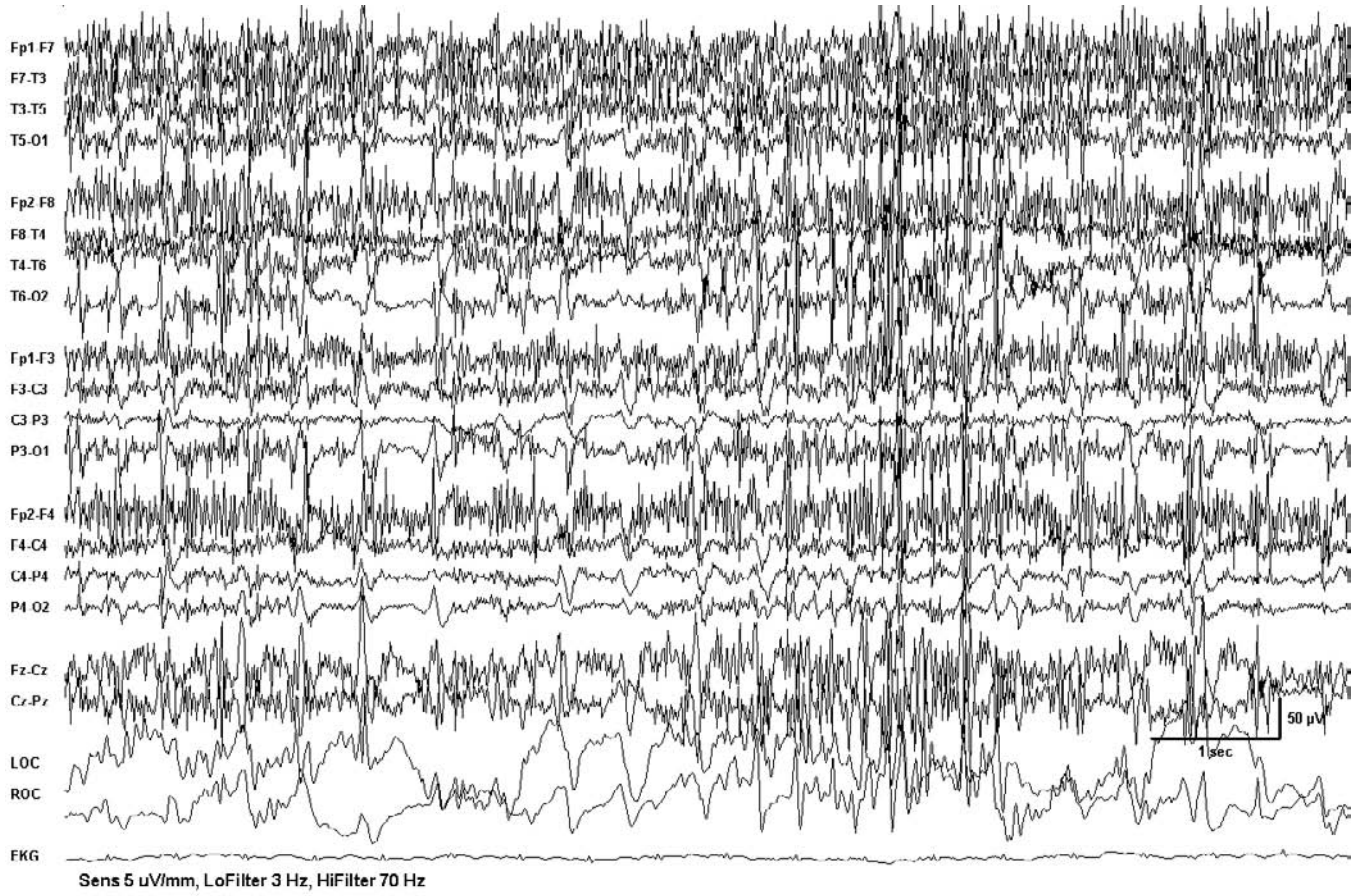

FIGURE 19-21. EEG from a patient in myoclonic SE before neuromuscular blockade.

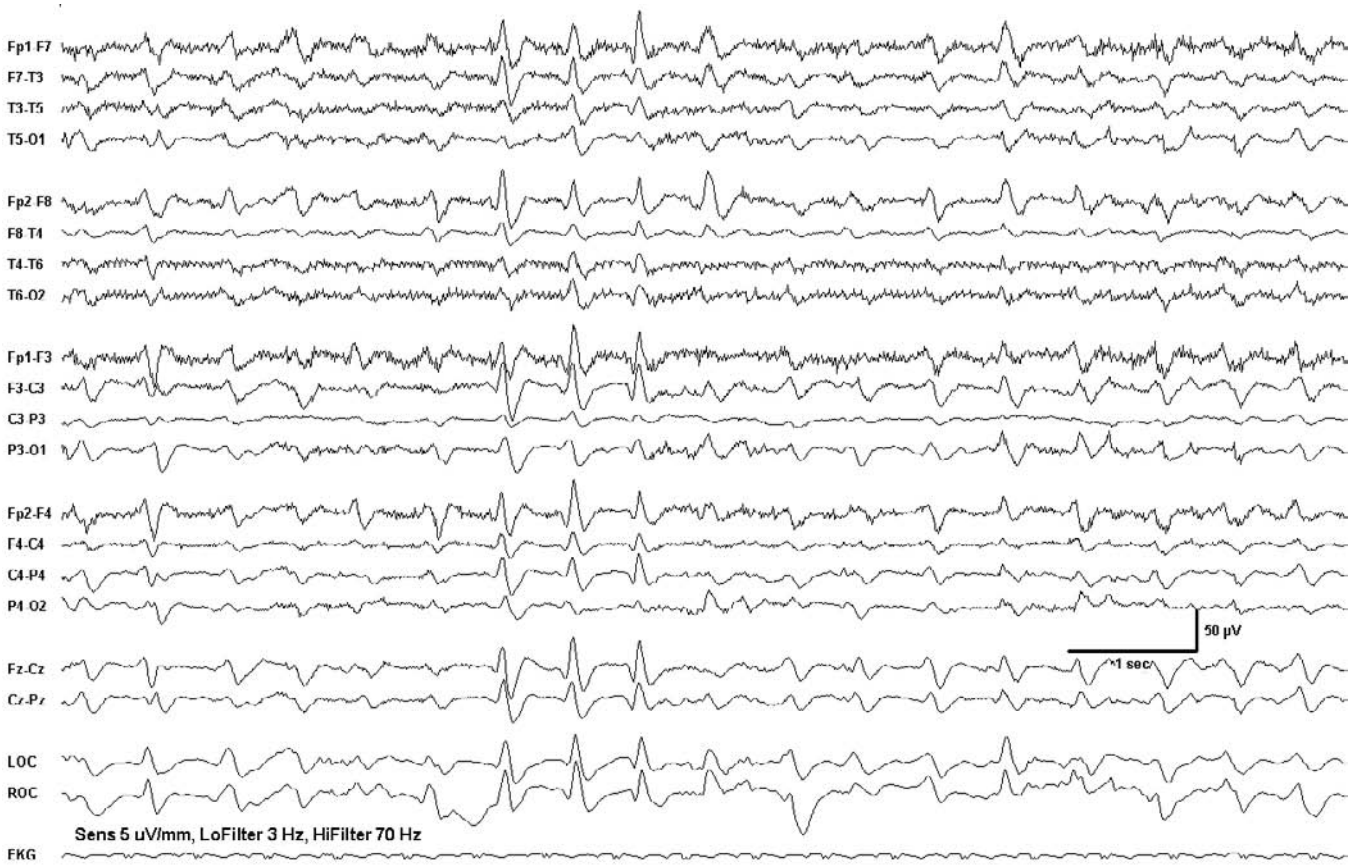

FIGURE 19-22. EEG from the same patient (in myoclonic SE) after neuromuscular blockade.

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NONCONVULSIVE SEIZURES AND STATUS EPILEPTICUS

FRANK W. DRISLANE
PETER W. KAPLAN

PREVALENCE AND DETECTION OF NONCONVULSIVE STATUS EPILEPTICUS IN THE ICU

Nonconvulsive seizures are more common than is usually suspected. While generalized convulsive seizures are usually apparent clinically, nonconvulsive seizures (probably the majority of seizures in adults) are harder to recognize. Paradoxically, nonconvulsive status epilepticus (NCSE) may be even harder to recognize because there may be no sudden behavioral change at presentation, the patient's condition may fluctuate very little over the course of a day, the significance of many EEG patterns is controversial, and the response to antiepileptic drugs may be subtle or delayed.

Gastaut defined status epilepticus (SE) as "an epileptic seizure that is so frequently repeated or so prolonged as to create a fixed and lasting epileptic condition" (1). No precise duration was specified. The International League Against Epilepsy specified "a single epileptic seizure of more than 30 minutes duration or a series of epileptic seizures during which function is not regained between ictal events in a 30-minute period" (2). Physiologically, there often appears to be a neurologic deterioration at about 30 minutes of continued seizure, at least for generalized convulsive status epilepticus (GCSE) (3). While there is no definite biological discontinuity at 30 minutes of a seizure, this criterion has been the standard in most clinical studies (4).

Clinically, seizures should be treated before they last 30 minutes. There is a substantial difference between the duration of SE that leads to neuronal damage in experimental animals and the shorter duration of SE now felt to warrant prompt treatment in patients. Prospective clinical trials must define SE as diagnosable within several minutes. The largest prospective trial of different antiepileptic drugs for the treatment of GCSE mandated treatment within 10 minutes, and yet retained the diagnostic label of SE (5). Subsequently, an "operational" definition was proposed for GCSE requiring a duration of 5 minutes—the time by which status should be interrupted to avoid morbidity, mortality, or refractory SE (6). This applies primarily to SE that is a serious threat to health or that presents a potential danger of neuronal damage. This includes GCSE, but evidence for cerebral damage following NCSE alone is much less convincing (7). For NCSE, 30 minutes may well be a better criterion for studies, but treatment should begin as soon as the continuing seizures are recognized.

Nonconvulsive status epilepticus has been defined as a "range of conditions in which electrographic seizure activity is prolonged and results in nonconvulsive clinical symptoms. [It is] . . . primarily as a form of epileptic cerebral response which is dependant largely on the level of cerebral development and integrity, the presence or absence of encephalopathy, the type of epilepsy syndrome, and the anatomical location of the epileptic activity" (8). This definition reflects the pleomorphic character of NCSE and provides good conceptual insight into its biology, but diagnosis of individual cases can remain challenging.

Nonconvulsive status epilepticus may constitute $\frac{1}{4}$ of all cases of SE (9), and thus has an incidence of about 10 per 100,000 persons per year in the general population (4). Among sick patients in hospitals and intensive care units (ICUs), however, it is much more common. Of 164 patients with earlier GCSE whose seizures had ceased clinically, EEG recordings showed ongoing seizure activity in 14% within the first 30 minutes and in 34% later, and 14% were considered to be in NCSE (10). In the Veterans' Affairs study of GCSE treatment, 20% of patients who had no further convulsions nonetheless had subsequent evidence of ongoing NCSE on the EEG (5). In another study, of 236 comatose patients without any clinical signs of seizures, 8% were shown to be in NCSE on EEG (11).

NCSE is not rare in ICUs. Using continuous EEG (cEEG), one group found that seizures were recorded in 19% of patients monitored in a neurological ICU over a 6-year period (for a question of seizures or to evaluate coma), and that 92% of these seizures were strictly nonconvulsive (12). Coma, prior epilepsy, age less than 18 years, and earlier convulsive seizures were risks for these seizures. Children also have a high prevalence of electrographic seizures in the setting of recent GCSE or altered mental status. In one pediatric neurological ICU, 44% of patients who underwent cEEG had electrographic seizures, 75% of which were entirely nonconvulsive (13). The same researchers found NCSE in 34% of pediatric patients following convulsive SE (14).

Many different structural and metabolic central nervous system insults can cause nonconvulsive seizures and NCSE. Patients with an acute neurologic injury are at particular risk, especially those with intracerebral or subarachnoid hemorrhage, central nervous system infection, brain tumors, severe head trauma, or prior neurosurgery. For each of these conditions, 20%–30% of monitored patients have had nonconvulsive seizures in different studies (15–18). Other risks include recent generalized convulsions, a history of epilepsy, and remote symptomatic central nervous system insults (e.g., stroke, neurosurgical intervention, tumor, etc.) (19), especially when the patient is encephalopathic.

TYPES OF NONCONVULSIVE STATUS EPILEPTICUS

Decades ago, NCSE was generally divided into two types: "absence SE" and complex partial SE. The former included all NCSE with generalized spike and slow-wave discharges on the EEG. Complex partial SE could have a clear focal onset clinically, or focal discharges, and was considered the equivalent of prolonged or repetitive complex partial seizures (20). This oversimplification is no longer tenable.

NCSE with generalized discharges and nonfocal clinical manifestations should be subcategorized further into (a) typical absence SE, occurring in patients with idiopathic (usually genetic) primary generalized epilepsies, and (b) the remainder of cases, with secondarily generalized seizures. Clinical manifestations may be very similar from one syndrome to another.

Absence SE is the classic form of generalized NCSE. "True" absence SE occurs in patients with earlier absence seizures in the idiopathic epilepsy syndromes (21). It has no features of focal epilepsy and exhibits rapid (about 3 Hz), generalized, epileptiform discharges on the EEG. Typical clinical manifestations include confusion or abnormal behavior, with occasional minimal motor abnormalities such as blinking or myoclonus; episodes can last up to days. Alertness may be preserved, often with just a minimal change in responsiveness (21). Typical absence SE is seldom, if ever, the reason for an ICU admission, but it may occur in the ICU in susceptible patients with an acute medical precipitant.

Typical absence SE with rapid, rhythmic generalized discharges also occurs in several other idiopathic generalized epilepsy syndromes, even though those epilepsies are usually manifested by other types of seizures—for example, myoclonus in juvenile myoclonic epilepsy (22). Episodes of SE are relatively uncommon in these syndromes.

Frequent episodes of NCSE have been reported in older patients with no prior epilepsy ("*de novo* absence SE of late onset"), often in association with withdrawal of benzodiazepines that are used at times for anxiety or sleep (23). Some of these patients may have had undiagnosed idiopathic generalized epilepsies, and others may have been misdiagnosed—it is unclear whether all of these cases are truly *de novo.* Almost all types of absence SE are relatively benign and easily treated. They would seldom necessitate an ICU admission, but they could appear in patients with earlier epilepsy admitted to the ICU for other reasons, and the NCSE could be difficult to recognize.

Atypical absence SE occurs primarily in children with cryptogenic and secondary generalized epilepsy such as Lennox-Gastaut syndrome, and often has slow spike and wave (< 3 Hz) discharges on the EEG. Patients often have other types of seizures and SE, and substantial neurologic deficits, including moderate to severe mental retardation. The EEG background is often markedly abnormal, even between episodes of seizures or status. The seizures and SE are often refractory to treatment (24). Children with these syndromes may well enter ICUs, often for other acute medical illnesses that may precipitate the SE.

Complex partial SE is more frequently encountered in ICU patients. It may occur as an "epileptic twilight state" with a lack of responsiveness or with confusion and bizarre, typically fluctuating, behavior (25–27). At times there are automatisms. Possibly because of the frequent association with vascular disease and prior focal epilepsy, complex partial SE is usually more resistant to antiepileptic drug treatment than most primary generalized SE and is more likely to recur (27). Complex partial SE may impair the level of consciousness sufficiently to prompt an ICU admission.

The most common form of NCSE in hospitalized and critically ill ICU patients is *secondarily generalized NCSE.* It may have a clinical and EEG expression not readily distinguishable from cases of primary generalized NCSE. It may be impossible to determine whether the seizures and EEG findings were generalized or focal at the onset, as the EEG no longer has (or never had) signs of the focal onset. With common underlying lesions such as encephalitis,

strokes, or other injuries, this form of NCSE is often much harder to treat and has the prognosis of the underlying illness. In particularly sick patients, this may progress to refractory NCSE.

THE DIFFICULTY OF DIAGNOSIS OF NONCONVULSIVE STATUS EPILEPTICUS IN THE ICU

The diagnosis of nonconvulsive seizures and NCSE derives from two major elements: an alteration in baseline cognition or behavior, and concurrent epileptiform seizure patterns on the EEG (28). Satisfying these criteria in the ICU is often complicated and difficult. In order to recognize the clinical features, one must maintain a high index of suspicion. The clinical signs of NCSE are not merely the abnormal behavior, but its change from a baseline state. Often, family members or caretakers are the first to spot particular changes that might escape the attention of hospital personnel seeing the patient for the first time. Nonconvulsive seizures and NCSE can have subtle presentations and include minimal movements of the face or eyes, such as blinking, hippus, nystagmus, or sustained eye deviation. Such movements are highly suggestive of NCSE in the appropriate clinical setting (19). Some NCSE patients have no such behavioral signs at all. Prolonged EEG monitoring can detect seizures (particularly nonconvulsive) and NCSE when clinical manifestations are subtle.

NCSE often occurs in a population of patients with other illnesses, thus obscuring the diagnosis (Table 20-1). Many patients are elderly and have dementia; others have mental retardation or psychiatric disorders making it difficult for unfamiliar observers or ICU physicians to notice a new perturbation in cognitive function (21,29–34). Therefore, it is important to consider questions such as whether a patient is "more confused than usual," is "inappropriately lethargic" after a tonic-clonic seizure, is confused above and beyond what might be attributable to a concurrent infection or electrolyte disturbance, and so on. Patients with long-standing psychiatric illness are at risk of delayed diagnosis of NCSE because their neuroleptic burden and propensity for starting and stopping benzodiazepines are triggers for *de novo* NCSE (23). Additional risk factors in psychiatric patients include greater age, female gender, cerebral atrophy, Alzheimer's disease, and microvascular cerebral disease (33). Other risks for NCSE are intercurrent electrolyte abnormalities, infections such as pneumonia or urinary tract infections, or abnormal glucose regulation (Table 20-1).

Many patients with NCSE have had their cognitive impairment attributed to other problems such as electrolyte imbalance, hyperglycemia, pneumonia, prior seizures, or alcohol (Table 20-2) (33). There is often little suspicion of NCSE when confusion, lethargy or inappropriate behavior can be ascribed to psychiatric conditions. Mutism from NCSE has been attributed to aphasia with stroke, and lethargy from NCSE has been attributed to an excess of alcohol. Such scenarios have led to a substantial diagnostic delay.

ICU patients have many reasons for altered mental status, including infections, severe metabolic dysfunction, sedating medications, postoperative encephalopathies (many due to medications), and other systemic illnesses. Patients in ICUs with impaired responsiveness have an increased likelihood of being in NCSE (10,11,16,25,35), especially when they have had earlier seizures or clinically evident SE (36–39). Coma is a particular risk for NCSE in the ICU, especially if the cause of coma is unclear. In one study, more than half of 97 comatose patients undergoing cEEG had electrographic seizures (12).

The patients at highest risk for unrecognized NCSE are those with who have had GCSE and are believed to have been treated successfully but, in fact, have not been. A prolonged "postictal" state after a convulsion should raise concern for possible NCSE (36,37). After generalized convulsions, most patients begin to recover responsiveness within 20 to 30 minutes, although there is a broad range of recovery times. If this does not occur, the patient may be in NCSE, and EEG is often the only way to make the diagnosis. Therefore, all patients with seizures or SE who do not return to a normal level of consciousness should have EEGs performed to see whether treatment was effective in stopping their seizures, or if they remain in NCSE.

Young and colleagues advised that nonconvulsive seizures and NCSE should be suspected in the ICU when (a) a prolonged encephalopathy follows generalized convulsions, an operation, or a neurologic insult; (b) there is acutely impaired or fluctuating consciousness interrupted by normal alertness; (c) there is impaired consciousness with facial myoclonus or nystagmus; (d) staring, aphasia, or automatisms (e.g., limb or facial) occur episodically; or (e) other acutely altered behavior has no obvious cause (40).

Making a diagnosis of NCSE usually requires the clinical picture of an abnormal mental status with diminished responsiveness (described above) and a supportive EEG (see next section). Even then, diagnostic uncertainty may persist in some patients, and a diagnostic challenge with benzodiazepines may be useful. If the patient and EEG improve rapidly after the benzodiazepine, a firm diagnosis can be made then. In many patients, however, the response is equivocal or substantially delayed, and the diagnosis must be made on clinical and EEG grounds alone. In all cases, the EEG is crucial. To diagnose NCSE, Tomson and colleagues required impaired consciousness for an hour and an EEG showing continuous seizure activity (20), while Kaplan sought impaired consciousness for 30 to 60 minutes with seizure activity on the EEG (28).

TABLE 20-1. CLINICAL FEATURES IN SYNDROMES RESEMBLING NONCONVULSIVE STATUS EPILEPTICUS

Distinguishing features	Nonconvulsive status epilepticus	Lithium toxicity	Neuroleptic malignant syndrome	Serotonin syndrome	Creutzfeldt-Jacob disease	Malignant hyperthermia	Baclofen toxicity
Clinical features	**Confusion***	**Confusion***	**Confusion**	**Confusion***	**Confusion***	**Rigidity***	**Confusion***
	Apathy	Apathy*	Drowsiness	Anxiety*	Agitation	**Fever***	Agitation*
	Agitation/ lability	**Agitation/ lability***	**Rigidity/ akinesia***	**Restlessness***	Hallucinations	Tachypnea*	Lethargy
	Rigidity	Spasticity/ **rigidity***	**Tremor**	**Rigidity***	**Rigidity***	Hypotension	Hallucinations
	Myoclonias*	**Myoclonias***	**Mutism**	**Myoclonias***	**Myoclonias***	Tachycardia*	**Myoclonias***
	Tremor	**Tremor***	**Dysarthria***	**Tremor***	**Tremor***		**Seizures**
	Catalepsy*	Intention tremor	**Fever***	**Mutism**	**Dementia***		Fever(?)
	Mutism*	Catalepsy	**Shuffling gait***	Shivering*	Spasticity		Visual blurring
	Seizures*	**Mutism***	Buccofacial dyskinesias	**Fever**	Wasting*		
	Ataxic gait	**Dysarthria***	**Sweating**	**Ataxic gait**	**Dysarthria***		
	Nausea	**Seizures**	Dysphagia	**Sweating***	**Seizures**		
	Anorexia	**Fever**	Incontinence	**Diarrhea**	**Ataxia***		
	Vomiting	**Ataxic gait**		**Hyper-reflexia***	Weight loss*		
	Constipation	Muscle twitching	Hypertension*		Visual loss		
	Hyper-reflexia	Asterixis/ choreoa-therosis	Tachycardia*		Sleep changes		
		Nausea	**Constipation**				
		Anorexia*	Pallor				
		Vomiting, drooling*					
		Papilledema					
		Nystagmus					
		Bradycardia					
		Diarrhea*					
		Hyper-reflexia					
Other tests		**Leukocytosis**	**Elevated creatine phosphokinase (CPK)**		**14-3-3 prion protein**	**Elevated CPK; Hyperkalemia**	
			Leukocytosis			Cyanosis	
			Myoglobinuria			Metabolic acidosis	
						Lactic acidemia	
						Myoglobinuria	
EEG	Seizure activity	Slow; triphasic waves (TWs); focal, multifocal or diffuse epileptic activity; seizures	Slow; TWs	Slow; TWs	TWs/Periodic waves		TWs
					Background slowing		**Periodic waves**

Bold=Frequently cited clinical features; *=Typical/cardinal features (91).

TABLE 20-2. REASONS FOR MISSED OR DELAYED DIAGNOSIS OF NONCONVULSIVE STATUS EPILEPTICUS

- Lethargy/confusion attributed to a postictal state
- Ictal confusion mistaken for metabolic encephalopathy
- Unresponsiveness/catalepsy presumed psychogenic
- Obtundation attributed to alcohol or drug intoxication
- Hallucinations/agitation mistaken for psychosis or delirium
- Lethargy presumed caused by hyperglycemia
- Mutism attributed to aphasia
- Laughing and crying ascribed to emotional lability
- Sudden focal weakness and aphasia attributed to stroke (with plans to give tissue plasminogen activator (tPA))

From Kaplan (33).

EEG FEATURES OF NONCONVULSIVE SEIZURES AND NONCONVULSIVE STATUS EPILEPTICUS

There are several problems in the use of EEG for the diagnosis of nonconvulsive seizures and NCSE in ICU patients. Sometimes, nonconvulsive seizures and NCSE are readily apparent on the EEG, but in many other cases the clinical significance of epileptiform and other EEG abnormalities is unclear.

Terminology

One factor impeding diagnosis in this area is the lack of a uniform terminology to describe electrographic seizures and other abnormal EEG patterns. EEG interpretation varies by reader, and there is a lack of consensus on the terms, descriptors, and electrographic definitions of NCSE, although some standardization of nomenclature is being formulated by the American Clinical Neurophysiology Society (ACNS). An ACNS committee recommended that EEG findings be described by morphology, location, frequency, and periodicity of waveforms, without using clinical overtones—with subsequent interpretation in the clinical context (41). The use of standardized terminology could facilitate studies of the clinical implications of epileptiform findings without the biases of some currently used terms.

EEG Evidence of Seizure Activity

The ascertainment of whether there is evidence of seizure activity on an EEG relies on the determination by an electroencephalographer that certain patterns are "ictal" in nature, that is, having to do with epileptic seizures. Some EEGs show NCSE very clearly, with characteristic or even "classic" features. Some formal criteria for definite NCSE, based on the ACNS committee work on EEG terminology, are in Table 20-3 (15). Straightforward examples of NCSE on EEG contain clear runs of high-frequency, epileptiform morphologies and patterns that evolve, continue for over 30 minutes, and possibly wax and wane (Figures 20-1 and 20-2).

Probably more common, however, are EEGs with ambiguous patterns (Figure 20-3). Some show rhythmic activity in temporal or frontal regions without clearly epileptiform morphology, sometimes alternating sides in a "ping-pong" pattern. Others show disorganized slowing, without rhythmicity or epileptiform abnormalities, more suggestive of encephalopathies than seizures (Figure 20-4). In well-established clinical cases of NCSE, the frequency of discharges within the electrographic seizure activity is seldom (<5% of the time) greater than 3 Hz, and is usually 1 to 2.5 Hz (42).

With regard to specific EEG morphologies (leaving aside the temporal or spatial evolution of discharges), there is ongoing controversy about sharp or rhythmic features that range from the nonictal "irritative" (post-, inter-, or pre-ictal) to the "actively seizing"—along an "ictal-interictal continuum" (see PLEDs, below) (43–46). Actual waveforms observed during well-documented NCSE vary remarkably and include rhythmic slowing, sharp waves, spikes, and mixtures of these features (42).

Some patients with less "classic" findings still show an EEG and clinical response to benzodiazepines or other anticonvulsant medication (28). Frequently, the EEG determination of seizures is not a blinded exercise. The interpreter may be aware of the patient's staring, facial twitching, or subtle myoclonus, and be predisposed to diagnose ambiguous patterns as NCSE. For example, the appearance of periodic discharges at 1 Hz in a patient with focal twitching would favor a diagnosis of seizure over that of an interictal periodic pattern (43,44).

Some EEG patterns do not meet the strict research criteria for a diagnosis of NCSE described above but are still strongly suggestive of seizure activity in the appropriate clinical setting. Many are associated with minimal or no motor convulsive activity, often following earlier generalized convulsions or GCSE, and often in the setting of severe medical illness such as anoxia, sepsis, or marked metabolic derangements. These patients have received many different diagnoses. Those with minimal movement after GCSE have been said to be in "subtle" SE (47); some are referred to as being in electrographic status epilepticus (37). Other practitioners refer to "status epilepticus in coma," but not

TABLE 20-3. PROPOSED RESEARCH CRITERIA FOR THE DIAGNOSIS OF NONCONVULSIVE STATUS EPILEPTICUS

An EEG pattern lasting at least 30 minutes, satisfying any one of the following three primary criteria:

Primary Criteria:

1. Repetitive generalized or focal spikes, sharp waves, or spike-and-wave complexes at ≥ 2.5 Hz.
2. Repetitive generalized or focal spikes, sharp waves, spike-and-wave or sharp-and-slow wave complexes at <2.5 Hz and the secondary criterion.
3. Sequential rhythmic, periodic, or quasiperiodic waves at ≥1 per second, with unequivocal evolution in *frequency* (gradually increasing or decreasing by at least 1 Hz, e.g., 2 to 3 Hz), *morphology*, or *location* (gradual spread into or out of a region involving at least two electrodes). Evolution in amplitude alone is not sufficient. Change in sharpness without other change in morphology is not sufficient to satisfy evolution in morphology.

Secondary Criterion:

Significant improvement in clinical state, or appearance of previously-absent normal EEG patterns (such as a posterior dominant alpha rhythm), temporally coupled to acute administration of a rapidly-acting antiepileptic drug. Resolution of the "epileptiform" discharges leaving diffuse slowing, without clinical improvement and without appearance of previously-absent normal EEG patterns, does not satisfy this criterion.

From Jirsch and Hirsch (15).

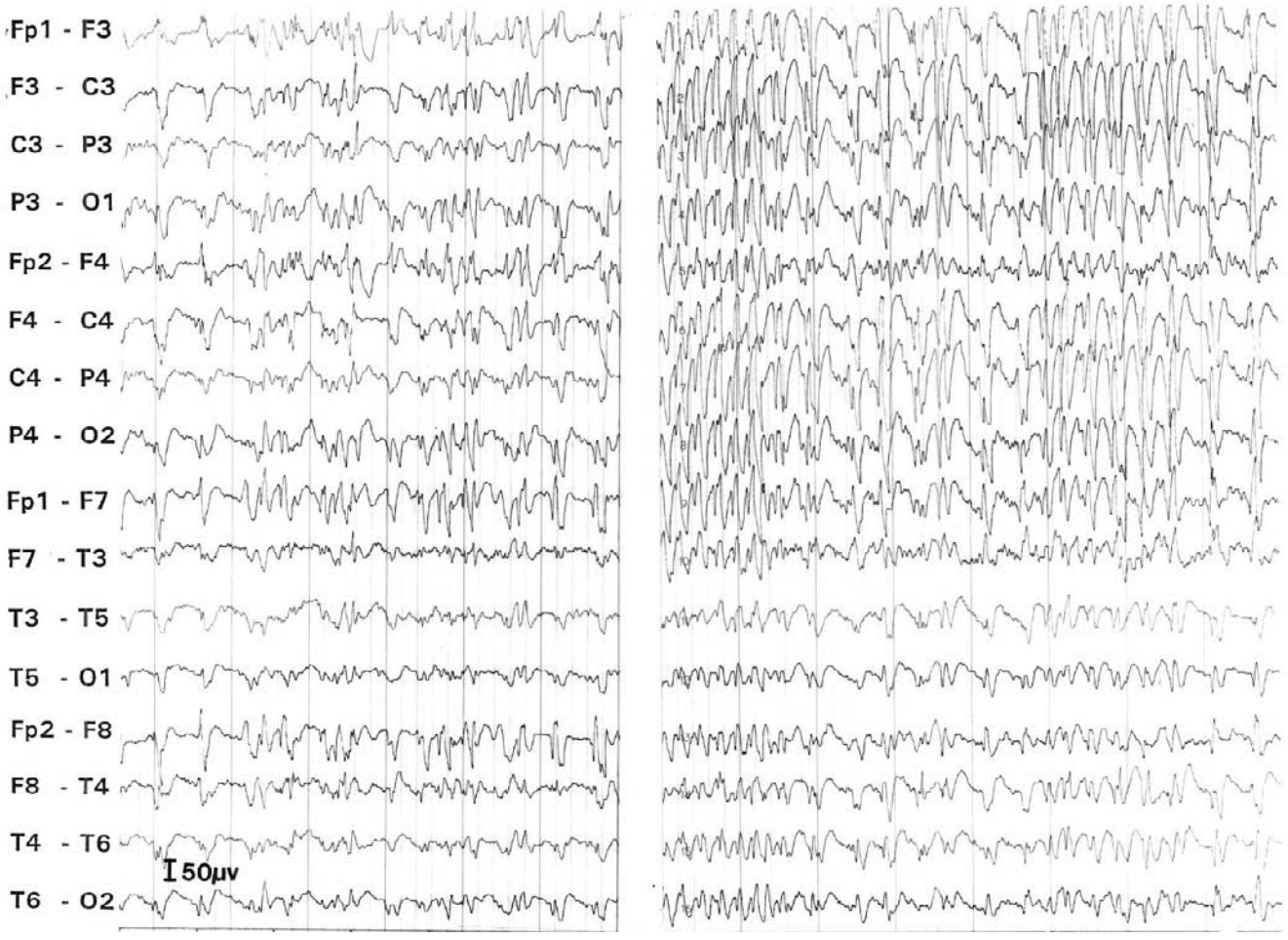

FIGURE 20-1. These EEG segments show generalized spike-wave discharges with some waxing and waning, typical of generalized nonconvulsive status epilepticus (GNSE). [From: Kaplan PW. Nonconvulsive status epilepticus. Sem Neurology 1996;16:33-40. Copyright permission granted by Thieme Medical Publishers.]

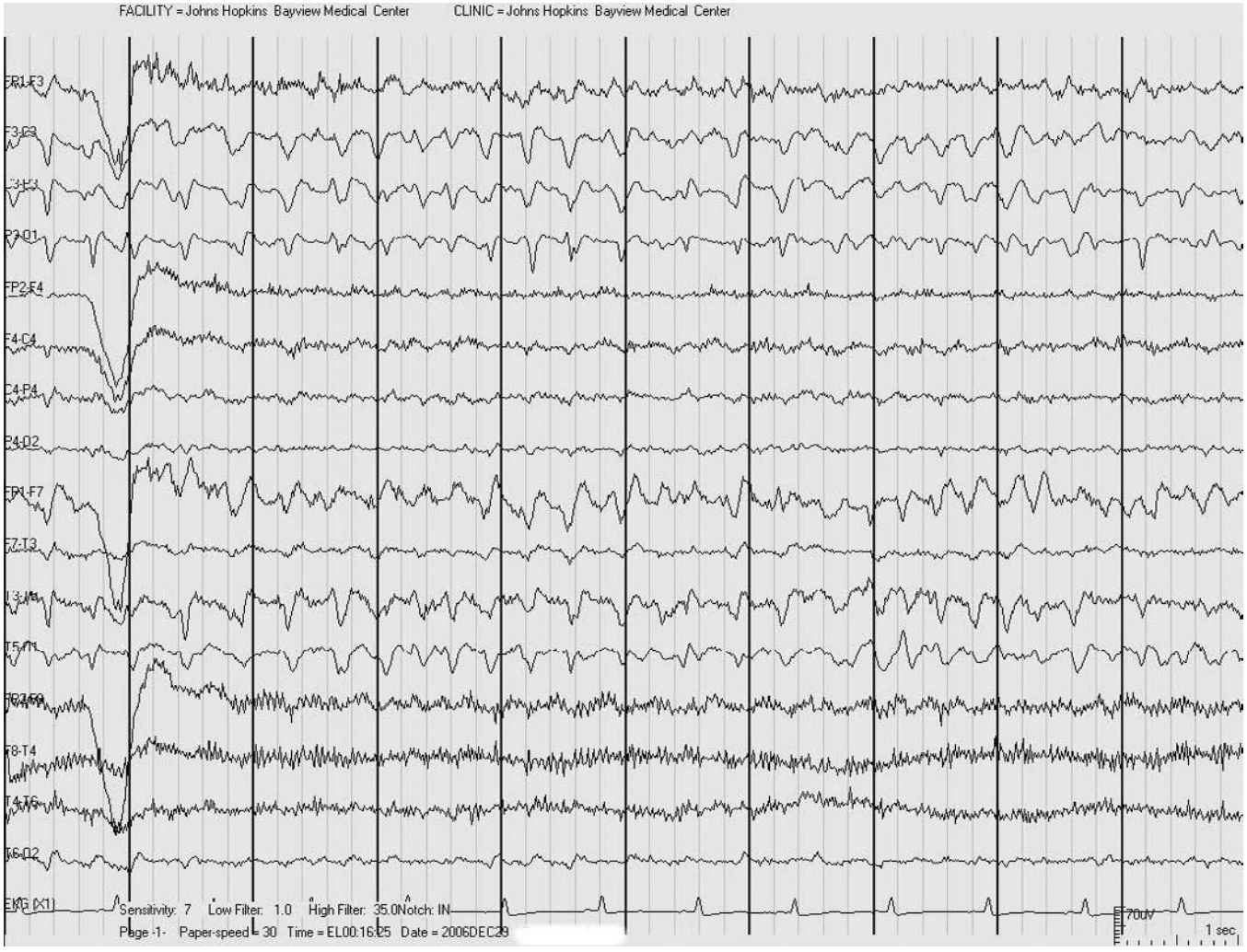

FIGURE 20-2. Ongoing epileptiform discharges at 3 per second, broadly over the left hemisphere in this awake but confused patient, indicative of complex partial status epilepticus (CPSE).

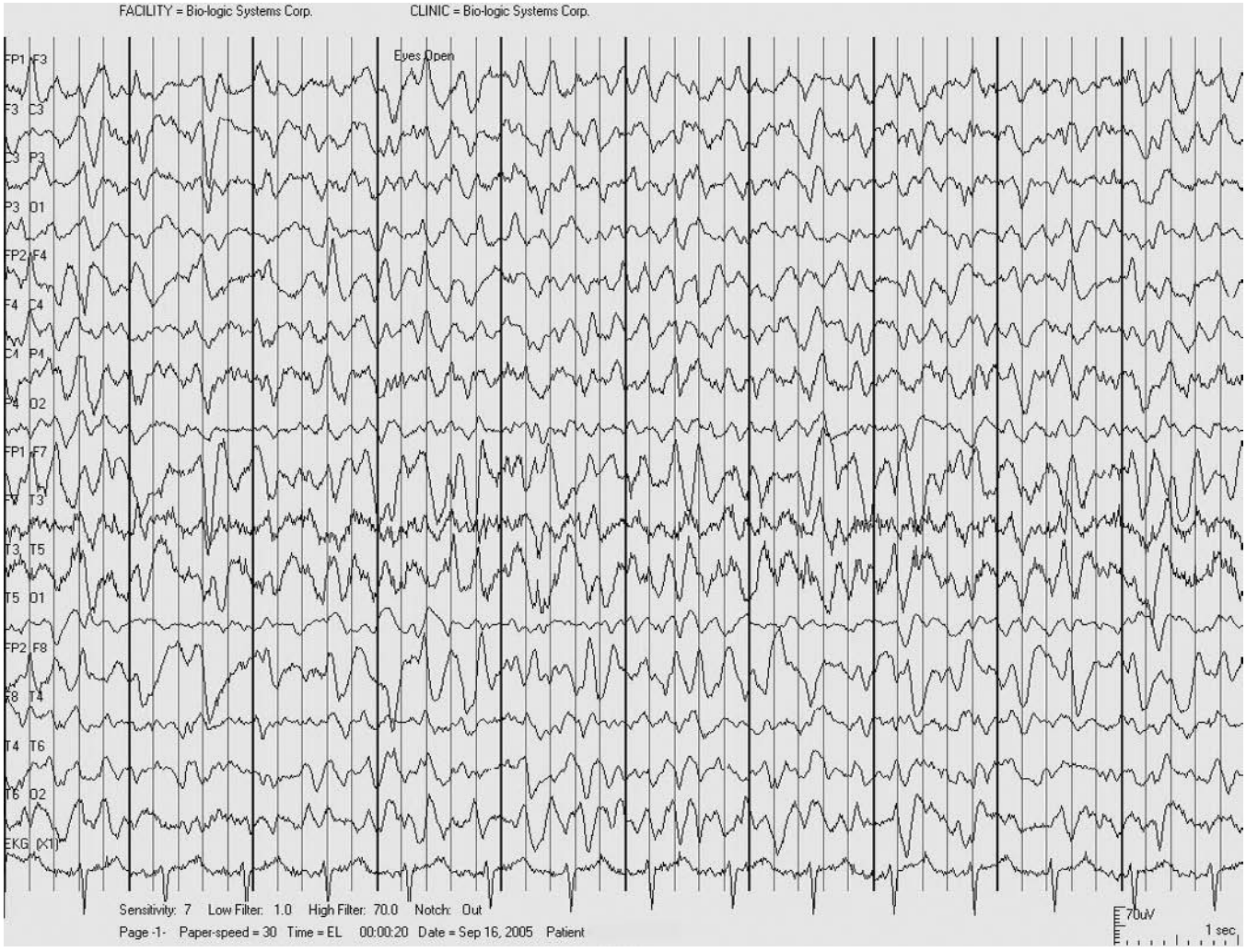

FIGURE 20-3. Atypical NCSE: this EEG shows a disorganized pattern with irregular, bilateral sharp-waves, both synchronously and asynchronously, with some triphasic morphologies. The EEG and the patient improved rapidly upon administration of lorazepam.

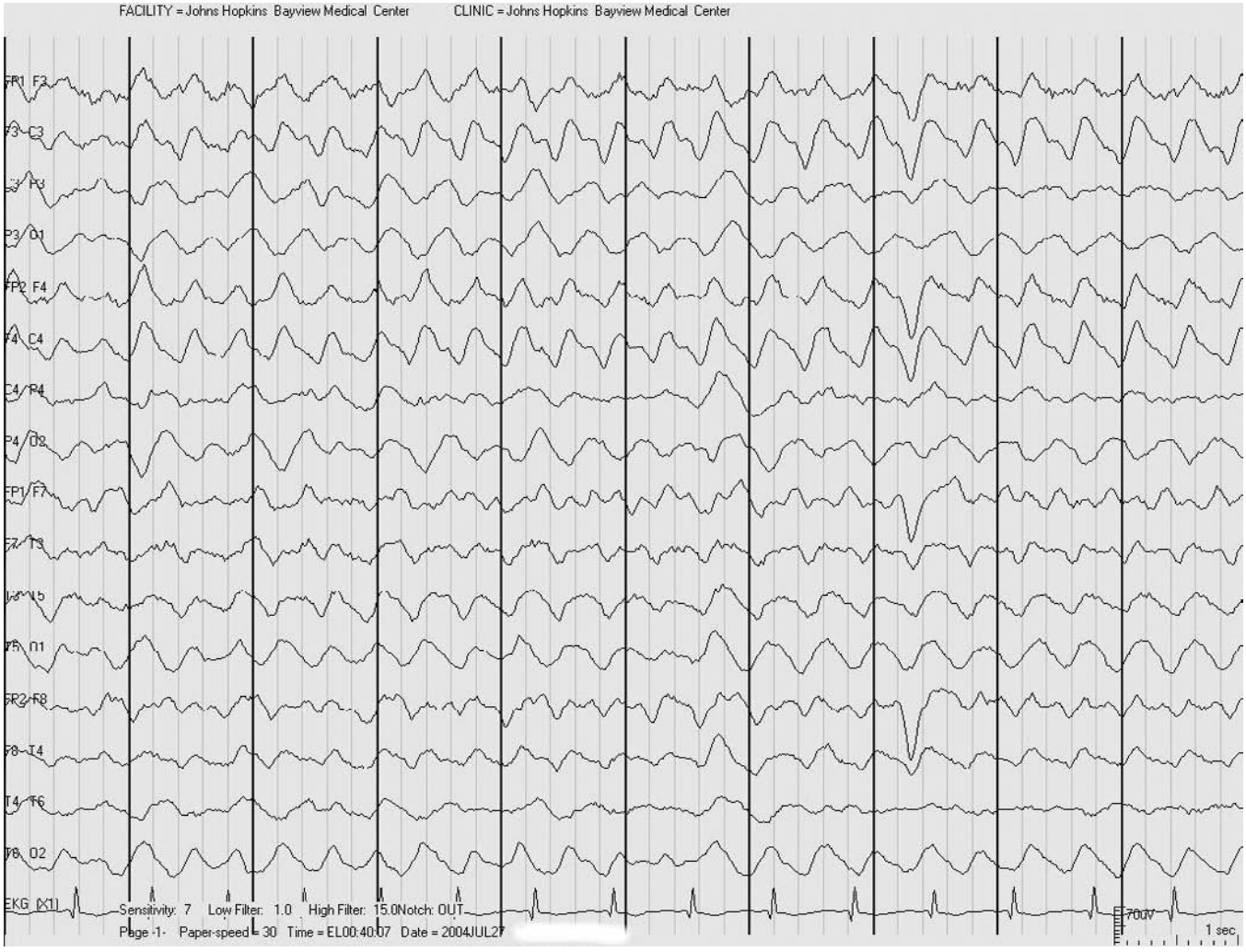

FIGURE 20-4. This tracing shows primarily frontal and more widespread rhythmic delta waves, varying from 2 to 4 Hz, indicative of (very) atypical nonconvulsive status epilepticus (NCSE).

all patients with ongoing electrographic seizures are comatose. Some refer to those patients with severe medical illness as having "epileptic encephalopathies," indicating that the underlying disease causing the encephalopathy is the key diagnosis, and that the epileptic component is not primary and may not respond to antiepileptic drugs. This term, however, is probably best reserved for childhood conditions such as Landau-Kleffner syndrome and electrographic status epilepticus in sleep ("ESES").

In actual clinical practice, electrographic status epilepticus (rhythmic, relatively rapid epileptiform discharges on the EEG, without obvious clinical manifestations) should be considered "true" status rather than "just an encephalopathy with some discharges"—even when treatment is unsuccessful in effecting a clinical improvement. The EEGs resemble those published in many NCSE studies. Also, patients with electrographic SE upon emergence from pentobarbital or midazolam infusion treatment usually go on to have clinically evident seizures (48,49), indicating that electrographic SE is not just an EEG aberration. Finally, some patients with electrographic SE do respond well to antiepileptic drugs (39).

Continuous versus Intermittent Seizure Activity

Is there a different clinical significance if NCSE is manifested on EEG by recurrent discrete electrographic seizures or by continuous epileptiform discharges of a certain frequency? In a series of focal SE (not all nonconvulsive), there was no significant difference in the etiologies and outcome of patients with either continuous discharges or recurrent discrete seizures on EEG (50). In another series, patients with continuous clinical seizures appeared to be sicker overall than those with discrete seizures (51), but the management and outcome did not appear to differ significantly between the two patterns.

Periodic Lateralized Epileptiform Discharges

Periodic lateralized epileptiform discharges (PLEDs) are generally not considered a manifestation of clinical seizures or SE, at least at the time of the EEG recording (52,53). Nevertheless, clinical seizures have occurred in at least 80% of patients with PLEDs, often before the EEG, and many had prior SE. PLEDs are associated with stroke (the most common cause), tumors, and occasionally, infections, metabolic disturbances, and a possible exacerbation of earlier epilepsy. In most cases there is an acute, serious neurologic illness. In one study, half of patients without prior epilepsy who survived the acute illness developed long-term epilepsy (52). PLEDs are considered by many as "the terminal phase of status epilepticus" (53).

Almost all reports of PLEDs show EEGs with relatively low-frequency epileptiform discharges, usually every 1 to 2 or 3 seconds (Figure 20-5). Most would not be considered indicative of clinical seizures, but those with more rapid discharges (at least 1 Hz and certainly >1.5 Hz) would be interpreted as representing seizures (and if prolonged enough, as SE) by most EEG-ers. Similarly, PLEDs associated with myoclonus are generally considered ictal.

There are also bilateral independent periodic lateralized epileptiform discharges (BiPLEDs) (Figure 20-6), often from infectious or vascular causes (54,55), and generalized periodic epileptiform discharges (GPEDs) occurring in patients who are obtunded (many with anoxia or other catastrophes, and a "flat" background) or in some patients with recent overt seizures (Figure 20-7).

Sometimes, PLEDs *are* a manifestation of seizures and NCSE. One report of seven patients over the age of 60 described recurrent confusional episodes associated with PLEDs, with EEG discharge intervals as long as 4 seconds (56). Clinical deficits resolved with a slowing of EEG discharges, either spontaneously or in response to benzodiazepines. Carbamazepine appeared to prevent recurrences, but patients relapsed when it was decreased. The authors considered PLEDs an "unusual status epilepticus of the elderly." Another group found classic PLEDs during clinically well-defined SE, with abnormal movements and response to antiepileptic drugs (57). They demonstrated that PLEDs could be an ictal EEG pattern when there are appropriate clinical signs. PLEDs may be seen during seizures or SE, and their clinical significance appears to differ in individual cases. Thus, the interpretation of the clinical significance of this EEG pattern must always consider the clinical context.

Triphasic Waves

Another controversial pattern in the EEG diagnosis of epileptiform activity is that of triphasic waves. These are complexes consisting of three phases, often sharply contoured (Figure 20-8), that can be considered epileptiform, particularly when very sharply contoured. They occur in a number of toxic or metabolic states, including uremia, hepatic insufficiency, and toxicity from lithium (Figure 20-9), baclofen (Figure 20-10), ifosfamide, tiagabine, and other medications (58). Usually of broader, more blunted, and slower frequency, triphasic waves may regress with intravenous benzodiazepines, but the patient does not improve then (59). Triphasic waves are generally an EEG expression of an encephalopathy and generated from deeper, subcortical structures and are not truly epileptic in nature (60). They have long been a source of confusion because of the overlap in clinical features among patients with encephalopathy and with NCSE, which is further complicated if the EEG "improves" after benzodiazepines in either (58,59,61). Other features distinguishing triphasic waves are their

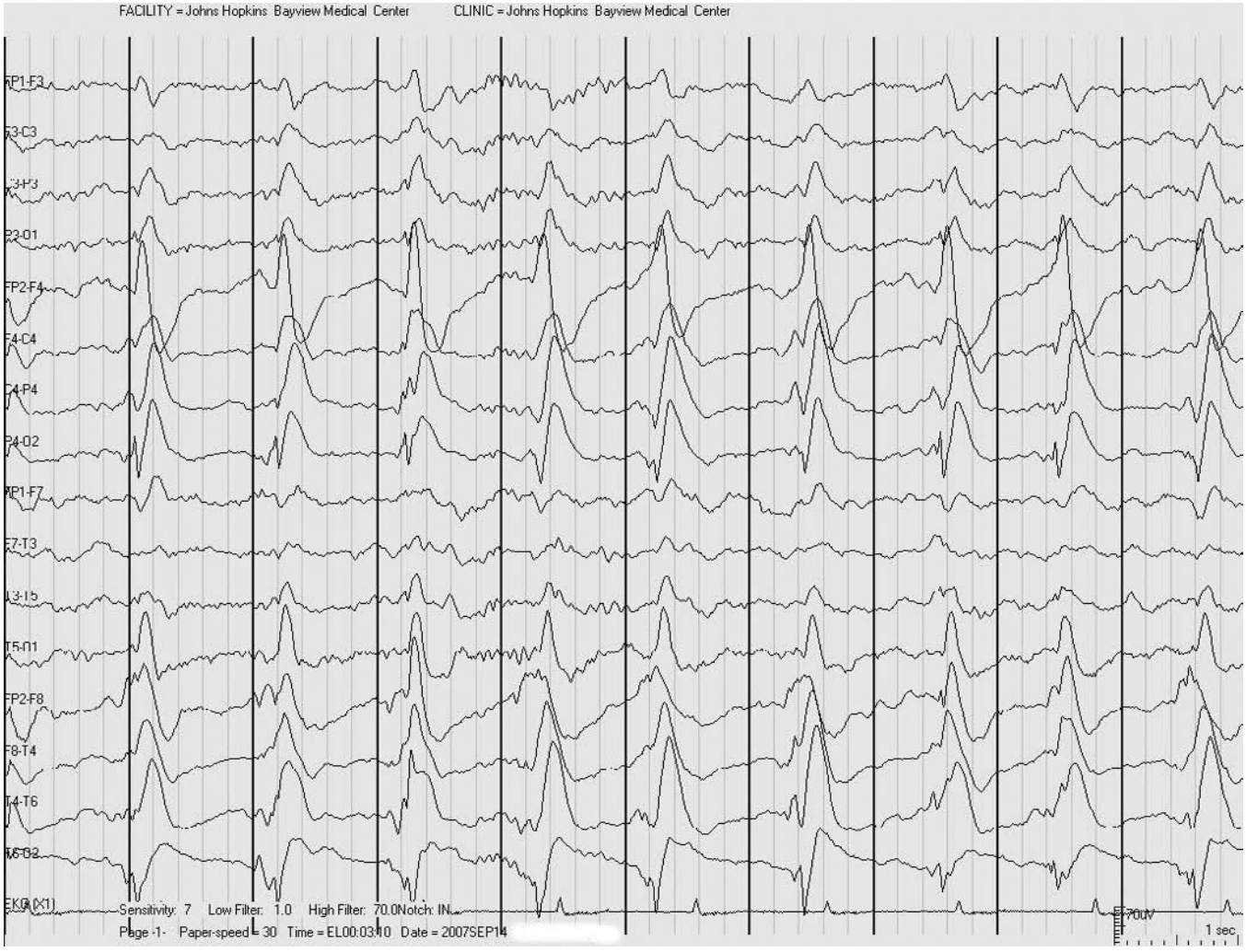

FIGURE 20-5. Periodic lateralized epileptiform discharges (PLEDs), over the right hemisphere, at about 1 per second.

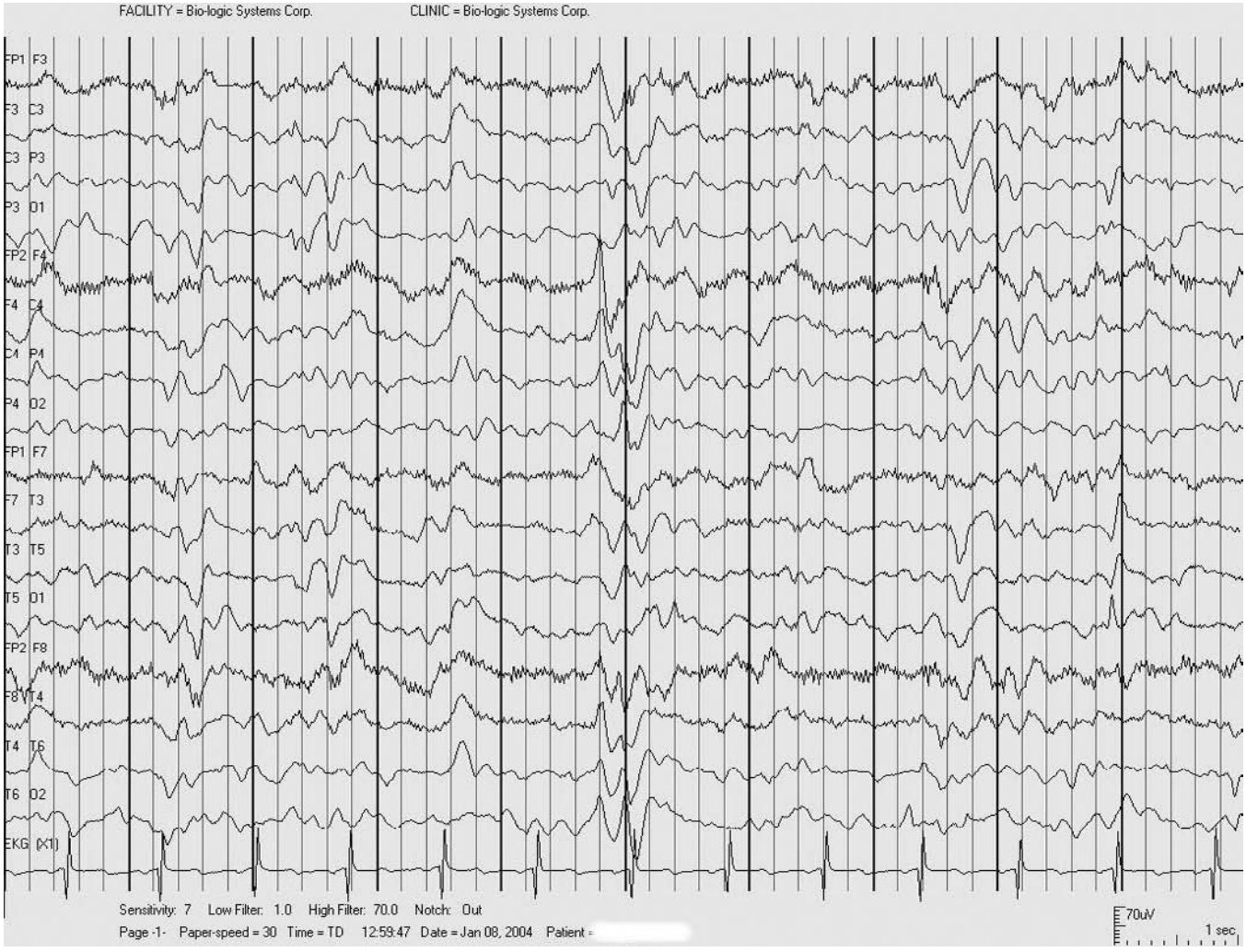

FIGURE 20-6. This EEG shows bilateral independent periodic lateralized epileptiform discharges (BiPLEDs) appearing over the frontal regions, and associated with coma in this patient. [From Kaplan PW. The EEG of status epilepticus. J Clin Neurophysiol 2006;23:p. 228. Permission granted from Lippincott Williams & Wilkins.]

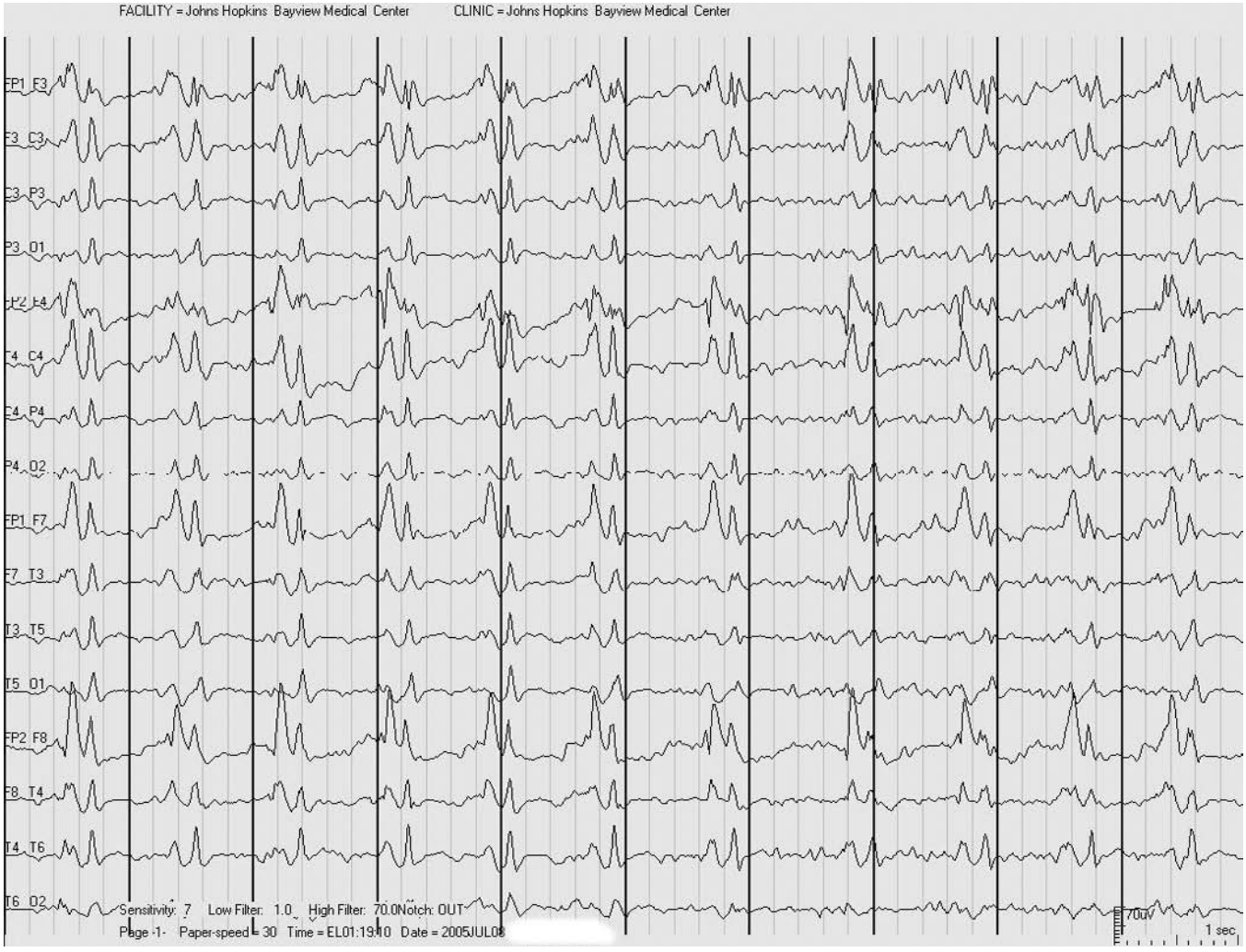

FIGURE 20-7. This EEG shows generalized, bilateral pseudoperiodic discharges at about 1Hz, in a patient with anoxia after cardio-respiratory arrest:; generalized periodic epileptiform discharges (GPEDs).

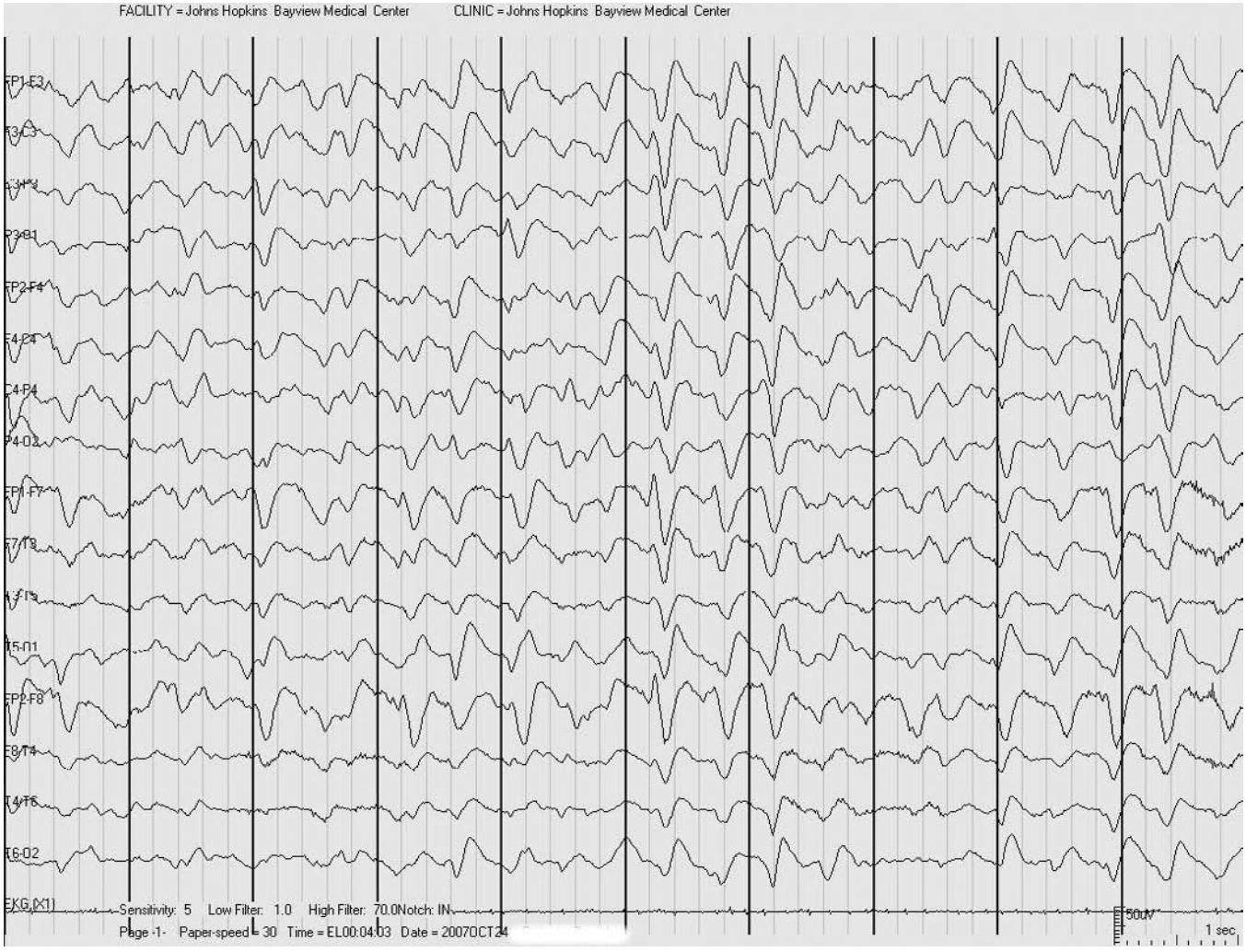

FIGURE 20-8. Runs of lateral fronto-cerebral synchronous biphasic and triphasic waves (TWs) in a man with liver failure and an ammonia level of 179 μg/ml.

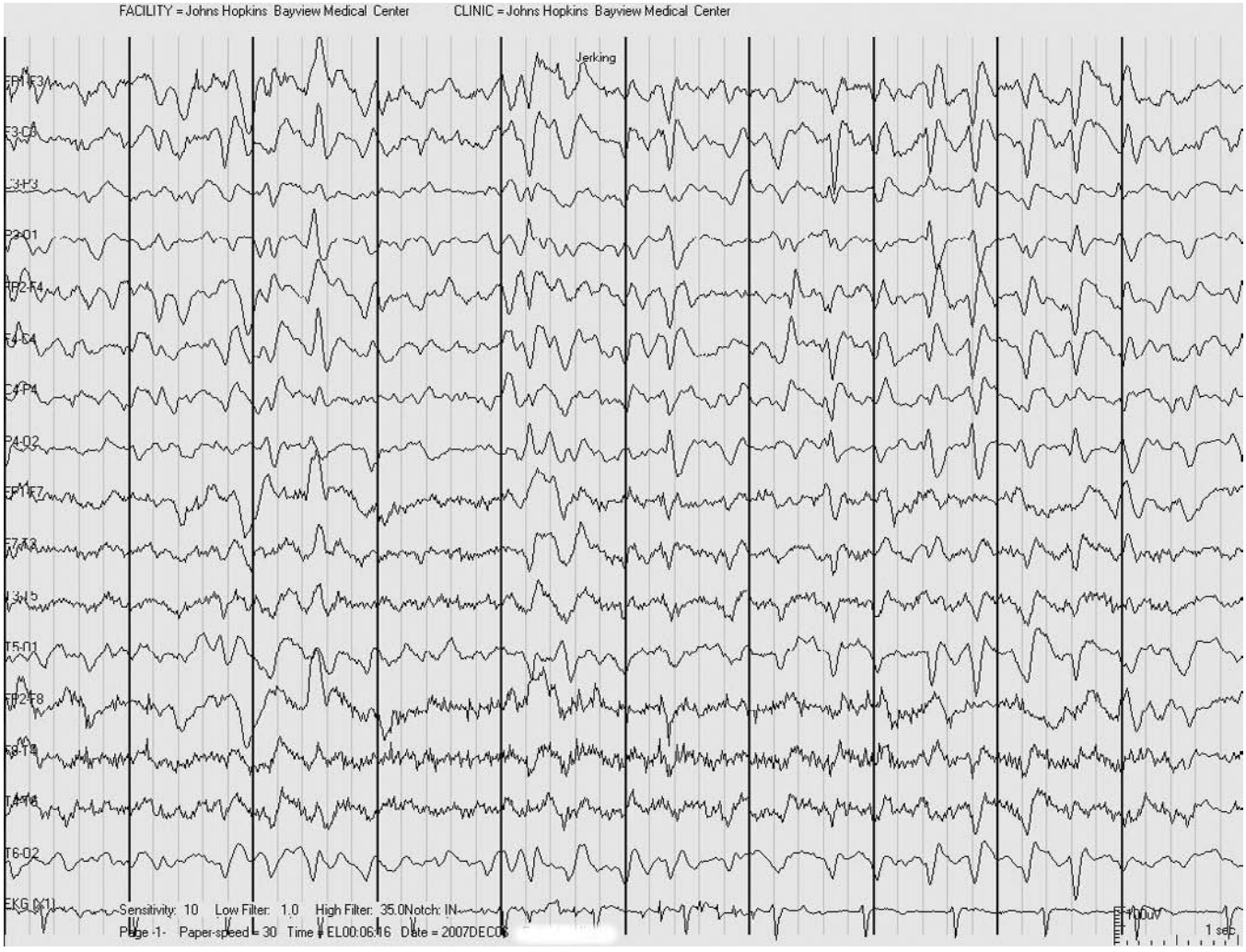

FIGURE 20-9. The EEG of a 62-year-old man admitted with a lithium level of 3.7 μg/ml, who was mute and had myoclonus and rigidity. There are synchronous runs of frontal triphasic waves intermixed with more diffuse higher voltage, briefer generalized epileptiform discharges.

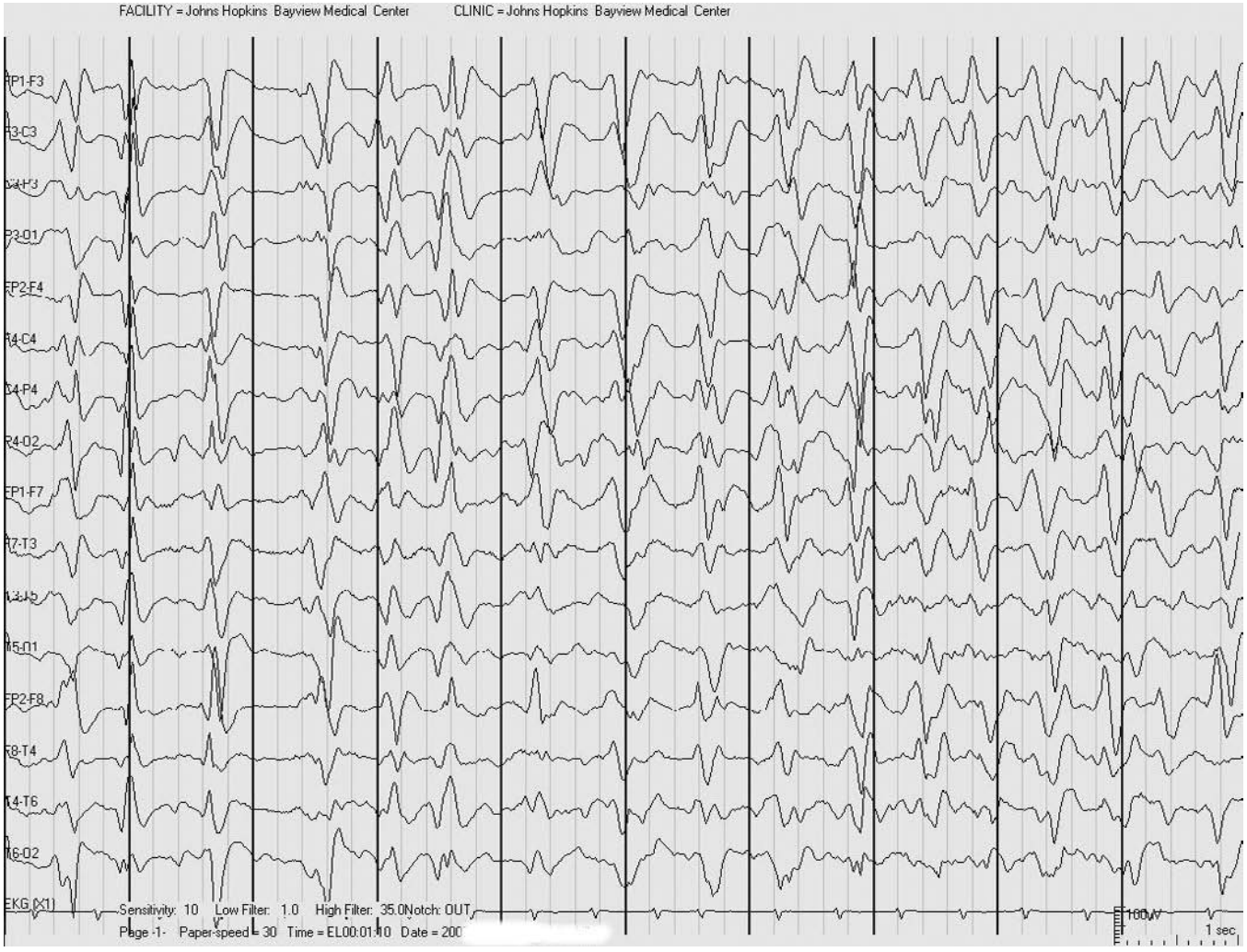

FIGURE 20-10. On the EEG of this patient with baclofen toxicity, there are disorganized, bilateral synchronous and asynchronous triphasic waves at about 2/sec.

slower discharge frequency (62), the usually apparent underlying toxic or metabolic state, and the absence of facial or limb myoclonus. Table 20-4 lists characteristics that can help to distinguish NCSE from triphasic waves.

Duration of cEEG Monitoring

Shorter periods of EEG monitoring are often insufficient to detect seizures. In one study, a routine 30-minute EEG identified electrographic seizures in 11% of 105 critically ill patients, while the subsequent cEEG (for a median of 2.9 days) found seizures in 27% (63). In another series, only half of 110 patients with seizures seen eventually on EEG had them during the first hour of recording (13). In that series, 95% of noncomatose patients had their seizures found in the first 24 hours, versus just 80% of comatose patients. After 48 hours, this increased to 98% and 87%, respectively. Among children with seizures, half had the first seizure detected in the first hour of EEG recording, and 80% within 24 hours (15). The Columbia group concluded that cEEG monitoring was appropriate for 24 hours in patients without coma, and for 48 hours in comatose patients, in patients with periodic discharges, or when antiepileptic drugs were being withdrawn (15).

Technology

A practical problem in the identification of NCSE in the ICU is that nonconvulsive seizures and NCSE exhibit very different electrographic patterns in critically ill patients from those in patients in standard EEG monitoring units being evaluated for epilepsy surgery or for a question of seizure versus pseudoseizure. For example, NCSE in ICU patients often includes lower discharge frequencies than are seen in seizures recorded in ambulatory or typical epilepsy monitoring unit patients. The difference in electrographic seizure morphology makes it harder for most seizure detection algorithms used in monitoring units to detect electrographic seizures in ICUs (15).

TABLE 20-4. DISTINCTION BETWEEN PERIODIC EPILEPTIFORM DISCHARGES AND TRIPHASIC WAVES

Periodic Epileptiform Discharges:
Surface-negative bi-, tri-, or poly-phasic discharges with spike, or sharp, or polyspike components and slow-wave complexes.
Complex duration: 60 to 600 msec (mean 200 msec).
Amplitude: 50 to 300 uV (usually up to 150 uV).
Frequency: 0.2 to 3 Hz (usually 0.5 to 2.0 Hz).
Persistence: minimum of 10 minutes in a recording.
Evolution: static, with only minor variability (<50%) in the above characteristics; if varying, more likely to be part of electrographic seizures.

Triphasic Wave Features:
Surface negative, blunted complexes with three phases:
a) a low-amplitude, blunted, negative first phase, often wide-based;
b) a dominant, steep, positive second phase; and
c) a slow-rising third "slow-wave" component. (may exhibit phase-lag, seen best on referential montage) NO polyspike component.
Complex duration: 400 to 600 msec.
Amplitude: 100 to 300 uV on referential montage; smaller on bipolar.
Frequency: 1.0 to 2.5 Hz (typically 1.8 Hz).
Persistence: wax and wane, but >10% of a standard 20 minute recording.
Evolution/reactivity: decrease with sleep, drowsiness, or after benzodiazepines; increase and reappear with arousal or noxious stimulation.

Also, monitoring units and cEEG systems must deal with very large amounts of data, and not all can be reviewed by a clinical neurophysiologist. Automated detection programs better suited to cEEG in ICUs (versus ambulatory or presurgical situations) will help with the enormous quantity of data produced by cEEG. Quantitative EEG methods including compressed spectral array can help to select episodes for review by the clinical neurophysiologist (15) (see also Chapter 7, Computerized Signal Analysis and Event Detection, and Chapter 22, Traumatic Brain Injury).

Monitoring Artifacts

EEGs in the ICU are particularly susceptible to contamination with a variety of artifacts (64) (see also Chapter 18, Events That Mimic Seizures during ICU Monitoring). Some are periodic or rhythmic and mimic epileptiform discharges or electrographic seizures. These include pacemaker, movement, and chewing artifacts. Artifacts more peculiar to the ICU setting include those from bed machinery and ventilators, and chest percussion from physical therapy. Recognition of these patterns as artifacts generated by external stimuli is facilitated tremendously by video and audio recording obtained simultaneously with the EEG (which is also often necessary for diagnosing pseudoseizures). Video is often helpful, even with routine EEG recordings, to examine for visible evidence of EEG artifacts and their causes. Similarly, comatose ICU patients may have clinical episodes of twitching, tremors, posturing, or sudden changes of heart rate or blood pressure that may appear to be seizures clinically (and by video), but that can be shown with EEG to be very unlikely to be epileptic and inappropriate to treat as seizures.

EEG MONITORING IN THE MANAGEMENT OF NONCONVULSIVE STATUS EPILEPTICUS

Once nonconvulsive seizures or NCSE has been diagnosed, most patients still need EEG monitoring to ensure successful treatment. The EEG guides the use of intensive treatments, assesses the effectiveness of treatment, and shows signs of any relapse. It may also provide important prognostic information.

It is important to follow the EEG during prolonged treatment of SE in the ICU. When NCSE follows GCSE, it must be suppressed for some time, usually 12 to 24 hours or more (especially during definitive treatment with midazolam, pentobarbital, or propofol) to ensure the absence of electrographic (and, of course, clinical) seizures. Nevertheless, the optimal electroclinical goal of treatment (simple cessation of seizures, both clinical and electrographic seizure control, or a certain degree of suppression of cerebral activity—usually a burst-suppression pattern) has never been studied well prospectively. In one study of 35 patients with refractory SE treated with pentobarbital, there were only three patients for whom the EEG showed simply freedom from seizures, and all survived (48). Of the others, those suppressed to the point of a "flat" background did substantially better than those whose EEGs showed a burst-suppression pattern. This was not a prospective study, and it is possible that patients thought to have a better chance of survival were treated more intensively. Another study found no clear difference in outcome depending on the depth of EEG suppression (65).

In a meta-analysis, patients treated (mostly with pentobarbital) with the goal of EEG background suppression (to a burst-suppression or nearly flat pattern) had a 4% chance of breakthrough seizures, versus a 53% chance for patients

treated to control clinical and electrographic seizures only (mostly with midazolam or propofol) (66). Correspondingly, patients treated to EEG background suppression had a 76% chance of significant hypotension, versus 29% for those treated to suppress seizures without such suppressed EEG backgrounds. Whatever the depth of suppression, mortality was the same, 48%, and always attributed to the severity of the underlying illness causing SE.

EEG can detect nonconvulsive, electrographic seizures even after treatment of SE has been initiated—for example, nonconvulsive seizures were found in 18% of patients within the first 6 hours of intravenous midazolam infusion for SE and in 56% of patients during continuous midazolam infusion later (49). When electrographic seizures appear, they are generally not an "innocent" EEG sign, but rather predict a relapse of clinical seizures and SE (49,67). Breakthrough clinical seizures essentially always warrant an increase in antiepileptic drug treatment. Most epileptologists re-treat with higher doses of definitive treatment, or for longer periods at doses that were successful earlier, and then have more antiepileptic drugs (or higher levels of other antiepileptic drugs) on board for the next attempt at tapering. This can lead to a long ICU course. Clearly, these seizures cannot be suppressed unless they are recognized (and probably, the sooner the better), so cEEG is the appropriate way to follow these patients. Isolated epileptiform discharges, however, do not appear to necessitate more treatment (48).

The duration of treatment (and monitoring with cEEG) is also inadequately studied. Many investigators have used 12 to 24 hours of seizure or EEG suppression and then a taper of medication, typically over 12 to 24 hours, although many trials of midazolam are shorter. One study of patients on pentobarbital raised the possibility that a prolonged period of seizure and EEG suppression could be beneficial (48).

ELECTRODIAGNOSTIC EVALUATION IN THE PROGNOSIS AND OUTCOME OF NCSE

It is clear that "not all status epilepticus is created equal," or is equally threatening. The best example is the difference between GCSE and NCSE. GCSE warrants aggressive treatment. Concern for overtreatment exists, but this is not the first priority. On the other hand, there is very little evidence of lasting harm caused by NCSE, so the treatment imperative is less strong, although not negligible. NCSE has therefore sometimes been referred to as "underdiagnosed and overtreated" (68).

In order to discuss prognosis and outcome, it is important to recognize the tremendous variety of illnesses that fall under the rubric of NCSE (see section 2). Like convulsive SE, NCSE includes those with a focal or generalized onset—although many generalized cases cannot be separated easily into those of a primarily generalized nature and those with a focal onset and secondary generalization. Focal NCSE includes aphasic, sensory, and autonomic SE. Secondarily generalized NCSE is the most common type of SE in ICUs. Prognosis for each varies tremendously, with etiology overwhelmingly the most important prognostic feature.

For typical absence SE as with other forms of SE, consequences also depend on the etiology—in this case, the epilepsy syndrome. No long-term morbidity can be attributed to absence SE (69) or any other idiopathic primary generalized SE. Similarly, reports of outcome for complex partial SE indicate that almost all patients return to normal or "baseline cognitive function" (70,71). This applies to complex partial SE as the primary illness; ICU patients are still subject to the effects of the underlying illness prompting the ICU admission. Some patients have prolonged memory deficits after complex partial SE and NCSE (26,72,73), but many such deficits are not permanent. In another study, there was no difference in mortality between patients with complex partial SE (with focal discharges on EEG) and those with GCSE, but the former likely included many patients with secondary generalization (74).

Most reports of NCSE (without specifying whether it is of focal or generalized-onset) show few long-term sequelae of the NCSE itself (20,31,75,76). Adachi and colleagues performed neuropsychological testing on 15 epilepsy patients (without underlying lesions or "symptomatic" causes) before and after episodes of SE (half nonconvulsive) (77). No mortality or significant cognitive morbidity accrued from the SE, suggesting that morbidity in other series comes from the underlying etiology, not from the SE itself (although these were not ICU cases). NCSE should be avoided, but the exact long-term risk from an episode of NCSE, without an acute brain lesion, is unclear.

In the ICU, however, secondarily generalized NCSE is the most common type of SE, and in the setting of severe medical or neurologic disease, morbidity and mortality can be substantial (78), similar to that from electrographic SE or "SE in coma" (37). In one series of 49 patients with nonconvulsive seizures, mortality correlated with etiology, age, and length of ICU stay, but only seizure duration and delay-to-diagnosis were significant predictors upon multivariate analysis (40). Patients with anoxia or multiple medical problems, including sepsis, fare poorly, while those with strokes, tumors, trauma, infection, or abuse of alcohol or other drugs have intermediate results (4). Generally, the most favorable etiology is epilepsy itself with some exacerbating factor (reduced antiepileptic drugs, fever, sleep deprivation, or some intercurrent illness or another precipitant) prompting the SE. Patients with electrographic SE in the setting of serious medical illness have a terrible prognosis, but dissecting out that portion of the long-term harm done by epileptiform discharges, seizures, or SE (37–39,79) from the damage caused by the underlying illness remains problematic (see also Chapter 22, Traumatic Brain

Injury). Usually, little of this morbidity can be attributed to the NCSE itself, and complications of treatment can also contribute to morbidity (80).

Longer SE duration is a risk for worsened outcome (74), but, again, it has been impossible to separate duration (beyond the first hour) conclusively from the influence of etiology, the primary determinant. There are several reports of SE (most of it NCSE) lasting over a month in critically ill patients (81,82). Morbidity and mortality are substantial, but recovery can be good, depending on the etiology (81). Correspondingly, the prognosis for most patients treated with prolonged courses of pentobarbital or other aggressive treatment for refractory SE is dismal (67,83–85), with the very high mortality usually attributed to the almost invariably severe underlying etiology. A longer duration of SE is rarely a good sign, but it is also unwarranted to conclude that the situation is hopeless when SE has continued for hours (or days), especially if the cause is relatively benign.

While risks of treatment exist, patients with NCSE should be treated quickly with antiepileptic drugs for several reasons. They are clearly ill with ongoing seizures and have impaired consciousness, and they may have other neurologic deficits that are potentially reversible and certainly treatable. NCSE, like other forms of SE, entails the attendant morbidity of incidental trauma, aspiration pneumonia, and so on. Also, many episodes of NCSE begin, and may end, with generalized convulsions that are in turn potentially harmful.

EEG findings help to predict outcome after SE. After carotid artery distribution strokes, subarachnoid hemorrhage, meningitis, encephalitis, or closed head injury, a diagnosis of SE increases the mortality rate above that associated with the precipitating event itself (86). Among 94 consecutive patients with moderate to severe traumatic brain injury, 22% had electrographic seizures on EEG, and six patients were in NCSE; those in NCSE all died, while 24% of patients without seizures died (16). The impetus to diagnose seizures and NCSE in acutely ill neurologic patients is increasing as the correlation between SE and poorer prognosis becomes apparent.

PLEDs after SE are associated with an increased mortality, typically attributed to more morbid primary diagnoses (87,88). Burst-suppression patterns are also associated with worse outcomes (whether pharmacologically-induced or due to hypoxia) (12,87), as is persistence of ictal discharges (i.e., electrographic seizures) after clinical control of SE (10,87). In children over 2 years old, lack of background reactivity after SE portends a poorer prognosis (13).

Continuous EEG monitoring aids in the recognition of nonconvulsive, electrographic seizures, influences clinical decision making, and helps predict outcome, but its actual effect on outcome has not yet been established (80,89). No prospective studies have evaluated the use of cEEG compared to routine EEG or other clinical measures in the setting of SE. Rapid diagnosis and EEG-guided treatment appear likely to improve the care of patients with SE. One study found that cEEG monitoring was "decisive" (54%) or "contributing" (32%) to neurologic ICU therapeutic and monitoring decisions (90). If earlier detection and better monitoring of treatment help to reduce the morbidity and mortality associated with SE, it might well be worth the expense engendered by neurologic ICUs, neurointensivists, epileptologists, and EEG technicians. Advances in technology, including the production of MRI/CT compatible EEG electrodes, more precise automatic seizure detection programs, and remote monitoring, is gradually making cEEG monitoring standard practice in the ICU treatment of nonconvulsive status epilepticus, and possibly in many other ICU patients.

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21

ENCEPHALOPATHY AND PROGNOSIS IN COMA

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RICHARD P. BRENNER

In the intensive care setting, EEG complements the history, the physical exam, and neuroimaging studies, and assists in the diagnosis and treatment of individuals in coma. EEG is a very sensitive technique for detecting cerebral dysfunction in patients with stupor and coma. The extent of alteration of EEG activity typically corresponds to the degree of brain dysfunction. Although EEG allows an objective assessment of the severity of central nervous system abnormality, it is not specific and cannot independently identify the etiology of stupor or coma. In addition, EEG cannot reliably distinguish between an acute or chronic process, but changes are typically more dramatic in an acute process. This chapter focuses on the role of conventional visual EEG analysis in the evaluation of adults in coma secondary to encephalopathy. Whether caused by a metabolic disturbance, drugs, or anoxia, encephalopathy is typically associated with generalized changes of background EEG activity.

In contrast to the lab setting, recording and interpreting EEG in the intensive care unit (ICU) can be especially challenging. From a technical standpoint, the ICU is a hostile environment and the EEG recording is often contaminated by artifacts arising from monitoring equipment, life support systems, and health care professionals. The use of additional electrodes for monitoring of the electrocardiogram (EKG), movements (body, tongue, and eye), respiration (as shown in the last channel in Figure 21-1), and the temporary disconnection of other equipment may be needed to identify the noncerebral origin of such activity. To complicate things further, patients in the ICU typically have multiple medical problems and are usually being treated with numerous medications that can affect the EEG.

When recording comatose patients, it is important to test for both variability and reactivity. Reactivity is defined as a change in EEG activity following stimulation (EEG response to painful stimulation to the left arm is shown in Figure 21-2). The recording should be continued for a sufficient period of time without stimulation so that the presence or absence of spontaneous variability can be accurately determined. Stimuli, both auditory and tactile, should be applied when the patient and surroundings are relatively quiet. If reactivity is present, the EEG changes in a consistent fashion. Following stimulation, background activity may show an attenuation of ongoing activity or an increase in amplitude, which is usually accompanied by the appearance of slower-frequency activity. Reactivity indicates a lighter level of coma, and as the prognosis in most cases of coma is related to severity more than etiology, this is generally a good sign.

There are however some exceptions. In an encephalopathy due to drug intoxication, in which recovery typically occurs with appropriate treatment, the presence or absence of EEG reactivity is of less value. In addition, in other cases reactivity is not necessarily a good sign. There are a number of controversial periodic EEG patterns, such as periodic epileptiform discharges (PEDs), which can be either generalized (GPEDs) or lateralized (periodic lateralized epileptiform discharges (PLEDs)); bilateral independent PLEDS (BIPLEDs), and triphasic waves (TWs) that may become prominent following stimulation. When induced by stimulation, these patterns represent stimulus-induced, rhythmic, periodic or ictal discharges (SIRPIDs) (1) (Figure 21-3). Technological advances have allowed continuous digital EEG and simultaneous video EEG monitoring in the ICU. Using these techniques, Hirsch et al. (1) noted striking EEG changes when stuporous or comatose patients were stimulated. In their study of 150 critically ill patients undergoing continuous EEG monitoring, 33 patients exhibited SIRPIDs. No significant difference was found in the incidence of clinical seizures in patients with SIRPIDs (30%) compared with those without (45%), nor did the researchers find any particular correlation between subtypes of SIRPIDs and clinical findings.

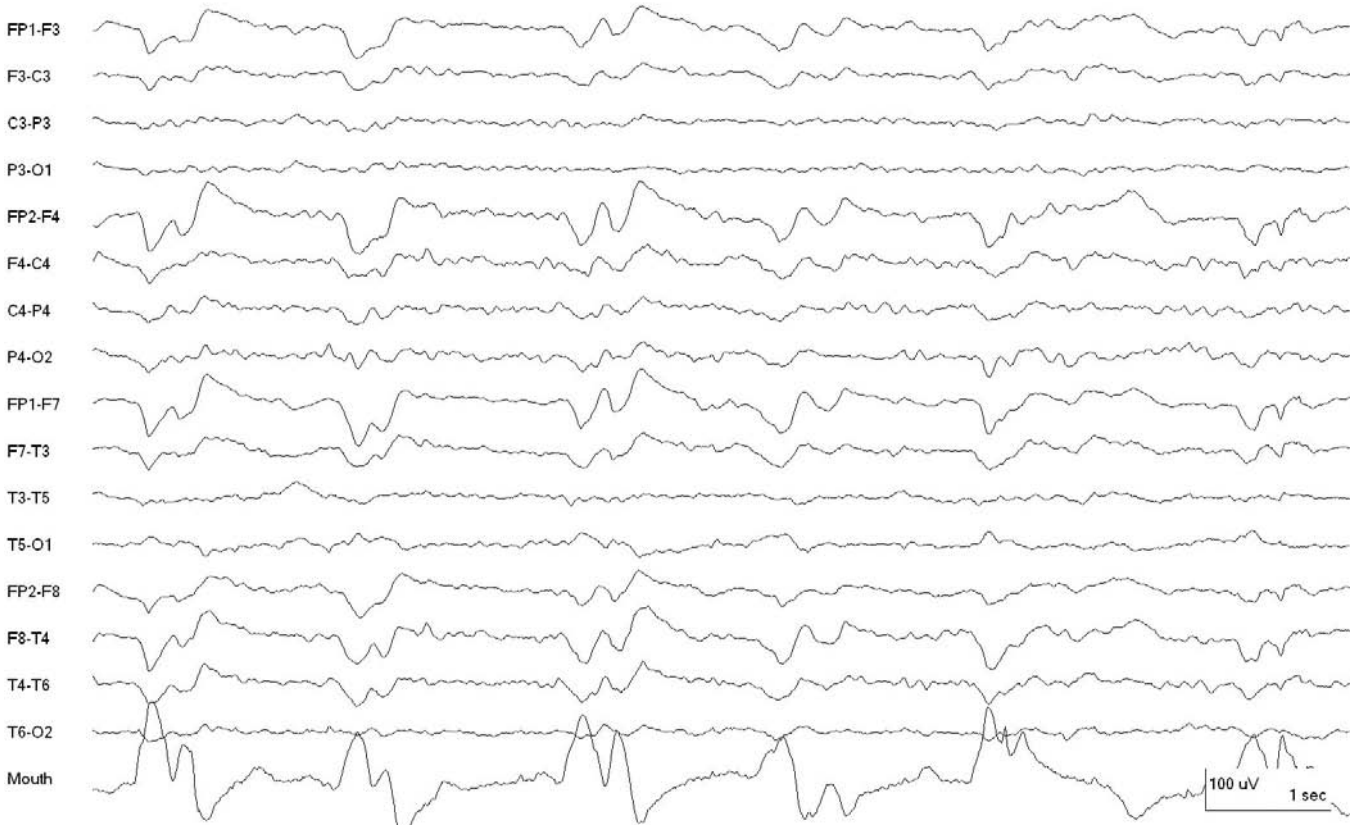

FIGURE 21-1. Respirator artifact in a 46-year-old woman. The derivation in the bottom channel consists of electrodes placed above and below the lips.

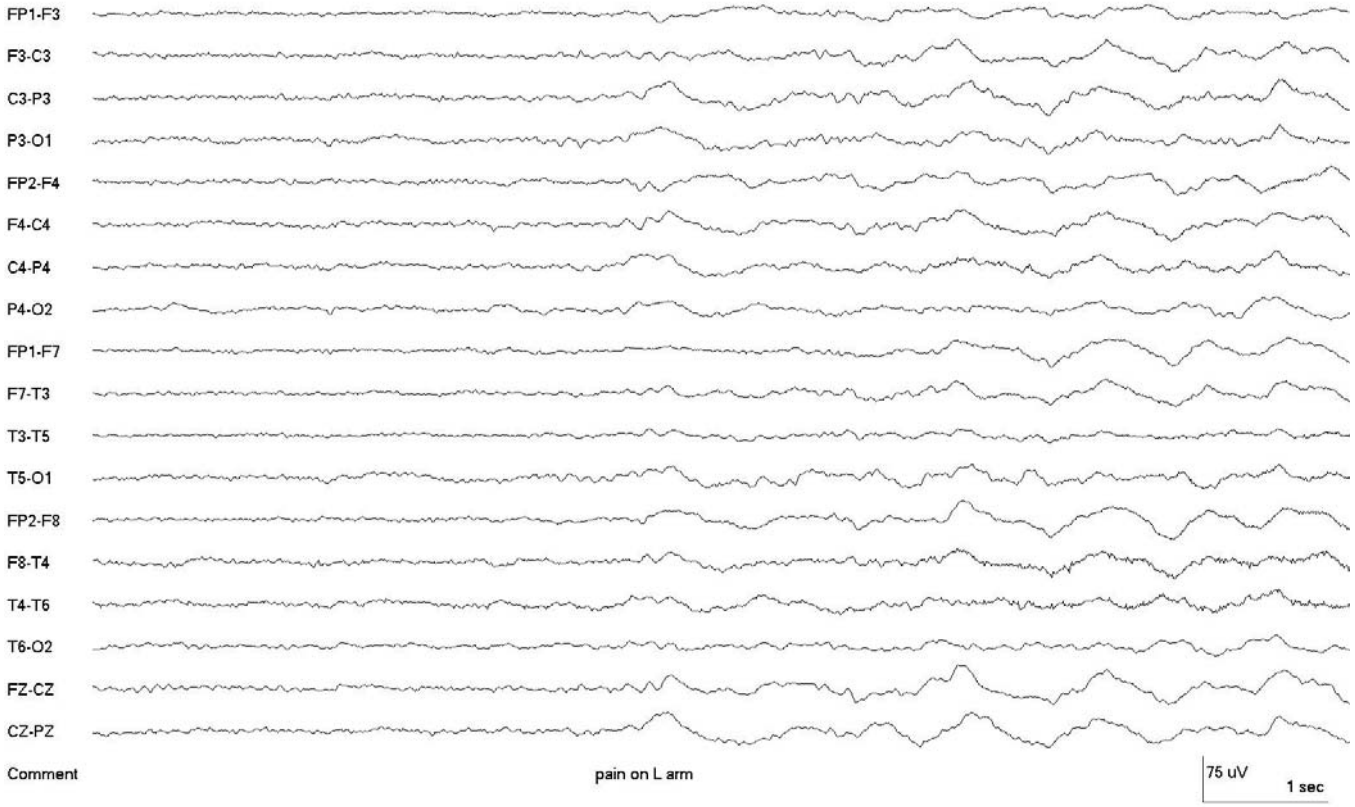

FIGURE 21-2. Reactivity in a 27-year-old-man with a heat stroke. There is an increase of generalized delta activity following tactile stimulation.

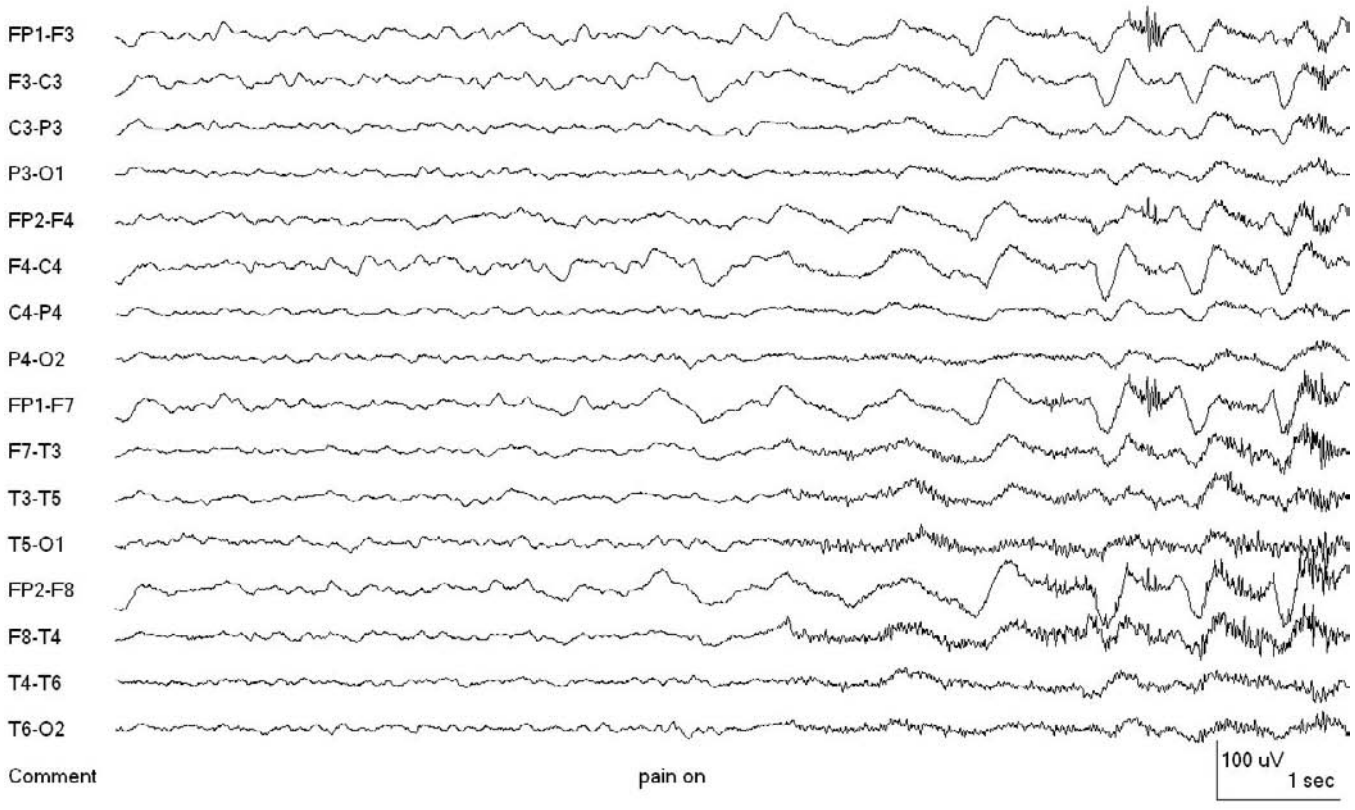

FIGURE 21-3. SIRPIDs, following tactile stimulation, in a 61-year-old man with listeria meningitis.

Although EEG patterns in patients with encephalopathy are suggestive of the degree of central nervous system impairment, none are specific and few can predict outcome. With progression from lethargy to coma, there is diffuse slowing of background rhythms from alpha to theta and subsequently, delta activity (2). The term frontal intermittent rhythmic delta activity (FIRDA) (Figure 21-4) is used to describe bursts of rhythmic delta activity, maximal over the anterior head regions. Triphasic waves, originally linked to hepatic failure, are also commonly seen in uremic and anoxic encephalopathies. Periodic patterns, which may include epileptiform transients, are usually indicative of an acute or subacute severe diffuse encephalopathy. Spindle coma contains features of stage 2 sleep, but the patient is not arousable; alpha and theta comas reveal generalized rhythmic activity predominantly in the alpha and theta range, respectively. This chapter will review EEG patterns commonly encountered in ICU encephalopathy.

METABOLIC ENCEPHALOPATHY

Metabolic brain dysfunction is a leading cause of coma (3). The degree of background slowing usually parallels the severity of the encephalopathy, although there are exceptions. One of the limitations of EEG is its lack of specificity. EEG cannot aid in distinguishing between metabolic encephalopathies caused by liver failure, by kidney failure, or by an electrolyte imbalance.

Hepatic Encephalopathy

Triphasic waves (Figure 21-5) are commonly associated with hepatic encephalopathy, but often occur in uremic encephalopathy or subsequent to anoxia. Foley et al. (4) described blunt spike-and-slow wave complexes in patients with liver disease. These waveforms were subsequently termed triphasic waves (5), and consist of bursts of moderate to high amplitude (100 to 300 uV) activity, usually of 1.5 to 2.5 Hz, often occurring in clusters. Although frequently predominant in the frontal regions, occasionally they are maximal posteriorly. A fronto-occipital lag may be present. The initial negative component is the sharpest component, whereas the subsequent positive portion of the complex is the largest and is followed by another negative wave. Triphasic waves are bisynchronous but may show shifting asymmetries. A persistent asymmetry of background EEG activity, not related to technical factors or a skull defect, suggests an underlying structural lesion on the side of the lower amplitude.

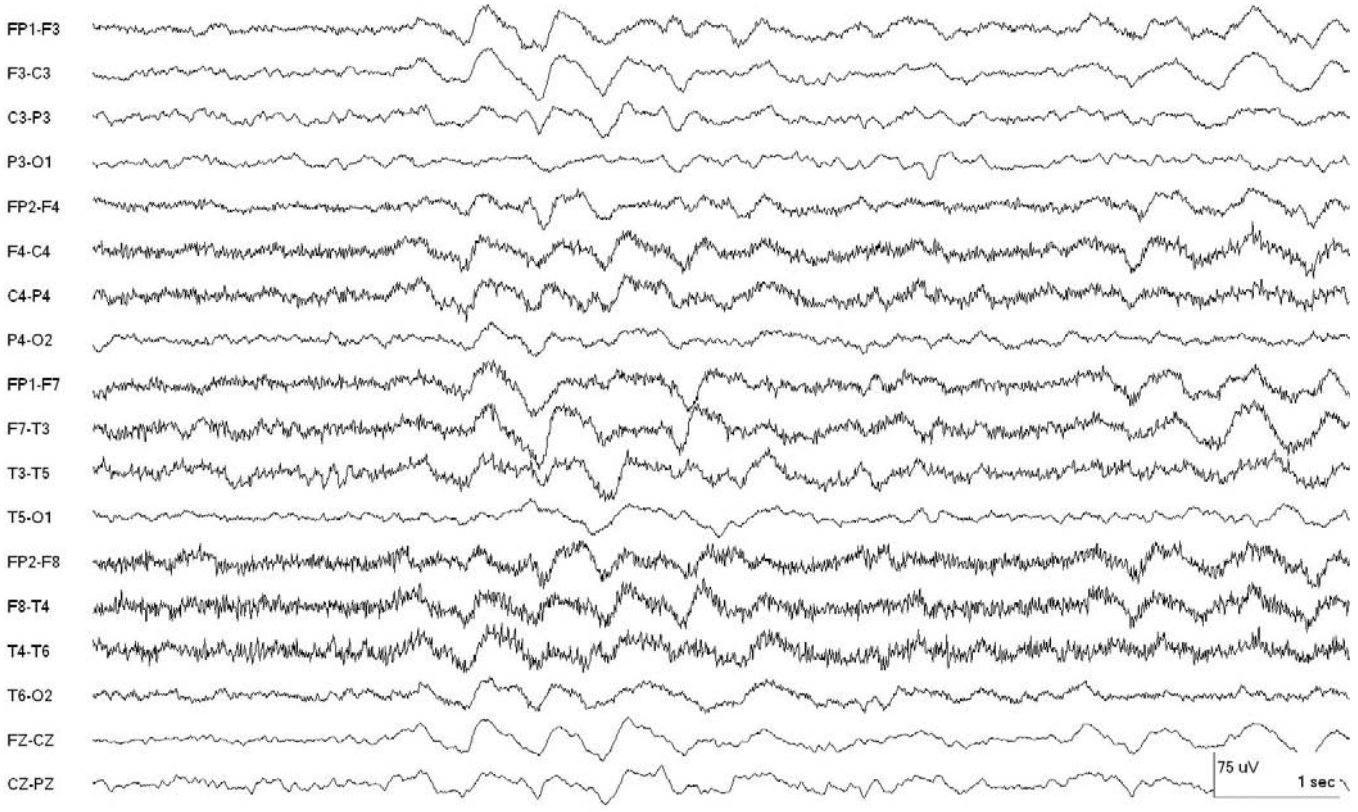

FIGURE 21-4. FIRDA in a 62-year-old with end-stage renal disease.

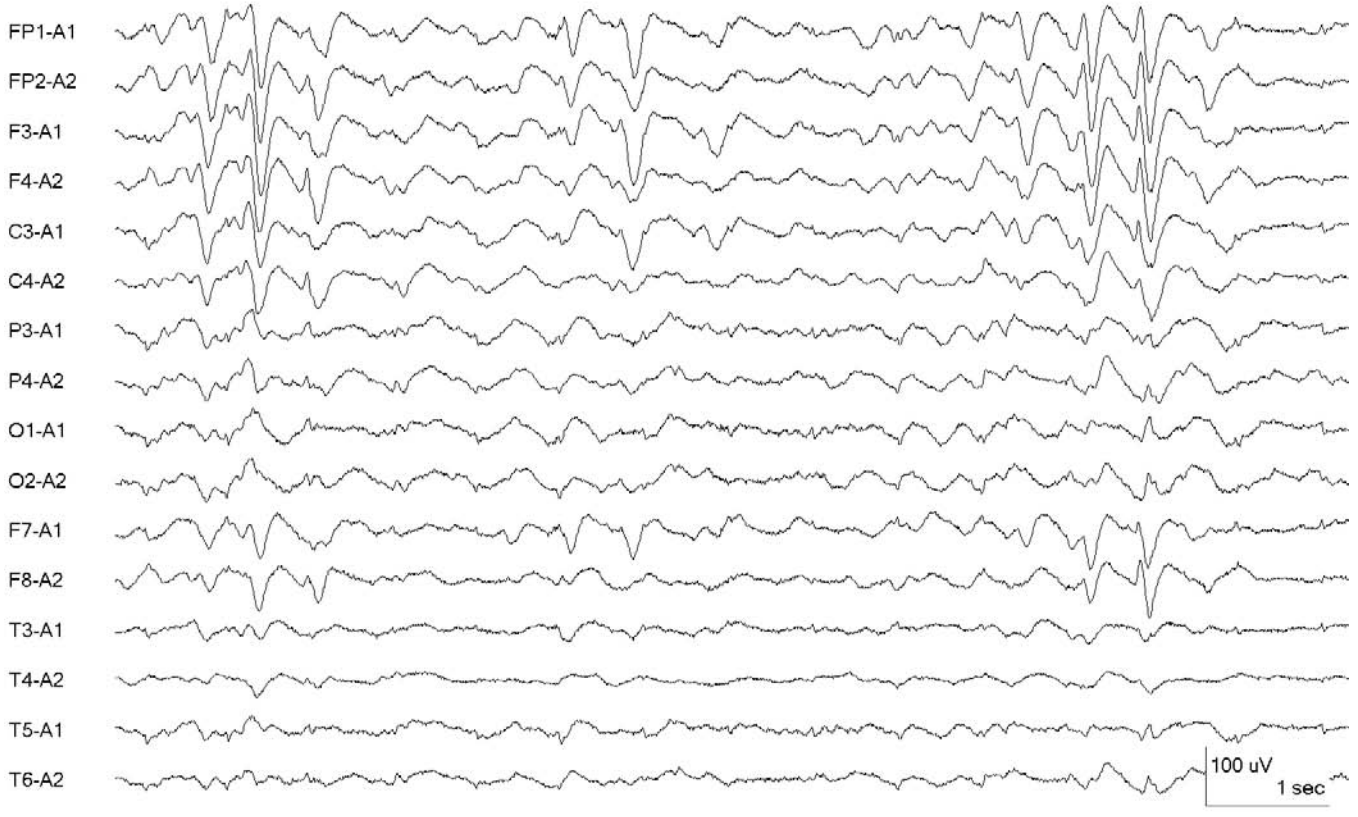

FIGURE 21-5. Triphasic waves, occurring in clusters, in a 58-year-old man with hepatic encephalopathy.

Initially, triphasic waves were believed to be highly specific for hepatic dysfunction, but subsequent studies identified numerous causes. Karnaze and Bickford (6), in a study of 50 patients whose EEGs showed triphasic waves, found the variety of etiologies to include hepatic dysfunction (28), azotemia (10), hypoxia (9), hyperosmolarity (2), and hypoglycemia (1). Bahamon-Dussan et al. (7) found multiple metabolic derangements to be the most common cause of triphasic waves, being present in 12 of 30 patients. Patients were either very lethargic or comatose, and the mortality was high (77%). Sundaram and Blume (8) found senile dementia of the Alzheimer type to be the most common diagnosis among 37 patients with triphasic waves who did not have a metabolic encephalopathy.

In a study of the diagnostic specificity of TWs, those occurring in hepatic encephalopathy were more likely to be associated with severe EEG background slowing than other encephalopathies with these waveforms (9). However, none of the morphological features of TWs (including longitudinal topography, phase lag, symmetry, and longitudinal bipolar phase reversal sites) reliably distinguished hepatic encephalopathy from other forms of metabolic encephalopathy. Sundaram and Blume (8) found the etiology of triphasic waves more closely related to the patient's level of consciousness at the time of recording than to any of the waves' morphological aspects or distributional features, or to the nature of EEG background activity. Awake but confused patients all had nonmetabolic encephalopathies, particularly Alzheimer's disease, whereas all unarousable patients had metabolic encephalopathies.

Triphasic waves and generalized spike-wave discharges in generalized nonconvulsive status epilepticus (GNCSE) can closely resemble one another. Difficulties in distinguishing triphasic waves from generalized epileptiform abnormalities were initially noted by Foley et al. (4), and recommendations to differentiate these entities were provided by several investigators (10–12). Kaplan (13) felt that triphasic waves might straddle the borders between epilepsy and encephalopathy and that the distinction between GNCSE and encephalopathy could be difficult; Litt et al. (14) felt that monorhythmic triphasic waves could be distinguished from ictal patterns. Clearly there are times when this distinction can be difficult; hence terms like "triphasic-like waves" and nonepileptiform "true triphasic waves" (15).

EEG features were felt to help differentiate triphasic waves from epileptiform discharges seen in GNCSE in a recent study (16). This retrospective study analyzed 87 EEGs (from 71 patients) with triphasic waves and 25 EEGs (from 13 patients) with GNSCE. The authors proposed that the morphological characteristics of the waveforms could distinguish triphasic waves from GNCSE. They reported that wave 1 is of shorter duration, and that the frequency of the complexes is higher, in GNCSE. In GNSCE, extra spikes preceding wave 1 and less prominent background slowing was present. In patients with triphasic waves caused by metabolic encephalopathies, phase 2 was maximal (exceeding by at least 50% all other waveforms), and this did not occur in the group with GNCSE. There was usually a lag of phase 2 in the encephalopathy group only, which most commonly was anterior to posterior, but could be posterior to anterior. Triphasic waves increased in a large percentage of cases following stimulation, whereas stimulation had no effect on the discharges in GNCSE. As noted by Young (17), the study had limitations. It was retrospective and used traditional differentiating EEG criteria that have never been subjected to pathophysiological investigations for confirmation. Thus, the study was almost tautological in its approach.

An unusual finding in hepatic encephalopathy is 14- and 6-Hz positive spikes (Figure 21-6). This pattern is commonly present in young children and adolescents in drowsiness and light sleep, and is considered a benign EEG variant. Yamada and coworkers (18) identified these waveforms in over 50% of their patients with Reye's syndrome who were comatose and whose EEGs were markedly abnormal, showing diffuse delta activity. This high incidence of 14- and 6-Hz positive spikes in hepatic encephalopathy contrasts with the scarcity of similar findings in other comatose patients.

Flumazenil competitively inhibits the activity at the benzodiazepine recognition site on the GABA/benzodiazepine receptor complex. Although benzodiazepine antagonists have been shown to improve background EEG activity and symptoms of encephalopathy in patients with hepatic failure, several studies have not supported a major therapeutic benefit of flumazenil in most patients with hepatic encephalopathy (19).

Renal Encephalopathy

Renal disease shows abnormalities similar to other metabolic encephalopathies, with progressive slowing of background rhythms and superimposed bursts of slow activity with worsening kidney function. Triphasic waves are also seen in renal encephalopathy, the incidence being similar to that with hepatic disease (approximately 20%). In contrast, seizures and epileptiform abnormalities are more common in uremic than hepatic encephalopathy. As discussed in the medication section of this chapter, there is an association of renal failure, treatment with cephalosporins, and GNCSE (20,21).

EEG changes are common in patients with renal failure requiring dialysis (Figure 21-7). Hughes (22) reviewed the correlation between multiple EEGs and chemical changes in 23 uremic patients undergoing chronic hemodialysis over long periods of time (up to 18 months). They found that 70% of patients had at least one abnormal EEG. The one single serum index that correlated best with the EEG was the blood urea nitrogen. This was especially true if the record showed a worsening. Other syndromes in patients with renal disease undergoing dialysis include the dialysis disequilibrium syndrome and progressive dialysis encephalopathy.

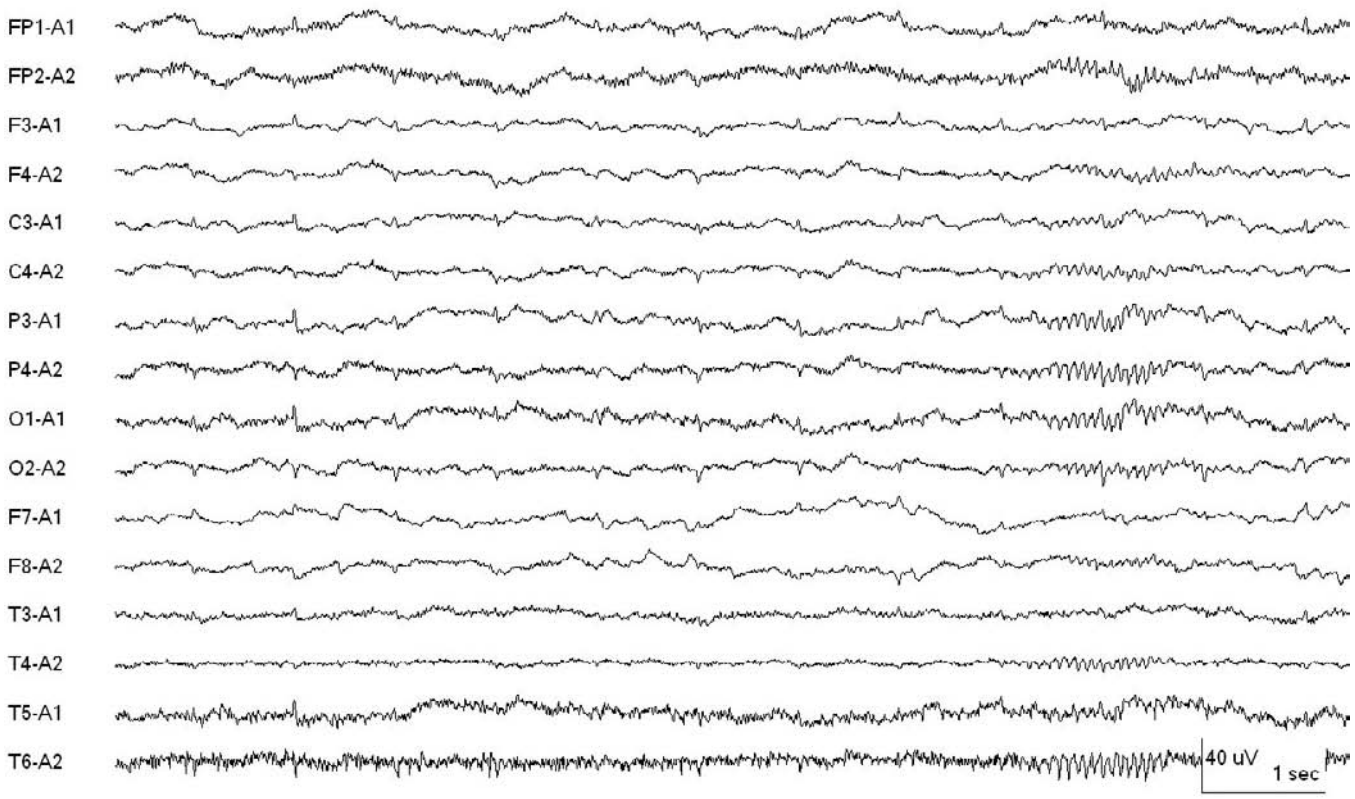

FIGURE 21-6. Fourteen-hertz positive spikes in a comatose 55-year-old woman with hepatic failure.

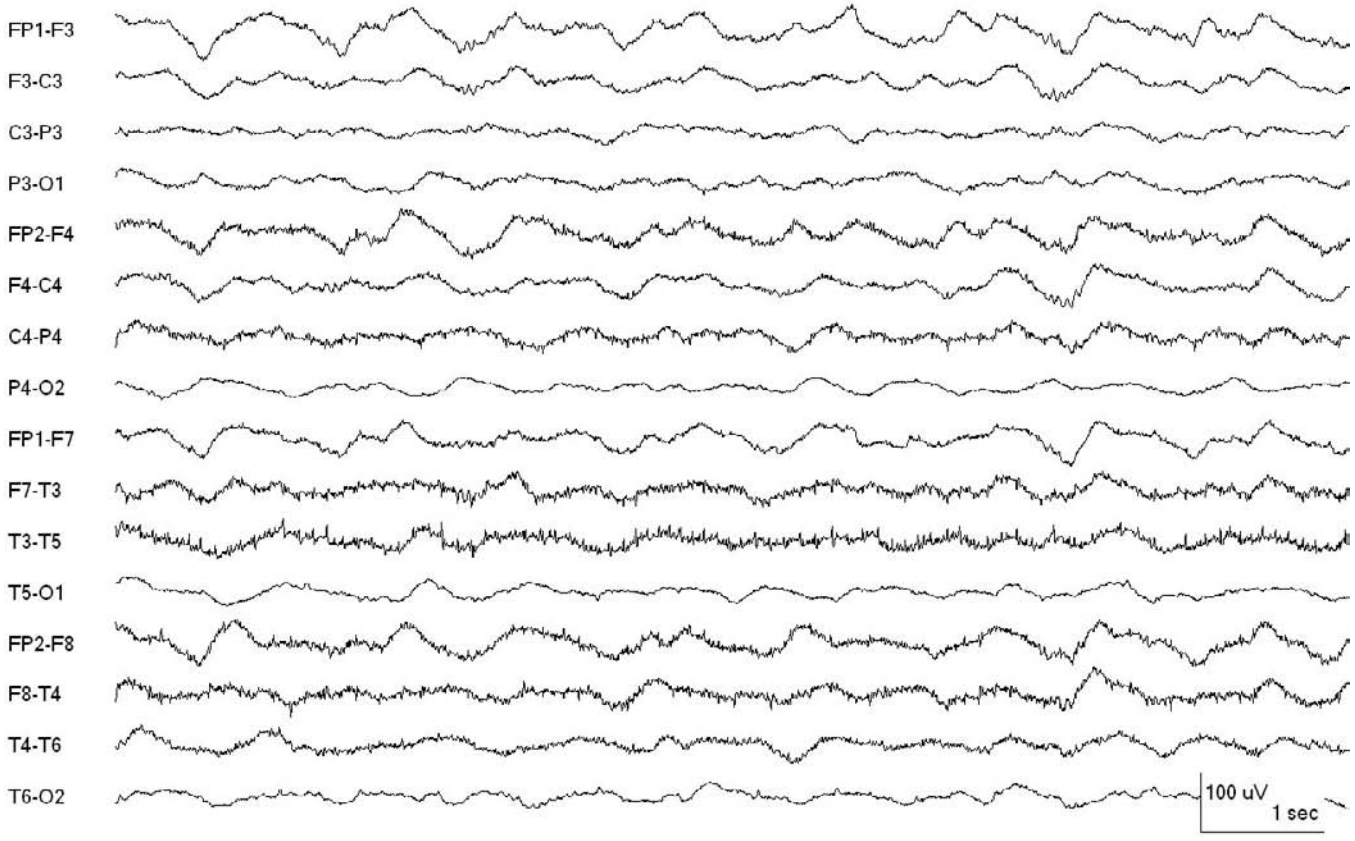

FIGURE 21-7. Diffuse slowing of background activity in a 33-year-old man with renal failure.

Dialysis disequilibrium (23) can be associated with multifocal myoclonus, muscle twitching, tremor, and disorientation. In patients who develop dialysis disequilibrium syndrome, there is a worsening of the clinical state and EEG following dialysis (24). The EEG can reveal background slowing and FIRDA. Progressive dialysis encephalopathy, also known as dialysis dementia, is a severe and frequently fatal disease characterized by memory loss, seizures, involuntary motor phenomena, and gait disturbance (23). Hughes and Schreeder (25) found bilateral spike-and-wave complexes in 77% of patients with dialysis encephalopathy syndrome, but found such complexes in only 2% of chronic renal patients without dialysis encephalopathy. Bursts of diffuse slow waves, usually maximal in the frontal area, were more frequent in dialysis encephalopathy patients, although common in both groups. In a review of EEG and clinical features in 14 patients with dialysis encephalopathy, the most characteristic EEG feature (12 patients) was paroxysmal high-voltage delta activity, usually maximal anteriorly. Spike-and-wave activity occurred in five patients; two patients had triphasic waves (26).

Encephalopathy Associated with Altered Glucose Metabolism

Cerebral function is dependent on glucose (Figure 21-8). Early studies revealed that cortical electrical activity is sensitive to serum glucose levels. However, level of consciousness, low blood sugar levels, and EEG changes do not always correlate (27). Diabetic coma is typically associated with acidosis and electrolyte abnormalities, and the EEG frequently shows diffuse continuous slowing. Localized epileptiform abnormalities, such as PLEDs, occur in association with partial seizures or epilepsia partialis continua, and are most common in nonketotic hyperglycemia (28–30). Nonketotic hyperglycemia-related epilepsia partialis continua has recently been correlated to ictal unilateral parietal hyperperfusion (31). Although atypical, a case of epilepsia partialis continua has been reported in ketotic hyperglycemia (32).

Encephalopathies Related to Electrolyte Abnormalities

As with alterations in blood serum glucose levels, changes in electrolyte or fluid balance can result in altered levels of consciousness and EEG changes. Fluctuations in sodium, calcium, hypophosphatemia, and hypomagnesaemia result in generalized EEG slowing. Electrolyte abnormalities, most commonly hyponatremia (<120 mmol/L), can be associated with seizures. Clinical and EEG changes are usually related to the rate of changes of electrolyte abnormalities (27).

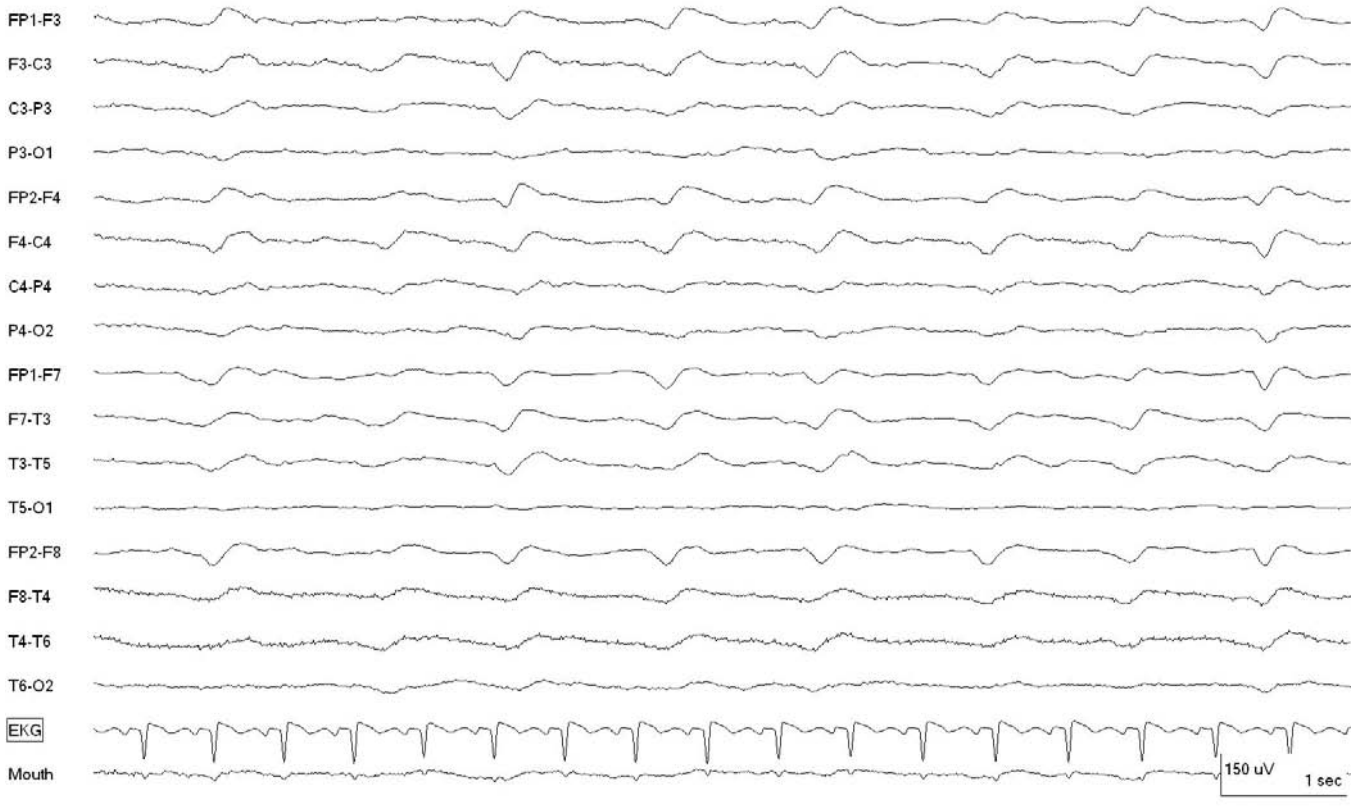

FIGURE 21-8. Generalized periodic complexes in a 50-year-old woman who was comatose as a result of severe hypoglycemia.

COMA SUBSEQUENT TO CARDIAC ARREST

Coma caused by hypoxic-ischemic insult encountered in the ICU most commonly follows cardiopulmonary resuscitation. The neurological examination in combination with EEG and somatosensory evoked potentials (SSEPs) can aid in determining the prognosis for recovery following cardiac arrest (33,34). A wide variety of abnormal EEG patterns (35,36) have been described following arrest. The EEG literature addressing the impact of hypoxia/ischemia on EEG activity is extensive and contains several grading systems that have been purported to aid in prognosis. However, the time between resuscitation and EEG testing was highly variable, limiting the value of these reports. EEG grading systems proposed to aid in prognosis following arrest (37–40) were recently reviewed (33,41). The EEG is helpful in prognosis of favorable and very poor outcomes, but less accurate in patients between these extremes. EEG will help to identify electrographic seizures or nonconvulsive status epilepticus following arrest.

Synek (42) classified patterns into benign, uncertain, and malignant groups. Benign patterns comprised the following: near normal; rhythmic theta, reactive; frontal rhythmic delta, reactive or nonreactive; and spindle coma. Uncertain patterns comprised mixed theta and delta, nonreactive; dominant delta, reactive or nonreactive; alpha-coma, reactive; and epileptiform discharges on a base of diffuse delta. Malignant categories comprised low-amplitude delta (<50 uV), nonreactive; burst-suppression; suppression (<20 uV); alpha-theta coma, nonreactive; and epileptiform discharges with burst-suppression. Further modification of the classification system resulted in greater interrater reliability (40). Several studies have reviewed early prediction of poor outcome in hypoxic-ischemic coma using clinical findings and electrophysiologic studies (EEG and SSEP) (34,41,43–49).

Recent practice parameters concluded that generalized suppression to less than or equal to 20 microvolts, or a burst-suppression pattern with generalized epileptiform activity (Figure 21-9), were strongly "but not invariably" associated with a poor outcome (33). In comatose patients having repetitive myoclonic jerks following an arrest, the EEG often shows the jerks to be associated with repetitive spikes, sharp waves, or triphasic-like waves occurring at approximately 1-second intervals with periods of suppression between the intervals, a burst-suppression pattern. This entity, which has gone under a variety of terms including myoclonic

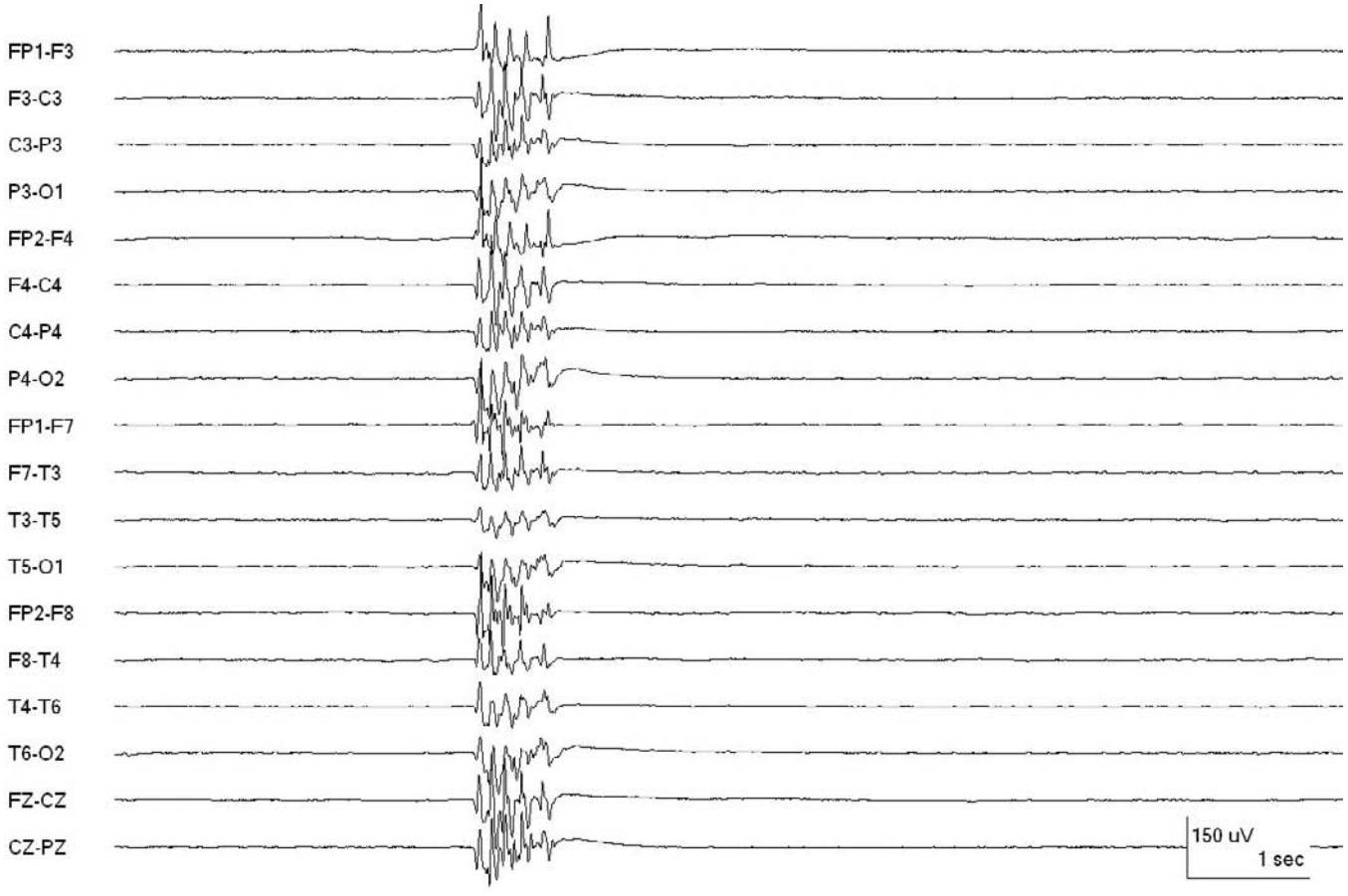

FIGURE 21-9. A burst-suppression pattern with epileptiform bursts in a 58-year-old man after a cardiorespiratory arrest.

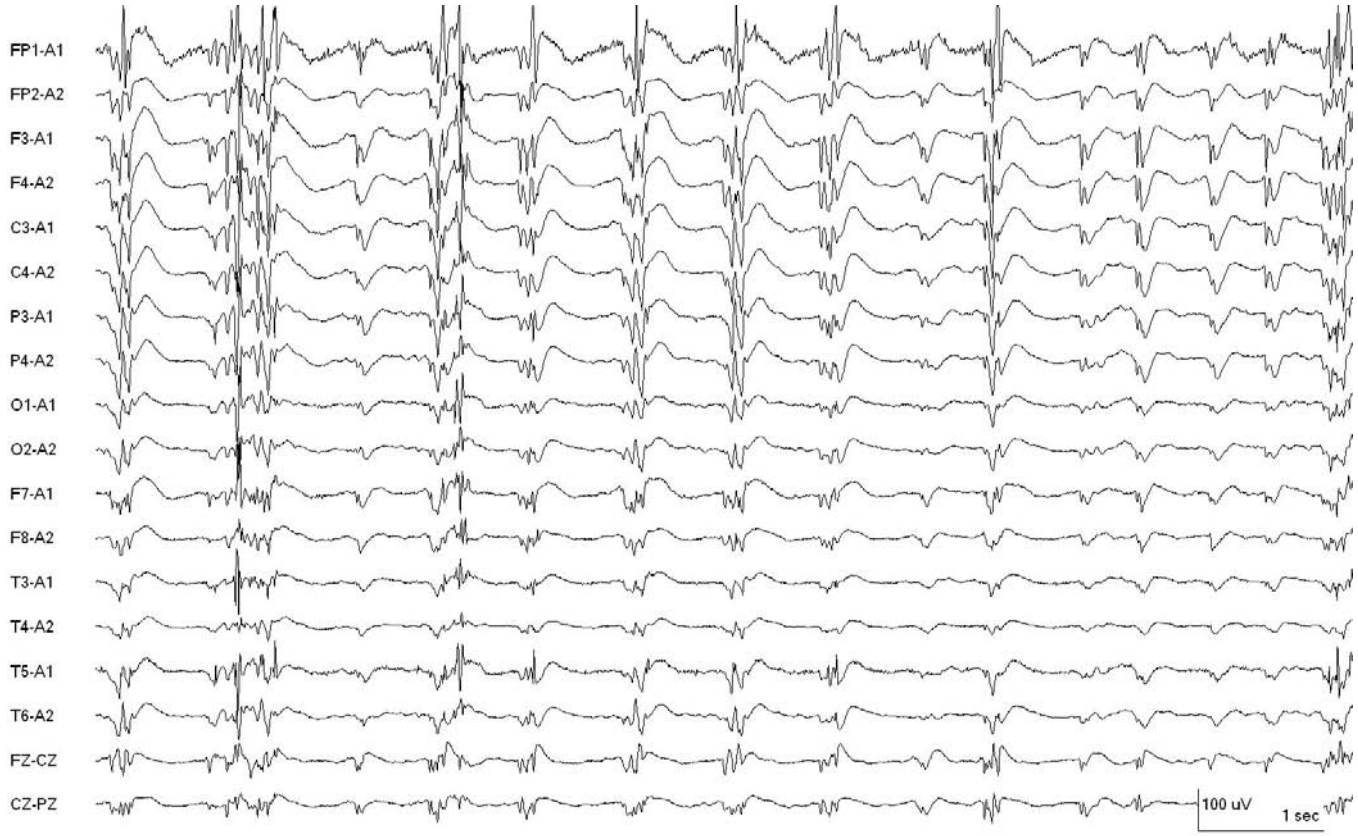

FIGURE 21-10. Generalized periodic polyspikes in a 69-year-old man in myoclonic status epilepticus after a cardiac arrest.

status epilepticus (50), status myoclonus (51), generalized status myoclonicus (52), and generalized myoclonic status epilepticus (53) (Figure 21-10), is usually associated with a fatal outcome (33,54–57). Some patients described as having subtle generalized convulsive status epilepticus have had similar clinical and EEG findings (58).

As indicated above, a burst-suppression pattern is associated with an extremely poor prognosis. Kuroiwa and Celesia (59) reviewed 11 patients of their own and previously published reports of 105 other patients with a burst-suppression pattern who were comatose after a cardiorespiratory arrest and not under the effects of central nervous system depressants. Of the 116 patients, 111 (96%) died. In some patients with a burst-suppression pattern, spontaneous movements can occur. These are usually orofacial-lingual movements, such as eye opening or chewing (Figure 21-11), and may be misleading regarding the patient's level of consciousness (60,61). A generalized periodic pattern following a cardiorespiratory arrest (Figure 21-12) also carries a poor prognosis (15,33,37,49,62). Often there are no associated clinical changes, other than a decreased level of consciousness. Another pattern that occurs in hypoxia, as well as in metabolic encephalopathies, consists of brief (up to several seconds), intermittent periods of generalized suppression without associated bursts; it is often associated with a poor prognosis (Figure 21-13) (63,64).

An alpha coma pattern (Figure 21-14) has been described following hypoxia (65), as well as with drug intoxications. Although the frequency of the activity is in the alpha range, it is widespread, is often of greatest amplitude anteriorly, and does not show the usual reactivity to passive eye opening and eye closure. Thus, the activity does not represent the normal physiologic alpha rhythm but rather is an abnormal pattern. In a review of 94 posthypoxic cases, only 10 of 86 patients survived when the pattern was secondary to cardiopulmonary arrest (66). In contrast, when the pattern was secondary to a respiratory arrest, seven of eight patients survived.

Unfortunately, there have been few studies comparing the outcome of patients with coma associated with alpha-frequency activity in the EEG with a clinically similar group of individuals who have other EEG findings after cerebral hypoxia from cardiac arrest. Some earlier studies (67,68) suggested that the prognosis in patients with alpha pattern coma was no worse than in other patients who had been comatose for more than 24 hours after cardiac arrest. Young et al. (69) reviewed alpha coma, theta coma, and alpha-theta coma patterns. They felt that these patterns represented transient clinical EEG phenomena that did not differ from each other in etiology or outcome and that indicated severe disturbance in thalamocortical physiology.

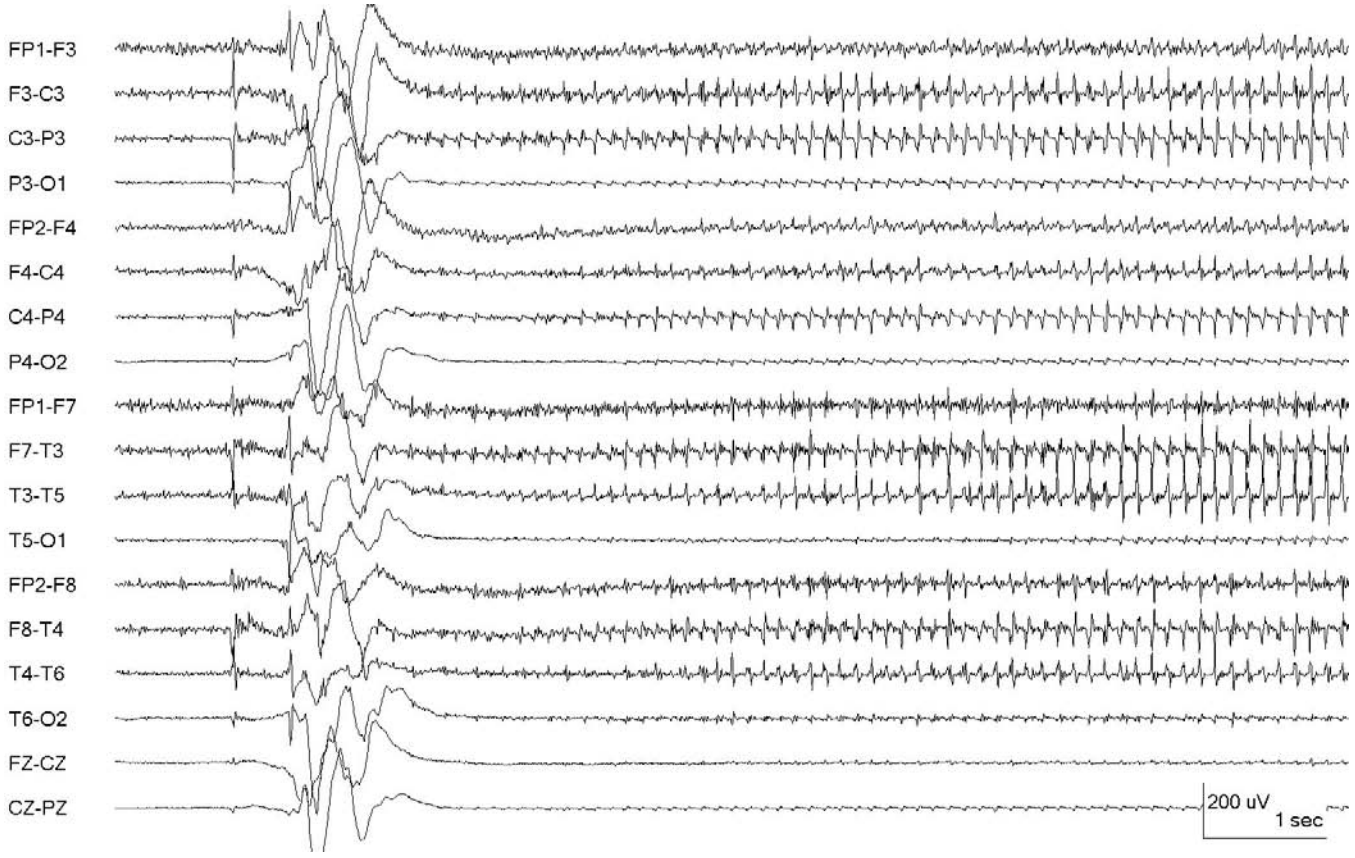

FIGURE 21-11. A burst-suppression pattern in an 80-year-old man one day after an arrest. Jaw movements were unassociated with EEG changes, aside from artifact.

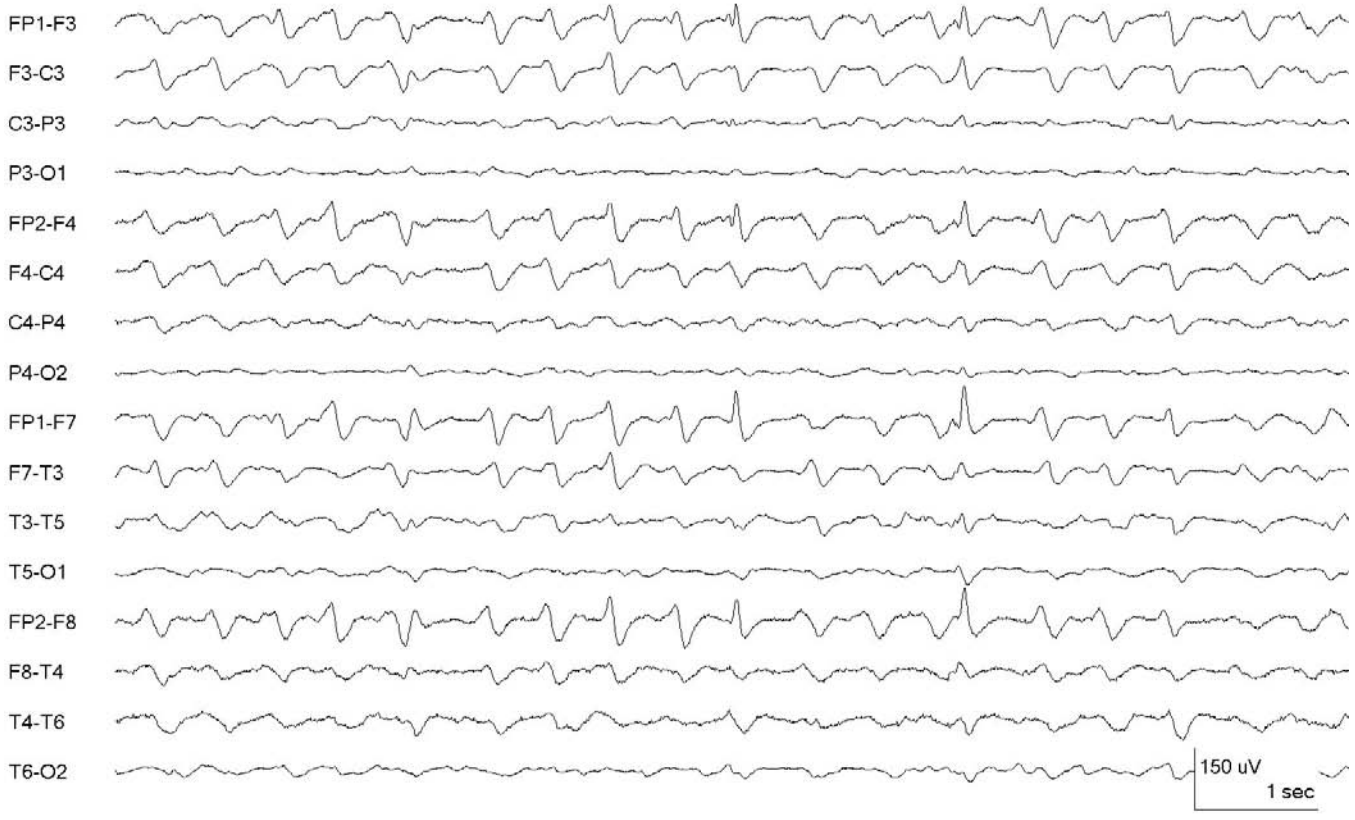

FIGURE 21-12. Generalized periodic pattern after an arrest in a 46-year-old man.

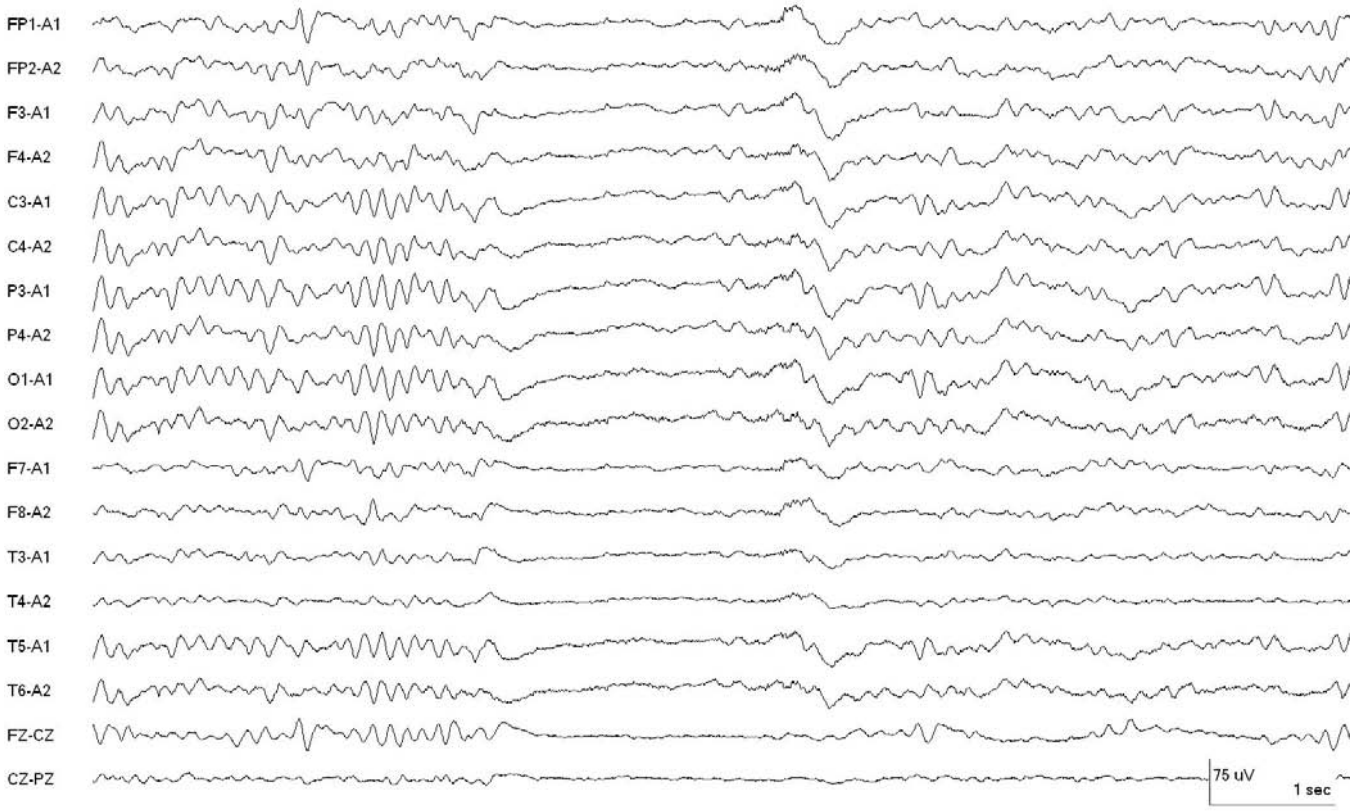

FIGURE 21-13. Intermittent suppression in a 44-year-old woman.

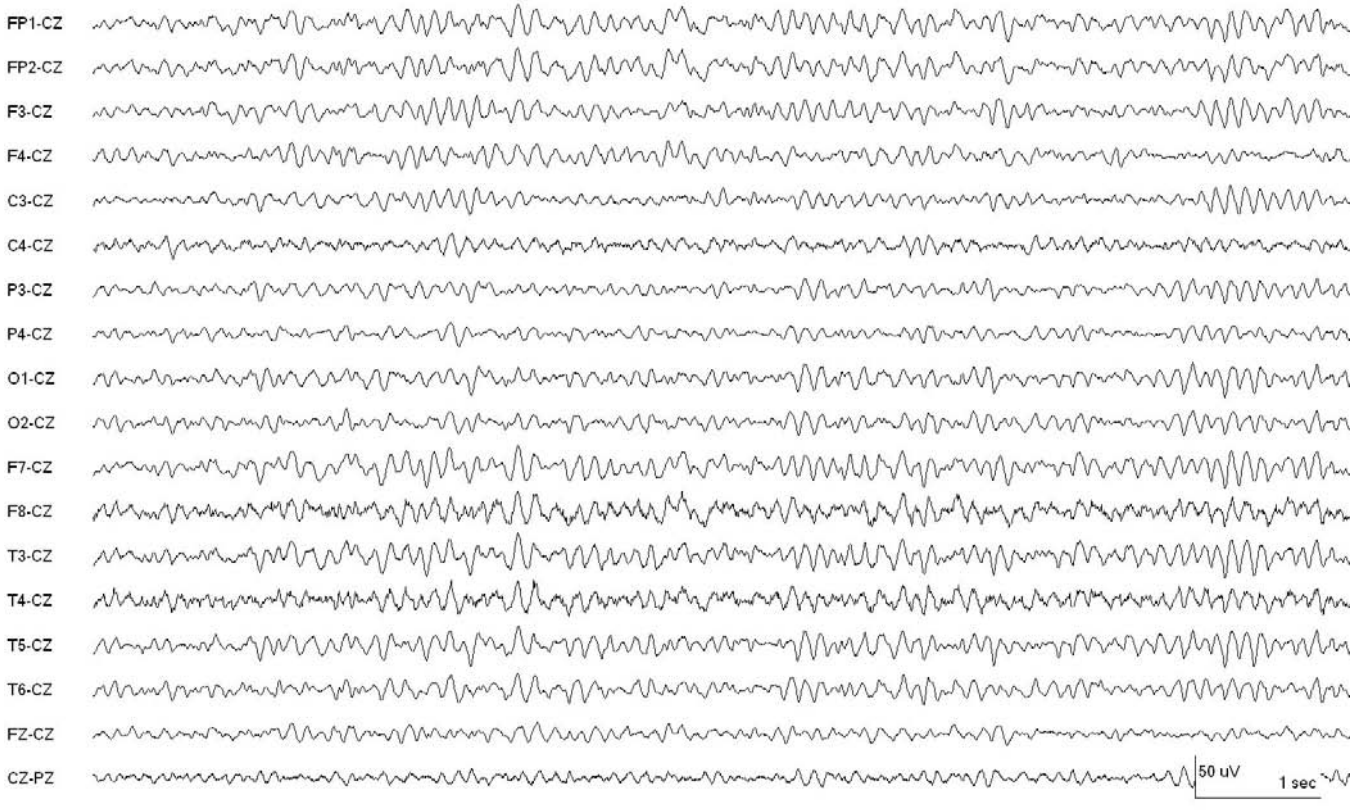

FIGURE 21-14. An alpha coma pattern in a 68-year-old man post–cardiorespiratory arrest.

Using serial recordings, the authors found that these patterns usually changed to a more definitive pattern within 5 days, and that EEG reactivity in subsequent tracings was relatively favorable.

A study of 14 comatose patients with an alpha-theta coma after cardiac arrest, and a review of 283 reported cases of posthypoxic alpha-theta coma, suggested the existence of incomplete and complete variants of alpha-theta coma (70). Incomplete alpha-theta coma (the alpha-theta EEG activity was not monotonous, was partially reactive, or was posteriorly dominant) was associated with a full recovery, whereas complete alpha-theta coma was invariably associated with a poor outcome. Kaplan et al. (71) retrospectively reviewed 36 patients with alpha coma pattern and performed a meta-analysis of 335 cases of alpha coma in the world literature, and found that it had an outcome of fatality or persistent vegetative state in 88% of cases. There was a very high mortality in patients with a cardiorespiratory arrest, whereas approximately 90% with drug-induced coma survived. The review authors stressed the importance of reactivity, as well as etiology. EEG reactivity to noxious stimuli favored survival; without it, most patients died, and this was independent of etiology.

Another type of alpha coma has been described with brainstem lesions, as a result of involvement of the upper pons and caudal midbrain, usually secondary to a vascular insult. With bilateral involvement of the pontine tegmentum, the patient is comatose with an EEG showing alpha activity (72). In contrast to the posthypoxic alpha coma pattern, the alpha frequency activity seen with a brainstem lesion is more posterior and shows more variability. In addition, there may be reactivity with sensory stimulation such as passive eye opening and eye closure or painful stimuli (65). Although the EEG resembles normal wakefulness, few patients survive. Patients with this type of alpha coma pattern need to be distinguished clinically from patients with a "locked-in" syndrome (73–75).The latter are conscious, although paralyzed and mute, and can often communicate with eye blinks; the lesion affects the ventral pons but does not involve the pontine tegmentum, and consciousness is not affected.

A spindle coma pattern is thought to be caused by altered function caudal to the thalamus but rostral to the pontomesencephalic junction (76). This pattern has been described in a variety of conditions including hypoxia, drug intoxications, diffuse encephalopathies, and subtentorial or supratentorial lesions. In a study of 22 patients with a spindle coma pattern, approximately one-third of cases were secondary to head injury, whereas another third were secondary to cerebral hemorrhage or cerebral hypoxia (77). The authors concluded that EEGs with spindle coma patterns are of dubious value in the prognosis of coma, because the outcome for patients with this EEG pattern was no better than those without it. In 14 posthypoxic patients, the presence of spindles did not indicate a favorable prognosis, but the absence of spindles or reactivity was associated with a poor outcome (death or persistent vegetative state) (78). Like other EEG patterns, spindle coma is not specific for a single etiology, and the prognosis is dependent on several factors including the type of injury, the severity of the insult, and the time of recording in relationship to insult.

In contrast to EEGs, somatosensory evoked potentials (SSEPs) are less impacted by metabolic abnormalities and medications. Many recent studies have examined the prognostic value of the loss of the cortical response (N20) to median nerve stimulation when earlier potentials (brachial plexus; dorsal root entry zone) are preserved. Several studies (34,43,45,49,79–82) have shown that the bilateral absence of the N20 component following median nerve stimulation has a good predictive value for poor outcome following anoxia. In a meta-analysis that included over 500 patients, no patient with absent cortical evoked potentials recovered to wakefulness. In individuals with a normal N20 latency, 60% awoke. In contrast, a delay of the N20 latency decreased the probability of awakening to 20% (83). The optimal time to perform SSEPs for prognostic purposes following arrest is unclear, because the N20 responses may initially be present and then disappear on follow-up testing (84). In the studies reviewed by the American Academy of Neurology (AAN) Quality Standards Subcommittee, the intervals from resuscitation to prognostic SSEP testing varied, but all studies were done within 3 days of arrest. Recent AAN practice parameters (33) concluded that the bilateral absence of the N20 SSEP component 1–3 days after cardiopulmonary resuscitation accurately predicts a poor outcome. Significantly, the preservation of the N20 component is not helpful in prognosis since many patients who fail to recover following arrest have preserved N20 components with median nerve stimulation.

MEDICATIONS AND DRUGS OF ABUSE

A drug's effect on background EEG activity is dependent on several factors including drug dosage and duration of exposure. Alterations of EEG activity may also reflect systemic effects of the medication; for example, generalized slowing may be secondary to central nervous system hypoperfusion associated with drug-induced hypotension. Individual patient characteristics, including pre-existing brain disease and EEG abnormalities, can influence the impact of drugs and toxins on EEG activity. EEG changes from a drug vary considerably from patient to patient and do not allow prediction of a specific drug's effect in a given individual.

Generalized slowing is the most commonly encountered EEG drug effect, but it is not specific for a particular drug. The presence of superimposed generalized fast activity on an EEG should arouse suspicion of drug toxicity, particularly from medications that increase beta activity, such as barbiturates or benzodiazepines. Focal slowing

or an asymmetry of EEG activity is usually not encountered in drug-induced encephalopathies, and suggests an underlying localized abnormality. Anesthetic agents and illicit drug intoxications can result in seemingly ominous EEG patterns, including alpha coma, spindle coma, burst-suppression pattern, and even electrocerebral inactivity (ECI). As was addressed in earlier chapters (Chapter 19, Convulsive Seizures and Status Epilepticus, and Chapter 20, Nonconvulsive Seizures and Status Epilepticus), many of the anesthetic agents are used in the treatment of status epilepticus, although no agent has been proven to be consistently superior (85,86). Intensivists have used quantitative EEG, including spectral analysis, to monitor the depth of drug-induced sedation in ICU patients (87,88). What follows is a review of some patterns that have been associated with drug-induced and toxic encephalopathies.

ICU Medications

Benzodiazepines, a large class of medications frequently encountered in the ICU setting, include diazepam, lorazepam, and midazolam. These drugs can be used as anesthetic agents and/or anticonvulsant agents, and produce hypnotic and amnestic states associated with muscle relaxation. Low-dose benzodiazepines increase beta activity and may cause mild generalized slowing of background EEG activity. Fast activity may persist for up to 2 weeks after drug administration. Benzodiazepine-induced fast activity can be reduced at the site of a focal cerebral lesion (89). Acute withdrawal can cause seizures and lead to *de novo* absence status in older individuals (90).

Most anesthetic agents used in the ICU produce similar EEG changes. Barbiturates and most of the nonbarbiturate agents (etomidate, propofol) (Figure 21-15) initially cause an increase in beta activity with a loss of the alpha rhythm. As the anesthetic dosage is titrated, the frequency of EEG activity decreases and the amplitude increases, accompanied clinically by a loss of consciousness. At high doses, a burst-suppression pattern (Figure 21-16) occurs, and if the dose is increased further, electrocerebral inactivity may be seen (91). Propofol is an ultra-short-acting intravenous agent commonly administered in the ICU. Used at doses appropriate for maintenance, propofol induces a regular, frontally dominant delta rhythm with superimposed faster frequencies. Like midazolam (92), propofol may produce an alpha coma, spindle coma (Figure 21-17), or a burst-suppression pattern.

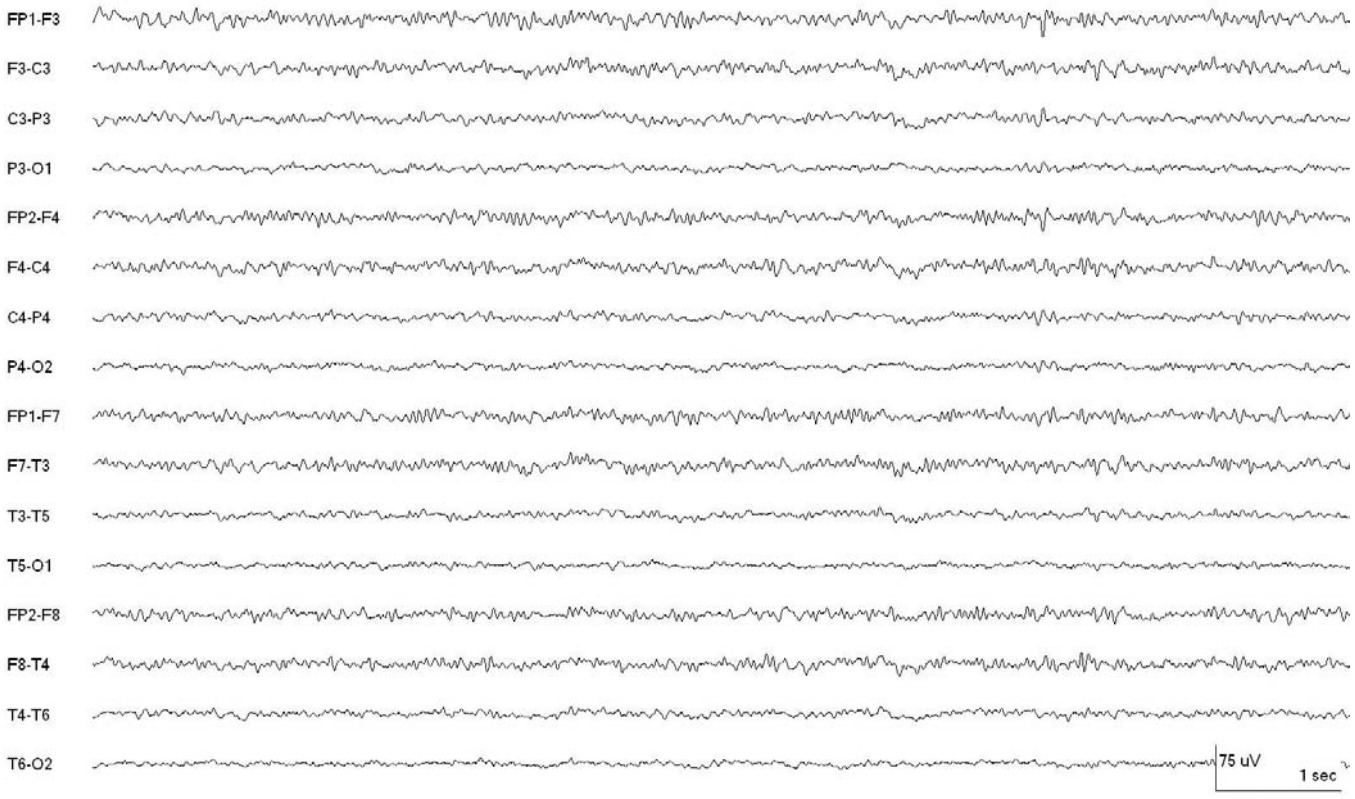

FIGURE 21-15. Anesthetic pattern in a 65-year-old man undergoing a carotid endarterectomy.

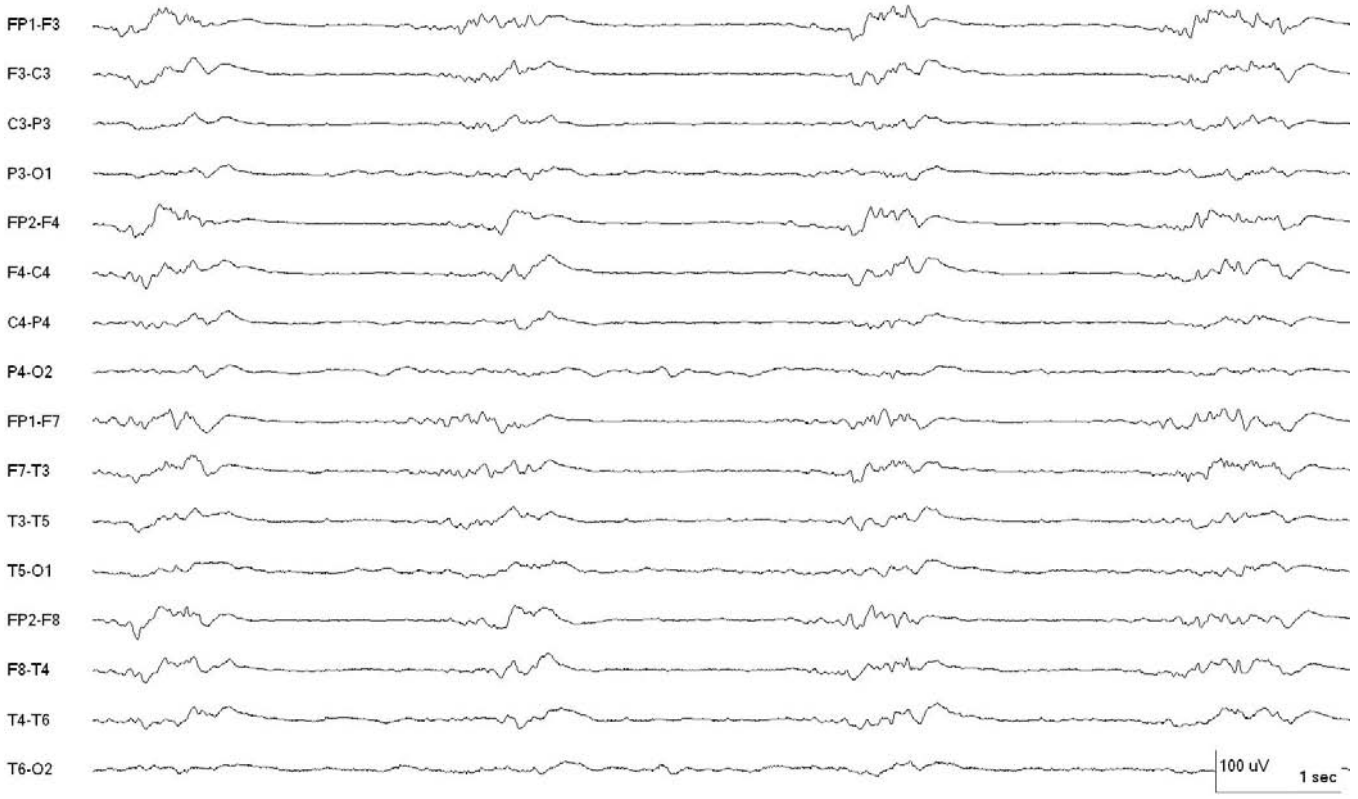

FIGURE 21-16. A burst-suppression pattern in the same patient (Figure 21-15) receiving sodium amytal.

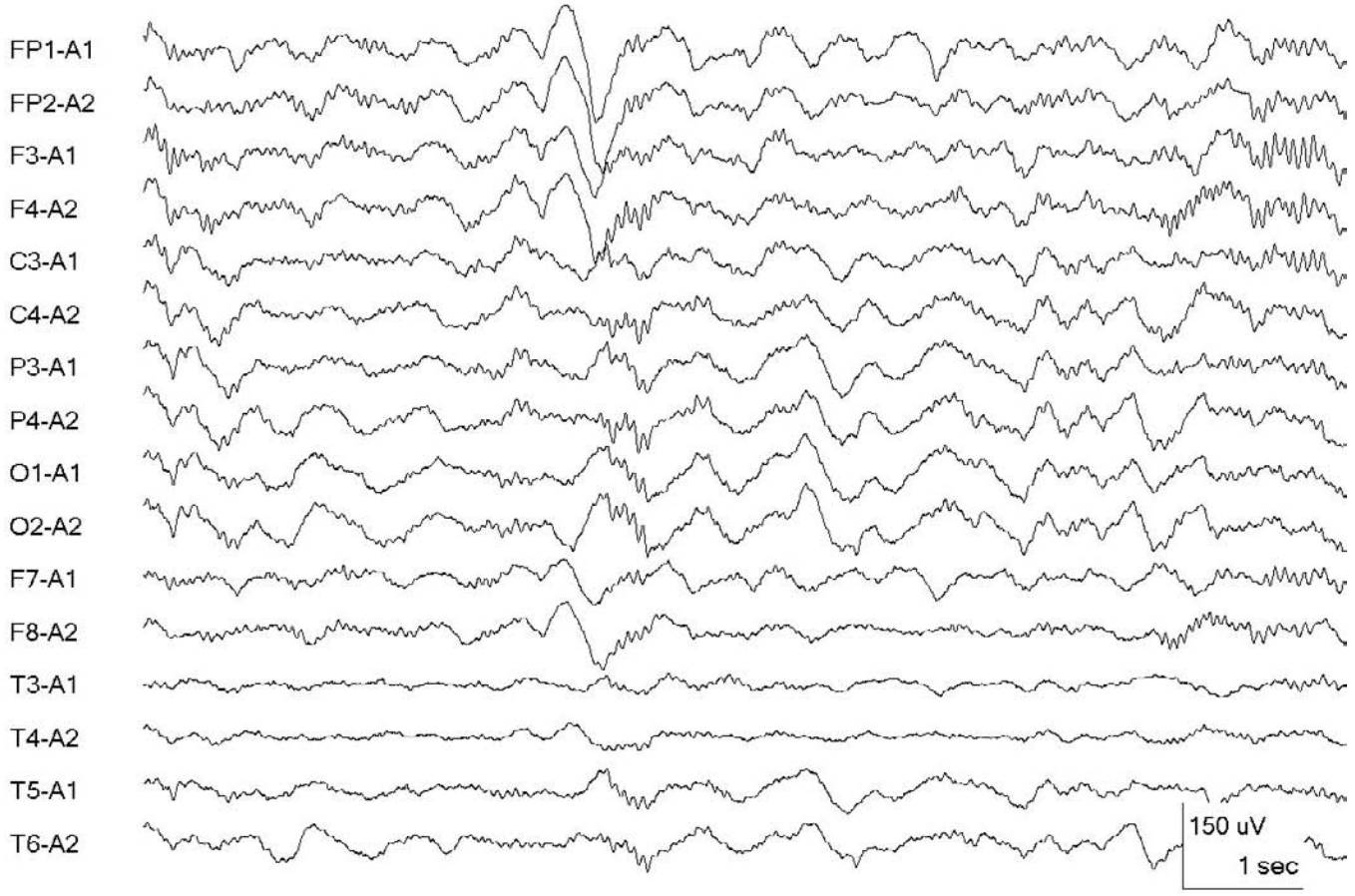

FIGURE 21-17. Sleep spindles in a comatose 33-year-old man receiving propofol.

Ketamine, which is structurally related to phencyclidine (PCP), is used for anesthetic induction and, rarely, in status epilepticus (93). Initially a loss of the alpha rhythm and a decrease in background amplitude are present. Increasing the dose further produces frontally dominant rhythmic theta activity. Higher doses produce high-amplitude theta activity accompanied by an increase in beta activity (94).

The effect on EEG activity of the short-acting synthetic opiates, including fentanyl, sufentanil, and alfentil, can be described based on dosage. At low concentrations, loss of beta activity and slowing of alpha activity occurs. With moderate doses, the amplitude increases while a decrease in frequency (diffuse theta with some delta activity) occurs. At high concentrations, delta activity—often synchronized, and of high amplitude—predominates. Burst-suppression or electrocerebral silence is not present at higher doses (91).

Drugs of Abuse

Frequently, patients with alcohol-related disorders are in the ICU because of seizures, intoxication/withdrawal, or head trauma. Patients with alcohol abuse may have EEG abnormalities related to intoxication (both acute and chronic) or withdrawal. Alcohol abusers are prone to a variety of central nervous systems diseases (e.g., traumatic brain injury) and systemic illnesses (e.g., hepatic failure) that may produce additional EEG changes, including focal and interictal epileptiform changes.

During acute alcohol intoxication, mild slowing of the alpha rhythm occurs. Quantitative EEG reveals spectral density shifts to lower frequency ranges (95). The effect of rising concentrations of alcohol is a generalized reduction in frequency of EEG activity. With severe intoxication, marked generalized slowing may be present. EEG slowing during intoxication diminishes as tolerance develops (96), and EEGs in alcohol abusers are normal or demonstrate only minor degrees of diffuse slowing (97).

Signs of alcohol withdrawal in chronic abusers usually begin within 24 hours after diminished consumption. Mild background EEG slowing may be associated with physiological artifact due to tremulousness and sweatiness (98). Abstinence may result in alcohol-related seizures, the majority being generalized tonic-clonic, 8 to 72 hours after discontinuation of alcohol (99). Generalized epileptiform discharges have been described during alcohol-related seizures (96). However, interictally, patients with seizures associated with withdrawal rarely (2%–12% of cases) have epileptiform discharges (97). Withdrawal seizures typically precede delirium tremens, during which time background EEG activity is low-voltage with a poorly developed dominant posterior rhythm (100). Patients with a history of alcohol use are at risk for a variety of medical conditions that may produce abnormalities of the EEG. Focal EEG abnormalities and seizures may result from head injury.

Central nervous system stimulants (amphetamines, cocaine, and methylphenidate) increase faster activity in the beta and alpha range and reduce voltage and the amount of slower frequencies (101). At toxic levels, cocaine produces a nonspecific pattern of generalized slowing with theta and delta activity (102). Cocaine can provoke seizures in nonepileptic patients and can exacerbate seizures in patients with a history of seizures (103). Other cocaine-induced neurological conditions also include vascular insults, including subarachnoid, intracerebral hemorrhages and vascultits, which can produce focal abnormalities on the EEG alerting the clinician to problems in addition to intoxication.

Conflicting information is available regarding the effects of cannabis on EEG activity. Inhalation of both hashish and marijuana produce little or no effect on EEG activity per visual analysis (104). In contrast, the use of methylenedioxymethamphetamine (MDMA, also known as ecstasy) has significantly increased, and seizures represent the most common neurological emergency in ecstasy abusers. Seizures are typically attributed to drug-induced hyponatremia and hyperthermia, and respond to correction of metabolic abnormalities (105). Lysergic acid diethylamide (LSD) and mescaline, potent hallucinogenic agents, can produce nonspecific changes with reduction in EEG voltage and slower frequencies during the psychotic state (106,107). Phencyclidine (also known as PCP, angel dust) is structurally related to ketamine and was introduced as an intravenous veterinarian anesthetic. Acute phencyclidine intoxication produces an unusual pattern of rhythmic nonreactive theta activity interrupted by periodic bursts of delta activity (108,109).

Miscellaneous Drugs and Toxins

Valproate-induced hyperammonemic encephalopathy is a rare, life-threatening adverse event of treatment with valproate that can be reversed if a timely diagnosis is established (110,111). The condition is characterized by an acute or subacute decrease in level of consciousness, and serum laboratory analysis typically shows normal liver function with hyperammonemia. Not surprisingly, the EEG findings are nonspecific, revealing generalized slowing and occasionally triphasic waves. If valproate withdrawal is prompt, these findings reverse and clinical improvement correlates with EEG normalization (112). The addition of topiramate to valproate therapy may increase the risk of valproate-induced hyperammonemic encephalopathy (113, 114).

Generalized, bisynchronous sharp complexes, at times periodic and often with a triphasic configuration, have been associated with cefepime, a fourth-generation cephalosporin. Patients with renal failure receiving this antibiotic have become unresponsive, and the EEG often shows triphasic activity (20,21,115,116). It is uncertain whether this is the result of an encephalopathy caused by

the drug, drug-induced nonconvulsive status epilepticus, or renal failure (although the condition has recently been reported in patients with normal renal function (117,118)) (Figure 21-18).

ENDOCRINE ENCEPHALOPATHIES

Hashimoto's encephalopathy is an uncommon disorder associated with Hashimoto's thyroiditis. Hypothesized to be an autoimmune syndrome, it may cause an alteration in level of consciousness, seizures, myoclonus, and hallucinations. Patients respond to immunosuppressive agents, and the term "steroid-responsive encephalopathy associated with autoimmune thryoiditis" (SREAT) has also been coined to describe this entity. Although not specific, the essential laboratory feature of this encephalopathy is an elevated serum level of antithyroid peroxidase antibody and/or antithyroglobulin antibody (119–121).

As in other encephalopathies encountered in the ICU, EEG abnormalities in Hashimoto's encephalopathy are not specific but are common, having been described in over 90% of patients. Most commonly, the EEG shows moderate to severe generalized slowing, although triphasic waves, epileptiform abnormalities, and photomyogenic and photoparoxysmal responses have also been described (122–124). Clinical improvement is associated with improvement of background activity, making EEG a potentially useful monitor for following the patient's clinical condition (123). A recent case report described rapid improvement in background EEG activity during continuous EEG monitoring following treatment of SREAT with steroid therapy (125). Schauble et al. (123) suggested that EEG may help to distinguish Hashimoto's encephalopathy from Creutzfeldt-Jakob disease (CJD), given that in Hashimoto's encephalopathy myoclonic jerks are not associated with EEG changes that are typically present in CJD patients. Others have proposed that the response of the EEG following immunosuppressive treatment can distinguish Hashimoto's encephalopathy from a rapidly progressive dementia (126).

Alteration in level of consciousness and seizures have also been described in patients with hypothyroidism. EEGs have shown low amplitude and generalized slowing of background EEG activity with a poor or absent alpha-blocking response. Not surprisingly, EEG slowing becomes more prominent with deeper levels of myxedematous coma (127).

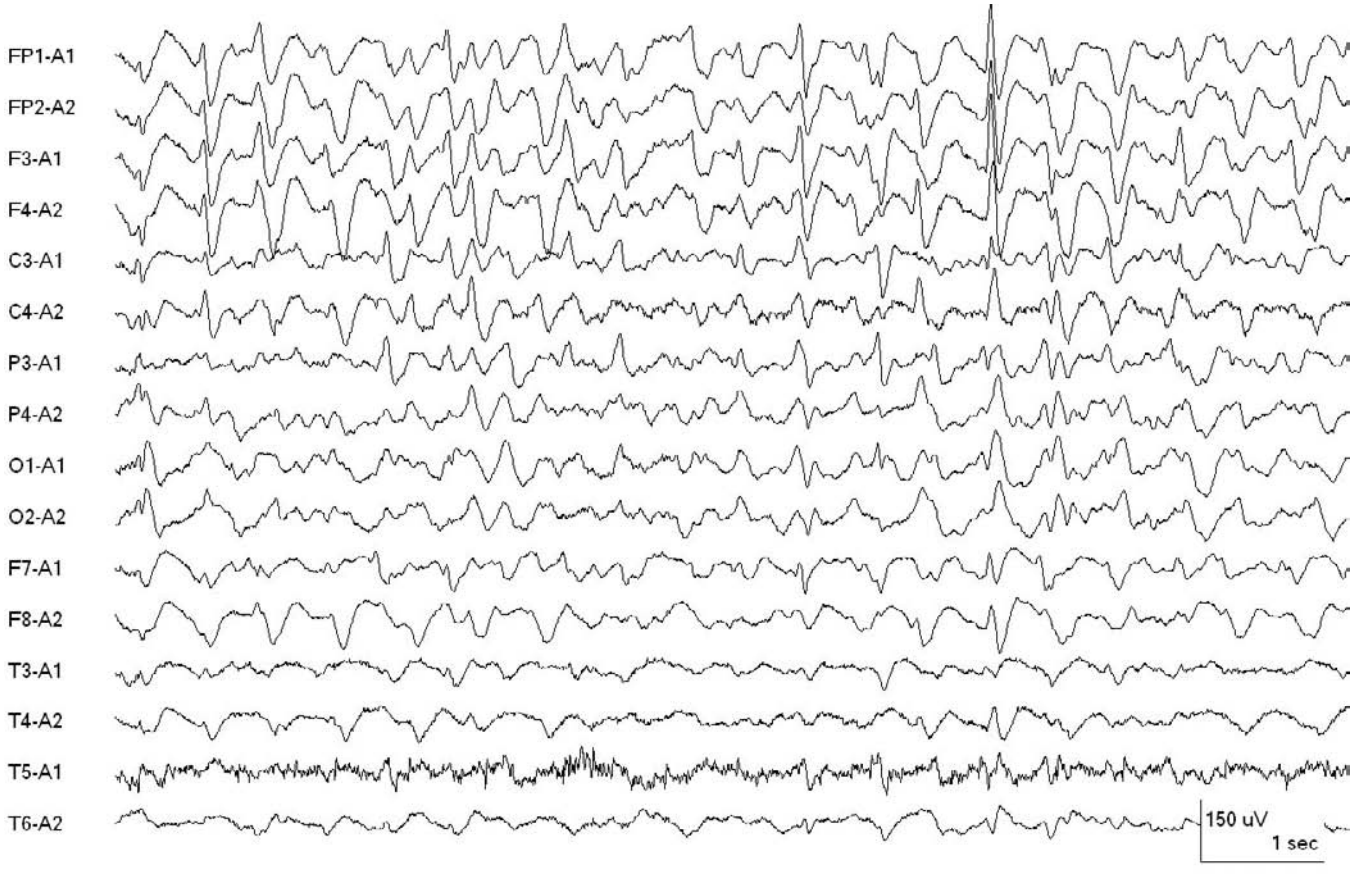

FIGURE 21-18. Nonconvulsive status epilepticus in a 40-year-old woman in renal failure receiving cefepime.

Hyperparathyroidism can lead to hypercalcemia associated with neurological deficits and mental impairment. Early studies (17) report slowing of rhythms associated with bursts of delta waves. EEG changes have been reported to appear when the serum calcium level reaches a concentration of 13 mg/100mL. With higher levels (>16 mg/100mL), hypercalcemia was associated with focal epileptiform abnormalities.

INFECTIONS

In central nervous system infections, both bacterial and viral, EEG abnormalities usually parallel the clinical picture. Abnormalities in meningitis and encephalitis are nonspecific, and usually consist of slowing and, in some cases, epileptiform findings. Continuous EEG (cEEG) monitoring, whose use in the ICU has increased greatly, has documented a high incidence of electrographic seizures (128). In a recent study of 42 critically ill patients with various central nervous system infections, electrographic seizures and/or periodic epileptiform discharges (PEDs) were frequent, occurring in 48% of patients. More than half the electrographic seizures had no clinical correlate. Both electrographic seizures and PEDs were independently associated with a poor outcome (129). As the authors indicated, a major limitation of this study was the selection bias: only patients in whom cEEG monitoring was requested were included in the study, and 14 (86%) of those with recorded electrographic seizures during cEEG had clinical seizures prior to EEG.

West Nile virus is now the most common cause of epidemic viral encephalitis in the United States. In addition to encephalitis, West Nile neuroinvasive disease includes syndromes of meningitis, acute flaccid paralysis/poliomyelitis, and movement disorders (including myoclonus) (130,131). Although EEG changes in West Nile encephalitis are common (present in over 70% of cases), they are not specific. Generalized slowing, often maximal over the frontotemporal head regions, is most common (132). As recently reviewed (133), convulsions occurred in up to 30% of patients in early reports, but were not common in recent studies.

Unlike West Nile virus, herpes simplex encephalitis (HSE) is associated with distinct EEG changes, but these are not pathognomonic for HSE. The majority of patients with HSE have periodic PLEDs (Figure 21-19), particularly when serial recordings are obtained. PLEDs are not unique

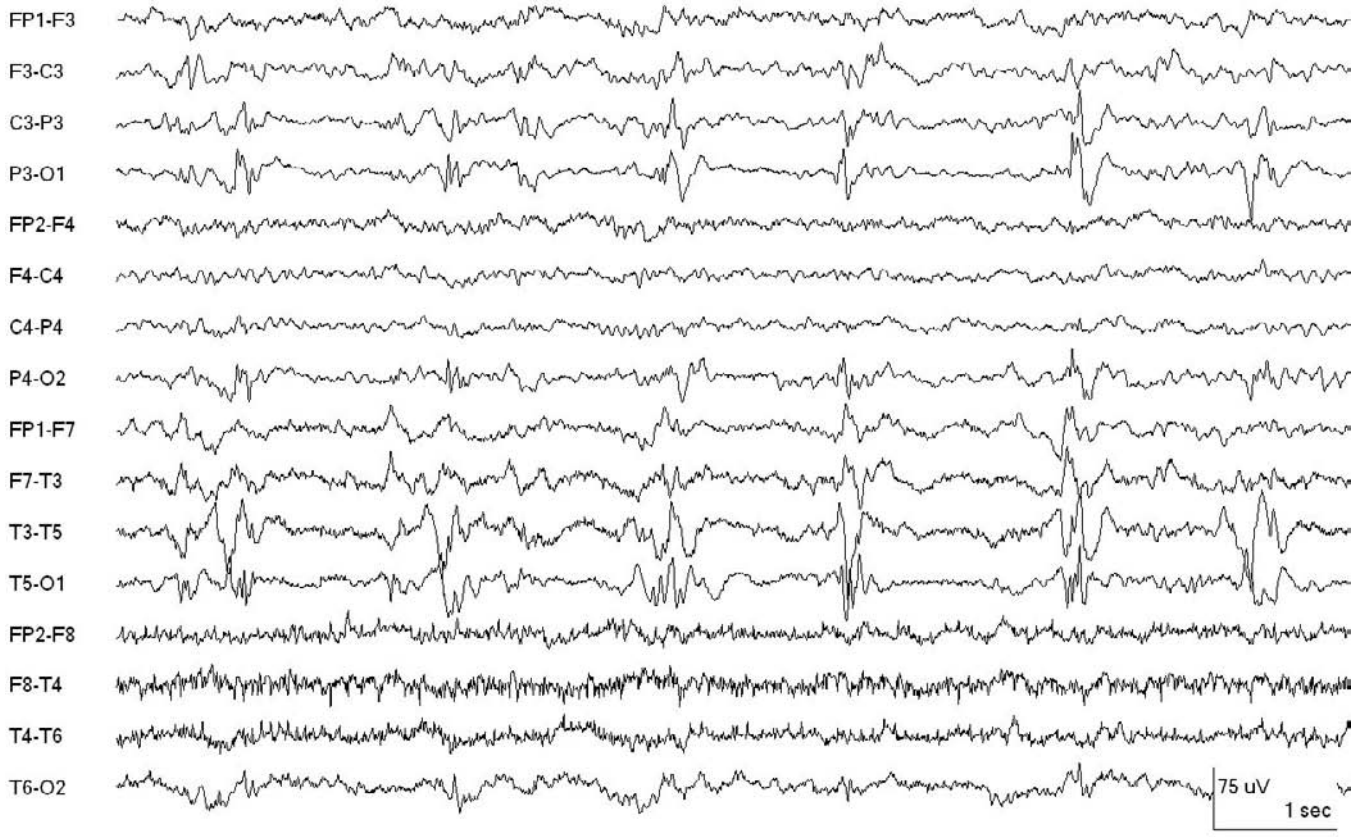

FIGURE 21-19. Left hemispheric PLEDs in a 73-year-old-woman with HSE.

to HSE and occur in a variety of disorders, most often infarcts or tumors. In a series of 147 patients, etiologies were cerebrovascular accident (35%), mass lesion (26%), infection (6%), hypoxia (2%), and other (22%) (134). PLEDs may also be seen in patients with chronic seizure disorders or old static lesions, especially when associated with recent seizures, alcohol withdrawal, or a toxic-metabolic disorder (135). PLEDs are a transient phenomenon in HSE. With time, the discharges usually decrease in amplitude, the repetition rate decreases, and ultimately the discharges cease.

Although EEG findings in HSE were once the most sensitive neurodiagnostic test in the acute stage of this disorder (136), the polymerase chain reaction (PCR) of the viral genome in cerebrospinal fluid is the most sensitive and specific of the diagnostic methods currently employed. In a recent study of patients with suspected HSE, PLEDs and/or focal temporal slowing were present in 90% of the PCR-positive patients at symptom onset compared with only 30% of the PCR-negative group (137). The presence of PLEDs in the EEG in a patient with suspected viral encephalitis should raise the suspicion of HSE; however, as has been indicated, it is not pathognomonic (138).

Neurological complications often occur in ICU patients initially admitted with non-neurological disorders. In one study, septic encephalopathy, which occurs with a systemic infection and no indication of another etiology, was the most frequently encountered neurological complication in the ICU (139). In patients with septic encephalopathy, the EEG was found to be a more sensitive index of brain function than clinical criteria, and the severity of the EEG abnormality correlated with mortality (140).

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CONTINUOUS EEG MONITORING FOR THE DETECTION OF SEIZURES IN TRAUMATIC BRAIN INJURY: DETECTING AND TREATING POST-TRAUMATIC EPILEPSY

PAUL VESPA

Neurocritical care for traumatic brain injury focuses on limiting the secondary injury that is related to brain swelling, elevated intracranial pressure, and cell death. For years, the etiology of brain swelling was thought to be based on early ischemia. More recently, other secondary insults have been recognized. These insults most commonly take the form of cytotoxic brain edema, repeat ischemia, fever-related injury, and seizures. Secondary insults frequently remain clinically silent until the problem becomes critical. Because these secondary insults are silent, and because they occur early on after the primary injury, there is a narrow window of observation prior to initiation of treatment. One of the principal secondary insults that occurs is the electrographic seizure. Seizures are usually readily treatable once they are diagnosed. However, the majority of seizures are nonconvulsive and therefore are truly silent or subclinical. Treatment can prevent the pathophysiological effects of seizures, which are exaggerated after a primary insult to the brain.

The purpose of this chapter is to outline the current state of knowledge about the usefulness of continuous electroencephalography (cEEG) in the acute setting in patients with cerebral trauma, stroke, and brain hemorrhage. The goal is to impress upon the reader five important concepts: (1) the optimum methodology for cEEG in the ICU, (2) the incidence of post-traumatic seizures, (3) the pathophysiological response in the brain that leads to endogenous neurotoxicity, (4) indications for cEEG in traumatic brain injury, and (5) how the treatment of seizures in the context of brain injury requires the use of cEEG.

METHOD FOR cEEG

The methods used in our ICU have been previously published (1,2) after being clinically established for routine brain monitoring at UCLA in 1994. The brain is monitored in essentially the same way that the heart is monitored in the cardiac care unit. Briefly, a14-channel EEG (F4-CZ, T4-CZ, P4-CZ, O2-CZ, F3-CZ, T3-CZ, P3-CZ, O1-CZ, F4-T4, T4-P4, P4-O2, F3-T3, T3-P3, P3-O1) is continuously recorded at the patient's bedside, beginning at the earliest opportunity after admission to the ICU. The cEEG is continuously displayed at the bedside, 24 hours per day, for moment-to-moment online observation by physicians and nurses. A physician trained in interpretation of EEG reviews the ongoing EEG activity at the bedside at least three times each day, and additionally when informed by the bedside nurse of suspicious EEG activity (Figure 22-1). Seizures are detected in one of three ways:

1. By online identification of seizures by the neuro-ICU nurse or neurointensivist
2. By the total power-trend seizure detection method
3. By detection during the regularly scheduled EEG segment review

The date and time of the seizure and the clinical behavior are noted by the bedside neuro-ICU nurse or neurointensivist and recorded. Each seizure is independently confirmed by an independent electroencephalographer blinded to the clinical condition. Seizure type is characterized as focal, hemispheric, or generalized according to the EEG at time of onset, as described by Drislane (3). The duration of individual seizures and the total (aggregate) duration of seizures during the ICU stay are recorded.

Others have made use of automated seizure detection software. Gotman and colleagues (see Chapter 7, Computerized Signal Analysis and Event Detection) have recently reported progress in creating an automated system using fuzzy logic and neural networks that can imitate an experienced electroencephalographer. This may decrease the time spent differentiating real from artifact-induced abnormalities in quantitative EEG (qEEG) trends (4). Several characteristic

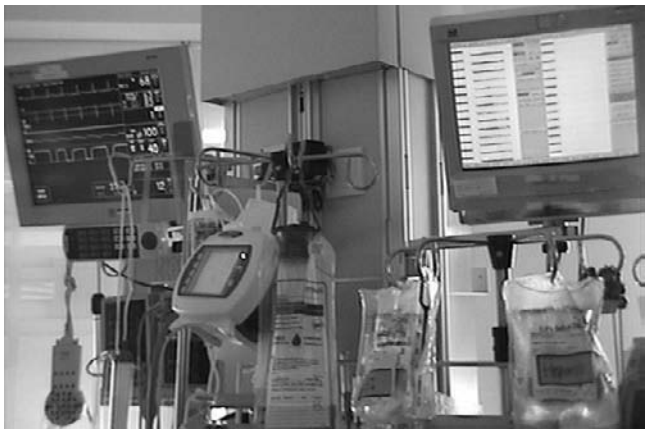

FIGURE 22-1. The figure shows cEEG continuously displayed at the bedside (monitor at the far right), 24 hours per day, for moment-to-moment online observation by physicians and nurses. The display is set to show spectral EEG trends and the ongoing routine can also be displayed or rapidly accessed for review to analyze specific behavioral or quantitative EEG events identified by nurses or ICU physicians. A physician trained in interpretation of EEG reviews the ongoing EEG activity at the bedside at least three times each day, and additionally when informed by the bedside nurse of suspicious EEG activity.

alterations in qEEG trends have been repeatedly recognized as markers of seizure activity. The finding of increases in amplitude of total power and/or in the alpha-delta ratio occur reliably with high-amplitude seizure or repetitive epileptiform spike discharges. Figure 22-2 shows one example of the use of quantitative EEG in detecting seizure activity. However, similar indiscriminant changes in total power and/or alpha-delta ratio occur with muscle activity or electrode artifacts. Reduction in the amplitude of total power occurs with burst-suppression and/or marked attenuation of the EEG. To date, there are no fully proven automated seizure detection algorithms, but several software packages employ versions that have a high sensitivity but low specificity for seizure detection, which help to reduce the amount of EEG being reviewed.

Unfortunately, there is little published literature about the number of electrodes and duration of monitoring of cEEG for brain injuries. In our experience, post-traumatic seizures can occur in a bimodal distribution across time, as early as a few hours and as late as 10 days after trauma (5). In a time-to-seizure study of a broad population of neurological ICU patients, most seizures occurred

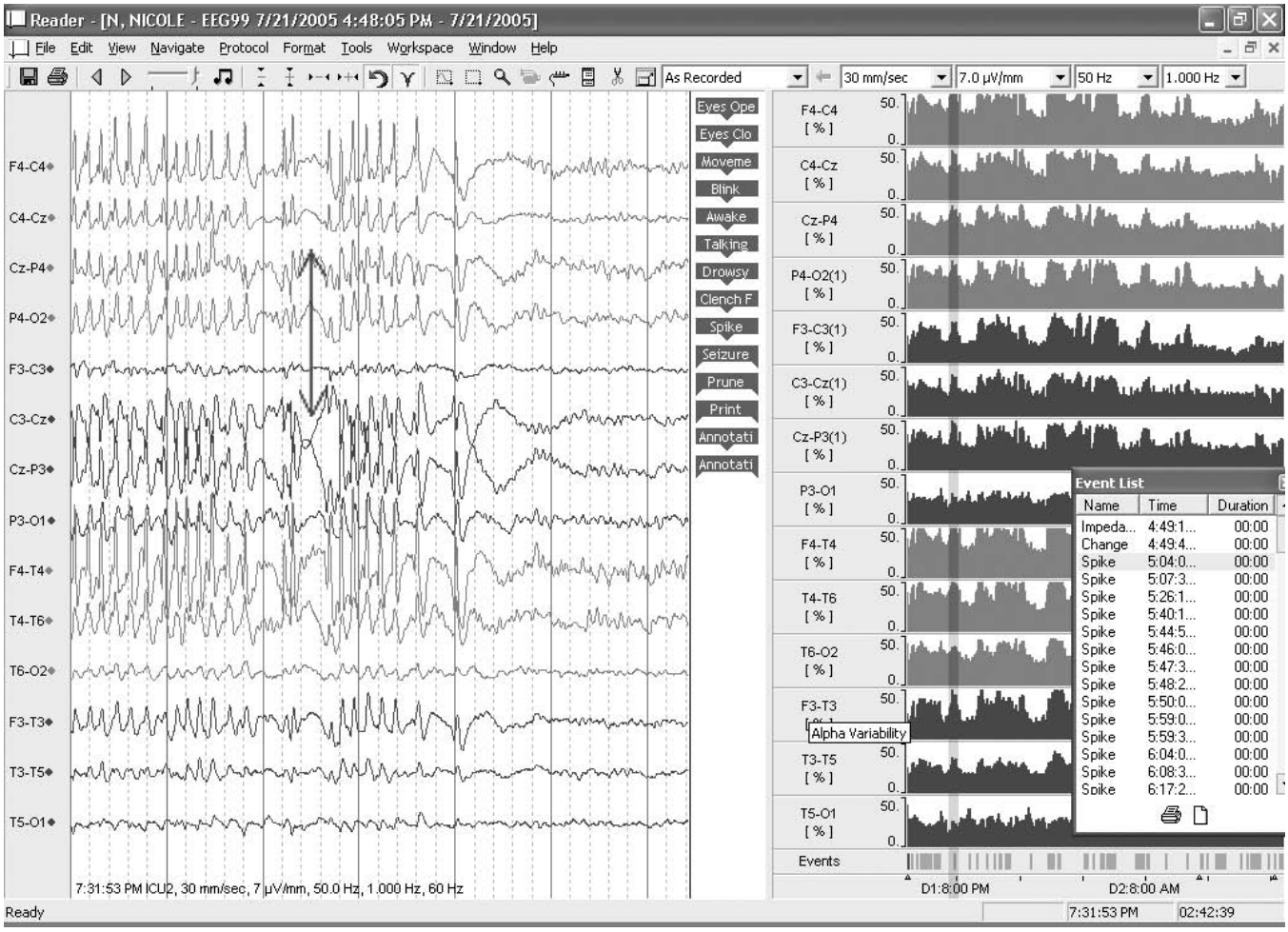

FIGURE 22-2. The recording shows an example of the use of quantitative EEG in detecting seizure activity. In many patients the finding of increased amplitude of total power and/or the alpha-delta ratio occur with electrographic seizures. Once identified, this spectral finding can be used to reliably and rapidly identify high-amplitude seizures or repetitive epileptiform spike discharges. The vertical highlight in the right panel that displays quantitative EEG changes corresponds to the EEG displayed in the left panel where high amplitude epileptiform activity is present during the first 4 seconds of recording. (*See color insert*).

within the initial 3 days of monitoring (6). It remains to be seen what the optimal duration of monitoring is, but we recommend at least 7 days for the comatose brain-injured patient.

RATIONALE FOR MONITORING: SECONDARY INSULTS IN THE ICU

The rationale for cEEG monitoring in the ICU is that (a) secondary insults frequently occur that further damage the vulnerable brain, and (b) early detection of conditions leads to prompt, and therefore more effective, treatment. The concept of secondary insults occurring after the primary neurological injury was put forth by Jennet and colleagues (7) and, later, by Miller (8). In a careful analysis of 124 brain trauma patients, Miller et al. (8) reported that the majority of patients (91%) suffered secondary insults. The most frequent secondary insults were raised intracranial pressure, hypotension, and pyrexia. Two of these, hypotension and pyrexia (temperature >38°C), were significant predictors of mortality. Similarly, Chan et al. (9) reported that a reduction in cerebral perfusion pressure to less than 70 mm Hg was associated with brain ischemia. Others have reported that reductions in global oxygen saturation increase mortality (10). Enblad and Persson (11) recently documented the occurrence of 164 secondary brain insults in 64 subarachnoid hemorrhage patients while the patients were in the ICU.

In addition to the aforementioned secondary insults, several investigators have reported ongoing transient and dynamic changes in brain metabolism (12) and neurochemistry (13–15) after brain injury. Dynamic increases in glucose metabolism and excitatory amino acids have been documented to occur in a majority of neurocritical care patients. Despite the fact that the occurrence of increased brain temperature, excitatory amino acid elevations, and secondary ischemia have been repeatedly documented, no comprehensive understanding of these secondary events has yet been put forth, and practical guidelines for responding to them have not been established. Based on this growing body of knowledge, monitoring of the brain is becoming more common, with treatment plans tailored to the individual patient based in part upon this physiological data. Thus it is rational to think that cEEG monitoring can not only assist the clinician in detecting some of these insults, but also lead to treatment or protective strategies (16).

A large literature regarding the incidence of clinical seizures following brain injury of varying severity exists. The incidence of early post-traumatic seizures is between 2.8% and 10% (17,18). Two early studies concluded that higher rates of seizures occur (15%) during the acute hospitalization in populations of severely injured patients who demonstrate seizures at or immediately after the moment of trauma (19,20). More recent studies confirm these initial findings. Lee et. al. (21) reported a 4.1% incidence rate of clinical seizures in the first week after brain trauma, and a 1.2% rate within the first 24 hours.

Continuous EEG after Brain Injury

Jordan (22) reported an initial study of continuous EEG monitoring in a neuroscience ICU population of 124 patients. The admission diagnosis of these patients included stroke, intracerebral hemorrhage, seizures, metabolic coma, brain tumors, and brain trauma. Overall, seizures occurred in 35% of patients during the ICU course, with over three-quarters demonstrating either nonconvulsive seizures or nonconvulsive status epilepticus. These seizures had no suggestive behavioral signs and were only diagnosed by EEG evaluation. The duration of monitoring was determined by the presence of epileptiform activity. The impact of cEEG on clinical decision making was evaluated by determining whether the available EEG information influenced the following decisions: (a) initiating or modifying anticonvulsants, (b) obtaining a CT or MRI scan, or (c) adjusting cerebral perfusion or mean arterial blood pressure. Overall, the cEEG strongly influenced these decisions in 51% of patients, and made a significant contribution in a further 31% of patients. Thus, cEEG monitoring detected abnormal subclinical pathophysiology that could be treated and contributed directly to patient care in a large proportion (82%) of patients. Other studies report a similarly high frequency of nonconvulsive seizures in neurocritical care patients, with the incidence ranging from 11% (23) to 55% (24,25).

More recently, the Mayo group reviewed the use of cEEG with video monitoring in the Neurointensive Care Unit setting (26). cEEG was used to guide patient care and clinical decision making in all cases. None of the patients with nonconvulsive seizures had an excellent outcome. Although the Glasgow Coma Scale was not predictive of outcome, refractory status epilepticus was significantly associated with mortality. The use of simultaneous video monitoring also allowed for the correct classification of non-epileptic behavioral events initially thought to be seizures by clinical observation alone.

The likely incidence of nonconvulsive seizures after traumatic brain injury has been recently established by Vespa et al. (1). cEEG monitoring was used in patients with moderate and severe traumatic brain injury (Glasgow Coma Scale 3–12) for 7–10 days after injury, beginning at the time of admission to the intensive care unit. The EEG was displayed at the bedside and the nurses were instructed to identify electrographic seizure activity. Electrographic seizures without clinical signs of convulsions were the most common form of seizure (Figure 22-3). Sudden increases in total power previously described in patients with electrographic seizures were used as a nonspecific marker of important EEG events that required review (Figure 22-4). Using these methods, 22% of 91 patients were found to have seizures, with a majority (57%) demonstrating nonconvulsive seizure activity. Most seizures occurred within the initial week after the brain injury,

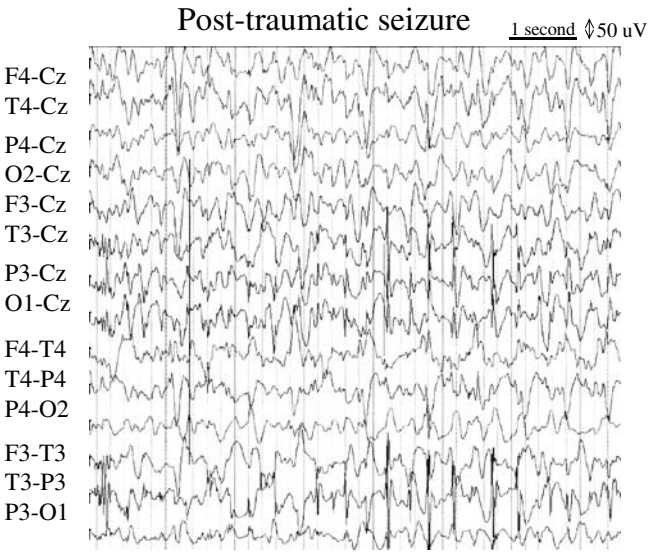

FIGURE 22-3. T Typical nonconvulsive event associated with electrographic epileptiform activity. High amplitude spikes are present with maximal amplitude at T3, P3, and O1 that gradually increase in amplitude.

and the incidence of seizures was not affected by therapeutic phenytoin levels, withdrawal of ethanol, or the type of brain injury. It should be noted that only moderate to severe brain injury patients were monitored, and that the incidence of nonconvulsive seizures in patients with mild brain injury is not well documented. The absence of overt clinical signs of seizure activity was consistent with the observations of Young (27), Grand'Maison (24), Scholtes (28), Vespa (15), and Claassen (25) in patients in other neurological populations with nonconvulsive status epilepticus. Patients who exhibited post-traumatic status epilepticus all died, whereas patients with isolated seizures had no apparent difference in mortality rate. In a follow-up assessment of 315 patients with moderate to severe brain injury, seizures were present in 27% of patients and were associated with increased mortality (29).

Continuous EEG after Infarction

The incidence of seizures after brain ischemia has relied upon studies of clinical signs of seizure activity (not EEG). The incidence of clinically defined seizures after bland ischemic stroke varies from 5% to 17% (30,31), with hospital-based studies

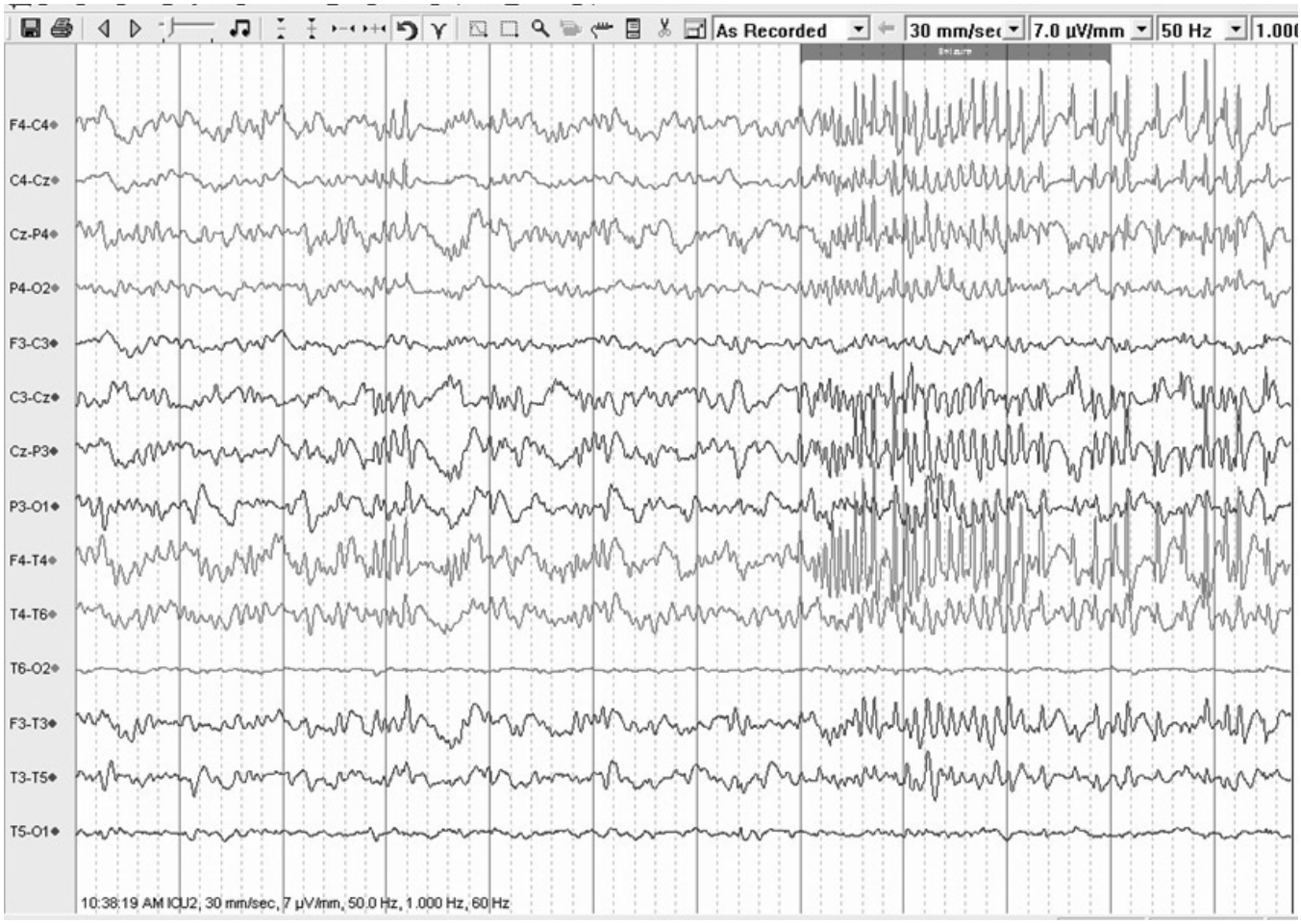

FIGURE 22-4. EEG monitoring in a patient with head trauma shows a nonconvulsive (subclinical) electrographic seizure clearly seen beginning in the eighth second of the recording (predominantly involving F4, C4, and Cz) that was easily and reliably identified by increases in quantitative EEG amplitude on the bedside spectral display. (*See color insert*).

demonstrating the highest rate of poststroke seizures (32–34). Indeed, the incidence of seizures after stroke increases with large-territory ischemic injury and with cardioembolic stroke. In contrast, the use of cEEG after ischemic stroke suggests that the incidence of nonconvulsive seizures is much higher than the previous studies without EEG monitoring would suggest. In the work of Jordan et. al. (22) using cEEG in 57 consecutive patients admitted to the ICU with cerebral ischemia, 26% of the patients had EEG-defined nonconvulsive seizures during the period of monitoring. In a recent study using cEEG, 6% of ischemic stroke patients demonstrated nonconvulsive seizure activity. This occurred in the setting of malignant brain edema, but not in conjunction with hemicraniectomy or specifically with arterial recanalization.

Continuous EEG after Nontraumatic Intracerebral Hemorrhage

The incidence of seizures after intracerebral hemorrhage has been noted to be higher than after ischemic stroke. Immediate and early seizures occur in the range of 2.8% to 18.7%, with the frequency of status epilepticus between 1.1% and 2%. In a recent study by Vespa (15), the incidence of seizures after intracerebral hemorrhage was 28%, compared with 6% incidence in ischemic stroke. In this study, cEEG was used to identify nonconvulsive seizures; this explains why the incidence rate is higher than in most previously cited studies. In a recent report from the Columbia group, Claassen et al. (6) used similar cEEG methods and detected a 28% incidence rate of nonconvulsive seizures in a mixed population including patients with intracerebral hemorrhage, subarachnoid hemorrhage (35), and ischemic stroke. Of 45 patients with ICH, 6 (13%) had nonconvulsive seizures, and 4 of these 6 had nonconvulsive status epilepticus. The seizure rate in brain hemorrhage patients may be higher given the relative toxicity of intraparenchymal blood. Blood products, especially thrombin and iron, are known to be pro-epileptogenic, and are often used for experimental models of epilepsy (36). The presence of blood may elicit seizures in the injured brain, given that the rate of seizures is higher in patients with nontraumatic and traumatic intraparenchymal bleeding than in patients with bland infarctions. It is clear that the use of cEEG monitoring has resulted in an increased number of seizures being detected, as reflected by the data in Table 22-1, which show that *with the use of cEEG monitoring, the incidence rate of seizures after intracranial hemorrhage is double that found in natural history studies before monitoring*. Thus, cEEG clearly detects unsuspected nonconvulsive seizures and permits treatment.

Patients admitted to the NICU with primary central nervous system infections may have an incidence of seizures detectable by cEEG that is equal to or greater than that found in brain trauma. Carerra and colleagues (37) found electrographic seizures or periodic epileptiform discharges in 48% of 42 consecutive patients with primary CNS infections. More than half of the electrographic seizures occurred in association with nonconvulsive seizures. This raises the likelihood that seizures may occur more frequently in traumatic brain injury complicated by infection.

Acute Symptomatic Seizures after Brain Injury are not Benign

Seizures occurring after brain injury or brain hemorrhage elicit a pathophysiological response at a time when the brain is most vulnerable. These seizures lead to additional secondary injury through a variety of mechanisms. Post-traumatic seizures give rise to increased levels of extracellular glutamate

TABLE 22-1. RATE OF SEIZURES IN NONTRAUMATIC AND TRAUMATIC INTRACEREBRAL HEMORRHAGE
Rate of seizures in Non-traumatic and Traumatic Intracerebral Hemorrhage

Study	N	Percentage with seizures	Principal Diagnosis
Berger 1988	112	17	brain trauma
Temkin 1990	208	3.6	brain trauma
Lee 1995	2574	4.1	brain trauma
Bums 1997	99	13	brain trauma
Arboix 1997	208	4.3	brain trauma
Bladin 2000	265	10.6	brain trauma
Labovitz 2001	200	7.5	brain trauma
ICU cEEG Studies	**N**	**Percentage with seizures**	**Principal Diagnosis**
Jordan 1995	124	35	neurologic critical illness
Vespa 1999	91	22	brain trauma
Vespa 1999	300	21	subarachnoid hemorrhage/brain trauma
Vespa 2003	65	28	primary intracerebral hemorrhage
Claassen 2004	204	17	subarachnoid hemorrhage
Pandian 2004	105	42	neurologic critical illness
Young 2005	55	20	neurologic critical illness
Ronne-Engstrom 2006	70	33	brain trauma
Claassen 2007	102	28	primary intracerebral hemorrhage

(38). This increase in glutamate concentration exceeds the concentration known to induce cell death and swelling, and is persistent across many days after the injury. The sustained excitotoxic injury associated with seizures gives rise to lipid peroxidation and membrane disruption (2) with resultant increases in levels of extracellular lipid breakdown products (e.g., glycerol). In addition, in the acute setting, seizures increase glucose metabolism and lead to an increase in the intracranial pressure. These mechanisms are most likely responsible for the observation that seizures after brain hemorrhage lead to increased brain swelling and midline shift (15). Compared with brain hemorrhage patients without seizures, patients who have post-hemorrhagic seizures have a dramatic increase in midline shift and increased mortality. Indeed, seizures alone are an independent factor in patient mortality, after controlling for traditional prognostic factors (Table 22-2). In a recently completed study, nonconvulsive seizures resulted in delayed and prolonged increases in intracranial pressure (5). The intracranial pressure increased during the seizure and was higher for longer periods of time in the group that had seizures. This effect did not appear to be caused by injury characteristics of the patients, because other patients with similar injury severity did not have a similarly prolonged increase in intracranial pressure. One can conclude that seizures in these cases led directly to worsened brain edema and poor outcome, and thus were not benign. The role of seizures in the natural history of brain injuries is not well established, but studies so far indicate that seizures enhance and worsen the natural history of brain injury. *It is safe to conclude that seizures occur commonly after hemorrhagic brain injury, and in this context are not benign and must be detected, treated, and, even better, prevented.*

TREATMENT OF TBI PATIENTS USING CONTINUOUS EEG

Since patients with TBI often have seizures, it is important to discuss how they should be treated. Seizures may result in no apparent clinical effect. However, TBI patients with seizures after brain hemorrhage or cerebral injury typically have worsened brain edema, midline shift, and elevated intracranial pressure (15). These events occur during the initial week after injury, which overlaps with the peak incidence of post-traumatic seizures. Several principals of goal-directed treatment for seizures can be derived from the current literature:

1. cEEG should be started immediately upon presentation of the brain trauma or hemorrhage.
2. Brain hemorrhage patients (traumatic or nontraumatic) have a higher risk than ischemic stroke patients and should get priority for monitoring if resources are limited.
3. Monitoring should continue for at least 5 days given the temporal course of seizures.
4. The lack of clinical seizure activity is not an indication to avoid cEEG, because the preponderance of seizures are nonconvulsive.

Treatment to avoid or limit the number of seizures includes the use of long-acting anticonvulsants as well as the use of continuous infusions of anticonvulsants such as midazolam, propofol, and pentobarbital. Continuous EEG is a useful monitor for titration of these medications. Anticonvulsants are typically quite effective at stopping the seizure activity when used as continuous infusions. However, the goal for the duration of continuous infusion is not clear, and recurrent seizures can occur when the continuous infusion is stopped, even when continued routine anticonvulsants are used. In part, this may be the result of persistent excitatory pathway activation that is self-sustaining.

TABLE 22-2. IMPORTANCE OF SEIZURES IN THE INTENSIVE CARE UNIT
Physiological Impact of Seizures after Cerebral Injury

Study	Effeft
Vespa 1998	Increase in glutamate
Vespa 1999	Increase in mortality with status epilepticus
Vespa 2002	Increase in lipid membrane breakdown
Vespa 2003	Increase in midline shift and mortality
Cury 2004	Increased regional cerebral blood flow
Vespa 2007	Increased ICP and metabolic distress

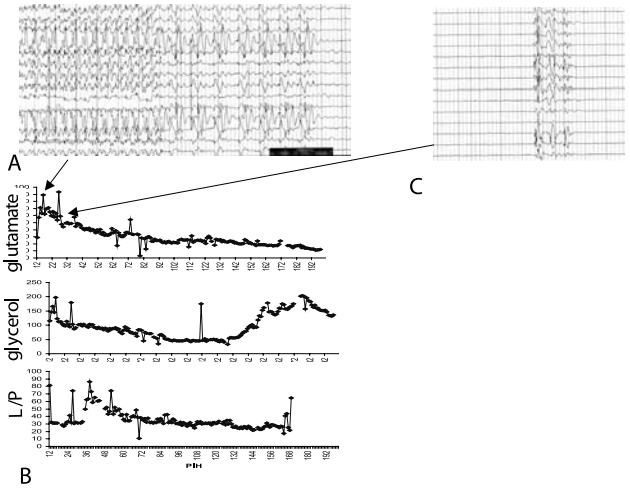

FIGURE 22-5. The figure shows a case example in which a brain injury patient experiences nonconvulsive status epilepticus (A) associated with prolonged elevations of excitotoxic neurotransmitters (glutamate) and extracellular lipid breakdown products (glycerol). Early during the status epilepticus, the extracellular levels of glutamate are increased (B) and remain elevated despite induction of burst-suppression using pentobarbital (C). This case underscores the significance of nonconvulsive (subclinical) seizures by showing that there may be long-lasting changes in brain neurochemistry and signs of injury that persist even after the initial successful resolution of seizure activity.

Figure 22-5 shows a case example in which a brain injury patient experiences nonconvulsive status epilepticus. Early during the status epilepticus, the extracellular levels of glutamate are increased and remain elevated despite induction of burst-suppression using pentobarbital. This illustrates the concept that there may be long-lasting changes in brain neurochemistry that occur in post-traumatic seizures and that cEEG is needed to detect recurrent seizures, even after the initial successful resolution of seizure activity. Goal-directed treatment using cEEG as a clinical guide was demonstrated to be effective in stopping seizures and led to an overall improvement in clinical outcome in a case-controlled cohort study (39). The net effect of this approach on patient care was to improve outcome while decreasing length of stay and being cost-neutral in the process.

TEN PRINCIPLES OF ICU cEEG IN THE EARLY POST-TRAUMA PERIOD

There are ten principles for the application of cEEG monitoring for the detection of early post-traumatic seizures, as follows:

1. Early post-traumatic seizures occur in roughly 20% of patients with moderate-to-severe TBI.
2. Most early post-traumatic seizures occur within the initial 10 days after TBI.
3. One-half of all post-traumatic seizures are nonconvulsive and are detectable only by cEEG monitoring.
4. The electrographic patterns of post-traumatic seizures are characterized by evolutionary spike-wave discharges that may lack a postictal compensatory suppression.
5. Early post-traumatic seizures result in prolonged and sustained elevations in intracranial pressure.
6. Early post-traumatic seizures result in worsening metabolic distress, as evidenced by positron emission tomography and cerebral microdialysis monitoring.
7. Early recurrence of seizures occurs often, despite therapeutic levels of anticonvulsants, requiring titrated continuous infusions of anticonvulsants with real-time monitoring of cEEG.
8. Rebound seizures, after withdrawal of common sedative drugs, may occur in traumatic brain injury patients.
9. The recommended duration of cEEG monitoring for the comatose traumatic brain injury patient is at least 7 days after injury.
10. Long-term effects of early post-traumatic seizures are not well known.

CONCLUSION

The future of neurological monitoring is quite bright. We anticipate that novel discoveries of functional pathways and specific brain electroencephalographic changes will provide clinicians with a better understanding of brain function in coma, enable us to detect and stop seizure activity, and yield important insights into how the brain adapts to and recovers from injury. Determining the effect of cEEG on clinical outcome requires further study. In addition to seizure detection, cEEG trend analysis, as first shown by Labar and colleagues (40) at Columbia and more recently by Claassen and colleagues at the same institution, appears to be useful for the early detection of vasospasm. Trend analysis may prove useful in detecting other secondary insults in trauma. Understanding how long-term epilepsy may or may not be directly related to specific aspects of early post-traumatic seizure activity has yet to be explored. But at present, cEEG is already an essential tool that allows us to improve immediate patient care and provide brain-directed therapy to patients in need.

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23

STROKE AND SUBARACHNOID HEMORRHAGE

JAN CLAASSEN
LAWRENCE J. HIRSCH

Recent technological developments have allowed the routine use of continuous EEG as a monitoring tool in the neurological intensive care unit (ICU). Initially applied primarily in patients with status epilepticus (SE), cEEG is increasingly being utilized in patients with other acute neurological diseases such as subarachnoid hemorrhage (SAH), acute ischemic stroke (AIS), and intracerebral hemorrhage (ICH). EEG is able to detect delayed cerebral ischemia from vasospasm in patients with SAH, recurrent or progressive ischemia in patients with AIS or transient ischemic attack, and electrographic seizures, which are particularly common with hemorrhagic strokes. Additionally, EEG may have some use for prognostication. In this chapter we will discuss current applications of EEG monitoring in patients with stroke and SAH, including detection of seizures and ischemia, prognostic implications, and the future role of EEG in the ICU.

PRINCIPLES OF EEG MONITORING IN STROKE PATIENTS

Principles of Seizure Detection with cEEG in the ICU

Seizures and status epilepticus are frequent among ICU patients, particularly those with acute brain injury. The majority of electrographic seizures in the ICU setting are nonconvulsive, and therefore can only be detected with EEG (1,2). Risk factors for nonconvulsive seizures include impaired mental status, a history of epilepsy or remote epilepsy risk factors, prior convulsive seizures, and ocular findings (2,3). In a mixed cohort of 570 neurological ICU patients undergoing continuous EEG monitoring, 19% (110 patients) had seizures, and the seizures in 92% of these patients (101 of 110) were purely nonconvulsive that could only be detected by EEG (2). Only half of these patients had their first seizure within the first hour of recording; thus, even a prolonged routine EEG would not have identified nonconvulsive seizures in half of these patients. Clinical correlates of nonconvulsive seizures and nonconvulsive SE may vary widely and may include negative symptoms such as coma, lethargy, confusion, aphasia, amnesia, and staring, or positive symptoms such as automatisms, blinking, facial twitching, agitation, nystagmus, eye deviation, and perseveration (4,5). In most cases it is impossible to confidently diagnose nonconvulsive status epilepticus without using EEG. It is crucial to recognize and treat nonconvulsive SE early, since prognosis worsens with increasing duration of seizure activity (6).

Principles of Ischemia Detection with EEG

Electrical dipoles, which are the basis for the EEG signal, are primarily generated by cortical layers 3 and 5 (7–9). These areas are selectively sensitive to oxygen deficits (10). EEG changes caused by energy and ion pump failure occur when cerebral blood flow falls below 25–30 ml/100 g/minute—a time when therapeutic interventions might prevent permanent brain damage, as infarction does not occur until cerebral blood flow falls below 18 ml/100 g/minute (11–13). Brain damage may be reversible down to a cerebral blood flow of 12 ml/100 g/minute (Table 23-1) (8). Mild hypoxia (cerebral blood flow at 25–35 ml/100 g/minute) may result in subtle decreases in the amplitude of fast activity (8,14). Worsening ischemia usually results in polymorphic delta activity, and more pronounced attenuation of fast frequencies, including sleep spindles (15–17). These EEG findings reflect disrupted metabolism (cerebral metabolic rate of oxygen) as seen with positron emission tomography (14) and abnormal cerebral blood flow as seen with xenon-enhanced computed tomography (XeCT) studies (18,19).

TABLE 23-1. RELATIONSHIP BETWEEN ISCHEMIA, EEG CHANGE, AND NEURONAL INJURY

CBF Level (ml/100 gm/min)	EEG Change	Degree of Neuronal Injury
35–70	Normal	No injury
25–35	Loss of fast (beta) frequencies	Reversible
18–25	Slowing of background to 5–7 Hz	Reversible
12–18	Slowing to 1–4 Hz delta	Reversible
<8–10	Suppression of all frequencies	Neuronal death

Adapted from Jordan (8).

Computer programs are also able to convert the raw EEG signal into quantitative EEG (qEEG) parameters, and display vast amounts of EEG data in a user-friendly way.

Several studies of patients with ischemic strokes have demonstrated a relationship between focal ischemia and qEEG monitoring parameters such as topographic power maps (16,20–22). Additionally, EEG is very sensitive for recovery and may demonstrate recovery of brain function from reperfusion earlier than the clinical exam (7). These observations make the EEG a potentially very useful tool to continuously monitor brain perfusion. For many years monitoring cerebral blood flow with EEG was exclusively done in the operating room, specifically during carotid endarterectomy (23,24). Increasingly, the EEG detection of ischemia in different clinical scenarios is used in the ICU.

Principles of Prognostication with cEEG

Many EEG findings have been associated with poor prognosis, including seizures, status epilepticus, generalized or lateralized periodic epileptiform discharges, nonreactivity, and absent sleep architecture (Table 23-2, 25–30). However, for many severely brain-injured patients it remains unclear whether these electrophysiological events are markers of the extent of brain injury or whether they cause additional brain injury. Accurate prognostication is further limited by the fact that the neurological outcome of many of these patients is heavily influenced by non-neurological complications such as pneumonia and myocardial infarction. These complications may not involve the brain, and therefore would not be expected to be reflected in the EEG.

TABLE 23-2. SUMMARY OF LITERATURE ON EEG FINDINGS AND THEIR SIGNIFICANCE IN SPECIFIC CLINICAL SCENARIOS

	AIS	SAH	ICH
Ischemia	• Increased delta, decreased alpha[16] • Brain symmetry index[44]	• Trend analysis of total power (1–30 Hz)[73] • Variability of relative alpha (6–14 Hz/1–20 Hz)[74] • Poststimulation alpha-delta ratio (8–13 Hz/1–4 Hz)[75]	• Not studied
Poor prognosis	• Background slowing[55,56] • Continuous polymorphic delta with depression of alpha or beta activity and background suppression[53] • Acute delta change index[36] • Z-values of absolute power from the four classic frequency bands[54] • Regional attenuation without delta (RAWOD) reflecting massive hemispheric infarction[38]	• Absent sleep architecture[29] • PLEDS[29] • Absent EEG reactivity[29] • GPDs[29] • BiPLEDs[29] • NCSE[29]	• Electrographic seizures[28] • PEDs[30] • PLEDs[30] • Focal SIRPIDs[30]
Others	• Acute delta change index reflecting effects of IV tPA[36]		• Seizures associated with increasing midline shift[28] • Seizures associated with secondary hematoma growth[30]

Emerging cEEG Techniques

Cortical spreading depression-like events have been documented on intracranial electrocorticographic recordings in patients with acute, focal brain damage using subdural strips (Figure 23-1) (31,32). Among 12 patients with acute brain injury (7 with spontaneous ICH, 5 with traumatic brain injury), electrocorticographic activity was recorded from the immediate vicinity of the injured cortex, detecting cortical spreading depression in 6 patients (4 of 5 traumatic brain injury, 2 of 7 ICHs patients) (32). In two of these patients, the authors also observed peri-infarct depolarizations in electrically silent cortical tissues at the margins of injury, and hypothesized that these may contribute further to tissue damage in acute brain lesions. Animal data suggests that in models of transient focal ischemia and reperfusion, similar peri-infarct depolarizations contribute to secondary injury such as delayed edema, intracranial hypertension, and hypoperfusion (33). If future studies confirm these findings, monitoring of cortical spreading depression and peri-infarct depolarizations may allow real-time detection of secondary injury in acutely brain-injured patients at a time when interventions such as NMDA antagonists (32) may alter the ultimate outcome.

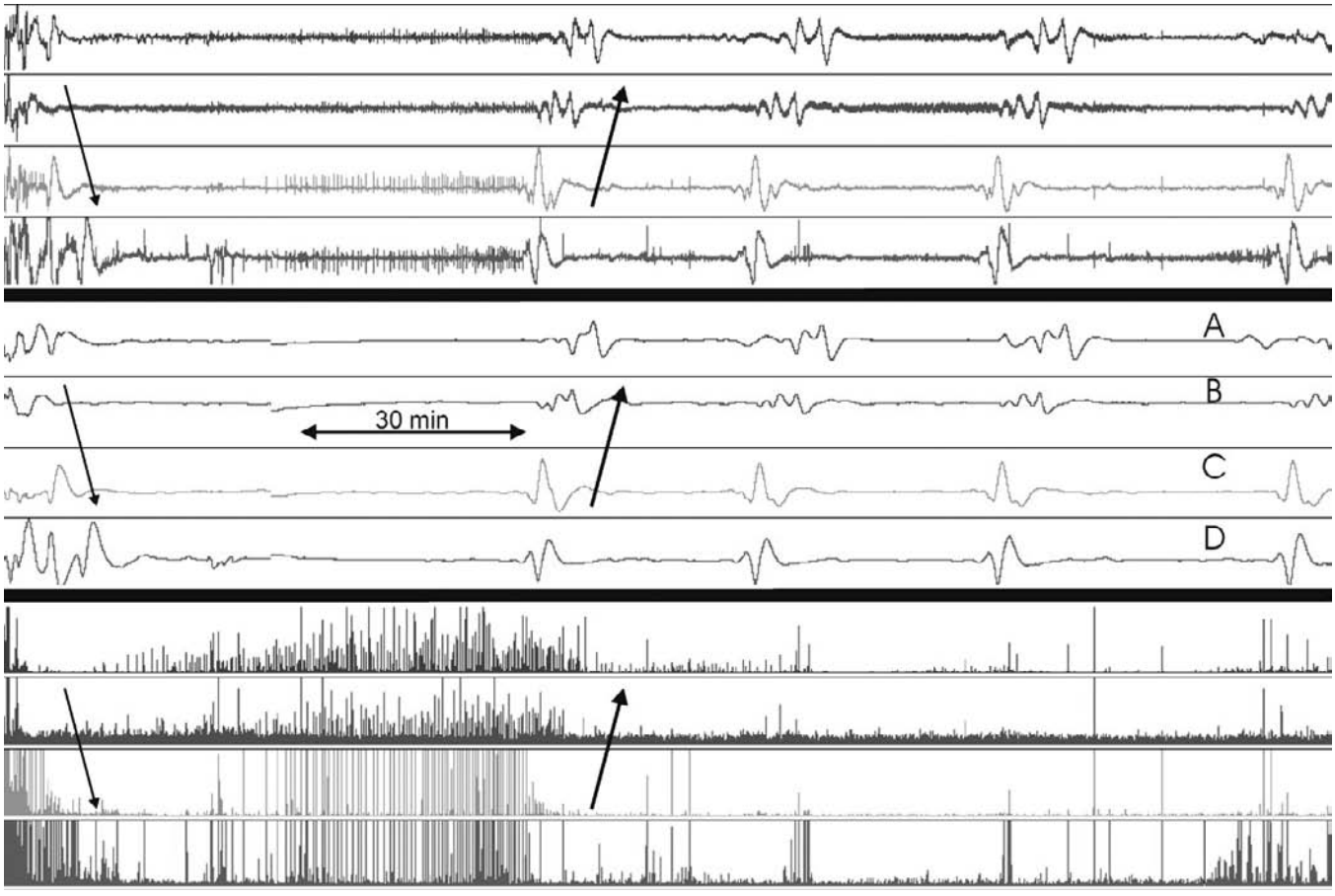

FIGURE 23-1. Cortical spreading depression and peri-infarct depolarizations (PIDs) in an acutely injured brain; three-hour recording of electrocorticography (ECoG) from channels A to D. The three sets of traces represent the same period: the upper four traces show the unfiltered signal (full scale: 3 mV); the middle four traces show the integrated signal (full scale: 100 mVs); and the lower four traces show the power of the 0.5–70 Hz band of the signal (full scale: 0.05 mV2). Baseline ECoG activity showed a burst-suppression pattern: 2-second bursts and 10- to 30-second suppressions, amplitude 300–1000 mV. Initially, a cortical spreading depression spreading from channel A to D depressed this ECoG activity for 30–40 minutes. The cortical spreading depression was accompanied by slow potential changes and spread from channels B to D at a velocity of 2–3 mm/minute (thin arrows). After ~1 hour, another cortical spreading depression accompanied by slow potential changes spread from D to A (thick arrows). This time, the ECoG activity did not recover. After 29 minutes, slow potential changes spread from channel D to A with exactly the same time sequence and shape as detected during the last cortical spreading depression. The ECoG remained depressed, indicating compromised metabolism. The event was therefore classified as a PID. Two stereotyped PIDs followed after intervals of 32 and 39 minutes. Just before the last of these PIDs, slight recovery of ECoG in channel D was noticed (lower right). During 5 hours, a total of 21 stereotyped PIDs were recorded. These PIDs were either similar to those in the figure or spread in the direction A to D in a second stereotyped pattern. (Adapted from Fabricius et al. (3).)

Recently, we have detected epileptogenic activity from miniature cortical depth electrodes in patients with acquired brain injury (34); this activity, including clear focal ictal activity, was undetectable on the scalp EEG in some cases (Figure 23-2). In one case, prominent changes were seen in the depth electrode only (suppression-burst, then attenuation, then periodic discharges with no obvious change in scalp EEG) while the patient sustained a hemorrhagic transformation of a large infarct (34).

ACUTE ISCHEMIC STROKE (AIS)

Ischemia Detection in AIS

The diagnosis of AIS is usually made under great time constraints in the emergency room based on a combination of the clinical history, the neurological examination, and the head computed tomography (CT) scan or, increasingly, the magnetic resonance image (MRI) scan. Prior to the advent of readily available neuroimaging techniques, there was a role for EEG in supplementing the physical examination to diagnose AIS (8). Among 91 patients with AIS, 36% initially had normal CT scans, and 48% (N=16) of these showed acute lateralized EEG abnormalities (35). All 16 showed cortical infarction on follow-up CT scans corresponding to the EEG findings. EEG is able to detect cortical infarcts with a much higher sensitivity (76%) than subcortical infarcts (30%) (35). A close topographic correlation between infarct location and focal increases in delta and decreases in alpha activity has been reported in 17 of 20 AIS patients measured by frequency analysis and topographic mapping (16). Quantitative EEG analysis (topographical maps based on absolute and relative power in the different frequency spectra) assisted in localizing focal hypoperfusion in AIS patients (20). At least 64 channel recordings are necessary to achieve adequate recording densities when EEG is compared to clinical and MRI standards in localizing acute ischemia (22). Among 11 patients with AIS, a close

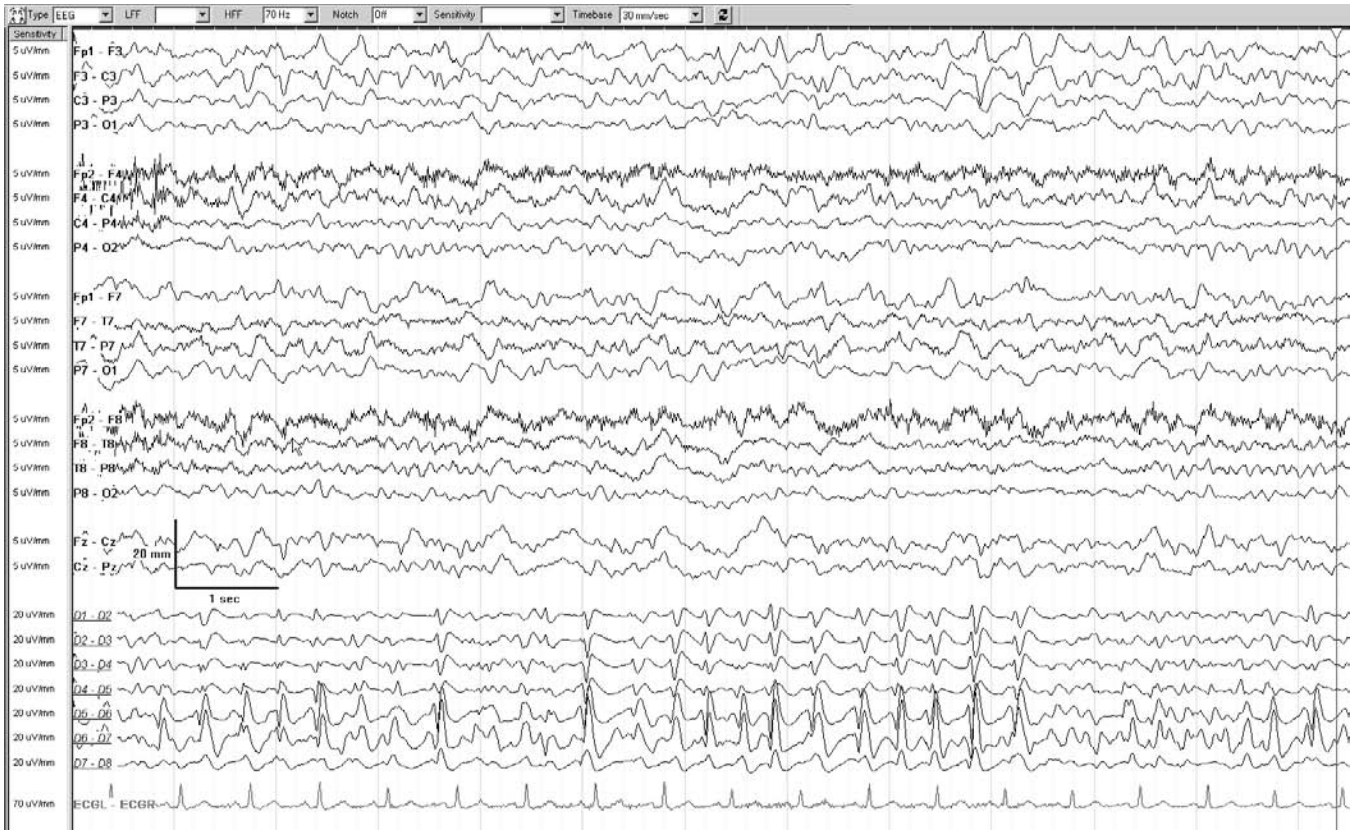

FIGURE 23-2. Epileptiform SIRPIDs on depth electrode but missed on surface EEG. 73-year-old woman, presenting with SAH from an anterior commissure aneurysm (Fisher grade 3, Hunt–Hess grade 3), who underwent clipping of her aneurysm. Intraoperatively, a depth electrode was placed into the right frontal lobe. On SAH day 3, the depth electrode shows frequent runs of repetitive epileptiform discharges (frequency 2–3 Hz, amplitude up to 560 uV). These decreased during sleep, and increased with stimulation (SIRPIDs). Many had the appearance of electrographic seizures, lasting 10 seconds to several minutes. There were no epileptiform discharges recorded from the surface EEG. Later, the surface EEG also showed periodic epileptiform discharges and electrographic seizures.

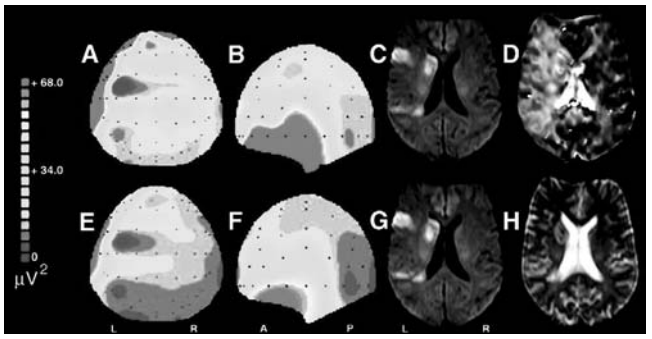

FIGURE 23-3. Correlation of early change in EEG focal delta power with outcome and imaging in acute ischemic change: example with early decreasing delta power and excellent early recovery. A and B: axial and left lateral EEG scalp delta power maps acquired 6.5 hours after onset of symptoms. C: initial DWI (6 hours). D: initial mean transit time (MTT) map. E and F: axial and lateral delta power maps at 13 hours. G: 15-hour DWI scan. H: 30-day T2 MRI. (Adapted from Finnigan et al. (36).) (*See color insert*).

relationship was seen between the perfusion-weighted image (PWI) lesion volume (mean transit time on MRI) and the acute delta change index (reflecting the rate of change of average delta power in the scalp EEG) (Figure 23-3) (36). Given the availability of MRI scanning, EEG is rarely used in diagnosing or localizing AIS—except perhaps in cases of laminar necrosis, in which MRI, including the diffusion-weighted image (DWI), may be negative or show only subtle findings for days (Figure 23-4) (37). However, certain EEG patterns (e.g., regional attenuation without delta (RAWOD)) may help in selecting patients in the emergency room who will benefit from thrombolysis (38).

More importantly, cEEG may be used as a continuous monitor of brain perfusion to detect progressive or recurrent ischemia (17). AIS patients with recanalization may have reocclusion in up to 34% of cases (39). Both patients with stroke and those with transient ischemic attack have an increased risk of early recurrent ischemic stroke (40), which may be picked up by cEEG. Despite theoretical advantages and some clinical evidence, today only a few institutions use cEEG for AIS patients (8). In AIS patients treated with hypervolemic hypertensive therapy, focal slowing in the raw EEG normalized once regional cerebral blood flow (measured with XeCT cerebral blood flow imaging) was elevated above the ischemic threshold (41). One study correlated qEEG monitoring (percentage of theta and delta activity over total activity) with baseline and post-treatment cerebral blood flow measured with 133-Xenon SPECT in patients with AIS in the middle cerebral artery territory during isovolemic hemodilution (42). Improved background activity was seen in response to increases in regional cerebral blood flow and clinical improvement. In patients with atherosclerotic AIS, a good correlation between topographic maps based on qEEG parameters (% time and amplitude obtained by the waveform recognition method) and controlled hypertension and hypotension was reported (43). Six of 11 patients (54%) showed qEEG improvement during hypertension, and 12 of 18 patients (66%) showed qEEG worsening with hypotension (43). The acute delta change index was found to mirror the effects of intravenous tissue plasminogen activator (tPA) in a patient with AIS (36). A close relationship was reported between the clinical condition of 21 AIS patients as determined using the National Institutes of Health Stroke Scale (NIHSS) score and the qEEG as quantified using the brain symmetry index (44). The authors of this last study suggest that changes in the continuously assessed brain symmetry index may alert clinicians to re-examine a patient and detect a clinical change as early as possible.

The patients who may be at highest risk of recurrent stroke and have significant function to salvage are patients hospitalized with transient ischemic attack or minor stroke. Using clinical parameters, a subset of patients at high risk of stroke after transient ischemic attack can be identified (40). EEG monitoring could be used in these patients to detect ischemia as it occurs in order to maximize the benefit from thrombolysis; however, this application has not been studied so far.

Seizures in AIS

Approximately 1.8% to 15% of AIS patients monitored with cEEG will suffer from acute seizures (8,45,46). Generalized convulsive SE has been reported in 0.1% to 0.9% of patients with AIS (45,47,48). Nonconvulsive seizures have been observed in 9% of AIS patients in whom cEEG was ordered, and nonconvulsive SE in 7% (2). In animals, seizures are associated with increased infarct size and increased mortality (49). In humans, epidemiological studies have demonstrated a threefold increase in mortality when status epilepticus complicated AIS, independent of infarct size or initial severity (50). It may be particularly important that AIS patients who received intravenous thrombolysis be monitored closely with cEEG, because in animal models tPA may cause seizures (51). The relationship between tPA and seizures in humans is less well understood. One study suggested an association between intravenous thrombolysis and electrical epileptic activity (46), but others have postulated that seizures during thrombolysis may represent reperfusion and neurological recovery (52).

Prognostication in AIS

Several studies have investigated the ability of acute or subacute EEG data to predict long-term outcome after AIS (36,53–56). Poor outcome was found to correlate with contralateral (55) and generalized background slowing (56). Among 55 patients with supratentorial ischemia, early EEG was able to differentiate between poor and good functional outcome more accurately than admission functional

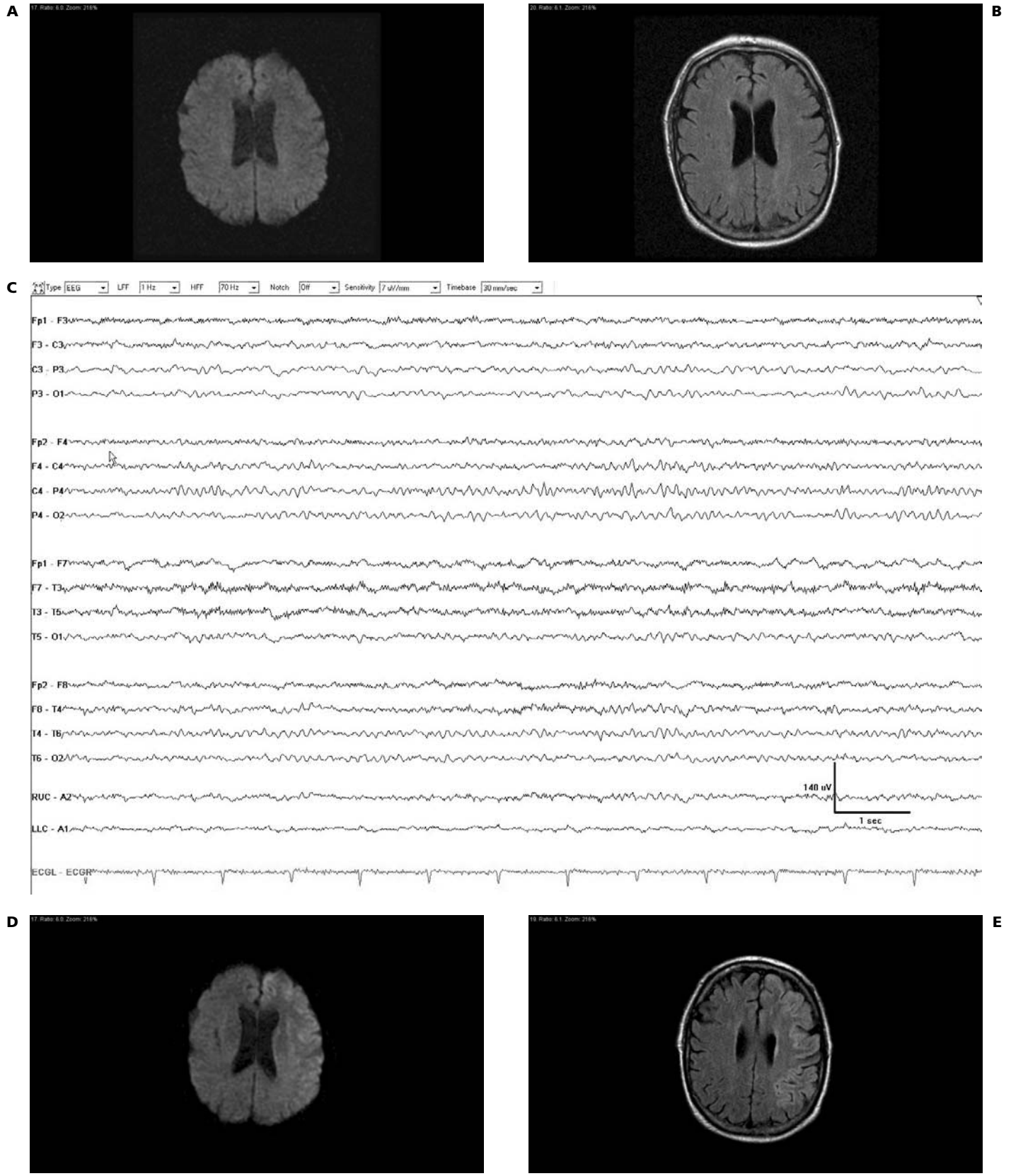

FIGURE 23-4. 70-year-old man with persistent left middle cerebral artery syndrome after left carotid endarterectomy; negative MRI with DWI two days in a row, but markedly asymmetric EEG, most likely due to laminar necrosis from intraoperative or perioperative ischemia. Postoperative angiogram, magnetic resonance perfusion, and transcranial Doppler studies showed no occlusion, major stenosis, or delayed perfusion. A: MRI with DWI obtained about 28 hours postoperatively, with no major abnormalities. B: MRI with fluid-attenuated inversion recovery (FLAIR), also at 28 hours postoperatively and with no major abnormalities. C: EEG from the same day (24 hours postoperatively), showing a clear asymmetry of faster activity consistent with diffuse cortical dysfunction such as from ischemia/infarct. This abnormality was persistent throughout the patient's recording, beginning at the time of EEG hookup less than 24 hours postoperatively. No other imaging or vascular study showed an abnormality to explain his clinical syndrome in the first several days. D: MRI with DWI 9 days postoperatively, now showing widespread abnormalities. E: MRI with FLAIR, also 9 days postoperatively and showing widespread increased signal in the left hemisphere cortex. (Adapted from Nuwer, in press.)

impairment (53). Continuous polymorphic delta with depression of alpha or beta activity and the degree of background suppression was related to poor outcome, whereas good outcome was seen in patients with the absent slow activity with minimal decrease in background frequencies, and intermittent theta-delta activity with slight asymmetry of background activity (53).

Recently, several quantitative EEG parameters were reported to predict outcome after AIS. Among 28 patients with acute MCA stroke, qEEG parameters (Z-values of absolute power from the four classic frequency bands, calculated from serially obtained EEGs within 72 hours of stroke onset) and a clinical examination scale (Canadian Neurological Scale) were used to predict functional disability (54). Remarkably, these qEEG parameters were more often able to correctly predict residual functional disability than the clinical scale. Similarly, among 11 AIS patients, a change in the power of slow frequencies (acute delta change index) based on EEGs obtained within 16 hours of stroke onset was highly related to the 30-day NIHSS score (36). This qEEG parameter correlated as closely with clinical outcome as did the lesion size on perfusion-weighted MRI scans, and (surprisingly) correlated more closely with outcome than did diffusion-weighted imaging.

Other Applications of cEEG in AIS

AIS patients are at risk for a number of other complications, including cerebral edema with increased intracranial pressure, intracranial hemorrhages, and side effects from treatment. All of these warrant close brain monitoring given that up to 43% of AIS patients have some degree of deterioration within the first 24 hours, with marked deterioration in 25% (57). Intravenous tPA therapy has a 7% to 10% complication rate of intracerebral hemorrhage (58). These patients are also at an increased risk of hypotension, fever, hyperglycemia, and other systemic perturbations (59). Although little data exists for AIS patients, hemorrhages (see section of this chapter on intracerebral hemorrhage) and intracranial pressure elevation may also be detected by cEEG.

SUBARACHNOID HEMORRHAGE (SAH)

Subarachnoid blood may cause diffuse background slowing in the theta and delta range, with the amplitude and frequency relating to the degree of impaired consciousness (60), and will also frequently lead to a disruption of the posterior dominant (alpha) rhythm (17). Focal or lateralized slowing appears with parenchymal extension of the hemorrhage, usually ipsilateral to the location of the ruptured aneurysm (61). In the pre-CT-scan era, research focused on using focal EEG findings to help in localizing the aneurysm location in these patients (61). With the advent of readily available CT scanning and angiography, this objective has become obsolete.

Detection of Delayed Cerebral Ischemia in SAH

Delayed cerebral ischemia is defined as clinical deterioration and/or infarction due to vasospasm after SAH, and is one of the major in-hospital complications of this disease. Angiographic vasospasm is detected in 50% to 70% of patients with SAH (62). Delayed cerebral ischemia occurs in 19% to 46% of SAH patients (63–68), and may be seen in up to 54% of poor-grade SAH patients (Hunt–Hess grade 4 or 5, i.e., stupor or coma) (69). Clinically silent infarction accounts for approximately one-fourth of patients with delayed cerebral ischemia (68,70). Hypertensive hypervolemic therapy and angioplasty are used to treat vasospasm and may potentially prevent infarction if started early enough. Therefore, timely diagnosis is crucial in these patients.

The gold standard to diagnose vasospasm in a patient with delayed cerebral ischemia is cerebral angiography, which cannot be performed frequently or continuously, cannot be performed onsite in the ICU, and carries a low but significant risk. Currently, patients are followed for delayed cerebral ischemia with serial clinical exams, which are particularly limited in poor-grade patients and only performed intermittently. Transcranial Doppler ultrasound (TCD) is often used to supplement the clinical examination, but the sensitivity and specificity of routine TCD testing are rather poor (71). Continuous EEG may be used to monitor the patient continuously. Suspected ischemia in the cEEG would ideally lead to rapid examination and confirmatory testing—for example, with cerebral angiography. Similarly, the EEG could be used to help guide therapy—for example, by monitoring the functional effect of blood pressure manipulations or changes in position (head elevation, Trendelenburg, etc.).

Raw EEG patterns such as broad, repetitive slow waves, termed "axial bursts," are highly correlated with clinical or angiographic evidence of vasospasm (up to 97% of the time) (72). Continuous visual analysis of raw EEG is unpractical. In an effort to make this technique both more sensitive for detecting vasospasm and more practical, quantitative analysis of cEEG has been used to detect delayed cerebral ischemia due to vasospasm in SAH patients (73–75). There is controversy over which qEEG parameter best correlates with clinically significant ischemia, but a ratio of fast over slow activity (e.g. alpha over delta activity) or the variability of such activity (e.g., relative alpha variability) appear to be effective measures (Figure 23-5) (74,75). A number of qEEG parameters have been shown to correlate with delayed cerebral ischemia or angiographic vasospasm: trend analysis of total power (1–30 Hz) (73), variability of relative alpha (6–14 Hz/1–20 Hz) (74), and poststimulation alpha-delta ratio (PSADR,

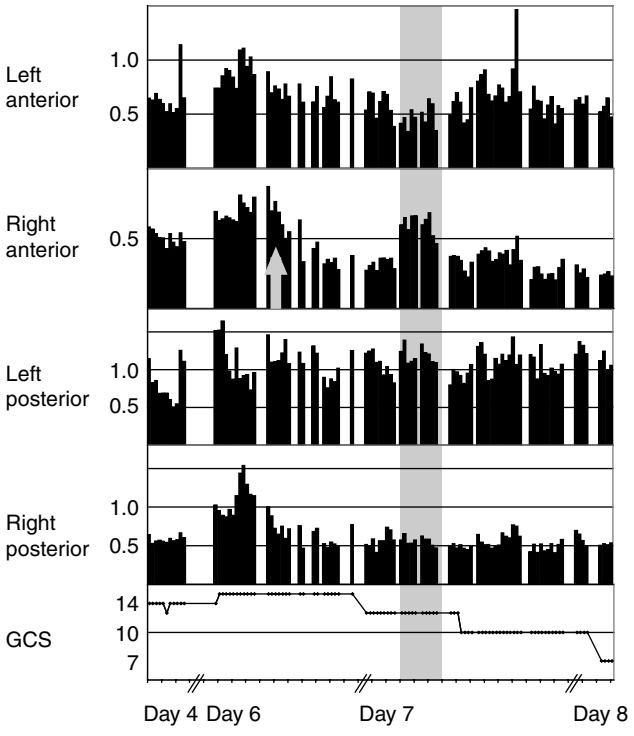

FIGURE 23-5. Detecting delayed cerebral ischemia (DCI) from vasospasm after subarachnoid hemorrhage (SAH). Alpha-delta ratio calculated every 15 minutes and Glasgow Coma Score shown for days 6–8 of continuous EEG (cEEG) monitoring. Fifty-seven–year-old woman admitted for acute SAH (admission Hunt–Hess grade 4) from a right posterior communicating aneurysm. Admission angiography did not show vasospasm. The aneurysm was clipped on SAH day 2. No infarcts were seen on postoperative CT. Postoperatively, the patient had a GCS of 14. Continuous EEG was performed from SAH days 3 to 8. The alpha-delta ratio progressively decreased after day 6, particularly in the right anterior region (thick vertical gray arrow), to settle into a steady trough level later that night, reflecting loss of fast frequencies and increased slowing over the right hemisphere in the raw cEEG. On SAH day 6 flow velocities in the right MCA were marginally elevated (144 cm/s), but the patient remained clinically stable with hypertensive, hypervolemic therapy. On day 7, the Glasgow Coma Score dropped from 14 to 12 and a CT scan showed a right internal capsule and hypothalamic infarction. Angiography demonstrated severe distal right middle cerebral artery and left vertebral artery spasm; however, because of the marked tortuosity of the parent vessels and the location of vasospasm, a decision was made not to perform angioplasty, but to infuse verapamil and papaverine. This resulted in a marked but transient increase of the right anterior and posterior alpha-delta ratios (shaded area). Later that day, the patient further deteriorated clinically to a Glasgow Coma Score of 7, with a new-onset left hemiparesis, and died on SAH day 9 from widespread infarction due to vasospasm. (Adapted from Claassen et al. (2).)

8–13 Hz/1–4 Hz) (75). These qEEG parameters may detect changes days prior to clinical changes (73,74). Among primarily good-grade SAH patients, changes in two-channel qEEG preceded clinical symptoms suggesting delayed cerebral ischemia in 4 of 11 cases (73). Another study found that a decrease in the visual scoring of the relative alpha variability preceded transcranial Doppler ultrasound or angiographic detection of vasospasm by at least 2 days in 10 of 19 patients. In this study, qEEG was 100% sensitive for angiographically defined vasospasm (19 of 19 cases) (74). Importantly, all of these studies found that focal ischemia sometimes resulted in global or bilateral changes in the EEG (74,75). Continuous EEG might also be better at detecting distal spasm that would not be picked up on routine transcranial Doppler ultrasound testing or MRA.

Seizures in SAH

Older studies reported generalized tonic clonic seizures at the onset of bleeding in 6% to 25% of SAH patients (76–79), with some of those episodes possibly representing nonepileptic tonic posturing related to herniation or intracranial hypertension. In-hospital seizures have been reported in up to 12% of SAH patients (77,80), often associated with rebleeding, which now occurs less frequently thanks to earlier treatment (surgical clipping or coiling). In modern studies, estimates of the rate of generalized tonic-clonic seizures after SAH range between 3% and 5% (76,78,79,81). In these studies, early in-hospital seizures after SAH were most frequently seen with large focal clots (78,80,82). Importantly, the diagnosis of seizures in all of the aforementioned studies (76–81) was based on the presence of overt focal or generalized tonic-clonic activity; none of these studies used cEEG to reveal nonconvulsive seizures.

Among 116 consecutive SAH patients that underwent cEEG at our center, 16% had periodic epileptiform discharges while undergoing cEEG (lateralized in 11%; generalized in 5%) (29). Nonconvulsive seizures (Figure 23-6) were seen in 6% and nonconvulsive SE in 4% of cases. In one study, aneurysmal SAH was among the most common acute symptomatic causes of nonconvulsive SE, representing 10% of consecutively diagnosed cases (5 of 49 patients) (6). Nonconvulsive SE has been detected with cEEG in 8% of patients with SAH and otherwise-unexplained coma or neurologic deterioration (83).

Prognosis in SAH

In a recent study by our group, cEEG provided independent prognostic information in poor grade SAH patients after controlling for age, clinical exam (Hunt–Hess grade), and the presence of intraventricular hemorrhage (IVH) on admission CT scan (29). Poor outcome (modified Rankin score 4 to 6, i.e., dead or severely disabled) was associated with the absence of sleep architecture (OR 4.3, 95%-CI 1.1–17.2) and the presence of periodic lateralized epileptiform discharges (PLEDs; OR 18.8, 95%-CI 1.6–214.6). In addition, all patients with absent EEG reactivity (N=8), or with generalized periodic epileptiform discharges (N=12) or bilateral independent PLEDs (N=5), and 92% (11 of 12)

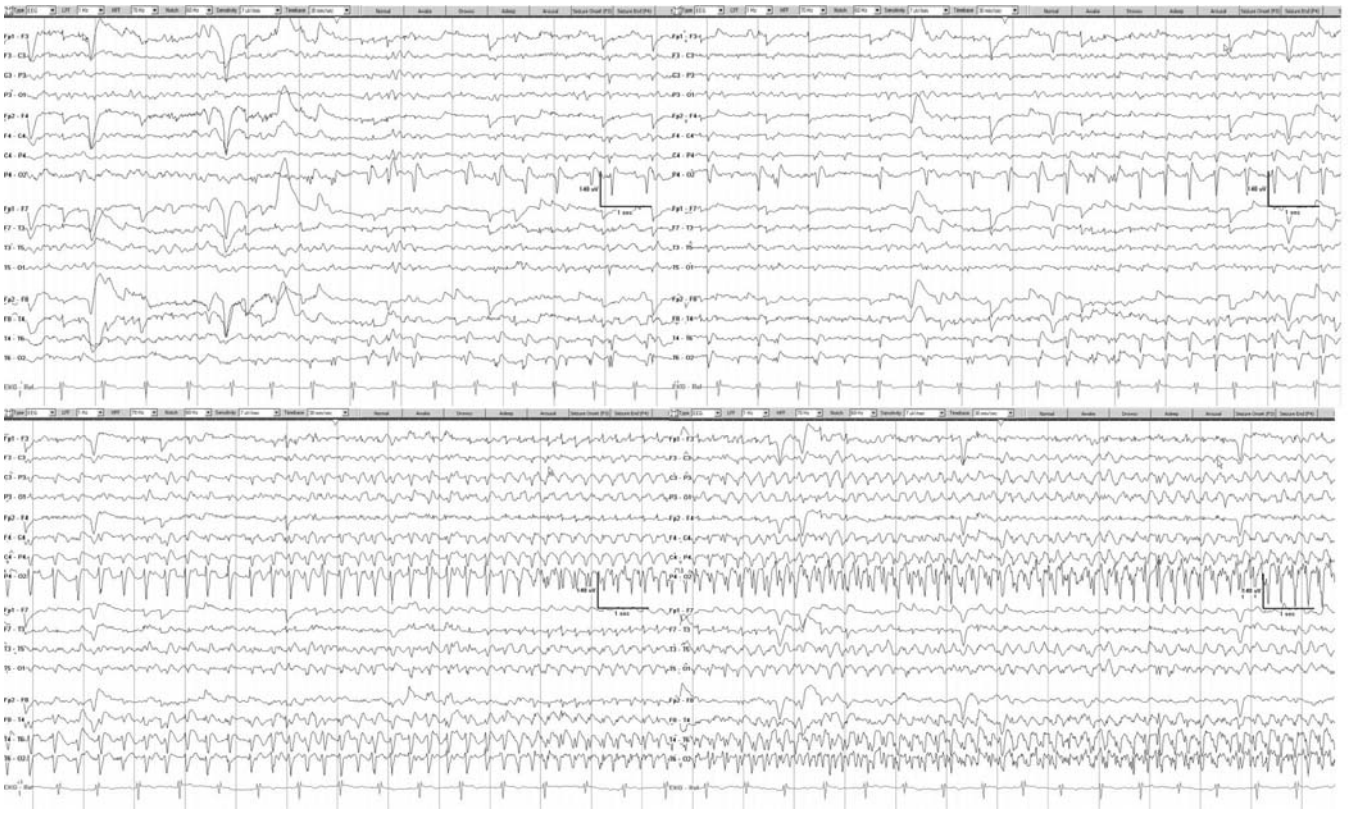

FIGURE 23-6. Seizure in patient with SAH. EEG demonstrating a nonconvulsive seizure in a 46-year-old woman with Hunt–Hess grade 3 SAH after endovascular coil-embolization of a right posterior cerebral artery aneurysm. (Adapted from Claassen et al. (29).)

of patients with nonconvulsive status epilepticus, had poor outcome (29). In an earlier study from our center, all eight SAH patients that were found to have nonconvulsive SE on cEEG died (83).

Other Applications in SAH

Though theoretically feasible, the ability of EEG to detect rebleeding after SAH is increasingly difficult to study, because it occurs in only approximately 7% of cases in more recent series (84). However, cEEG may be a very sensitive tool to detect rebleeding in real time. The aforementioned ability of cEEG to detect elevated intracranial pressure and edema in AIS patients also applies to SAH patients.

INTRACEREBRAL HEMORRHAGE (ICH)

Depending on the ICH location, varying raw EEG patterns have been observed. In deep capsular hemorrhages, delta activity is seen over the affected hemisphere, at times occurring in rhythmic runs of moderate amplitude (17,85). Thalamic hemorrhages may lead to ipsilateral delta activity, a reduction or enhancement of the alpha rhythm depending on the precise location within the thalamus, and lack of sleep spindles (17,86). Bleeds located in the mesencephalon may cause diffuse theta activity (17). Hemorrhages in the mid-lower brainstem can cause diffuse attenuation or a lack of reactivity (17,87).

Ischemia, Hematoma Growth, and Midline Shift in ICH

In ICH patients, electrographic seizures have been associated with increasing midline shift ($p<0.03$) (28) and secondary hematoma growth (OR 9.5) (30). The cause-and-effect direction of this relationship remains unclear. Perilesional ischemia that may be associated with edema is seen in patients with ICH (88). This has not been studied well with cEEG and may be a target for more interventional EEG techniques such as depth electrodes.

Seizures in ICH

Acute clinical seizures have been reported in 2.8% to 19% of patients with ICH (30,82,89–91). Generalized convulsive SE is rare and depending on patient selection and data acquisition ranges between 0.3% and 2% (48,82,89–91). Few studies have used cEEG to study nontraumatic ICH patients (Figure 23-7). In these studies, electrographic

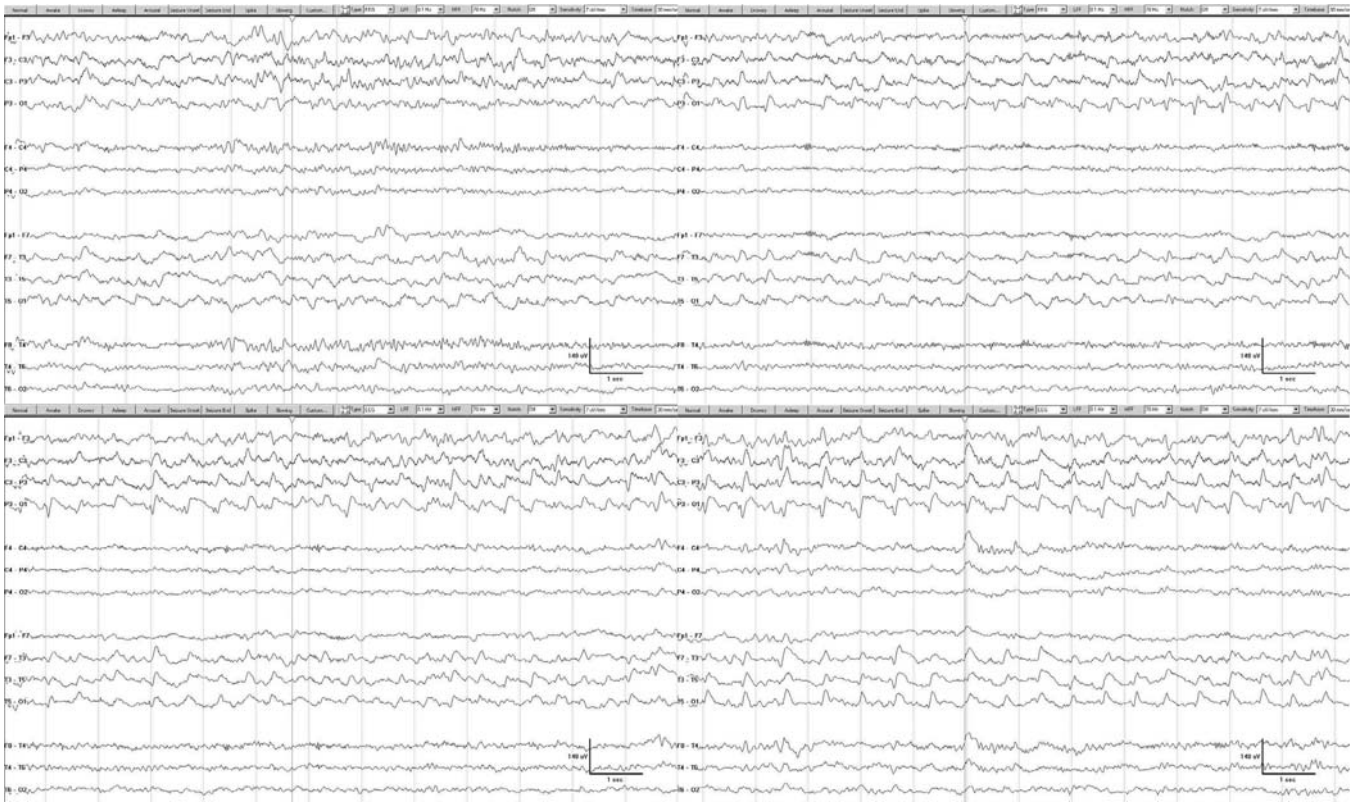

FIGURE 23-7. Seizure in patient with ICH. 72-year-old woman admitted with a 65-cc left temporoparietal lobar ICH with 5.7-mm midline shift secondary to a vascular malformation. EEG recording of an evolving electrographic seizure in the left hemisphere maximal in the parasagittal region. Panels A, B, and C are continuous clips of the seizure developing in the left hemisphere. Panel D demonstrates the fully developed seizure approximately 1.5 minutes later. There was no clinical correlate observed on video. After electrographic seizures were recorded, there was no further increase in ICH volume or midline shift. (Adapted from Claassen et al., in press.)

seizures have been reported in 13% to 28% (7,28,30) and nonconvulsive SE in 7% of ICH patients (30). In patients with seizures, the first seizure was recorded within one hour in 56% of patients and within 2 days in 95% (30).

Prognosis in ICH

One study found a trend for poor outcome (P<0.06) for patients with electrographic seizures after ICH (28). This was not corroborated in a subsequent larger study, in which seizures did not remain associated with poor outcome after controlling for demographic, clinical, and radiological variables (30). Despite being almost twice as large as the first study (28), this study may have been underpowered to detect this difference (30). This study did, however, find that any periodic epileptiform discharges (OR 7.6, 95%-CI 2.1–27.3), periodic lateralized epileptiform discharges (OR 11.9, 95%-CI 2.9–49.2), and focal stimulus-induced rhythmic, periodic, or ictal discharges (SIRPIDs; OR 15.6, 95%-CI 2.7–90.5) were associated with poor outcome (30). SIRPIDS are rhythmic, periodic, or ictal-appearing discharges consistently induced by alerting stimuli (e.g., auditory stimuli, sternal rub, examination, suctioning, turning) (92).

It remains unclear whether seizures or periodic discharges cause additional damage or are surrogates of brain injury. However, there is a significant body of data suggesting that seizures do cause additional brain injury (93–95).

FUTURE OUTLOOK ON cEEG

cEEG will become an essential part of multimodality monitoring of ICU patients. Important questions remain unanswered to date. Do subclinical seizures or periodic discharges cause additional harm in severely brain-injured patients? Do these patients benefit from more aggressive treatment? Is it practical to implement treatment decisions based on cEEG data in real time? So far the quality of the data supporting the widespread application of cEEG is poor, and most studies are retrospective, often drawn from heterogeneous patient populations using a small sample size. There are a number of reasons for this lack of good evidence that include the following: (a) few centers are performing cEEG, (b) consent issues complicate research of brain-injured patients, and (c) cEEG is very labor-intensive, and may be very expensive. Automated seizure and ischemia

detection as well as artifact rejection need to be improved. To maximize the clinical utility of cEEG as a continuous monitor of brain activity, around-the-clock real-time "brain telemetry" is needed. Specially trained personnel need to be available to respond to computer alarms and to monitor the studies, as is done with cardiac telemetry in virtually every hospital in the United States. Once this is in place, and more is known about which EEG patterns require treatment, prospective, randomized controlled trials will need to be conducted to see whether cEEG improves outcomes.

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SECTION

VI

SPECIAL LOCALIZING PROCEDURES

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24

NEUROIMAGING LOCALIZING PROCEDURES

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Structural and functional imaging has revolutionized the evaluation and management of patients with epilepsy. Structural imaging of patients with new-onset epilepsy is standard practice, helping to identify etiology, detect potential foci, and provide prognostic information. Advanced imaging techniques—including high-resolution structural magnetic resonance imaging (MRI) at 1.5 T, and increasingly at 3.0 T; special MRI sequences such as diffusion tensor imaging (DTI), magnetization transfer, and functional imaging (magnetic resonance spectroscopy (MRS)); positron emission tomography (PET); and ictal (subtraction interictal) single photon emission computed tomography (SPECT)—are performed in patients with medically refractory epilepsy to identify surgical candidates, help estimate the chance of surgical success, and plan resection. Structural and functional imaging has reduced the need for invasive monitoring and has improved surgical outcomes. Improved MRI technology has reduced the clinical need for functional imaging (particularly PET receptor imaging), but such imaging retains an important role in identifying seizure foci among MRI-negative patients, and in the study of epilepsy pathophysiology.

STRUCTURAL IMAGING

Technical Considerations for Magnetic Resonance Imaging

The usefulness of MRI in patients with epilepsy depends on the sequences employed. Although this is an area of continuing debate, there is general agreement that the following sequences should be obtained for evaluating patients older than 24 months with epilepsy:

1. Anatomic, thin-slice (1–1.5 mm) volumetric T1-weighted gradient-recalled echo sequence
2. Axial and coronal T2-weighted sequence
3. Fluid-attenuated inversion recovery (FLAIR) sequence (axial, and coronal if possible)
4. High-resolution oblique coronal T2-weighted imaging of the hippocampus (fast or turbo spin-echo weighted sequence)

Routine administration of gadolinium contrast provides little advantage in patients with epilepsy, but it may be used where tumor, vascular malformations, inflammation, or infection are suspected based on noncontrast studies (15).

Children younger than 2 years require special sequences, because immature myelination affects the ability to identify common causes of epilepsy (5). Lesions may appear or disappear with the changing patterns of myelination (33,143,154). In addition to a three-dimensional dataset, imaging in children younger than 2 years should include sagittal, axial, and coronal T1-weighted sequences. Volumetric T1-weighted sequences are less useful prior to age 1 because of incomplete myelination on T1 sequences. MR imaging (especially high-resolution T2 images) performed early in the first year of life in infants with epilepsy is important to identify areas of cortical or subcortical dysplasia, which can become difficult to identify after myelination. Conversely, if MR imaging before the age of 2 is normal, and seizures persist, then MRI may be repeated at 6- to 12-month intervals, and certainly after age 24–30 months when more mature myelination can reveal suspected but unappreciated cortical dysplasia.

New-Onset Seizure and Newly Recognized Epilepsy

Imaging is recommended for the evaluation of patients with recently diagnosed epilepsy (62). Computed tomography (CT) is able to identify blood (acutely), intracranial calcifications (congenital infection, tumor), and large

tumors or large stroke (46,62). However, MRI is superior to CT for the identification of most causes of epilepsy (15). CT may therefore be used as a screening tool in the acute setting when MRI is unavailable, but yield is low when the clinical exam is normal (107). Imaging with either CT or MRI is invariably normal in the primary generalized epilepsies or localized genetic epilepsies such as benign focal epilepsy of childhood with centrotemporal spikes (BECTS) (6,47,82).

Patients with an underlying structural etiology (who have remote symptomatic epilepsy) have reduced likelihood of long-term seizure control (147,149). Although lesions such as tumors are rare (1%–2%) in new-onset epilepsy, their identification alters management (6). A vascular anomaly such as an arteriovenous malformation or recent stroke will also alter management. Patients with an abnormal neurological exam, or a risk factor such as AIDS or residence in a cysticercosis-endemic region, are more likely to have a structural lesion on initial seizure presentation (57).

Chronic Localization-Related Epilepsy

Imaging in chronic epilepsy is primarily pursued to evaluate patients for, and to plan, epilepsy surgery. When the MRI demonstrates a clear focal anomaly (such as focal cortical dysplasia, mesial temporal sclerosis, tumor, or vascular anomaly) and imaging findings are congruent with the ictal EEG, it is unusual for the lesion not to be the focus of seizure onset, and surgical outcome can be expected to be excellent (63,164). Nonspecific findings such as encephalomalacia or atrophy are less helpful for seizure focus localization.

The most common MRI findings in patients with chronic epilepsy (15) are

1. Malformations of cortical development
2. Mesial temporal sclerosis
3. Tumor
4. Vascular abnormalities (stroke, arteriovenous malformations, angioma)
5. Infection (e.g., cystercircosis)
6. Nonspecific abnormalities (atrophy, encephalomalacia)

Malformations of cortical development are generally categorized by developmental timing of the abnormality: abnormal cell proliferation/apoptosis (hemimegalencephaly, balloon cell of Taylor, tuberous sclerosis), cell migration (lissencephaly, heterotopia), and late migration and organization (polymigrogyria, schizencephaly, focal cortical dysplasia without balloon cells). Other schemes use the location, pathological organization, or genetics of the abnormality, and are the topic of recent reviews (4).

Mesial temporal sclerosis (MTS) is the most common pathological substrate in adolescents and adults with temporal lobe epilepsy. MTS can be seen in children and may be associated with so-called dual pathology, especially in younger children, when the primary pathology is not MTS but usually dysplasia, stroke, or, less commonly, tumor (50). MTS is characterized by loss of internal architecture, atrophy, and increased T2 signal (Figure 24-1) (19,69,70). When found, *unilateral MTS is associated with 67% complete seizure freedom (Engel 1) and 90% excellent surgical outcome (Engel 1 or 2)* (156,175). The atrophy is best demonstrated on T1-weighted images, whereas signal changes are best demonstrated on fast spin-echo (FSE) or FLAIR images. The yield is highest when images are acquired perpendicular to the long axis of the hippocampal formation and are 3 mm thick. Thin-cut (1–1.5 mm), T1-weighted gradient-recalled-echo sequence images can be reformatted for optimal orientation. Hippocampal volumes may also be measured, especially from T1-weighted anatomical sequences, to provide a quantitative measure of atrophy (absolute and relative by use of an asymmetry index) as well as to identify evidence of bilateral involvement when unilateral volumes are corrected for whole-brain volume. Hippocampal volumetrics show several patterns of atrophy; usually the head of the hippocampal formation is affected, but atrophy of the entire hippocampal formation can also be seen, and, less often, atrophy restricted to the posterior segments (167). The signal change found in MTS may also be identified and quantified by T2 relaxometry (27,177). Evidence of bilateral MTS is found in approximately 10%–15% of patients, particularly when T2 relaxometry and magnetic resonance spectroscopy are obtained and vary with primary pathology. Occurrence of MTS is highest in stroke and dysplasia, and lower in tumor and

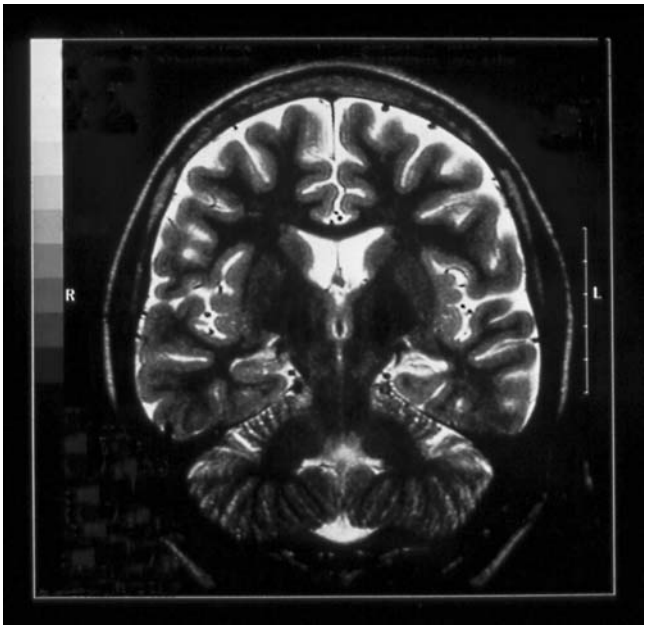

FIGURE 24-1. An 8-year-old with left mesial temporal sclerosis (MTS). Fast spin-echo sequences perpendicular to the long axis of the hippocampal formation demonstrate the characteristic findings of MTS: atrophy and increased signal. Right image is left brain. (*See color insert*).

vascular malformation (21). In expert hands, visual rating is comparable to volumetrics (22) even though it lacks the precision of quantitative analysis. It is also important that developmental variants not be misinterpreted as hippocampal formation atrophy or dysplasia.

Tumors are less common causes of epilepsy, but represent up to 25% of pathological substrate in some epilepsy surgery series (89). The most common mass lesions identified by imaging are gangliogliomas, oligodendrogliomas, astrocytomas/gliomas, and dysembryoplastic neuroepithelial tumors (DNETs) (168). These tumors vary in contrast enhancement. Seizures usually derive from the margins of such lesions. Vascular malformations that are associated with local ischemia (arteriovenous malformation) or hemorrhage (cavernous hemangiomas, which are often multiple) may also cause epilepsy.

Focal cortical dysplasia is found in 40% of pediatric epilepsy series. Widespread and diffuse malformations of cortical development, such as lissencephaly, are not amenable to resective surgery. In patients with multiple focal areas of dysplasia, such as periventricular heterotopia, surgical outcome is also poor (see below). The findings of clear, isolated, focal abnormalities may provide an 80% or greater Engel 1 or 2 outcome (Figure 24-2) (164). However, outcome is based on the ability to resect the lesion completely. When this is not possible because the lesion rests in eloquent cortex, then the frequency of good outcome is lower (52). Patients with a seemingly isolated malformation of cortical development may harbor other less apparent anomalies that result in a poorer surgical outcome. The long-term rate of seizure-free surgical outcome for malformations of cortical development in childhood is closer to 40%, but this includes patients with incomplete resections (52). For patients with more than one focal abnormality, such as children with tuberous sclerosis and multiple epileptogenic tubers, there is increasing experience with multiple resections to suggest that outcome may not be bleak (135). This experience may be applicable to a minority of children with other clearly defined areas of focal cortical dysplasia. Other focal cortical dysplasias deserve special consideration, given that increasing experience with hypothalamic hamartomas also suggests that appropriately selected children may benefit from resection or ablation of the hamartoma (118,133). In children considered for hemispherectomy or multilobar resection, surface EEG may show generalized or nonlocalizing patterns, yet resection or surgery results in favorable outcome in a high proportion of children (181). Children with Rasmussen's encephalitis, porencephaly (congenital stroke), extensive malformations of cortical development, or hemimegalencephaly have good surgical outcomes (29,71). *There are rare circumstances in which clear lesions are not the epilepsy focus* (63), but in these circumstances surface ictal EEG and clinical characteristics have suggested a focus elsewhere.

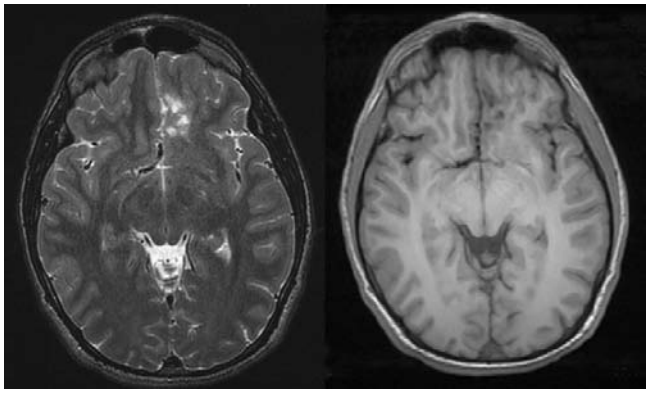

FIGURE 24-2. A 16-year-old with pathologically confirmed left mesial frontal dysplasia. T2-weighted sequence on left, Ti-weighted sequence on right. The lesion did not enhance with contrast. For MRI, right image is left brain.

The improved outcome when focal lesions are identified continues to drive the investigation of advanced and new imaging techniques toward identifying small or subtle focal abnormalities. Voxel-wise comparison (statistical parametric mapping (SPM), originally designed for PET; see below) has been used in functional imaging and more recently applied to MRI (7,138,139). In these methods, individuals may be compared statistically on a voxel-wise basis to probabilistic atlases based on a large sampling of normal volunteers. These methods do not show any clear superiority to skilled visual reading, but may provide additional insights under certain circumstances. They have also been employed to investigate structural brain injury as a response to chronic epilepsy (102).

Diffusion tensor imaging identifies areas with altered diffusability and also anisotropy (i.e., the preferential direction of water molecule diffusion). Epilepsy may be associated with loss of white matter structural integrity that may also represent a functional state influenced by ongoing or recent seizures. DTI imaging shows abnormalities in a minority of patients (139,172), but has no clear advantages in predicting surgical outcome. Aniosotropy maps may be used to identify white matter fiber tracts to be spared during surgery—primarily optic tracts, sensorimotor tracts, or important long tracts such as those connecting Wernicke's area to Broca's (13,119,131). In a few patients, magnetization transfer imaging may identify subtle focal cortical dysplasia, particularly at the base of sulci, that cannot be noninvasively identified by other means (138). Imaging seizures is rare, but postoperative imaging in patients with (prolonged) seizures may identify increased T2 signal and altered diffusability representing edema and cytotoxic injury (120,165).

Thin-cut curvilinear reconstruction of thin-cut high resolution (1-mm) images has also been advocated as a means to identify small focal cortical dysplasias, particularly gyral thickening or blurring grey-white junction (111). The efficacy of these methods for surgical outcome has not been validated. Similarly, it is not yet clear to what extent imaging

at higher tesla will improve identification of small areas of abnormality, mostly focal cortical dysplasias. There are reports of increased yield of high-resolution imaging at 3 T (83), and human studies at 7 T are under investigation. There is always the risk that subtle abnormalities will be found that are incidental and have no relation to epilepsy. It remains important to place imaging evidence in the context of clinical characteristics of the seizure and electrophysiological studies.

FUNCTIONAL IMAGING

Two opposing trends have affected the role of functional imaging techniques for localization of seizure foci. Advances in structural MRI have reduced the number of patients with "normal" studies. At the same time, higher-resolution PET cameras, combined PET-CT equipment, and cyclotron-produced ^{18}F-fluorodeoxyglucose (FDG) are becoming more widely available, as a result of their increasing roles in cardiology and oncology. Single photon emission computed tomography resolution is improving as well.

Data Acquisition and Analysis

In order to make optimal use of functional imaging in epilepsy, it is important to consider some technical aspects of image acquisition.

Positron Emission Tomography (PET)

Although PET is capable of measuring a wide variety of physiological processes, only cerebral glucose metabolism (CMRglc) measured with ^{18}F-FDG, and a variety of ^{18}F or ^{11}C-labeled neuroreceptor ligands or precursors, are important for epilepsy. The half-life of ^{11}C is 20 minutes, so an on-site cyclotron is needed to produce it, but ^{18}F (half-life 110 minutes) can be brought in from outside the scanning facility. State-of-the-art PET scanners produce sets of 30 to 50 images that can be reconstructed with true three-dimensional resolution. The spatial resolution of the newest PET scanners is 2–3 millimeters.

FDG-PET reflects cerebral glucose metabolism during the 30–40 minutes isotope uptake and fixation period, weighted toward the beginning. Ictal scanning is not practical with rapidly decaying cyclotron-produced radiopharmaceuticals, because one cannot wait for seizures to occur after tracer production. However, it is very important to have good clinical or EEG monitoring of patients during PET scans; a seizure occurring 3 minutes after injection would have a very different effect than an identical event occurring 25 minutes later.

PET data can be analyzed with quantitative, "semi-quantitative," or purely visual methods. Purely visual PET interpretation does not reveal all the information in the images. Absolute CMRglc measurement is not necessary for clinical localization, and values relative to the cerebellum, the whole brain, or a right-left asymmetry index can be calculated. More sophisticated approaches, using programs such as statistical parametric mapping, allow comparison with normal control databases on a voxel-wise basis (40).

Single Photon Emission Computed Tomography (SPECT)

SPECT blood flow measurements use commercially available tracers, ^{99m}Tc-ethyl cysteinate dimer (ECD) or the older ^{99m}Tc-HMPAO. ^{99m}Tc has a 6-hour half-life; the tracer can be kept premixed on a monitoring unit to be injected as soon as a seizure is detected. The actual scan can be performed at a delay after tracer injection. In order to allow proper interpretation of the scans, video EEG monitoring should be in progress when the tracer is injected. In contrast to PET, SPECT can be used for ictal scans. The major disadvantages of SPECT are lower resolution than PET, the lack of clinical value for interictal CBF studies (see below), and inability to perform quantitative studies, which is a particular disadvantage for neuroreceptor-ligand and research purposes.

Coregistration of Multimodality Images

PET and SPECT fusion with MRI has become a standard technique. Image registration errors are less than 3 mm (180). EEG data can be integrated with MRI or PET by digitizing individual electrode positions using a digitizing wand, or using fiducial markers (especially for magnetoencephalography).

PET Localization of Epileptic Foci

Interictal Glucose Metabolism

Even in the early studies performed with relatively low-resolution scanners, a high proportion of patients with temporal lobe epilepsy had unilateral temporal hypometabolism on FDG-PET scans (Figure 24-3) (34,35,160). Sensitivity increased to about 80% with high-resolution scanners (121). The hypometabolism usually was lateralizing, rather than localizing, as extension to ipsilateral temporal neocortex, frontal lobes, and thalamus was common (3,60,61). Moreover, it was difficult to distinguish lateral from mesial temporal hypometabolism (141). In patients with temporal lobe seizure onset, ^{18}FDG-PET results show a close correlation with video EEG monitoring and can be used to predict the outcome of temporal lobectomy (34,132,162). The greater the ^{18}FDG-PET asymmetry, the greater the chance of becoming seizure-free (162).

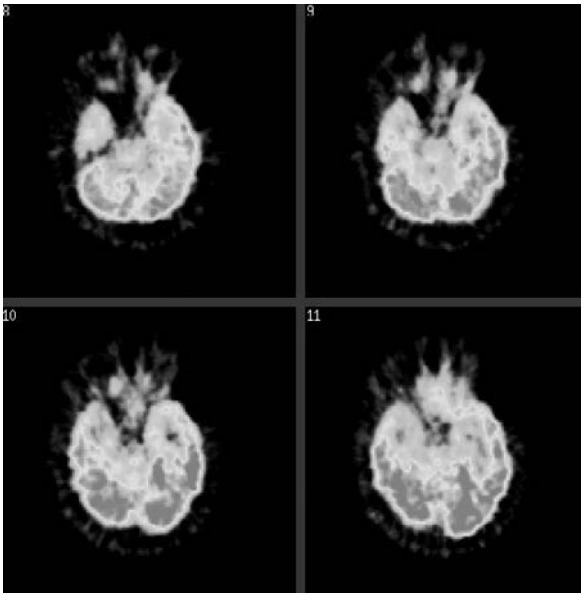

FIGURE 24-3. ^{18}FDG-PET scan showing focal hypometabolism.

The incidence of hypometabolism ipsilateral to EEG foci in patients with "MRI-negative" mesial temporal lobe epilepsy reportedly varies from 30%–90%, and probably depends on subject selection (91,146,153). Some studies have suggested that hippocampal atrophy and neuronal cell loss are primary factors for decreased metabolism (84). Others suggest that the relation between glucose metabolism and tissue volume breaks down in epileptic foci, and that decreased synaptic activity or areas of microdysplasia not detected on MRI could lead to hypometabolism (122,158) Reduced glucose metabolism did not correlate closely with cell loss measured in resected specimens (38,59). Recent studies using partial volume correction suggest that about 20% of the hypometabolism may be the result of volume loss (49).

Studies using scanners with improved resolution and new analytic techniques have attempted to distinguish mesial from lateral temporal hypometabolism. Patients with mesial foci defined by foramen ovale electrodes had greater mean depression of mesial metabolism than the group with lateral foci, but within the mesial focus group itself lateral hypometabolism was as prominent as mesial (51). Patients with hippocampal sclerosis and microdysplasia may have greater lateral temporal hypometabolism than those with hippocampal sclerosis alone (30). A study using statistical parametric mapping found that medial hypometabolism was less extensive or severe in the lateral than medial temporal lobe epilepsy patients, and patients with lateral temporal neocortical foci, as a group, had relatively greater lateral temporal hypometabolism. However, individual variation was too great for ^{18}FDG-PET to be used for clinical localization (81).

Several clinical factors may affect hypometabolism. In some studies, patients with uncontrolled temporal lobe epilepsy being considered for surgery (153), or with chronic rather than new-onset temporal lobe epilepsy and greater seizure frequency (105), were more likely to have hypometabolism. Others found that hypometabolism had only weak prognostic value (173). Increasing epilepsy duration over decades, but not over a few years, is associated with increasing hypometabolism (158). Patients with epilepsy and depression are more likely to have ipsilateral or bifrontal hypometabolism (14,142,170).

Children with temporal lobe epilepsy who are referred for surgical evaluation for uncontrolled seizures have hypometabolism nearly as frequently as adults, compared with only about 20% of children with new onset epilepsy (42,43). In a study in which repeated scans were performed over 3 years, children with initial normal PET scans were more likely to remain in good seizure control than those with abnormal initial PET, and patients with higher seizure frequency were more likely to have abnormal PET scans (44). These studies suggest that the presence of hypometabolism predicts intractable seizures and should lead to early surgical consideration.

Contralateral lateralization, compared with depth EEG, has been reported to occur in a small percentage of patients (148). Prior depth electrode implantation, unrecognized ictal activity leading to the false impression of an incorrect lateralization, and failure to perform quantitation where a visually identified hypometabolic region is actually within normal limits for asymmetry are all possible reasons for misreading scans (81). Increased interictal metabolism has been described in large cortical malformations; the contralateral cortex could be erroneously judged hypometabolic (130). The time since last seizure, and the nature of the last seizure, have been reported to affect the presence and patterns of hypometabolism (44,99). These phenomena may be related to occasional reports of increased interictal metabolism, either widespread or focal, and in the context of associated hypometabolism (39). FDG-PET should be interpreted in the context of clinical data.

Well-localized hypometabolism is less frequent with extratemporal EEG foci (153). In 29 patients with frontal lobe epilepsy who showed good outcome after surgical resection, focal hypometabolism was seen in 73% of patients with, and 36% of patients without, MRI structural lesions (80).

^{15}O-water PET–measured cerebral blood flow (like interictal SPECT) is not helpful for seizure focus detection. It has also largely been supplanted by functional MRI (fMRI) for mapping language, motor, and sensory function, but remains useful when contraindications to fMRI are present, such as claustrophobia, ferromagnetic implants, or a need for overt responses.

Receptor Studies

Although a variety of receptors—including mu, delta, and kappa opiate (41,157,106); H1-histamine (67); MAO-B

(88); NMDA (using ^{11}C-ketamine) (87); muscarinic (113); nicotinic acetylcholine (129); and dopamine (8) receptors—have been studied in patients with epilepsy, only benzodiazepine and serotonin 1A ligands, as well as the serotonin precursor alpha-methyltryptophan, may be of potential clinical value.

Benzodiazepine receptor binding is reduced ipsilateral to both frontal and temporal epileptic foci, may be confined to mesial temporal regions even when hypometabolism is widespread, and has as much localizing value as FDG scans (145,60,16). One study reported that ^{11}C-flumazenil PET (FMZ-PET) can detect abnormalities in 30%–40% of MR-negative mesial temporal lobe epilepsy patients (91). In a study of 100 patients, FMZ-PET was slightly more sensitive than FDG-PET or MRI for temporal lobe foci, and delineated the site of seizure onset more precisely, but showed reduced binding contralateral to the side of hypometabolism and ictal EEG focus in several cases (140). Rare MRI-negative, FDG-PET-negative patients had abnormal FMZ-PET. Other investigators found that focal FMZ binding increases as well as decreases, with no consistent localizing value (85,56). Detection of increased periventricular white matter flumazenil binding may be an adverse prognostic factor, even when MRI shows mesial temporal sclerosis (55). Binding variations that could lead to clinically significant changes in interpretation were reported in 5 of 10 patients who had two scans one week apart. Hippocampal binding was reduced when patients had shorter intervals since their last seizure (10).

^{11}C-flumazenil (FMZ) PET was more sensitive than FDG-PET for detection of neocortical seizure onset in children with extratemporal lobe epilepsy (114). Larger preoperative flumazenil abnormalities, and unresected regions, predicted a poor surgical outcome; there was no relation between the extent of FDG-PET hypometabolism and surgical success (73). However, FMZ did not detect abnormalities when FDG-PET was normal. Regions of hypometabolism were less likely to show spiking on subdural electrodes than were nearby normal cortex or "border zones." Benzodiazepine receptor binding may correlate well with the ictal onset zone within the dysplastic region (2). In children with clear structural lesions, the value of flumazenil PET was less clear, and "false positive" scans (altered binding not associated with spiking cortex) were more common (74).

Several studies have shown reduction of $5HT_{1A}$ receptor binding in patients with temporal lobe epilepsy (49,109,144,163). The magnitude of reduction appears greatest in the zone of seizure onset, usually in hippocampus (Figure 24-4) (49,109). There is a strong correlation between depression in temporal lobe epilepsy and the extent of $5HT_{1A}$ binding reduction (58,159). Preliminary data suggest that $5HT_{1A}$ receptor PET may be more sensitive than FDG for detecting temporal lobe foci.

^{11}C-alpha methyltryptophan (AMT) uptake is increased in epileptogenic tubers, and may help to identify lesions for resection (23,36,76). In children with neocortical malformations, increased AMT uptake appeared less sensitive but more specific than FDG-PET, showing more closely delineated abnormalities (72). It may identify nonresected epileptic neocortex in patients with unsuccessful surgery (75). In patients with partial epilepsy, AMT uptake was increased in patients with normal MRI (including several with negative FDG-PET), but not in those with hippocampal volume loss; partial volume correction was not performed in these studies (36,115). AMT, designed as a 5HT precursor, may also measure synthesis of kynenurine pathway metabolities implicated in excitatory neurotransmission.

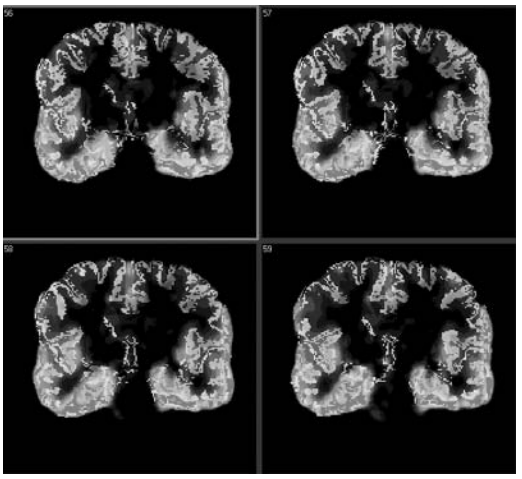

FIGURE 24-4. FCWAY PET. (*See color insert*).

Magnetic Resonance Spectroscopy (MRS)

Clinical use of MRS has concentrated on measurement of relative concentrations of N-acetylaspartate (NAA), a compound found in high levels in neurons; choline (Cho); and creatine (Cr). Spatial resolution with current techniques is inferior to PET or SPECT, but it has the advantage of being totally noninvasive.

In temporal lobe foci, decreased NAA to Cho + Cr ratios probably reflect altered mitochondrial metabolism, as well as neuron loss and gliosis (11,20,28,45,65,90,128). "Correct" lateralization judged by EEG recording and surgery ranges from 60% to 90%, although bilateral NAA decreases are common, as are hemispheric reductions, probably in part as a result of partial volume effects and the large MRS voxel size (18,95). NAA/(Cho + Cr) ipsilateral to the seizure focus should be 15%–20% lower. After successful temporal lobectomy, metabolic recovery in the reduced contralateral hippocampal NAA may increase to control levels, suggesting functional impairment by seizures (169). However, symmetric bilateral abnormalities may predict poor surgical outcome (97).

MRS may detect abnormalities in a proportion of patients with temporal lobe epilepsy and normal structural MRI

(53,152). In one series, MRS localization correlated well with ictal SPECT and subdural mapping, and with focal cortical dysplasia as found at surgery (86). Using multivoxel ^{1}H-MRS, which does increase imaging time, it may be possible to differentiate mesial and lateral temporal lobe epilepsy (54).

A meta-analysis of temporal lobe epilepsy MRS studies from 1992 to 2003 found marked methodological heterogeneity, suggesting that optimal MRS procedures are uncertain (176). Seventy-two percent of patients with good surgical outcome had an ipsilateral MRS abnormality concordant with the seizure focus; positive predictive value was 82%. However, there were not enough data to assess the role for MRS in structural MRI–negative cases. A recent study found that MRS and ictal SPECT each detected EEG-concordant abnormalities in about 75% of patients with, and 65% without, structural MRI findings; each modality found 25–30% contralateral abnormalities as well, however (32).

Similar clinical factors are associated with reduced NAA/(Cr + Cho) and FDG-PET hypometabolism. Patients with refractory, as compared to nonrefractory, temporal lobe epilepsy, have been found to have lower hippocampal NAA/(Cr + Cho) (103). The degree of NAA reduction has been correlated with interictal spiking (12,126). Some (32,155) but not all studies have found a significant correlation epilepsy duration and mean hippocampal NAA/Cr or NAA/(Cr + Cho) ratio (17). Reduced NAA has been correlated with severity of depression in temporal lobe epilepsy (48).

Reduced NAA/creatinine has been detected in 40%–50% of patients with presumed frontal lobe foci, but there are fewer data on surgical outcome in these patients, and MRS may be less reliable than for temporal lobe epilepsy; about 50% of these patients have bilateral dysfunction (45,97).

Single Positron Emission Computed Tomography (SPECT)

SPECT measurements of interictal cerebral blood flow have also been unreliable for seizure focus localization, possibly because of interictal uncoupling of perfusion and metabolism in epileptic foci, although they should be obtained as baseline data for comparison with ictal SPECT scans (11,42,92,100,108). In a small preliminary study, MR arterial spin-labeling measurements of cerebral perfusion showed a good correlation with ^{18}FDG-PET hypometabolism; both were superior to volumetric MR for lateralizing temporal lobe foci (178).

Ictal SPECT has proved to be a reliable method for localizing epileptic foci (116,136,137,150). It is important to inject the tracer as soon as possible after seizure onset, while patients are being monitored with video EEG. Initially (in patients with mesial temporal foci), relative hyperperfusion of both mesial and lateral temporal cortex (30%–35% compared to the opposite side) is seen, followed by persistent mesial hyperperfusion and lateral hypoperfusion (117). Spread of activation to ipsilateral basal ganglia, brainstem, and bilateral thalamus does not suggest a more diffuse epileptogenic zone or influence surgery outcome (78). Contralateral hyperperfusion may occur in a "mirror image" of the seizure onset zone, but is of lower intensity (64). Temporal lobe foci may be localized in up to 90% of patients, and false positives are rare. However, if injection is delayed, only hypoperfusion may be found, leading to potential errors. SPECT has lower resolution than PET, and quantitative data cannot be obtained.

SPECT image subtraction and MRI coregistration appear to improve detection of epileptic foci (125). Most investigators now use this approach, often coupled with image analysis strategies such as statistical parametric mapping (Figure 24-5). Occasionally subtraction may introduce confusion, and images should be compared with originals (101). Combing hyperperfusion and hypoperfusion images by ictal-interictal and interictal-ictal subtraction may improve distinction of lateral from mesial temporal foci (93).

In cryptogenic neocortical epilepsy, rates of detection of hyperperfusion and concordance with invasive video EEG monitoring data vary from 40% to 80% (1,84,97,98,123,124). When MRI lesions are present, concordance with SPECT localization is about 90% (123).

In general, ictal SPECT and FDG-PET provide similar sensitivity and specificity for detection of temporal lobe epileptic foci (9,94,104). Some studies report an advantage for either PET (79,97) or SPECT (151) for neocortical foci.

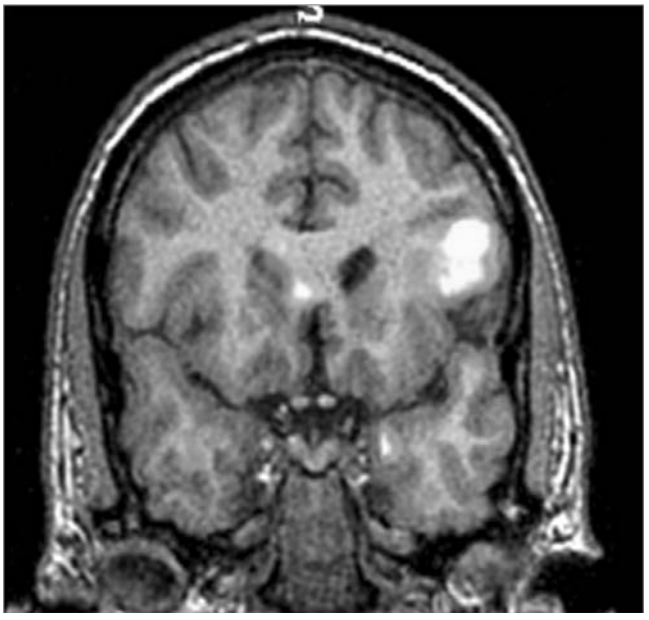

FIGURE 24-5. Ictal SPECT. Prominent left frontal hyperperfusion (right side of photo). MRI and routine EEG were normal. Intracranial monitoring confirmed the left frontal localization of seizures. Pathology was focal cortical dysplasia with balloon cells. The patient had been seizure-free for 9 years after surgery in 1998. Courtesy of Dr Gregory Cascino, Mayo Clinic. (*See color insert*).

The difference may depend in part on relative familiarity with the techniques. SPECT is a less forgiving technique, and the timing of injection in relation to seizure onset is an important factor (77). Automatic pump injectors (37) and self-injection (166) have been used to reduce delay. Postsurgical imaging has shown unresected regions of ictal hyperperfusion in patients with persistent seizures (174).

SECONDARY GENERALIZED EPILEPSY AND INFANTILE SPASMS

Secondary generalized epilepsies are a more prominent problem in child than in adult neurology. In patients with the Lennox-Gastaut Syndrome, initial FDG-PET studies showed variable patterns of either global or multifocal hypometabolism that were related both to the presence or absence or structural lesions and to the underlying etiology (24,161). Little localizing information was obtained in nonlesional patients. Children with a variety of congenital or acquired lesions and generalized epileptiform discharges had PET hypometabolism that matched MRI abnormalities but did not add to surgical planning; ictal SPECT showed variable ipsilateral or contralateral hyperperfusion (181). In children with hemimegalencephaly, FDG-PET hypometabolism contralateral to the hemimegalencephalic side is associated with poor surgical outcome (134). In infants and children with this spectrum of disorders, concordance between functional imaging and EEG localization should encourage, and discordance discourage, consideration of surgery.

MRI may be less sensitive for identifying malformations of cortical development in children under 2 years of age, given that myelinization is incomplete. In these circumstances, FDG-PET may provide advantages in identifying cortical dysplasia. Some studies suggest that FDG-PET hypometabolism in children with infantile spasms and normal structural MRI suggests surgical options. Hypometabolism may be present in parieto-temporo-occipital cortex without underlying MRI lesions; at surgery, dysplastic cortex is usually found (25,26). Others report that hypometabolism present at epilepsy onset may resolve spontaneously; persistent hypometabolism may (68) or may not (110) predict clinical outcome. In children with Sturge-Weber syndrome, FDG-PET may be more sensitive to the presence of the lesion, but give less specific information on its nature, than MRI (31). SPECT has not been helpful in infantile spasms (112).

CHOOSING FUNCTIONAL IMAGING FOR FOCAL EPILEPSY

Comparisons among imaging techniques for surgical localization are hard to perform, because few research groups have optimal software and hardware for each modality. Moreover, investigators usually have more experience with one approach than another, which may introduce subtle biases into studies. For temporal lobe and neocortical epileptic foci, ^{18}FDG-PET and subtraction ictal SPECT appear to have approximately equal reliability, and can detect abnormalities in 50%–80% of patients with normal MRI (66,179). The increasing sensitivity of structural MRI, however, may reduce the number of patients with negative scans (83). MRS may be equally reliable for seizure focus lateralization, although fewer data are available, and bilateral findings more common (127).

Functional studies probably do not add anything to seizure focus localization in patients with clear focal MRI abnormalities. The severity and extent of hypometabolism was not related to surgical outcome in one study of patients with mesial temporal sclerosis (96), but resection of hypometabolism beyond the limits of the structural lesion did improve outcome in another (171). It is possible that the concurrence of a structural and a functional imaging study with focal interictal EEG, in a patient with typical clinical features of mesial temporal lobe epilepsy, could obviate the need for ictal video EEG recording, but the presence of actual seizures may remain in doubt. In contrast, when both structural and functional imaging are normal, the chance of a good outcome is markedly reduced (to as low as 30% in some pediatric series).

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LANGUAGE AND MEMORY TESTING

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The Wada test is the standard by which many clinicians identify cerebral language laterality preoperatively. Developed in the 1950s, the Wada procedure involves the administration of a short-acting barbiturate into the internal carotid artery via a transfemeral catheter. This injection anesthetizes the anterior two-thirds of the ipsilateral cerebral hemisphere, and cognitive testing is conducted during this anesthesia. Although the Wada test was originally introduced as a procedure only to establish cerebral language representation (1), a memory component was later included to predict risk for developing severe anterograde amnesia (2). The most common anesthetic agent is amobarbital, although other drugs are successfully used including etomidate (3), methohexital (4), and propofol (5). These newer agents have a shorter duration of action than amobarbital, and in the case of etomidate, a constant infusion of the drug is necessary to produce a sufficient length of anesthesia to permit language and memory testing. Because of the variety of drugs in contemporary use, we will use the term "Wada test" to refer to the family of approaches using intracarotid anesthesia to identify language and memory representation, rather than more specialized terms such as intracarotid amytal test (IAT) or etomidate speech and memory test (eSAM).

During the period of hemispheric anesthesia, language testing is performed, and memory items are introduced for subsequent recall. Although the specific assessment protocols vary across centers, most language approaches include counting, confrontation naming, comprehension, reading, and repetition. Memory may be assessed using a variety of stimuli, including real objects, pictures, words or sentences, and geometric designs. In addition to differences in stimuli, other procedural variations across sites include drug dose, the choice of which hemisphere is tested first or whether both hemispheres are tested, the interval between hemispheric injections, and the scoring criteria for determining language and memory results.

The overall risk of Wada testing is generally considered comparable to that of arteriography, with greater risk associated with increasing age. One empirical report described the risk of carotid artery dissection to be 0.7% (6). In light of this risk, and because Wada testing has limited spatial resolution that provides information on hemispheric lateralization of language and memory only, functional MRI is increasingly being advanced as a noninvasive alternative (7). Other advantages of fMRI include a potentially less stressful procedure for the patients, and potentially smaller overall costs given the multidisciplinary team necessary for Wada testing (8). In addition, fMRI has much greater spatial resolution compared to the Wada, offering the ability to localize language to particular regions within the brain, and because it is noninvasive, it can be repeated as needed more easily than the Wada, and normal/reference values from healthy controls can be obtained. However, fMRI has a greater degree of bilateral activations during language processing, and the decision whether activations in the non–language-dominant hemisphere reflect critical language regions is often based solely on somewhat arbitrary asymmetry score thresholds.

The cognitive neuroscience literature using fMRI to investigate language mechanisms is extensive, although the clinical experience using fMRI to identify language regions is more limited. There are also important differences between experimental and clinical protocols. For clinical applications, the protocol task needs to be simple enough to be performed by patients with neurological disease, and in certain circumstances, may need to be adapted to accommodate differences in ability. It is also critical that the task (and analytic procedure) elicit sufficiently robust blood oxygenation level–dependent (BOLD) signal changes that results can be applied reliably on an individual-patient basis. This contrasts with applications in which group fMRI data are often used to illustrate brain-behavior relationships.

Approaches to data analysis differ between experimental and clinical application because, in presurgical evaluations, false negative errors failing to identify eloquent cortex (Type II error) will have significant adverse implications for clinical outcome. There may also be greater concern about monitoring performance in clinical contexts, not only to ensure that patients are adequately engaged in task performance, but also to create implicit demand characteristics regarding task engagement, because some patients will be more likely to comply if performance is being monitored. It should be noted, however, that covert word-generation tasks are among the most robust and reliable fMRI tasks for identifying cerebral language laterality (9,10), and consequently, performance monitoring, although optimal, may not always be feasible.

LANGUAGE

Wada Language

At some centers, the standard for determining cerebral language representation is cortical stimulation mapping. Focal electrical stimulation is applied to the cortex during language tasks (typically naming), and regions in which language disruptions occur are considered to reflect language-specific cortical areas (11). The limitations of cortical stimulation mapping, however, include that it can be conducted only where electrodes have been implanted (or in open craniotomies, only in exposed cortical regions); that it can be conducted only with distinct language site distributions based upon either the modality of assessment (e.g., auditory or visual) (12) or the specific language task employed (13); and, most importantly, that reliable language disruption does not necessarily indicate that resection of the identified region will result in postoperative language decline (14).

Because of the above limitations associated with stimulation mapping, Wada language assessment is considered by many to be the gold standard for determining cerebral language representation, and consequently it has been used as the criterion against which other approaches for language determination, including magnetoencephalography and fMRI, have been contrasted. There are reports, however, of cases in which drug effects failed to identify clinically relevant cerebral language representation despite the development of appropriate motor deficits following drug administration (15–17). In some situations to be discussed, fMRI has provided clarification of specific aspects of Wada language testing protocols.

Varying operational definitions of language dominance and of language representation exist; so do disagreements concerning whether multiple language components need to be formally assessed during the Wada test (e.g., repetition, comprehension of complex syntax), and whether similar criteria are necessary to make inferences for both left and right hemisphere language representation. All of these factors have contributed to variability in reported Wada language results in the literature.

These methodological and definitional issues directly affect the detection of bilateral language representation, because it is possible to have language dominance of one hemisphere with fewer language errors present during injection of the "nondominant" hemisphere (e.g., in the case of bilateral but asymmetrical language, L>R). Different frequencies of atypical language representation will be obtained depending on whether dominance is used to infer relative superiority of one hemisphere over the other, or to imply *no* language representation in the contralateral hemisphere (18). In one survey of epilepsy surgery centers performing Wada testing in the late 1980s, the prevalence of mixed (i.e., bilateral) language representation varied from 0%–60% of cases evaluated (19). Presently, language dominance is generally conceptualized as a continuous rather than discrete variable in much the same way as is handedness, and this approach has been subsequently adopted in multiple fMRI language studies (20). Functional MRI has shown that speech arrest alone following initial administration of amobarbital is not by itself a reliable index of language representation, with a more comprehensive language assessment during the Wada test correlating with fMRI language activations (21).

Although patients with bilateral language would be expected to be at smaller risk for postsurgical declines in naming following left anterior temporal lobectomy, the Wada evidence for this relationship is surprisingly sparse. Multiple clinical series have demonstrated the greater risk of language change after left temporal lobectomy involving the language-dominant hemisphere than after non-language-dominant resection (22,23), but the degree of language representation as determined by Wada testing and language outcome has been described in only one report (24). In that report, a language asymmetry score was calculated based upon the degree of language impairment across multiple Wada language tasks, and patients with less strongly left-lateralized language hemisphere displayed less postoperative confrontation-naming decline on the Boston Naming Test following left anterior temporal lobectomy than did patients with more strongly lateralized left-hemisphere language representation. However, when compared to fMRI, this association was smaller than that between fMRI language asymmetry and postoperative naming outcome.

The other source of data supporting the validity of Wada language studies comes from cases with atypical language representation. One case report described bilateral language representation indicated by Wada (R>L) that was confirmed with cortical stimulation mapping of the right hemisphere (25). In another larger series, five of six patients showed evidence of bilateral language representation by Wada testing that was confirmed with cortical stimulation mapping (26). In that series, for the single patient in whom right-hemisphere language was not identified with corti-

cal stimulation mapping, the failure to identify language regions was thought to reflect placement of an electrode array that did not cover classic language regions.

Functional MRI Language

Because of the risks associated with Wada testing, functional MRI is increasingly being advanced as a noninvasive alternative to establish cerebral language representation preoperatively (7). In addition to being noninvasive, fMRI may be less stressful for many patients, and may impose a smaller cost than that associated with the multidisciplinary team necessary for Wada testing (8).

A major advantage offered by fMRI is the potential to localize language to particular regions within the brain, whereas Wada testing provides only lateralized findings (Figure 25-1). Although dissociations between expressive and receptive components to language may be identified with Wada testing (27), Wada language results are intended to only reflect hemispheric language involvement. The greater spatial resolution of fMRI provides the potential to identify specific cortical language regions, and to fractionate language components not only with respect to traditional receptive-versus-expressive dichotomies but also into modality or domain-specific language regions (e.g., reading comprehension versus auditory command comprehension).

One of the primary differences between fMRI and Wada testing is the method of obtaining clinically relevant data. The Wada test creates a reversible pharmacological lesion in which induced behavioral deficits are thought to reflect the risk of including these areas in a surgical resection. Functional MRI is an activation procedure in which small task-related increases in blood oxygenation are elicited and are either contrasted with a resting (or directed) baseline, or contrasted post-hoc based upon an *a priori* performance criterion (e.g., event-related design). Thus, fMRI reflects a relative change in blood flow, and there is no intrinsic way to establish whether areas significantly associated with task performance are necessary to task performance (i.e., their resection will result in postoperative deficit) or simply associated with the task in a noncritical but supportive role. Conversely, there is no inherent procedural technique to determine whether critical regions have been adequately identified, in part because thresholds and criteria used to identify significant activations are user-selected (28,29).

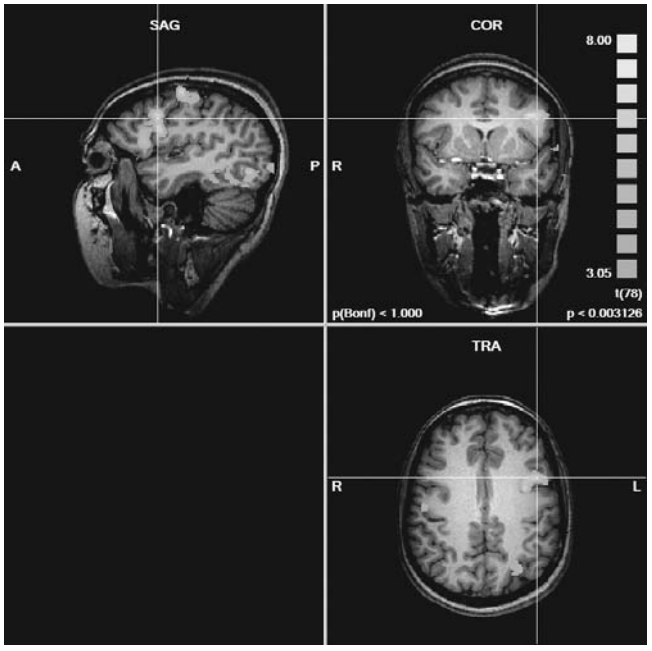

FIGURE 25-1. Left hemisphere language activation using a noun–verb association task, demonstrating prominent left frontal task-related activation (Loring et al. (28)). (*See color insert*).

Despite these limitations, clinical language fMRI has matured into a reliable and reproducible technique for cerebral language identification. There have been multiple independent reports of reliable fMRI language determination in epilepsy patients (10,30–32). As with Wada testing, there is considerable variability in the specific protocols used across centers. Although common language activation protocols include semantic decisions (30) and word generation (31), multiple other approaches including reading (33), naming (34), and listening (10) have been used. In centers that rely on baseline neuropsychological testing as a primary predictor of memory risk, fMRI language testing has greatly reduced the need for Wada testing, with significantly fewer Wada studies being conducted (35). In these cases, only patients with ambiguous fMRI language images will undergo Wada testing (typically only unilateral Wada injection) in order to identify eloquent language cortex.

One of the factors contributing to ambiguous language fMRI results is varying degrees of bilateral activations during language task performance (Figure 25-2), making it difficult to determine whether the smaller activations contralateral to the primary language regions reflect critical language cortex. Functional MRI studies typically employ laterality ratios to indicate degree of language representation, and ratios that do not exceed a specific criterion are generally interpreted to reflect bilateral language representation. This is one approach used to establish the concordance between Wada and fMRI language findings, and it has identified patients in whom clinically relevant mismatches occur (10,31). Across multiple studies examining the relationship between fMRI and Wada language outcomes, however, good agreement has been reported, with a discrepancy between Wada and fMRI on the order of 10%–15% (30–32,36). Yet these figures can be misleading, because the degree of concordance does not necessarily reflect the relative infrequency of atypical (i.e., mixed or right-cerebral-dominant) language representation. For example, if we can assume that 90% of all patients have left cerebral language dominance, then simply assuming that *all* patients have left cerebral language results in a 90% positive predictive value.

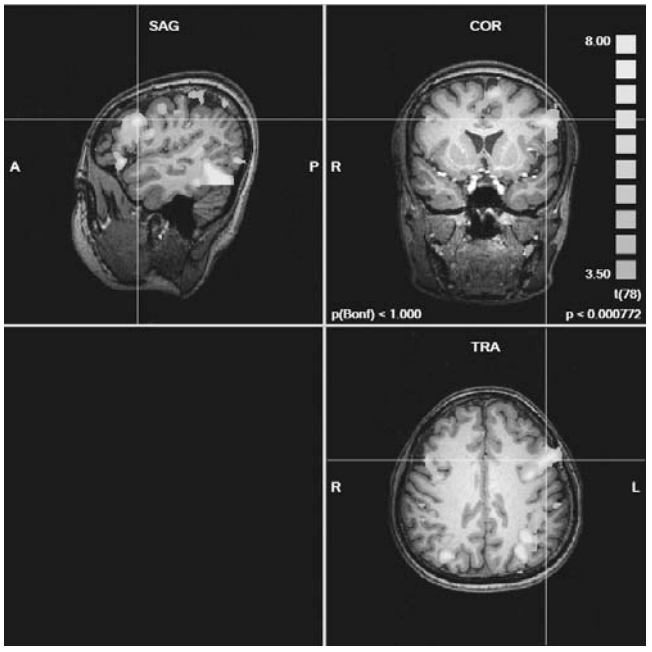

FIGURE 25-2. Language activation using fMRI noun–verb associating tasks in a left-handed patient. Note bilateral language activation (L>R). (*See color insert*).

Despite the high inter-rater agreement for assigning fMRI language laterality ratings, one relatively large series of 68 consecutive patients reported a more modest relationship between Wada and fMRI language in patients with left temporal lobe epilepsy, finding 72% concordance, but also found 89% concordance in right temporal lobe epilepsy patients (37). This suggests that the greater variability in language representation associated with left temporal seizure onset corresponds to poorer clinical ability to judge clinical fMRI representation. A lower relationship between fMRI and Wada language findings is present with atypical language, and yet it is precisely patients with atypical language whose language representation needs to be identified preoperatively.

One approach to overcome some of the variability in language fMRI scans has been to obtain results from a panel of tasks (9,32). Multiple tasks reduce the likelihood of nondiagnostic findings, improve inter-rater reliability, and help confirm language laterality by establishing a consistent pattern across multiple language activation protocols. However, it is likely that as language fMRI is more widely adopted clinically, inferences of cerebral language dominance will be based on visual inspection of results. This will permit statistical threshold adjustments to accommodate individual differences in activation patterns (32,37) and avoid conditions in which the presence or absence of activations is based upon threshold choice rather than on clinical judgment that draws on information from multiple sources. Although the magnitude of activation may be dependent on task performance, performance levels do not appear to be a primary factor contributing to lateralization of activation (38).

MEMORY

Wada Memory

Memory testing is the second primary goal of Wada testing at most centers, and was originally added to the Wada test to identify patients at risk of becoming amnesic following unilateral resection (2). The role of Wada memory testing has evolved since its introduction, and there are now other methods contributing to memory outcome prediction such as MRI hippocampal volumes (39), clinical history/age of seizure onset, EEG findings, and preoperative neuropsychological profile. Wada memory results, however, continue to be widely used to counsel patients regarding the likelihood of memory decline that, even if not frank amnesia, is of sufficient severity to interfere with quality of life or factors such as employment or school enrollment (40).

The Wada test evaluates each hemisphere in isolation, helping to disentangle the effects of parallel distributed brain networks. When the hemisphere ipsilateral to a medial temporal lobe focus is anesthetized, the *functional reserve* capacity of the contralateral temporal lobe to sustain memory function in isolation is assessed (41). Assessing functional reserve was the original goal of the Wada memory test when the procedure was developed to avoid postoperative amnesia. There are also varying degrees of residual function in the diseased temporal lobe, termed *functional adequacy;* therefore, there is a potential contribution of resection from the temporal lobe ipsilateral to the seizure focus to postoperative memory decline, and this must be assessed. Functional adequacy of the area to be resected is assessed during the injection contralateral to seizure onset.

Several approaches have been used to validate Wada memory testing. Although postoperative memory outcome might be considered the ideal variable for validation, Wada memory findings are used clinically to establish surgical candidacy, which confounds the predicative and outcome variables. Although there are reports of successful memory outcomes following Wada memory failure (42), there are also cases of amnesia in which Wada memory results appeared to predict that outcome (43). In addition to memory outcome studies, there have been numerous reports suggesting a relationship between Wada memory scores and hippocampal volume or cell counts (44–48). Both hippocampal volumes and Wada memory asymmetries are related to postoperative verbal memory decline (48–54).

Although intact baseline verbal memory function and Wada memory performance after injection contralateral to the seizure focus both make independent contributions to verbal memory outcome prediction beyond laterality of resection and presence of lesions other than mesial temporal

sclerosis, baseline delayed verbal memory predicted postoperative outcome at a higher level of statistical significance than did Wada memory (52). In a separate report, Wada memory scores were superior to baseline neuropsychological test findings in predicting verbal memory change following left temporal lobectomy, although the magnitude of this improvement was sufficiently small that the authors did not feel that sufficient "added benefit" was obtained to justify subjecting all patients to Wada testing (55). Wada memory asymmetry scores that are inconsistent with the side of seizure onset appear to be predictive of postoperative verbal memory change (53,55). Wada memory testing suggests that verbal memory Wada results (right-hemisphere injection) are moderately correlated with baseline neuropsychological verbal memory results (56).

Because Wada protocols are not standardized, it is sometimes difficult to estimate to what degree method variance contributes to some of the reported variability in memory outcome prediction. We have shown that Wada memory correlations with seizure onset laterality are related to factors such as stimulus type (real objects are superior to line drawings) (57), timing of stimulus presentation (early object presentation for memory testing is superior to later object presentation) (58), mixed stimuli requiring a verbal response, and amobarbital dose (higher doses, greater than 125 mg, increase the risk of producing impaired memory performance of the nonepileptic hemisphere) (59). The potential confound of aphasia on certain verbal memory stimuli is well recognized (60), and generalizations of specific results to other Wada memory protocols must necessarily be made cautiously (61).

Functional MRI Memory

While there has been considerable progress in the development and implementation of fMRI language protocols for clinical evaluation, development of reliable memory procedures to evaluate medial temporal lobe function has lagged behind. There are multiple contributing factors for this, ranging from behavioral activation (the hippocampus is always "on," making new memories) to physical resolution (the small size of the hippocampus) to technical difficulties (static susceptibility gradients).

Nevertheless, initial reports continue to suggest that with continuing protocol refinement, reliable and valid fMRI memory protocols can be developed for clinical application. As with early fMRI language studies, an initial approach to validating fMRI memory results has been to correlate fMRI with Wada memory findings. In healthy controls, scene memory tasks, with activations contrasted with a repeating pixilated/scrambled image (Figure 25-3), produced relatively symmetric bilateral medial temporal lobe activation (62). In patients with temporal lobe epilepsy, there was concordance between the fMRI memory and Wada memory asymmetry scores in nine epilepsy patients. Noteworthy was the consistency of fMRI and Wada laterality scores across patients with atypical Wada memory findings, with agreement present in two patients with "reversed" Wada memory scores. In a similar small patient series, concordance with Wada memory results was reported in eight of nine patients using a variety of different activation materials as stimuli for the fMRI (63).

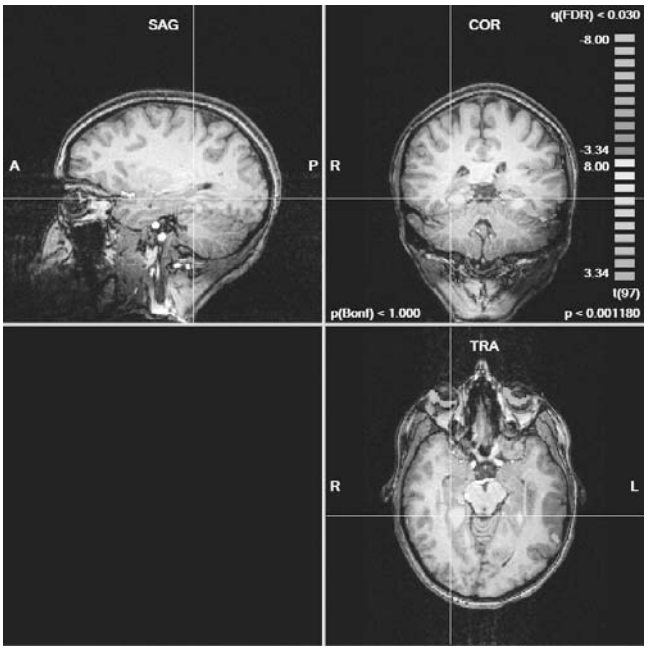

FIGURE 25-3. Bitemporal activation using scene encoding and tasks with pixilated scene control. Note bitemporal (R>L) activations involving the mesial temporal lobe region (Binder et al. (73)). (*See color insert*).

Although the hippocampal role in memory acquisition and new learning is typically emphasized in epilepsy contexts, there is also a hippocampal contribution to information retrieval. One approach relying on this relationship has been to activate hippocampal regions using a spatial navigation task based upon an imagined walk through multiple hometown landmarks. Reliable activations of medial temporal lobe regions as well as parietal areas have been described with this task in both healthy volunteers and patients with unilateral temporal lobe epilepsy (64). The fMRI asymmetries corresponded to seizure onset laterality in 90% of unilateral temporal lobe epilepsy patients. This approach differs from other fMRI memory tasks in that it involves recall of visuospatial information from long-term memory, and may represent a nonverbal analogue of verbal semantic memory rather than relying on episodic memory as the activation procedure. Although postsurgical changes in verbal memory are generally a greater clinical concern than nonverbal memory decline, this approach using spatial navigation may be useful in predicting postoperative nonverbal memory changes in right temporal lobe epilepsy patients (65).

Although semantic decision tasks reliably elicit fMRI language-related changes, such tasks may also have utility in demonstrating lateralized temporal lobe dysfunction. In one small series of lateralized temporal lobe epilepsy patients, patients with right temporal seizure onset showed greater activation of the left medial temporal lobe, including the hippocampus, parahippocampal gyrus, and collateral sulcus, than did patients with left temporal seizure onset (66). The hippocampal contribution to semantic memory in temporal lobe epilepsy has been demonstrated clinically with correlations with the Boston Naming Test, a measure of semantic memory. These studies indicate a correlation between naming and hippocampal volume (67), functional measures such as magnetic resonance spectroscopy (68), naming decline following left anterior temporal lobectomy (69), and greater sensitivity of the Boston Naming Test to lateralized temporal lobe dysfunction than traditional verbal episodic memory measures (70,71). Consequently, the use of nonepisodic memory tasks as activation protocols merits continuing study.

In addition to semantic memory as an alternative to episodic memory tasks to elicit fMRI activation of the medial temporal region, a different approach has used fearful faces obtained from episodes from thriller and horror films contrasted with dynamic landscape viewing to produce bilateral amygdalar activation in controls (72). When combined with results from the hometown spatial navigation task discussed above, the findings improved the lateralization of the side of seizure onset. Dissociations between emotional and spatial navigation tasks were described in three patients.

These studies, although few in number and with relatively small sample sizes, support the continuing development of fMRI protocols to assess medial temporal lobe function. The control condition is critical, and, as already suggested, the hippocampus appears to be always processing information during consciousness so that it is always ready to lay down new memory traces. The hippocampus not only responds to stimulus novelty—which provides the rationale for using repeating stimuli as the control task in fMRI memory protocols—but also is actively involved in relational processing as concepts and other bits of information are bound during the process of memory formation. Both important factors were compared against a scene-encoding task to determine whether significance differences in hippocampal fMRI activation could be altered by choice of control condition alone. Two contrast conditions were employed: a novel task in which the same stimuli were repeated throughout, and a superficial processing task that was intended to disrupt ongoing conceptual processing associated with memory formation (structural processing) (73). In both tasks, subjects viewed novel pictures and determined whether the image depicted an indoor or an outdoor scene. The first contrast presented the same indoor and outdoor scene in alternating fashion, whereas the second contrast had subjects examine two halves of scrambled/pixelated pictures to determine whether both halves were identical. Both tasks resulted in bilateral hippocampal activation, although the contrast emphasizing the relational aspects of processing (scrambled pictures) produced greater activation in anterior hippocampus. This not only addresses the issue of functional specialization of the hippocampus, but also has important clinical relevance because the anterior hippocampus is a common area of seizure onset and is almost always included in temporal lobe epilepsy resections. A similar methodological adjustment intended to increase the likelihood of anterior hippocampal activation has been event-related testing, in which contrasts are made between items that are successfully encoded and remembered versus those that are subsequently forgotten. This approach has yielded greater activation of anterior hippocampus than block-design approaches (74).

The potential clinical utility of fMRI has been hinted at with several studies demonstrating predictive value for postoperative memory change. The first report described the relationship between scene memory protocol and outcome, finding that fMRI asymmetry ratios correlated with change in memory performance on the scene memory task when re-administered outside the scanner approximately 7 months following surgery (75). However, no information about fMRI and the prediction of independent measures of memory function (e.g., neuropsychological memory measures) was presented.

Because verbal memory decline is a more serious concern than nonverbal memory decline, one approach is to use a verbal memory fMRI protocol (76). In a sample of 10 right-handed temporal lobe epilepsy patients with left hippocampal sclerosis who underwent surgery, postoperative verbal memory decline was predicted by fMRI memory asymmetries obtained using an event-related verbal word learning/recall design. Functional MRI provided the strongest independent predictor of memory outcome after surgery, and could be applied at the individual patient level. In an additional analysis of these same patients, left hippocampal activity was the strongest predictor of postoperative memory outcome, consistent with the functional adequacy model of hippocampal function (77).

MCG WADA PROTOCOL

General

The examiner stands next to the patient ipsilateral to the side of injection because the patient may develop a contralateral field defect. Patients begin counting aloud from 1 to 20 with their hands held up and their palms turned rostrally and fingers spread. An injection of 100 mg amobarbital sodium is administered by hand over a 4–5-second interval via a percutaneous transfemoral catheter. Following demon-

stration of hemiplegia and evaluation of eye gaze deviation, the patient is requested to execute a simple midline command (e.g., "touch your nose").

Beginning approximately 30–45 seconds after injection, eight common objects are presented for 4–8 seconds each, and the object names are repeated twice to the patient. Examples of Wada memory items include a combination of ordinary household items (e.g., fork, mousetrap), small toys (e.g., doll, ball), and plastic food (e.g., hotdog, pizza). At times, because of patient confusion, inattentiveness, or nonresponsiveness, the patient's eyes are held open. Language is assessed in detail following presentation of the memory items. Recognition memory of material presented during the procedure is tested after amobarbital effects have worn off, as demonstrated by return to baseline language performance on all tasks described below, return of 5/5 strength, and absence of pronator drift, tactile extinction, asterixis, and bradykinesia.

Language

Language rating is based upon performance on five linguistic tasks (counting disruption, comprehension, naming, repetition, and reading). Although we have developed a formalized approach to calculate a language laterality ratio, this is for research purposes and is not routinely used clinically.

Expressive Language/Counting

The expressive language score (0–4) is based upon disruption of counting ability at the initiation of the Wada test (4 = normal, slowed, or brief pause < ~20 seconds; 3 = counting perseveration with normal sequencing; 2 = sequencing errors; 1 = single number or word perseveration; 0 = arrest > ~20 seconds). We have adopted a period of speech arrest of 20 seconds' duration as a criterion to ensure that counting interruption is not merely caused by acute generalized disruptive effects of the medication. If speech arrest occurs, patients are repeatedly urged to begin counting again from 1, because the more overlearned portion of the sequence will be less likely disrupted from generalized medication effects.

Comprehension

Simple comprehension is assessed after assessment of eyegaze deviation. The patient is requested to execute a simple midline command (e.g., "stick out your tongue"). After object memory stimulus presentation, comprehension is more systematically assessed by a modified token test. The token test consists of four geometric shapes of different colors that are presented vertically to the subject's ipsilateral visual field.

Comprehension is rated based upon the level of syntactic complexity in the command that is correctly executed: (1) "point to the blue circle after the red square," (2) "point to the red circle and then point to the blue square," (3) "point to the red square." A score of 3 is awarded for completion of a complex two-stage command with inverted syntax, a score of 2 reflects a successful simple two-stage command, 1 is scored for one-stage commands, and 0 is scored if the subject cannot perform any commands.

Confrontation Naming

Two line drawings of common objects (e.g., watch and jacket) are presented, and the subject is asked to name the objects and parts of the objects (e.g., watchband, collar). Performance is qualitatively scored on a 0- to 3-point scale.

Repetition

Following object naming, the patient repeats phrases (e.g., "No ifs, ands, or buts") and repetition is graded on a 0–3 rating scale. If unable to provide any response, the patient is asked to repeat "Mary had a little lamb."

Reading

Patients are asked to read either "The car backed over the curb" or "The rabbit hopped down the lane." Performance is rated on a 0- to 3-point scale.

General Language Considerations

When language impairments are present, language stimuli are presented throughout the recovery phase to monitor drug effects, and the time of complete language recovery is noted. The same stimuli as those employed during the initial assessment are used, with the exception of those for the repetition tasks. Repetition is a very sensitive measure of mild language impairment, and additional repetition items such as "Methodist-Episcopal" and sentences from the Boston Diagnostic Aphasia Examination are used to monitor recovery (e.g., The spy fled to Greece). *Positive paraphasic responses are considered the single strongest evidence of language representation in the hemisphere being studied.*

Memory

A minimum of 10 minutes' delay after amobarbital injection is required before memory assessment. Although free recall of object memory stimuli is obtained, interpretation of Wada memory performance is based solely on object recognition.

Ipsilateral Performance

Each of the eight objects is presented randomly interspersed with 16 foils, and forced choice recognition is obtained.

One-half the number of false positive responses is subtracted from the number of objects correctly recognized to correct for possible response bias and guessing. Thus, the expected score in the absence of true recognition is 0.

Laterality Scores

Because Wada memory scores are used to assist in seizure onset lateralization by demonstrating lateralized dysfunction, the order of injection is randomized across subjects and memory results are interpreted in a blind fashion. To assess lateralized asymmetries, interhemispheric Wada memory difference scores (i.e., [left injection] – [right injection]) derived from corrected memory performances are computed; positive scores suggest left temporal lobe dysfunction, and negative scores suggest right temporal lobe impairment.

General Memory Considerations

Fixed pass/fail criteria are not employed for memory performance after injection ipsilateral to the seizure onset. However, we generally require a score of at least 2/8 correct in order to not repeat the Wada memory assessment, and are more comfortable with scores of at least 3/8 correct. Asymmetries of at least 2 are interpreted as evidence of lateralized impairment, although greater asymmetries are interpreted with more confidence.

As with the ipsilateral performance, the asymmetries scores are not considered absolute, and memory performance is always considered in the context of other clinical factors, such as consistency of seizure onset or presence of a structural lesion such as tumor or hippocampal atrophy on MRI. Although asymmetries in the "wrong" direction are sometimes observed, when they are present, they are cause for particular concern and the procedure may be repeated bilaterally using a 75-mg dose and beginning on the side ipsilateral to the presumed seizure onset.

At many centers, simultaneous EEG is performed to help document the effects of amobarbital (ipsilateral slowing and increased beta activity) and to interpret unusual behavioral responses (e.g., detect the occurrence of a subtle seizure prior to or during testing).

CONCLUSIONS

The Wada test continues to be a critical component of the preoperative evaluation for epilepsy surgery at most centers. The development of robust language fMRI tasks has decreased the number of Wada procedures performed at selected epilepsy centers that rely primarily on neuropsychological assessment and other measures (e.g., hippocampal atrophy) for determination of postoperative memory risk rather than on Wada memory. The development of robust fMRI memory protocols continues to be an area of significant interest, although presently there does not appear to be a sufficient number of studies with adequate sample size to expect that fMRI memory results will begin to displace the need for Wada memory testing in centers that rely on Wada memory for outcome prediction.

Because both Wada and fMRI are imperfect tests of language laterality as well as memory function, it is likely that both approaches will be used to provide complementary information (78). Their combined use appears particularly promising for clarification of ambiguous results, which collectively should minimize cognitive risk and increase the likelihood of good behavioral outcomes. Because of significant protocol differences across Wada and fMRI procedures, however, individual centers should not assume that any specific procedure described in the literature will yield comparable results at their institution, and each center should continue to establish the relationship between specific Wada and fMRI procedures employed, not only with each other, but also with language and memory outcomes.

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APPENDICES

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REPORT OF THE NATIONAL ASSOCIATION OF EPILEPSY CENTERS

GUIDELINES FOR ESSENTIAL SERVICES, PERSONNEL, AND FACILITIES IN SPECIALIZED EPILEPSY CENTERS IN THE UNITED STATES

THE NATIONAL ASSOCIATION OF EPILEPSY CENTERS
MINNEAPOLIS, MINNESOTA, U.S.A.

PREFACE

The treatment of seizure disorders requires more than the right choice of an antiepileptic medicine, or even the ability to perform epilepsy surgery. Seizures and their treatment affect many aspects of health and the ability to function in modern society. These needs have been rec-ognized by the formation of specialized epilepsy centers. Initially the emphasis of these centers was necessarily on arriving at an accurate diagnosis and choosing the best acute intervention medical or surgical. This attitude was reflected in the initial set of guidelines published by the National Association of Epilepsy Centers in 1989. Today the emphasis should shift to a systematic ap-proach to chronic disease. The resources required for modern treatment are so great that only a few major centers can hope to provide all that any patient might need. The revised guidelines reflect these new condi-tions. The National Association of Epilepsy Centers be-lieves that the year 2001 guidelines will set a new direc-tion, helping to improve access to safe and effective treatment for all patients with seizure disorders.

Robert J. Gumnit, M.D., President
National Association of Epilepsy Centers

Eleven years ago, the National Association of Epilepsy Centers (NAEC) established an initial set of guide-lines for services, personnel, and facilities that should be available at specialized epilepsy centers (1). We now present an updated version for the beginning of the 21st century. The purpose of this document is to assist existing and developing epilepsy centers to obtain and organize the components necessary for comprehensive epilepsy care. This document also provides consumers and purchasers of health care with criteria to evaluate the appropriateness and quality of specialized epilepsy care.

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The last "Decade of the Brain" has seen an explosion in the diagnostic and treatment options available to people with epilepsy. Both consumers and purchasers of health care services have increasingly demanded that these treatments clearly and directly improve quality of life. The goal of treatment, no seizures and no side effects (2), is increasingly achievable and expected. At the same time, purchasers of health care expect this goal to be achieved more efficiently and at lower costs. The convergence of these three forces has increased the need for a well-organized approach to subspecialty epilepsy care and provides the motivation for these revisions of the guidelines.

We define a specialized epilepsy center to be a program providing comprehensive diagnostic and treatment services primarily or exclusively to people with intractable epilepsy. Such a program is staffed by physicians, psychologists, nurses, technologists, and other personnel with special training and experience in the treatment of epilepsy. It includes facilities and equipment necessary to provide appropriate care or has well-established patterns of access to necessary facilities. An established administrative system assures that these services are delivered appropriately and efficiently. Contemporary diagnostic and treatment options are so numerous that it is not realistic to expect any center to provide them all. Local needs will and should lead to differences in services provided as well. These guidelines list the essential services that two levels of specialty epilepsy centers should provide.

Epilepsy care can be divided into four levels. First-level care is provided by the primary care physician. Second-level care is provided by a general neurologist. Most patients with epilepsy are adequately treated at these levels. Patients with persisting seizures or side effects have failed standard treatment and should be referred to a third- or fourth-level specialty epilepsy center. Suggested criteria for referral are included in these guidelines.

A third-level epilepsy center should provide the basic range of medical, neuropsychological, and psychosocial services needed to treat patients with refractory epilepsy. Third-level medical centers provide basic neurodiagnostic evaluation, as well as basic medical, neuropsychological, and psychosocial services. These centers do not perform resective epilepsy surgery, although some may implant vagus nerve stimulators. Third level medical-surgical centers provide basic diagnostic and treatment services. In addition, these centers offer noninvasive evaluation for epilepsy surgery, straightforward resective epilepsy surgery, and implantation of the vagus nerve stimulator. These centers do not perform intracranial evaluations or other more complex resective epilepsy surgery. Knowledge and experience with epilepsy surgery has become sufficiently widespread that straightforward surgical interventions at the third level are now reasonable. However, third-level centers that offer such surgery should meet additional requirements. It is important that physicians making health care decisions at such centers be fully knowledgeable regarding all surgical options available and establish appropriate referral arrangements with fourth-level centers. If surgery is required, the best surgical procedure for the particular situation must be recommended, and this may not necessarily be the procedure that can be provided locally. Third-level centers will typically be found at many universities and some large community hospitals.

A fourth-level epilepsy center serves as a regional or national referral facility. This center should provide the more complex forms of intensive neurodiagnostic monitoring, as well as more extensive medical, neuropsychological, and psychosocial treatment. Fourth-level centers also offer a complete evaluation for epilepsy, surgery, including intracranial electrodes, and provide a broad range of surgical procedures for epilepsy.

It is important that these specialized resources be used appropriately. Although specialized epilepsy centers are not needed by most people with epilepsy, they must be available to patients with seizures or side effects after a reasonable period of care at the first and second levels. We strongly believe that early specialized intervention is more likely to achieve the best results and to be more cost effective over the long run. Patients requiring these services should therefore be identified and referred without undue delay. This argument is further developed in the section on referral guidelines.

This document was developed by the members of the Committee to Revise the Guidelines for Services, Personnel and Facilities at Specialized Epilepsy Centers. After discussions with the general membership, they were adopted by the Board of the National Association of Epilepsy Centers. The Guidelines may be reviewed and updated as considered necessary by the Board.

Thaddeus S. Walczak, M.D., Committee Chairman
Committee to Revise the Guidelines for Services
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I. THIRD LEVEL—MEDICAL CENTER FOR EPILEPSY

A. SERVICES PROVIDED

1. Electrodiagnostic

a) Minimum 8-h video-electroencephalogram (EEG)with surface electrodes. Supervision by EEG technologist and assistance by epilepsy staff nurse or monitoring technician if necessary

2. Epilepsy surgery

a) Emergency or elective neurosurgery, including biopsy and removal of incidental lesions and treatment of cerebral complications of epileptic seizures. Resective epilepsy surgery (surgery whose primary aim is treatment of seizures rather than of the lesion) will generally not be performed at third-level medical centers
b) Management of surgical complications
c) An established referral arrangement with a third-level medical–surgical or a fourth-level center for resective or other epilepsy surgery when indicated
d) Implantation and management of vagal nerve stimulator are reasonable although not required

3. Imaging

a) Magnetic resonance imaging with appropriate magnet strength and sequences for the sensitive detection of mesial temporal sclerosis and common epileptogenic lesions
b) Computerized axial tomography
c) Cerebral angiography

4. Pharmacologic expertise

a) Quality-assured antiepileptic drug levels
b) 24-h antiepileptic drug level service
c) Pharmacokinetic expertise by at least one member of the team

5. Neuropsychological/psychosocial services

a) Comprehensive neuropsychological test batteries for evaluation of cerebral dysfunction for vocational and rehabilitative purposes. Basic assessment of psychopathologic and characterological issues
b) An established referral agreement for comprehensive management of psychogenic nonepileptic seizures
c) Clinical psychological services for assessment and basic treatment of emotional disorders associated with chronic epilepsy
d) Basic assessment of social and vocational needs

6. Rehabilitation (inpatient and outpatient)

a) Physical, occupational, and speech therapy for basic evaluation and treatment of multiply handicapped individuals
b) Sufficient physical, occupational, and speech therapy for managing complications of surgeries performed at the center

7. Consultative expertise

a) Neurosurgery (if not program director)
b) Psychiatrist, board-certified (ABPN), with interest and expertise in treatment of epilepsy patients with psychiatric disorders
c) Internal medicine
d) Pediatrics
e) General surgery
f) Obstetrics/gynecology
g) Neuroradiology

B. PERSONNEL

1. Physicians

a) Any licensed physician could be program director, but ordinarily a neurologist or neurosurgeon with special expertise in epilepsy should serve as program director
b) Board certified neurologist(s) with expertise in epilepsy, clinical neurophysiology, video-EEG monitoring, pharmacology of anticonvulsant drugs, and the vagus nerve stimulator. Generally, neurologist(s) would have undergone fellowship training in these topics. At least two such individuals would be desirable. At least one of these individuals should be board certified in clinical neurophysiology by either the American Board of Clinical Neurophysiology or the American Board of Psychiatry and Neurology with added qualifications in Clinical Neurophysiology. Appropriate experience may substitute for clinical neurophysiology certification
c) Neurosurgeon, board certified

2. Neuropsychologist/neuropsychometrist

a) Neuropsychologist: Ph.D. in clinical psychology with specialization in clinical neuropsychology as evidenced by pre- or postdoctoral training and/or work experience; or, a Ph.D. in psychology withpostdoctoral training from an APA-approved clinical neuropsychology program. This individual would supervise neuropsychological evaluations and assessments and may also supervise interventional psychologists
b) Psychometrist: A bachelor's degree in a behavioral science plus supervised experience in neuropsychometric instrument administration and scoring under the direction of a qualified neuropsychologist. This individual would administer and score the neuropsychological tests

3. Psychosocial

a) Clinical psychologist/counseling psychologist: Ph.D. from an APA-approved clinical or counseling psychology program and a special interest in epilepsy
b) Social worker: ACSW preferred with experience coordinating case services for epilepsy patients in an outpatient setting
c) School services for children

4. Nursing

a) Clinical nurse specialist/nurse clinician: qualifications include R.N. with experience in epilepsy. Responsibilities are to provide patient and family education and coordinate nursing services for the epilepsy center
b) Head nurse/staff nurse: qualifications include R.N. with experience in epilepsy. This individual would coordinate nursing functions for the inpatient service

5. EEG Technologist and personnel

When intensive neurodiagnostic monitoring of patients is performed, an EEG technologist, monitoring technician, or epilepsy staff nurse must observe the patient and maintain recording integrity. An EEG technologist attaches electrodes, maintains integrity of the recording, is capable of observing for seizures and examining patients during seizures, and operates recording equipment. A monitoring technician is defined as an individual trained in seizure observation and capable of maintaining recording integrity in the temporary absence of an EEG technologist.

All technologists and technicians should be certified in basic life support. All technologists preferably would be

board-eligible or certified by the American Board of Registration for EEG Technology (ABRET). All technologists should meet American EEG Society long-term monitoring qualifications (3). The chief technologist should be ABRET-registered and have additional training in long-term monitoring

6. Rehabilitation services

a) Registered occupational therapist
b) Physical therapist supervised by physician
c) Speech therapist and vocational counselor desirable

7. Other support services available on a consultative basis

a) Biomedical engineer

II. THIRD LEVEL MEDICAL–SURGICAL CENTER FOR EPILEPSY

A. SERVICES PROVIDED

1. Electrodiagnostic

a) 24-h video-EEG with surface electrodes supplemented with sphenoidal or appropriate additional electrodes. Continuous supervision by EEG technologist or epilepsy staff nurse, supported when appropriate by monitoring technician or automated seizure detection program
b) Intracarotid amobarbital (Wada) testing
c) Intraoperative electrocorticography

2. Epilepsy surgery

a) Emergency or elective neurosurgery, including biopsy and removal of incidental lesions and treatment of cerebral complications of epileptic seizures
b) Management of surgical complications
c) Surgical resection of epileptogenic structural lesions with the goal of treating seizures ([a]straightforward lesionectomy[o]). See comment below
d) Standard anterior temporal lobectomy in the presence of mesial temporal sclerosis. See comment below
e) Experience in resective epilepsy surgery
    i) A clinical experience of at least 20 resective epilepsy surgery cases per year on average over the last4 years, or
    ii) staff members of epilepsy center will include a neurosurgeon with a cumulative experience of 50 resective epilepsy surgery cases over the last 4 years and a physician who has evaluated at least 50 people for epilepsy surgery over the last 2 years
f) Implantation and management of vagus nerve stimulators

3. Imaging

a) Magnetic resonance imaging with appropriate magnet strength and sequences for the sensitive detection of mesial temporal sclerosis and common epileptogenic lesions
b) Computerized axial tomography
c) Cerebral angiography

4. Pharmacologic expertise

a) Quality-assured anticonvulsant serum drug levels. Levels of newer anticonvulsant drugs and free drug levels should be readily available
b) 24-h antiepileptic drug level service
c) Pharmacokinetic expertise by at least one member of the team

5. Neuropsychological/psychosocial services

a) Comprehensive neuropsychological test batteries for
    i) evaluation of cerebral dysfunction for vocational and rehabilitative purposes; and
    ii) localization of cerebral dysfunction in evaluation for epilepsy surgery. Basic assessment of characterologic and psychopathologic issues
b) An established referral arrangement for comprehensive management of psychogenic nonepileptic events
c) Clinical psychological services for assessment and basic treatment of emotional disorders associated with chronic epilepsy
d) Basic assessment of social and vocational needs
e) Inpatient school services

6. Rehabilitation (inpatient and outpatient)

a) Physical, occupational, and speech therapy for basic evaluation and treatment of multiply handicapped individuals
b) Sufficient physical, occupational, and speech therapy for managing complications of surgeries performed at the center

7. Consultative expertise

a) Psychiatrist, board-certified (ABPN), with special interest in treatment of people with epilepsy and psychiatric disorders
b) Internal medicine
c) Pediatrics
d) General surgery
e) Obstetrics/gynecology
f) Neuropathology
g) Neuroradiology

B. PERSONNEL

1. Physicians

a) A neurologist or neurosurgeon with special expertise in epilepsy should serve as program director
b) At least two board-certified neurologists with expertise in epilepsy, clinical neurophysiology, video-EEG monitoring, selection of patients for epilepsy surgery, and the pharmacology of anticonvulsant drugs. Generally neurologists would have undergone fellowship training in these topics. At least one of these individuals should be board certified in clinical neurophysiology by either the American Board of Clinical Neurophysiology or the American Board of Psychiatry and Neurology with added qualifications in clinical neurophysiology. Appropriate experience may substitute for clinical neurophysiology certification. At least one of these individuals should have experience in the selection of patients for and the adjustment of the vagus nerve stimulator
c) At least one board-certified neurosurgeon with special interest in epilepsy, experience in resective epilepsy surgery, and in the implantation of the vagus nerve stimulator

2. Neuropsychologist/neuropsychometrist

a) Neuropsychologist: Ph.D. in clinical psychology with specialization in clinical neuropsychology as evidenced by pre- or postdoctoral training and/or work experience; or, a Ph.D. in psychology with postdoctoral training from an APA-approved clinical neuropsychology program. This individual should have specific experience
   i) in use of neuropsycho metric tests in evaluation for epilepsy surgery; and
   ii) interpreting results of intracarotid amytal tests. The neuropsychologist would supervise neuropsychological evaluations and assessments and may also supervise interventional psychologists

b) Psychometrist: A bachelor's degree in a behavioral science plus supervised experience in neuropsychometric instrument administration and scoring under the direction of a qualified neuropsychologist. This individual would administer and score the neuropsychological tests

3. Psychosocial

a) Clinical psychologist/counseling psychologist: Ph.D. from an APA-approved clinical or counseling psychology program with a special interest in epilepsy
b) Social worker: ACSW preferred, with experience coordinating services for epilepsy patients in an outpatient setting

4. Nursing

a) Clinical nurse specialist/nurse clinician: qualifications include nursing with experience in epilepsy. Responsibilities include providing patient and family education and coordinate nursing services for epilepsy center
b) Head nurse/staff nurse: Qualifications include R.N. with experience in epilepsy. Responsibilities include coordinate nursing functions for inpatient service

5. EEG Technologist(s)

As in I, B, 5. Additionally, at least one technologist should have experience with the technical and safety issues encountered during electrocorticographic recordings in the operating room

6. Rehabilitation services

a) Registered occupational therapist
b) Physical therapist supervised by physician
c) Physiatrist with special interest in neurologic dysfunction
d) Speech therapist and vocational counselor preferred

7. Support services

a) Biomedical engineer

COMMENT

Knowledge and experience with resective epilepsy surgery have disseminated widely since the 1990 guidelines were published (1,4). We define resective epilepsy surgery as resection of cerebral cortex with the primary aim of treating epilepsy. Epilepsy training programs have increased the number of individuals capable of performing epilepsy surgery. When the facilities, personnel, and expertise detailed above are available, it is reasonable to perform

straightforward lesionectomy and straightforward anterior temporal lobectomy at the third level of epilepsy care. The availability of the resources necessary to evaluate patients for these surgeries and the ability to perform these surgeries distinguishes third-level medical–surgical centers from third-level medical centers.

We define lesionectomy as resection of a structural epileptogenic lesion and surrounding tissue that is performed primarily to treat epileptic seizures. In excellent candidates for lesionectomy, a single epileptogenic lesion is present, the lesion is an appropriate distance from cerebral regions necessary for normal function, and noninvasive electrophysiologic evaluation indicates that the lesion and surrounding area is responsible for the patient's seizures. Straightforward lesionectomy, defined in this manner, can be performed at a third-level medical–surgical center. If these criteria are not met, the situation is usually not straightforward, and intracranial evaluation will probably be necessary. Such patients should generally be referred to a fourth-level epilepsy center.

We define anterior temporal lobectomy as the removal of a small amount of lateral temporal cortex followed by aggressive hippocampal resection. In excellent candidates for anterior temporal lobectomy, magnetic resonance imaging detects unilateral mesial temporal sclerosis, noninvasive electrophysiologic evaluation indicates that the same temporal lobe is responsible for the patient's seizures, and neuropsychometric evaluation including intracarotid amytal testing indicates that temporal lobectomy can be safely performed. Straightforward anterior temporal lobectomy, defined in this manner, can be performed at a third-level medical±surgical center. If these criteria are not met, the situation is usually not straightforward. Further evaluation is necessary, often including intracranial recording. Such patients should generally be referred to a fourth-level epilepsy center.

Current experience indicates that the vagus nerve stimulator rarely cures epilepsy. In contrast, straightforward lesionectomy and straightforward anterior temporal lobectomy as defined above cure epilepsy in the large majority of cases. Patients with refractory epilepsy should therefore be evaluated for resective epilepsy surgery before the vagus nerve stimulator is considered. This approach has been strongly endorsed by the Health Care Finance Administration (5).

Physicians making health care decisions at third-level medical and medical±surgical centers should be fully knowledgeable regarding all surgical options available and establish formal referral arrangements with fourth-level centers. If epilepsy surgery is required, the best surgical procedure for the patient's particular situation must be recommended, and this may not necessarily be the procedure that can be provided at third-level centers. When fourth-level care is required, appropriate referral must not be delayed. Cooperating third- and fourth-level centers should attempt to standardize data collection so that all studies do not have to be repeated in referred patients. This might include uniform imaging protocols, uniform video-EEG monitoring protocols, easy access to referring physicians, and agreements to send all appropriate information with the patient.

III. FOURTH-LEVEL CENTER FOR EPILEPSY

A. SERVICES PROVIDED

1. Electrodiagnostic

a) 24-h video-EEG with surface electrodes supplemented with sphenoidal or appropriate additional electrodes. Continuous supervision by EEG technologist or epilepsy staff nurse, supported when appropriate by monitoring technician or automated seizure detection program
b) 24-h video-EEG recording with intracranial electrodes (subdural, epidural, or depth electrodes) under continuous supervision and observation as above
c) Intracarotid amobarbital (Wada) testing
d) Functional cortical mapping by stimulation of subdural electrodes either extraoperatively or intraoperatively
e) Evoked potential recording capable of being used safely with intracranial electrodes
f) Electrocorticography

2. Epilepsy surgery

a) Emergency or elective neurosurgery, including biopsy and removal of incidental lesions and treatment of cerebral complications of epileptic seizures. Management of surgical complications
b) Open and stereotactic biopsy
c) Surgical resection of epileptogenic structural lesions with the goal of treating seizures ("lesionectomy") d) Anterior temporal lobectomy with or without mesial temporal sclerosis
e) Placement of intracranial electrodes
f) Resection of epileptogenic tissue in the absence of structural lesions
g) Implantation and management of the vagus nerve stimulator
h) A clinical experience of at least 25 resective epilepsy surgery cases and 5 cases evaluated by intracranial electrodes per year on average over the last 4 years, or staff members of epilepsy center will include

i) A neurosurgeon with a cumulative experience of 50 resective epilepsy surgery cases over the last 4 years and 10 intracranial electrode implants, and
ii) a neurologist or neurosurgeon who has evaluated at least 50 people for epilepsy surgery over the last 2 years
i) If the center does not offer corpus callosotomy and hemispherectomy, it should establish a referral arrangement with fourth-level centers offering these services

3. Imaging

a) Magnetic resonance imaging with appropriate magnet strength and sequences for the sensitive detection of mesial temporal sclerosis and common epileptogenic lesions
b) Computerized axial tomography
c) Cerebral angiography
d) Access to one or more of the following either on site or by established arrangement:

i) interictal positron emission tomography
ii) ictal single-photon emission computed tomography

4. Pharmacologic expertise

As in II, A, 4

5. Neuropsychological/psychosocial services

a) Comprehensive neuropsychological test batteries for

i) evaluation of cerebral dysfunction for vocational and rehabilitative purposes; and ii) localization of cerebral dysfunction for evaluation for epilepsy surgery. Complete assessment of characterological and psychopathologic issues

b) Inpatient and outpatient psychological services for assessment and treatment of emotional disorders associated with chronic epilepsy
c) Assessment of social and vocational needs. Interventive social services
d) Comprehensive management of psychogenic nonepileptic seizures
e) Inpatient school services for children

6. Rehabilitation (inpatient and outpatient)

a) Physical, occupational, and speech therapy for evaluation and treatment of multiply handicapped individuals
b) Sufficient physical, occupational, and speech therapy for managing complications of surgeries performed at the center

7. Consultative expertise

a) Psychiatrist, board-certified (ABPN), with special interest in treatment of people with epilepsy and psychiatric disorders
b) Internal medicine
c) Pediatrics
d) General surgery
e) Obstetrics/gynecology
f) Neuropathology
g) Neuroradiology

B. PERSONNEL

1. Physicians

a) A neurologist or neurosurgeon with special expertise n epilepsy should serve as program director
b) At least two board-certified neurologists with expertise in epilepsy, clinical neurophysiology, video-EEG monitoring, selection of patients for epilepsy surgery, and the pharmacology of anticonvulsant drugs. Generally neurologists would have undergone fellowship training in these topics. At least one of these individuals should be board certified in clinical neurophysiology by either the American Board of Clinical Neurophysiology or the American Board of Psychiatry and Neurology additional qualifications in clinical neurophysiology. Appropriate experience may substitute for clinical neurophysiology certification. At least one of these individuals should have experience in the interpretation of intracranial EEG recordings and cortical stimulation studies. At least one of these individuals should have experience in the indications for and the adjustment of the vagus nerve stimulator
c) At least one board-certified neurosurgeon with special interest in epilepsy, experience in resective epilepsy surgery, placement of intracranial electrodes, and insertion of the vagus nerve stimulator. Generally neurosurgeons would have undergone fellowship training or additional training beyond residency in these topics

2. Pharmacologist or Pharm. D.

a) With special interest and training in epilepsy

3. Neuropsychologist/neuropsychometrist

a) As in II, B, 3

4. Psychosocial

a) Clinical psychologist/counseling psychologist: Ph.D.from an APA-approved clinical or counseling psychology program and a special interest in epilepsy

b) Social worker: ACSW preferred with experience coordinating case services for epilepsy patients in an outpatient setting
c) School services for children

5. Nursing

a) Clinical nurse specialist/nurse clinician: qualifications to include nursing with experience in epilepsy (M.S.N. desirable). Responsibilities include providing patient and family education and coordinate nursing services for epilepsy center
b) Head nurse/staff nurse: Qualifications include R.N. with experience in epilepsy. Responsibilities include coordinating nursing functions for inpatient service

6. EEG Technologist(s)

As in II, B, 5. Additionally, several technologists should have experience with long-term monitoring with intracranial electrodes and the safety and recording issues occurring during cortical stimulation. At least one technician should have experience with electrocorticographic recordings in the operating room

7. Rehabilitation services

a) Registered occupational therapist
b) Physical therapist supervised by physician
c) Physiatrist with special interest in neurological dysfunction
d) Speech therapist and vocational counselor also preferred

8. Support services

a) Biomedical engineer

COMMENT

It is our impression that corpus callosum section is being performed less frequently. Hemispherectomy is indicated infrequently. Consequently, we do not recommend that fourth-level centers must be able to perform corpus callosum section or hemispherectomy. However, physicians making health care decisions at these centers should be aware of the indications for these procedures. They should establish referral arrangements with fourth-level centers performing these procedures and refer patients requiring these procedures when necessary

IV. EPILEPSY-MONITORING UNIT FACILITIES

Inpatient or outpatient units evaluating or boarding patients with epilepsy require features beyond those needed for routine patient care. Unit layout, unit furnishings, and personnel needs must be considered. Protocols for situations frequently encountered in the care of epilepsy patients are advisable. Finally, emergency and intensive care should be readily available. Requirements for epilepsy-monitoring units vary by level of the epilepsy center

A. OUTPATIENT VIDEO-EEG MONITORING UNITS

1. Layout and furnishings should

a) Allow nursing or monitoring staff easy access to patients to facilitate examination and first aid
b) Minimize risk of injury due to falls

2. Personnel

a) Continuous observation by qualified providers such as EEG technologists is mandatory. Additionally, physician or staff epilepsy nurse should be readily available

3. Protocols addressing the following are useful. These can be modified as necessary to account for individual situations

a) Examination during seizures
b) Number or duration of seizures over given period requiring physician notification
c) Transportation and designated provider of emergency services in the event of emergencies
d) Medication reduction to increase seizure yield is not recommended in the outpatient setting. It should not be done without physician or extensively trained nurse clinician on premises

4. Access to additional care

a) Ready access to emergency resuscitative equipment in the monitoring unit
b) Arrangement with nearby hospital to provide emergency services when needed

B. INPATIENT UNITS AT THIRD-LEVEL MEDICAL AND SURGICAL CENTERS

1. Layout and furnishings should

a) Minimize risk due to injury and falls. Measures taken should be more thorough than in the outpatient setting because likelihood of seizures occurring is greater with medication reduction

b) Decrease risks for leaving unit or confused wandering in the postictal state
c) Allow continuous observation of patients for the purposes of safety and examination during video-EEG monitoring. Observation should be possible during wakefulness and sleep. Arrangements should assure privacy when appropriate (e.g., when patients use the bathroom) but rapid access must be available at all times

2. Personnel

a) Continuous observation by EEG technologists or epilepsy staff nurses is highly recommended, supplemented as appropriate by frequently reviewed spike and seizure detection. Reliable and appropriately trained family members or nursing assistants may assist in some situations. A higher nurse-to-patient ratio than in standard care is necessary
b) Epilepsy staff nurses must be continuously present on site. EEG technologists must be continuously available
c) 24-h physician on site. 24-h availability of epileptologist

3. Protocols addressing the following are useful. These can be modified as necessary to account for individual situations

a) Examination during seizures
b) Number or duration of seizures over given period requiring physician notification
c) Measures to be taken if number, duration, or severity of seizures observed is excessive

4. Access to additional care

a) Ready access to intensive care unit and anesthesia services in the event of status epilepticus

C. INPATIENT UNITS AT FOURTH-LEVEL CENTERS

1. Layout and furnishings

As in IV, B, 1, a–c. Additionally neurodiagnostic equipment and furnishings must meet electrical safety and other standards of the American EEG Society's Recommendations for Intensive Neurodiagnostic Monitoring (2).

2. Personnel

a) For scalp video-EEG monitoring, continuous observation by EEG technologists or epilepsy staff nurses is highly recommended, supplemented as appropriate by frequently reviewed spike and seizure detection. Reliable and appropriately trained family members or nursing assistants may assist in some situations. A higher nurse-to-patient ratio than in standard care is necessary. For video-intracranial EEG monitoring, continuous observation by EEG technologists or epilepsy staff nurses is mandatory
b) Epilepsy staff nurses must be continuously present on site. EEG technologists must be continuously available
c) 24-h physician on site. 24-h availability of epileptologist

3. Protocols addressing the following are useful. These can be modified as necessary to account for individual situations a–c) As in IV, B, 3, a–c

d) Care of head-dressings in patients studied with in tracranial electrodes
e) Measures to prevent postoperative infections or other complications in patients studied with intracranial electrodes

4. Access to additional care

a) Ready access to intensive care unit and anesthesia services in the event of status epilepticus

SPECIALIZED EPILEPSY CENTERS REFERRAL GUIDELINES

Many, and perhaps most, patients with seizures can be initially evaluated and managed by a primary care physician or a general neurologist in their local community (the first or second level of care) (Fig. 1). Typically, epilepsy care starts with an evaluation at an emergency room or a primary care physician's office and proceeds to consultation with a general neurologist or a specialized epilepsy care center if considered necessary or locally available. If seizure control is obtained, no further specialized epilepsy evaluation may be warranted. If seizures persist and cannot be brought under control by the primary care provider within 3 months, further neurologic intervention is appropriate; the neurologist should assume management of the patient's seizures at this point (6).

Once seizures are under control, care can be transferred back to the primary care provider. Alternatively, if the diagnosis of epilepsy is in question or if psychogenic nonepileptic events are suspected, a referral to an epilepsy center is appropriate early in the evaluation process for diagnostic purposes. Early diagnosis of nonepileptic events is associated with improved outcome (7). There also is some evidence that expert evaluation shortly after the onset of epileptic seizures improves outcome (8). Accurate diagnosis of the epilepsy syndrome and rapid treatment with the best possible medication may minimize the number of seizures and anticonvulsant trials and minimize impact of the seizures

on quality of life. Referral to specialized epilepsy centers if locally available should therefore be considered shortly after seizure onset even if local practitioners are reasonably secure that the diagnosis of epilepsy is correct.

Somewhat more difficult to define is the appropriate time for a general neurologist to refer a patient to a specialized epilepsy center. With multiple new medications available, some have argued that adequate medication trials may now take longer to achieve. Recent evidence suggests that up to 70% of patients have seizures fully controlled with medication (9). However, it also shows that only a small percentage of patients in whom the first antiepileptic drug was ineffective would ever become seizure free with additional anticonvulsant drug treatment. The authors concluded that patients with inadequate response to initial medical therapy likely had refractory epilepsy that would persist even when newer medications were tried. Therefore, referral to specialized epilepsy centers should occur when a patient's seizures are not fully controlled with the resources available to the general neurologist after 1 year. The flow sheet outlines the evaluation and treatment process that ultimately leads to referral to a specialized epilepsy center.

Somewhat less controversial are referrals to specialized epilepsy centers for acutely ill patients with uncontrolled seizures, status epilepticus, or patients with epileptic foci adjoining eloquent cortex. As with all patient care, referrals for all epilepsy patients should focus on what is in the best interest of the patient and emphasize treatment that is likely to improve the patient's quality of life. Very often, an objective assessment of the patient's situation will lead to an early referral to a specialized epilepsy center. Delayed or denied referral may be detrimental to the patient's health, safety, and quality of life.

The NAEC believes very strongly that the needs of the patients with seizures can best be met through well well-developed cooperative relationships between primary care physicians, general neurologists, and specialized epilepsy centers. It is the responsibility of the epilepsy center to develop a clear specific treatment plan. The center and the primary care physician or general neurologist should form a team to carry it out.

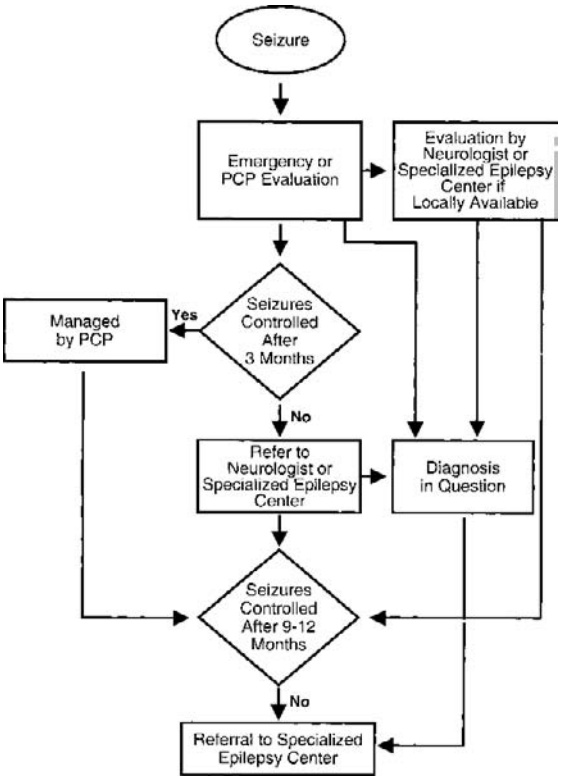

FIG. 1. Suggestions for appropriate level of care according to degree of seizure control. Flow chart indicates points at which referral to a Specialized Epilepsy Center should be considered. PCP, primary care physician.

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AMERICAN CLINICAL NEUROPHYSIOLOGY SOCIETY

GUIDELINE TWELVE: GUIDELINES FOR LONG-TERM MONITORING FOR EPILEPSY

I. INTRODUCTION

Long-term monitoring for epilepsy (LTME) refers to the simultaneous recording of EEG andclinical behavior over extended periods of time to evaluate patients with paroxysmal disturbances of cerebral function. LTME is used when it is important to correlate clinical behavior with EEG phenomena. EEG recordings of long duration may be useful in a variety of situations in which patients have intermittent disturbances that are difficult to record during routine EEG sessions. However, as defined here, LTME is limited to patients with epileptic seizure disorders or suspected epileptic seizure disorders. These guidelines do not pertain to extended EEG monitoring used in a critical care, intraoperative, or sleep analysis setting.

Although LTME can, in general, be considered to be longer than routine EEG, the duration varies depending on the indications for monitoring and the frequency of seizure occurrence. Since the intermittent abnormalities of interest may occur infrequently and unpredictably, the time necessary to document the presence of epileptiform transients or to record seizures cannot always be predetermined and may range from hours to weeks. Diagnostic efficacy requires the ability to record continuously until sufficient data are obtained. Consequently, "long-term monitoring" refers more to the capability for recording over long periods of time than to the actual duration of the recording. The term "monitoring" does not imply real-time analysis of the data.

Developments in digital technology have enhanced the ability to acquire, store and review data in LTME to such a degree that digital systems are now the industry standard. These guidelines will therefore focus on these systems. It is expected that further advances in digital technology will make it necessary to review these standards on a regular basis.

Guideline Twelve: Guidelines for Long-Term Monitoring for Epilepsy is reprinted with the permission of the American Clinical Neurophysiology Society (from the Journal of Clinical Neurophysiology, Volume 25, Number 3, 2008, pages 170-180).

II. INDICATIONS FOR LTME

This listing of indications is not meant to be all-inclusive, since special circumstances may warrant additional considerations.

A. Diagnosis

1. Identification of epileptic paroxysmal electrographic and/or behavioral abnormalities. These include epileptic seizures, overt and subclinical, and documentation of interictal epileptiform discharges. EEG and/or behavioral abnormalities may assist in the differential diagnosis between epileptic disorders and conditions associated with intermittent symptoms due to nonepileptic mechanisms (e.g., syncope, cardiac arrhythmias, transient ischemic attacks, narcolepsy, other sleep disturbances, psychogenic seizures, other behavioral disorders).
2. Verification of the epileptic nature of the new "spells" in a patient with previously documented and controlled seizures.

B. Classification/Characterization

1. Classification of clinical seizure type(s) in a patient with documented but poorly characterized epilepsy.
2. Characterization (lateralization, localization, distribution) of EEG abnormalities, both ictal and interictal, associated with seizure disorders. Characterization of epileptiform EEG features, including both ictal discharges and interictal transients, is essential in the evaluation of patients with intractable epilepsy for surgical intervention.
3. Characterization of the relationship of seizures to specific precipitating circumstances or stimuli (e.g., nocturnal, catamenial, situation-related, activity-related). Verification and/or characterization of temporal patterns of

seizure occurrence, either spontaneous or with respect to therapeutic manipulations (e.g., drug regimens).
4. Characterization of the behavioral consequences of epileptiform discharges as measured by specific tasks.

C. Quantification

1. Quantification of the number or frequency of seizures and/or interictal discharges and their relationship to naturally occurring events or cycles.
2. Quantitative documentation of the EEG response (ictal and interictal) to a therapeutic intervention or modification (e.g., drug alteration).
3. Monitoring objective EEG features is useful in patients with frequent seizures, particularly with absence and other seizures having indiscernible or minimal behavioral manifestations.

III. QUALIFICATIONS AND RESPONSIBILITIES OF LTME PERSONNEL

A. Chief or Medical Supervisor of LTME Laboratory

Qualifications

1. A physician with appropriate qualifications to be chief of an EEG laboratory [e.g., as outlined in Guidelines for Laboratory Accreditation, Standard I, published by the American Clinical Neurophysiology Society (ACNS)].
2. Certification by the appropriate national certifying group in EEG.
3. Special training in the operation of LTME equipment, which is typically more complex than that used for routine EEG recording. Special knowledge of the technical aspects of data recording, storage, and retrieval is required, and formal training or equivalent experience in electronics and/or computer science is strongly recommended.
4. Special training in the interpretation of EEG and video data generated in an LTME laboratory. Experience beyond routine EEG interpretation is necessary, since much of the analysis involves complex ictal and interictal features, as well as artifacts, seldom encountered in a standard EEG laboratory. Long-term monitoring systems can utilize methods of data display or formats of data review (e.g., discontinuous segments). The analysis of LTME data requires as well the simultaneous interpretation and correlation of EEG data and behavioral events.
5. As a minimum, it is recommended that experience in the practical use of specialized LTME equipment and in data interpretation be gained by working in a major LTME laboratory, preferably under the direction of an individual who meets the qualifications for chief or medical supervisor of an LTME laboratory.

Responsibilities

1. The chief or medical supervisor of an LTME laboratory should have the same responsibilities and authority as the chief of an EEG laboratory. They must possess the training and necessary skills needed to care for a person having seizures.
2. Additional responsibilities include the final interpretive synthesis of LTME data with diagnostic and pathophysiological formulations.

B. LTME Electroencephalographer

Qualifications

1. A physician with the qualifications to be a clinical electroencephalographer (e.g., as outlined in Guideline Four: Standards of Practice in Clinical Electroencephalography, published by the AEEGS).
2. Specialized training and experience in the use of LTME equipment and in the interpretation of LTME data is necessary, preferably under the direction of an individual who meets the qualifications for chief or medical supervisor of an LTME laboratory.

Responsibilities

1. Responsibilities include the analysis of, at minimum, pertinent segments of collected electrographic and behavioral data reviewed in all appropriate formats, the writing of LTME reports, and the final interpretive synthesis of LTME data with diagnostic and pathophysiological formulations in the absence or in lieu of the chief or medical supervisor.

C. LTME EEG Technologist I-III

Qualifications

1. A technologist with the minimal qualifications of an EEG technologist as set forth by the appropriate national body (e.g., as outlined in Guideline Five. Recommended Job Description for Electroencephalographic Technologists, published by the ACNS). In the LTME laboratory

EEG technologists should be supervised or managed by Registered EEG Technologist (R. EEG T.)
2. Special training in the use and routine maintenance of LTME equipment in the laboratory of employment, with particular emphasis on techniques for monitoring the integrity of data recording.
3. Special training and resultant expertise in the recognition of ictal and interictal electrographic patterns and in their differentiation from artifacts.
4. Special training and resultant expertise in the management of clinical seizures and seizurerelated medical emergencies. Successful completion of training in cardiopulmonary resuscitation is necessary.

Responsibilities

1. LTME technologists I-Ill should have the same responsibilities and authority as EEG technologists (e.g., as outlined in Guideline Two: Recommended Job Description for Electroencephalographic Technologists, published by the ACNS). Competencies in EEG and LTME supported by The American Society of Electroneurodiagnostic Technologists (ASET) are embraced by LTME technologist
2. Additional responsibilities include the technical operation of LTME studies (e.g., patient preparation, equipment set-up, and data recording). Overall management of these is the responsibility of a technologist III.
3. Under the supervision of the electroencephalographer in charge, data retrieval and reduction operations may be performed and EEG records prepared in a form suitable for interpretation, by LTME technologists II and III. This may include a prescreening of EEG and behavioral data to define segments for later analysis.

D. Monitoring Technician

Qualifications

1. Special training with resultant expertise in recognition of clinical ictal behavior and interaction with patients during seizures to elucidate specific ictal symptoms.
2. Special training and resultant expertise in aspects of use of monitoring equipment dependent on specific functions of technician.
3. If direct patient observation is involved, special training and resultant expertise in the management of clinical seizures, seizure-related emergencies, and cardiopulmonary resuscitation is necessary.
4. The monitoring technician position is exclusive of the operating room.

Responsibilities

1. Patient observation (direct or several patients at a time via video monitoring) to identify and note ictal events and interact with patients during seizures and to alert appropriate personnel (e.g., physician, EEG technologist, nursing staff) to the occurrence of each seizure.
2. Depending on specific training and requirements, the monitoring technician may also adjust video cameras to keep patient in view and in focus, oversee the adequate function of EEG recording equipment, administer or monitor continuous performance tasks, and otherwise maintain the integrity of the monitoring procedure, calling appropriate personnel to assist when problems occur.
3. Due to the need for continuous observation during most LTME procedures, monitoring technicians provide essential specialized services that do not require the expertise of physicians, nurses, or EEG technologists, but medical and technical personnel must be immediately available when called by the monitoring technician. If the monitoring technicians are the first responders on site, they must possess the training and necessary skills needed to care for a person having seizures.
4. Assess and respond to integrity of digital recording equipment including the integrity of electrodes.

IV. LONG-TERM MONITORING EQUIPMENT AND PROCEDURES

The following is a discussion of the EEG equipment that is available for long-term neurodiagnostic monitoring and the variety of ways it may be used. Unless otherwise stated, these are not meant to be strict requirements, but only guidelines to appropriate usage.

A. Electrode Types

Scalp

1. Disk

a) Used for scalp LTME and ambulatory EEG recording
b) Electrodes should be applied with collodion/gauze for effective long-term results
c) Electrode with hole in top is best, since it permits periodic refilling with electrode conductant.

2. Needle electrodes are not recommended for long-term recordings.

Basal Extracranial Electrode Positioning

1. Sphenoidal locations are used to record epileptiform activity from the mesial or anterior aspects of the temporal lobe in the region of the foramen ovale. Solid needle or wire construction is not recommended; fine flexible braided stainless steel wire, insulated except at the tip, is best and can be used for periods of days to weeks.
2. Other locations, such as nasoethmoidal, supraoptic, and auditory canal electrode positions, have also been employed under special circumstances to better record focal discharges; however, the indications for these placements are not well-defined. These electrodes are not recommended for routine use.
3. There is increasing evidence to suggest that earlobe, anterior or subtemporal electrode placements are, in most cases, as good as sphenoidal electrodes.
4. Nasopharyngeal locations should not be used in LTME because of the resultant irritation and the demonstrate superiority of other electrode positions.

Intracranial

1. Epidural and subdural electrodes are used to record over the surface of the brain. Electrode "grids" are made of small platinum or stainless steel disks that are embedded into soft silastic. Each grid has 4-64 contact points, a few millimeters to about 1 cm apart. Grids are placed epi- or subdurally over the cerebral cortex and require a craniotomy. Electrode "strips" consist of a row of disks embedded in silastic, or a bundle of fine wires, each tip of which is a recording point. Strips are usually inserted through a burr hole.
2. Intracerebral or depth electrodes are used to record from within the brain. Procedures and types of electrodes used vary widely. Two major types include rigid and flexible probes. Most probes are "multi-contact" with up to 16 recording points arranged along the shaft, constructed of either stainless steel or magnetic-resonance-imaging-compatible metals such as nichrome.
3. Foramen ovale electrodes are used to record from mesial temporal structures without

requiring penetration of the skull. A one- to four-contact flexible electrode is placed in the ambient cistern with the aid of a needle inserted through the foramen ovale. These electrodes are not as close to hippocampal structures as intracerebral electrodes and do not allow as large a recording field as grids and strips but detect mesial temporal EEG discharges better than sphenoidal and scalp electrodes. When extracranial recordings are equivocal, foramen ovale electrodes offer a less invasive alternative to a more complete intracranial evaluation or can be used in association with grids and strips. Foramen ovale electrodes may also be constructed from MRI-compatible metals.

4. All intracranial electrodes applications must be used with proper infection control policies and procedures
5. All intracranial electrodes and interelectrode connectors to LTME equipment must be "anchored" securely or wrapped to the scalp. This is normally done after checking intracranial electrode integrity with a second bandage over that applied by the neurosurgeon.

B. EEG Amplifiers

1. The following are recommended performance specifications:

a) Low-frequency response of 0.5 Hz or lower.
b) High-frequency response of 70 Hz or higher.
c) Noise level less than 1 μV rms
d) Input impedance of at least 1 M
e) Common mode rejection of at least 60 dB
f) Dynamic range of at least 40 dB

2. Frequency filters and gain of the recording system should be set up to obtain maximum information, rather then clean tracings, when these recordings can be modified as necessary upon replay of recorded EEGs.

C. EEG and Video Recording/Storage and Retrieval/Review

The method of EEG recording/storage has changed from analog to digital equipment. Please refer to Guideline Fourteen for recording clinical EEG in digital media.

1. For LTME, digital equipment must be able to record a minimum of 24 hours of Video and 32-64 channels of EEG. However, the capacity for 128 channels or more are found in the majority of LTME recording equipment.
2. Storage systems should normally support 24 hours of Video/EEG.
3. The retrieval and review systems should be capable of storing a minimum of 30 gigabytes or 24 hours of Video/EEG. Review can be performed on the same LTME monitoring equipment but a separate system is recommended for physician review as clinical circumstances often make more then 24 hour recording necessary. In either case, all data should be reviewed prior to any pruning and archiving of data.

V. EQUIPMENT AND PROCEDURES FOR LTME OF BEHAVIOR AND CORRELATION WITH EEG

A major objective of LTME is the correlation of behavior with EEG findings. Systems should allow the marking of relevant evens by patients or other observers and annotation

of the tracing by staff. Behavioral and EEG data are truly complementary. Bizarre ictal behaviors that are not easily recognized as seizures are appropriately identified by a simultaneous epileptiform discharge on EEG. Conversely, video evidence of classic behavioral manifestations of a seizure may be sufficient to diagnose epilepsy even in the absence of a clearly defined epileptiform EEG abnormality during such an episode. A variety of techniques for behavioral monitoring and its correlation with EEG may be employed. This section will discuss the advantages and disadvantages of each and provide recommendations as to their proper use.

A. Types of Behavioral Monitoring

1. Self-reporting

a) Features—a daily diary or log in which the patient notes the occurrence of behavioral episodes in question. This is the principal form of behavior monitoring in ambulatory EEG recording and an adjunct to in-patient LTME. A more advanced form of self-reporting includes the use of a pushbutton event marker on the ambulatory EEG recorder or by the bedside for the patient to signal the occurrence of an episode.
b) Advantages—simple, requires little special equipment, easy to implement, practical way to monitor patients with infrequent seizures for which they have warning or memory. When used with ambulatory recordings, it can provide information regarding the effect of circadian cycles, environmental factors, and anti-epileptic drug fluctuations on seizure activity.
c) Disadvantages—correlation is subjective, record of behavior not available for detailed visual analysis, temporal correlation may be inaccurate even when event marker is used, not possible with seizures for which the patient has no warning or memory, ictal descriptions usually not obtained, not suitable for final correlation in a presurgical workup, but, with 16-24-channel ambulatory recording. It may provide preliminary data that can minimize inpatient monitoring.

2. Observer reporting

a) Features—observer reporting complements self-reporting in daily diaries. Observer reporting by trained hospital personnel can be objective and includes the use of standardized checklists of information to be recorded, direct interaction with the patient to assess mental function (level of consciousness, language function, memory) and neurological deficits. A pushbutton event marker, activated by a family member, friend, or LTME staff, can provide temporal correlations of clinical episodes on ambulatory or inpatient EEG recordings. This is a major form of behavior monitoring in ambulatory EEG recording, particularly in young children or in mentally retarded patients who cannot reliably self-report. It is also used in inpatient settings when personnel are available to monitor patient activity.
b) Advantages—simple and inexpensive, requires little specialized equipment, easy to implement interactive assessments provide critical information about functional deficits accompanying episodes. Since it can be used with seizures for which the patient has no warning or memory, it provides a practical way to monitor patients with infrequent seizures.
c) Disadvantages—correlation is subjective, record of behavior not available for detailed visual analysis, temporal correlation may be inaccurate even when event marker used, not sufficient for presurgical evaluations. Seizures may be missed if observer is not continuously observing patient.

3. Video recording

a) Features—principal and most effective means of behavior monitoring in in-patient setting. Patient behavior is continuously recorded on video simultaneously with EEG (vEEG) Observations of LTME personnel, self-reporting by patients, or automated computer analysis of EEG identify episodes that are potentially seizures that require detailed analysis. Direct assessment of neurological function of patient by LTME staff adds to other recorded data. A succinct event list can be posted for physician review of events and patient push buttons.
b) Advantages—objective record of behavior, available for replay and associated direct EEG correlation, temporal correlations accurate when synchronization achieved with time code generators or same tape recording, useful in seizures of all types even if minimal behavioral manifestations are initially unrecognized, since permanent record allows subsequent review of behavior associated with EEG changes. The interaction between monitoring personnel and the patient, when properly structured, defines the events more explicitly than other mechanisms.
c) Disadvantages—specialized equipment required, can be time-consuming to implement. When recording without personnel present, interactive assessments of neurological function are unavailable. A major problem is that freedom of movement is limited by the necessity for the patient to stay in view of the camera.

4. Polygraphic and reaction time monitoring. A variety of approaches can be used to record aspects of ictal behavior along with the EEG. Monitoring of specific physiological functions such as eye movement of electromyography (EMG) may provide useful information for characterizing the behavioral manifestations of ictal events. Cognitive disturbances can be documented by reaction time tasks, with stimulus and response times recorded on an

event marker channel. This technique can also be used to demonstrate that discharges that would ordinarily be thought of as interictal can interfere with cognitive processing on a transient basis. Selection of appropriate tasks that can be maintained for prolonged periods, recorded, and quantified allows time indexing to the EEG, and, in essence, may extend the definition of what is ictal for a given patient. LTME personnel should test awareness, memory, language and gross motor function using a standard protocol during ictal events.

B. Equipment—Behavioral Data Acquisition

1. Video cameras

a) Standard monochrome (black and white)— requires illumination of 0.5 footcandle, satisfactory for daylight monitoring conditions, unsatisfactory for nocturnal monitoring under reduced lighting conditions
b) Low light level monochrome—allows monitoring in only 0.03 footcandles of illumination, particularly sensitive to red light, useful for nocturnal monitoring under reduced lighting conditions, automatic iris needed to compensate for sudden increases in light level, especially focal, which can cause "blooming"
c) Silicon intensified target ("starlight")—effective in as little as 0.000025 footcandles of illumination, image intensifier technology, high resolution for nocturnal monitoring, expense is substantial, value for increased resolution is not established
d) Color, current preferred technique—requires 25 footcandles of illumination, better resolution of facial features than black and white, valuable for perceiving certain autonomic changes (e.g., blushing, pallor), not suited to nocturnal monitoring but continuous auto-white balance improves resolution during changes in ambient light, exclusive color systems may be impractical
e) Low-light level color—requires 1-10 footcandles of illumination, can be used for nocturnal monitoring with small night light, increased expense, value not established in nocturnal conditions except to attempt exclusive use of color cameras
f) Solid-state sensor monochrome—longer lasting than tube cameras, good resolution, no "blooming" and no image retention ("burn in"), tolerates difficult lighting conditions, is available with built-in infrared illuminators for night monitoring

2. Video camera lenses—irises

a) Standard—iris requires manual adjustment for changing light conditions, inconvenience may lead to neglect of this factor, minimally acceptable for LTME
b) Automatic—iris automatically adjusts to changing light conditions, facilitates prolonged monitoring under varying conditions, "blooming" may still occur with a sudden focal increase in light (such as from a match), manual override can compensate for unusual light conditions

3. Video camera lenses—field of view

a) Standard—size of viewing field fixed relative to distance between camera and object
b) Fixed wide-angle—increases the area monitored at the expense of detail, patient more easily keep within field of view
c) Remote zoom—allows personnel to obtain close-up view of area of particular interest (e.g., motor onset of simple partial seizure), utilizes separate 6-V AC power unlike 24-VAC power to camera and remote pan/tilt
d) Remote zoom wide-angle—allows variable area to be monitored depending on clinical situation, 15-mm focal length preferred

4. Video camera mobility

a) Fixed position camera—requires that the patient remain within the camera's unchangeable field of view; this degree of restriction of patient mobility difficult to maintain over long monitoring periods, particularly if close-up of face is required
b) Mobile or portable camera—provides a changeable field of view to allow some patient mobility, necessitates intrusion into monitoring room and physical repositioning of camera by personnel for each change
c) Remote pan/tilt device—allows personnel to keep patients in view of the camera as they move about the room by moving camera side to side or up/down; recommended for permanent monitoring rooms, separate remote control panel may activate combined focus, zoom, and pan/tilt functions of camera
c) Reformatted EEG does not provide adequate or sufficiently long segments of recording to make official EEG interpretations; reformatted EEG cannot be transcribed back into analog signals for paper writeout; separate EEG recording facilitates are also required for most purposes

5. Audio—microphones. In addition to the video image of patient behavior, it is important to have an audio record of clinical episodes, which includes not only the patient's verbalizations, but also a description of behavior and neurological function as assessed and related by LTME personnel attending to the patient during the episode.

a) Unidirectional—picks up only sound coming from directly in front of the microphone head, eliminates extraneous noise, requires readjustment with patient movement, usually attached to video camera, which is aimed at patient, unsatisfactory for recording nearby LTME personnel
b) Omnidirectional—picks up sound in roughly a spherical distribution around the microphone, eliminates need

for directional readjustment, subject to interference from extraneous sounds, recommended as a minimal standard

c) Pressure zone—mounts to flat surfaces for reduced echo-reverberation, but picks up extraneous sound; discrete and less vulnerable to handling

d) Sound mixer—combines multiple audio sources into a single signal for recording on videotape; unidirectional and omnidirectional microphone inputs may be combined to obtain improved audio recording capability

C. Equipment—Behavioral Data Storage and Retrieval

1. Digital Storage- This is the current industry standard for LTME. Digital storage provides more reliable storage with no degradation of copies. Sufficient storage space to allow for 24 hours of continuous video-EEG information is essential.

2. Display monitors

a) Monochrome—perceived optical resolution is 525 line pairs, satisfactory for LTME, higher optical resolution of up to 1,000 line pairs available in some monitors.

b) Color—perceived optical resolution of 250 line pairs, minimal acceptable standard for LTME. The current optimal standards are 1600 X 1200 pixels with a screen diagonal size of 20 inches or more.

D. Behavioral Data Storage Protocols

1. Storage for initial analysis

a) All video/audio monitoring data as well as associated EEG recordings should be saved until appropriately analyzed and reduced by trained personnel.

b) When long-term monitoring is only for the purpose of recording clinical episodes, partial data reduction can be performed online. Data containing no episodes may be erased.

c) If a clinically significant event has occurred, the data should be retained for later analysis.

2. Archival storage

a) When it has been determined upon analysis that a behavioral episode is clinically relevant, video-recorded data should be copied onto a durable medium for long-term storage.

b) Edited data to be stored should include a short period (approximately 2 mm) prior to and after the event, as well as the entire episode. A log of the contents of all edited data should be maintained, preferably as part of the detailed report.

E. Behavioral Data Analysis and Correlations with EEG

1. Event analysis

a) Using the appropriate review options, a detailed characterization of the temporal sequence of the patient's behavior during each clinical episode should be accomplished under the direct supervision and review of the LTME electroencephalographer.

b) Attention should be paid to the sequence and character of motor activity, verbalizations, responsiveness to stimuli, and any other noteworthy features.

2. Correlation of behavior and EEG

a) EEG that is temporally concurrent with the clinical episode in question should also be analyzed in detail for significant change of progression in pattern, with particular emphasis on those that are ictal in character.

b) The progression of behavioral alterations as outlined in the event analysis can be correlated to any EEG changes by utilizing synchronous time codes recorded on each. Times codes should be accurate to less than 0.5 s.

VI. TECHNICAL AND METHODOLOGICAL CONSIDERATIONS

A. Electrode Locations

1. Use of the International 10-20 System with supplementary positions is suggested in order to maintain standardization. Additional electrodes are often helpful in the evaluation of patients for epilepsy surgery.

2. Atypical electrode positions such as F9, F10, and Nz (nose tip), as well as special electrodes such as sphenoidal may be used depending on the clinical indications.

3. Intracranial electrode placements (epidural, subdural, intracerebral, foramen ovale) are used in candidates for surgical resection of an epileptic lesion. They are indicated to answer specific questions about the localization of discharges determined to be of focal origin by surfacerecording techniques, but insufficiently defined to direct surgical interventions. Use of nonferrous metals such as platinum and nichrome allows MRI verification of electrode location. In these instances of intracorporeal recording sites, the guidelines for patients with in-dwelling devices should be followed in the United States, UL, Type A patient). They are not appropriate when surface EEG recordings provide no clues to the presence or location of a focal lesion. Due to the diversity of the techniques in use, specific recommendations concerning electrical and mechanical safety precautions are beyond the scope of this discussion.

B. Electrode Application/Insertion

1. Disk—Collodion technique is currently the only method that will insure a stable long-term recording. Application by electrode paste alone is not recommended. Collodion should be dried slowly to make a film over the electrode, which prevents the electrode jelly from drying out. This may be facilitated by the use of pressured air. Underlying skin should not be unduly abraded when electrodes are to remain in place several days. Electrode jelly that is used should not contain irritants or dry out quickly. A felt pad may be used under a disk electrode to prevent pressure breakdown of the skin.
2. Sphenoidal—inserted bilaterally through the skin below the zygomatic arches in the direction of the foramen ovale by an electroencephalographer or qualified physician, with or without local anesthetic. Flexible wire electrodes are placed 3-4 cm deep, within or alongside a needle, and the needle is then removed. The external wire should be coiled, to relieve tension, and fixed to the cheek with collodion and/or tape at the point of exit from the skin.
3. Epidural and subdural—inserted during a neurosurgical procedure. Epidural and subdural electrode grids are directly placed over accessible areas of the cerebral cortex through a craniotomy. Strip electrodes are usually placed freehand through burr holes.
4. Intracerebral—inserted stereotactically into bilateral temporal and/or extratemporal sites.
5. Foramen ovale—inserted bilaterally through the skin using an approach similar to that for percutaneous trigeminal rhizotomy, by a qualified neurosurgeon. A 1-4-contact flexible electrode remains in the ambient cistern after the insertion needle is withdrawn.

C. Electrode Maintenance

1. Disk-recording characteristics of electrodes should be checked every day so that electrode contact deterioration can be detected and corrected without interruption of the recording. Impedance should be checked periodically, and if recording characteristics change. Refilling of the electrodes with conductant gel should be performed as necessary to maintain low impedance. If electrode conductant is applied via blunted tip syringes; they are appropriately disposed of after each use.
3. Sphenoidal—care must be taken to relieve stress on the recording wires. External wires should be inspected periodically to insure proper fixation to the skin and minimize the possibility of breakage or accidental removal. Inspect that the tip of sphenoid is still intact and that the length of the sphenoid is the same as the length of sphenoid upon insertion.
4. Epidural, subdural, intracerebral, foramen ovale—once inserted for chronic recording, electrode malfunction cannot be corrected, although its condition can be assessed through the quality of the recording. The special connectors used with these electrodes are liable to cause problems and must be inspected periodically.

D. Electrode Impedance

1. Disk-impedance should be measured at the beginning, periodically during, and with ambulatory EEG at the end of the recording. Initial impedance should be less than 5,000 ohms. During in-patient LTME, attempts should be made to maintain this level.
2. Sphenoidal—impedance can be measured in routine fashion and maybe of help in verifying the cause of a change in recording characteristics.
3. Epidural, subdural, intracerebral, foramen ovale—impedance measurements can be safely performed with currents in the range of 10 nA for electrodes inserted intracranially. This is 1,000 times less voltage than the normal 5-10 Kohm impedance measurements of scalp electrodes. Care must be taken not to polarize intracerebral electrodes. Electrode conductivity and integrity of insulation should be checked prior to sterilization of the electrodes.

E. Digital Equipment and Calibration

Digital Equipment and Calibration are addressed in Guideline 1

1. Before beginning LTME and periodically during the monitoring, the integrity of the entire recoding system from electrode to storage medium should be checked by observing ongoing EEG, tapping electrodes or connectors, and/or by having the patient generate physiological artifact. The resultant signals should be examined online and offline and compared to baseline recordings.

F. Recording Techniques

1. Number of channels—standard LTME

a) Telemetered EEG long-term monitoring requires a minimum eight channels, similar to the guideline for routine clinical EEG. Twelve or more channels are routinely used and are in particular necessary for accurate localization when additional electrodes are employed.

b) A large number of EEG channels is essential for obtaining accurate localization, as is required in a presurgical evaluation. Thirty-two to 64 channel recordings are recommended for this purpose.

2. Number of channels—ambulatory EEG

a) Fewer than eight EEG channels are usually not sufficient for a primary EEG evaluation.

3. Montages—extracranial recordings

a) Montages should be appropriate for the abnormalities anticipated and should be determined on the basis of previously documented EEG findings. Guidelines for montages can found in other ACNS guidelines. An important aspect of montage design for LTME is to clearly separate activity from the basal temporal electrodes from the remainder of the standard 10-20 derivations.
b) Simultaneous electrocardiographic (ECG) recording is recommended, since cardiac arrhythmias may produce artifacts that mimic epileptiform EEG transients.

4. Montages—intracranial recordings

a) Montages depend upon the type and location of the implanted electrodes.
b) Common approaches include linking adjacent contact points in a linear bipolar chain to survey a large area, defining well a small area with closely spaced bipolar derivations or referring all contact points to a least active point to obtain a referential recording.
c) Montages may include some scalp derivations to assure adequate characterization of abnormalities.

5. Montages—ambulatory EEG

a) Montage selection for a given patient should be guided by previously documented abnormalities on routine EEG and by clinical history. Guidelines for montages can be found in other ACNS guildelines.

6. Use of filters and sensitivity—EEG signals

a) Low linear filters and sensitivity settings should be adjusted to optimize review, but it is best to record information in as wide a frequency band as possible and selectively filter the signals, as necessary upon playback.
b) Filter settings in most cases are the same as those used in standard laboratory EEG, i.e., high linear frequency filter of at least 70 Hz, but preferably higher, and a low linear frequency filter at 0.5-1 Hz. More selective filtering may enhance the information obtained from intracranial recording.
c) Certain environments may require the use of a 50-60-Hz notch filter. This should only be applied after inspection of the recording without a notch filter in order to detect electrode artifacts. Under certain unavoidable conditions, more restrictive filtering than that above may improve the recording.
d) Sensitivity settings for extracranial recording should be equal among channels and follow the recommendations for routine EEG. For intracranial recordings, equal sensitivity settings are recommended, if possible, as when using equally spaced chain linkage bipolar or common reference montages. Sensitivity can be set independently for each channel to obtain the best relative signal when closely or irregularly spaced bipolar intracerebral derivations are used.

7. Monitoring of other physiological parameters

a) Recording of the ECG, electrooculogram (EOG), EMG, or respiration may be indicated for particular clinical situations. Recording techniques are the same as in standard polygraphy.
b) In ambulatory EEG systems, the use of more than one channel for other physiological monitoring may limit the usefulness and validity of the EEG data.

G. Artifacts

The differentiation of artifacts and normal EEG transients from EEG abnormalities poses an increased problem in LTME, particularly in ambulatory EEG recordings with a limited number of channels. Unusual artifacts not seen in standard laboratory EEG recording are commonly encountered.

1. Biological

a) In addition to the normally recognized eye movements, blinking, muscle tension, ECG, respiration, sweating, and tremor, activities such as chewing, talking, and teeth brushing can produce EMG, glossokinetic, and/or reflex extraocular movement potentials and result in potentially confusing patterns.
b) Standard disk electrode recordings are very susceptible to biological artifact. Sphenoidal electrodes are associated with less artifact. Intracranial electrode recordings are usually free of biological artifacts, except for pulsation.

2. Mechanical or external

a) The main mechanical artifacts of telemetry originate from altered electrode/scalp contact or intermittent lead wire disconnection induced by body movement. Direct connection with standard cable imposes additional artifacts from movement of the cable itself.
b) Artifacts produced by rubbing or scratching of the scalp and other rhythmic movements of head or extremity can, in association with accompanying biological artifact, result in particularly confusing patterns that must be differentiated from ictal discharges.
c) The most common external artifact in surface recordings is 50- or 60-Hz interference. Electromagnetic fields due to nearby fans, air conditioning, or ballasts of fluorescent lights and vertical alignment of LTME power cable and pneumonic pressure boots can produce interference of 50- or 60-Hz plus harmonics. A crossing of cables

can eliminate some artifact interference. Electrostatic potentials due to nearby movement of persons with dry clothing or telephone ringing may produce spurious transients.

d) In intracranial recording, mechanical artifacts due to body movement are usually negligible and those due to electrical interference are usually less than with extracranial electrodes.

3. Instrumental

a) Any part of the recording and playback system, e.g., electrodes, wires, amplifiers, etc., can be a source of artifact.

b) Common sources of spurious transients are electrode popping, faulty switches or connectors, or touching of dissimilar metals. Rhythmic slow waves can be due to chipped silver—silver chloride coating, instability of the electrode scalp interface, and electrode wire movement.

4. Recognition/interpretation

a) A conservative interpretation of unusual or equivocal EEG events is mandatory in LTME, particularly in instances in which the patient's activity at that moment cannot be verified for possible artifact production.

b) Personnel should familiarize themselves with the common artifacts of active wakefulness and EEG transients of normal sleep. Recognition of the instrumental artifacts of a particular laboratory or recording arrangement is equally necessary to insure reliable differentiation from cerebrally generated events.

c) In ambulatory EEG monitoring, all common biological and mechanical artifacts should be produced by the patient and/or technologist at the beginning or the end of the recording, where they can serve as a reference for confusing transients noted on review of that particular tape.

d) When simultaneous video-recorded behavior is available, artifacts due to biological and mechanical disturbances, particularly rhythmic ones, can usually be verified by review of the videotape.

e) When patient behavior is not being video recorded, identification of a rhythmic discharge as an epileptic seizure can be made by recognition of well-formed epileptiform spike-and-wave patterns with a believable field and typical ictal progression (for partial and convulsive seizures, the ictal discharge usually begins with low-voltage fast activity and becomes slower with higher amplitude), as well as postictal slowing, appropriate interictal abnormalities in other portions of the record, and an appropriate episode noted in the patient's diary or by an observer.

f) Interictal epileptiform EEG abnormalities should be identified as recurrent independent transients in artifact-free portions of the record, such as quiet wakefulness or sleep. Sharp waveforms noted only during active wakefulness should be interpreted as abnormal with caution.

H. LTME Quality Assurance

1. Periodic checking of the status of ongoing EEG recording is essential and should be performed at least once a day.

VII. RECOMMENDED USES OF SPECIFIC LTME SYSTEMS

Although the large numbers of different EEG and behavior monitoring components create the possibility of many combinations that could comprise an LTME system, there are only a small number of configurations in general use. Listed below are recommended basic system configurations along with indications (refer to Section II) for which each is appropriate and not appropriate. Combinations of these systems are commonly used.

A. Monitoring with Continuous Storage of Video and EEG Data

1. EEG transmission— most often achieved using cable connection or radio telemetry
2. EEG recording/storage—mostly often acquired using digital systems
3. EEG review/analysis—review of all episodes and random samples of background, although complete review of all EEG data is possible.
4. Behavior monitoring—self, observer, and video
5. Clinical indications

a) Appropriate—documentation, characterization, and quantification of clinical ictal episodes and their EEG features over days to weeks and assessment of their relationships to behavior, performance tasks, naturally occurring event or cycles, or therapeutic intervention.

b) Comment—at least 16 channels of EEG data and synchronized video monitoring are required for presurgical localization of epileptogenic regions.

c) Not appropriate—for evaluation benefiting from complete freedom of movement

B. Computer-Assisted Selective Monitoring

1. EEG transmission—cable or radio telemetry
2. EEG recording/storage—digital tape/disk, computer-assisted selective storage

3. EEG review/analysis—selective analysis of clinical and computer-recognized ictal and interictal events
4. Behavior monitoring—self, observer, and video
5. Clinical indications

a) Most appropriate—documentation, characterization, and quantification of ictal (clinical and subclinical) and interictal EEG features and assessment of their relationship to behavior, performance tasks, naturally occurring events or cycles, or therapeutic intervention.
b) Comment—computer recognition programs have not been perfected and are subject to a variable amount of false-negative and false-positive error. At least 16 channels of EEG data and synchronized video monitoring are required for presurgical localization of epileptogenic regions. Radio telemetry provides more mobility than cable telemetry; however, video monitoring becomes difficult or impossible when this degree of mobility is required.
c) Not appropriate—evaluations benefiting from complete freedom of movement

C. Ambulatory Continuous EEG Recording

1. EEG transmission—ambulatory
2. EEG recording/storage—digitally stored
3. EEG review/analysis—events reviewed in detail, random samples of EEG analyzed..
4. Behavior monitoring—self report, observer log comments.
5. Clinical indications

a) Appropriate—documentation and quantification of ictal (clinical and subclinical) and interictal EEG features and assessment of their relationship to reported behavior.
b) Comment—also applicable in an in-patient setting, particularly when mobility is of benefit.
c) Not appropriate—detailed characterization of EEG features as is required in presurgical evaluation

D. Ambulatory —Selective, Computer Assisted

1. EEG transmission—ambulatory (16-24 channels)
2. EEG recording/storage—digitally stored
3. EEG review/analysis—selective analysis of computer-recognized ictal and interictal events
4. Behavior monitoring—self, observer
5. Clinical indications

a) Appropriate—same as C, except that seizures without an obvious behavioral change may be detected
b) Comment—same as C
c) Not appropriate—same as in C.

VIII. MINIMUM STANDARDS OF PRACTICE FOR SPECIFIC INDICATIONS

When in-patient LTME is performed, an EEG technologist, monitoring technician, epilepsy staff nurse, or other qualified personnel must observe the patient, record events, and maintain recording integrity.

A. Presurgical Evaluations

The most exacting evaluation in LTME is the attempt to localize, by means of surface and/or intracranial electrodes, a region of epileptogenic brain tissue that is the site of origin of recurrent seizures and that is amenable to surgical removal. The following are minimum acceptable standards.

1. EEG transmission—standard cable ("hard wire") or telemetry EEG with at least 16 channels of EEG data. Cable telemetry is the most common technology. Ambulatory EEG is not acceptable for final evaluation, but may serve a useful triage function.
2. EEG recording storage—continuous digital storage with synchronization of video data.
3. EEG review/analysis—detailed visual analysis of all seizures and representative interictal abnormalities from a high-quality display is required. Additional computer analyses of EEG abnormalities (temporal and distribution characteristics) may be beneficial.
4. Behavior monitoring—continuous video recording with a time code synchronized to EEG. Observer or self-reporting of behavior is not sufficient. Time-lapse video recording is discouraged.

B. Diagnosis of Nonepileptic Seizures

Minimum standards of practice in the differentiation of nonepileptic seizures from epileptic seizures are the same as above, although eight channels of EEG data can be adequate to identify most epileptic events. Regardless of the number of channels, however, absence of clear ictal EEG abnormalities during a behavioral event must be interpreted with reference to the complete clinical evaluation before a diagnosis of nonepileptic seizures can be made.

C. Classification and Characterization of Epileptic Events

Only systems with eighteen or more channels (16 EEG, 1 eye and 1 EKG) can provide basic characterization of epileptic EEG events;

IX. GUIDELINES FOR WRITING REPORTS ON LTME

A. General Considerations

1. The LTME report should consist of four principal parts.

a) A statement of the clinical problem and overall intent of LTME Background information should include a brief summary of the clinical history avnd physical findings, the reasons for referral and a brief review of current medications and other existing conditions that might alter recorded EEGs or behavior. The purpose of the LTME (e.g., diagnostic study, presurgical evaluation) should be clearly stated.

b) An explanation of technological aspects of the recording, such as number of channels of EEG recorded, type and location of electrodes (e.g., scalp, sphenoidal, intracranial, multiple EMG, ECG, etc.) and the use of manual and/or automated seizure and/or discharge detection should be documented. Special observations (oximetry, sleep assessment, blood pressure or cardiac arrhythmia monitoring) are indicated. Activation procedures (drug injection, suggestion, hyperventilation, exercise, reenactment of precipitating events), testing of reaction times, etc., should be fully described. The reduction of medications, especially those intended to increase or decrease the incidence of seizures, is described.

c) A description of the findings should include a statement concerning waking and sleeping EEG patterns, magnitude and location of nonepileptiform abnormalities, and the presence of artifacts that might reflect upon the overall quality of the recording. The frequency of occurrence, character, topographic distribution and propagation of interictal epileptiform discharges should be reported. Behavioral and electrographic ictal events should be emphasized and described in detail. Descriptions of patient behavior should include portrayal of activity immediately preceding the attack, characteristic features of the onset, course, and termination of the episode, and ictal and postictal behavior evident spontaneously, as the result of examination, and as supplemented by reports of observers. Specifically, responsiveness, orientation, language, memory, motor activity, and other neurological functions are to be reported. The electrographic findings to be reported should include descriptions of background activity and epileptiform discharges preceding the seizure, the mode, pattern, and location of onset of ictal activity, the propagation and termination of seizure discharges, and postictal changes. The durations, relative times of onset, and significant changes in clinical and electrographic ictal events should be presented. The temporal relationship between behavioral manifestations and ictal electrographic events should be noted.

d) An interpretation, stating the overall impressions gained from, and clinical significance of, the electrographic and behavioral correlations. This portion of the report should be an interpretive synthesis rather than a reiteration of the description. Seizures and epilepsy syndromes should be classified wherever possible according to the guidelines developed by the International League Against Epilepsy. Overall pathophysiological and diagnostic formulations should include reference to available data on the quantitative and topographic features of interictal epileptiform and nonepileptiform, as well as ictal, abnormalities. Inferences as to the site of origin and propagation of seizures should be made when this is justified by the findings. Suggestions for subsequent studies are stated.

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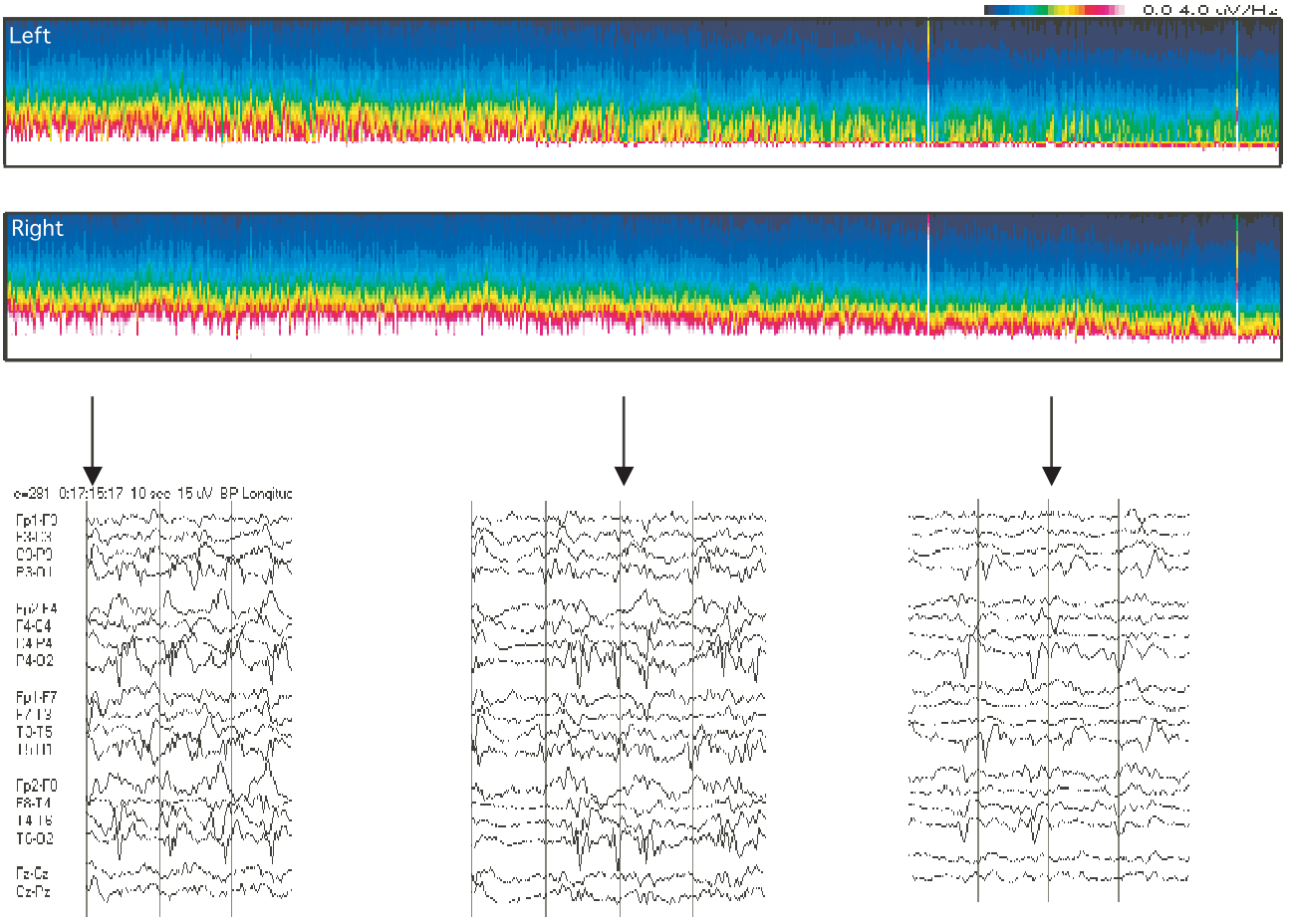

FIGURE 2-3. Resolution of nonconvulsive status epilepticus shown on compressed spectral array (CSA). CSA showing gradual resolution of nonconvulsive status epilepticus over 11 hours. CSA is particularly useful for recognition of such long-term trends. Arrows indicate approximate time periods in the CSA from which the EEG samples were taken. Y-axis: frequency, 0 Hz at bottom, 60 Hz at top. X-axis: time (approximately 11 hours shown). Gray scale (z-axis, typically displayed in color) power of given frequency (scale in upper right; microvolts/Hz). Z-axis: voltage, measured in microvolts/Hz (22).

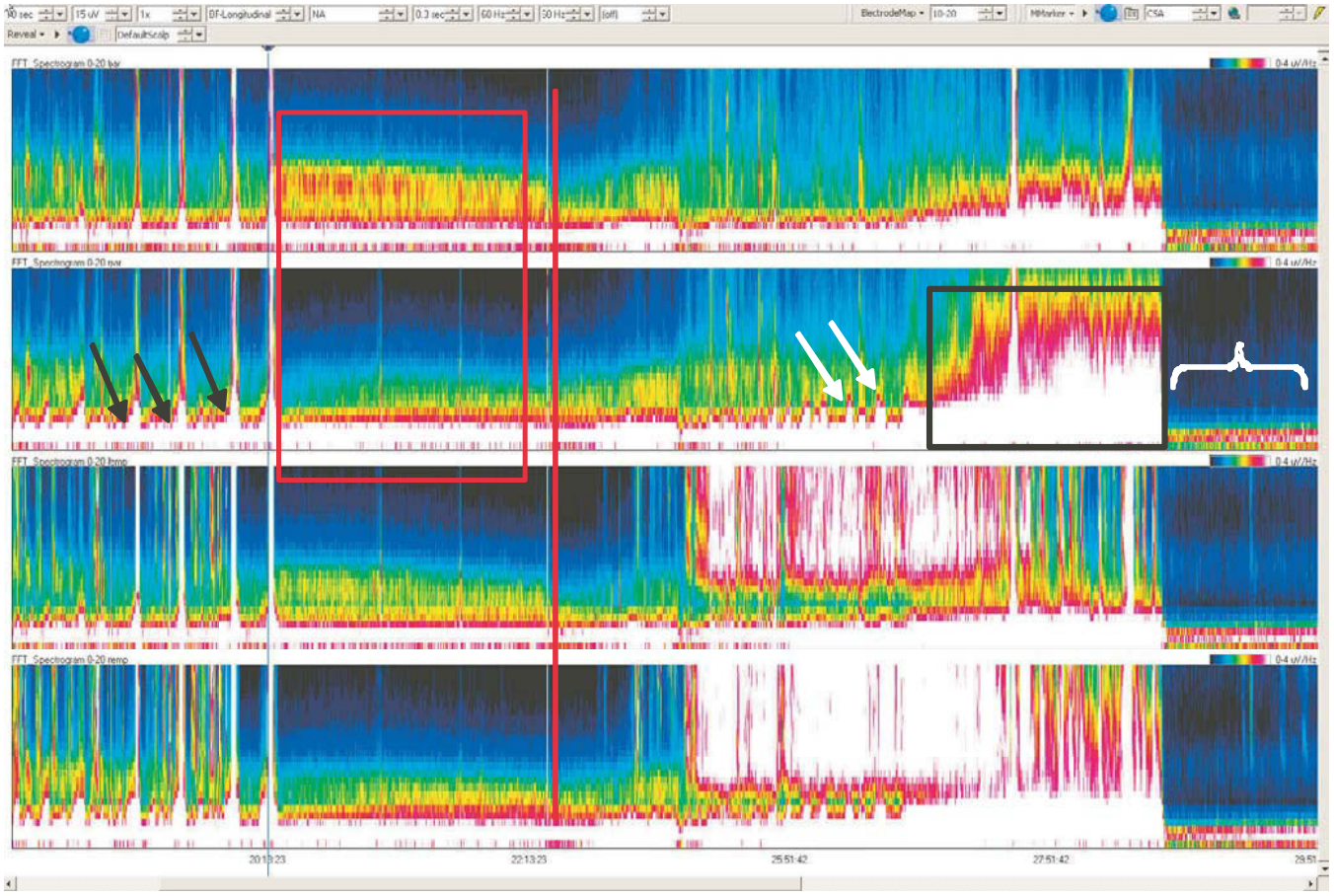

FIGURE 2-4. CSA detection of respiratory failure: a 10-hour case summary. CSA showing 10 hours of EEG in a 76-year-old patient with atrial fibrillation, on warfarin, who was admitted with a small right subdural hematoma. Continuous EEG monitoring was initiated after the patient became lethargic for an unknown reason (there were no clinical seizures). Initially the CSA revealed recurrent right>left hemisphere nonconvulsive seizures (black arrows). Seizures ceased for several hours without any change in antiepileptic medications (taller box). Clinical assessment at that time revealed respiratory failure, with pH 7.1; presumably, the acidosis led to fewer seizures. After intubation (dark line) and improvement of acidosis, CSA activity gradually increased, but was followed by gradual recurrence of nonconvulsive seizures (white arrows), and eventually nonconvulsive status epilepticus (black box). A midazolam infusion was begun (white bracket), with subsequent resolution of electrographic epileptic activity and diminished activity on CSA. Y-axis: frequency, 0 Hz at bottom, 20 Hz at top. X-axis: time (approximately 10 hours shown). Color scale (z-axis): power of given frequency (scale in upper right) measured in microvolts/Hz.

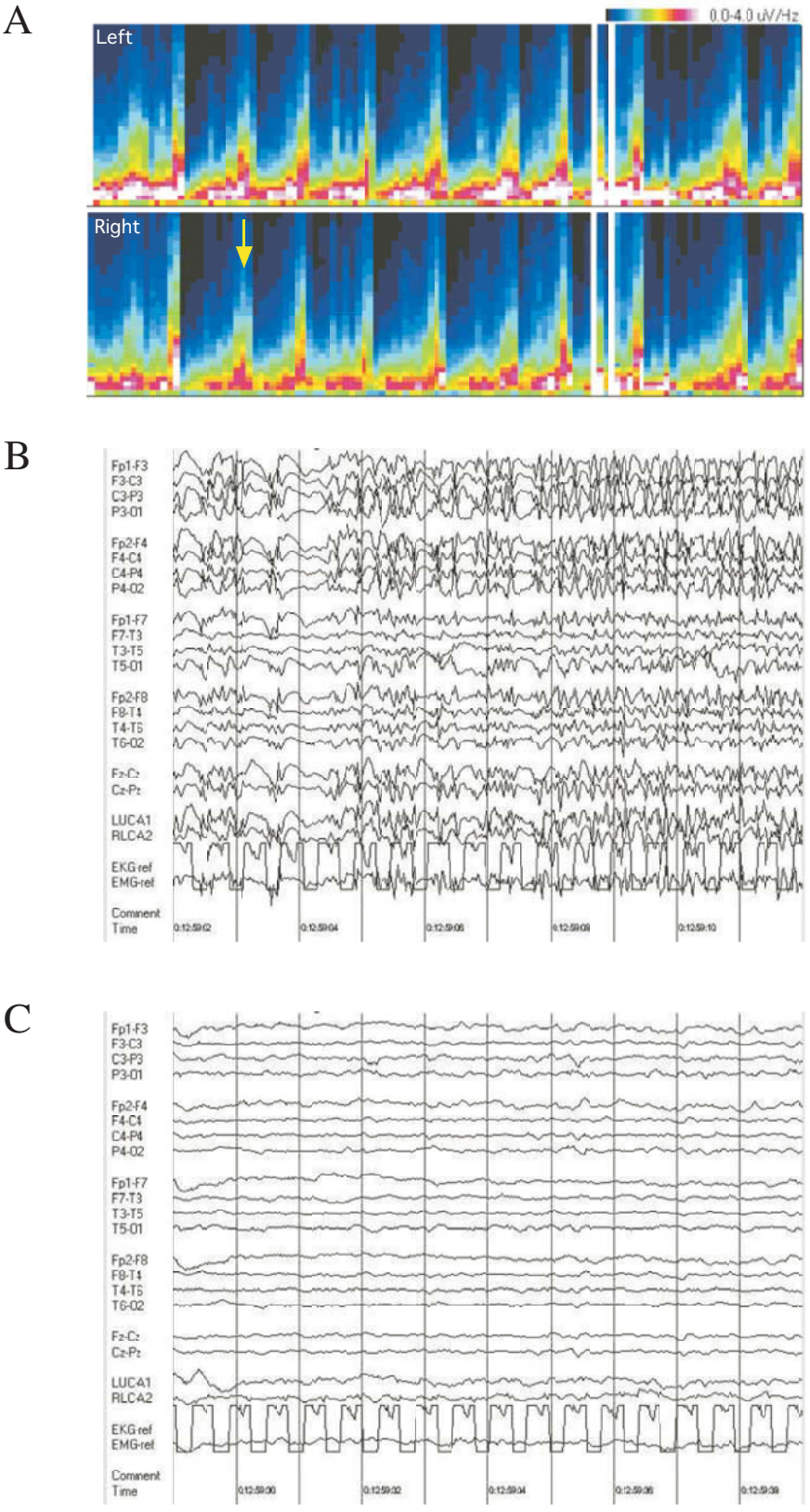

FIGURE 2-6. Cyclic seizures. (A) CSA in a patient demonstrating a cyclic seizure pattern, with a gradual buildup of voltage, followed by the seizure (arrow). This is again followed by seizure offset, which is then followed by the gradual buildup of voltage again. The seizures occur at a rate of approximately one every 3 minutes. (B) Ictal EEG from same patient, corresponding to the peak labeled with the arrow on CSA. (C) Postictal EEG, corresponding with the postictal attenuation of activity on the CSA, just after the arrow (58).

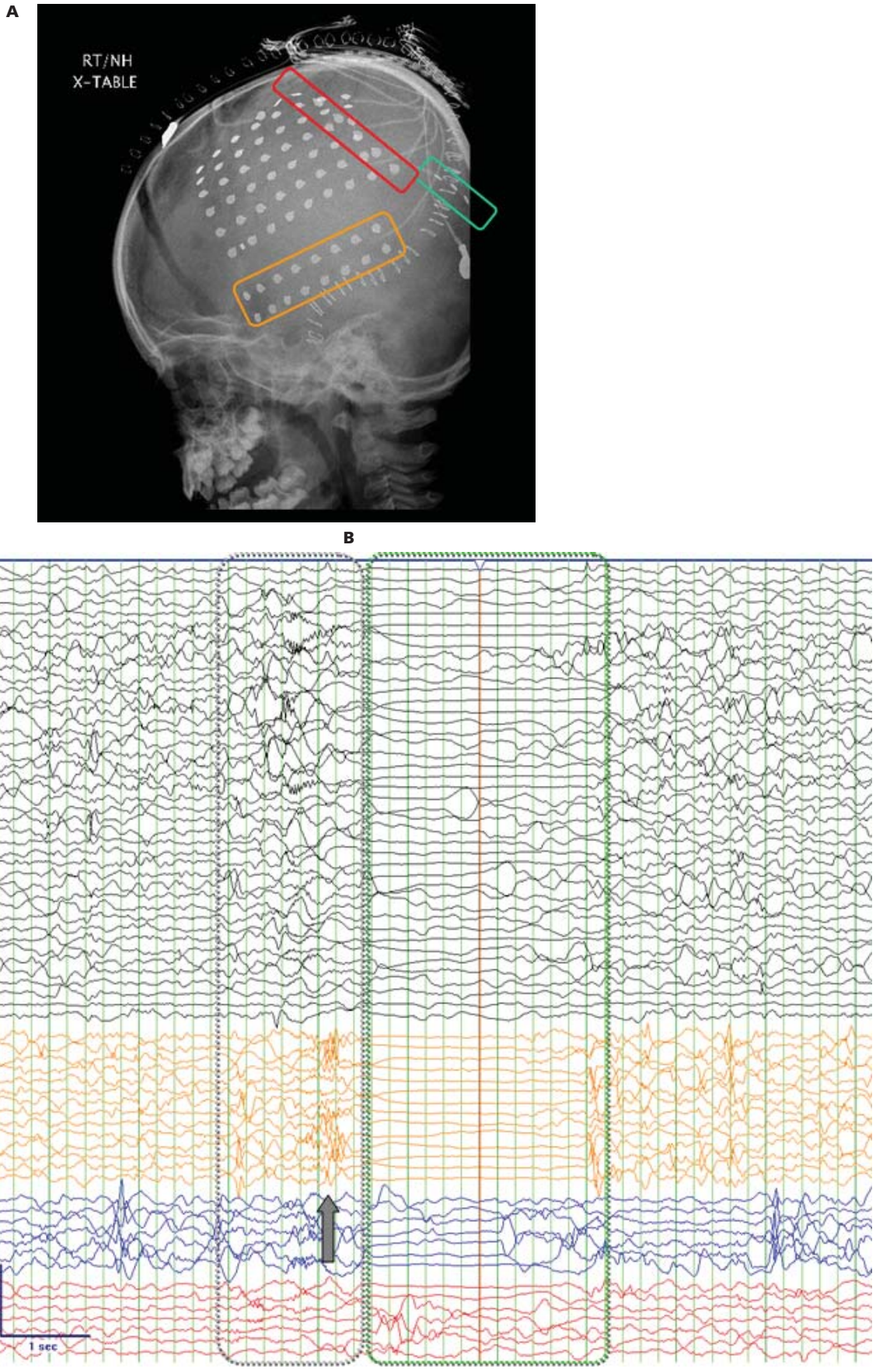

FIGURE 16-5. a. Lateral skull x-ray revealing subdural electrodes consisting of a 48-contact grid over right frontoparietal cortex, a 16-contact grid over right temporal cortex (orange), and two 8-contact strips over the interhemispheric region (red) and occipitotemporal cortex (blue). b. EEG showing seizure onset with a burst of high-amplitude paroxysmal discharges in the right temporal region (arrow, surrounded by purple line), followed by widespread suppression of background activity throughout the convexity (green).

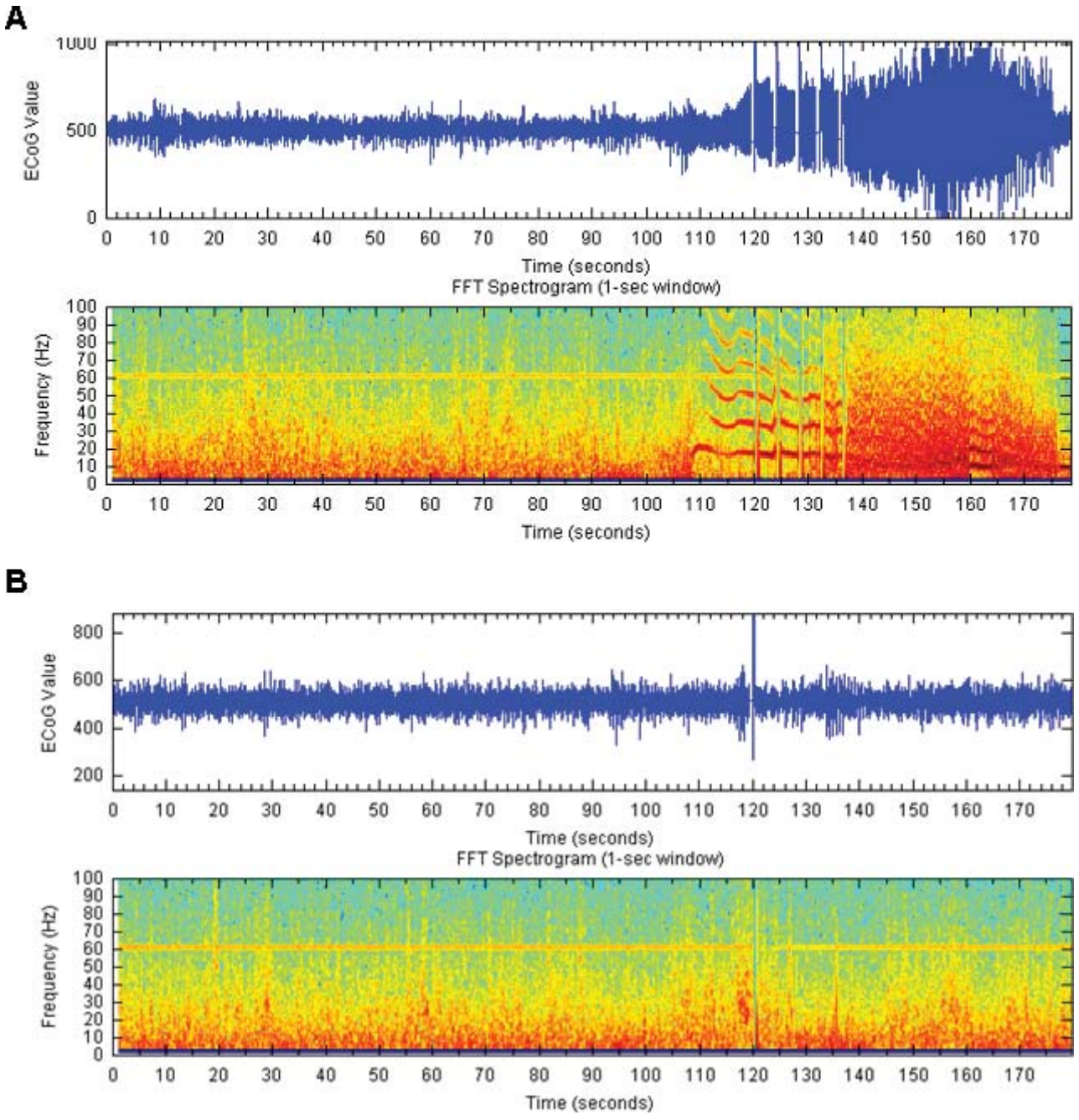

FIGURE 17-4. Time series and spectrograms of electrographic seizures receiving late (A) and early (B) stimulation relative to the seizure onset, using the implantable RNS System. Note that the seizure continues to evolve when focal stimulation is delivered several seconds after the onset of the seizure (A), whereas the electrographic activity does not evolve when focal stimulation is delivered earlier (B).

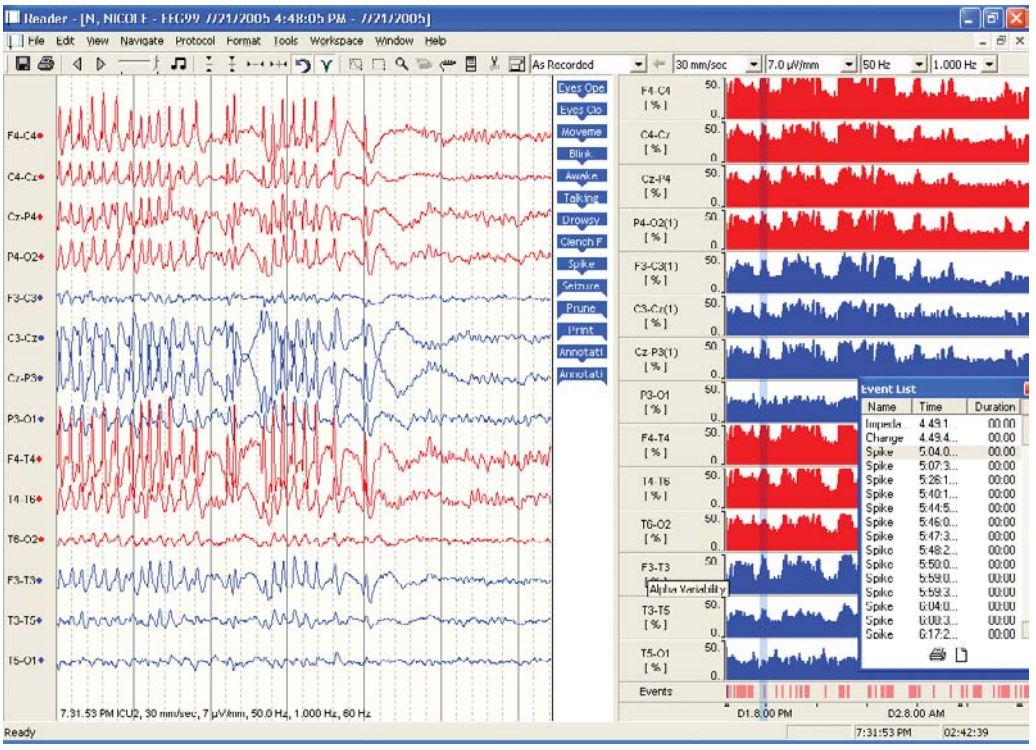

FIGURE 22-2. The recording shows an example of the use of quantitative EEG in detecting seizure activity. In many patients the finding of increased amplitude of total power and/or the alpha-delta ratio occur with electrographic seizures. Once identified, this spectral finding can be used to reliably and rapidly identify high-amplitude seizures or repetitive epileptiform spike discharges. The vertical highlight in the right panel that displays quantitative EEG changes corresponds to the EEG displayed in the left panel where high amplitude epileptiform activity is present during the first 4 seconds of recording.

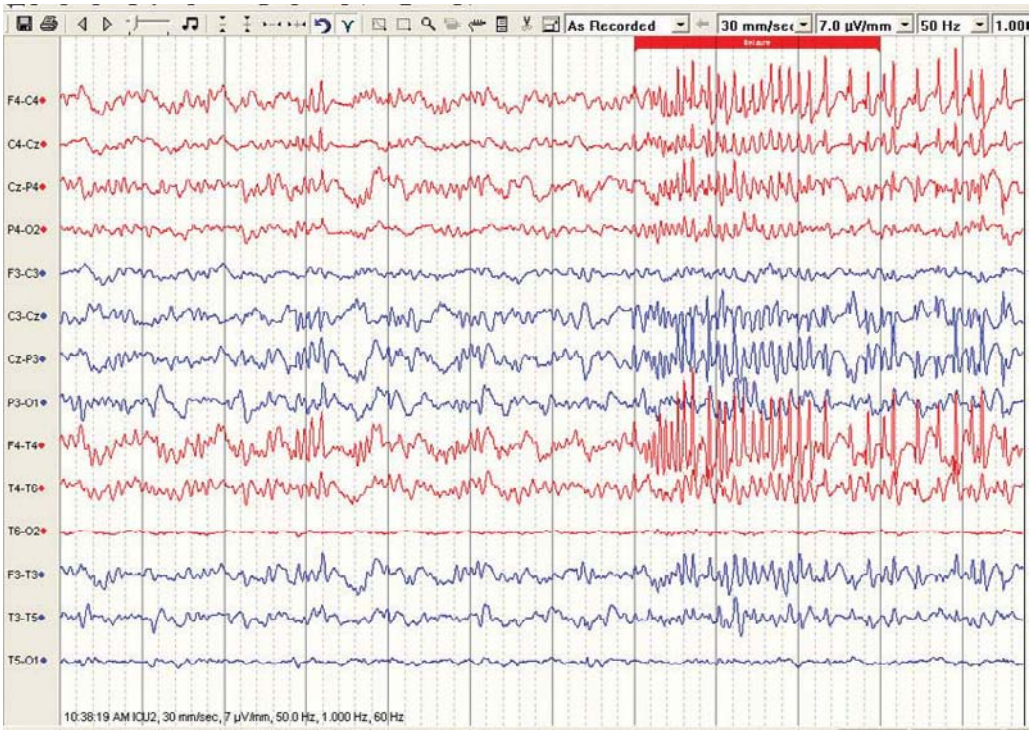

FIGURE 22-4. EEG monitoring in a patient with head trauma shows a nonconvulsive (subclinical) electrographic seizure clearly seen beginning in the eighth second of the recording (predominantly involving F4, C4, and Cz) that was easily and reliably identified by increases in quantitative EEG amplitude on the bedside spectral display.

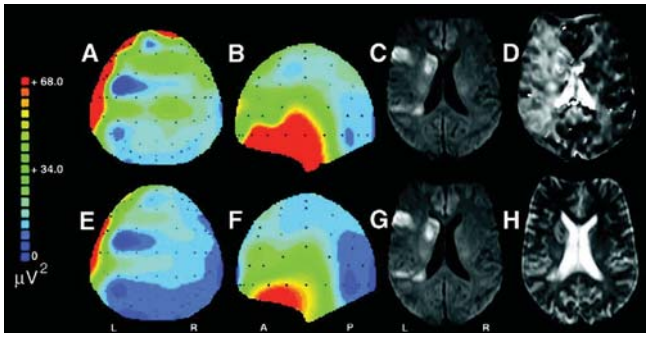

FIGURE 23-3. Correlation of early change in EEG focal delta power with outcome and imaging in acute ischemic change: example with early decreasing delta power and excellent early recovery. A and B: axial and left lateral EEG scalp delta power maps acquired 6.5 hours after onset of symptoms. C: initial DWI (6 hours). D: initial mean transit time (MTT) map. E and F: axial and lateral delta power maps at 13 hours. G: 15-hour DWI scan. H: 30-day T2 MRI. (Adapted from Finnigan et al. (36).)

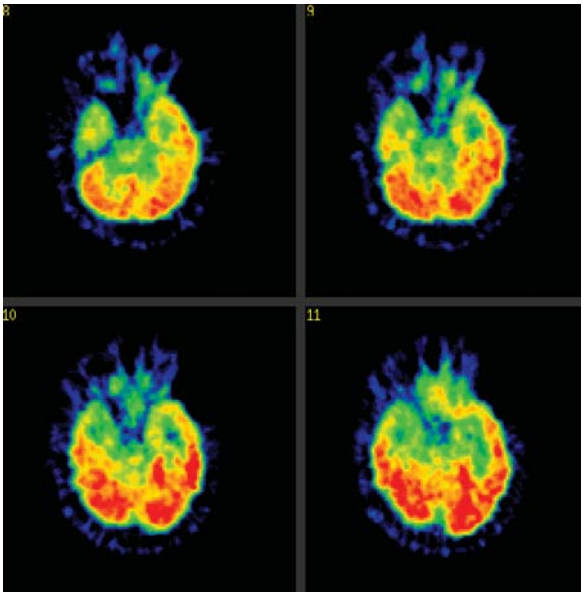

FIGURE 24-3. ^{18}FDG-PET scan showing focal hypometabolism.

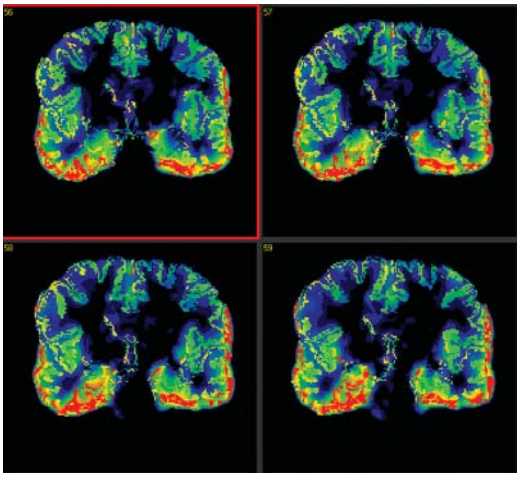

FIGURE 24-4. FCWAY PET.

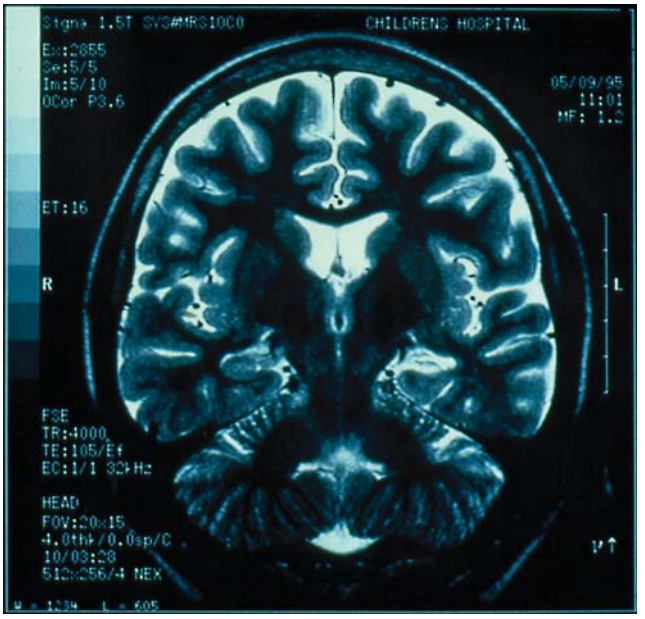

FIGURE 24-1. An 8-year-old with left mesial temporal sclerosis (MTS). Fast spin-echo sequences perpendicular to the long axis of the hippocampal formation demonstrate the characteristic findings of MTS: atrophy and increased signal. Right image is left brain.

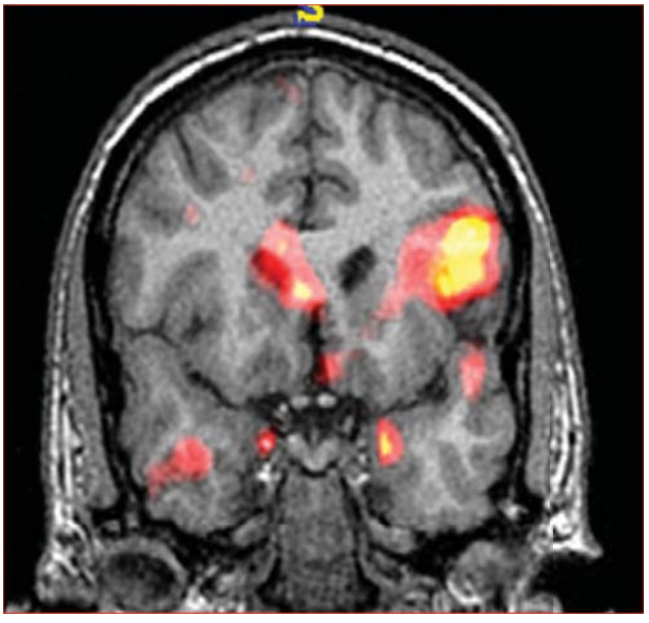

FIGURE 24-5. Ictal SPECT. Prominent left frontal hyperperfusion (right side of photo). MRI and routine EEG were normal. Intracranial monitoring confirmed the left frontal localization of seizures. Pathology was focal cortical dysplasia with balloon cells. The patient had been seizure-free for 9 years after surgery in 1998. Courtesy of Dr Gregory Cascino, Mayo Clinic.

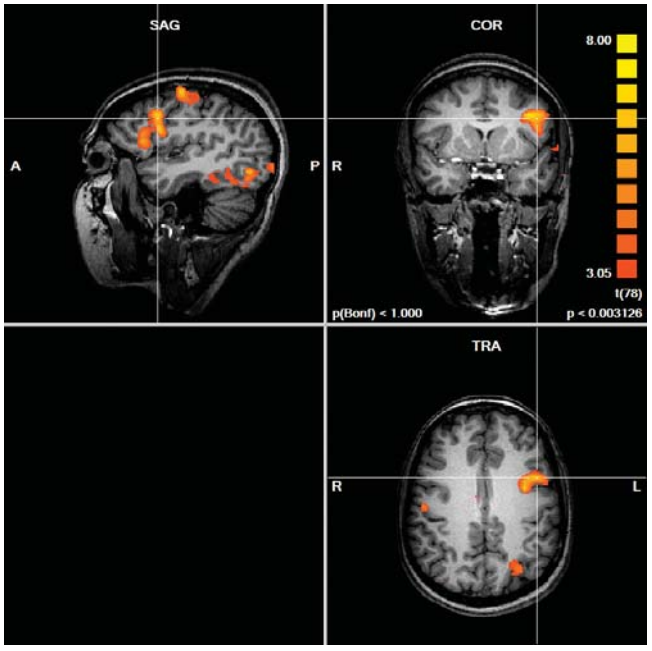

FIGURE 25-1. Left hemisphere language activation using a noun–verb association task, demonstrating prominent left frontal task-related activation (Loring et al. (28)).

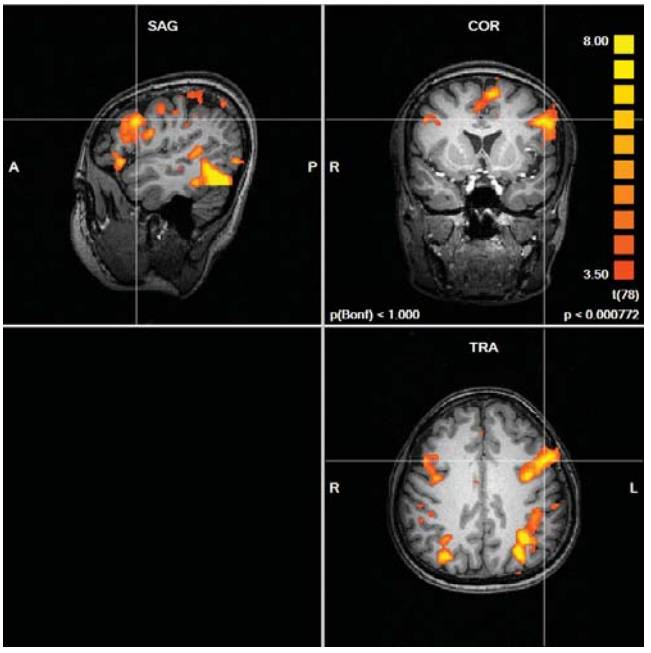

FIGURE 25-2. Language activation using fMRI noun–verb associating tasks in a left-handed patient. Note bilateral language activation (L>R).

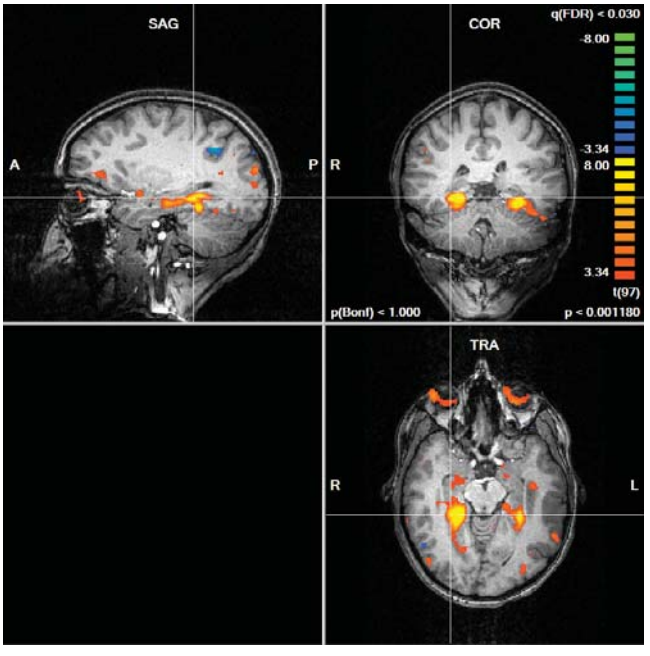

FIGURE 25-3. Bitemporal activation using scene encoding and tasks with pixilated scene control. Note bitemporal (R>L) activations involving the mesial temporal lobe region (Binder et al. (73)).