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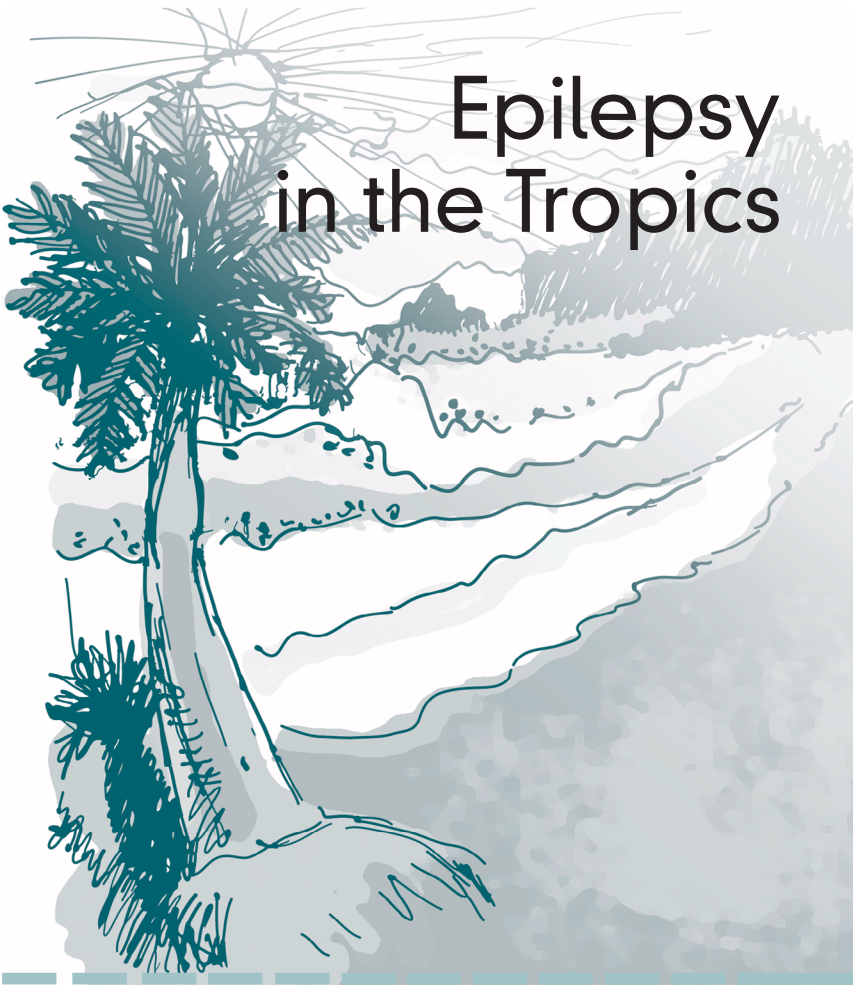

Epilepsy in the Tropics

J.M.K. Murthy
Nimal Senanayake

v a d e m e c u m

Epilepsy in the Tropics

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Dedication

To all people with epilepsy in the tropics

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Preface

The global belt demarcated by the Tropics of Cancer and Capricorn includes a large part of Asia, and most of Africa and Latin America where more than a third of the world's population live. In this tropical belt, epilepsy is a major public health problem, in terms of the numbers affected as well as in terms of its impact on the affected individuals and their families.

Epilepsy in the tropics has features that are distinct to those seen in the temperate zones. The prevalence is higher, as much as ten-fold in certain localities; as to the reason for this high prevalence there is no scientifically validated explanation. The manifestations show clear-cut differences with symptomatic epilepsies and therefore partial seizures accounting for a higher percentage in the tropics than in the temperate countries. Also, acute or remote symptomatic seizures are a dominant feature in the symptomatology of most tropical diseases. Peculiar forms of reflex epilepsies such as hot water epilepsy and eating epilepsy confound the spectrum of clinical presentation. On the other hand, facilities for investigation and treatment of epilepsy in the tropics are meager. In many areas, clinicians have no access to neuroimaging or electroencephalography. Even the basic antiepileptic drugs may be in short supply. To complicate matters, the stigma of the disease renders patients social outcasts, and therefore they hide the disease and avoid medical care. These factors make the care of patients with epilepsy in the tropics a challenge. This book is an attempt to look more closely at these many facets, which make epilepsy in the tropics a subject by itself.

Epilepsy in the Tropics, to our knowledge, is the first and the only book written on this subject. The chapters are arranged in seven sections focusing on epidemiology, diagnosis, symptomatology, clinical biology, treatment, economics, and health care. Authorities from different parts of the world who have made significant contributions in the respective fields have contributed to these chapters bringing out the distinct features, patterns, problems, and the economics of epilepsy and epilepsy care in tropical countries. This will be a guidebook for professionals in tropical countries engaged in the care of people with epilepsy. We also believe that this book will be of

relevance to all those who are interested in tropical medicine and neurology as well as epilepsy, irrespective of whether they belong in the tropics or in the industrialized world. It is our fervent hope that this book, while revealing the spectrum and the scope of seizure disorders in the tropics, will serve as a foundation for further studies and research in this field.

J.M.K. Murthy, M.D., D.M.
Nimal Senanayake, M.D., Ph.D., D.Sc.

Chapter 1

Epilepsy in Developing Countries: Historical Perspective

Nimal Senanayake

'The ocean,
who embraced the land,
crying out loudly,
its high waves fluttering like hands,
throwing out foam,
He (Krishna) suspected to be
a person suffering from Apasmara'

Magha, the great Sanskrit poet of the seventh century A.D., in his famous epic-*'Sisupalavadha'*, giving a vivid description of the island, *Dwarakapuri* on the Western coast of Gujarat in India, compared the ocean with a patient having an epileptic seizure.

Epilepsy, or the falling sickness, not only has a much older history than any of the other individual nervous or mental disorders, but it has also occupied people's minds to a much larger extent than the majority of ailments to which the genus *Homo sapiens* is susceptible.[1] A recently discovered tablet in *Sakikku* or 'all diseases', a Babylonian 'textbook' of diagnostic medicine, appears to provide one of the oldest accounts of epilepsy in existence, written originally in the reign of the king Adad-aplaiddina between the years 1067 and 1046 BC. Referring to *antasubbu*, a Sumerian term meaning 'the falling disease', the tablet contains descriptions of what today we would call tonic-clonic, absence, Jacksonian, complex partial and even gelastic seizures. Also described are prodromal symptoms, auras, postictal phenomena, provocative factors, interictal emotional disturbances, and temporal and prognostic aspects of epilepsy. Throughout the text, the ancient conception of epilepsy as a supernatural disorder due to invasion of the body by demons is very evident, sometimes with individual names for the demons associated with particular seizure types.[2]

The ancient Hebrews regarded convulsive seizures and epilepsy as sacrosanct with religious, magical or divine causes, and called it *morbus sacer*, the 'sacred illness' or the 'holy illness'.[3] This tradition persisted until the 17th century, though the effort to counter it with rational explanations also began very early. One of the Hippocratic writers in the fourth century B.C. denied that epilepsy was sacred in any sense, asserted that its seat was in the brain, and, as a humoralist, diagnosed its cause as an excess of phlegm in the brain rushing into the blood vessels of the body. Another writer in the same tradition ascribed seizures to a mixture of blood and air.[4]

Hindu mythology has a deity specializing in convulsions by the name of *Grahi*, which means 'she who seizes'. She had never been very popular among the people,

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1 for she had a more successful competitor in *Kurkura*, the dog-demon, who was frequently invoked in cases of the falling sickness.[1] Epilepsy, no matter what its immediate causation may be, was frequently thought of as a punishment inflicted upon the individual for evil deeds or for the breaking of certain taboos. As related in the Nidanam Sthanam section of *Charaka-Samhita,* epilepsy, like the other diseases mentioned in the legend, is evidently a punishment for participation in the forbidden sacrifice. Daksha is one of the sons of Brahman, the Grandsire of the universe. He made preparations to perform a grand sacrifice without giving to *Mahadeva* any share of the offerings. *Mahadeva,* whose ire was aroused, came with his ghostly army and destroyed the sacrifice. Everybody flew away in fear.

"…In consequence, again, of their contact with various kinds of noxious creatures and impure objects arose the different varieties of epilepsy…"

Another Hindu belief is that *apasmara* in this life is the result of cheating in a previous state of existence. *Kamma* is a concept in Buddhist philosophy, but epilepsy is not singled out. The *Culakamma-vibhanga Sutta* of the *Majjhimanikaya,* states that if anyone causes injury to other beings and torments them with hands, clubs or weapons, such a person, when reborn as a human being, may be subject to many diseases as a consequence of his bad *kamma*. In the *Sivaka Sutta* of the *Samyutta Nikaya* it is mentioned that some diseases that people suffer may be due to their past *kamma,* but *kamma* is only one explanation. There is also a reference to a *Bikkhu,* whose good *kamma* made him free of diseases such as *apasmara* in numerous rebirths.

Apasmara is mentioned along with, leprosy abscess, skin disease, and asthma, as *panca-abadha*. Ordination was prohibited for people suffering from those five diseases. The circumstances which led to this prohibition are mentioned in the *Vinayapitaka.* At one time, these five diseases became very common in *Magadha.* Many patients wanted Jeevaka- the famous physician, to treat them. Jeevaka refused, because he was fully engaged with service as the royal physician and also, being a devoted Buddhist, looking after the health of the *bhikkhu* community. The patients thought that the best way to get Jeevaka's attention was to become Buddhist monks. They began to enter the Buddhist order of monks in large numbers. Many of them, once cured, reverted to the lay life. This was reported to the Lord Buddha and the Buddha laid down the regulation that people suffering from these diseases should not be ordained. However, the *Vinayapitaka* also rules that if a monk is admitted to the Buddhist order and suffers from such a disease, no ordained monk should, when he wants for some reason to silence another monk, disparagingly refer to him as an epileptic etc. There is also the requirement that, if anyone gets such a disease after being admitted to the Order, the teacher or the preceptor should take proper care of him as long as he lives.

Epilepsy, on various occasions, has been looked down upon as a transmissible, contagious disease. Rhazes, in Arabic medicine, included epilepsy among the eight cardinal contagious diseases, the others being bubonic plague, phthisis, scabies, erysipelas, anthrax, trachoma, and leprosy.

The Bassa and Kpelle people in Liberia believe that the foam of an epileptic person is contagious. This has grave social consequences in that the patient is socially isolated and stigmatized.

For the Bassa and Kpelle tribesmen in Liberia, the evil spirits or *'ginna'* consist of dead family members who can harm those who are still alive, and *'mame wata'*- water spirits- conceptualized as a white lady, a mermaid, who lives in the water.

Mame wata is believed to transform into a handsome man who can harm people and cause epilepsy.

The Wapogoro tribesmen in Tanganyika consider epilepsy as a possession by the devil- *'shetani'*. Touching the patient during a seizure is considered very dangerous, because the spirit could then leap over into the other person. People specially fear the excretions, particularly the saliva, which froths from the mouth. If an epileptic patient falls into the fire, nobody dares to pull him out.

Belief in witchcraft is part of a religious thought system, and is common throughout Africa. Water or food poisoned by witchcraft may cause epilepsy. Often, the actions of the witches happen when a person is asleep. The Bagandas, living in rural areas of Uganda, believe that epileptic seizures are caused by the movement of a lizard within the head, present since birth or "sent" through the agency of witchcraft. Treatment comprises shaving the scalp and applying a horn to suck the lizard out.

The Indian medical system, however, began to leave the dim borderland of the supernatural to find a rational habitation. *Vedas* (veda = knowledge), the ancient Indian texts written in the period c1500 to c800 BC, include the *Atharveda* and *Rigveda* which specifically mention the healing arts, *Athavale*.[5] *Ayurveda* ('the science of life'), designated epilepsy *Apasmara*: *apa* meaning negation or loss of, and *smara* meaning recollection or consciousness. Atreya, the father of Indian Medicine, defined *Apasmara* as a 'paroxysmal loss of consciousness due to disturbance of memory and (of) understanding of mind attended with convulsive seizures'. This places on record the origin of epilepsy in the mind, about 500 years before Hippocrates (460-355 BC), the father of Greek medicine, placed the 'sacred disease' in the mind.[5]

The seizure itself was thought by Atreya to be set off by the 'morbific humours', which normally lay dormant above the heart, but could be aroused by a sudden overwhelming emotion. They then entered the heart, and via the circulation reached the brain where they triggered off a seizure. 'Morbific humours' were called *vata, pitta* and *kapha*. The Indian medicine believed that molecules of five basic elements constituted the body mass of all living creatures, viz space, air, energy, water and earth. *Vatha* contained molecules of air, wind or ether, and was constantly moving, a stimulus. *Pitta,* with molecules of energy, heat or fire, was the impulse (which travelled to the brain). *Kapha* was earth, solid, and was the brain and nervous tissue. Atreya regarded that one and the same cause may lead to many diseases; or, many causes may lead to one and the same disease. Accordingly, it was suspected that epilepsy could have many causes.[5]

Four different types of *apasmara* were described, the *vata, pitta* and *kapha* and the tridiscordant, the last being the worst of all.[5] An actual attack of *apasmara* consisted of falling down, shaking of the hands, legs, and body, rolling up of the eyes, grinding of the teeth, and foaming at the mouth. Aura was recognized, and was called *apasmara poorva roopa*. A large number of symptoms indicative of aura included subjective sensation of sounds, sensation of darkness, feeling of delusion, and dream-like state. *Apasmara* was considered a dangerous disease that was chronic and difficult to treat. Among the causes mentioned were transgression of dietary rules, eating of contaminated food, abuse of rules of hygiene, weakness and extreme mental agitation by lust, fear, anxiety or anger. Treatment included correcting the etiological factors and dietary regimen, and avoiding dangerous places that may result in injuries.[6]

In the West, the 19th century produced a transformation in thinking about the brain and neural system. Studies by physicians and neuroscientists of the calibre of

W.R. Gowers, Sir Charles Locock, Charles Edward Brown Sequard, John Hughlings Jackson, Jean Martin Charcot, Paul Broca, Carl Wernicke, Gustav Fritsch, Edward Hitzig, and David Ferrier contributed to that revolution, and a better understanding of epilepsy followed. In the early part of the 20th century, the development of effective medication paralleled progress in surgical techniques, especially the improvement in diagnostic insight provided by the electroencephalogram (EEG), which Johannes Berger developed between 1929 and 1938. Wilder Penfield and Hubert H. Jasper became the leading authorities on surgical treatment of epilepsy since World War II.[7]

The Greek word *epilepsia* means 'a taking hold of, a something seizing the subject as though that "something" were outside himself'.[8] Since the time of Hughlings Jackson, epilepsy had been defined in physiological terms, being 'the name for occasional sudden, excessive, rapid and local discharges of grey matter'.[9] An epileptic seizure, therefore, is a symptom of disease, produced by an abnormal, excessive neuronal discharge within the central nervous system (CNS). A comprehensive clinical definition of seizures and epilepsy is more difficult, because of the varied clinical manifestations produced by cerebral neuronal discharge. However, an epileptic seizure may be defined as an intermittent, stereotyped, disturbance of consciousness, behaviour, emotion, motor function, or sensation that, on clinical grounds, is believed to result from cortical neuronal discharge. Epilepsy can then be defined as a condition in which seizures recur, usually spontaneously.[9]

After a long circuit through ages of magic, black humours, and blank disinterest, medical thought has returned to the affirmation that epilepsy, like many other diseases, is rooted in natural causes. In terms of today, epilepsy is not cryptogenic, born of ignorance, but is merely a disturbance of the normal rhythm of the brain. In nature, rhythm is inherent; in man, dysrhythmia means disease; in brain, paroxysmal dysrhythmia spells epilepsy.[7]

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Chapter 2

Epidemiology of Epilepsy in Developing Countries

Nimal Senanayake

The impact of geographic, climatic, demographic, social, and economic characteristics in developing countries is adverse in terms of the frequency of epilepsy. Information is relatively limited, and actions have to be based frequently on dramatic numbers; in Malawi between 1983 and 1986, 60% of psychiatric outpatients and 30% of all psychiatric and neurological cases were related to epilepsy.[1] Most of the earlier epidemiological studies on epilepsy in developing countries derived the information from hospital-based data, which made extrapolation to the general population highly conjectural. Both the hospital-based and recent population-based studies reported a higher prevalence of epilepsy when compared to developed countries. The reasons for this high prevalence are not precisely known, but is attributed to some of the geographically specific etiological factors such as premature birth and birth-related injuries, traumatic brain injury, and infections including multiple parasitism.[2] This chapter reviews the epidemiology of epilepsy in developing countries.

Definitions

Definitions are of crucial importance in epidemiological studies. Neurosciences Program research protocol of the World Health Organization (WHO) designed to study the prevalence of neurological disorders in developing countries,[3,4] defines epilepsy as two or more afebrile seizures unrelated to acute metabolic disorders or to withdrawal of drugs or alcohol. Most, but not all, epidemiological studies on epilepsy have adopted similar such definitions. However, some studies particularly lacked distinction between provoked (acute symptomatic) and unprovoked seizures. There is also a failure to define criteria for disorders related to seizures. "Active epilepsy", a concept that better reflects the segment of epilepsy population that needs allocation of health care resources, is defined as those persons who have had seizures during the previous one to five years or those receiving antiepileptic drugs (AED). However, there is no consensus on the maximum duration since the last seizure (for those not on AED) to be called active epilepsy. This lack of uniformity in the definitions and in the methods employed in different studies needs consideration while interpreting the data presented below.

Incidence

In developed countries, the reported age-adjusted incidence of epilepsy ranges between 24/100,000 and 53/100,000 person-years. In the studies, which included persons with a single unprovoked seizure, the incidence ranged between 26/100,000 and 70/100,000.[5] Relatively few incidence studies are available in developing countries. Probably in these countries it will be methodologically difficult to conduct

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prospective longitudinal studies of large population samples. In Mariana islands in 1960s, three separate community-based studies reported different incidence rates,[6-9] the range varying from 30 to 47.3 per 100,000 population. However, more recent studies reported much higher incidence rates when compared to developed countries: 114/100,000 in a rural community in El Salvador district in Chile;[10] 73.3/100,000 in Ulanga, a rural district in Tanzania;[11] and 122 to 190/100,000 in a rural Andean region in Ecuador.[12] In the Ecuador study, the incidence for neurologically confirmed cases was about 30% lower. The study also took into account all persons with new onset nonfebrile seizures (including acute symptomatic seizures) and some children with multiple febrile seizures. However, the Yelandur, rural community-based study in south India,[13] reported an incidence of 49.3/100,000, which is similar to the observed incidence in developed countries.

Because of the possible differences in the case-inclusion criteria and methodology, comparison across these studies is difficult. Nonetheless, it appears that the incidence of epilepsy is higher in the tropics than in countries with temperate climates.

Age-Specific Incidence

In developed countries, epilepsy is a disease with onset at extremes of life.[5] However, incidence studies in Tanzania,[11] Chile,[10] and Ecuador[12] reported a single peak in young adults with no increase in later life. The Yelandur study,[13] however, is an exception. In this study, the age-specific incidence was similar to the observed age-specific incidence in developed countries.

Sex-Specific Incidence

Incidence of epilepsy or of unprovoked seizures, in most studies in developed countries, is higher in males. This seems true even after correction for the higher incidence of definitive risk factors for epilepsy in males, such as head injury, stroke, and central nervous system (CNS) infection.[5] The few studies in developing countries reported similar observations. The exception is the Andean study in Ecuador[12] with a male to female ratio of 0.8. This study, however, also included persons with acute symptomatic seizures.

Prevalence

Prevalence of a disease in a community is a measure of interaction of factors such as incidence, remission and mortality. It is also affected by factors such as migration or access to multiple sources of healthcare. Prevalence reflects survival and chronicity of an illness than frequency.[5] With a chronic disease like epilepsy, the number of patients accumulates with time; hence the prevalence tends to be high even if the incidence is low. Conducting a prevalence survey is logistically less demanding than conducting an incidence survey. Many prevalence studies in diverse populations have been reported during the past few decades, providing intriguing clues to guide hypotheses that can be tested in properly designed studies and proved valuable in planning healthcare.[5]

In developed countries the prevalence of epilepsy is about 3 to 9 per 1000 population,[14] although figures as low as 1.5/1000[15] and as high as 18.6/1000,[16] have been reported. These variations are often related to differences in the methodology of case detection and definition of epilepsy, rather than true differences in the prevalence.

Data Collection

Most of the prevalence studies in developing countries have concentrated on rural populations. Some studies were restricted to selected populations such as certain occupational[17] and ethnic[18] groups or to a particular age category.[19] In most community-based surveys, door-to-door inquiries by health workers have been the most widely employed method for case detection. Some studies have depended on the medical records maintained at hospitals, general practitioners' clinics or health insurance offices. The use of medical records for case detection is far less reliable, particularly so in developing countries where there is no well-organized healthcare delivery systems or comprehensive record keeping systems. Ignorance, stigma or superstition may prevent patients from seeking medical advice. Also, for a disorder such as epilepsy, many patients may choose to go to a traditional healer rather than to a western medical practitioner. A community survey in Sri Lanka revealed that only half of the persons with epilepsy were attending a western medical practitioner for treatment at the time of the survey. This was in spite of the availability of a state-run, free health care service.[20]

Community surveys, in general, adopt a two-phased design, the first phase screening interviews by field workers, and the second phase medical evaluation by neurologists. The successful case finding depends on the screening questionnaire, and how it is administered. A common problem is the under-reporting of cases. Because of the associated stigma, patients and their families tend to conceal information about the illness. In a study in Sri Lanka, some of the persons with epilepsy revealed their epilepsy only when they had sufficient confidence that the information about their epilepsy would be treated confidentially and also when they had seen the benefits of the program.[20] Another source of under-reporting is the possible exclusion of certain seizure types, absences and complex partial seizures of temporal lobe origin, as these may not be readily recognized as forms of epileptic seizures by the patients and their family members or by the field workers. In some communities, patients with epilepsy may be expelled from their homes as outcasts and may not be available for case ascertainment.[19] Notwithstanding these shortcomings, this form of survey is considered to be the optimum method to detect most of the active cases of epilepsy in the community.[21] Guidelines for such epidemiological surveys and the details of the methodology are available in several excellent publications.[22-26]

Prevalence Rates

Selected community-based prevalence data on epilepsy in developing countries are summarized in Table 1 and Figure 1. Most of the studies prior to 1980, including some pioneer studies, have been omitted because the results of more recent and well-designed surveys have become available. Most of the recent studies have followed the WHO protocol or a similar such protocol. Even then, it should be remembered that the results are not necessarily comparable, because of other compounding factors. These data, however, provide a measure of the magnitude of the problem of epilepsy in developing countries and highlight certain geographic trends at a global level.

Areas of Low Prevalence

Some of the studies in developing countries have reported very low prevalence rates, 3 per 1000 in south India[54] and 2.47 per 1000 in the Kashmir valley.[55] The study in the Kashmir valley used the WHO protocol for the survey. One of the

Table 1. Prevalence studies of epilepsy from developing countries

Ref. ID	Country	Method	U/R	Year	n	P	Range	
	Africa							
27	Bénin (Agbogbomé)	HHS	R	1995	530	24.5	10.9-38.1	
28	Bénin (Savalou)	HHS	R	1996	1443	15.2	8.7-21.7	
29	Benin (Zinvie)	HHS	R	2000	3134	15.9	(33.5-35.1)	Range: Capture -recapture method
30	Burkina Faso	HHS	R	1993	16627	10.6	9- 12.2	
31	Cameroon	HHS	R	1989	500	70	46.3-93.7	
32	Cameroon (Bilomo)	HHS	R	1998	1900	58	46.9-69.1	
33	Ethiopia (Butajira)	HHS	R	1990	60820	5.2	4.6-5.8	
34	Ivory Coast	HHS	R	1988	1176	7.6	2.5-12.7	
35	Ivory Coast	HHS	R	1990	309	74	43-105	
36	Ivory Coast (M'Brou)	HHS	R	1995	920	59	43-75	
37	Kenya	HHS	R	1988	2960	18.2	13.2-23.2	
38	Libéria	HHS	R	1983	4436	28	23-33	
39	Mali	HHS	R	2000	5243	15.6	12.2-19	
40	Mali (Bamako)	HHS	U	2000	4074	11.3	8-14.6	
41	Nigéria (Aiyete)	HHS	R	1982	903	37	24.2-49.8	
42	Nigéria (Igbo-Ora)	HHS	U	1987	18954	5.3	4.2-6.4	
43	Nigéria	HHS	R	1989	2925	6.2	3.3-9.1	
44	Sénégal	HHS	R	1986	7682	8.3	6.2-10.4	
45	Sénégal	HHS	R	1996	2803	21	15.5-26.5	
11	Tanzania	HHS	R	1992	18183	10.2	8.7-11.7	
46	Togo (Akebou)	HHS	R	1996	4182	13.1	9.6-16.6	
47	Togo (Kloto)	HHS	R	1991	19241	12.3	10.7-13.9	
48	Togo (Kozah)	HHS	R	1989	5264	16.7	13.1-20.3	
49	Togo (Tone)	HHS	R	2000	9143	18.6	15.7-21.5	
50	Uganda	HHS	R	1996	4743	13	9.7-16.3	
	Asia							
51	India (Bangalore)	HHS	U/R	1996	51502		5.8 U, 11.9 R	Act ep
52	India (Bengal)	HHS	R	1996		3.06		

Table continued on next page

Table 1. Continued

Ref. ID	Country	Method	U/R	Year	n	P	Range	
	Asia							
18	India (Bombay)	HHS	U	1987		4.7		Select group- Parsis
53	India (Chandigarh)	HHS	R	1993		8.7		
54	India (Gowribadanur)		R	do	39926	5.58		
54	India (Gowribadanur)	HHS	Semi-U	1987	17734	2.48	1.8-3.3	
55	India (Kashmir)	HHS	R	1988	63645	2.47	2.1-2.9	
56	India (Kerala)	HHS	Semi-U	2000	238102	4.9		
13	India (Yelandur)	HHS	R	1998	64963	4.38	3.91-4.63	Act ep
57	Pakistan	HHS	U/R	1994		9.99	7.4 U, 14.8 R	
20	Sri Lanka	HHS	R	1989	80408	9.02		
58	Vietnam	HHS	R	2001	80,557	4.9		4.6 for Act ep
	Latin America							
59	Bolivia	HHS		1999	10,000	12.3		Act ep 11.1
60	Brazil	HHS	U	1987		13.3	10.8-16.2	
61	Colombia	HHS	U	1978		19.5	16.5-22.6	
62	Colombia	HHS	R	1984		17		
63	Ecuador	HHS	R	1985		17.1	10.1-26.7	
12	Ecuador	HHS	R	1992			12.2-19.5	Act ep 6.7-8.0
64	Guatemala	HHS	R	1996	1882	8.5		
65	Mexico	HHS	R	1990		8		
66	Panama (Panama City)	HHS		1988		22		
67	Panama (Changuinola)	HHS	R	1990		57	33.5-88.2	Select group-Guaymi Indians
68	Venezuela	HHS		1985		17.5		
69	Venezuela	HHS		1991			4.1-22.6	
	Oceania							
9	Guam	HHS	R	1968		3.4	2.2-5.1	
7	Guam	HHS	R	1972		4.9	3.4-6.7	

U/R = urban and rural, n = number of patients, P = prevalence, HHS = house-to-house survey

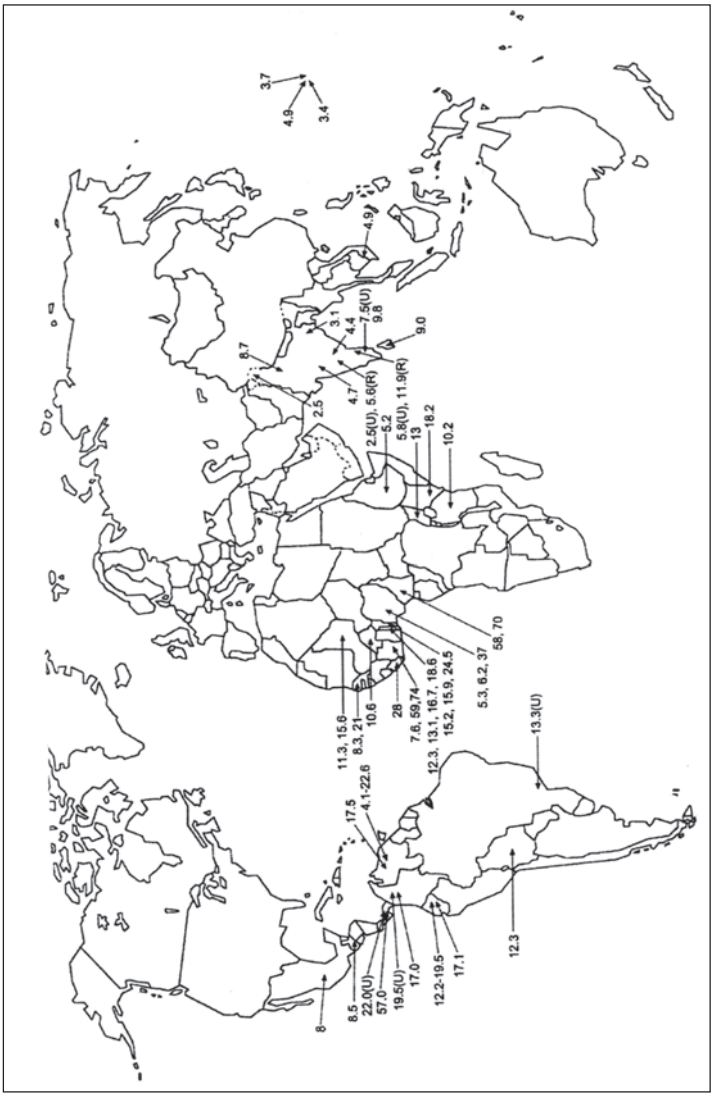

Figure 1. World map showing prevalence rates of epilepsy in the tropics.

possible reasons for this low prevalence rate in this study may be failure to detect epilepsies with absences, simple partial and complex partial seizures. But this shortcoming is applicable to all surveys of this nature. The other possible reason could be high infant mortality rate observed in this region. However, in a community with such a high infant mortality and morbidity, the prevalence of epilepsy is likely to be high.

Areas of High Prevalence

Studies in Nigeria

Aiyete, about 100 km southwest of Ibadan, recorded a prevalence of 37/1000[41] and Igbo-Ora town found a prevalence of 5.3/1000.[45] Both studies were conducted by the same author using the WHO protocol. Aiyete and Igbo-Ora are inhabited by the same ethnic group and are only 20 km apart. One plausible explanation for this marked difference in the prevalence rates is concealment of the illness because of the stigma associated with epilepsy among the residents of Igbo-Ora and a positive attitude of residents of Aiyete to declare their illness. But, a more possible logical explanation for the low prevalence in Igbo-Ora may be the availability of effective primary healthcare systems with emphasis on prevention of childhood infectious diseases, improved antenatal care, and health education.[42]

Studies in Liberia

In Liberia a very high prevalence rate has been reported in two remote inaccessible districts of Grand Bassa County.[38] The calculated prevalence rate from these studies was 49/1000.[70] The diagnosis of epilepsy (locally termed *see ee*) was based on clinical examination and witness of seizures. In a separate study in the same region, Goudsmit et al[38] reported a prevalence of 28/1000. No tribal group was preferentially affected. A positive family history of epilepsy was recorded in 53% of the cases. An etiologic factor could be documented in 47% of the cases. Infections of the CNS preceded the onset of the seizures in 38%. Seizure disorders appeared to have been introduced in the area approximately 30 years ago as computed from the year of onset and retrospective information provided by the elders in the community. Possible cause suggested for the high prevalence of this seizure disorder is exposure of genetically susceptible individuals to an environmental factor.

Studies in Tanzania

In Tanzania, Jilek and Jilek-Aall[71] reported a prevalence of 20/1000 in a Bantu population in Mahenge region. This figure, based on voluntary attendance to their clinic, was considered an underestimate. Possible causes suggested for the high prevalence were: birth related brain trauma, syphilis, malaria, parasitic infections, meningo-encephalitis, toxic enteritis in children, and chronic malnutrition. These factors, however important, do not fully explain the unusually high frequency of epilepsy observed in the tribal population. Owing to its marked geographical, cultural, and social isolation, the Wapogoro society is traditionally an endogamous system, which encourages marital union within the kin group, even between first cousins. This trend is more pronounced among families with epilepsy. Low social prestige and poor financial status prevent them from marrying brides from healthy families. Of the 201 patients, a family history of epilepsy was found in 154 (76.6%).

These findings strongly support a genetic basis for the high prevalence of epilepsy in the Tanzanian tribe. The authors revisiting the area 30 years later found that

over two thirds of the patients had died. In more than half of them the cause of death was related to epilepsy.[72]

Studies in Latin America

Highest prevalence rates have been observed in two studies in the Republic of Panama. A study in Panama City[66] using the WHO protocol documented a prevalence of 22/1000 for active epilepsy. A subsequent survey,[67] using the same methods, estimated a prevalence of 57/1000 among a select group of Guaymi Indians living on banana plantations in Changuinola. The two main risk factors identified were family history of epilepsy and history of febrile seizures. Assay of serum antibody to *Cysticercus* in patients and in control subjects excluded neurocysticercosis as an important etiological factor. Further investigations are needed to identify the possible etiological factors for the high prevalence of epilepsy in Latin American countries.

Age-Specific Prevalence

Prevalence rates increase with age, and in most studies in developed countries they reach their highest in the third and fourth decades[15,73] or later.[74,75] Age-specific prevalence in developed and developing countries is difficult to compare, given the marked differences in the age structure of the populations and the wide variation in the age-specific prevalence.[5] Most studies in developing countries have found highest prevalence in the second[20,33,41,42] and third decades,[9,11] but a few in the fifth decade or later.[63,76]

Sex-Specific Prevalence

Prevalence of epilepsy, similar to incidence, is higher in males than in females. However, this difference never reached statistical significance.[77] There are exceptions. In southeast England[78] and northern Norway[73] the reported prevalence is higher in females. Studies in developing countries have produced varying results, some recorded a high prevalence in males and others an equal prevalence in either sex, but some studies in Nigeria,[41,42] Tanzania,[11] Pakistan,[76] and Latin America[59,61,79] recording a higher prevalence in females. In one of the Nigerian studies,[42] however, the male to female ratio reversed when the prevalence rates were age-adjusted to the1970 U.S. population. A possible reason for high prevalence in females is that the social stigma associated with epilepsy might have made males to deny their illness during epidemiological surveys.[41]

Seizure Type

The proportion of cases with a specific seizure type based on the International Classification of Epileptic Seizures[80] is provided in several incidence and prevalence studies. In both Rochester[81] and Faroes Island studies,[82] partial seizure is the common seizure type accounting for slightly more than 50% of the incidence cases. Data from developing countries, several hospital-based studies, are presented in Table 2.

There are several possible sources of inaccuracy in these studies. One needs to consider these facts while interpreting the data. Partial seizures with secondary generalization can erroneously be diagnosed as primary generalized, if the symptomatology of focal onset before secondary generalization is missed or ignored. Certain seizure types: simple partial seizures, complex partial seizures of temporal and frontal lobe origin, absences, and myoclonic jerks, which do not manifest with marked

Table 2. Seizure type in the prevalence studies from developing countries

Ref.ID	Country	Author(s)	Year	n	Partial			Generalized					Unclass.		
					SP	CP	SGP	Total	GTC	Abs.	Myo.	Other	Total	Other	
	Africa														
83	Liberia	van der Waals et al	1983	123		17.9	44.7	62.6	37.4				37.4		
84	Nigeria (Ibadan)	Ogunniyi et al	1987	155	0.7	43.2	15.5	59.4	40.6				40.6		
42	Nigeria (Igbo-ora)	Osuntokun et al	1987	101	4	52		56	23	3			26		
85	Nigeria (Lagos)	Danesi	1985	945	24.7	32.9	16.7	74.3	17.4	1.2	0.9	2.9	22.4	3	
86	Tanzania	Matuja	1989	428	18	42.1	9.8	70	19.6	1.4	0.9	7.9	30		
11	Tanzania	Rwiza et al	1992	207	0.5	9.2	22.2	32 0 0	54.1	1	1	1.9	58 0 0	10.1	
	Asia														
87	India (Varanasi)	Joshi et al	1977	1000	46.6	5.8	12.2	64.6	5.4	2.8	1.2	4.2	16.3	19.1	Hospital -based
88	India (Bombay)	Bharucha et al	1988	66	1.5	6	47	54.5	42.4	1.5	1.5		45.4		Limited to the Parsis
55	India (Kashmir)	Koul et al	1988	157	3.2	1.9	6.4	11.5	72.6		1.9	4.5	79	9.6	

Table continued on next page

Table 2. Continued

Ref.ID	Country	Author(s)	Year	n	Partial			Generalized						Unclass.	
					SP	CP	SGP	Total	GTC	Abs.	Myo.	Other	Total	Other	
56	India (Kerala)	Radhakrishnan et al	2000	1175				58.8				30.6			
89	India (Yelandur)	Mani	1997		10.7	22.6		33.3				0.3	66.4		HWE excl.; *SP incl. SGP; **CP incl. SGP
89	India	Mani	1997		5.6	52.9		58.5	41.7			0.2	41.9		HWE incl.; *SP incl. SGP; **CP incl. SGP
76	Pakistan	Aziz et al	1997	241	4.9	4.9		9.8	80.5	0.8	5.8	11.6	98.7		
90	Sri Lanka (Kandy)	Senanayake	1993	1250	0.4	8.8	64.6	73.8	7.4	1.3	14.6		23.3	2.9	Hospital-based
								0					0		
	Latin America								0					0	
59	Bolivia	Nicoletti	1999	124	8.1		45.2	53.3	34.7	7.3		4.8	46.8		SP includes CP
64	Guatemala	Mendizabal	1996	16	6.2	37.5		43.7	50			6.2	56.2		

n = number of patients, SP = simple partial seizures , CP = complex partial seizures, SGP = secondry generalized seizures, GTC = generalized tonic-clonic seizures, Abs = absences, Myo = myoclonic

loss of consciousness or convulsions can easily be overlooked or misdiagnosed by field workers. Most of the studies did not utilize EEG routinely, limiting the diagnostic accuracy. Partial seizure with or without secondary generalization is the commonest seizure type. Complex partial seizures seem to be commoner than elementary seizures. High frequency of partial seizures probably suggests a high incidence of symptomatic epilepsy secondary to cortical damage caused by various insults in developing countries. Of the generalized seizures, tonic-clonic seizures are by far the commonest. But some studies reported a higher proportion of myoclonic epilepsies, mostly juvenile myoclonic epilepsy (JME), as in our own series from Sri Lanka.[90,91] The reported frequency of JME in developed countries in patients with epilepsy is 4% to10%.[92] Typical absences (petit mal) are under-represented in developing countries.[90,91,93,94] The frequency of these seizures in temperate countries is approximately 6%.[93] An EEG study in children in Nigeria[94] suggests that the frequency of absences is really low in developing countries.

Conclusion

The above observations highlight some of the difficulties in the neuroepidemiology of epilepsy. These problems are compounded in developing countries, particularly in places where physicians and neurologists may not reach large segments of the population, and where diagnostic methods such as EEG and neuroimaging may not be readily available. Other problems include the fact that the diagnosis of epilepsy is not always easy and may require EEG or video-EEG confirmation; classification of epilepsy and epilepsy syndromes has become complicated and poorly suited for field studies; the definitions change according to the different studies; and the inclusion criteria are not always clear. To complicate matters, in many cultures the stigma of having epilepsy renders persons with epilepsy into social outcasts or leads the family to conceal the disease resulting in under-reporting of cases. In many places in developing countries, due to cultural factors or to the simple fact that medications may not be available, the treatment of epilepsy is highly unsatisfactory. Some of these elements may also explain the reports of higher incidence and prevalence of epilepsy in developing countries. Further well-designed neuroepidemiological studies of epilepsy are mandatory to determine the magnitude of the problem, the economic burden, and the social perception in developing countries for implementation of appropriate public health measures.

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Chapter 3

The Prognosis of Epilepsy in Developing Countries

Samden D. Lhatoo and Josemir W. Sander

Prognosis in epilepsy is defined as the prospect of attaining complete freedom from seizures once a pattern of recurrent epileptic seizures has been established. Between 70 and 80% of people developing epilepsy will remit, while the remainder continue to have seizures despite optimum treatment. Remission usually occurs in the first five years. Thus for the majority of people, epilepsy is a short-lived condition.[1] The vast majority of studies on prognosis are from the developed world and there are few studies from the developing world. This highlights a real need for comprehensive studies to address this hiatus in our knowledge of the epilepsies in the developing world where the distribution of etiologies in particular and health care infrastructures in general vary in many ways.

There are several aspects of prognosis that must be considered. These include the risk of seizure recurrence after a first seizure, and the natural history of the condition, the influence of etiology and treatment on outcome.

Recurrence after a First Seizure

The view that single seizures should not be equated with epilepsy originates from earlier recurrence studies, which suggested that the majority of patients with a single seizure had no further attacks. In population studies, however, the incidence of epilepsy is greater than single seizures. There is conflicting evidence with regard to the recurrence of first seizures, with estimates varying between 27% to 81%.[1-3] Hospital-based estimates are usually higher than community studies. The most plausible reason for this is the bias caused by the "time of entry to study" bias. The risk of seizure recurrence is highest in the first few weeks or months after the first seizure.[1,2] Thus if there is a long interval between the first seizure and recruitment into a study as is often the case with hospital-based studies, patients are likely to have had a recurrence before being seen and therefore will be excluded. This will artificially lower recurrence rates. A large hospital-based study demonstrated this quite clearly where there was a 15% recurrence rate in patients recruited eight weeks after the first seizure compared to 50% in patients recruited within four weeks.[4] There are no published studies of single seizures from the developing world, and there are therefore no reliable estimates of first seizure recurrences.

Even in the developed world, there are few studies that reliably estimate the effect of treatment on prognosis. In one particular study, which examined convulsive seizures, recurrence in the treated group was 26% in patients randomized to treatment compared to 51% in patients not randomized to treatment.[5] What still remains unknown is the impact of early treatment on the long-term prognosis of epilepsy although preliminary findings from this study suggest that it has no effect.[6]

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The Natural History of Treated Epilepsy

Newly Diagnosed Epilepsy

Usually when a patient has had two or more seizures, a working diagnosis of epilepsy is made and antiepileptic drug (AED) treatment is started. Again, there are few comprehensive studies from developing countries that address prognosis in these patients and current knowledge relies largely on studies from western countries. A number of hospital-based prospective studies have reported the effect of treatment in newly diagnosed cases.[1,2] Despite differences in case ascertainment between these studies, outcome is usually discussed in terms of a seizure remission period. Overall, the one-year remission rates in these studies have varied between 58 and 95%, with most studies reporting rates between 65 and 80%.

The prognosis of remission from partial seizures is less good. In one large study, complex partial seizures were controlled only in 16-43% of patients, while for those with only secondarily generalized seizures, control was achieved in 48-53% at one year.[7] Most studies have reported outcome to be less favorable in patients with multiple seizure types, associated neurological deficit and behavioral or psychiatric disturbance.[1,2] Two large community based studies have looked into the long term remission of treated epilepsy. In Rochester Minnesota, 76% of patients were in five year remission 15 years after onset.[8] In Tonbridge, UK, 73% of patients entered remission.[9] In both studies, most patients who entered remission did so in the first two years and as time elapsed, the prospect of entering remission diminished. Most patients who entered remission had suffered a small number of seizures, usually less than ten. Indeed a recent study has found that the number of seizures in the first six months is the single most important predictive factor for both early and long term remission of seizures.[10]

No report has yet associated good outcome with any particular AED. Although there are individuals who respond better to a particular drug, on a population basis all first line drugs appear to be equally effective.

Chronic Epilepsy

All hospital studies of newly diagnosed epilepsy have consistently demonstrated that 20-30% of patients do not enter remission.[2] This has been confirmed by community studies.[8,9] Only 20% of these patients with chronic epilepsy have periods of seizure freedom and even short term remission is unlikely to occur in the majority of them.[11] Suggested risk factors for the development of chronic epilepsy have included partial epilepsy, more than one seizure type, the presence of additional handicaps, long duration of active seizures and frequent seizures at onset.[2,10] A recent study has suggested that lack of response to the first two AEDs is also a strong predictor of intractability.[12]

Drug Withdrawal and Seizure Relapse

Of the patients on AED treatment, 70-80% will eventually become seizure free.[1] Because of the possibility of long-term side effects of drugs, it is good practice to consider drug withdrawal after a substantial remission period. There are risks of relapse, however, in doing so and several studies have addressed this issue.[13-17] The probability of relapse has varied between 11 and 41%. Most studies in children have reported figures at the lower end of the spectrum while studies in adults tend towards the higher end. A number of risk factors for seizure recurrence after discontinuation of treatment have been identified.[14,15] These include a long history of

seizures before remission, the occurrence of more than one seizure type, learning difficulties, a past history of remission and relapse and juvenile myoclonic epilepsy. Whether EEG in adults is helpful in predicting recurrence remains controversial. In children, the presence of background slowing or frankly abnormal discharges in the record indicates and increased risk of recurrence.

The Natural History of Untreated Epilepsy

The natural history of untreated epilepsy is unknown as most patients in the modern era can avail of treatment.[1] Even though the treatment gap in developing countries can be large in some instances, for various reasons, it is not easy to describe the natural history of untreated seizure disorders. Outcome studies of epilepsy have almost invariably been of the treated condition. Consequently two important questions remain unanswered: what is the possibility of spontaneous remission and what is the effect of early treatment on outcome. The answers to these questions are important in view of the suggestion that the failure to treat epilepsy in its early stages could lead to later intractability.[18,19]

Spontaneous Remission Rate in Epilepsy

In developing countries, patients may have had epilepsy for long period of time.[1] If these patients never remit, prevalence rates for epilepsy in developing countries should be much higher than those found in the developed world.[20,21] Indeed some studies in developing countries have reported higher prevalence rates for epilepsy. However, these were all small scale studies of selected populations that may have high rates of CNS degenerative diseases, parasitic diseases or specific epilepsy syndromes.[21-24]

Large-scale prevalence rates in largely untreated populations in several developing countries have reported rates that are similar to those found in developed countries despite higher incidence rates.[21,25-30] One explanation could be that epilepsy has a higher mortality rate in these countries, but this is unlikely to account for the whole difference. Another possible explanation is that case ascertainment for active seizures, was not optimal. However, cases in remission are more likely to be missed than active seizures in such studies.[1,20,21] A more plausible explanation would be that some patients enter spontaneous remission. Two small retrospective studies, one carried out in a hospital clinic in Finland[31] and the other in rural community in Southern India,[32] seem to support this explanation: both reported a remission rate of 50% in untreated patients.

The Yelandur study from India observed treatment outcome prospectively on 135 children as well as adults with definite partial or generalised epilepsy treated with phenobarbital or phenytoin, or both drugs.[33] Single, absence, myoclonic and atonic seizures were excluded as were patients with progressive neurological disease. Terminal remission was defined as seizure freedom for more than 2 years. Seizures in the first three months (the "stabilisation" period) after enrolment were excluded from analysis, but annual follow-up was calculated from the end of this period. Patients already on treatment at entry were not excluded. Patients were given long-term treatment with phenobarbital (n = 68), phenytoin (n = 60) or both (n = 7), given once daily at the lowest effective dose. The daily maintenance dose of phenobarbital ranged from 30-90mg and phenytoin from 50-250mg. Terminal remission rates ranged from 58-66% in patients who were drug compliant and who had a lifetime total of 30 or less generalised tonic clonic seizures, as opposed to 6-16% for patients who were nondrug compliant and who had suffered more than

30 seizures. Multivariate analysis appeared to confirm that drug compliance and early treatment were important predictors of seizure remission. These findings are not dissimilar to those reported in the west[10,34] and emphasise the importance of effective care delivery and the encouragement of compliance. They confirm the usefulness of phenobarbital in developed countries.

Effects of Early Treatment on Prognosis

Observations on the efficacy of treatment in patients with chronic epilepsy who had not previously received AED treatment have now been made in three different studies from developing countries.[35-37] These studies, involving more than 1000 patients, have found that neither the duration of the condition nor the number of seizures before treatment were predictors of outcome. This finding offers some evidence against the view that unless treatment is given early, chronic epilepsy will develop. The ideal method top test the hypothesis that AEDs influence the prognosis of epilepsy would be to randomly allocate patients developing cryptogenic epilepsy to two groups—early treatment and delayed treatment—and to compare long-term prognosis.

Heterogeneity of Epilepsy: Epilepsy Syndrome and Prognosis

Certain conditions may express themselves solely by the occurrence of repeated epileptic seizures, thus qualifying for the label of epilepsy.[1] Few studies have assessed outcome of epilepsy according to epilepsy syndromes. Most studies of prognosis have been reported according to seizure type rather than by syndromic classification.

It is important to categorize epilepsy into an appropriate syndrome where possible. A syndrome is a group of symptoms and signs which, when taken together, form the description of an illness. In the case of epilepsy, the features which usually define a syndrome, are seizure type, age at onset, family history and EEG findings.[38]

Some of the epileptic syndromes are clear-cut. The majority, however, has considerable overlap or may be based on a loose association of clinical features. There may be disagreements about the precise limits of a syndrome, or a particular syndrome may have more than one etiology. In many cases a syndromic diagnosis can only be made retrospectively. Some syndromes may not yet have been defined.

With regard to prognosis, epileptic syndromes may be classified into one of four groups.[1] These groups to some extent are static and self contained, and migration from one group to another is unlikely unless new factors vary, for instance exposure to a new AED, surgical treatment or the widening of a lesion. Patients will fall into one of these prognostic groups predetermined by the epileptic syndrome.

Excellent Prognosis

In this group, comprising 20-30% of all people who develop epileptic attacks, syndromes and conditions are self limiting and very benign. Usually only a few seizures occur. Patients commonly require no AED treatment, as spontaneous remission is the rule. Conditions include benign neonatal convulsions, fifth day seizures, benign partial epilepsies, benign myoclonic epilepsy of infancy and some of the epilepsies precipitated by specific modes of activation (acute symptomatic seizures).

Good Prognosis

Epilepsies in this group are usually benign, short lived, and comprise 30-40% of all people who develop epileptic seizures. Seizures are usually easily controlled with AEDs. Remission once achieved, is permanent and AEDs can be successfully tapered off. It could be argued that in this group AEDs are curative or suppressant until the epileptic diathesis resolves spontaneously. Conditions include childhood absence epilepsy, epilepsy with generalized tonic clonic seizures on awakening, non-specific generalized tonic clonic seizures in patients with no neurological signs, and some of the localisation related epilepsies (both cryptogenic and symptomatic types).

Uncertain Prognosis

This group, with a long-term tendency towards seizures, comprises 10-20% of people who develop epilepsy. AEDs in this group are suppressive treatment rather than curative. Patients may achieve remission but have a tendency to relapse if AEDs are stopped and therefore usually require lifelong treatment. Conditions include juvenile myoclonic epilepsy, and the bulk of the localization related epilepsies (both cryptogenic and symptomatic). Some patients in the latter group may be amenable to surgical treatment, with subsequent changes in prognostic group.

Bad Prognosis

This group comprises up to 20% of all people who develop epileptic seizures. AEDs in this group are palliative rather than suppressive of seizures. There is a continuous tendency to have seizures despite intensive treatment with all AEDs, although occasionally patients may move to the uncertain prognosis group when exposed to a novel AED. Some patients in this group may also be amenable to surgical intervention with subsequent change to prognostic group. Conditions include seizures associated with neurological deficit present from birth (tuberous sclerosis, Sturge Weber syndrome, cerebral palsy etc), epilepsia partialis continua, progressive myoclonic epilepsies, West syndrome, Lennox Gastaut syndrome and others in which atonic/tonic seizures are a prominent feature, partial seizures associated with gross structural lesions and some of the localization related cryptogenic seizures.

Thus, the outcome of epilepsy is determined to a large extent by its etiology although some unknown factors may modify this. Unfortunately there is a serious shortage of studies from the developing world where etiologies and treatment may differ from the west. Needless to say, further studies are required and should be encouraged.

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Chapter 4

Mortality Associated with Epilepsy: Developing Countries Perspective

Nadir E. Bharucha, Arturo Carpio, W. Allen Hauser and Nimal Senanayake

Studies consistently suggest that patients with epilepsy have higher mortality rates than the general population. This is true for all types of epilepsy, especially among younger patients and those with severe epilepsy. Age, sex, race, socioeconomic status, interval from the diagnosis, seizure frequency, and seizure type have all been suggested to be relevant factors affecting mortality.[1] A higher mortality rate is expected in developing countries, because of the high incidence of symptomatic epilepsies, high proportion of generalized seizures, marked treatment gap, and poor social standards. But reliable mortality data from developing countries are sparse. Annual age-adjusted mortality rates related to epilepsy for 33 countries[2] show that developing countries tend to occupy the base of the pyramid.

In Ethiopia of the 316 persons with epilepsy followed for two years, 20 (6.3%) died.[3] Death was attributable to epilepsy in nine of them; eight related to status epilepticus (SE) and one related to severe burns from falling into a domestic fire during a seizure. In a follow-up study of 164 patients with epilepsy in the tribal population of Mahenge Mountains in Tanzania, 110 died in the preceding 30 years. In more than 50% of them the deaths were epilepsy-related. Some of the common causes included status epilepticus (14.5%), drowning (4%), burns (5%), and death during a seizure (2.7%).[4]

There are numerous measures of mortality. Cause specific mortality deals with the increased risk of someone with a particular disease dying as compared with someone without it. In the case of epilepsy, people with acute symptomatic seizures particularly those with status epilepticus have the highest mortality rates. Patients with remote symptomatic seizures make the next biggest contribution to mortality. Cerebral palsy and mental retardation would possibly be important coexisting factors in developing countries. In the case of progressive diseases, such as brain tumor obviously mortality will be high. Those with idiopathic epilepsy probably have the lowest mortality rates. In the symptomatic group, death is usually related to the underlying condition rather than epilepsy per se. Even in the case of status epilepticus mortality is highly related to the underlying cause of SE. The risk of death in SE associated with anoxic/hypoxic ischemic encephalopathy following cardiac arrest is very high.

Sudden unexpected death in epilepsy (SUDEP) is defined as sudden unexpected nontraumatic, nondrowning, nonstatus related death in a person with epilepsy in which postmortem does not reveal a toxicological or anatomical cause of death. Usually the autopsy reveals pulmonary edema. The reported annual incidence of SUDEP varies from 3 per 10,000 in the general population to 150 per 10,000 in those who have undergone epilepsy surgery, yet continue to have seizures.[5] The only

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available data on SUDEP from developing countries is by Carpio et al.[6] In Ecuador, they carried out a prospective hospital based study of mortality among 412 newly diagnosed patients with epilepsy and reported a SUDEP rate of 2.9 per 1000 patient years. This is higher than the rates reported in developed countries. The Standardized Mortality Ratio (SMR) of epilepsy was also higher, 6.3 when compared with an SMR of 2 to 3 in developed countries.[5]

It is important to distinguish between mortality rate, which is usually population based and gives the individual risk of dying from epilepsy and case fatality rate which is often clinic based and gives the average risk of dying within an epilepsy population. In Mali, Beghi et al[7] carried out a prevalence survey for epilepsy and identified 36 epilepsy cases in Bandiagara city and a corresponding rural sample population. In the year 2000 they traced 31 of 36 cases and found that 13 had died yielding a case fatality ratio of 5.31 or 16%.

Proportionate mortality ratio, which may be population or clinic based and Standardized Mortality Ratio or SMR are other indices of mortality. Proportional mortality ratio is the proportion of deaths in the community due to epilepsy compared with deaths due to other causes. SMR is the ratio of observed deaths in the study group to the number of expected deaths. The number of expected deaths is calculated by applying age and sex specific death rates of the general population to the group with epilepsy. In the year 2000, we followed up Parsis with epilepsy who had originally been identified in a community-based study carried out in 1985.[8] We found an SMR of 0.76. This unexpectedly low value may be attributed to the fact that most of the cases are prevalence cases rather than incidence cases. Prevalence cohorts include survivors and hence underestimate mortality. In 2000 we also looked at the mortality among 51 patients with epilepsy in the semi-urban district of Vasai.[8] These patients were originally identified in 1989 and have been followed continuously to the present. For the first 5-year period, the SMR was very high, 7.81, but for the whole 10-year period, it was only 3.9. The higher initial mortality could be attributed to the fact that those who are going to die, die within the first few years. SMR from a developing country should in general, not be compared with the SMR from a developed country because in SMR we compare the mortality of those with epilepsy with the death rate of the general population. If the death rate of the general population is high, as is likely in developing countries, the SMR will be relatively lower than the SMR of a developed country where the death rate of the general population is low.

One other way of looking at mortality is the study of death certificate data. In developing countries such as India, death certificates do not exist in rural areas. Moreover, even in developed countries, epilepsy is not listed in death certificates in more than 10-20% of patients with epilepsy. The technique of verbal autopsy, which involves approaching relatives and associates to ascertain the history of illness before death, is now being employed to a greater extent in developing countries.

In Sri Lanka, in an analysis of 37,125 death certificates issued in the Kandy District over 20 years beginning from 1967,[9] there were 881 (23.7 per 1000) deaths in whom the illness was associated with convulsive disorder, the highest number being in infancy (35.8%). Most of the deaths occurred in the periphery (51.6%) and in the tea estates (36.3%) as opposed to urban areas (12.0%). "Febrile convulsions" was the commonest diagnosis in 44.9% of deaths. "Convulsions" which included neonatal and infantile convulsions accounted for 21.1% of deaths. Status epilepticus accounted for 2.3% of deaths. Other causes included chest complications (60, 6.8%), drowning (28, 3.2%), asphyxia (20, 2.3%), burns (7, 0.8%), and

poisoning (2, 0.2%). There was a decline in the death rates over the 20 years period. In 1967 the death rate was 37.28 per 1000 while it was 9.55 per 1000 in 1987. The decline was more evident in rural areas, from 60.49/1000 in 1967 to 13.19/1000 in 1987. This drop in death rate paralleled a drop in the proportion of deaths attributed to "febrile convulsions" and "convulsions".

In Martinique, Jallon[10] collected all patients with seizures who had been hospitalized or seen by neurologists and pediatricians over one-year period. He also looked at all the death certificates for the same year and found the mortality rate for those with epilepsy to be 5.73 and estimated an SMR of 4.25.[10] Data from other developing countries is not available, but in general the death rates in countries in Africa, are likely to be high due to burns, drowning and status epilepticus.[11]

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Chapter 5

Knowledge, Attitude, and Practice of Epilepsy in Developing Countries

Hasan Aziz and Zarin Mogal

Epilepsy is a worldwide problem with a major impact on the personal, family, and social life of the affected individual and also on the society. The reported prevalence rates of epilepsy in various epidemiological studies vary from 1.5 to 19.5 per 1,000 population with higher prevalence rates in developing countries.[1-5] The average accepted prevalence rate is ~ 5 per 1000.[2] Stigmatization, low literacy, sub-optimal employment, and social and economical marginalization are the commonly faced problems by people with epilepsy, both in developed and developing countries. This attitude of the public significantly contributes to high rates of anxiety, depression, dejection, feeling of deprivation, and low self-esteem in people with epilepsy.[6,7] This is much more so in developing countries.[8-11] Even in the present era when the civic sense of tolerance and acceptance to accommodate people with handicaps is high, people with epilepsy are socially isolated and discriminated.[12,13] However, in the developing countries this social isolation and discrimination is much less when compared to people with acquired immune deficiency syndrome (AIDS) or leprosy.[14] The encouraging aspect is, increasing acceptance of epilepsy among people with high level of eduction.[15]

The 'tropical countries' or 'developing world' represents a large, kaleidoscopic group of nations with varied economies[16] and many cultures and sub-cultures within one country. The population density, some social indicators related to literacy, unemployment, income, and economic activity are similar.[17] Here people with epilepsy encounter several significant barriers. These include: (1) inadequate manpower with expertise in clinical neurosciences; (2) regular availability of antiepileptic drugs (AEDs); (3) substandard drugs; (4) meager health budgetary allocation, epilepsy being a low priority; and (5) inadequate infrastructure in regards to communication and transportation. In addition, poor drug compliance related to cultural beliefs and beliefs in culture bound traditional systems of medicine are also likely to have a negative impact.

Epilepsy - Knowledge and Attitude

Over all the level of knowledge and awareness of epilepsy is poor in developing countries. Many might have heard or read about epilepsy, but a majority lack adequate information about its cause, nature and treatment. Even among parents of a child with epilepsy, understanding of the disorder is inadequate and negative.[18] The knowledge of epilepsy is also low among highly educated groups,[19-21] professors,[20,21] and school teachers.[22,23] In a study in Senegal, 25% of primary school teachers considered epilepsy as a contagious disease.[23] The perception was similar among medical students in Nigeria.[24] In Sri Lanka, knowledge is found to be deficient in many

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aspects among teachers, school children, university/medical/nursing students, participants attending adult education programs, and army personnel.[10] In India, of the 92% who have heard or read about epilepsy, 85% are unaware of the cause of epilepsy and 20% are ignorant about its treatment.[25] The knowledge of epilepsy in Africa is inadequate among both rural[26] and urban population.[27]

When compared to developing countries knowledge about epilepsy is much better in developed countries and varies from 50% to 97%.[28-30] However, in some studies marked deficiency was observed in respect to the cause and treatment of epilepsy. In Finland, of the 95% who have heard or read about epilepsy, only 15% were familiar with the cause.[26] A survey among the junior medical staff of a teaching hospital in Australia observed negative attitude and also lack of knowledge about epilepsy.[31] In a survey in Wales, 34% general practitioners lacked confidence about their knowledge of epilepsy.[32]

Awareness of epilepsy amongst Chinese is much more than that observed in developed countries, but the attitude is more negative.[33] The favorable attitude observed among people of Taiwan is attributed to the western culture and socioeconomic system.[34] In India although the awareness of epilepsy has been found to be comparable to that in the western countries, the attitudes are much more negative.[25] A positive attitude can be developed in the community if people are well informed about epilepsy. A research among teachers in Zimbabwe demonstrates the same.[35]

Perception of Epilepsy

In developing countries epilepsy still remains in the shadows of myths, superstitions and stigma. Fear, shame and mysticism surrounds epilepsy even today. Families of patients with epilepsy often make references to black magic, witchcraft, voodoo or evil/ancestral spirit possession, a divine punishment, and poisoning.[26,27,36,37] The mysterious stormy events of an epileptic seizure have compelled many to associate it with a supernatural cause.[36-39] In Pakistan, only 3.1% population surveyed associated epilepsy to a supernatural cause as against 71% in Turkey.[40] In traditional Africa epilepsy is linked to the evil eye. The curative rituals range from complete shaving of entire body with glass and affliction of burns to banishment of the person causing the evil influence.[38,41] The saliva, flatus, breath, and other secretions of the patient are thought to be highly contagious.[38,42] Epileptic seizure is thought to signify escaping of a demon or an evil spirit and hence one is not allowed to touch a convulsing person.[9,27,43] The notion that epilepsy is a contagious disease and spreads by contact still persists and person with epilepsy is isolated or avoided.[24,26,27,36] In the Moorish population of Central African Republic, there is a belief that wrong food or excessive eating causes epilepsy.[44] Abstinence from certain foods and use of laxatives to purge the evil spirits is a way of treatment.[38,44] Barbaric practices exists in Nigerian backwoods and other African countries to bring out the patient from the post-ictal stupor state.[9] These practices include thrusting a limb into boiling water or over a flame and instilling pepper in the conjunctival sacs which would only add to the physical suffering and pain of the seizures. In Central African Republic, various parts of the body of patients with epilepsy are burnt in an attempt to remove the occult, supernatural cause; a reflection on the immense physical and moral suffering of the epilepsy patient.[38,44] '*Holy Man*' of rural Pakistan claims to specialize in exorcising the evil spirits responsible for epilepsy. Person with epilepsy is chained to a tree and deprived of food. Patients who are already on treatment and seeking added 'spiritual' help are denied medications, many ending in status epilepticus and death.

In many Southeast Asian countries, there is gender bias and females are discriminated. Because of culture bound beliefs women are not allowed to move out of their homes, even to seek treatment. It is the prerogative of the male member of the family to decide if her illness is worth a visit to a doctor or can be treated by a traditional healer or a local clergyman within the four walls of the house. Epilepsy is usually considered the work of the demons, due to some wrong doings of the female and she is de-possessed by gruesome methods of the local spiritual or traditional healer. Many equate epilepsy with insanity.[25,30,33] In Zimbabwe, teachers too associate epilepsy with a type of insanity.[35]

Epilepsy and Education

For persons with epilepsy, there is no legal restriction on education. Most of the problems are related to the societal attitude. Educational opportunities are usually denied to persons with epilepsy[42] and are not allowed to attend school.[38] Even, teachers who are aware of the nature of the medical condition, insist on complete control of seizures before allowing the child to school. This is probably due to the pressure from parents of other children.[45] In China a sizeable number of parents would not like their children having any association with persons with epilepsy in school or at play.[33] Similar attitude is also observed in Denmark, a developed country.[29] In Senegal epilepsy is considered contagious, forcing children with epilepsy to stay away from school.[23] It appears that there is a change in this trend with time. Well-educated people in high positions are less prejudiced against their children studying and having friendship with children with epilepsy.[25] However, many teachers have misconceptions about epilepsy. In Zimbabwe many school teachers, associate epilepsy with a type of insanity.[35] Some teachers in Thailand prefer to place all the children with epilepsy in a special classroom[22] while in Cantabria,[21] 25% of professors felt schooling of people with epilepsy should be done in special schools. In Sudan, more than a quarter of primary school teachers showed rejection towards children with epilepsy.[46] Poor scholastic achievements of many patients with epilepsy may be due to the sentiment of shame expressed by parents, parental over-protection, or parental fear of the child's infectivity to others.[18,43] In rural Tanzania,[43] 68% of parents would not allow to send the child with epilepsy to school, while 40% of parents in India[25] felt that children with epilepsy should not be sent to school. In Pakistan there is a marginal association between epilepsy and educational possibilities; 27% of patients with primary education felt they were being avoided by their classmates.[47] On the other hand in developed countries like Japan the general attitude of education towards younger people is seemingly generous.[48]

Epilepsy and Marriage - Legal and Social Issues

In many parts of the developing world epilepsy is still equated to temporary insanity,[25] a perception fast changing.[30] In persons with epilepsy, marriage may not have a legal sanction. In India till the end of 1999, epilepsy was a valid ground for seeking divorce[49] and it probably still exists in Brazil.[50] Many parents have objections to having their children married to persons with epilepsy.[25,27,33,34,45] In a study in Brazil, senior medical students having excellent level of familiarity and knowledge about epilepsy expressed objection to marry their children to person with epilepsy.[51] In the Indo-Pak subcontinent, marriages are normally arranged. Matrimony is still eagerly sought by females; educated or otherwise, working or not. Revelation of illness would spoil prospects of getting married and also profoundly affect social status of women with epilepsy. Concealment of the disorder is common among

parents of a young girl of marriageable age in order to get an ideal partner. There is also a popular misconception that marriage cures epilepsy. The actual suffering of parents with daughters having epilepsy starts when her condition gets revealed after marriage. There have been instances when the in-laws, potentiate the physical agony of seizures and overall psychological stress by physically abusing the daughter-in-law. Many women with epilepsy are neglected after marriage and a sizable number are divorced.[52] In Pakistan despite the belief that people with epilepsy should not marry, 20.3% of persons with epilepsy are married.[47] In China while education has shown to reduce prejudice against play and employment, the objection to marriage still persists.[33] The marital status of both the sexes has been found to be far from satisfactory even in a developed country like Japan.[48]

Epilepsy and Driving

Epileptic seizures are accountable for a small proportion of road traffic accidents. Driving laws for persons with epilepsy vary in different countries, from a life-term ban to no regulations at all. In the United Arab Emirates and Sri Lanka there are no laws restricting a person with epilepsy from driving.[53,54] In most countries, patients with good seizure control for at least one year and also with good drug compliance are allowed to drive a private vehicle, but professional driving is denied.[55] The ban on driving is life long in Pakistan as in some other Asian countries. In these regions professional drivers especially flout laws, as it may cost their job. It is quite possible that a number of fatal road accidents are related to epileptic seizures while driving. In India, law pertaining to driving and epilepsy has been at absolute extremes during the last century. The Motor Vehicle Act of 1939 prohibits a person with even a single seizure from driving at any time,[56] while the revised Motor Vehicle Act of 1988 has completely done away with the term epilepsy permitting patients with epilepsy to drive irrespective of the status of seizure control.[57] In Japan, Taiwan, Singapore there is an absolute prohibition on driving.[58-60] In Australia, a person with chronic active epilepsy must be seizure free for at least 2 years before getting a driving license, but a recently diagnosed person with epilepsy who is under treatment of a physician, needs to be seizure free for only 3 months.[61] In very few countries there are statutary laws requiring the doctors to notify a person with epilepsy or his fitness to drive to the concerned authorities. In Canada, while it is mandatory in five provinces, it is discretionary in the other provinces. In the provinces with mandatory laws, seizure reporting was more than 80% and it was less than 20% in provinces with discretionary laws.[62]

Epilepsy and Insurance

In most of the developing world the concept of having a health insurance is alien or nascent. There is often no national health insurance cover. Many insurance companies do not provide cover for epilepsy. In India, until recently medical insurance was under complete state control. Medical insurance with the state owned companies, specifically excludes epilepsy.[63] In Pakistan, the situation is similar. Persons with epilepsy are denied health insurance by the private as well as state owned insurance companies; many considering epilepsy as a congenital disorder.

Epilepsy and Employment

There is no legal bar on employment of persons with epilepsy, however discrimination towards their employment is highly prevalent. World-over persons with epilepsy are sub-optimally employed. This is more so in developing countries. Employers

are found to be unaware of employment problems faced by people with epilepsy.[64] The seizure status is a major factor determining employment opportunities of a patient with intractable epilepsy. Persons with good seizure control and with no other handicap usually face lesser employment problem.[65,66] Intellectual impairment, physical disabilities, psychological and psychiatric disorders further influence the employment status. Perception of the illness by the employer and coworkers is of great significance in all parts of the world, more so in the developing world. Various misconceptions associated with epilepsy deny patients with epilepsy employment or are under-employed with restricted career development.[66] Persons with epilepsy have to battle against the wrong, but a common notion, that they are intellectually not up to the mark. They have to struggle against stigma and misconceptions to prove their capabilities and avoid getting socially and economically marginalized. Disappointment, deprivation, feeling of unworthiness and paranoia often creep in, resulting in psychological and/or psychiatric problems interfering with the quality of life. In United Arab Emirates, 10% of study population believe, that persons with epilepsy should not be employed in jobs like others[45] and in China it is ~50%.[33,34] In Finland ~1% of people studied would prefer to leave their jobs if they had to work with a person with epilepsy,[28] while in Denmark 7% have objection to equal employment.[29] In Italy 70% of study population believed that epileptic persons should be employed in jobs like any other people.[67] In USA there has been an increasing trend towards employment of persons with epilepsy.[30]

Epilepsy and Law

The general public has callously treated persons with epilepsy over the centuries and worst would be if law should sanctify these attitudes due to ignorance, prejudice and lack of communication between the concerned authorities. Epilepsy and law have never found it easy to understand each other. In Spain, the Supreme Court defined epilepsy as a typical endogenous psychosis, equating it with insanity. This can prove to be a double-edged sword; on one hand it can be the grounds for acquittal from criminal responsibility and immunity from prosecution for many offenders, while on the other the concept of insanity leads to the patient suffering social rejectment.[68] Contrary to the popular belief, epilepsy is not equated with insanity in Indian law; past or present.[69] The reference to 'epileptic insanity' has been made in one of the judicial pronouncements of the Supreme Court while discussing the relationship between epilepsy and premeditated murder with special reference to a plea by the defense for an epileptic automatism.

Treatment-Seeking Behavior

Drug noncompliance is highly prevalent in persons with epilepsy in the developing world. The reasons are multiple. Poor health infrastructure, scarcity of trained medical personnel, poor doctor-patient rapport, poor socio-economic status, high costs, nonavailability or inconsistent supply of anti-epileptic drugs, lack of treatment seeking behavior, traditional concepts and seeking of alternative treatment methods are some of the many reasons. All can result in poor seizure control and consequent impact on the quality of life.

Traditional beliefs have an important influence on the treatment seeking behavior of persons with epilepsy. There are people who hold both medical and traditional beliefs and seek both types of treatment.[46,70,71] Multiple agencies are usually consulted including spiritual/faith healers and traditional local nonmedical practitioners.[72,73] In many of the developing countries, the first contact of treatment is

usually with an indigenous healer and alternative medicine.[39] A supernatural belief combined with family decision is associated with this choice. Relatives, friends and neighbors have a marked influence on the treatment-seeking behavior. In Nigeria,[73] 86% of the patients are influenced to use alternative medicine, while in Turkey 65% have visited religious figures at onset or during the course of the disease.[74] Alternative treatment includes traditional healers, herbal medicine, spiritual healing, faith healing, cautery, aryuveda and homeopathy.[27,41,43,45,73] In India, in spite of being well informed of this disorder, alternative treatment methods are often sought.[70] The proportion of patients treated by traditional healers and herbal remedies was 70% in Mauritania[44] and 11.5% in Pakistan.[3] Mystical beliefs about this disorder make many patients and families to visit a community spiritual healer, a holy person or a shrine while receiving allopathic medical care.[74] Involvement of multiple agencies usually results in contradictory advice, confusing the patient with resultant poor seizure control. Alternative medicine especially spiritual healing should not be considered irrelevant in the management of epilepsy in the Indo-Pak subcontinent and the African regions where strong religious/mystical/spiritual beliefs prevail. Medically trained personnel dealing with epilepsy must work in tandem with these spiritual/local healers.[73,75] Skilful practitioners will not contradict the patient's belief, however, stress on the importance of anti-epileptic drug therapy along with a diplomatic but firm stand against negative traditional advice like placing the arm of a seizing child into fire and putting of pepper in the conjunctival sacs.

Treatment and management of epilepsy cannot be solely the domain of a neurologist, especially in developing countries where there is a gross deficit in manpower in the overall health sector. The concept that only the specialist must treat epilepsy patients has no practical use in the developing world presently or even in the near future. Although the number of neurologists in the developing world is increasing, there is still a significant deficiency in the desired number of experts who can take care of patients with neurological disorders, especially epilepsy. In 1975, there were two neurologists in Syria for a population of 8,000,000; after two decades there were 30 neurologists for a population of nearly 13,000,000. In 1977, Nigeria had a population equivalent to a quarter of all of Africa's population but had only seven neurologists. In Ghana, with a population of 8,000,000, there were only two neurologists.[75] A recent epilepsy care status survey in developing countries conducted by International League Against Epilepsy (ILAE)[76] reveals that there are five neurologists for the 11 million inhabitants of Cambodia and six for the three million population of Congo. In the Asia Pacific region, Papua New Guinea has no trained neurologist while Nepal has ~1 per 22 million and Pakistan ~1 per 6.6 million inhabitants.

Lack of informed knowledge regarding the goal of treatment and consequences of sudden stoppage is one of the many reasons of treatment failure.[70] Inability of the treating physician to stress the importance of continuous long-term treatment, in the prescribed dose is a major factor. Patient load and stiff professional competition are the major reasons for the physician sparing very little time to the patient. Sub-optimal drug dosage, intermittent use of medicines, sudden stopping of drugs or change to other modes of treatment are major reasons for poor seizure control. Recurrent seizures interfere with the quality of life of the patient.

Governments in developing countries allot meager resources to health budget. Patients are either provided no free antiepileptic drugs or intermittently.[76] Often patient has to pay for the treatment out of his pocket, which may be high with respect to his earnings. In Western India, the cost of AED includes a 40% of

government-levied tax.[50] This may result in poor drug compliance, poor seizure control and poor quality of life.

Conclusion

Epilepsy has been known for many centuries. Remarkable advancement on different aspects of this disorder has helped in reducing the associated physical agony to a considerable degree. However, scientific advancements have not yet succeeded in penetrating and eradicating the deep-rooted myths, misconceptions, superstitions and stigma which go hand in hand with epilepsy resulting in enhanced physical, psychological and social scarring, thus multiplying the sufferings of the patient. Bringing 'epilepsy out of the shadows' should be the goal of all concerned health care personnel in the new millennium. This is only possible by public awareness...health education to the masses.

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Chapter 6

Epilepsy in Developing Countries: Clinical Evaluation

Agnon Ayélola Koffi Balogou, Macharia Waruingi, Michel Dumas and Pierre-Marie Preux

Epilepsy is a major public health problem worldwide and over 80% of people with epilepsy, are thought to be in developing countries. Reported prevalence of epilepsy is very high in some developing countries and varies from 5 to 20‰.[1-4] The climatic, economic, and cultural conditions are quite different from developed countries and provide epilepsy a unique profile.

Diagnosis of epilepsy is essentially clinical and the diagnostic approach depends on the clinical setting, availability and access to various diagnostic facilities, and economic factors. Limited resources and poorly developed health care infrastructure make the case ascertainment, seizure monitoring, and drug therapy, at times, very difficult in developing countries. Clinical profile of epilepsy has been studied in several hospital-based studies in developing countries. However, most of the earlier studies lack clarity and quality, mostly related to definitions and methodology. Studies on epilepsy, in developing countries can be divided into three distinctive periods. Studies before 1980s were based on the individuals' collection of cases and experience. In 1980s most of the studies were based on screening protocols developed for common neurological disorders by World Health Organization for use in developing countries.[5] Most of the current studies, particularly in African countries, are based on the Questionnaire of Investigation of Epilepsy in Tropical Countries developed by the Research Network in Tropical Neurology (RERENT).[6] This chapter will discuss the clinical evaluation pathways of diagnosis of epilepsy in developing countries.

Clinical History

Screening Questionnaire

Diagnosis of epilepsy is fundamentally a clinical judgment. Clinical history should elicit details of seizure semiology, seizure provoking factors, and seizure frequency in the preceding five years.[7] At times there can be discrepancy in the diagnosis of epilepsy when it is based only on a screening questionnaire. In a recent epidemiological survey in Togo of the 9,155 subjects screened by a screening questionnaire, 285 subjects (3.1%) reported loss of consciousness, 263 (2.9%) had seizures and 142 (1.5%) had foaming and urinary incontinence during the seizure; 74 (0.8%) had absence seizures, 68 (0.7%) had focal symptoms. During case ascertainment of the 304 subjects studied, diagnosis of epilepsy could be established in only 170 patients.[8] Documenting seizure provoking factors like sleep deprivation, photic stimulation, and hyperventilation, helps the clinician in the management of people with epilepsy.[9]

Epilepsy in the Tropics, edited by J.M.K. Murthy and Nimal Senanayake.

Past and Personal History

Family history of epilepsy, past neurological and medical history must be documented in detail and may give clue to the underlying mechanisms of the disease. In developing countries, some studies reported low incidence of family history of epilepsy,[10-12] whereas others reported a high incidence.[13-18] One study in Tanzania reported an extremely high incidence of 75%.[13] Studies carried out in 9 different African countries, between 1996 and 1999, using the Questionnaire for Investigation of Epilepsy in Tropical Countries found a positive family history of epilepsy in 34% of the first-degree relatives among the 1374 patients with epilepsy interviewed.[6,9] According to Farnarier et al,[3] traditionally sanctioned consanguinity in endogamous relationship is very common in many developing countries. In certain situations, consanguinity could be the consequence of tribal isolation or the result of social rejection, which diminishes the possibility of a patient with epilepsy to obtain a healthy spouse, with eventual marginalization of the later.

Relevant past history should concern enquiry about the progress of mother's pregnancy, the circumstances at birth, psychomotor development, diseases during infancy and childhood, neurological sequel consequent to these diseases, and the time interval before the appearance of the symptoms. The place and the conditions during birth should be documented. The psychomotor development must be evaluated according to age specific milestones including but not limiting to sitting, walking, talking etc. A developmental abnormality is probably a sign of central nervous system (CNS) disease. In developing countries obstetrical trauma and perinatal hypoxic-ischemic brain insults are frequent. Multiparity, prematurity, malnutrition, anemia, lack of hygiene and neonatal infections are highly prevalent and may result in many types of cerebral lesions that could result in seizure disorder in later life.[19] Of the 1374 patients with epilepsy studied in the community in 9 African countries, mother's pregnancy was abnormal in 14% of patients with epilepsy.[9] In this study 48% were born at home, 6% had birth trauma, 7% were premature, 11% did not cry immediately after birth, and 12% had abnormal psychomotor development. In a study in Tanzania 12.1% of patients with epilepsy were products of abnormal pregnancy when compared to 1.8% in the control group.[17] In many developing countries children are born at home, without qualified assistance. In a study done in Burundi, 79.1% of children aged less than 15 years were born at home.[18] Prenatal, perinatal, and postnatal causes are probably the most frequent predisposing factors for epilepsy in childhood in developing countries[3] and account for about 13-14% of the causes.[20]

Certain diseases of the young, particularly infectious diseases can predispose to epilepsy. Measles, encephalitis and meningitis are among the most serious illnesses that may be accompanied by acute symptomatic seizures, focal or global neurological deficits and later epilepsy. In the study conducted in 9 African countries, severe measles was reported in 22%, while 3% had encephalitis or encephalopathies and 3% had meningitis. Of the 300 patients with epilepsy studied in the Democratic Republic of Congo, 66 children had measles or whooping cough encephalitis and 44 had other encephalitis and meningoencephalitis.[21] Japanese encephalitis is a common cause of encephalitis worldwide and endemic in most of the Asian countries and survivors may later develop epilepsy. The reported incidence of epilepsy following Japanese encephalitis ranged between 1.3%[22] and 20%.[23] Meningococcal meningitis is endemic to Sub-Saharan Africa and Brazil. In a study from Cameroon, of the 101 infants treated for meningitis 17.8% later developed epilepsy.[24] Seizures can

be a feature of any febrile illness and febrile seizures are a major risk factor for epilepsy (odds ratio 11.0, $p < 0.01$).[25] In a study from Tanzania, history of febrile seizures was found in 44% of patients with epilepsy when compared to 23% in the control group.[17] Other childhood infections and parasitic diseases may be risk factors for epilepsy. Of the 38 patients studied by Debouverie et al[26] in Burkina Faso, 11 had infectious and parasitic diseases.

In developing countries HIV infection is highly prevalent and is a major public health problem. About 60% of patients with HIV infection may have epileptic seizures during the course of the illness.[27] Epileptic seizures may be manifestation of HIV encephalopathy, lymphoma, or opportunistic infections: toxoplasmosis, cryptococcosis, tuberculosis, and progressive multifocal leukoencephalopathy. Patients with HIV infection may present with new onset epileptic seizures.[28,29]

In the clinical evaluation, history of traumatic brain injury should be elicited and details should be documented. The reported frequency of traumatic brain injury as a putative risk factor in community-based studies in developing countries varied between 8%[9] and 9%.[25]

History of alcohol consumption, substance abuse and exposure to various toxins should be elicited and documented. Whether consumption of large amount of alcohol, especially adulterated alcohol, is a risk factor for epilepsy is not certain.[19] But in a study in Togo,[15] attributed epilepsy to alcohol consumption in 8 of the 237 patients studied. The tropical world is the major region for the production and distribution of narcotics. In the developing world psychotropic drug consumption is on the rise. Over indulgence of substance abuse can provoke epileptic seizures.[30] Benzene hexachloride, a pesticide used in India, has been associated with seizures.[31] Consumption of certain fruits can result in fatal convulsive encephalopathy, this is more often described during famine. In Burkina Faso and other African countries epidemics of fatal convulsive encephalopathy in children have been reported following consumption of unripe ackee fruit (*Blighia sapida*).[32,33] The traditional healers provoke seizures and even status epilepticus by administering some of the herbals.[34,35]

Physical Examination

Inspection

Inspection is the key step in the diagnostic evaluation as certain findings; burn scars and amputations can give a clue to the epileptic nature of seizures. In developing countries due to high usage of unattended open fires, patients with epilepsy are at a higher risk of burns. Burns from falling into domestic fires are very common. When a patient with epilepsy falls into a fire or on a hot object he may be deserted by the entourage (Fig. 1). In India forehead of a child with febrile seizures is often burnt with a belief that it will prevent further seizures or such phenomenon. Burn scars can identify a patient with epilepsy, in Ethiopia of the 316 patients with epilepsy studied, 8.5% had burn scars.[12] Epilepsy related burns account for a significant proportion of admissions, 24/183[36] - 11%,[37] to the hospitals in developing countries and is a major cause of mortality.[38] In certain cultures, burn scar has grave implication the subject with burns is considered incurable.[3]

In developing countries neurocysticercosis is a common cause of epileptic seizures. Patients with cysticercosis may have subcutaneous cysticercal cysts in the body (Fig. 2). Sometimes these cysts are easily visible and palpable. They can be millet size

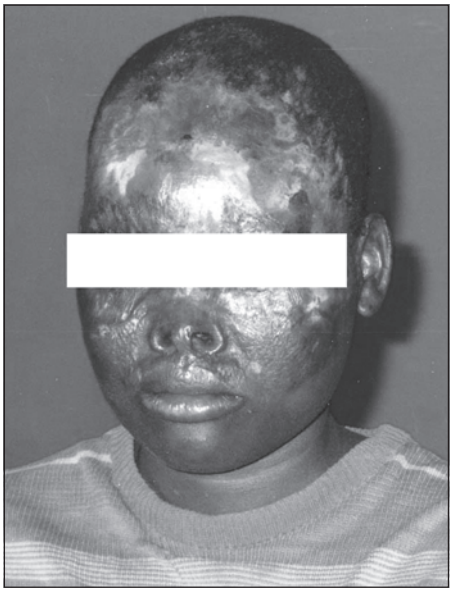

Figure 1. Photograph of a patient with epilepsy showing facial burn-related scars following an epileptic seizure.

or may be much larger and can be rolled between the thumb and the index finger. Live cysts have a soft rubbery consistency and calcified cysts are hard in consistency. Subcutaneous cysticercosis is most frequently observed in Africa and Asia than in South America.[39,40] The reported frequency of subcutaneous cysticercal cysts in African countries endemic to cyticercosis varied between 0.3% and 1%.[41,42] In patients with epilepsy the reported frequency varied between 29% and 70.6%.[42,43] Whereas in the series from Mexico,[44] Colombia,[45] and Ecuador[46] subcutaneous cysticercal cysts were reported in less than 5% of cases. In Burundi, of the 422 patients seropositive for cysticercosis, subcutaneous cysts were noted in 4.7% of patients.[18] Since subcutaneous cysticercosis is a common finding among Africans; it has been a common practice to consider neurocysticercosis in patients with subcutaneous nodules and epileptic seizures.[47-49]

In African population other causes of subcutaneous nodules include onchocerciasis and other nonparasitic lesions. In endemic areas, because of high prevalence of epilepsy, onchocerciasis has been incriminated as a putative risk factor for epilepsy. Some preliminary studies have suggested the relation, but till date the association has not been proved in most rigorous epidemiological studies.[50,51]

Muscular pseudohypertrophy is a feature of disseminated cysticercosis. Patients with disseminated cysticercosis present with uncontrolled seizures, progressive dementia, behavior disorder, muscular pseudohypertrophy, and a relative paucity of localizing neurological signs or signs of raised intracranial pressure.[52] Most of the reports of disseminated cysticercosis with muscular pseudohypertrophy have been reported from India.[53-58]

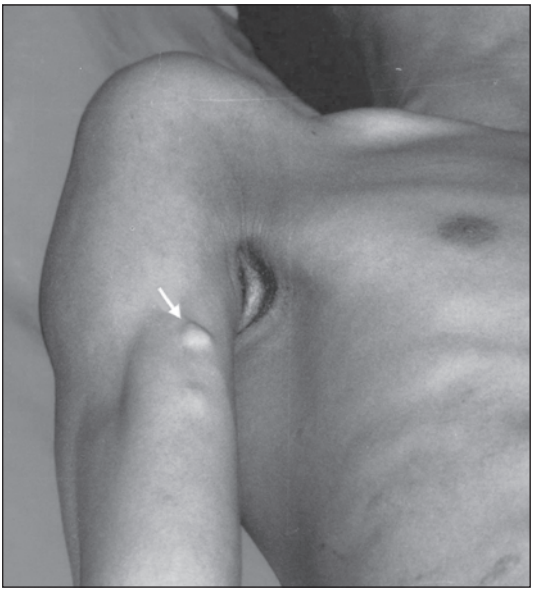

Figure 2. Photograph of subcutaneous cysticercal cysts in a patient with epileptic seizures associated with neurocysticercosis.

Traditional Therapeutic Scarification on Patients with Epilepsy

A major problem of epilepsy in developing countries is its social implications. Prejudice against the disease is common and patients with epilepsy are marginalized and discriminated. Epilepsy is often concealed. The very pronunciation of the word "falling disease" (as epilepsy is called) is a taboo. Many regard epilepsy as supernatural. This negative attitude will have considerable biases in hospital and population-based studies. Patients often consult traditional doctors. Traditional scarification is used for the treatment of epilepsy. In Togo,[29] examined the skin of 36,000 patients in the neurological department of a teaching hospital in Lome between 1985 and 1995 and conducted a similar population-based study on about 20,000 inhabitants in the Kloto district of southwestern Togo and on 10,000 inhabitants in the Tone district of northern Togo. Interviews with traditional doctors revealed that forehead scarifications are characteristic of epilepsy treatment. More than 80% of patients with epilepsy in Togo have forehead scarifications. When the seizures are infrequent, scarifications are slim, short (1-3 mm), near the forehead hairline and concealed. But when seizure frequency is high and many in the community are aware of the disease in the individual, scarifications are large, long, and visible over forehead and cheeks, a sign of social sentence of the patient. In Togo, the diagnosis of epilepsy is written on the skin, it only needs to be seen and read.

Physical Examination

The general status of the patient must be appreciated. In developing countries, malnutrition is highly prevalent and the body mass index (BMI) must be calculated. Low BMI is a frequent finding in patients with epilepsy in these countries, 21% to 61%.[9,18]

Mental retardation needs to be evaluated and this can be assessed using the intelligence quotient (IQ) system. IQ system is not watertight and a global examination by the physician is a must in order to have a clear impression. This has relevance as epilepsy and epilepsy syndromes related to prenatal and perinatal brain trauma is common in developing countries. The physical examination should consist of detailed neurological examination and examination of other systems. In most studies, authors rarely report the results of physical examination. In the study in 9 African countries, of the 1374 patients with epilepsy, only 58% were in good general status, 29% had an abnormal neurological examination, and 23% had mental retardation.[9]

Conclusion

Diagnosis of epilepsy is fundamentally a clinical judgment. Meticulous clinical evaluation often confirms the diagnosis of epilepsy. In developing countries certain clinical features will be of help to confirm the diagnosis of epilepsy and also epileptic nature of the seizures. This has much relevance in developing countries where availability of various investigative modalities is limited. Even if such facilities are available, affordability will be a problem. Clinical evaluation by the physician should give a good description of seizure onset, progression, and termination and also detailed account of seizure semiology. Such description should help to distinguish between different provoking factors and/or intercurrent situations. It is also important to distinguish between acute symptomatic seizures, single seizures and epilepsy. In developing countries, all investigators should use a common questionnaire. Investigators in developing countries are recommended to use the Questionnaire for Investigation of Epilepsy in Tropical Countries. The questionnaire is available in French, English, Spanish, Vietnamian, Arab languages (www-ient.unilim.fr). This will allow standardization of clinical data for a better comparison, which is so crucial for formulating the action plans and policy for community and also individual care of patients with epilepsy. Such an approach will expedite the process of bringing people with epilepsy out of the shadows and keeping them in the light.

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Chapter 7

Epilepsy in Developing Countries: Diagnostic Evaluation

P. Joseph Cherian and Kurupath Radhakrishnan

"Careful history taking and interpreting, and minute and repeated clinical examinations are time consuming. It is particularly the busy physician who is inclined to delegate the diagnosis to the laboratory in the vain hope of saving time. Laboratory procedures often seem necessary because the clinical examination has not been adequate. They are all too often superfluous, and a thorough clinical examination would have provided grounds for correct management of the patient. The more clinical neurology we know, the less need there is for laboratory procedures and more valuable these procedures become when they are necessary."

Robert Wartenberg, 1953

Epilepsy is a major health problem worldwide with a prevalence rate of ~5 per 1000.[1] Developing countries carry more than 90% of epilepsy burden.[2] Most studies from developing countries have reported high prevalence rates.[3,4] However, some of the recent community-based surveys from India have shown prevalence rates similar to that of developed countries.[5,6] The high prevalence of epilepsy in developing countries is attributed to some of the geographically specific etiological factors such as neurocysticercosis,[7] other infections of central nervous system (CNS), and hot water epilepsy.[8]

With better understanding of the etiopathogenesis and natural history of various epilepsies and epilepsy syndromes, there is an increasing need for specialized care of people with epilepsy. A wide variety of electrophysiological, and structural and functional neuroimaging modalities and also molecular genetic investigations are now available for the clinician to provide an accurate diagnosis and he is also has different treatment options like antiepileptic drug (AED) therapy, epilepsy surgery, and nonpharmacological interventions for optimal care of people with epilepsy. Often considerable expertise is required to make a judicious choice from this bewildering array of investigations. Data regarding the sensitivity, specificity, predictive power and cost-effectiveness of various investigative modalities are limited.

Resource constraints are universal, but more so in developing countries. The developed world is slowly getting used to the limits set by managed care and the availability or not of the medical insurance for a patient. The problems in developing countries are different. Investigations considered very basic like an electroencephalogram (EEG) are not available in many regions or may not be affordable to a large segment of patient population. Even in the few centers where EEG equipment is available, the technical expertise required for recording and interpreting EEGs may be lacking. Computerized tomography scan (CT) facility is available in most of the big towns in developing countries. But magnetic resonance imaging (MRI) is

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available only in a few regional centers or metropolitan cities. The number of centers where single photon emission computed tomography (SPECT) and positron emission tomography (PET) are performed in India are very few. Long-term video-EEG monitoring and epilepsy surgery programs are restricted to few selected centers.[9-11] Absence of statutory bodies enforcing quality control and lack of trained personnel lead to overuse as well as abuse of the available investigative facilities.

Diagnosis of epilepsy is fundamentally a clinical judgment based on history. The accuracy of diagnosis of epilepsy depends on the skill and experience of the physician and the quality and reliability of the witness information available. The diagnostic questions that a physician, caring people with suspected seizure disorder, encounter would include: (1) Is it an epileptic seizure? (2) What is or are the seizure types? (3) What is the syndrome or type of epilepsy? (4) What is the cause? The diagnostic approach to a patient with epilepsy depends on the clinical setting, availability and access to investigative facilities and economic factors. When compared to well-structured health care and reimbursement systems in developed countries, in developing countries, a majority of people with epilepsy pays for investigations from their own pocket. In this chapter, we describe the investigative facilities available for patients with epilepsy in tropical countries and critically examine how these facilities can be utilized in a cost-effective way.

Electroencephalography

The EEG provides specific information about epileptogenesis. Normal EEG findings, however, do not exclude the possibility of epilepsy, and epileptiform discharges can rarely occur in normal subjects without epilepsy.[12,13] The objectives of obtaining EEG in people with suspected epilepsy are two: (1) to gather information to support the clinical diagnosis of epilepsy; and (2) to aid in the syndromic classification of epilepsy.[14]

Epileptiform discharges are distinct paroxysmal EEG waveforms that have a high degree of association with epileptic seizures.[12] The common types of interictal epileptiform discharges (IEDs) are spikes (Fig. 1A), sharp waves, and spike/multiple spikes and wave discharges. The IEDs may occur singly or in bursts. By contrast, a seizure-related (ictal) discharge usually consists of rhythmic sinusoidal activity that has an abrupt onset and termination and is associated with clinical manifestations of a seizure (Fig. 1D).[12,15] Epileptiform activity is localized in partial seizures[12] and generalized if associated with generalized seizures.[12] However, focal IEDs have been reported in up to one-thirds of patients with juvenile myoclonic epilepsy,[17,18] and the IEDs in localization-related epilepsies may become secondarily generalized.[12,16] The focal IEDs may arise from temporal (Fig. 1A), frontal, occipital, centrotemporal, centroparietal and midline regions of the brain. Generalized IEDs consist of 3-Hz (typical) spike-and-wave, slow (atypical) and fast spike-and-wave, rhythmic fast spikes, and hypsarrhythmic patterns.[12]

Diagnostic Sensitivity

An awake standard EEG record will record IEDs in ~50% of adults with epilepsy.[12] The chance of recording IEDs increases with multiple EEGs and it is 92% with four recordings.[19] The yield substantially increases by recording during sleep, more so after overnight sleep deprivation.[20,21] Sleep recordings are of special value for ascertaining focal IEDs in partial epilepsies[22,23] and establishing the presence of generalized IEDs in patients with idiopathic generalized epilepsy syndromes.[12,13] A single wake and sleep EEG provides information supportive of diagnosis and also

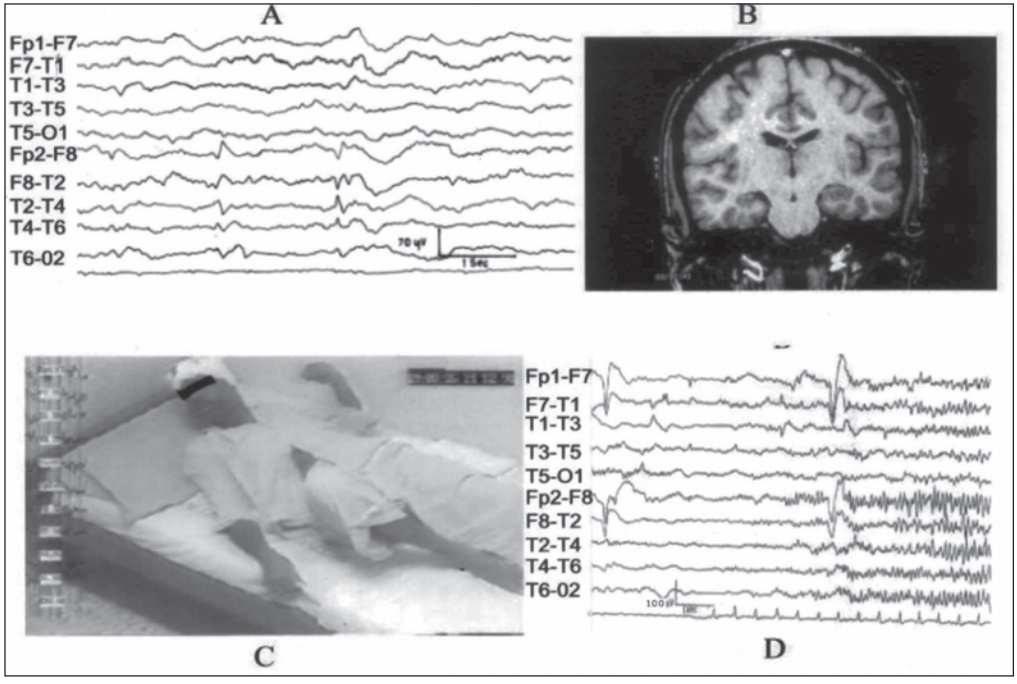

Figure 1. EEG - MRI - video-EEG correlation in a patient with medically refractory temporal lobe epilepsy. Shows (A) right anterior temporal spike discharges; (B) small right hippocampus on T1-weighted coronal MRI sequence; (C) dystonic posturing of the left upper extremity during video recorded complex partial seizure; and (D) rhythmic right temporal EEG activity during the seizure.

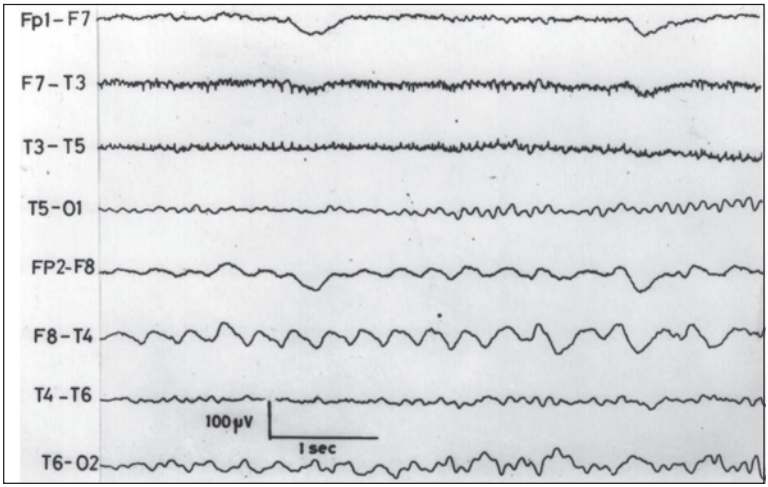

Figure 2. Right temporal intermittent rhythmic delta activity (TIRDA) in a patient with medically refractory complex partial seizures.

classification of epilepsy in ~80% of patients.[12,13,16] Temporal intermittent rhythmic delta activity (TIRDA) consists of trains of rhythmic, sinusoidal 1-4 Hz activity of 50-100μV in amplitude lasting 3 seconds or more in duration and occurring more frequently during drowsiness and light sleep and has a high diagnostic specificity for temporal lobe epilepsy (Fig. 2).[24,25] The frequency of IEDs in elderly persons with epilepsy is substantially low when compared to the frequency reported in the epilepsy population as a whole.[26]

Diagnostic Specificity

Benign epileptiform variants (Table 1) are waveforms that have an epileptiform appearance but are not epileptogenic.[12,27,28] Misinterpretation of benign epileptiform variants such as benign sporadic sleep spikes (Fig. 3) is one of the common causes for wrong diagnosis of epilepsy. Understanding of age-dependent EEG characteristics of infants and children is essential to avoid misinterpretation of pediatric EEGs.[29] It is often difficult to distinguish the sharp contoured waveforms overlying a skull defect (breach activity) from IEDs.[30,31] When these phenomena are carefully excluded from the category of epileptiform activity, the incidence of epileptiform abnormalities in the EEGs of healthy subjects is almost zero.[32]

Recording and Interpretation

Diagnostic value of scalp EEG depends upon the strict protocols followed in recording and interpretation. A sleep recording should be an essential part of EEG recording protocol. Mayo Clinic EEG Classification System[33] provides a consistent reporting with very little inter-observer variability of the visual analysis of the EEG findings. A computer-coded version of this classification system is valuable in data collection and analysis.[34]

The quality of EEG recording and interpretation in developing countries leave much to be desired. Standardized EEG laboratories and qualified technologists and electroencephalographers (EEGers) are nonexistent in most of the regions of the

Table 1. Common sources of misinterpretation of scalp EEGs

Artifacts
Electrode artifacts
Myogenic artifacts
ECG and pulse artifacts
Benign epileptiform variants
Benign sporadic sleep spikes
Wicket waves
14 and 6 Hz positive spikes
6 Hz spike-waves
Rhythmic temporal theta burst of drowsiness
Subclinical rhythmic electroencephalographic discharge of adults
Miscellaneous
Atypical responses to photic stimulation
Bifrontal delta activity on hyperventilation
Posterior slow waves of youth
Breach activity

ECG: electrocardiogram

tropical world. In India, there are no defined minimum standards for EEG laboratories and there are no governmental or professional authorities to ensure quality control. A majority of EEG laboratories are managed by a variety of laboratory technologists and paramedical personnel with no formal training. Majority of EEGs are of only eight channel recordings and often the recordings are done for less than

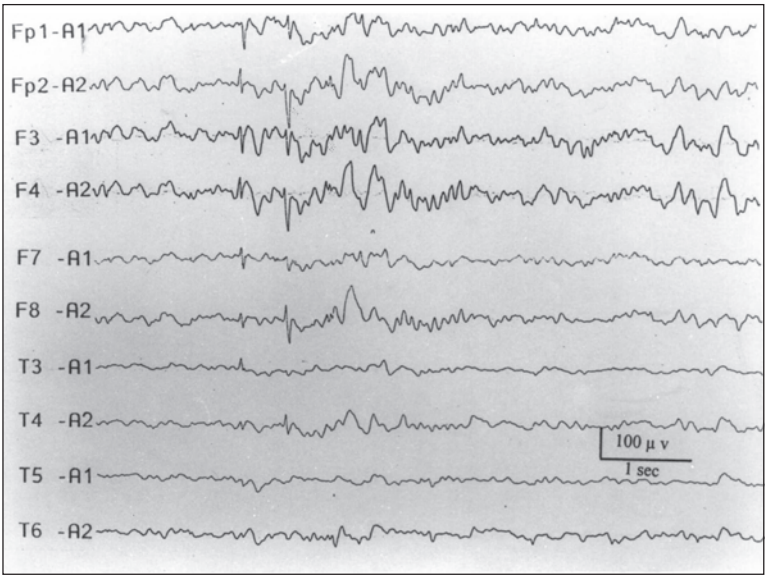

Figure 3. Benign sporadic sleep spikes (BSSS) in the EEG of a 31-year old male during light sleep.

Table 2. Utility and limitations of the EEG

Utility
Support the diagnosis of epilepsy
Classification of epilepsies and epilepsy syndromes
Identify seizure-precipitating factors
Exclude nonepileptic events
Detect subclinical seizures
Predict relapse following AED withdrawal.
Detect AED intoxication
Monitor therapy of status epilepticus.
Limitations
Normal interictal EEG cannot exclude epilepsy
Ictal EEG may not show epileptiform activity
Amount of IEDs does not correlate with seizure frequency or treatment response
IEDs may not dictate prognosis.

IEDs: interictal epileptiform discharges; AED: antiepileptic drug

30 minutes and do not include sleep. There are no formal training programs for professionals. Reading EEG is learned through apprenticeship and experience. The postgraduates undergoing training in neurology even in the best of the institutions in India receive inadequate exposure to EEG and epileptology. Post-doctoral fellowship programs in clinical neurophysiology and epileptology are not as yet available in India.

Availability and Affordability

Facilities for EEG recording are not available for most patients with epilepsy in developing countries in the tropics. Even if available they are mostly located in urban areas. In India there are a total of approximately 1000 EEG machines, which works out to be one EEG machine per 5000 people with epilepsy. EEG facilities available in selected governmental institutions remain underutilized because of the poor quality of services and long waiting periods. In developing countries majority of persons with epilepsy are treated by primary care physician, without an EEG study. In a study in South India, among the 100 patients with epilepsy (mean disease duration ~ 2 years), only 25 had an EEG recording before referral to a tertiary referral center.[35]

Cost-effective Utilization

Interpretation of EEG is best achieved by good interaction between the referring physician and the EEGer regarding the clinical details and the question(s) the EEG is expected to answer (Table 2).[13,36,37] Such an approach will improve the cost-effective utilization of EEG in the diagnosis and management of seizure disorder and is especially relevant to developing countries. Based on the published evidence EEG should not be a part of evaluation of a neurologically healthy child with simple febrile seizures.[38] Even in children with complex febrile seizures the yield of abnormalities on an early postictal EEG is low if the neurological status is normal.[39] All children with an apparent unprovoked seizure should have an EEG. The risk of seizure recurrence is higher in children whose EEGs show abnormalities.[40,41] The role of EEG in predicting relapses following AED withdrawal in patients in remission, particularly

in adults, is uncertain.[42,43] The epilepsy syndromic diagnosis, rather than the EEG finding, should dictate the decision to withdraw AED.

In developing countries most often patients are managed without recourse to EEG. In the Yelandur study in south India, of the 203 patients with tonic-clonic seizures, both partial and generalized were diagnosed clinically without EEG and treated; 40% attained complete seizure remission and an additional 32% had significant reduction in seizure frequency.[44] Based on a study from a tertiary referral center, Sawhney et al[45] concluded that EEG made a positive contribution in the management of epilepsy in only 15% of patients.

Digital EEG

The advantages of digital EEG over analog EEG include paperless storage, quantification, automatic event detection and networking capabilities.[46,47] The flexibility of digital EEG allows modification of the recording parameters, such as montage, filters, amplitude and duration display scales retrospectively during review of the recording. These capabilities allow for more accurate interpretation of the EEG data.[48] Since digital EEG machines are comparable in cost to analog EEG machines, they are slowly replacing the analog EEG machines in developing countries as well.

Special EEG Procedures

Activation Procedures

Activation procedures, hyperventilation, intermittent photic stimulation and sleep enhance the epileptiform abnormalities and also help to identify seizure precipitating factors. Absence seizures have a special tendency to get precipitated during hyperventilation. The photoparoxysmal response, defined as the occurrence of generalized spike, spike-wave or polyspike wave discharges consistently elicited by intermittent photic stimulation,[49] has a high correlation with primary generalized epilepsy.[13,50] A proportion of patients with photosensitivity may exhibit a similar EEG response to geometric patterns.[13,50] There are some racial differences in the reported prevalence of photoparoxysmal response. In White subjects with epilepsy it varied between 4 to 6%.[49-51] A lower prevalence was reported in the African and Asian population with epilepsy, 0.4% to 1.6%.[52-54] However, in a recent study from south India, the prevalence was similar to the studies among Whites, 3.5%.[55] The wide variations observed in these studies may be related to the differences in the characteristics of the patient group studied and the study protocol. Patients with suspected reflex epilepsies should be subjected, during EEG recording, to appropriate stimuli that precipitate seizures.[56] Cognitive tasks should include reading, speaking, listening to conversation, arithmetic calculation, writing, drawing and working crossword puzzles.[57-60]

Long-term Monitoring

Some diagnostic problems require prolonged observation of both behavior and EEG until sufficient number of the events in question has been recorded. The two commonly utilized methods are: video-digital EEG cable telemetry and ambulatory EEG monitoring (without video). Ambulatory EEG is most useful for investigating the patient in a natural environment, such as to determine whether a child suffers from absence seizures at school. It is important to recognize, in order to avoid misuse, that long-term EEG monitoring is not an alternative, but complimentary to careful clinical assessment.

Video-EEG monitoring provides long-term recording of EEG and time-locked video of the patient in a dedicated recording room. It is the most definitive method for differentiation between epileptic and nonepileptic events, categorization of seizure types, and localization of seizure onset (Fig. 1C, D). The investment in equipment and the time for monitoring make this procedure expensive as well as labor intensive. By carefully selecting the patients to answer specific questions, video-EEG monitoring can be utilized in a cost-effective manner in a developing region.[61]

Intensive Care EEG Monitoring

Neurophysiologic monitoring is increasingly utilized in intensive care units particularly in the detection of nonconvulsive status epilepticus.[62] In generalized convulsive status epilepticus, EEG is a valuable means of monitoring the effects of intravenous antiepileptic medication and is the only reliable guide in an anesthetized, paralyzed and ventilated patient as to whether seizures are continuing.[63]

Special Problems

Epileptic Seizure versus Nonepileptic Attack Disorders

Video-EEG monitoring is the most reliable investigation that can distinguish nonepileptic paroxysmal events from epileptic events. A patient may suffer from both psychogenic and epileptic seizures. The reported prevalence of psychogenic seizures in patients with epilepsy varied between 4% to 11% and that of epilepsy in subjects with psychogenic seizures was 8% to 36%.[64] However, frontal lobe seizures may still be misdiagnosed as psychogenic seizures. Occurrence of both false positive and false negative results limits the utility of prolactin assay for separating epileptic seizures from pseudoseizures.[65]

Epileptic Seizure Versus Syncope

EEG along with simultaneous electrocardiographic (ECG) monitoring is helpful in distinguishing syncopal events due to cerebral hypoperfusion from epileptic seizures. Regardless of the cause of cerebral hypoperfusion, EEG after an initial period of theta slowing, reveals high amplitude, frontally dominant delta activity.[66] If the hypoperfusion persists, there is subsequent flattening of the EEG. The EEG returns to normal in the reverse sequence. In case of profound and prolonged cerebral hypoperfusion, convulsions (convulsive syncope) may occur at the time of EEG flattening. Convulsive syncope and epileptic disorders associated with ictal bradycardia[67,68] may be difficult to differentiate, if attention is not paid to the chronology of the development of clinical, EEG and ECG phenomena.

Nonconvulsive Status Epilepticus

Nonconvulsive status epilepticus (NCSE) accounts for over one-quarter of all cases of status epilepticus and is more common in patients admitted to intensive care units.[69] The most important diagnostic procedure in the evaluation of patients with NCSE is the EEG. In a recent study, 8% of patients in altered sensorium with no overt seizure phenomena were found to have NCSE by EEG monitoring.[70]

Nonconvulsive status epilepticus is broadly divided into generalized (absence) or partial (complex partial) forms, although the electro-clinical differentiation is often indistinct.[69] The characteristic EEG features in patients with generalized (absence) NCSE is generalized spike and slow wave discharges and in complex partial status epilepticus EEG features are variable and may show irregular, asymmetric or focal

spike, multiple spikes and slow waves in various combinations or may be indistinguishable from that of generalized NCSE.[69,71] Attenuation of epileptiform activity with intravenous administration of benzodiazepines with marked improvement in consciousness and responsiveness is characteristic of NCSE.

Medically Refractory Epilepsy

Epilepsy surgery is an option for selected patients with medically refractory epilepsy. Temporal lobe epilepsy is the commonest form of medically refractory localization-related epilepsy and over 80% of epilepsy surgery involves the temporal lobe.[9,72] Seventy to 80% of patients with medically refractory temporal lobe epilepsy become seizure-free after epilepsy surgery.[10,11,72]

Success of epilepsy surgery depends on the accurate localization of the epileptogenic zone (the area necessary for initiating seizures and whose removal is necessary to achieve a seizure-free outcome).[73] Selection of ideal candidates for epilepsy surgery requires a careful correlation between clinical, neuropsychological, interictal scalp EEG, structural magnetic resonance imaging (MRI), ictal video-scalp EEG, interictal positron emission tomography, and ictal single photon emission computed tomography (SPECT) data.[9,73]

Today, a majority of patients with temporal lobe epilepsy are selected for surgery based on information gathered on noninvasive evaluation comprising clinical, and interictal and ictal scalp EEG, and MRI findings (Fig. 1).[74,75] Concordance of MRI and scalp interictal and ictal EEG abnormalities correlates with excellent postoperative seizure outcome.[75,76] Patients with strictly unilateral IEDs are more likely to have consistent ictal onset patterns than patients with bilateral independent temporal IEDs.[77] However, bilateral independent temporal IEDs can occur in ~50% of patients with medically refractory temporal lobe epilepsy.[78,79] Patients may require invasive EEG monitoring with subdural or depth electrodes when the results of noninvasive monitoring are not localizing or conflicting.[80] Invasive EEG monitoring escalates the cost of epilepsy surgery and is associated with increased morbidity.[80,81]

Role of Sphenoidal Electrodes

Since the International 10-20 System of electrode placement does not provide adequate coverage of the mesio-basal temporal lobe, several types of additional electrodes including anterior temporal, zygomatic, cheek, mandibular notch surface and subdermal, nasopharyngeal, sphenoidal, mini-sphenoidal, and cavernous sinus electrodes, have been developed.[82-84] The Modified Combinatorial System of electrode placement provides more extensive coverage of the scalp.[85]

The anterior temporal and sphenoidal electrodes are widely used during prolonged video-EEG monitoring. Several studies have compared sphenoidal electrodes with anterior temporal, cheek and other surface electrodes for the detection of interictal and ictal abnormalities with inconsistent results.[83,86,87] It appears that anterior temporal scalp electrodes are as effective as sphenoidal electrodes in detecting IEDs. Kanner et al[87] have emphasized that the position of the tip of the sphenoidal electrode, close to foramen ovale (preferably under fluoroscopic control, plays a crucial role in its efficacy to detect mesial temporal IEDs and ictal activity. We have also found sphenoidal electrodes placed close to foramen ovale under fluoroscopic control useful in patients with temporal lobe epilepsy whose initial scalp recorded ictal EEG pattern was poorly visualized or contaminated by myogenic artifacts.[82]

Neuroimaging

In most developing countries CT scans are more widely available than MRI scans. Although the most effective brain imaging study for a person with epilepsy is a MRI, in tropical countries, because of the cost, CT scan is often the first brain imaging study performed. A majority of the MRIs, done outside the comprehensive epilepsy care center, do not conform to the specifications laid down for patients with refractory epilepsy. Repeating another MRI will add to the financial hardship of the patient.

Indications

The goals of neuroimaging in persons with epilepsy are: (a) delineation of structural and functional abnormalities in the suspected epileptogenic region, (b) prediction of the nature of the structural pathology, (c) detection of abnormalities distant from the putative epileptogenic region (diffuse or dual pathology), and (d) identification of eloquent brain regions, such as language, memory, and sensorimotor areas, and the relation of these regions to the epileptogenic lesion.[88] Every patient with adult onset partial seizures and those with medically unsatisfactorily controlled seizures, irrespective of seizure type, should have a neuroimaging. Neuroimaging studies may not be necessary in patients with well-characterized generalized idiopathic epilepsies and epilepsy syndromes. Similarly, children with uncomplicated febrile seizures and normal neurological examination do not require imaging studies.[89]

Neuroimaging Modalities

Several imaging modalities are available to evaluate persons with seizure disorders (Table 3). The two commonly utilized imaging modalities are CT and MRI.

Computed Tomography Scan

The CT can detect only gross structural abnormalities. A negative CT in a patient with chronic epilepsy conveys little information. The use of CT in epilepsy today is restricted to emergency setting and in patients presenting with recent onset seizures.

In a review, of the 766 patients who presented to emergency departments with seizures, CT was abnormal in 27% of patients.[90] Patients with focal neurological deficits had more chances of having an abnormal CT than patients without deficits, 41% vs 13%. In a prospective study, of the 66 children presented to emergency department with seizures, 78.8% of children had normal CT. Of the children with suspected symptomatic seizures, 60% had abnormal CT whereas it was 6% in children with cryptogenic seizures. None of the children with complex febrile seizures had an abnormal CT.[91]

In developing countries infections of the central nervous system account for significant proportion of risk factors for both acute symptomatic seizures and epilepsy. CT can be an appropriate initial imaging modality to demonstrate infective pathology. Neurocysticercosis is a major cause of epileptic seizures in developing countries and most of the lesions due to brain cysticercoids can be demonstrated by a contrast CT.[92] Single small enhancing lesions (SSEL)[93] and single small cerebral calcific lesions[7] are common findings in the brain CTs of patients with epilepsy in India and in other developing countries endemic to neurocysticercosis. The pathological substrate of SSLE, in majority of cases, is solitary cysticercus granuloma and small calcific lesion(s) is evidence of cysticercal parenchymal brain involvement previous to the calcification becoming evident in the CT.[7,93]

Table 3. Imaging modalities and their yield in epilepsy

Computed tomography
Emergent situations
Recent onset seizure (suspected single small enhancing lesion)
Structural magnetic resonance imaging (MRI)
Mesial temporal sclerosis
Developmental cortical malformations
Vascular malformations
Low-grade neoplasms
Atrophic lesions
Functional imaging/procedures
MRI T2-relaxometry
Functional MRI
Magnetic resonance spectroscopy
Single photon emission computed tomography
Positron emission tomograpy
Magnetoencephalography
Intracarotid amobarbital (Wada) procedure

Magnetic Resonance Imaging

Structural MRI is the best tool available to define the normal brain structure and to identify the abnormal structure and is the investigation of choice in patients with medically refractory epilepsy.[94] During presurgical evaluation, modern imaging modalities play an important role in the selection of ideal surgical candidates.[95,96] The common lesions identified by structural MRI in patients with chronic epilepsy are mesial temporal sclerosis (Fig. 1B), cortical developmental and vascular malformations, low-grade neoplasms and focal atrophic lesions (Table 3).

Several MRI techniques are utilized in the evaluation of patients with medically refractory epilepsy (Table 3). In developing countries, one has to utilize the available MRI facilities in a systematic cost-effective manner to obtain optimum results.[96] A dedicated team of neuroradiologists interested and experienced in imaging in epilepsy will bring more dividends than expensive software meant for volume acquisition. For these reasons it will be most cost-effective to do imaging evaluation of patients with medically refractory epilepsy in centers involved in epilepsy surgery.

The commonest surgically remediable lesion in patients with medically refractory epilepsy is mesial temporal sclerosis, characterized by atrophy and sclerosis involving predominantly the hippocampus, but often extending to amygdala and the rest of the mesial temporal structures (Fig. 1B). The routinely used MRI protocol for structural imaging in patients with medically refractory epilepsy is aimed at defining this lesion, and should include T1-weighted images in axial and sagittal planes, and T2-weighted and proton density sequences in axial and coronal planes, with 3 mm thickness and zero spacing, and T1-weighted three dimensional spoil gradient echo (3D SPGR) images in coronal plane with 1.5 mm slice thickness.[96] Fluid attenuated inversion recovery (FLAIR) images are often helpful to clarify the significance of a focal abnormality. To an experienced epilepsy radiologist, visual analysis of MRI provides as much information as can be obtained by volumetry.[95] However, in patients with bilateral MTS, volumetry helps to identify the side maximally affected.[97]

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Chapter 8

Etiological Implication of Prenatal and Perinatal Brain Injury

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Most of the epilepsy has long been believed to commence in childhood and thereafter decline with age. However, in developed countries increased incidence of epilepsy in the elderly has been reported with the progressive aging of the population,[1,2] whereas that in childhood has decreased nearly by 40%.[3] Two incidence peaks early in the childhood and in the senescence over 60 years of age has been observed.[3,4] When compared to developed countries the incidence of epilepsy in childhood in developing countries is higher by a factor of 20 to 50%.[5-8] Similarly the reported prevalence rates are also one-and-half to three times higher, 3.5 to 17 per 1000 population.[7,8] The increased incidence of epilepsy in childhood in developing countries has been attributed to higher incidence of pre and perinatal acquired brain injury, endemic infections of central nervous system (CNS), and poor socio-economic conditions prevailing in these countries.[9,10]

Etiologically, pre and perinatal factors are involved in the majority of children with epilepsy. Those with onset in adolescence or later life may have causative factors in early stage of life, but it is often difficult to confirm pre and perinatal events precisely. Until recently, causes of perinatal brain damage are considered more important than prenatal factors. However, technological advances in neuroimaging and molecular genetics have attracted the attention of prenatal causes. Even in those with brain damages supposedly caused by neonatal asphyxia, not a few may be vulnerable to perinatal distress because of prenatal cerebral dysgenesis.

In this chapter, pre and perinatal acquired causes of epilepsy with special reference to developing countries are discussed.

Etiology - Classification

It is well known that both endogenous, i.e., genetic, and exogenous causative factors are related to epilepsy, and their relative importance is individually different. The latter consists of not only acquired brain damages, which mostly occur intrauterine, peri- and postnatally, but also neuronal damage due to inherited metabolic disorders or degenerative diseases. Accordingly, exogenous factors are classified into static and progressive pathologies.

International classification of epilepsies and epileptic syndromes proposed by International League Against Epilepsy[11] classifies epilepsies etiologically into idiopathic, cryptogenic and symptomatic. Idiopathic epilepsy is virtually synonymous with genetic epilepsy. Symptomatic seizures are further divided into provoked or acute symptomatic seizures, and unprovoked or remote symptomatic seizures. Acute symptomatic seizures are those reactively caused or provoked by an acute medical or neurological insult. Remote symptomatic seizures are those that occur in association

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with nonprogressive static encephalopathy or sometimes with progressive cerebral pathologies. However, it should be noted that not all etiologies work in isolation; some occur in association with others. Thus, finding out a single etiologic factor does not always mean the end of evaluation.

Etiology of Epilepsy - Epidemiology

Most of the community-based epidemiological studies of epilepsy in all age-groups suggest that in about 40-80% of people with epilepsy no known etiology could be established.[1-8] There is no remarkable difference in the studies exclusive to childhood epilepsies.[12-16] In the developed world cerebrovascular diseases are important putative risk factor for epilepsy in the elderly.[2,3] Recently, human immunodeficiency virus (HIV) infection has gained significance among progressive conditions.[2] In childhood epilepsy prenatal etiologies such as neuronal migration disorders, congenital syndromes, chromosomal abnormalities and prenatal CNS infections, prenatal and perinatal birth related antecedent events account for a significant proportion of known etiology of epilepsy, more so in developing countries.[9,10] In addition, mental retardation and cerebral palsy of unknown etiology account for about 20%.[12]

In the earlier years when proper investigative facilities were not available, perinatal etiologies often exceeded prenatal etiologies.[13,16] However, with availability of more advanced investigative facilities prenatal factors are more frequently observed.[12,14,15] The reported relative frequency of pre-, peri-, and postnatal risk factors for epilepsy by Eriksson and Koivikko[14] was 15%, 9%, and 12% respectively. This study includes patients with prolonged isolated seizure also. Prematurity and small-for-dates (SFD) were considered by Van den Berg and Yerushalmy,[17] as risk factors for afebrile seizures. Nelson and Ellenberg[18] stressed the importance of neonatal seizures and congenital malformations for later development of epilepsy but not SFD and low Apgar scores. Hypoxia, however, may be an indirect risk factor for epilepsy, considering its importance as the causative factor for neonatal seizures.

The prevalence study on childhood epilepsy in Okayama Prefecture in 1999[19] showed a decline in the perinatal factors such as birth asphyxia and abnormal deliveries to 5.0% when compared to 15.8% in the study performed in 1978.[20] On the other hand, there was an increase in the prenatal factors from 3.2% to 4.3%. Oka[19] interpreted these findings to the technological developments in the investigative workup. Prospective follow-up cohort studies have also suggested the larger effect of prenatal etiologies than those of perinatal.[18,21]

In developing countries the scenario is totally different and pre and perinatal antecedents and infections of central nervous system (CNS) account for the much of the known putative risk factors for epilepsy.[7,22,23,25] Unprovoked seizures can be the sequelae of CNS infection and the risk is increased by 10-fold during the first 5 years after infections of CNS.[24] Endemic infections like cerebral malaria are almost exclusively observed in this area.[7,22,23,25-27] Cerebral malaria is an acute encephalopathy caused by plasmodium falciparum and leads to acute symptomatic generalized seizures in 20-50% of adults and in the majority of children.[22,23,27] Remote symptomatic epilepsy may develop by the astrocytosis due to vascular invasion of the organisms.[23,27] Malaria is also the commonest cause of fever in febrile convulsions; almost 50% of febrile convulsions in Africa are closely related to malaria.[25] Febrile convulsions tend to be prolonged and later may evolve as mesial temporal lobe epilepsy.[25] It may be difficult to differentiate febrile convulsions triggered by fever of common malaria from cerebral malaria with generalized seizures.[23] Japanese B encephalitis is the most frequent viral encephalitis in developing countries and up to

20% of survivors may later develop remote symptomatic epilepsy.[23,28] Many parasites can cause seizures, but neurocysticercosis represents a major risk factor in developing countries; nearly 30% of seizure disorders are related to neurocysticercosis.[23,25-27] Meningitis and infections related to HIV are very frequent in developing countries.[25-27] Seizures are attributable either to HIV encephalopathy, or to an associated opportunistic infection, such as tuberculosis and toxoplasmosis. About 25% of patients with acquired immunodeficiency syndrome (AIDS) have toxoplasmosis.[23] Tuberculosis is responsible for certain partial seizures due to intracerebral tuberculomas or sequels of tuberculous meningitis.[23,25,26]

High prevalence of epilepsy in developing countries generally has to do with such specific etiologies, but also with other socioenvironmental factors, such as undernuturition and poor sanitation, consanguinity, and pre and perinatal complications. With head injury, traffic accidents are becoming much commoner in developing countries with poor safety measures, road conditions, driving habits, and accessibility to emergency medical care, in which rural and urban differences are also big.[27]

Prenatal Factors

Prenatal etiologic factors include gene abnormalities, chromosomal abnormalities and various prenatal environmental factors affecting embryo and fetus. Prenatal factors usually cause developmental brain abnormalities, patterns of which are mainly depend on the timing of CNS development that the causative factors are applied, usually not specific to the kinds of insults. Gross brain malformations are caused by the teratogenic factors during organogenesis, mainly 3 to 8 weeks of conception, or by the destruction of once normally formed structure due to vascular events, teratogens, and others. In the fetal period, migration disorders occur, ranging widely from lissencephaly to microdysgenesis. Abnormalities of gyral formation may be found in a number of metabolic disorders, congenital syndromes like Aicardi syndrome, neucutaneous syndromes, and other genetic conditions, due to secondary morphogenetic abnormalities. In cortical malformations, abnormal and unwanted neuronal circuits may easily become epileptogenic and may be reinforced by seizure discharges, inhibiting the development of more desirable pathways. Neurophysiologically, high amplitude rhythmic activities and focal rhythmic spikes are somewhat characteristic in extensive and focal dysplasia, respectively.

Recent progress in molecular genetics has been disclosing gene abnormalities of idiopathic epilepsies as well as inborn errors of metabolism and degenerative diseases which may cause symptomatic epilepsies. Chromosome abnormalities of high association with epilepsy, such as Angelman (del 15q11-13), Wolf-Hirschhorn (del 4pterm-p15), Miller-Dieker (del 17p13.3) syndromes, ring chromosome 20, may be an efficient clue to epilepsy genes. Already disclosed epilepsy genes of idiopathic epilepsies are mostly related to ion-channels of Na, K, Cl, which may suggest epilepsy as channelopathy. The finding that the same abnormality is observed in various types of epilepsy may suggest the genetic heterogeneity or contribution of polygenes. The etiology of epilepsy may be multifactorial and genetic traits may interact with environmental factors to lower the seizure threshold. These genetic abnormalities may accumulate in some localized area in the developing countries due to poor movement or interchange among population.

Prenatal environmental factors such as maternal infection, nutritional conditions or other diseases and their treatment, ischemia, irradiation, and chemicals

affect embryo and fetus. These will be referred more to the condition of developing countries.

Prenatal Infections

Maternal infections during pregnancy are known to affect the embryo and cause brain damage resulting in various malformations according to the critical timing of organogenesis.[29] Toxoplasmosis, syphilis, rubella, herpes, cytomegalovirus (CMV), and other viruses are known to affect central nervous system prenatally.

Newly acquired toxoplasmosis occurs in about 0.1~2% of all pregnancies[30] and mental retardation and epilepsy (80%) were frequently reported in cases with congenital toxoplasmosis.[23,29,30] This etiology accounted for 6.8% of putative risk factor for epilepsy in inmates of an institute for the mentally handicapped.[27] Acute and remote symptomatic seizures can be associated with congenital toxoplasmosis in up to 50% of affected children, who are often associated with chorioretinitis and a variety of CNS abnormalities including microcephaly, hydrocephalus, cerebral calcification, cerebral palsy and blindness.[23,29,30]

Congenital rubella occurs in more than 80% of infants of maternal rubella during the first 12 weeks of pregnancy, in 54% during 13 to 14 weeks, and in 25% at the end of the second trimester.[31] The infection rate increases again during the last month of pregnancy. Histologically three types of neuronal damage have been identified: cellular growth retardation or inhibition, cellular necrosis related to vascular lesions and inflammation.[32] Seizures occur in 25% of the affected children.[33] West syndrome and Lennox-Gastaut syndrome (LGS) may be the presenting epileptic syndrome. Another type of seizures are abrupt vasomotor changes.[33] About one-third of affected children demonstrate a variety of EEG abnormalities, including hypsarrhythmia.

Prenatal cytomegalovirus (CMV) infection occurs through the first to third trimesters in symptomatic patients. CMV has an affinity for the rapidly proliferating subependymal cells lining the ventricles. Viral multiplication and subsequent calcium deposition result in brain disruption or dysgenesis with periventricular or diffuse calcification. Microcephaly (50%), hydrocephalus, neuronal migration disorders, porencephaly, and polycystic encephalomalasia are observed. Mental retardation, visual disturbance, hearing loss, language disorders, and epilepsy can be observed.[23,29,30]

Varicella embryopathy occurs in approximately 2% of infants born to mothers infected with varicella during the first 20 weeks of gestation[34] and is associated with microcephaly, porencephaly, and cerebral calcification and subsequent mental retardation and seizures (26~50%).[29]

Transplacental infection of herpes simplex type 2 has been recognized in the primary maternal infection during pregnancy, resulting in microcephaly, intracranial calcifications, epilepsy, microphthalmos and retinal dysplasia.[29,30]

Hypoxia and Ischemia

Hypoxia and/or ischemia due to threatened abortion or premature delivery, maternal hypotension, placental dysfunction, or maternal hormonal environment and other illnesses are risk factors for abnormal fetal development and epilepsy.

Other Factors

Besides infections, maternal diseases, metabolic disorders, and hormonal derangement are also risk factors for abnormal fetal development and epilepsy. Irradiations, food additives, insecticides, medicines, and other chemicals, narcotics, nicotine and alcohol are known to affect the morphological and functional development of the embryo and fetus.[35] Fetal brain was most vulnerable to irradiation at the 8th to 15th week of conception.[36]

Perinatal Factors

Proper antenatal care, advances in fetal monitoring, supervised deliveries, and specialist care in case of high-risk pregnancies have considerably reduced birth related brain injuries in the developed world. In the developing world maternal and child health care systems are poorly developed and not yet optimal. Perinatal morbidity and mortality is still very high because of a variety of factors, poor maternal health at the start of pregnancy, lack of antenatal and postnatal care, large family size, home deliveries by traditional birth-attendants, and high frequency of preterm deliveries.[10,27]

In the developed world survival of very-low-birth-weight (VLBW) and extremely-low-birth-weight (ELBW) infants is not unusual. With development in the treatment of respiratory distress syndrome, the incidence of ventricular hemorrhages, an important prognostic factor in these infants, has been considerably decreased.[29] The reported incidence of periventricular leukomalacia (PVL) in premature or low birth weight infant varied between 4% and 15%.[29,37,38] However the scenario is totally different in the developing world. Deliveries in developing countries are often conducted by traditional birth-attendants in difficult environments; the frequency of preterm deliveries is twice as high as that in developed countries; and mothers are malnourished and exposed to violence and infection.[27]

In developing countries, the most common cause of epilepsy in the very young is perinatal brain damage.[23,27] Most of the data from developing countries is from the descriptive studies. In these studies perinatal brain damage would account for 13-14% of the etiology of epilepsy observed in children.[25] Prenatal and perinatal pathology was felt to be associated with epilepsy in 11% of patients in the studies from Chile, Brazil, and Ecuador.[10] In the neonatal period, delay of first cry, abnormalities of tone, neonatal seizures, and meningitis were leading predictors of late seizures.

Premature Birth / Low Birth Weight

With improvement in the survival of very premature, the risk of epilepsy has been shown to be high in infants with low birth weight. The risk of developing epilepsy in the later life is very high in neonates with gestational age less than 27-weeks and birth weight less than 1000 g.[39] Of the 29 neonates with ELBW (<1,000 g) followed for a period of 11 to 14 years, 17.2% had epilepsy and 10.3% with active epilepsy. The corresponding figures for the 197 neonates with VLBW (<1,500 g) were 4.1% and 2.5% respectively.[39] Causes of brain damages in low birth weight children include hypoxia-ischemia, PVL, intracranial hemorrhage such as subependymal hemorrhage (SEH) and intraventricular hemorrhage (IVH).[29]

Periventricular Leukomalacia

Periventricular leukomalacia (PVL) is a ischemic cerebral white matter disorder and occurs in the premature brain of about 24-35 weeks of gestation.[29,38] In addition to arterial ischemia, other factors involved in the pathophysiology of these changes include immaturity of the brain, underdeveloped cerebral vasculature and nature of cell component such as intrinsic vulnerability of the oligodendroglia, hemorrhage during later pregnancy and perinatal period, vascular anastomosis in the placenta, and hypotension. Factors relating prenatal infections, such as chorioamnionitis, may also play a role through cytokines.[29,37,38,40] Hypocapnia due to mechanical ventilation is one of the risk factors for ischemia.[38]

In acute phase neuro-sonography shows periventricular echodense and/or echolucent cystic lesion and in chronic phase MRI reveals signal changes or decreased volume of periventricular white matter.[29,40] Reduction in cortical gray matter volume presumably secondary to axonal loss is also detected.[41] Spastic diplegia is the main clinical outcome, often associated with epilepsy.[40,42] Sprouting following axonal damage may result in reorganization of neuronal network and probably may contribute to the epileptogenicity.[43]

Intracranial Hemorrhages and Ischemia

Incidence and the type of intracranial hemorrhages depend on the maturity of the fetus and newborn. In the mature fetuses asphyxia and traumatic delivery can result in subdural or subarachnoid hemorrhage, whereas SEH and IVH occur exclusively in the premature babies.[29] IVH dominantly occurs in the newborns with gestational age ≤ 32 weeks and incidence is inversely related to birth weight. The highest incidence is in the newborns with ELBW. The incidence in the newborns with VLBW is 20% to 30%. About 50% germinal matrix (GM) hemorrhages, i.e., SHE, occur on the first day of life and 90% by the fourth day. It relates to the immaturity of the vasculature in the germinal matrix. Other factors that predispose to hemorrhage include vascular congestion; underdeveloped supporting tissues, poorly developed autoregulation and also not so well developed coagulation mechanism.

Approximately 80% of bleeding in the GM extends into the ventricles (IVH), and may also be associated with intracerebral hemorrhage. Intraventricular hemorrhage may lead to ventricular dilatation (posthemorrhagic hydrocephalus), periventricular cerebral infarction (~10-15%), concomitant periventricular leukomalacia, local hemorrhagic injury to the subependyma (GM) and focal ischemia and injury. Severe bleeding is associated with higher mortality and progressive ventricular dilatation with serious neurological sequels.[29] Those with periventricular hemorrhagic infarction (PVHI) have particularly poor prognoses. In very premature newborn, unstable hemodynamics due to anemia, hypotension, acidosis and disseminated intravascular coagulation is associated with very poor prognosis. Pre or perinatal ischemic stroke, both arterial and venous, presumably related to coagulopathies is also a rare but important risk factor of neurological disorders including epilepsy.[44]

Neonatal Asphyxia, Hypoxic (Anoxic)-Ischemic Encephalopathy

Hypoxia and/or ischemia often cause brain insult (hypoxic-ischemic encephalopathy) which may be transient or permanent.[29,45] The risk of epilepsy was 5.1 times higher in the group of newborns with acute neurological disorders related to fetal

and/or neonatal hypoxia than in the control group.[46] Although the incidence of epilepsy is higher in the first year of life, epileptic seizures associated with perinatal hypoxia may occur in early childhood or later in life. However, there is no difference in the incidence of febrile seizures between the two groups.[46]

Neonatal Seizures

Neonatal seizures are more often provoked (acute symptomatic) seizures due to an acute neurological insult or systemic illness. The etiological factors include perinatal hypoxic-ischemic encephalopathy, infections (meningitis, encephalitis), intracranial hemorrhage (intraventricular, intracerebral, subarachnoid), cerebral infarcts, metabolic disorders (hypoglycemia, hypocalcemia, hypomagnesemia), inborn errors of metabolism, congenital brain anomalies, drug and drug withdrawal.[29,47-49] Severity of CNS insult and probably the underlying genetically determined lowered seizure threshold determine the severity of acute seizures. The etiological factors for acute symptomatic seizure may later predispose to epilepsy. Prolonged seizures or status epilepticus may result in further brain damage and later epilepsy,[50] although still controversial.[29,47,49]

Thus, prognosis of neonatal seizures depends on the underlying etiology and the associated brain damage. Few studies examined the relationship between neonatal seizures and development of epilepsy in later life. The reported frequency of development of epilepsy in the survivors with neonatal seizures is about 20-30%.[18,47] One study[51] reported an exceptionally high rate of 56% and probably it was related to the inclusion of high-risk population in the study. Coma and background EEG abnormalities are the risk factors for development of post-neonatal epilepsy.

Perinatal Infection

Bacterial (pyogenic) meningitis, due to group *B Streptococcus*, *E. Coli*, *Klebsiella*, rarely *Listeria Monocytogenis* in neonates, may lead to acute and chronic symptomatic seizures, typically partial with or without secondary generalization.[29] Seizures in acute phase may be related to the extension of the pathology beyond meninges. Inflammatory process may involve both small and large arteries and veins often leading to cerebral infarction.[23,29] About 30% of patients with gram-negative bacterial meningitis may develop remote symptomatic seizures.[29] Tuberculous meningitis in early stage leads to vasculitis, cerebral infarction and obstructive hydrocephalus resulting in severe multiple handicaps and epilepsy. Epilepsy can be the sequelae of tuberculous meningitis in about 10% of patients.[23]

Infectious encephalitis are mainly caused by viruses, such as enteroviruses, mumps, measles, lymphocytic choriomeningitis and herpes viruses, arboviruses, HIV and CMV, but other diseases, particularly Lyme disease and mycoplasma pneumonia can sometimes cause a similar picture. Most cases of herpes infection including type 1 and 2 develop in the neonatal period.[29,52] A 16-fold increase in unprovoked seizures was reported with viral encephalitis and the risk was more when associated with early seizures.[24]

In approximately 80% of the infected offspring (with infection rate of 10-40%) of HIV infected mothers, transmission of virus occurs just before or at the time of the delivery, and in 20% the virus may infect the fetus during intrauterine life. Infants born before 34 weeks gestation have a higher rate of vertical transmission of HIV-1.[29,52]

Conclusions

In developing countries the prevalence and incidence of epilepsy in childhood is significantly very high when compared to developed countries. Much of the etiology of epilepsy in this age group is preventable and includes pre and perinatal brain injury and CNS infections. Still perinatal factors account for a significant proportion of the etiology of epilepsy in developing countries. To some extent the burden of epilepsy related to these etiological factors, could be prevented by establishing effective maternity and child health care systems.

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Chapter 9

Remote Symptomatic Epilepsies and Epileptic Syndromes: Etiological Spectrum

Arturo Carpio and W. Allen Hauser

Most of the tropical countries in the world are underdeveloped or developing countries that form part of the so-called "Third World". These countries not only have geographic but also social, economic, and ethnic differences as compared to the northern countries of the world. Consequently, there are substantial differences in the relationship between health and disease. The socioeconomic structure of developing countries is marked by profound contrasts. A small percentage of the population has access to institutions, frequently privately owned, equipped with the latest and most sophisticated methods of diagnosis, which offer high quality service. But the majority of the populations seek health care from the few public institutions that cannot provide optimal services because of economic and administrative limitations. Most of the population suffers the effects of poverty, illiteracy, and malnutrition. Infectious and parasitic diseases remain the leading cause of mortality in these developing countries.[1]

Epilepsy is a major health problem worldwide, however, the burden frequency of epilepsy appears to be greater in developing countries than in developed countries.[2,3] Whether this difference is related to methodological issues or to the factors that potentially increase the risk of epilepsy such as poor perinatal care, head injury, and infectious and parasitic diseases, remains to be unanswered. Worldwide epilepsy carries a strong social stigma, but factors such as poor education and superstition in developing countries lead to even greater stigma, as a consequence, the majority of the population with epilepsy in these countries remain untreated.[4,5] These circumstances have an impact on both medical and social approaches to epilepsy. Poor health-care facilities and lack of technology not only reflect the quality of health care; but also make research in this area very difficult. There is a relative absence of reliable medical records and hospital registers for use in epidemiological and clinical studies. As a consequence, information related to causal or risk factors of epilepsy in developing countries is very scarce.[6,7] This chapter reviews the available information about the clinical studies of epilepsy syndromes and the etiology of epilepsy in tropical and developing countries.

Definitions and Classification

The International Classification of Epileptic Syndromes and Epilepsies was first proposed in 1970.[8] This classification takes into consideration the fundamental dichotomy between partial and generalized seizures, and also a second essential dichotomy between age-related idiopathic or cryptogenic epilepsies on the one hand, and symptomatic epilepsies on the other. The revised classification in 1985[9] created two new categories: "epilepsies undetermined as to whether focal or generalized,"

Epilepsy in the Tropics, edited by J.M.K. Murthy and Nimal Senanayake.

and "special syndromes." The 1989 proposal[10] gave a more precise meaning to the terms "idiopathic," "symptomatic," and "cryptogenic." International League Against Epilepsy (ILAE) recently appointed a Task Force on Classification and Terminology to review the current classification system for epileptic seizures and syndromes,[11] considering the advances in the understanding of the pathophysiology and anatomic substrates of epileptic seizures, and also several recently described new epileptic syndromes. The Task Force maintains the term "symptomatic epilepsy" and is used to define a syndrome in which the epileptic seizures are the result of one or more identifiable structural lesions of the brain. "Idiopathic epilepsy" indicates that etiology is presumed to be genetic and is usually age dependent, with no underlying structural brain lesion or other neurologic signs or symptoms. "Cryptogenic epilepsy" is defined as a syndrome that is believed to be symptomatic; but no etiology has been identified. The Task Force proposes "probably symptomatic epilepsy syndrome" instead of cryptogenic epilepsy.

In accordance with the above concepts, and to make the studies that have been published so far comparable, we can also maintain the definitions suggested by the ILAE - Commission on Epidemiology and Prognosis in 1993,[12] regarding the differentiation between "provoked or acute symptomatic seizures" and "unprovoked seizures". Acute symptomatic seizures occur in close temporal association with an acute systemic, metabolic, or toxic insult. Symptomatic unprovoked seizures (epilepsy, if seizures recur) may occur subsequent to a well-demonstrated antecedent condition, known to substantially increase the risk of epileptic seizures. Similarly, cases of idiopathic or cryptogenic unprovoked seizures are recognized according to the above definitions. Symptomatic unprovoked seizures are categorized into two major subgroups: (1) remote symptomatic unprovoked seizures following conditions resulting in a static encephalopathy, such as infection, cerebral trauma, or cerebro-vascular disease, which are generally presumed to be the result of this nonprogressive (static) lesion; (2) progressive symptomatic unprovoked seizures occurring in association with progressive central nervous system (CNS) disorder, such as degenerative brain diseases. Most of the published studies include both categories, remote and progressive, under "symptomatic epilepsy".

Epilepsy Syndromes

Classification of epilepsies is important in clinical practice and research because the etiology, treatment, and prognosis differ remarkably with the type of epilepsy.[13] The main objective of the International Classification of Epilepsies and Epileptic Syndromes (ICEES) proposed by ILAE is to provide a common language for clear communication among physicians.[11] This classification is widely accepted and it is applied in clinical research as well as in daily clinical practice by epileptologists; however, some general neurologists and practicing physicians still find it difficult to apply in many patients. This classification is seldom used in clinical practice because there is confusion between seizure type and epilepsy syndrome.[14] The task force of ILAE is at present revising the current classification in order to provide a universal vocabulary that not only facilitates communication among clinicians, but also establishes a taxonomic foundation for performing quantitative clinical and basic research in epilepsy.[11] Additionally, studying epilepsy in terms of syndromes rather than symptoms could provide a much better approach to understand pathophysiology, treatment and prognosis of patients with epilepsy.

Table 1. Distribution of epilepsies and epilepsy syndromes in children

	Carpio et al[15] (Ecuador)		**Berg et al[16] (USA)***		**Sillanpa et al[17] (Finland)****		**Shah et al[21] (India)****	
	181	(%)	613	(%)	245	(%)	1742	(%)
1. Localization-related	**86**	**(48)**	**359**	**(59)**	**95**	**(63)**	**954**	**(55)**
1.1 Idiopathic	10	(6)	61	(10)	14	(9)	69	(4)
1.2 Symptomatic	29	(16)	195	(32)	75	(50)	466	(27)
1.3 Cryptogenic	47	(26)	103	(17)	6	(4)	419	(24)
2. Generalized	**67**	**(37)**	**178**	**(29)**	**40**	**(27)**	**620**	**(36)**
2.1 Idiopathic	52	(29)	126	(21)	33	(22)	252	(14)
2.2 Cryptogenic or symptomatic	7	(4)	43	(7)	7	(5)	159	(9)
2.3 Symptomatic	9	(5)	9	(1.5)			209	(12)
3. Undetermined whether focal or generalized	**28**	**(15)**	**71**	**(12)**	**7**	**(4)**	**168**	**(10)**

* Newly diagnosed unprovoked seizures; ** Prevalent unprovoked seizures

Table 2. Distribution of epilepsies and epilepsy syndromes in patients with newly diagnosed unprovoked seizures (all age groups)

	Carpio et al[15] (Ecuador)		Manford et al[24] (England)*		Jallon et al[13] (Switzerland)	
	310	**(%)**	**594**	**(%)**	**1016**	**(%)**
1. Localization-related	**179**	**(58)**	**252**	**(42)**	**482**	**(47)**
1.1 Idiopathic	10	(3)	7	(1)	48	(5)
1.2 Symptomatic	84	(27)	96	(16)	137	(13.5)
1.3 Cryptogenic	85	(27.5)	146	(24.5)	297	(29)
2. Generalized	**93**	**(30)**	**66**	**(11)**	**343**	**(34)**
2.1 Idiopathic	75	(24.2)	55	(9)	278	(27)
2.2 Cryptogenic or symptomatic	7	(2.3)	0	(0)	39	(4)
2.3 Symptomatic	11	(3.5)	11	(2)	26	(3)
3. Undetermined whether focal or generalized	**38**	**(12)**	**190**	**(32)**	**177**	**(17)**

* Excluding patients with special syndromes

Table 3. Distribution of epilepsies and epilepsy syndromes in prevalent unprovoked seizures (all age groups)

	Senanayake[19] (Sri Lanka)*		**Murthy et al[18] (India)***		**ILAE[20] (Italy)***	
	1250	(%)	2531	(%)	6889	(%)
1. Localization-related	**917**	**(73)**	**1591**	**(63)**	**4323**	**(63)**
1.1 Idiopathic	24	(2)	18	(1)	375	(5.4)
1.2 Symptomatic	133	(11)	997	(39)	1991	(29)
1.3 Cryptogenic	760	(61)	456	(23)	1957	(28.4)
2. Generalized	**228**	**(18)**	**299**	**(12)**	**1750**	**(25)**
2.1 Idiopathic	214	(17)	162	(6.5)	1272	(18.5)
2.2 Cryptogenic or symptomatic	0	(o)	64	(2.5)	287	(4)
2.3 Symptomatic	14	(1)	73	(3)	152	(2)
3. Undetermined whether focal or generalized	**104**	**(8)**	**503**	**(20)**	**227**	**(3)**

* Excluding special or unclassified syndromes

Table 4. Etiology of symptomatic epilepsies

	Carpio et al[15] (Ecuador)	Hauser et al[29] (USA)
Idiopathic/cryptogenic	65.9%	65.5%
Symptomatic	34.1%	34.5%
Perinatal brain damage	7.7%	
Neurocysticercosis	8.7%	
CNS infections	4.2%	2.5%
Stroke	4.8%	10.9%
Head trauma	3.8%	5.5%
Tumors	1.6%	4.1%
Others	3.1%	11.5%*

* Includes congenital 8% (mental retardation and cerebral palsy)

It is important to consider the differences among studies using prevalent cases of epilepsy and those who recruit newly diagnosed epilepsy specially when considering etiology. In a design to analyze etiology, it is desirable to select incident cases instead of prevalent cases, because it is very difficult to distinguish potential etiology that preceded the disease from that which occurred after the disease developed, thus making it hard to differentiate between cause and effect.

There is also a substantial difference in the distribution of syndromes in the first seizures when compared with the newly diagnosed epilepsy groups. Certain seizures types, which are characteristic of specific syndromes, are less likely to present to medical attention at the time of an initial event, such as absence, myoclonic, infantile spasms, and partial complex seizures, whereas generalized tonic-clonic seizures are most likely to come to medical attention.

There is a good agreement across studies in the criteria used to classify idiopathic syndromes. These syndromes are very specific and well defined with respect to several clinical factors, such as age at onset, seizures type, and specific EEG abnormalities (e.g., 3-Hz generalized spike and wave). The proportion of patients with generalized idiopathic epilepsy in childhood series is fairly similar (Table 1) in the studies from Ecuador[15] (29%), USA[16] (21%) and Finland[17] (22%). On the contrary, symptomatic localization-related epilepsies are a group of more diverse syndromes and the criteria for the classification of these epilepsies are somewhat more subjective to interpretation[13] and it is probably due to differences in the risk factors for epilepsy between developed and developing countries.

Localization-related Epilepsies

The reported frequency of localization-related epilepsies in the series from developing countries varies between 57.7% per cent in Ecuador,[15] 62.9% in India,[18] and 73.4% in Sri Lanka.[19] These differences are probably related to methodological issues. The Ecuadorian study included only newly diagnosed patients whereas the data from India and Sri Lanka was based on the prevalent cases. However, the reported frequency of localization-related epilepsies in developing countries is similar to the reported frequency in developed countries, 62.8% in Italy[20] (Italian study 1995) and 58.6% in France.[13] All these studies included patients of all age groups. In the childhood, localization-related epilepsies accounted for 54.7% in India[21] similar to the reported frequency in the studies in USA[16] (58.6%) and Finland[17] (61%).

The Ecuador study,[15] which included only patients with more than one seizure, reported the lowest frequency (Table 1).

In developing countries the reported frequency of idiopathic localization-related syndromes is very low in all the age groups, including children and varied from 0.7-3.9%[15,18,21] whereas the reported frequency has been higher in developed countries, 8%[22] to 10%.[16]

Symptomatic localization-related epilepsies, all age groups, accounted for 39.4% in the series from India,[18] which is much higher than the reported frequency from France (13.5%),[13] and Italy (28.9%).[20] However, the reported frequency in the Ecuadorian study (27.1%)[15] and another Indian study (26.7%)[21] are similar to the reported frequency from developed countries. Cryptogenic localization-related epilepsy accounted for 22.8% in the Indian study,[18] 27.4% in Ecuador,[15] 29.2% in France,[13] and 28.4% in Italy.[20] These results are quite similar in developing and developed countries (Tables 2 and 3), in spite of the boundary of cryptogenic epilepsy is somewhat arbitrary because it depends on the extent of the diagnostic evaluation.

Generalized Epilepsies and Epilepsy Syndromes

In the studies from Ecuador[15] generalized epilepsies and epilepsy syndromes accounted for 30% whereas it was 11.8% in the Indian[18] series. This difference is probably related to the patient population studied. However, in the study in the childhood population from India, generalized epilepsies and epilepsy syndromes accounted for 35%.[21] Idiopathic group formed 24.2% in the Ecuadorian study,[15] similar to the reported frequency in the French (27.4%)[13] and Italian (18.5%)[20] series. Childhood absence epilepsy is the most frequent idiopathic generalized epilepsy. In many studies, the reported frequency of "other idiopathic generalized epilepsies" is high, 10% to 12%.[13,15,20-22] This only confirms the difficulty to categorize all patients with idiopathic epilepsy in the current ICEES classification.

In the series reported from developing countries cryptogenic or symptomatic generalized epilepsy syndromes accounted for ~ 2% epilepsies[15,18] and in developed countries for ~ 4%.[13,20] The frequency was also low, 1.7%, in a population-based study.[23] The frequency of West syndrome, 1.3 to 3.9% is also constant worldwide. Similar low numbers account for Lennox-Gastaut syndrome. Symptomatic generalized epilepsies were reported in 3.5% in the Ecuadorian study,[15] whereas the Indian study[18] reported 2.9%, similar to developing countries (Tables 2 and 3).

Epilepsies and Epilepsy Syndromes Undetermined Whether Focal or Generalized

There is a wide variation in the reported frequency of this group of epilepsies and epilepsy syndromes from both developing countries, 8% to 20%[15,18,19] and also from developed countries 3% to 32%.[13,20,24] Again, this may be due to the inability to define the epilepsy and epilepsy syndrome more precisely to group into one of the categories of the ICEES classification.

The diagnostic categories defining various age-related partial and generalized idiopathic epilepsies appear to be similar in both developed and developing countries and also the frequency of symptomatic and cryptogenic localization-related epilepsies. However, there are differences among the symptomatic group probably due to different risk factors.

We agree with some authors as to the limited applicability of some specific diagnostic categories in the general population, as their recognition requires an experienced neurologist or epileptologist. Nevertheless, we assume that the clinical pictures classified within these syndromic groups are also very important because of their prognosis and therapeutic specificity.[24-27] On the basis of the most recent publications from developed and developing countries, it is considered that the ILAE Classification of Epilepsies and Epileptic Syndromes is satisfactorily applicable to the large majority of cases observed at tertiary centers. Classification of epilepsies in population-based surveys using syndromic classification involves difficulties because patients should be studied in comprehensive epilepsy centers equipped with EEG and imaging technology. Obviously, this is difficult to obtain in developing countries.

Symptomatic Epilepsies

It is extremely difficult to compare the results of the studies of etiology of epilepsy. In addition to broad differences in the definition of seizures there is also a failure to define criteria for disorders related to seizures.[28] In most studies from developing countries the information on the latency between the first acute symptomatic seizure and the first unprovoked seizure and age at onset of seizures in relation to the age of the patient at the time of diagnosis is lacking.

Despite the lack of uniform criteria upon which to base attribution of etiology, the ratio of idiopathic/cryptogenic to symptomatic epilepsy remains fairly constant across the studies of etiology in both developed and developing countries. In the Rochester study[29] 65.5% of newly diagnosed cases of epilepsy were idiopathic. New available information in developing countries also shows similar proportion of idiopathic/cryptogenic (60-70%) to symptomatic epilepsy (30-40%).[15,28] However, the etiological spectrum is quite different in developing countries when compared to developed countries (Table 4). Cerebrovascular diseases account for a significant proportion of putative risk factors in developed countries.[24,29] Whereas perinatal brain damage, neurocysticercosis, central nervous system infections, and traumatic brain damage are the most frequently reported putative risk factors from developing countires.[3,15,28]

Proportion epilepsies related to remote symptomatic etiology increases with age. Remote symptomatic epilepsies accounted for 18% in a cohort of children with newly diagnosed epilepsy.[16] The reported incidence of epilepsy related to remote symptomatic etiology in adults was 39% in the incidence study in Switzerland[30] and 49% of newly diagnosed epilepsy in the Swedish study, the etiology was remote symptomatic.[25] In the Ecuadorian study[15] 25% of children and 53% of adults had symptomatic epilepsy.

Prenatal and Perinatal Pathology

Poor prenatal or perinatal care resulting in brain damage of the child is often claimed to be a reason for the high prevalence of epilepsy in the tropics.[3,31] Unfortunately, very few studies in the tropics define inclusion criteria for this category. In studies in developed countries the presence of prenatal and perinatal events do not appear to be associated with the occurrence of childhood epilepsy when children with cerebral palsy and mental retardation are excluded.[32]

The USA Collaborative Perinatal Project,[33] which prospectively followed a large population, found that 14% of children who had nonfebrile seizures also had cere-

bral palsy to some degree. Conversely, 21% of children with cerebral palsy had at least one nonfebrile seizure by the age of seven years. Low birth weight is a well established and an important risk factor for infant mortality and also cerebral palsy. However, seizure disorders in children with low-birth weight without cerebral palsy were not found to be significantly more frequent. Of the late pregnancy and birth conditions evaluated, including conditions considered to be associated with anoxia and markers of fetal distress, none were found to be important antecedents for seizure disorders in children without motor handicap. Among factors observable in the neonatal period, delay of first cry to three minutes or longer, abnormality of tone, and neonatal seizures or meningitis were leading predictors of later seizures.

We cannot extrapolate these findings to the situation in developing countries, where the health care system is quite different. In many developing countries, most deliveries in rural areas are conducted by traditional birth-attendants, the families are large, and the frequency of preterm deliveries is at least twice as high as in developed countries.[6] Many of the mothers are malnourished and exposed to a variety of infections that may affect the baby in utero or at the time of delivery. These factors need further studies to evaluate their contribution to perinatal brain damage. In developing countries perinatal brain damage would account for 13 to 14% of the putative risk factors for epilepsy in children.[7] (Commission ILAE 1994) In a hospital-based study from south India, static encephalopathy related to perinatal brain damage accounted for 9% of putative risk factors. This pathology was the risk factor for 13.5% remote symptomatic epilepsies.[26]

Infections of the Central Nervous System

Infectious and parasitic diseases are the most common causes cited for the higher incidence of seizures in developing countries. Acute infections of CNS are significant risk factors for both acute symptomatic seizures and epilepsy. In a retrospective cohort study from Rochester, Minnesota, CNS infections increased the risk for the development of unprovoked seizures by 11-fold.[32] In the Ecuadorian study infectious diseases were the antecedent events for the development of epilepsy in 4.5% of cases.[15] Majority of patients, particularly children, had tuberculous or bacterial meningitis. Epilepsy was the sequela of tuberculous meningitis in 8%.[28] Seizures are also common manifestations of intracranial tuberculomas. Bacterial meningitis is endemic in tropics and also occurs in epidemics. However no reliable data are available on the long-term sequelae.

Toxoplasmosis of CNS is epidemic in patients with AIDS.[6] With the increasing incidence of AIDS in tropical countries, such as Brazil toxoplasmosis may become a more important cause of epilepsy in the tropics. Epilepsy is a well recognized consequence of toxoplasmosis, reported in about 25% of the affected individuals.[6] Mental retardation and seizures are the sequelae of brain damage associated with congenital toxoplasmosis; 6.8% of patients with epilepsy from an institution for mentally handicapped children had congenital toxoplasmosis.[1]

Neurocysticercosis

Neurocysticercosis (NCC) is not necessarily a tropical disease, it is related to unsanitary conditions, poverty and poor health-care systems of a country, regardless of its geographical location. Studies of highly selected patients with epilepsy (or seizures?) in neurologic services of hospital settings from some developing countries report NCC as the main cause of epilepsy, accounting for 30% to 50% of patients.[16,31]

However, in the recent prospective multicenter study carried out in Ecuador, NCC was the putative risk factor for epilepsy in 8.3% of newly diagnosed patients with epilepsy.[15] In other studies in which acute symptomatic seizures were excluded, only 5.3%[34] and 11%[35] of patients with epilepsy had NCC It seems that most of the patients with NCC have acute symptomatic seizures which do not evolve into epilepsy. High incidence of epilepsy related to NCC, reported in some studies, probably related to failure to differentiate between epilepsy and seizures.[36,37] Although NCC is one of the most frequent antecedents among the symptomatic group, this disease is not the main cause of epilepsy.

Surprisingly, the proportion of epilepsy cases associated with cysticercosis using immunological tests as diagnostic tools is considerably lower than the proportion of NC using CT. Only 12% of patients with epilepsy attending an outpatient clinic in Peru had serological evidence of *T. solium* by enzyme-linked immunotransfer blot (EITB) test.[36] There are also clinical inconsistencies in the link between epilepsy and NCC. Parasite location may be remote from the apparent epileptogenic region.[38] There is no correlation between the NC burden of lesions and the severity of the epilepsy. Patients with severe refractory seizures may have only one calcified lesion. On the other hand, there are patients with multiple cysts or calcifications but no epilepsy. NC and epilepsy are common diseases in most developing countries. Because of their high prevalence, a causal as well as fortuitous relationship between the two conditions might independently exist.[35,39,40]

Cerebrovascular Diseases

In developed countries, cerebrovascular disease is the most commonly identified cause of epilepsy (Table 4), accounting for about 11% of all new cases and about one third of cases with any identifiable cause,[32] whereas in Ecuador cerebrovascular diseases accounted for only 4.4% of new cases.[15] In developing countries cerebrovascular diseases account for a small proportion of putative risk factors for epilepsy.[6]

Other Tropical Diseases

Malaria is endemic in tropical America, Africa, and some Asian countries. Cerebral malaria is an acute encephalopathy, which occurs only with infection by *Plasmodium falciparum.*[41] Clinically, cerebral malaria presents itself with fever, headache, delirium and confusion progressing to coma. Despite appropriate treatment, cerebral malaria carries a mortality of 22%.[42] Generalized seizures occur in 40% of adult patients and in most children. Epilepsy has long been recognized as a late sequel of cerebral malaria.[41] Pathological examination of the brain in fatal cases has shown severe vasculopathy with hemorrhages, and granuloma of Durck formed by astroglial reaction.[42] These lesions may act as epileptogenic foci in those who survive, giving rise to chronic epileptic seizures. A special relationship has been described between cerebral malaria and febrile convulsions. Together they may lead to 5% of pediatric emergency consultations in endemic areas such as central Africa and the Amazon forest.[4] However, it is difficult to ascertain whether these convulsions are in fact febrile seizures or are secondary to the cerebral malaria.

Frequently seizures may occur during the acute meningoencephalitic phase of schistosomiasis, but only 2.4% and 3.8% of patients are reported to have seizures during the chronic phase of schistosomiasis with confirmed cerebral ova deposition. Paragonimiasis is another nematode infection prevalent in South America. Lung is

the primary site of infection; but brain is also involved in many cases. Seizures, usually focal motor are the commonest manifestation of cerebral paragonimiasis.

American trypanosomiasis (Chagas' disease), a zoonotic disease caused by *T. cruzi*, is a public health problem in rural areas of Central and South America.[43] Involvement of the CNS is secondary to cerebral embolization of cardiac blood clots.[44] Immunologic reactions probably underlie the pathological characteristics of the disease including anaemia, thrombocytopenia, glomerulonephritis, pancarditis and a late-evolving diffuse meningoencephalitis with edema and arachnoiditis. These may cause late-onset epilepsy, with a high frequency of partial seizures.[6]

Approximately one-third of patients with cerebral hydatid cysts develop epilepsy, the majority before and some after surgery.[45] The relationship between epilepsy and cerebral hydatid disease was investigated by Saus et al.[37] Seizures were partial with or without secondary generalization in almost all the cases. Signs of focal cerebral involvement or of raised intracranial pressure were found at the onset of epilepsy in all the patients. Recurrence of seizures after surgery frequently indicated recurrence. Partial status epilepticus was common before and after surgery. Focal motor deficits related to seizures were frequent.

Seizures secondary to cerebral amoebiasis and cerebral toxocariasis have also been described,[15] but their contributions, as an etiology of epilepsy requires further study.

Conclusions

The frequency of epilepsy appears greater in tropical and developing countries than in developed countries; however, there are no studies to show differences between these countries on potential factors for increasing the risk to develop epilepsy. The utilization of the current International Classification of Epileptic Syndromes and Epilepsies proposed by ILAE seems appropriate in order to make studies over the entire world comparable. At the present time, there are some clinical studies that provide reliable information about classification of epilepsy. In order to analyze etiology, which is one of the components of this classification, it is important to differentiate between incident and prevalent studies.

The diagnostic categories defining various age-related partial and generalized idiopathic epilepsies appear to be similar in developed and developing countries. The frequency of localization-related epilepsies in newly diagnosed epilepsy is more or less similar among all the reported studies. This similarity is more consistent when considering children. Prevalent case series show a higher frequency of localization-related epilepsies when compared to the case series with new-onset epilepsy. There is also a good agreement across studies in the criteria used to classify idiopathic syndromes. However, there are differences when differentiating symptomatic and cryptogenic seizures. This is probably due to the fact that criteria for classifying epilepsies are subject to interpretation from one investigator to another, and somewhat arbitrary because it depends on the extent of the diagnostic evaluation.

New available information in developing countries shows that the proportion of idiopathic/cryptogenic (60-70%) to symptomatic epilepsy (30-40%) is similar to that reported in the studies from developed countries. However, there are differences among the symptomatic group probably due to different risk factors. Poor prenatal or perinatal care, infectious and parasitic diseases are the most common causes cited for the higher incidence of seizures in developing countries. Neurocysticercosis is not necessarily a tropical disease, it is related to unsanitary conditions, poverty and poor health-care systems, regardless of its geographical lo-

cation. Recent prospective studies carried out in newly diagnosed patients with epilepsy, NC was the cause of epilepsy in 8.3%. Seizures secondary to some tropical diseases such as malaria, trypanosomiasis, cerebral amoebiasis and toxocariasis, have also been described, but their contribution, as an etiology of epilepsy requires further study.

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Chapter 10

Neurocysticercosis and Epilepsy

Oscar H. Del Brutto

Neurocysticercosis (NCC) is defined as the infection of the central nervous system (CNS) by the larval stage of the tapeworm *Taenia solium*. The disease constitutes a threat to millions of people all over the world, and is endemic in Central and South America, the southwestern United States, the sub-Saharan Africa, and in some regions of Asia, including the Indian subcontinent, Indonesia, Korea, and China.[1-3] Conservative figures mention that more than 2 million people harbor the adult tapeworm and that many more are infected with cysticerci.[4] In endemic areas, NCC accounts for 10% to 12% of all hospital admissions to neurological services. In addition, this disease is a major cause of epilepsy in developing countries, where the prevalence of active epilepsy is almost twice the prevalence than in the developed nations.[5] It is estimated that 50,000 new deaths due to NCC occur every year, and many times that number of patients survive but are left with irreversible brain damage.[4] This is an important public health problem since most people are affected in productive ages. Despite the alarming magnitude of these numbers, they are but the "tip of the iceberg" since the actual prevalence of NCC is not known due to the lack of a reliable diagnostic test that permits a worldwide survey to assess the proportions of the problem.

Etiopathogenesis

Life Cycle of T. Solium

Humans are the definitive hosts for the adult *T. solium*, whereas both pigs and humans may act as intermediate hosts for the larval form or cysticercus.[6] The adult cestode inhabits the small intestine of humans, where it is attached to the intestinal wall by its suckers and hooks. Every day, gravid proglottids containing thousands of eggs are detached from the worm and are passed with the feces. In places with deficient disposal of human feces, porks are nourished with human feces containing *T. solium* eggs.[7] Once in the intestinal tract, the eggs lose their coat and liberate oncospheres which cross the intestinal wall, enter the bloodstream, and are carried to the tissues of the host where embryos evolve forming larvas (cysticercus). Human consumption of improperly cooked pork meat results in release of cysticerci in the small intestine. Here, by the action of digestive enzymes, their scolices evaginate and attach to the intestinal wall. After the scolex is attached, the proglottids begin to multiply and will become mature enough to be excreted in feces a few months after infection.[6] Humans can also act as intermediate hosts for *T. solium* after ingesting its eggs. Under these circumstances, human cysticercosis develops. The mechanisms by which eggs cross the intestinal wall and lodge in human tissues are the same as those described in the pork. The two main sources from which humans acquire cysticercosis are ingestion of food contaminated with *T. solium* eggs and the fecal-oral route

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in individuals harboring the adult parasite in the intestine.[8] The former was considered the most common form of transmission; however, recent epidemiological studies showing clustering of cysticercosis patients around taeniasic individuals, have changed previous concepts crediting the environment as the main source of human contamination with *T. solium* eggs.[9,10]

Characteristics of Cysticerci

Cysticerci are vesicles consisting of two main parts, the vesicular wall and the scolex.[6] The scolex have a similar structure than the adult *T. solium*, including an armed rostellum and a rudimentary body. The macroscopic appearance of cysticerci varies according to their location.[11,12] Cysticerci in brain parenchyma rarely measure more than 10 mm, and tend to lodge in the cerebral cortex or the basal ganglia due to the high vascular supply of these areas. Subarachnoid cysticerci may be located within cortical sulci or in the CSF cisterns at the base of the brain. Cysticerci located at the cortical surface of the brain are small while those located within the cisterns may attain a size of 50 mm or more. These parasites usually lack the scolex and are composed of several membranes attached to each other (racemose form of cysticercus).[13] Ventricular cysts may be small or large, are usually single, and may or may not have a scolex; these cysts may be attached to the choroid plexus or may be freely floating within the ventricular cavities. Other less common locations of cysticerci within the nervous system include the sellar region, the retro-orbital space, the eye, and the spinal cord.[12]

Stages of Involution of Cysticerci

After entering the nervous system, cysticerci are in a *vesicular stage* in which the parasites are viable and elicit little inflammatory changes in the surrounding tissues; in this stage, parasites have a transparent membrane, a clear vesicular fluid, and a normal invaginated scolex. Cysticerci may remain for years in this stage or, as the result of a complex immunological attack from the host, enter in a process of degeneration that may end with the death of the parasite[11] (Fig. 1). The first stage of involution of cysticerci is the *colloidal stage*, in which the vesicular fluid is replaced, by a viscous and turbid fluid, and the scolex shows signs of hyaline degeneration; colloidal cysts are surrounded by a thick collagen capsule and by a mononuclear inflammatory reaction associated with edema, neuronal degenerative changes, and perivascular cuffing of lymphocytes. Thereafter, the scolex is transformed into coarse mineralized granules; this stage, in which the cysticercus is no longer viable, is called the *granular nodular stage*. Finally, in the *calcified stage* the parasite remnants appear as a small mineralized (calcified) nodule. When parasites enter into the granular and calcified stages, the edema subsides but the astrocytic changes in the vicinity of the lesions become more intense than in the preceding stages.

Clinical Features

Individual differences in the number and location of the lesions within the nervous system makes NCC a highly pleomorphic disease.[14,15] Epilepsy, focal neurological deficits, intellectual deterioration, and increased intracranial pressure are the most common clinical manifestations of NCC, but these are also observed in many other neurological disorders. This underlines the lack of specificity of the clinical picture of NCC and stresses the need to perform complementary studies in every patient to confirm the diagnosis.

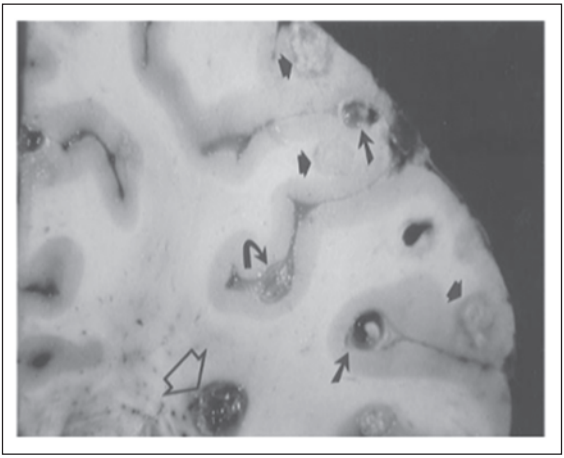

Figure 1. Brain slice showing the four stages of evolution of cysticerci in the same patient, including vesicular cysts, colloidal cysts, granulomas, and calcifications. (Reproduced from: Del Brutto OH, Sotelo J, Román GC. Neurocysticercosis: a clinical handbook. Lisse: Swets & Zeitlinger, 1998, with permission).

Epilepsy is the most common clinical manifestation of NCC and usually represents the primary manifestation of the disease.[16] Before the introduction of CT scan, the prevalence of epilepsy in patients with NCC ranged from 25% to 35%.[17] In more recent series, however, epilepsy has been reported in more than 70% of patients.[14] This disease is considered a leading cause of adult-onset epilepsy in developing countries of Latin America, Asia, and Africa.[18-24] Most patients with adult-onset epilepsy due to NCC have a normal neurological examination, and differ from patients with adult-onset epilepsy due to other type of cerebral lesions who usually present with focal neurological signs.[20]

As previously noted, intracranial cysticerci may be located in the brain parenchyma, the subarachnoid space, the ventricular system, or the sellar region. Epilepsy is more frequently observed in patients with cysticerci in the brain parenchyma or in the depth of cortical sulci between two cerebral convolutions. Cysticerci in all stages of involution - even in the vesicular stage - may induce seizures, although the mechanisms of epileptogenesis are different. It is believed that vesicular cysts cause seizures due to compression of the surrounding brain parenchyma and that colloidal cysts cause seizures due to acute inflammatory changes. In contrast, granular and calcified cysticerci usually cause seizures due to the intense astrocytic gliosis that usually surrounds these lesions.[16,25]

Seizures due to NCC are most commonly simple partial or generalized tonic-clonic, although some patients may present with complex partial or myoclonic seizures. The type of seizure has been considered to be related to the number and location of the parasites, whereby patients with a single lesion present with partial seizures, while patients with multiple lesions have generalized seizures.[19] However, other studies have shown no difference in the frequency of partial seizures in patients with single cysts as compared with those with multiple cysts.[16] It is possible that most NCC patients with generalized seizures actually have partial seizures

with rapid secondary generalization, an assumption based on the fact that focal brain lesions rarely, if ever, course with genuine generalized seizures.

Not all patients with NCC-related seizures develop epilepsy. Indeed, there are some patients with a single colloidal cyst who after a bout of two or three seizures remain free of seizures even without antiepileptic drug therapy (AEDs).[26] According to the classification of seizures of the International League Against Epilepsy (ILAE), these patients have "acute symptomatic seizures", a term coined to define seizures presenting in close temporal relationship with acute central nervous system lesions.[27] Nevertheless, if we consider the population of patients with NCC-related seizures at large, it is probably that the vast majority actually have "recurrent unprovoked seizures" (epilepsy) since the epileptogenic focus is already developed when the patient comes to the attention of the physician.

Diagnosis

Accurate diagnosis of NCC is possible only after proper interpretation of clinical and epidemiological data together with the findings of neuroimaging studies and the results of specific immunological tests.[28] In addition, the finding of cysticerci outside the central nervous system can be a great aid to the diagnosis of NCC in patients with seizures and suggestive but inconclusive CT scan or magnetic resonance imaging (MRI) abnormalities. Such parasites may be located in the posterior chamber of the eye where they can be identified by direct ophthalmoscopic examination, or in muscles and subcutaneous tissues where they can be palpated or visualized on plain X-ray films.[29]

Neuroimaging Studies

Both CT and MRI have drastically improved our diagnostic accuracy for NCC by providing objective evidence about the topography of the lesions and the degree of the host inflammatory response against the parasite.[30,31] CT scan and MRI findings in parenchymal NCC depend on the stage of development of cysticerci, and include cystic lesions imaging the scolex as a brilliant nodule ("hole-with-dot" image), ring like or nodular enhancing lesions, and punctate calcifications (Fig. 2). Neuroimaging findings in subarachnoid NCC include hydrocephalus, abnormal enhancement of the leptomeninges at the base of the skull, subarachnoid cysts, and cerebral infarcts (Fig. 3). Ventricular cysticerci appear on neuroimaging studies as cystic lesions that distort the anatomy of the ventricular system and cause asymmetric hydrocephalus (Fig. 4). With the exception of cystic lesions showing the scolex, most of these findings are nonspecific and represent a diagnostic challenge. In some of these cases, the diagnosis is not possible even after an exhaustive investigation including cerebrospinal fluid (CSF) analysis, cerebral angiography, and other complementary studies.[28,30]

A rather common neuroimaging finding in patients with epilepsy due to NCC is the so-called "single enhancing lesion".[32,33] These lesions represent cysticerci in the acute encephalitic phase (colloidal stage) and have generated a great debate concerning diagnosis and treatment.[34,35] In a recent study, Rajshekhar and Chandy[36] established solid diagnostic criteria to differentiate cysticerci-related single enhancing lesions from other intracranial pathologies that may course with similar clinical and neuroimaging findings (Table 1). As will be discussed later, such differentiation has important therapeutic implications.

On general terms, MRI is better than CT scan for the diagnosis of NCC, particularly in patients with lesions in the base of the brain, brainstem cysts, and

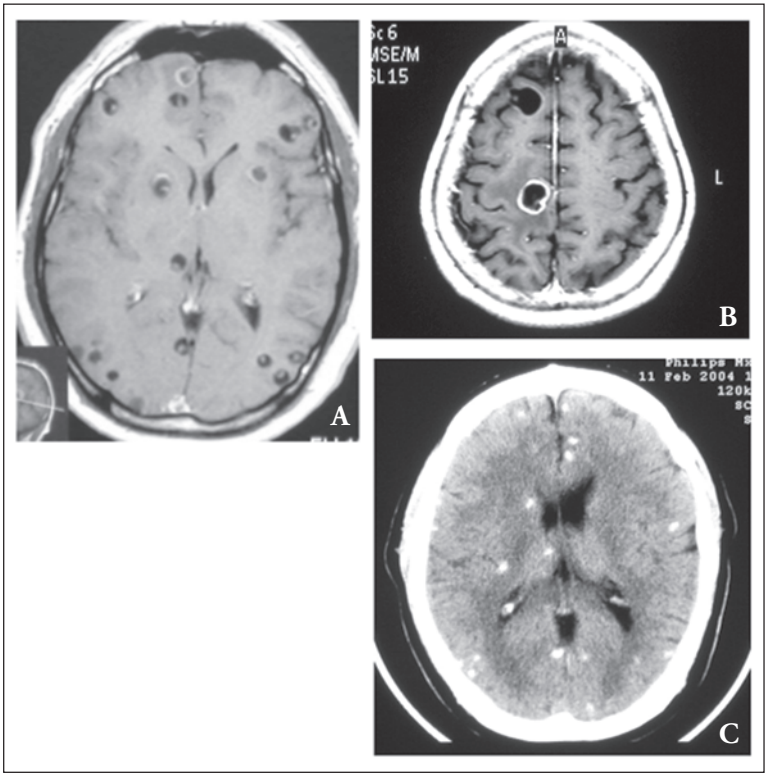

Figure 2. Neuroimaging findings in parenchymal neurocysticercosis: A) CT showing vesicular cysts appearing as well-defined cystic lesions with scolex; B) T2-weighted MRI showing a colloidal cyst visualized as a ring-enghaninc lesion surrounded by edema; and C) CT showing multiple small calcifications.

intraventricular cysts.[31] An important shortcoming in the accuracy of MRI for the diagnosis of NCC is the detection of small calcifications. Since many patients with NCC have parenchymal calcifications as the sole evidence of the disease, this condition may escape detection if only MRI is performed. CT scan is still the best screening neuroimaging procedure for patients with suspected NCC; MRI may be reserved for patients with normal CT scan or for those who have inconclusive CT scan findings.

Immunological Tests

Tests directed to the detection of anticysticercal antibodies in serum and CSF are a valuable complement to neuroimaging in the evaluation of patients with suspected NCC, but they should never be used alone to exclude or confirm the diagnosis of the disease.[28] From the many tests performed in serum, current data indicate that the most effective is the enzyme-linked immunoelectrotransfer blot (EITB). Such assay has been claimed to have 100% specificity and 98% sensitivity.[37] However the serum EITB may give positive results in patients with taeniasis or in those who have

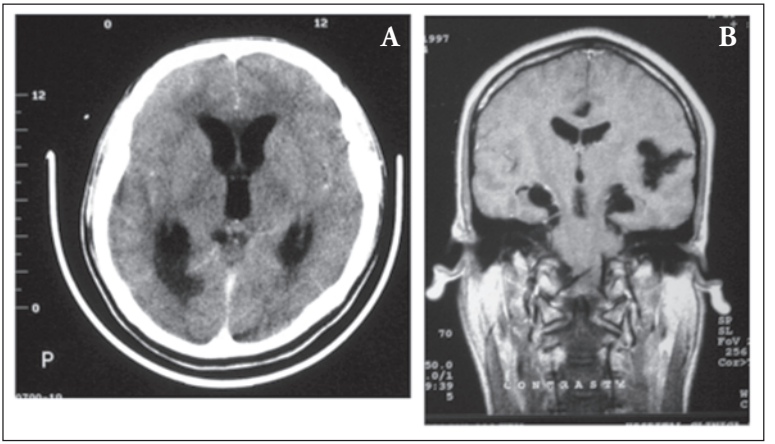

Figure 3. Neuroimaging findings in subarachnoid neurocysticercosis: A) CT showing hydrocephalus; and B) Contrast-enhanced CT showing subarachnoid cysts and abnormal enhancement of leptomeninges at the base of the brain.

cysticerci lodged outside the nervous system (false positive results). In addition, the sensitivity of EITB is low in patients with a single intracranial cysticercus (false negative results).[38] Another widely used test is the enzyme-linked immunosorbent assay (ELISA). The reliability of this test in CSF is higher than that performed in serum; however, its accuracy depends on the viability of cysticerci and their location within the nervous system. The ELISA is highly sensitive in cases of active subarachnoid NCC. Such sensitivity decreases considerably when the lesions are calcified or when viable parenchymal cysts are not in contact with the brain parenchyma.[39,40]

Figure 4. T1-weighted MRI showing asymmetric hydrocephalus in a patient with a lateral ventricle cysticercus.

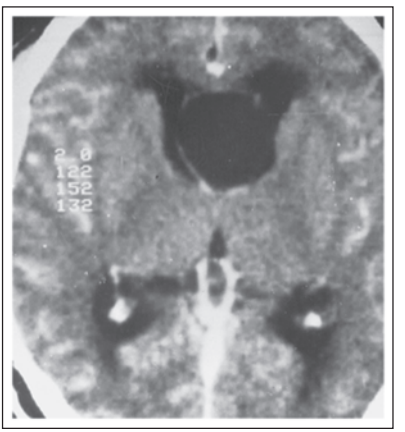

Table 1. Clinical and tomographic criteria for diagnosis of solitary cysticercus granuloma

Clinical criteria:
Presence of seizures as the initial symptom
Absence of signs of intracranial hypertension
No history of progressive neurological deficit
No evidence of active systemic disease
Tomographic criteria:
CT showing a single enhancing lesions
CT lesion should measure less than 20mm in diameter
Edema should not be severe anough to displace the midline

*Adopted from the criteria proposed by Rajashekhar V and Chandy MJ.[36] All criteria must be satisfied to make a diagnosis of solitary cysticercus granuloma

Electroencephalogram

All patients with NCC-related seizures must undergo an EEG as part of their evaluation. However, the EEG may be normal in up to 50% of cases. Moreover, there is poor correlation between seizure type and EEG findings in these patients.[16] It is common to find diffuse EEG abnormalities in patients with a single intracranial cysticercus and focal paroxysmal activity in patients with massive and disseminated infections.[40] Such incongruence may be related to the natural resistance of some cerebral areas to the epileptogenic effect of cysticerci, to the generation of local epileptogenic activity by the parasite with the subsequent activation of distant sites by cortical or subcortical spread, or to the low sensitivity of scalp EEG to detect epileptogenic activity.[42] It has recently been suggested that more sensitive methods such as magnetoencephalography may improve the detection of focal abnormal brain activity surrounding parenchymal brain cysticerci.[43]

Therapy and Prognosis

Characterization of NCC in terms of cysts' viability, location of the lesions, and clinical manifestations is of major importance for a rational therapy of this parasitic disease.[44] Therapy includes a combination of symptomatic drugs, specific cysticidal drugs, surgical resection of lesions, and placement of ventricular shunts. Two drugs, praziquantel and albendazole, may be used for therapy of intracranial cysticerci. Praziquantel destroys up to 70% of parenchymal brain cysticerci after a 15-day course of treatment at daily doses of 50 mg/kg.[45] Albendazole destroys 75% to 90% of parenchymal cystic lesions after a one-week course of treatment at daily doses of 15 mg/kg,[45,47] and has proved to be more effective than praziquantel in several comparative trials.[48-50]

Patients with epilepsy due to NCC should be treated with AEDs regardless of the use of cysticidal drugs. In such patients, standard doses of a first-line AEDs such as phenytoin, carbamazepine or valproic acid reaching therapeutic serum levels usually provide adequate control of seizures.[16] However, there are patients with parenchymal brain cysts who continue with seizures despite AED therapy. Retrospective studies have shown that a therapeutic trial with cysticidal drugs result in adequate seizure control in such cases.[16,51,52] In one of these studies, the group of patients who received cysticidal drugs had a 95% reduction in the number of seizures per year, while the group of untreated patients did not experience reduction in the number of

seizures despite several adjustments in the AED regimen.[51] While the retrospective and nonblinded nature of these studies have been criticized by some authors,[26] there is no reason to leave parenchymal brain cysts untreated when an effective and safe therapy is available.[53]

Another use of cysticidal drugs is their role as a diagnostic tool in patients with seizures and single enhancing lesions on CT scan or MRI. While most of these lesions are dying cysticerci in the acute encephalitic phase, some single enhancing lesions are not cysticerci but tuberculomas, mycotic granulomas or low-grade gliomas; therefore, a passive follow-up may allow the progression of another disease requiring urgent treatment.[54] Administration of cysticidal drugs to these patients permits prompt detection of those who need further investigation by hastening the resolution of cysticerci-related lesions.[35,55] Such approach obviates both the hazards of prolonged delays and the unnecessary practice of invasive diagnostic procedures.

The optimal length of AED therapy in patients with neurocysticercosis has not been settled. A recent prospective study showed that up to 50% of these patients had relapses after withdrawal of AEDs.[56] Such patients had been free of seizures during two years, and their parenchymal brain cysts had been successfully destroyed with albendazole. Prognostic factors associated with seizure recurrence included the development of parenchymal brain calcifications as the result of albendazole therapy, and the presence of both recurrent seizures and multiple brain cysts before the institution of anticysticercal therapy.

Several reports have documented transient neuroimaging changes around previously inert calcified cysticerci shortly after a seizure.[56-59] These changes may be related to a breakdown in the blood-brain barrier around an epileptogenic focus, in the same way as that observed in some patients with epilepsy from other causes. According to this hypothesis, transient neuroimaging changes around calcifications are the result and not the cause of the seizure. However, others believe that intermittent release of antigens by calcified lesions may induce transient inflammatory responses from the host that are, in turn, responsible for those neuroimaging changes and the seizures.[59] Irrespective of their pathogenesis, such findings suggest that even calcified cysticerci are potentially active epileptogenic foci that may cause recurrent seizures after withdrawal of antiepileptic drugs. While epilepsy due to NCC is easily controlled with antiepileptic drugs, a seizure free state without medications seems to be difficult to achieve in many patients.

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Chapter 11

Reflex Epilepsies in the Tropics: The Three Common Types

Nimal Senanayake

Reflex epilepsies encompass epilepsies in which seizures are regularly provoked by a specific stimulus or event. Among the reflex epilepsies, photosensitive epilepsy (PSE) where visual stimuli trigger seizures, is the most extensively studied.[1-4] A variety of other 'external stimuli' such as auditory, vestibular, olfactory, gustatory, and somatosensory, as well as 'internal' stimuli such as visceral and cognitive functions are also known to precipitate seizures.[5]

Epidemiology

The pattern of reflex epilepsies shows geographic variations, not only between countries with temperate climate and the tropics, but also within different regions in certain tropical countries. In countries with temperate climate, photosensitive epilepsy is the most common reflex epilepsy and the reported frequency is about 5% of all epilepsies.[4] It accounted for 53.4% of reflex epilepsies in United States of America.[6] Photosensitive epilepsy is less frequent in Africans and tropical Asians. However, in Peradeniya, Sri Lanka, a high frequency of photosensitive epilepsy has been recorded.[7] This may partly be related to the large number of patients with juvenile myoclonic epilepsy (JME) in the series. In India eating epilepsy (EE) is the most frequently reported reflex epilepsy.[8-10] In a study in Kerala, a province in south India, eating epilepsy accounted for 37.4% of reflex epilepsies.[8] Whereas in Karnataka, another province in south India, hot-water epilepsy was the commonest reflex epilepsy and accounted for 73.2% of reflex epilepsies.[11] At our center also eating epilepsy is the commonest type of reflex epilepsy and accounts for 85.7% reflex epilepsies.

This chapter will discuss three unusual forms of reflex epilepsies commonly seen in some of the Asian countries. (See Chapter 12 for Hot-Water Epilepsy.)

Eating Epilepsy

In 1945, Allen[12] first documented eating as a precipitating factor for epileptic seizures in a 35-year old male. Later in 1951 Boudouresques and Gastaut[13] documented the electroencephalographic (EEG) correlate of eating epilepsy. They reported epileptiform activity in the temporal leads in four patients with postprandial seizures attributed to gastric distension. Symonds[14] stressed the need for detailed interrogation of patient with epilepsy for seizure precipitants like eating. Subsequently several cases have been documented from different parts of the world.[9,15-20] Since then the condition came to be known as 'Prandic Epilepsy' or 'Eating Epilepsy' (EE).[21] Since EE does not represent a distinct nosologic entity, Aguglia and Tinuper[22] suggested the term 'eating seizures' specifying the clinical context. While subscribing to this view, for economy of words we have retained the term 'eating

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epilepsy' (EE) to mean epilepsy where majority (50%) of seizures are related to the act of eating.

Seizures occurring during eating or in the postprandial period are considered eating-related. The time relation between eating and seizure onset has not been defined precisely. We considered 30 minutes within eating as the postprandial period in our studies and any patient with more than 50% seizures during eating and/or in the postprondial period were considered to have eating epilepsy.[23-26] The minimum time to have an Eastern meal will be 10-15 minutes and can be up to 30 minutes. We considered 30 minutes within eating as the postprandial period. Thus the total duration of meal-related behavior is 3 hours for three meals. The probability of having a seizure during meal-related behavior is 0.125 (three attacks within 24 hours) and the probability of a patient having 2 seizures, both related to meal, is 0.0156, which is much less than the conventional chance probability, 0.05. For a patient having both eating-related and noneating-related seizures to consider the diagnosis of EE, he/she needs to have a minimum of six seizures of which at least 3 should be eating-related. Applying the binominal test[27] and these calculations, the probability that 3 or more of the seizures will be meal-related is 0.042, again much less than the conventional chance probability. When we applied these statistical exercises to patients in our series, the results suggest that the relation between seizures and eating could not have been by chance alone.

Epidemilogy

Eating epilepsy is more frequently reported from tropical Asian counties, It is rarely reported from temperate countries; of the 20,000 EEG examinations reviewed in an university hospital in Italy, Vizioli[15] found only 9 patients with a seizure disorder related to eating. In India, the reported prevalence in an university hospital-based study was 1.1 per 1000 patients with epilepsy[28] and it was 12 per 1000 patients with epilepsy in a clinic-based study.[11] The highest prevalence was however reported from the Kashmir valley in north India, 50 per 1000 patients with all types of seizure disorder.[10] In our study the prevalence was 148.4 per1000 patients with epilepsy. In view of this clustering and high prevalence in the Indian subcontinent, eating epilepsy may justifiably be called a tropical disorder (Table 1).

Patient Characteristics

In our study of the 120 patients with EE, 33% of patients had seizures exclusively related to eating and 67% had both eating-related seizures and noneating-related seizures. The mean age at onset was 23.7 years (range 13-43 years) and 80% had onset in the second decade. Like in other series,[28,37] there was male preponderance, 3:1 and this was highest in patients with seizures exclusively related to eating, 6:1.[26]

Etiology of Epilepsy

No etiological factor is specific for EE. Etiological factors reported in association with EE include mental retardation,[10,28] head injury, cerebral infarct, and infections of central nervous system (CNS).[41] Robertson and Fariello[38] reported a 14-year-old boy with a deep forebrain astrocytoma with partial seizures consistently triggered by eating. In our case controlled study there was no significant difference in the frequency of perinatal brain damage, febrile seizures, CNS infections, and traumatic brain injury between patients with EE and the control group, patients with other epilepsies.[26] The only significant finding in the patient group was a higher frequency of left-hand dominance.

Table 1. Geographic distribution of eating epilepsy

Country/City	Reference	No. of Cases
Brazil	Sepulveda et al[29]	1
England	Symonds[14]	2
	Abenson[17]	1
France	Boudouresques and Gastaut[13]	4
	Nick and Grasset[30]	1
	Aguglia and Tinuper[22]	3
	Loiseau et al[31]	1
Germany	Kerschensteiner and Dorstelmann[18]	1
Hungary	Jeno and Katalin[32]	1
India	Mani and Rangan[11,33]; Mani[34]	24
	Nagarajah and Chand[28]	13
	Chemburkar and Desai[9]	7
	Radhakrishnan et al[35]	1
	Devi and Iyer[8]	31
	Velmurugendran[36]	14
	Ahuja et al[21,37]	17
	Koul et al[10]	50
Italy	Vizioli[5]	9
	Cirignotta et al[20]	1
New Zealand	Allen[12]	1
Sri Lanka	Senanayake[23-26]	191
Switzerland	Scollo-Lavizari and Hess[16]	1
U.S.A.	Forster[6]	2
	Robertson and Fariello[38]	1
	Reder and Wright[39]	1
	Fiol et al[40]	1

Family History

The reported frequency of epilepsy among family members of patients with EE varied between 6% and 50%.[10,28,37] In our study 16.7% of patients had male sibling(s) with epilepsy and 7.5% had female sibling(s) with epilepsy. This was significantly higher when compared to patients with other epilepsies, 3.3%. An interesting feature was that 13 of the male siblings and 8 of the female siblings, belonging to 9 different families, had EE. A remarkable degree of intra-family consistency was observed with regard to the age at onset, the seizure semiology, and the timing of eating seizures. This phenomenon is known as sibling clustering and suggests probable genetic susceptibility in EE.[42]

Seizure Type and EEG

Seizure type includes simple[10,17,38,39] or complex partial seizures[6,9,10,13,15,17,22,28,37] with or without secondary generalization. Rarely it can be myoclonic and/or atonic.[10,20] Partial complex seizure with or without secondary generalization is the common seizure type in our patients. In our series, seizure semiology included epigastric sensation (10%), gustatory/olfactory hallucinations (8.3%), fear (32.5%), dreamy states (32.5%), abnormal speech (36.7%), and automatisms of face and mouth (38.3%) and limbs (16.7%).

Relation to Eating

In our series, in the majority of patients, seizures related to eating accounted for more than 90% of seizures. Seizures more often occurred during night meal. Seizures were specific to one of the three meals in 28% of patients. Others have also observed similar association.[20,22] Of the 120 patients in our series, 88% had seizures while eating (within five minutes of starting the meal), 39% had seizures immediately after the meal, and 32% had during postprandial period, within 10 minutes of eating. Twenty-one patients (17.5%) experienced occasional seizures while getting ready for a meal, even before touching the meal. Some reports observed such a phenomenon,[16] while others had not.[28,37] During the course of the seizure disorder, in some patients, the eating-related seizures were replaced by random seizures and vice versa.[20,21]

Food and Eating Habits

The relation between the seizures and the type of food, time of eating, eating pattern, and environment is uncertain.[26,28,37] In our series 55% observed that the seizures occurred only when they ate a rice meal and in three patients the seizures were related to eating fish. No such consistent relation has been found in other studies.[43] One of the earlier reports documented a patient in whom eating apple consistently precipitated seizures.[17] Rice is the staple diet that makes the bulk of the meal in Sri Lanka and other Asian countries from where EE epilepsy is frequently reported.

Pathogenic Mechanisms

What precipitates seizures in EE is uncertain. Pavlov's experiments in dogs suggest that EE is probably a conditioned reflex and mere sight of food is sufficient to provoke seizures.[15] In man all the stages of eating - mastication, swallowing,[16] food passing the esophagus,[18] and gastric distension[13,14] have been suggested as possible stimuli for provoking seizures. Possible role of peripheral inputs has been suggested by report of a patient[39] in whom seizures were always precipitated by cutting food with knife and lifting food with a fork and eating. He had seizure remission following accidental amputation of the hand. In a more recent study[44] none of these factors were found to trigger seizures. It appears that the entire process of eating is probably the provoking factor for eating-related seizures.[22,26,28]

Diencephalon,[38] hypothalamus,[29] and amygdala,[21,40] have been suggested as the brain regions responsible for initiating eating seizures. In animals kindling of amygdala at low intensity stimuli can result in seizures.[45,46] Amygdala is involved in the masticatory movements during seizures.[47] It is possible that in patients with EE, repeated acts of eating may kindle the amygdala resulting in seizures.[26]

Treatment and Prognosis

EE is considered a difficult to treat epilepsy.[6,10,21,28,48] However, in our series 86% of patients were either seizure-free or had satisfactory seizure control with conventional antiepileptic drugs (AEDs). In our experience, clobazam is a promising drug in the treatment of eating-related seizures. Behavioral therapy using vigilance inhibition method[6] and distraction-arousal technique,[44] one patient each, have been found successful in preventing eating-related seizures.

Epileptic Seizures Evoked by Higher Cerebral Functions

The phenomenon of seizure precipitation by higher cerebral functions had been appreciated for many decades.[14] Reading epilepsy was one of the earliest examples.[49-51] Geschwind and Sherwin[52] introduced the concept of language-induced epilepsy to include other language-related triggers such as writing. Ingvar and Nyman[53] described arithmetic problem solving as a provoking stimulus for seizures, "epilepsia arithmetices". Calculation[24,54-56] as well as other functions such as decision making,[6,57-59] playing cards and board games,[60-63] and performing spatial tasks,[64-66] which involve higher cerebral processing have since been recognized to precipitate epileptic seizures.

Epidemiology

Seizures precipitated by higher cerebral functions are considered rare. Mental arithmetic is performed as a standard activation procedure during EEG recording at the Mayo Clinic since 1951. Of the 100,000 such recordings, mental arithmetic provoked epileptiform activity in only one recording.[54] Forster,[6] in his series of 73 patients with reflex epilepsy, recorded only two patients with "decision making epilepsy". Of the 83 patients with reflex epilepsy studied by Devi and Iyer,[8] in 5 (6%) the provoking factor was solving arithmetic problems or games such as chess and cards. In our series of 1298 patients with epilepsy, 21 (2.7%) patients had seizures predominantly provoked by calculation, problem solving, spatial tasks or playing cards or draughts (checkers). In 12 (52%) patients all the seizures were consistently related to such activities involving higher cerebral functions.

Clinical Features

In our series of 21 patients, all except one had onset of seizures in the second decade (range 12-28 years) and there was no specific sex predilection. Six of them had febrile seizures in childhood. Primary generalized seizure was the seizure type in 14 patients and partial seizure in seven. Of the 14 patients with generalized seizures, juvenile myoclonic epilepsy (JME) was the epilepsy syndrome in 13 patients.[67,68]

Illustrative Case[56]

A 27-year old male, schoolteacher, presented with a history of attacks of generalized jerky movements of the body, accompanied by transient thought block since the age of 21 years. He used to get these attacks whenever concentrating on a problem, usually a mathematical calculation. At the Chartered examination, he failed to complete the mathematics and the accounts papers because of frequent jerks. As a teacher he used to experience jerking of the body whenever he taught commerce and mathematics classes, causing him much embarrassment. During these attacks his speech would be interrupted with an explosive 'ah'; while writing on the blackboard, he would drop the chalk. He also had several falls. He never experienced tonic-clonic convulsions or loss of consciousness. Other activities, which occasionally evoked jerks, included playing cards, draughts and carom. He was on diazepam two mg thrice daily for three years with some improvement. His past history was otherwise normal. Family history for epilepsy was negative. Physical examination was essentially normal. He was right-handed and of normal intelligence.

EEG Studies

Routine EEG, including hyperventilation and photic stimulation, showed no significant abnormality. However, a written arithmetic test provoked generalized

bisynchronous spike or poly-spike and wave discharges and minor spike-discharges within three minutes of testing. In 30 minutes, there were two major and three minor discharges. Most remarkable abnormalities on Raven's (progressive matrices) IQ testing appeared within five minutes of start of the test. During 30 minutes there were 45 major discharges accompanied by visible jerks and mental block, and many minor discharges.

Other tests of intelligence carried out included: (1) analogy tests- finding a comparative relationship existing between ideas and words, e.g., *fur is to animals as clothes are to*; (2) series tests- in an arithmetical series, indicating the next number in the order, e.g., *1, 5, 9, 13, 17,* (3) figures tests- similar to Raven's progressive matrices; and (4) logic tests, e.g., *A is older than B, but younger than C. D is older than A. If D is not the eldest, who is the youngest?* These were written tests, administered in Sinhala- the mother tongue of the patient. The duration of each test was six minutes, and during this period the patient was asked to answer as many test items as possible. Test periods were interposed with rest periods of 3 minutes each. He performed the tests well and scored 50% or more in each category: analogy test- 50%; series test- 67%; figures test- 60%; logic test- 80%. During the 3 tests EEG showed generalized bisynchronous spike or poly-spike wave discharges, some accompanied by clinical jerks and mental block, and also minor spike discharges. The number of major discharges during each test was: analogy test- 0; series test- 17 (jerks+); figures test- 8 (jerks+); logic test- 1. During the rest periods he showed no abnormality. EEG studies, repeated on the same day and 18 days later, produced similar results.

Patient was prescribed clobazam 10 mg twice daily. At review two weeks later, his condition had improved remarkably. He was free of symptoms except for a few instances of slight interruption of speech during teaching mathematics lessons. The test procedures repeated failed to provoke any EEG abnormality. Subsequently, the palatal myoclonia also disappeared. On clobazam he has been symptom-free.

Pathogenic Mechanisms

The pathophysiological mechanisms involved in the induction of seizures by cognitive functions have not yet been established. In reading epilepsy, several factors such as pattern vision,[69] proprioceptive inputs from the jaw and eye muscles, attention to reading, and conditioning to the circumstances of reading may be involved.[70] However, these concepts do not adequately explain the seizure-evoking mechanisms in all the patients. In some of our patients and in other reports,[54,55,57,59] mental arithmetic was equally or sometimes more effective as a trigger than tasks involving visual stimuli. It has also been demonstrated that attention to task by itself is not sufficient,[59] and conditioning of the patient during a long-lasting task is unlikely to be a major factor in the pathogenesis of the seizures.[53]

Our view is that in patients with seizure susceptibility to higher cortical functions, cortical areas responsible for various tasks have low seizure threshold. These cortical areas become hyperexcitable when various tasks are given for a prolonged period resulting in seizures.[56] This hypothesis, in fact, is similar to the mechanisms involved in eating epilepsy where the anatomical substrate is the amygdala, and the stimulus is eating.

Treatment

In patients with epileptic seizures induced by higher cerebral functions, the drug treatment depends on the type of epilepsy or epilepsy syndrome. As the seizure type, in most instances, is primary generalized, many with features of JME, valproate or

clonazepam has been found effective.[24] We have used clobazam in most of our patients with good seizure control.[56,63] Behavioral therapy, vigilance inhibition, signaling of occurrence of seizures while playing chess, has not been found successful.[6]

Self-Induced Epilepsy

The phenomenon of self-induced seizures has been recognized as a specific clinical entity, since the first description of a patient with 'reflex epilepsy provoked by optic excitation from sunrays' by Radovici et al[71] in 1932. Majority of patients with self-induced epilepsy are photosensitive, and induce seizures by gazing at the sun or a bright light and waving one hand in front of eyes.[72] Blinking movements[72-74] and eye closure with forced upward deviation of eyes[75,76] have also been employed as stimuli.

Epidemiology

Self-induced epilepsy is a rare condition.[5,77] This phenomenon was observed in only one patient, of the 10,000 patients with epilepsy studied,[78] in only two records, of the 20,000 EEG records studied,[79] and in five patients, of the 460 patients with photosensitivity.[1] Of the 22 patients with epilepsy and photosensitivity, studied by Darby et al,[76] seven had self-induced paroxysmal activity and/or seizures by slow eye closure. Self-induced epilepsy is more frequently reported from the Indian subcontinent. In a study in south India by Iyer,[80] of the 2000 patients with epilepsy 11 patients satisfied the criteria for photosensitive epilepsy. All but one had features of self-induced epilepsy. Hand waving and rubbing and flickering of eyelids were the techniques employed to induce seizures. Six patients in addition had heliotaxis, impulsive attraction to sunlight. In our study, of the 1298 patients with epilepsy, eight had self-induced epilepsy.

Clinical Features

Of the 8 patients in our series, five were males. The age range at presentation was 9-38 years and the age at onset of epilepsy was between 6-16 years. Three patients were mentally subnormal. Generalized seizure was the seizure type in five, and in three the seizure type could not be classified. Photosensitivity was demonstrable on EEG in four.

Illustrative case[81]

A female aged 22 years had her first seizure at the age of nine years. It happened one morning when she was in the schoolyard. She felt a 'funny sensation' in her forehead and began to rub the forehead, looking up. This resulted in a generalized tonic-clonic seizure. Similar attacks occurred subsequently, mostly in school, when she was outdoors on sunny days. While in the garden on a sunny day, she would suddenly look up and begin to rub her forehead. Within 2-3 min she would get a convulsion and fall unconscious. She reported a sensation of a worm wriggling in the middle of her forehead making her rub. She denied experiencing any pleasure during or after the act. All her self-induced attacks occurred only during daytime, outdoors, on sunny days. She had experienced a few spontaneous seizures in her sleep, usually around midnight, when the room was dark. When seen by us, she was taking phenytoin 200 mg/day with some reduction in the frequency of her seizures. Physical examination was essentially normal. She was right-handed and of average intelligence (IQ 73 on Raven's scale). Psychological assessment showed that she was a shy, timid and over-protected person who lacked self-confidence.

Routine EEG showed a symmetrical dominant alpha rhythm of 10 Hz and a slight excess of generalized theta activity. Hyperventilation induced occasional sharp and/or slow wave complexes bilaterally. Photic stimulation at 6-22 flashes/sec (fps) frequently evoked generalized spikes or polyspikes with or without slow after-waves. The following tests were carried out using a Flectalux 1000 MLA, 1000 W lamp placed in front of the patient at a distance of two meters. Rubbing the forehead with her left hand with spread out fingers crossing her open eyes horizontally, without the light for five min produced no abnormality. Looking at the light for five min without rubbing also produced no abnormality. However, rubbing with the light on constantly evoked generalized bisynchronous irregular polyspike and wave discharges immediately or within two minutes. While rubbing, when the lamp was switched on, similar discharges occurred immediately (Fig. 1) or within six seconds. These discharges disappeared when the light was switched off and reappeared when the light was switched on (Fig. 1). A similar response was seen with regard to rubbing, when the discharges disappeared when the rubbing was stopped and reappeared when the rubbing was restarted. Constant rubbing with the light on made the patient giddy and uncomfortable within 1-2 minutes, and the test was never continued for more than three minutes because of the fear of a clinical seizure. The abnormal discharges often continued throughout the 3-minute period but at times waxed and waned. These tests repeated one week later produced similar results.

Clobazam 10 mg twice daily was added to the treatment regimen. At review 1 week later, frequency and duration of rubbing had markedly decreased. She volunteered that the compulsion to rub was also much less even when she stayed in the hot sun, and the sensation of a worm wriggling in the forehead was no more present. Even when she rubbed the forehead, seizures did not occur. Repeat EEG tests with photic stimulation or rubbing up to 10 min. with the light on failed to produce significant abnormalities. At two months of follow-up she was seizure free and the frequency of rubbing had decreased further.

Pathogenic Mechanisms

As to why some patients with epilepsy deliberately evoke seizures remains a puzzle. Most of these patients are compulsively attracted to sunlight. They cannot offer a good explanation for their abnormal behavior, although some admit that it gives them a pleasurable or relaxing feeling. Many authors, including Radovici,[71] have thought that psychological factors and stressful situations influenced the frequency of self-induced seizures. Associated behavioral abnormalities leading to social isolation and learning problems are also seen in these patients. Mental retardation was found in 30% of patients with self-induced epilepsy.[82]

Hand waving and blinking are the commonest techniques employed to evoke seizures.[4] In our patient, rubbing the forehead was the maneuver and EEG (Fig. 1) clearly shows an eye movement artifact before the onset of epileptiform activity. This may suggest that the epileptiform activity is probably related to slow eye closure.[76] Seizures induced by eye closure are not rare.[75,76] They may occur in patients who have a history of seizures induced by techniques such as hand waving. Hand waving provides an intermittent retinal stimulation.[76] Some authors have suggested that the hand movement is part of an ictal phenomenon rather than the stimulus.[1,83] In our patient, movement of hand in the absence of a bright light failed to induce epileptiform activity. This suggests that hand movement is voluntary, and this view is supported by intensive monitoring.[82]

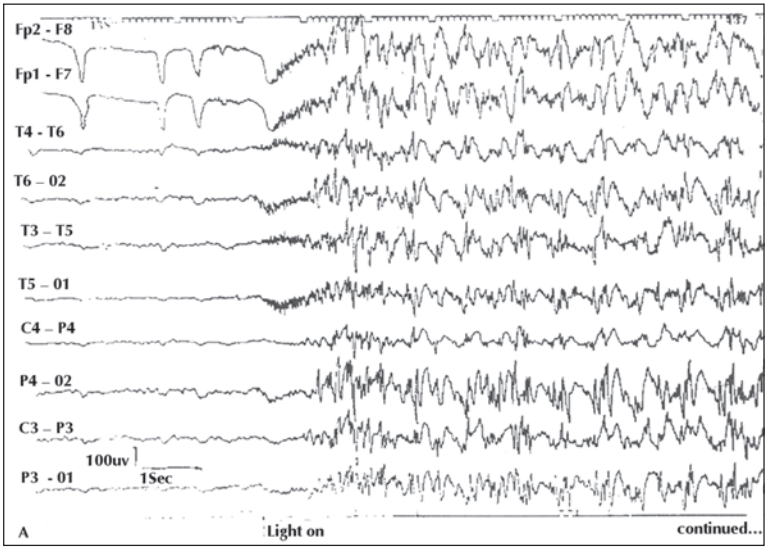

Figure 1A. EEG recording while patient rubbing the forehead- light switched on. Reproduced with permission from Senanayake N. Self-induction of seizures in photosensitive patients in a tropical country. Epilepsy Res 1988; 2:61-64.

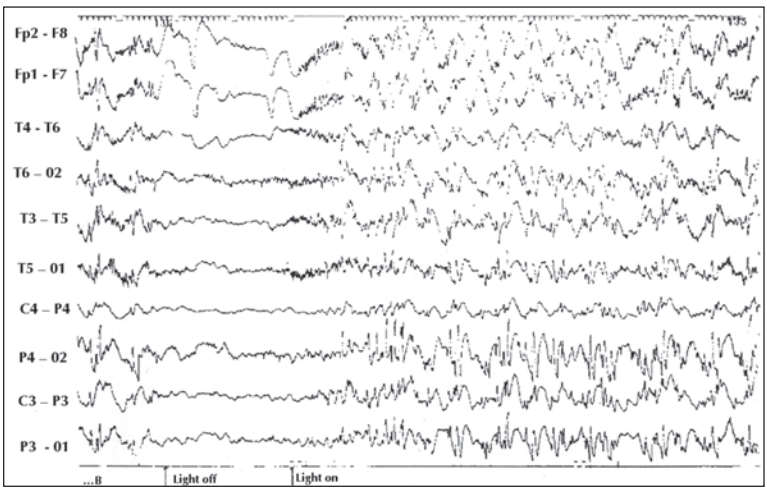

Figure 1B. EEG recording while patient rubbing the forehead- light switched off and then switched on. Reproduced with permission from Senanayake N. Self-induction of seizures in photosensitive patients in a tropical country. Epilepsy Res 1988; 2:61-64.

Treatment

Self-induced epilepsy is considered very difficult to treat.[4] Drugs, particularly valproate,[84] benzodiazepines and succinimide[1,85] which are effective in suppressing photosensitive and visually induced seizures have been tried with varying response. Clobazam, in some of our patients including the one illustrated in this chapter, has been found to be effective in reducing the seizure frequency. Wearing dark glasses have been shown to successfully reduce the seizure frequency. However, noncompliance with treatment is a major problem. Psychotherapy has been tried in some patients with varying success.[4]

Conclusion

In this chapter, certain forms of reflex epilepsies frequently reported from tropical Asian countries are discussed. More epidemiological studies are needed from other Asian countries and also from African and Latin American countries to determine the differences and peculiarities in the pattern of reflex epilepsies seen in developing countries, between countries and also within the countries. Such studies should take into cognizance the environmental factors responsible for reflex seizures. A case in point is eating epilepsy, which, in our opinion, is related to carbohydrate-rich bulky meals consumed by people of the Indian subcontinent. Information from other developing countries will possibly help to identify the seizure-provoking factors for these reflex epilepsies in more specific terms.

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Chapter 12

Hot-Water Epilepsy: A Geographically Specific Epilepsy Syndrome

P. Satishchandra, Gautam R. Ullal and S.K. Shankar

Seizures precipitated by a sensory stimulus are described as reflex or sensory epilepsy. Reflex epilepsies are interesting, not merely as 'collector's item' but provide extremely important information regarding the pathogenesis of epilepsy in general, and reflex epilepsy in particular. As the seizure-inducing mechanisms rather than the etiology constitutes the common factor in these seizures, the term 'sensory precipitation of seizures' proposed by Penfield is probably more appropriate.[1] Epilepsy precipitated by the stimulus of hot-water poured over the head is known as 'hot-water epilepsy' (HWE).[2-9] These are also known as 'water-immersion epilepsy'[10] or 'bathing epilepsy'.[11-12] HWE has been included under reflex epilepsies in the proposed new classification of epilepsies and epilepsy syndromes by the task force International League Against Epilepsy (ILAE).[13]

Epidemiology

Since the first description of HWE in 1945 from New Zealand,[14] cases have been reported from all the regions of the world; Australia,[15] United States of America,[15] Canada,[5] United Kingdom,[17] Japan,[18-21] and Turkey.[22] However, there is an over-abundance of reports of patients with HWE from south India, mostly hospital-based series.[2-4,6-9] Community based studies in Karnataka, a province in south India suggest geographical clustering of this epileptic disorder in this region of the world. In the Bangalore Urban-rural Neuroepidemiological (BURN) study the reported prevalence was 60 per 100.000 (P. Satishchandra, Bangalore, India, unpublished data), while in the Yelandur study, a rural community-based study, the reported prevalence was 255 per 100,000.[23]

Clinical Features

In HWE, seizures are precipitated by hot water bath or immersion in hot water. Though it is customary practice to bathe everyday among south Indians, head bath is done generally once in 3-15 days. Temperature of the hot water used for bathing ranges between 40-50°C (ambient room temperature - 25-30°C). Usually water is poured over the body or head using a μg. A proportion of patients, 5-10% may have seizures even when hot water is not poured on the head and only on the body. Isolated cases of HWE have been reported in people taking showers or tub baths.[7] HWE epilepsy is more commonly reported in children. It has also been reported in adults from south India.[2,4,6-9] In almost all the series there is a male preponderance (2-2.5: 1). Seizure frequency is more related to the frequency of head bathing. Mostly the seizure type is complex partial seizure with or without secondary generalization. Seizure semiology includes dazed look, sense of fear, irrelevant speech, visual and

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auditory hallucinations with complex automatisms. Primary generalized tonic clonic seizure is the seizure type in about one-third of the patients. Seizures usually last for 1-3 minutes. Video recording of seizures have been done in the laboratory in a few cases.[5,7,15,17] About 10% of patients express intense desire/pleasure and continue to pour hot water over the head until they lose consciousness and could be considered as 'Self induced HWE'.[7] In patients with HWE neurologic examination is essentially normal. Positive family history of epilepsy has been reported in 7-22.6% of probands. Nonreflex epilepsy occurs in 16% - 38% of patients with HWE.[3-4,7]

Electroencephalography

Interictal scalp electroencephalography (EEG) is usually normal, but diffuse abnormalities may be seen in about 15-20% of the records.[3-4,6-7] Lateralized or localized spike discharges in the anterior temporal regions have been reported in a few cases.[2,3,5,18] Ictal EEG recording has technical limitations and are often difficult to obtain. There are seven published reports of ictal EEG recordings during seizure provocation. The observed ictal EEG abnormalities include: rhythmic delta in temporal leads,[16] sharp and slow waves in the unilateral hemispherical leads,[17] bilateral spikes,[20] and temporal activity.[11-12] Video-EEG recording in one patient of 'bathing epilepsy' had demonstrated delta activity starting in the right hemisphere with rapid spread to the other hemisphere.[24]

Pathogenesis

Exact pathogenesis of this unique form of reflex epilepsy is not yet known and various pathophysiological mechanisms have been suggested. Steersman and Ursing[16] suggested that the seizures in HWE are precipitated by complex tactile and temperature dependent stimuli. The fact that the seizures can only be provoked by pouring hot water on the head but not by hot water towels, sauna or hot air blowing suggests that the triggering stimulus is complex and involves combination of factors such as (a) contact of scalp with hot water, (b) temperature of water and (c) specific cortical area of stimulation etc. Seizure semiology, ictal EEG activity in the temporal and frontal leads made Syzmonowicz and Meloff[5] to suggest that HWE may be related to a structural lesion of temporal lobe. But CT scan and magnetic resonance imaging (MRI) are essentially normal in patients with HWE. Even if such a lesion is present, it is not yet clear whether the seizures are due to increased excitability of temporal cortical neurons or due to pathological involvement of lower centers such as hypothalamus or both.[17] We studied the brain pathology in three patients with history of HWE and later developed nonreflex epilepsy.[25] They were aged 12 years, 23 years and 65 years and the duration of nonreflex epilepsy was 1 year, 15 years and 53 years respectively. The patient aged 23 years with 15 years duration of nonreflex epilepsy at autopsy had a thalamic astrocytoma, evolving from low grade to high grade and spreading to temporal lobe and adjacent subarachnoid space breaching the piaglial barrier, without evidence of calcification. It is very difficult to attribute causal relationship of this lesion to the seizure provoked by hot water in the early period of his life. In the child of 12 years, there was moderate degree of depletion of granule cell in dentate gyrus and loss of large neurons in CA4 zone. In CA1 zone of Ammon's horn neuronal loss was variable on both the sides, with reactive gliosis, right more than the left. The patient aged 65 years died of posterior circulation stroke. In him there was moderate neuronal loss and gliosis in dentate gyrus and Ammon's horn. These changes were much less pronounced when compared to features in the child with epilepsy of one-year duration. The neuronal loss and gliosis

observed in the anterior hippocampus of these brains were similar to the one described with chronic temporal lobe epilepsy.[26] This needs further validation by stringent quantitative evaluation.

The reported frequency of febrile seizures in patients with HWE is high, 11% to 27%.[3-4,7,9] Febrile seizures is an important risk factor for complex partial seizures. In a case control study, the frequency of febrile seizures in patients with complex seizures was 20%.[27] The clinical behavior of patients with HWE during incidental febrile episodes with respect to susceptibility to seizures activity is still under investigation.

Experimental Studies

Seizures can be provoked by repeated hot water (45°C) exposure to the head of an adult rat, the phenomenon similar to kindling. Klauenberg and Sparber[28] called this 'hyperthermic kindling'. We hypothesized that similar phenomenon of 'hyperthermic kindling might be responsible for the development of HWE in humans.[7] To further understand the pathophysiological and pharmacological mechanisms underlying HWE, we developed an experimental animal model which has similarities to human HWE: (a) precipitating stimulus; (b) the ictal events; and (c) EEG.[29,30] The rectal temperature rise is too rapid in seizure susceptible adult Wister rats when compared to 'nonseizure susceptible' rats. This may suggest the possible role of the abnormal thermoregulatory centers in initiating the seizure discharges.[30] Seizure susceptibility among the Wistar rats may be determined by certain constitutional genetic traits.[31] In the closely bred colony of Wistar rats that we have studied, nearly 30% were resistant to seizure initiation. In the 'seizure prone' rats, the succeeding progeny also had seizure susceptibility, highlighting the probable genetic basis. Pathological studies of brain in rats subjected to repeated seizure activity by hot water stimulation revealed shrinkage of neurons in cingulate gyrus and parieto-temporal cortex and atrophy of the pyramidal neurons, without much gliosis. In the hippocampus the neurons were depleted in addition to neuronal shrinkage and atrophy. There was granule cell loss in the dentate gyrus. Some of the neurons revealed apoptotic bodies. Reactive gliosis or microglial response was conspicuously absent. Some of the large reticular neurons in the brainstem, the cerebellar Purkinje cells and neurons in the thalamus were shrunken and basophilic indicating anoxic damage. There was no evidence of focal myelin loss or oligodendroglial changes. In contrast the brains of seizure resistant rats and controls not exposed to hot water stimulation were essentially normal but for occasional anoxic neurons randomly distributed in hippocampus and cerebral cortex.

Hyperthermic Kindling in Animal Model

In seizure susceptible rats stimulating at predetermined frequency of once in 2 to 4 days followed by delayed 8th and 9th stimulation on 15th and 30th days after 7th stimulus resulted in the progressive increase in seizure duration and severity and also lower temperature threshold. This feature persisted even after 30 days, suggesting a phenomenon of 'hyperthermic kindling' in these animals. Similar phenomenon has not been investigated in humans, though 'kindling' has been suggested as the possible pathophysiological mechanism for progression of 'hot water bath' induced partial seizures to nonreflex seizures with time.[7]

These animals were sacrificed and the brains were perfused with sodium sulfide. The sections were stained with Tim's silver stain. In the control animals Tim's staining in the hippocampus was noted in the mossy fiber axons of dentate granule cells,

which heavily innervated the hilus and extend into statum lucidum of CA_3, zone. In the animals with seizures 'Tim' silver staining was observed essentially in the internal and external molecular layer at the tips of dentate gyrus. In rats with single seizure, fine granular deposits were discernable at the tips of dentate gyrus and internal molecular layer. In the rats with multiple seizures and clinical and electrophysiological evidence of kindling, the silver staining density in the internal molecular layer at the tips and blades of dentate gyrus was dense, extending to the external molecular layer. In the stratum lacunosum also similar Tim positive reaction product was seen. Straturn lucidum of CA3 zone had a dense cap of staining, in contrast to minimal and focal labeling in the animals experiencing single seizure (Ullal et al, pending publication). The presence of sprouting in the rats in a graded manner as shown by Tim's silver staining indicates abortive reparative process in the neurons leading to kindling. Antiepileptic drugs like phenobarbital and benzodiazepines, but not phenytoin and calcium channel blocker, nifidipine, could block the seizure activity in the animal with hyperthermic seizures.[32]

Experimental studies in patients with HWE, during hot water head bath revealed 'rapid spurt' in the auditory canal temperature, 2-3°F, within a short span of 2 minutes. Further it took 10-12 minutes for the temperature to return to the base line after the bath. In comparison in normal volunteers the temperature rise was 0.5-0.6°F and it returned to base line immediately at the end of the bath.[33] It is possible that the rapid raise in temperature may be the provoking factor for seizures in these patients. We postulate that patients with HWE probably have an aberrant thermoregulatory system and are extremely sensitive to the rapid rises in temperature during hot water head bath. This aberrant thermoregulation seems to be genetically determined and further work to elucidate this hypothesis is under investigation. The rat model described simulates human HWE and gives new evidence that human HWE is a 'hyperthermic' seizure.[30]

Magnetic resonance imaging (MRI) in patients with HWE is essentially normal. It is possible that in patients with HWE pouring hot water on head may produce functional changes in certain brain areas provoking seizures. To test this hypothesis we studied functional imaging studies in ten patients with HWE who had seizures provoked only by hot water bath. All the patients had interictal EEG, MRI, and interictal SPECT study using Ehylene cysteine dimmer (ECD). Patients were given hot water baths after obtaining written consent in the laboratory to provoke seizures. Of the ten patients studied, seizures could be provoked in five patients. All of them were administered intravenous 99m TC ECD at the onset of ictal event and peri-ictal SPECT scans were obtained. These scans were subtracted from corresponding inter-ictal SPECT scans. Subtracted scans showed ictal hypermetobolism, low uptake of the isotope, in the medial temporal structures and hypothalamus on the left side in three and on the right in two patients with spread to the opposite hemisphere. These preliminary observations clearly demonstrate involvement of these structures in the initiation and propagation of seizures in patients with HWE.[34]

Genetics of Hot-Water Epilepsy

Reported family history of HWE epilepsy in patients with HWE varied between 7% and 15%.[3,4,7-9] In the community-based study, 18% of probands with HWE had positive family history of HWE.[9] Hot-water epilepsy has also been described in monozygotic cotwins by Itoh et al[35] from Japan. In our series, there were three dizygotic twins each with one member affected.[7]

We have identified in our series[7] five families with two to three affected members with HWE. In two of the families there was coexistence of HWE and febrile seizures.[36-37] Febrile seizures is a classic example of hyperthermic seizures. There is now a convincing evidence to suggest that at least some of the febrile seizures have genetic basis. Recently Wallace et al[38] have reported a large family from Australia in which febrile convulsions appear to result from autosomal dominant inheritance at a single major locus on chromosome 8Q13-21.

The genetic mechanism underlying the expression of HWE in humans is not known. Studying the first five families closely, we postulate that autosomal recessive mutation as a distinct possibility.[37-39] We speculate that although the frequency of such a mutation in a particular population would be fairly low, the high frequency of consanguineous marriage in many South Indian communities[40] could explain the high prevalence of HWE in this population. The single locus model is, however, insufficient to explain any genetic linkage between these conditions and the influence of a modifier locus (or loci) or of environmental factors that may need to be invoked to account for their co-occurrence.[39]

Management

Common practice by most of the practicing physicians is to advise patients with HWE to use luke warm water for head bath or sponging with hot towels[2-4] and also AEDs.[6-7] We followed 208 patients with HWE treated with conventional AEDs for a mean period of 14 ± 12.9 months (range 6 to 60 months). Complete seizure control could be achieved in 60% of patients and18.3% of patients had 50% reduction in seizure frequency.[7] It is of interest that 10% of patients exhibited compulsive behavior to pour hot water to provoke seizures, 'self-induced hot water epilepsy'.[7] About 16-38% of subjects with HWE continue to get seizures even during regular bath and develop nonreflex seizures during follow up Table 1. This may be considered as an indirect evidence for the phenomenon of 'hyperthermic kindling' in humans, though the concept of kindling in humans is still highly controversial.

In view of the observations that HWE is a type of hyperthermic seizure like febrile seizures, we have evolved a newer method of treatment, intermittent prophylaxis with benzodiazepines. Patients are advised to take 5-10 mg oral clobazam, 90 to 120 minutes before every head bath. Conventional AEDs are prescribed only if and when the patients develop nonreflex seizures apart from HWE. This approach has a dual advantage of minimizing the cost of therapy and reducing the side effects associated with AED use.[36]

Conclusion

Development of experimental animal model and careful analysis of clinical profile of patients with HWE has given a new insight into the possible pathogenesis of this unique type of epilepsy. These observations suggest that HWE is a type of hyperthermic seizure. Aberrant thermoregulation in the genetically susceptible population with possible coexisting environmental influence could be the probable mechanisms responsible for this epilepsy. The concept that HWE is a type of hyperthermic seizure has therapeutic implications. These patients may not require regular prophylactic AED use and seizures can be aborted by intermittent prophylaxis with benzodiazepines. Further work is in progress to identify the gene responsible for this interesting type of epilepsy with higher incidence among south Indian population and the role of chanelopathies in the pathogenesis.

Table 1. Clinical features of hot-water epilepsy in the published literature

Author Name and Reference	Country	No. of Cases	Sex M/F	Age of Onset (yrs/m)	Seizure Type	Temp. of Water in ˚C	Development of Non-Reflex Epilepsy (%)
Allen[14]	New Zeeland	1	M	10	CPS	?	NO
Mofenson et al[10]	-	1	M	7m	GTCS	37-48	NO
Mani et al[3]	India	108	72:28	6-15	CPS,	40-50	16
Keipert[15]	Australia	1	M	5m	CPS	?	NO
Stensman and Ursing[16]	USA	1	M	7m	CPS	37.5	NO
Onuma[21]	Japan	1	F	2	CPS	>39	NO
Subramanyam[4]	India	26	58:42	3m-35	CPS, GTCS	40-55	38
Parsonage et al[17]	UK	3	2:1	5.21	CPS	?	NO
Szymonowicz & Meloff[5]	Canada	1	M	18 m	CPS	37-38	100
Itoh et al[35]	Japan	1	M	5.5	GTCS	39	N0
Kurata et a1[7]	Japan	12	1:2	5m-9y	GTCS/ATONIC	40-43	100
Miyao et al[8]	Japan	3	2:1	3	GTCS	?	100
Satishchandra et al[7]	India	279	72:28	2m-58y	GTCS, CPS	40-50	25.4
Roos et al[24]	USA	1	M	8m	CPS	40	?
Shaw et al[11]	UK	1	M	5m	CPS	37	NO
Lenior et al[2]		2	1:1	1	CPS	37	NO
Gururaj & Satishchandra[9]	India	78	61:17	6m-58y	CPS, GTCS	40-50	12.8
Bebek et al[22]	Turkey	21	3:1	19m-27y	CPS, GTCS SPS	?	62

m: month, y: year, CPS: complex partial seizures, SPS: simple partial seizures, GTCS: generalized tonic-clonic seizures

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Chapter 13

Neonatal Seizures: Developing Countries Perspective

Surekha Rajadhyaksha and K.N. Shah

Seizures in the newborn period are a frequent clinical problem and represent the most distinctive signal of neurological disease. Neonatal seizures are usually related to specific illness requiring prompt therapy. Early diagnosis of underlying cause is important, as some of the risk factors are associated with high mortality or adverse neurological sequelae. Neonatal seizures show clearly differentiated characteristics from seizures in older children. Several unique characteristics of neonatal seizures warrant a separate classification from the classification of epilepsies and epileptic syndromes proposed by International League Against Epilepsy (ICE-1989).[1]

Incidence

Seizures manifesting in the first month of life is greater than at any time later in childhood.[2] Studies from the developed world indicate that seizures occur in 1.8 to 8.6 per 1000 live births and these studies also show increasing trends in the incidence rates.[3-6] The increase in the incidence rates has been attributed to increased survival of preterm and sick babies.[4] Data from developing countries is limited. Any incidence studies in developing countries will have significant limitations, mainly because of methodological issues. Health care systems are poorly developed and there are hardly any neonatal intensive care units, particularly in the rural areas. Most often births take place at home and problems exist in the recognition and documentation of subtle neonatal seizures. In Nigeria, an incidence of 7.5 per 1000 live births has been reported. The incidence was high in preterm infants than full-term infants, 47.6 vs 8 per 1000 live births.[7] Hospital based studies involve more high-risk newborn evaluation and are likely to report a higher incidence[8,9] (Table 1).

Clinical Seizure Semiology

Seizures manifest differently in newborn and seizure semiology depends on the neuroanatomical and neurophysiological development. In the perinatal period cortical organization, dendritic ramification, synaptic connections, and myelination of efferent systems and inter-hemispheric commissures is less advanced, while cortical development of the limbic system and its connection to the diencephalon and brainstem are well developed.[10]

Newborns rarely have well-developed generalized tonic-clonic seizures and preterm babies have even less organized spells. Focal clonic activity, rapidly shifting from one part of the body to another could be misinterpreted as generalized tonic-clonic seizures. Essentially four clinical seizure types are usually recognized in the neonates: subtle, clonic, tonic and myoclonic. They further can be categorized into multifocal and generalized. Multifocal refers to seizure activity that is asynchronous, migratory

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Table 1. Incidence of neonatal seizures

	Incidence/1000 Live Births		
Type of Study	**Total**	**Full-Term**	**Pre-Term**
Nigeria[7]	Community	7.5	8.0	47.6
South Africa[8]	Hospital-based	140	-	-
India (Kanpur)[9]	Hospital-based	100	-	-
Our series	Hospital-based	62.5	-	-

and involves more than one area while generalized denotes activity which is synchronous, bilateral and non migratory.[10] Subtle seizures are paroxysmal alteration in the neonate's behavior such as slight posturing of limbs, apnea, deviation of eyes with or without nystagmus, eyelid fluttering, abnormal cry or vasomotor changes. Aberrant behavior may manifest as oro-buccal lingual movements such as yawning, lip smacking, chewing and wincing of facial muscles or apparent as limb movements like pedaling, rowing, or rotating arm movements. These are considered as clinical seizures because of their repetitive, rhythmic and stereotype nature. Myoclonic seizures are distinguished from clonic seizures by the rapid speed of the jerks and their predilection to the flexor group of muscles. Focal myoclonic jerks involve flexor group of muscles of upper extremity while multifocal myoclonic jerks are asynchronous twitching of several parts of body. Most often seizure diagnosis in neonates is based on the clinical observations of the ictal events and interictal electroencephalogram (EEG). However, sometimes clinical observations alone are not sufficient, video-EEG improves the descriptive accuracy of the clinical event.

The reported frequency of various seizure types varied in different series (Table 2). In the series reported from India, multifocal seizures were the most common seizure type, whereas generalized tonic seizures were more frequently observed in the study in Nigeria.[7] Focal clonic seizures were more common in the study from Brazil.[11] These differences may be related to the characteristics of patient population studied and the study methodology.

Clinical Seizures versus EEG Diagnosis

Clinical observation alone may not be adequate to distinguish behavioral events as epileptic or nonepileptic activity. Understanding of neonatal seizures and descriptive accuracy has improved by video-EEG with polygraphic recording. The major EEG correlates of neonatal seizures include (a) focal or multifocal spikes or sharp waves or both; (b) focal monorhythmic discharges. Abnormal background activity is a determinant of outcome. Mild to moderate EEG abnormalities include voltage asymmetry and delayed maturation patterns. Severe EEG abnormalities include marked decrease in voltage, burst suppression patterns, and electro-cerebral silence.

Focal clonic, focal tonic and generalized myoclonic jerks are more often associated with synchronized abnormal electroencephalographic activity.[12] By contrast the relationship between EEG discharges and generalized tonic, focal and multifocal myoclonic paroxysms and also subtle seizures is inconsistent. The frequency of subtle seizures having EEG correlates (epileptiform activity) is variable. Ocular phenomenon such as sustained eye opening, ocular fixation and tonic horizontal eye deviation are associated with EEG abnormalities.[10] Apnea in a full term infant has EEG correlate and often associated with other subtle phenomenon such as staring, eye deviation or mouthing movements, but not bradycardia.[13] Synchronized generalized myoclonic jerking with flexion of both limbs resembling infantile spasms

heralds West syndrome and is associated with EEG discharges. A recently proposed classification of neonatal seizures is based on clinical seizure characteristics and EEG abnormalities; (a) clinical seizures with epileptiform discharges in the EEG; (b) epileptiform discharges in the EEG with no clinical seizures; and (c) clinical seizures with no epileptiform discharges or abnormalities of uncertain nature in the EEG.[14]

In one study electrographically confirmed seizures were correlated to clinical events in 92 preterm and term neonates.[15] Clinical criteria contemporaneous with electrographic seizures were noted in only 28 (45%) of 62 preterm neonates, and 16 (53%) of 30 full-term neonates. Subtle seizures coincident with electrographically confirmed seizures were the most predominant clinical type for both term and preterm neonates (71% and 68%, respectively). We studied clinical seizures and EEG correlates in 28 neonates born outside the hospital admitted to our neonatal intensive care unit. Fourteen neonates had clinical seizures with associate EEG correlates, 2 neonates had clinical seizures without any EEG correlates, and 3 had seizure mimics, hyperekplexia and sleep myoclonus. Epileptiform discharges were recorded in 2 neonates without coincident seizures and in 3 the background activity was grossly abnormal.

International Classification of Epilepsies and Epileptic Syndromes (ICE) 1989

Of the 2060 children with various epilepsies and epilepsy syndromes in our series, 988 (48%) had symptomatic epilepsies. Similar were the observations in the series from Italy (44%)[16] and Finland (36%).[17] Birth related trauma was the putative risk factor for 14.6% of the symptomatic epilepsies in our series and it was 18% and 15% in the series from Italy[16] and Finland[17] respectively. Birth related trauma is an important cause of symptomatic epilepsy in the later life. In our series, of the infants who sustained insult in the neonatal period 59% later developed localization-related epilepsy and 16% developed symptomatic West syndrome. In the study from Japan 41% of the infants with symptomatic neonatal seizures later developed West syndrome and 50% of them later evolved into localization-related epilepsies.[18]

Very few epilepsies and epilepsy syndromes recognized in the International Classification of Epilepsies and Epileptic Syndromes (ICE)[1] occur in the neonatal period. In our series 94 neonates could be grouped into one of the categories proposed in the syndromic classification (Table 3).

Etiology

Neonatal seizures are often related to specific illness (Fig. 1). Prompt identification of a treatable cause and rapid institution of etiology-specific therapy may decrease the chance of long-term neurologic sequelae. Such an approach may effectively control the seizures and there may not be the need for antiepileptic drug (AED) medication. In developing countries prenatal and perinatal insults and postnatal acquired infections of central nervous system (CNS) account for a significant proportion of etiological factors (see the Chapters 8 and 9).

Hypoxic-Ischemic-Encephalopathy

It is estimated that 2-4 full-term neonates per 1000 sustain perinatal asphyxia and the associated mortality is ~ 30%. Of the survivors a quarter develop hypoxic-ischemic-encephalopathy (HIE).[19] In developed countries due to effective antenatal care and improved obstetric monitoring there is a steady decline in the

Table 2. Clinical seizure types

	Multifocal Clonic (%)	Focal Clonic (%)	Generalized Tonic (%)	Focal Tonic (%)	Myoclonic (%)	Subtle/Minimal (%)
Our series	44	11.5	19	4	-	21
India (Kanpur)[9]	40.8	45.6	5.6	-	1.6	6.4
Nigeria[7]	-	23	51	-	11	16
NCPP data[3 +]	75•	33	25	2.5	10	-

+ Infants manifested more than one seizure type. • generalized clonic

Table 3. Neonatal epileptic syndromes (ICE 1989 classification)[1]

ICE Classification		Name of Condition	Prognosis-No. of Cases	Prognosis Seizure	Neurological
2.1	Generalized idiopathic	Benign neonatal familial convulsions	1	Controlled	Normal
		Benign neonatal convulsions	—		
23.1	Generalized symptomatic of nonspecific etiology	Early myoclonic encephalopathy (Aicardi)	3	Uncontrolled	Grossly abnormal
		Early infantile epileptic encephalopathy (Ohtahara)	10	Uncontrolled	
2.3.2	Generalized symptomatic of specific etiology	Diseases states in which seizures are predominant features;			
		a. Aicardi syndrome	4	Uncontrolled	Abnormal
		b. Holoprosencephaly	6		
		c. Lissencephaly/pachygyria etc	1		
2.2	Generalized symptomatic	Early presentation of West and/or cryptogenic	5	Variable	Abnormal
3.1	Undetermined whether focal or generalized	Neonatal seizures of other etiology	64	Variable	Abnormal
Total			94		

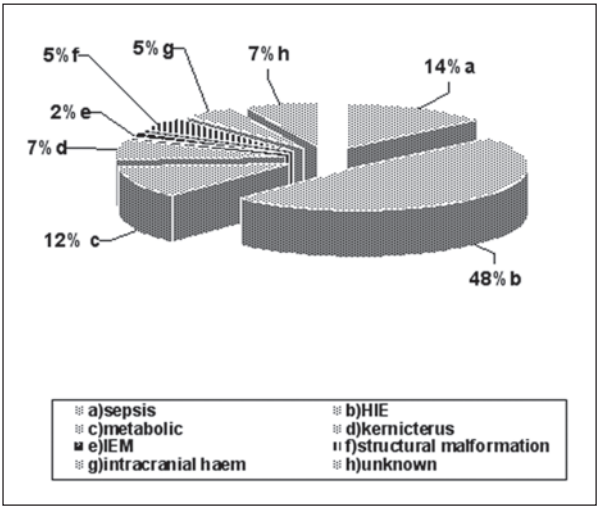

Figure 1. Etiology of neonatal seizures.

incidence of severe birth asphyxia[20] and HIE.[21] Comparing two time periods, Gunn et al[22] found little change in the overall incidence of neonatal seizures in term infants with birth asphyxia. However, there was a marked reduction in small for date infants with seizures between the two periods. This was attributed to the improved obstetric monitoring.

Birth asphyxia still remains a leading cause of perinatal mortality in developing countries. HIE following perinatal hypoxia is the leading cause of neonatal seizures in term and preterm newborn and accounted for 48% of etiological factors in our hospital-based series (Fig. 1). In a study in Nigeria the reported incidence of birth asphyxia was 26.5 per 1000 live births. In this study for every 1000 neonates with birth asphyxia 12.1 neonates had persistent seizures and coma.[23] Two independent studies in Nigeria, conducted in the same decade showed no change in the incidence of perinatal asphyxia and hypoglycemia, 47% and 19% respectively.[23,24] In Asian countries low birth weight is the most important independent risk factor for birth asphyxia[25] and is associated with high perinatal mortality.[26]

Diagnosis of HIE is based on: (1) complications of pregnancy, labor, delivery with evidence of fetal hypoxia, abnormal fetal heart rate pattern, low cord pH, low Apgar scores; (2) neurological signs of encephalopathy; and (3) associated metabolic, electrophysiological and neuroimaging abnormalities.[27] Seizures associated with HIE are frequently subtle, mixed or fragmentary and usually occur in the first 6 to 12 hours and are maximum over 24-36 hours. Response to antiepileptic drug therapy is poor. Early and prolonged seizures are associated with high mortality and neurological sequelae.[28] Similarly for full-term newborn with HIE, abnormal neurological behavior at 7th day of birth is a predictor of adverse outcome.[29]

Infections of Central Nervous System

Intrauterine and postnatal acquired infections of the CNS are important causes of neonatal seizures in developing countries and in our series these two etiologies accounted for 13% of risk factors. Neonatal meningitis is common in developing

countries. A hospital-based study in Ethiopia reported an incidence of 1.37 per 1000 live births, both preterm and term.[30] The clinical presentation of neonatal meningitis is often subtle and indistinguishable from that of neonatal sepsis without meningitis. Seizures are more common with gram-negative meningitis and can be the presenting symptom in 20% to 50% of neonates with meningitis.[31] Neonatal meningitis is associated with high mortality and morbidity. In the Ethiopian study, 40% of neonates with neonatal meningitis died and 21% developed neurological sequelae such as hydrocephalus, spastic paresis and seizures.[30]

Metabolic Disturbances

A variety of metabolic disturbances, including inherited metabolic disorders are associated with neonatal seizures. Hypoglycemia and hypocalcemia account for a significant proportion of metabolic disturbances. In the Nigerian study hypoglycemia accounted for 19% of provoking factors[7] and in our series it accounted for 11%. In developing countries hypoglycemia is more commonly observed in small-for-gestation age (SGA) newborns. The condition occurs in later part of the first or second post-natal day. Duration and severity of hypoglycemia determine the neurological outcome.[32] Of the SGA newborns with hypoglycemia, 80% exhibit neurological symptoms and 50% of symptomatic cases experience seizures. Symptomatic hypoglycemia is associated with ~ 50% chance of normal development.[10] In developing countries the most effective management approach is prevention of hypoglycemia. Of particular relevance is identification of high-risk infants, prevention of hypothermia, implementation of early oral feeding, surveillance for clinical symptoms, and serial blood glucose monitoring. Hypoglycemia can accompany with disorders such as trauma, HIE, intracerebral hemorrhage, and infection.

Hypocalcemia with or without hypomagnesemia is another common metabolic cause for neonatal seizures and accounted for 28% of provoking risk factors in a study in India.[33] Hypocalcemia is more common in neonates with low birth weight, particularly in the first 2 to 3 days of life. Pyridoxine dependency can result in severe seizures in the neonatal period. Diagnosis can be suspected from the characteristic EEG findings, paroxysmal bilateral synchronous high voltage 1 to 4 Hz burst activity intermixed with spike and sharp wave activity and EEG normalization with intravenous administration of pyridoxine.[34]

In developing countries kernicterus is often related to blood group incompatibility.[10] In our series kernicterus accounted for 5% of metabolic disturbances. In Saudi Arabia severe neonatal jaundice and kernicterus is related to high prevalence of G6PD deficiency in the general population.[35] In China, brain damage and poor outcome was noted with the use of a herbal medicine used to treat neonatal jaundice.[36]

Prognosis

In developed countries the outlook for infants with neonatal seizures has improved over the years. This is partly related to better antenatal care and improved obstetric monitoring and also to intensive monitoring of high-risk neonates. Neonatal seizures and intracranial hemorrhage are independent predictors of poor neurological outcome.[37] Seizures occurring in the first few days of birth and prolonged and repetitive seizure activity are associated with high mortality and abnormal neurological sequel. Neurological outcome is better in full-term babies with neonatal seizures than in preterm babies. Apgar score of less than 7 at 5 minutes in newborn with neonatal seizures is associated with high mortality and neurological impairment.[38-40]

Do We Need to Treat All Neonatal Seizures with Antiepileptic Drugs?

The immediate goals of therapy are seizure control and identification and treatment of etiological factor or factors. When potentially treatable causes are identified, etiology-specific treatment should be initiated to limit ongoing CNS injury. Not all seizures warrant AED treatment because they may not be epileptic. Epileptic seizures should be treated as continued seizure activity as it can result in brain injury and also can have adverse effects on respiratory function, circulation and cerebral metabolism. A more controversial issue centers around criteria applied for adequacy of treatment. Is it clinical or electrophysiological? Since there is no conclusive data, treatment is aimed to abolish the clinical seizures. The AEDs typically used in the acute treatment of neonatal seizures are phenobarbital, phenytoin, or a benzodiazepine (diazepam or lorazepam). Phenobarbital still remains the drug of choice and is administered in dosages to attain adequate blood levels with minimal risk to cardiovascular and respiratory function.

Conclusion

Seizures in the newborn period are a frequent clinical problem and represent the most distinctive signal of neurological disease. Much of neonatal seizures in the developing world, result from preventable causes prenatal and perinatal insults and postnatal acquired infections of central nervous system (CNS). Hypoxic-ischemic-encephalopathy following perinatal hypoxia is the leading cause of neonatal seizures in term and preterm and still remains a leading cause of morbidity and perinatal mortality in developing countries. The other important cause of neonatal seizures in developing countries is hypoglycemia commonly observed in small-for-gestation age (SGA) newborns. With effective antenatal care and improved obstetric monitoring some of the burden of neonatal seizures can be reduced. Fortunately in developing countries the concept of perinatal health is receiving much attention and also the awareness of the value of statistical indicators of health. With better allocation of resources and rationalization of services for maternal and child health a better picture is likely to emerge in future.

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Chapter 14

Febrile Seizure: Developing Countries Perspective

Jing-Jane Tsai

Introduction

Febrile seizure is the most common seizure disorder in childhood. Often the terms "febrile convulsion" and "febrile seizure" are used synonymously or interchangeably. In the newly proposed classification this seizure disorder has been recognized as a special syndrome and the term "febrile seizures" (FS) has been proposed.[1,2] Epidemiological studies of FS are very few from the developing countries and show some differences not only in the incidence and prevalence rates but also in the clinical features, etiology, management, and outcome when compared to developed countries.

Epidemiology

Epidemiological studies from developing countries are mostly prevalence studies and the reported prevalence varied between 1.33% and 11. 61% (Table 1),[3-9] whereas the reported prevalence rates from developed countries was between 2% and 5%.[10-12] The lowest prevalence rate was reported from Saudi Arabia.[13] However, studies from some Asian countries[7] reported prevalence rates similar to those reported from developed countries. The wide range in the prevalence reported from the developing countries is probably related to the methodological issues.[14] The reported higher rates from the non-Occidental countries are attributed to high incidence of childhood infections and environmental factors and also probably to genetic factors.

Clinical Manifestations

The core entity of the clinical features of FS includes the relevant issues in the child, the illness and the seizures. Various definitions of FS have been developed for the convenience of clinical study,[10-15] thus the natural history of FS is artificially and unavoidably distorted. FS are classified as simple (typical) and complex (complicated or atypical) FS without uniform definition. Simple FS is usually a brief generalized tonic-clonic seizure and occurs only once in 24 hours during fever, whereas complex FS have focal onset, longer (> 15 minutes) seizure duration, or more than one seizure during 24 hours.[16] A higher frequency of complex FS, 13.6%[9] and 30%[17] have been reported from the developing countries, whereas in a more recent population-based study from a developed country, complex FS was the initial FS type in only 8.6% of the patients.[18] The possible explanations for the differences include time delay in seeking medical attention, less frequent use of diazepam, ineffective routes for administering diazepam, and probably the cause of the febrile episode.[17]

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Table 1. Selected recent reports of the prevalence of febrile seizure in some developing countries

Author, Year	Prevalence Rate (%)	Community/ Country	Subject	Number with FS/ Number Surveyed
Bharucha et al, 1991[3]	1.77	Parsis/India	<14 yrs	28/1581
Iloeje, 1991[4]	11.61 8.05	Amokwe/Nigeria Enugu/Nigeria	6 mos-6 yrs	72/620 172/2135
Aziz, et al, 1994[5]	1.33	Sind/Pakistan	All age	322/24130
Okan, et al, 1995[6]	4.48	Gemlik/Turkey	5 yrs	224/5002
Tsai, et al, 1996[7]	3.2	Taiwan	6 mos-6 yrs	111/3462
Hackett et al, 1997[8]	10.1*	Kerala/India	8-12yrs	120/1192
Yakinci et al, 2000[9]	3.24	Malatya/Turkey	7-12 yrs	118/3637

* life time incidence

Predisposing Factors

Family history of FS is the most consistent and significant predisposing factor.[19,20] History of FS in a first-degree or a higher degree relative was found in most studies.[10,21,22] Familial aggregation of FS is more evident in the siblings than in the parents.[21-23] Several prenatal and perinatal factors have been described as predisposing risk factors for FS.[19,21] However, their role seems to be minor. Some of the perinatal risk factors like low birth weight, breech delivery, neonatal discharge time of at least 28 days, neonatal sepsis, difficult birth, and neonatal asphyxia are more likely to be associated with the poor socioeconomic state.[19] Some of the described predisposing risk factors may have a potential negative effect on the developing brain. Neurological abnormalities, including developmental delay also predispose to FS.[19] Recently an association between iron-deficiency anemia, a common disorder of children in the developing countries, and FS has been reported.[24] Most of the risk factors described are more frequent in the developing countries and may be improved by the integrated maternal, obstetric and perinatal care.

Precipitating Factors

The significant precipitating risk factors for FS include the degree of fever[20] and the frequency of febrile illnesses.[21] The most commonly reported febrile illnesses are upper respiratory tract infections and otitis media.[10] Children with primary infection with human herpes virus-6 (HHV6) often develop FS.[2] The pattern of the underlying febrile illness is similar in both developed and developing countries.[10,26] However, certain infections like exanthematous fevers and malaria are still endemic in the developing countries. In Central Africa, malaria accounts for five per cent of pediatric emergencies.[27,28] Vivax malaria is a frequent cause of typical FS in the endemic regions and FS can be the presenting feature of Falciparum malaria.[14,27]

FS following immunization is well known. The significance of immunization as a risk factor for FS has been the focus of debate. However meta-analysis of the data suggests diphtheria-tetanus-pertussis (DTP) vaccination is associated with a relative risk of FS.[29] FS following immunization has the highest incidence at the age when children are most susceptible to seizures from febrile illnesses of any cause.[30] The risk to develop FS is high in children with a family history of seizures.[31] Though there is a small risk of FS following immunization, the benefits of vaccination with DTP and MMR vaccines should not be deprived to children in the regions endemic to these diseases.

Diagnostic Evaluation

The diagnostic criterion for FS is, seizures in children in association with fever and absence of central nervous system infections. However, acute symptomatic seizures associated with acute febrile medical or neurological disease may pose difficulties in the diagnosis. Detailed analysis of the history, fever characteristics, physical and neurologic examination findings may differentiate the two conditions. In children with fever and acute seizures, age less than 6 month, complex FS, unarousable coma, or presence of extracranial focus of infection should warrant exclusion of CNS infection, more so in developing countries.[32]

In developing countries lumbar puncture is frequently performed in children in the presence of fever and seizures to rule out CNS infections. The yield for bacterial meningitis is less than 5%.[32,33] However, lumbar puncture is indicated in certain clinical circumstances, which include signs of meningism or clinical suspicion of meningitis, complex FS, prolonged sensorial alterations, and age less than 18 months, more so if the age is less than 12 months.[34] Clinical signs of meningitis may not be present in about 25% of the children.

Knowledge, Attitude and Practice

Ongoing seizure is a frightening scene for the parents. The parents will also be anxious about the affect of seizure on the brain and cognitive development. Their concerns also include chance of recurrence and subsequent epilepsy. The reasons for these concerns among the parents include lack of knowledge about FS, high concerns, and improper first-aid practices.[35] Studies from the developing countries have shown that at times some of the parents felt as if the child is dying or dead during the attack.[37,38] Active educational intervention has been found to have a positive effect on the parental concerns.[35,38,39] Parents need to be educated about the benign nature of FS, recognition and management of fever, use of antipyretic medication, home management of seizures, and timing of bringing the child to the hospital.

Pharmacotherapy

Drug treatment of FS, especially simple FS, has long been a controversial issue. Recently consensus recommendations have been evolved.[40,41] However, these recommendations are not absolute but only guide the practicing physicians to treat the child with FS.

Antipyretics are used to control the temperature and thus to prevent seizure recurrence. Although antipyretics may also improve the comfort of the child, vigorous reduction of fever does not influence the chance of seizure recurrence.[42]

Prophylactic use of anticonvulsants to prevent recurrence of FS is unclear. Prophylactic treatment with phenobarbitone[43] or valproic acid[44] and intermittent therapy

with diazepam[45,46] are effective in reducing the risk of recurrence. However, the efficacy of phenobarbitone and sodium valproate in preventing recurrence is found to be uncertain when trials are analyzed on an intention to treat basis.[47,48] Furthermore, compliance is usually poor and the potential side effects outweigh the relatively minor risks associated with simple FS in the long-term prophylactic therapy.[15] Prophylactic therapy does not influence the later development of epilepsy.[49] Thus the general consensus is against prophylactic anticonvulsant therapy.[50] Situations whence most authorities would consider prophylaxis are among children with complex FS, children in isolated remote areas, or very high parental anxiety despite appropriate counselling and reassurance.[51-53] If the parental anxiety is severe, intermittent oral diazepam at the onset of febrile illness may be advised.

Prognosis

FS are benign with excellent prognosis.[54-56] Short-term morbidity and mortality of febrile status epilepticus is low[57] and the mortality of febrile status epilepticus is primarily related to the underlying cause.[58]

Recurrence of Febrile Seizures

About one-third of children with FS experience one or more recurrences.[10,11,15,16,59-62] A higher recurrence rate (66%) has been described in some studies from developing countries.[63,64] Independent risk factors predicting likelihood of recurrence are young age at time of first FS (< 18 months), history of FS in a first-degree relative, low degree of fever while in the emergency department, brief duration between onset of fever and the FS.[15,59-62,65] Risk of recurrence is significantly high if the child has more than one risk factor.[61,65] In a study in south India perinatal adversity has been found to be associated with recurrence of FS.[64] These observations suggest chance of recurrence of FS is a complex interaction between genetic and environmental factors.[50]

Risk of Epilepsy

In the population-based studies the reported chance of developing epilepsy following FS varied between 2 to 6%.[16,66-68] Children who have a single, brief generalized seizure (simple FS), a negative family history of epilepsy, and no preexisting neurologic handicap have no or minimal increased risk of developing epilepsy. The risk factors associated with developing epilepsy include seizure duration greater than 15 minutes, focal seizures, abnormal preexisting neurologic deficit, seizure recurrence in the first 24 hours, and history of epilepsy in a parent or sibling.[12,16,68] However, the risk of occurrence of late epilepsy in children with febrile status epilepticus is different. In the British study of the 19 children with febrile status epilepticus, four (21%) developed subsequent afebrile seizures and two of them developed epilepsy.[69]

The type of epilepsy that develops after FS can be generalized or partial epilepsy. The association between mesial temporal scleroses with intractable complex partial seizure is well documented. However, the cause-effect relationship between the two is still unsolved.[70]

Behavior and Cognition Outcome

The behavior and cognition outcome of FS is a subject of controversy for a long time. Earlier hospital-based studies observed a relatively high incidence of mental retardation, behavioral disturbances, and academic difficulties in children with a history of FS.[71,72] Adverse outcome on intelligence has been

observed in children with prolonged FS.[73] However, these observations have not been substantiated in population-based studies.[56,64,74-77] Furthermore, children with FS have been shown to have significantly better mnemonic capacity, more flexible mental processing and higher impulsivity, better control of distractibility, and attention.[76,77] Onset of ---FS before one year of age has been found to be associated with compromised mnemonic function and prior neurodevelopmental delay was associated with defects in executive function.[76,77]

Conclusions

Inadequate knowledge, improper attitude and practice dealing with FS still prevail in every corner of the world. These greatly hamper the quality care of FS. The strategy of planning educational intervention becomes an important issue for modern care of FS. Medical personnel in tropical countries can take advantage of the experiences from developed countries for daily practice of the diagnosis and management of FS in general which should be adjusted with special consideration of local/regional specific problems. The researches specifically designed for the investigation of the significantly controversial issues can be conducted in tropical countries and may contribute to the comprehensive understanding of FS.

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Chapter 15

Acute Symptomatic Seizures: Clinical and Etiological Profile in Developing Countries

J.M.K. Murthy

Acute symptomatic seizures are those caused or provoked by an acute medical or neurological insult[1] and, in the aggregate are almost as common as febrile seizures or epilepsy.[2] They make up ~ 40% of all the newly diagnosed seizure disorders.[3] Acute symptomatic seizures show clearly differentiated characteristics with regard to true epileptic seizures; (1) a clearly identified causal association, (2) generally tend not to recur, (3) usually long-term antiepileptic drug (AED) treatment is not necessary.

Incidence

The incidence of acute symptomatic seizures has been reported in a few epidemiological studies. In Rochester, Minnesota, U.S.A, the age-adjusted incidence rate for 1955-1984 was 39.0/100,000 person-years. The incidence was considerably higher in men, 52.0 as compared with 29.5 in women. And the cumulative incidence in patients up to 80 years of age was 3.7%.[2] In Gironde, Bordeaux, France, the incidence was 28/100.000 person-years.[3] The only incidence study from developing country is from Taiwan in young children and reported an incidence of 46.0/100,000.[4] In a hospital-based study in south India, acute symptomatic seizures accounted for 22.5% of total population studied.[5] A similar incidence, 21%, was reported in the British community-based study of newly diagnosed epilepsy.[6] In a hospital-based prospective study of 1,000 consecutive patients with seizure disorder in Saudi Arabia, acute symptomatic accounted only for 3%.[7]

Acute symptomatic status epilepticus can be the presenting feature of acute medical or neurological illness. The incidence of acute symptomatic status epilepticus in French-speaking Switzerland was 62/100,000.[8] In a hospital-based study from south India of the 527 patients with acute symptomatic seizures, 3% of patients presented with status epilepticus.[5] Of the etiology of status epilepticus, acute symptomatic status epilepticus formed 54% in both the series from Argentina[9] and south India.[10]

In Rochester, Minnesota study age-specific incidence was highest during the first year of life.[2] In the Taiwan study age-specific incidence was highest in the group aged 1-12 months.[4] The highest incidence in young children is probably because of high incidence of seizures due to encephalopathies, metabolic disorders, and infections.

Classification

Provoked or acute symptomatic seizures are those caused by an acute medical or central nervous system insult.[1] There are distinct differences between the two provoking factors. Provoked seizures caused by acute medical illness are self-limited and there is no underlying permanent brain damage. The primary consideration in such

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patients should be the identification and treatment of underlying disorder. If AEDs are used to suppress acute seizures, generally they do not need to be continued after the patient has recovered from the primary illness. The prognosis is excellent and the risk of later epilepsy is virtually none,[4] whereas in patients with acute central nervous system (CNS) insult, each etiological factor is a significant risk factor for both acute symptomatic seizures and epilepsy. Although AEDs are effective in treating acute seizures, none have yet been shown to delay or reduce the development of later epilepsy. However, the prognosis is substantially different when compared to remote symptomatic epilepsy.[11]

In the syndromic classification proposed by International League Against Epilepsy (ILAE)[12] seizures related to acute metabolic or toxic factors and eclampsia fall into category 4.1, situation-related seizures. Epileptogenic zone in patients with acute symptomatic seizures caused by acute CNS insult is likely to be structural and as such may be categorized under symptomatic localization-related epilepsies (2.2) of syndromic classification.[5]

Etiology

The relative frequency of different etiologies may vary according to geographic location. Much of the acute symptomatic seizures in the developing world are from preventable causes, CNS infections.[2,5,13]

Infections of Central Nervous System

About 5% of people with CNS infections can be expected to experience an acute symptomatic seizure(s).[14] In a hospital-based study from south India, CNS infections were the provoking factors in 71% of patients with acute symptomatic seizures,[5] whereas in the Rochester, Minnesota study they accounted for only 15%.[2] The pattern of infections differs according to geographic regions. Neurocysticercosis and neurotuberculosis are the common infections in developing countries.[2,5]

Neurocysticercosis

Neurocysticercosis is the most common cause of provoked seizure(s) in developing countries (see Chapter 10). All the evolutive stages of parenchymal brain cysticerci, from viable cysts to calcifications, may be associated with seizures. Seizures in patients with degenerating cyst are a consequence of inflammation around a cyst(s) and these seizures as such may be categorized under acute symptomatic seizures.[15] In our study of acute symptomatic seizures, neurocysticercosis was the etiological factor in 66% of the patients.[5] Nearly 100% of patients with solitary cysticercus granuloma, present with seizures.[16,17] Seizures are either the presenting feature or occur during the course in 92% of patients with intraparenchymal lesions, and in 74% of patients with mixed intra- and extraparenchymal involvement.[18] Multiple cysts, parenchymal and extraparenchymal, are more common in Latin American countries,[15] whereas there is an over abundance of reports of solitary cysticercal lesions from India.[17]

Japanese Encephalitis

Japanese encephalitis is the most common cause of encephalitis, worldwide with an estimated 50,000 cases and 15,000 deaths annually.[19] Most of China, Southeast Asia, and the Indian subcontinent are affected by the virus.[20] Seizures have been reported in up to 85% of children and in 10% of adults in acute phase of the illness.

In some children a single seizure is followed by a rapid recovery. Multiple or prolonged seizures and status epilepticus are associated with a poor outcome.[20]

Central Nervous System Tuberculosis

The incidence of tuberculosis has increased drastically in recent years both in areas that were traditionally endemic and in areas where the incidence of tuberculosis is declining. About 2000 million people in the world today are infected with tuberculosis but only 10% develop clinical disease.[20] Coinfection with HIV increases the lifetime risk of developing clinical tuberculosis 1 to 3 times.[22] It has been estimated that about 10% of the immunocompetent patients who have tuberculosis will develop central nervous system disease.[23] HIV also predisposes to the development of extra pulmonary tuberculosis, and in particular tuberculous meningitis.[24] In our study of acute symptomatic seizures, 16% of provoked seizures were related to neurotuberculosis.[5]

In tuberculous meningitis seizures can occur at any stage of the illness and about 10% of adults and 55% of children develop seizures in the acute phase of illness.[25] Seizures can be the presenting feature in about 10% of patients with tuberculous meningitis.[26] The cause of seizures is attributed to associated, inflammatory response of the brain, tuberculomas, vasculitis and associated infarcts, and metabolic disturbances.

Intracranial tuberculomas account for less than 0.2% of intracranial mass lesions in developed countries, while it still represents a major neurosurgical finding in developing countries.[27] In the earlier studies in India tuberculomas accounted for 30% of pathologically verified intracranial mass lesions in adults and 50% of those of children.[28] Seizures occur in more than 60% of patients with intracranial tuberculoma, almost always with signs of focal CNS involvement.[29]

Malaria

Malaria is still one of the world's major killing disease and most of the malaria endemic area is confined to tropics. There may be as many as 300-500 million infections per year, 90% in Africa, with 1.5-3 million fatal cases most of which are African children.[30] Vivax malaria is a frequent cause of typical febrile seizures in children in tropical endemic region. Rarely children may have status epilepticus and it may be difficult to differentiate from malignant cerebral falciparum malaria.[13,18] Seizures commonly complicate cerebral falciform malaria. Majority of children and 40% of adults with cerebral malaria develop seizures. Possible causes of seizures include cerebral hypoxia associated with cerebral malaria, hyperpyrexia, hypoglycemia and other metabolic disturbances, and antimalarial drugs.[31] Seizures are associated with an increased risk of death and neurological sequelae.

Cerebrovascular Diseases

Early seizure(s) has been reported to occur with a frequency of 2.5 to 5.7% within 14 days after stroke and is a predictor of recurrent seizures.[5] and status epilepticus. Lesion location and stroke subtype are strong determinants of early seizure.[32] In one study initial stroke severity has been shown as a predictor of early seizure.[33] However in The Northern Manhattan Stroke Study (NOMSS) NIH stroke scale score was not an independent predictor of early seizure in multivariate analysis.[32] The incidence of acute symptomatic seizures with stroke increases rapidly with increasing age.[2] Like in developed countries, in developing countries also, stroke is

the leading cause for provoked seizures in the elderly.[5] In developing countries cortical sino-venous thrombosis is an important cause of acute symptomatic seizures among young patients with cerebrovascular diseases. And early seizure(s) has been reported in 46 -79% of patients.[34] In our series 14% of acute symptomatic seizures were related to stroke and cortical sino-venous thrombosis accounted for 37% of strokes.[5]

Seizures Associated with Fever in Children

There is a probability of a child with fever and seizures having primary CNS infection and in developing countries this probability is high. This is much more so in infants under 12 months.[35-37] In a study in Nigeria, of the 522 children, aged one month to 6 years, who presented with convulsions and fever of acute onset at the emergency department of a university hospital, bacterial meningitis was diagnosed in 22 (4.2%) children on bacteriological and/or biochemical evidence. The prevalence declined sharply after six months of age. Six (27%) of the children with meningitis lacked meningeal signs.[35]

Clinical Features

Acute symptomatic seizures may be single or repetitive. Single seizure may be brief or prolonged. Repetitive seizures may be serial, clustered, or crescendo. Status epilepticus may be the presenting feature. In our study, of the 572 patients, 7% had single seizure, 90% had two or more seizures and 3% developed status epilepticus. Repetitive seizures included seizure clusters.[5] Seizure type can be simple partial, complex partial (CPS) with or without secondary generalization, or generalized tonic-clonic seizures (GTCS). The most common seizure type is GTCS (including secondary generalization). In particular, alcohol or drug withdrawal, drug toxicity, or systemic metabolic disorders typically present as GTCS. Whereas patients with acute primary CNS insult may trigger simple or complex partial seizures depending on the site of pathology.

Nonconvulsive seizures and status are common in patients with acute neurological or systemic illness admitted to intensive care units. In one series of neurological ICU patients in coma, the incidence of nonconvulsive seizures (NCSzs) was 34%.[38] In a university hospital-based study the incidence of NCSzs in patients with CNS infections was 26% and two-thirds of them had nonconvulsive status epilepticus.[39] Clinical descriptions of nonconvulsive seizures cover a broad range. By definition there must be impairment of consciousness. This can vary from mild clouding of consciousness to unresponsive obtundation. Impairment of consciousness is accompanied by automatisms, agitated unresponsiveness with bizarre, almost psychotic activity, aphasia, amnesia, and twitching or myoclonic face or limb movements. Clinical seizure manifestations may be minimal and the diagnosis may be easily missed. Diagnosis of nonconvulsive seizures is critically dependent on EEG.

Diagnostic Evaluation

The primary consideration in patients with acute symptomatic seizures is identification of underlying cause. Laboratory screening should be ordered based on individual clinical circumstances to make diagnostic workup more cost-effective. Such an approach is of much relevance for developing countries.

Laboratory workup should include complete blood picture, serum electrolytes, blood urea nitrogen, creatinine, glucose, calcium, magnesium, arterial blood gas

(ABG), and toxicology screening. There are no studies that systematically evaluated the yield from doing routine laboratory screening in children and adults with acute symptomatic seizures.

Lumbar puncture is frequently performed in children in the presence of fever and seizures to rule out CNS infections. However, clinical features should guide decision on the need for lumbar puncture. Diagnostic lumbar puncture is indicated when the diagnosis of infectious meningitis or encephalitis is considered. In children with fever and acute seizures, age less than 6 months, complex febrile seizures, unarousable coma, and presence of extracranial focus of infection should warrant a lumbar puncture.[36]

Routine use of electroencephalogram is of limited value in the evaluation of acute symptomatic seizures. However, continuous EEG monitoring is of help in the evaluation of nonconvulsive seizures or status epilepticus. In patients with nonconvulsive seizures when the EEG demonstrates typical ictal patterns, the diagnosis is usually straightforward. However, in many circumstances the EEG has to be differentiated from encephalopathic patterns, and this differentiation can prove troublesome, although the clinical and electrographic response to treatment can prove helpful.

Commission on Neuroimaging of ILAE recommends, in acute circumstances, computed tomography (CT) scan as an appropriate initial investigation if magnetic resonance imaging (MRI) facility is not available.[40] Abnormal neurologic examination is the most important criterion available to select patients for emergency cranial CT in patients with acute seizures.[41,42] In developing countries CNS infections account for a significant proportion of acute symptomatic seizures and the pathology related to CNS infections can easily be demonstrated by a contrast CT scan. Contrast CT scan demonstrates most of the pathology of neurocysticercosis. Partial seizures with no obvious cause may be the presenting feature of neurocysticercosis and other CNS infections.[43] In developing countries endemic to neurocysticercosis it will be prudent to get contrast CT scan in patients with acute onset seizure(s) or cluster seizures.

Treatment

Acute seizure(s), seizure clusters, and acute symptomatic SE, are neurological emergencies that are typically first encountered in the prehospital environment. Management of acute symptomatic seizures should proceed on three fronts: (1) termination of acute seizure(s), (2) prevention of recurrence, and (3) identification, and management of underlying disorder.

Termination of Seizure

Single Seizure

Most acute single seizures (perhaps excluding febrile seizures) last about two minutes. A seizure lasting less than five minutes may not be treated. The chance in adults and older children, that a seizure lasting 5 minutes will self-terminate before 30 minutes is very small.[44] However, there is minimal evidence to support that immediate treatment of prolonged seizure prevents progression to status epilepticus. Nevertheless, it is generally accepted that prolonged seizure episodes should be treated, and that such treatment may prevent progression to status epilepticus.[44]

Seizure Clusters

Seizure clusters include repetitive series or clusters of seizures that occur within a short period of time but that do not meet the criteria for a diagnosis of status epilepticus. Patient recovers to the baseline between the seizures. Temporary treatment to terminate the cluster is often necessary, even though the evidence that such treatment prevents progression to status epilepticus is lacking.[46]

Status Epilepticus

Status epilepticus is defined as more than 30 minutes of: a) continuous seizure activity, or b) two or more sequential seizures without full recovery of consciousness. Recently proposed operational definition of generalized convulsive SE in adults and older children (> 5 years old) refers to > 5 minute of (a) continuous seizures or (b) two or more discrete seizures between which there is incomplete recovery of consciousness.[44] Acute symptomatic status epilepticus is associated with higher mortality, almost a 100 fold increased risk of dying compared to that expected in the general population.[47] Treatment protocols are similar to any status epilepticus.[48]

Treatment Options

Clusters and Prolonged Seizures

Various types of benzodiazepine delivered via diverse routes have been reported to be efficacious in treating seizure clusters and prolonged seizure. Commonly used benzodiazepines include diazepam, midazolam, or lorazepam. For patients who have a single seizure, it is important to identify and deal with possible provocative factors. In patients with acute seizure clusters, intermittent therapy is never enough. An acute loading dose of phenytoin/fosphenytoin or valproic acid can provide temporary additional protection while provocative factors are corrected or while the natural history of the patient's cluster pattern runs its course, The plan in such a patient would be to continue maintenance treatment with whatever AED is deemed best. If antiepileptic drugs are used to suppress recurrence of seizures, they generally do not need to be continued after the patient has recovered from the primary illness.[46]

Intramuscular midazolam is very effective in stopping seizure activity within 5 to 10 minutes and is more than 90% bioavailable after intravenous and intramuscular administration. In a prospective randomized study (intramuscular midazolam versus intravenous diazepam) of children requiring acute treatment for seizures, there was approximately a 4-minute difference in both the times for drug administration and seizure cessation in favor of intramuscular midazolam.[49] In patients in whom prolonged sedation may seriously confound neurological management, initial treatment of seizure(s) may be instituted with midazolam.

Status Epilepticus

Acute symptomatic status epilepticus is a neurological emergency and treatment protocols are similar to status epilepticus. Randomized double-blinded studies in adults[50] and nonrandomized studies in children.[51,52] supports the use of lorazepam as monotherapy. If status epilepticus persists this should be followed by phenytoin or fosphenytoin is effective. In case of refractory status epilepticus one of the anesthetic agents, midazolam, propofol, or pentobarbital, are the drugs of choice.[53]

Eclampsia of Pregnancy

Preeclampsia-eclampsia is a major problem in developing countries. Magnesium sulphate is clearly superior to phenytoin as an anticonvulsant in preeclampsia-eclampsia and it is preferred agent for this purpose. Clinical trails comparing magnesium sulphate with placebo or no anti-convulsant for women with preeclampsia provide promising evidence that magnesium sulphate reduces the risk of elcampsia.[54-57]

Prehospital Treatment

Recent studies have shown that the administration of benzodiazepines by paramedics is an effective and safe means of treating status epilepticus in adults[58] and children.[59,60] In the prehospital setting. These studies also suggest prehospital therapy shortens the duration of status epilepticus and simplifies subsequent management in the emergency department. It is reasonable to extend these conclusions to the treatment of acute symptomatic clusters and prolonged seizures since rapid, maximal control is desired. In developing countries poor health care delivery systems and logistic difficulties in transporting patients to a center with adequate facilities, make prehospital administration of benzodiazepines by paramedics a viable option. The potential benefits of such approach include the prevention of systemic and neurologic sequelae of prolonged convulsive seizures.

Rectal diazepam is effective in aborting seizures and preventing febrile seizures.[61] Prehospital intravenous and rectal diazepam therapy were initially effective in terminating SE in 100% and 81% of children, respectively. However, seizure recurred in 60% of the children treated with intravenous diazepam, as opposed to 30.8% of children treated with rectal diazepam.[60] In a retrospective case-control study design of prehospital treatment of SE in children rectal or intravenous diazepam was associated with SE of shorter duration (32 minutes – diazepam group versus 60 minutes – standard emergency department (ED) AED therapy group) and a reduced likelihood of recurrent seizures in the ED (58% versus 85%).[59] Prehospital administration of lorazepam for adult patients in SE by paramedics was found to be safe and effective.[58] Status epilepticus had been terminated on arrival at the emergency department in more patients treated with lorazepam (59.1%) or diazepam (42.6%) than patients given placebo (20.1%). The rates of respiratory and circulatory complications after the study treatment was administered were 10.6% for the lorazepam group, 10.3% for the diazepam group, and 22.5% for the placebo group ($P < 0.05$). Results of both the studies suggest lorazepam is likely to be a better therapy for acute seizures than diazepam.

CNS Infections: Antimicrobials, Provoked Seizures, and AEDs

While prescribing antimicrobials in patients with CNS infections and provoked seizures the issues that need to be considered include: (a) proconvulsant activity of the antibiotics, (b) adverse effect of the antimicrobials on the safety and efficacy of the concurrent AED therapy, and (c) the effect of concurrent AED therapy on the safety and efficacy of the antimicrobials.[62]

The antimicrobials associated with proconvulsant properties include pencillins, cephalosporins, carbapenems, quinolones, and antimalarial drugs.[62] Renal failure and hypoalbuminaemia when present will increase the risk for antimicrobial induced seizures.[63-65]

Fluconazole and iniconazole inhibit cytochrome P2C9 isoenzyme and may increase the plasma levels of phenytoin, which is a substrate of this isoenzyme. Isoniazide

is a broad ranging metabolic inhibitor and increases the plasma levels of phenytoin, carbamazepine, and valproic acid.[66] Risk of phenytoin toxicity will be high when given in combination with isoniazide than when given alone.[67] Rifampicin reduces the concentration of valproic acid, phenytoin, and carbamazepine.[66]

Carbamazepine, phenytoin, and barbiturates by hepatic enzyme induction may decrease the plasma levels of praziquantel and albendazole resulting in therapeutic failure if dosage is not adjusted appropriately.[66]

Conclusion

Acute symptomatic seizures in the aggregate are almost as common as febrile seizures or epilepsy and make up ~ 40% of all the newly diagnosed seizure disorders. Much of acute symptomatic seizures in the developing world result from preventable causes, CNS infections. Neurocysticercosis is the most common cause of provoked seizure(s) in developing countries.

Recent studies have shown that the administration of benzodiazepines by paramedics is an effective and safe means of treating status epilepticus. It is reasonable to extend these conclusions to the treatment of acute symptomatic seizure clusters and prolonged acute seizures. In developing countries poor health care delivery systems and logistic difficulties in transporting patients to a center with adequate facilities, make prehospital administration of benzodiazepines by paramedics a viable option. The potential benefits of such an approach include the prevention of systemic and neurologic sequelae associated with prolonged convulsive seizures or seizure clusters and may prevent progression to status epilepticus.

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Chapter 16

Status Epilepticus in Developing Countries: An Account

Pierre-Marie Preux, Mouhamadou Diagana and Michel Druet-Cabanac

Status epilepticus is a common neurological emergency and is associated with a significant mortality. It may occur in association with epilepsy and in the context of acute central nervous system insults and the systemic illness.[1] There is very few published data about status epilepticus in developing countries. Generalized tonic-clonic status epilepticus is readily recognized. But other forms of status epilepticus may not be recognized in developing countries due to the lack of specialized and trained personnel and also the investigative facilities like continuous EEG monitoring. Furthermore, in developing countries health care infrastructure is poor. Patients with status epilepticus may not have an access to the specialist care in time and also to the drugs, which could influence the outcome.

Definition and Classification

The definition of status epilepticus is evolved over the years, and is still a matter of controversy. Status epilepticus was defined in the first International Classification of Epileptic Seizure[2] as a condition in which "a seizure persists for a sufficient length of time or is repeated frequently enough to produce a fixed and enduring epilepticus status." Slight modifications in 1981[3] still left practical uncertainty on the duration of seizure activity. The other definition suggested by Shorvon[4] is "status epilepticus is a state in which one seizure follows another without the patient regaining consciousness between seizures". This definition could be extended to the occurrence of neurological signs in the interictal period, which mark the alteration of neurons in the cortical areas involved. Epilepsy Foundation of America defined "status epilepticus as more than 30 minutes of a, continuous seizure activity, or b, two or more sequential seizures without full recovery of consciousness".[5] This definition has been generally accepted. However, it has been proposed to change the definition of status epilepticus to incorporate a shorter duration.[6] The operational definition for generalized convulsive SE in adults and older children (>5 years old) proposed by Lowenstein et al[6] refers to ≥ 5 minutes of (a) continuous seizures or (b) two or more discrete seizures between which there is incomplete recovery of consciousness.

Status epilepticus can occur with any seizure type. Many classifications of status epilepticus have been proposed.[4,7] None are really satisfactory[8] because of their too elementary structure, or, of their complexity. A simple and decisional classification could be proposed, considering convulsive, either partial or generalized, and nonconvulsive status epilepticus. Convulsive status epilepticus is the most common type and is, in general, easily diagnosed but is associated with significant mortality despite recent advances in the diagnosis and treatment. On the other hand recogni-

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tion of nonconvulsive status epilepticus is difficult and the diagnosis can only be made by EEG. Outcome of nonconvulsive status epilepticus depends on the underlying etiology.

Epidemiology

Epidemiology of epilepsy in developing countries is yet very complex for many reasons and this is indeed even more true in status epilepticus. There is hardly any published data on status epilepticus and most of the available data is retrospective hospital-based studies. The recorded data is incomplete and definitions and classifications are often different making comparisons very difficult. There are no population-based incidence studies. Evaluating incidence needs specific and complex epidemiological survey methods including a follow-up, which is very difficult to establish in developing countries.

The reported incidence of status epilepticus in developed countries varied between 14.4 and 18.3 per 100 000 per year.[1,9-11] Recent study from Rochester, Minnesota suggests increase in the annual incidence rates of status epilepticus.[12]

There are no incidence studies in the developing world. However, the magnitude of status epilepticus associated with epilepsy and antiepileptic drug (AED) noncompliance can be assessed from the community-based prevalence studies of epilepsy. About 5% of all adult epilepsy clinic patients will have at least one status in the course of their epilepsy.[4,13] Somewhat similar frequency has been reported in the population-based prevalence studies in developing countries. In the population-based studies the reported frequency of patients experiencing at least one episode of status epilepticus varied from 4% to 11%.[14-16] In a hospital-based study in Tunis, Tunisia, of the 582 newly diagnosed patients with epilepsy, 4% had an episode of status epilepticus.[17] The reported frequency of status epilepticus in the meta-analysis of the nine studies of epilepsy in Africa varied between 2-25%.[18] In this study, history of status epilepticus was significantly higher in population-based surveys (18%) than in hospital-based studies (5%).[19]

Status epilepticus accounts for 1-8% hospital admissions[13] and 3.5% of intensive care unit admissions.[20] There is hardly any published data in this regard from developing countries. In the only study in south India, status epilepticus accounted for 11% of admissions to neurological intensive care unit.

Acute symptomatic status epilepticus accounts for a significant proportion of cases of status epilepticus. The incidence of acute symptomatic status epilepticus in French-speaking Switzerland was 62 per 100,000.[21] In a hospital-based study in south India, of the 572 patients with acute symptomatic seizures, 3% presented with status epilepticus.[22]

In developed countries age and sex adjusted figures suggest higher incidence in children, elderly, and men.[1,9-12,23] The mean age of the population in the hospital-based studies in developing countries ranged between 24-44 years[24,25] (G. Arunodaya, Bangalore, India, unpublished data). In the Senegal study, 48.2% of patients were below 5 years of age.[26] This young age may reflect the young age of the population in these countries. A slight male predominance was observed in all these hospital-based studies.

Clinical Features

Convulsive status is the predominant type of status epilepticus reported in developing countries.[17,24,26] The seizure type is both, generalized or partial with or without generalization. Descriptions of nonconvulsive status epilepticus are rare. This may probably be related to physician's failure to recognize the condition and also

Table 1. Distribution of status epilepticus according to etiology in tropical countries

Etiologies	Senegal (Mbodj et al)[26] n = 697	India (Arunodaya, Personal Commun., 2000) n = 155	Nigeria (Ogunniyi et al)*[27] n = 41
Infection of CNS	467 (67.0%)	43 (27.7%)	17 (41.5%)
Epilepsy	69 (9.9%)	46 (29.7%)	-
Vascular	56 (8.0%)	9 (5.8%)	6 (14.6%)
Expansive intracranial process	8 (1.2%)	-	4 (9.8%)
Metabolic / Toxic	30 (4.3%)	18 (11.6%)	14 (34.1%)
Traumatic	7 (1.0%)	-	-
Hyperthermia	60 (8.6%)	-	-
Unknown	-	39 (25.2%)	-

* pathological study, CNS = central nervous system

nonavailability of continuous EEG monitoring facilities in most of the intensive care units in developing countries. In the series reported in developing countries there was considerable delay between the onset and institution of appropriate treatment. The mean interval between onset of status epilepticus and appropriate treatment was 16.6 hrs in the series from Senegal,[26] and it was 18.2 hrs in the series from India.[24] In the series from Senegal, only 4.6% of patients arrived in the emergency department within 6 hours of onset, and it was 50.6% in the series from India. The proportion of patients arriving in the emergency department after 24 hours of onset of status epilepticus varied between 19% and 52%.[24] (G. Arunodaya, Bangalore, India, unpublished data).

Etiology

There is a distinct difference in the etiological spectrum of status epilepticus in developing countries when compared to developed countries. Acute symptomatic status epilepticus formed 54% of etiology in the series from south Indian[24] and also Argentina.[25] Infections of central nervous system form a significant proportion etiology of status epilepticus, 28% to 68%.[26,27] (G. Arunodaya, Bangalore, India, unpublished data) (Table 1). In the series from India, geographically endemic infections (neurotuberculosis, neuro-cysticercosis and Japanese encephalitis) accounted for 92% of these infections.[24] In children infections were the predominant risk factors in the Senegal study[26] and also in the study in Saudi Arabia.[28] In a study in China, acute central nervous system insults were the precipitating factors in 60% of status epilepticus in pediatric age group.[29] Other etiologies, AED noncompliance, cerebrovascular diseases, degenerative diseases were reported in adults with status epilepticus.[24-26] In the south Indian study drug noncompliance was the precipitating factor in 19% of patients.[24]

Treatment

In developing countries patients with status epilepticus encounter several significant barriers to adequate treatment. Extremely limited resources exist in most of the rural areas and patients with status epilepticus may not be able to reach centers with adequate facilities in time, whereas patients in the urban areas will have ready access

to medical centers with adequate facilities. The other limiting factor is costs involved in caring for such patients. Health insurance is virtually nonexisting. Furthermore, developing countries often lack personnel with neurologic expertise who can recognize and appropriately treat patients with status epilepticus. In most of the rural areas in developing countries, availability of injectable formulations of antiepileptic drugs is a major problem.[30] Of the benzodiazepines, diazepam is the only drug available in most of the rural areas. In a survey in Cameroon, diazepam was the most commonly used drug among the injectable formulations and 46% of the physicians prescribed it frequently.[31]

In developing countries patients with status epilepticus are managed by physicians with least experience with status epilepticus and management is not often evidence-based. In the series in Senegal 23% of patients were only treated by neurologists.[26] The other limiting factor is late referral. The reported mean delay in the institution of appropriate treatment varied between 16.6 hrs and 18.2 hrs.[24,26]

In the series reported by Mbodj et al[26] from Senegal, the drugs utilized were diazepam and phenobarbitone, administered by injection. With this drug regimen seizure control could be achieved in a significant proportion of patients. The specialist care in intensive care area did not have mechanical ventilator facilities. In the series reported by Maharaj et al,[32] bolus doses of diazepam were used in 62 of the 63 episodes, phenytoin in 18, diazepam infusion in nine and phenobarbitone in nine. No patient was ventilated or even admitted to the intensive care unit. Seizures were controlled within half-hour of starting treatment in 87% of the episodes. In only three episodes in two patients, control was poor and seizures persisted for 18 hours. Intravenous diazepam followed by intravenous phenytoin was the first line treatment schedule in the study in south India. With this schedule status could be terminated in 88% of patients.[24] The length of hospital stay was less than ten days in 79% of patients in the Senegal study[26] and in the Trinidad study it was only 2.9 days.[32]

Out-of-Hospital Treatment

Status epilepticus is typically encountered in the prehospital environment. Potential benefits of out-of-hospital treatment of status epilepticus include the prevention of systemic and neurologic sequelae. Several recent studies found that intravenous benzodiazepines are safe and effective when administered by paramedics for the treatment of out-of-hospital status epilepticus in both children[33,34] and adults.[35] Rectal and intravenous diazepam was effective in terminating status epilepticus in 81% and 100% of children respectively. Only two children treated with intravenous diazepam and none treated with rectal diazepam needed intubation prior to arrival in the emergency department.[33] Prehospital rectal or intravenous diazepam was associated with status epilepticus of shorter duration, and reduced likelihood of recurrent seizures in the ED.[34] In adults both lorazepam (59.1%) and diazepam (42.6%) were found safe and effective in terminating status epilepticus when compared to placebo, 21.1%. The rates of respiratory or circulatory complications were 10.5% for the lorazepam group, 10.3% for diazepam group, and 22.5% for the placebo group.[35] These results suggest that prehospital intravenous lorazepam therapy for adults and rectal diazepam therapy for children by paramedics are safe and effective. There is an urgent need to implement these protocols for the treatment of out-of-hospital status epilepticus in developing countries. The likely benefit will be substantial reduction in the duration of status epilepticus and reduced risk of recurrence of seizures. The indirect effect will be reduced mortality and morbidity associated with convulsive status epilepticus.

Prognosis

In developed countries the mortality of generalized convulsive status epilepticus has been estimated to be about 20% (3-35%).[13] Older age, acute symptomatic status epilepticus, female sex, increased seizure duration, and continuous (vs intermittent) seizures have been identified as predictors of mortality after status epilepticus.[12,36,37]

In developing countries data on the mortality related to status epilepticus, in the community is very limited. Of the 37,125 death certificates issued in Kandy district in Sri Lanka, death was related to status epilepticus in 2.2%.[38] In Ethiopia, of the 316 patients with epilepsy, 8 (2.5%) died during a two years follow-up period.[39] In the hospital-based studies the reported mortality varied between 10% and 35.5%.[24-26] (G Arunodaya, Bangalore, India, unpublished data). In the series in Senegal the overall mortality was 24.8%. In this study the mortality rates were different depending in which ward the patient was treated. The mortality was 13% in patients treated in the neurology wards whereas it was 27% in patients treated in infectious disease wards and 29% in patients treated in pediatric wards. This difference may be related to the underlying cause of status epilepticus and also the treatment protocols instituted.[26]

Older age and acute symptomatic etiology were the predictors of mortality in the series in Tunisia,[17] and in the series in south India history of epilepsy and abnormal CT scan were the determinants (G. Arunodaya, Bangalore, India, unpublished data). Failure to respond to first line drug therapy was the independent risk factor for poor outcome in the patients studied by Murthy et al.[24] In this study the first line drug therapy included Intravenous diazepam followed by phenytoin loading. In the pathological studies of patients with status epilepticus, pathologies associated with death were cerebral edema, pulmonary edema, and pulmonary embolism.[27] In this study in 17/41 of patients, infections of CNS were the etiology for status epilepticus.

Predictors of functional deterioration after status epilepticus are poorly understood. Using variety of definitions, studies in developed countries indicate that approximately 10% of patients who survive status epilepticus are left with disabling neurologic deficits.[40-42] In the series in Senegal, 18.1% of patients had significant neurologic deficit or epileptic seizure.[26]

Conclusion

In developing countries data on incidence of status epilepticus is limited. Most of the studies are hospital-based retrospective studies. Geographically prevalent infections account for a significant proportion of etiology. Most of them are preventable or containable. There is significant delay between the onset and institution of appropriate treatment. Patients with status epilepticus encounter several significant barriers to adequate treatment. These include poor health care infrastructure, nonavailability of injectable formulations of antiepileptic drugs, and lack of personnel with neurologic expertise who can recognize and appropriately treat patients with status epilepticus. In spite of these limitations, the mortality related to status epilepticus is quite comparable to that reported in developed countries. The place of prehospital administration of benzodiazepines by paramedics needs to be studied.

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Chapter 17

Women with Epilepsy: Special Issues in Developing Countries

J.M.K. Murthy and S.V. Thomas

Introduction

Epilepsy is one of the most common chronic disorders affecting women of childbearing age and 3 to 5 of every 1000 births are to mothers with epilepsy.[1] Women with epilepsy (WWE) in developing countries have many concerns and face many social and cultural taboos related to the diversity in ethnic, racial, religious, economic, educational, and cultural spheres. In addition, in developing countries childbearing for WWE has not always been acceptable because of prejudice directed towards persons with epilepsy.

Physicians caring WWE should have adequate knowledge of health issues for this patient population. The results of two recent surveys conducted in United States[2] and United Kingdom[3] suggest that specialists providing care for WWE are not optimally informed regarding health issues for this patient population. The British Epilepsy Foundation surveyed its female members.[4] They reported marked lack of advice on contraception and pregnancy. There are no such studies from developing countries, but the scenario is likely to be much worse. In developing countries primary-care provider for most patients with epilepsy including WWE is the primary-care physician. Unfortunately he/she is not equipped with adequate knowledge of practical epileptology.[5]

Management Issues during Reproductive Years

Antiepileptic Drug Selection

There are some specific dilemmas while selecting appropriate AED in WWE. Weight gain and weight loss has been associated with AEDs. Other adverse effects that may limit the use of the drug in WWE are hair loss and excessive hair growth.[6] Acceptance of drug-related cosmetic side effects to some extent may also depend on the socio-economic-cultural factors.[7] In developing countries cost factors and easy availability of the drug need to be considered in addition to effectiveness for seizure control and cosmetic side effects.

Mineral Metabolism

Long-term treatment of epilepsy with AEDs causes multiple abnormalities in calcium and bone metabolism. The mechanism of these abnormalities is unclear and has been attributed to AED related accelerated vitamin D metabolism or inhibition of intestinal calcium absorption.[8-10] Recent study suggests that all AEDs, including newer drugs, are risk factors for low bone density, irrespective of vitamin D

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levels. Patients taking enzyme-inducing medications tend to have a lower bone mineral density than those taking noninducing drugs.[11]

Ricketts and osteomalacia of nutritional origin are common in developing countries, more so in women in childbearing age who wear purdha.[12-15] Osteomalacia in India is common especially in females who are under purdah, repeated childbirth with prolonged lactation and poor intake because of economic and sociocultural reasons.[12] Reports from northern India revealed low serum 25 (OH) vitamin D in healthy individual which, has been attributed to low intake of calcium and poor sun exposure especially in adolescents females.[16,17] WWE with preexisting nutritional osteomalacia when exposed to AEDs, particularly to enzyme-inducing AEDs are at a greater risk of developing abnormalities in calcium and bone metabolism.

Contraception

Enzyme inducing AEDs (phenobarbital, phenytoin, carbamazepine, topiramate, and oxcarbazepine) increase the hepatic synthesis of sex hormone binding globulin (SHBG) and increase the metabolism of sex hormones and contraceptive hormones.[18] The failure rate for oral contraceptives in women receiving enzyme-inducing AEDs is 3.1 per 100 women years compared to 0.7 per 100 women years in the general population.[19] In addition, in developing countries, contraceptive pill discontinuation is a major problem exposing WWE to risk of unwanted conception.[20] Recommendations include possible use of a nonenzyme inducing AED or use of an oral contraceptive containing higher content of estrogen. Injectable long-term contraceptives are a useful alternative contraception. A barrier method of contraception can be an alternative method to be considered in developing countries.

Marital Status and Fertility

Marriage rates in individuals with epilepsy and without other neurological deficits are lower – the probability of being single is 2.7 time that of controls. Patients with epilepsy have a 3.6-fold increased probability of being childless.[21] The fertility rate in WWW is only 60-80% that of the nonepileptic female population.[22] Similar were the observations in the studies from developing countries. In a retrospective study from south India the proportion of married WWE was 59% and the mean family size was 1.6. The corresponding figures for women without epilepsy were 65% and 2.3. The proportion of WWE without child was 13.9% when compared to 9.8% in the community.[23]

The problem of infertility in WWE is clearly complicated. In addition to the hormonal effects, psychosocial and socio-economic-cultural factors may have a contributing role for lower fertility in WWE. In developing countries fertility behavior depends on literacy, women's autonomy and polygamy, which is prevalent in some of the sub-Saharan Africa.[24,25] In many developing countries objection to marry people with epilepsy still persists and a sizeable number of WWE with epilepsy are divorced (see Chapter 5). Strong social pressures on WWE to refrain from reproducing could also be a factor.

Pregnancy-Related Management Issues

Seizure Frequency during Pregnancy

Women with epilepsy are at risk for changes in seizure frequency during pregnancy. Three prospective studies report 0 to 37% of pregnancies resulting in an increase in maternal seizure frequency.[26,27] In a prospective population-based study,

(Tomson et al[28] found worsening of seizures in only 15%). Clinic-based studies done in developing countries, report 39 to 49% of pregnancies resulting in an increase in maternal seizure frequency.[29,30]

Although a range of possible risk factors for increased seizure frequency during pregnancy have been proposed, the biggest problem is poor compliance with drug therapy. In one study, medication noncompliance occurred in 68% of those WWE with worsened seizure control.[26] In developing countries obstetricians and primary care physicians are not well informed about health issues of WWE. Authors' experience in India suggests that drug compliance is poor in pregnant WWE. They often stop drugs on the advice of obstetrician and/or primary-care physician or because of concern regarding the effect of AEDs on their unborn children.

Birth Defects and AED Use

There have been consistent findings of high incidence of congenital malformations of AED treated mothers with epilepsy.[31] The overall malformation rate is 9.7% in offspring of mother with epilepsy compared with 4.8% in the control population in 12 prospective studies.[32] Anticonvulsant embryopathy includes major malformations (structural abnormalities with surgical, medical, or cosmetic importance), growth retardation, and hypoplasia of the mid face and fingers. The combined frequency of anticonvulsant embryopathy in singleton infants has been found to be higher in infants exposed to AEDs than control infants. Cleft lip, cleft palate, or both, and congenital heart diseases account for many of the reported cases of major malformations.[33] Oro-facial clefts are responsible for 30% of the increased risk for malformations in these infants.[34,35]

In developing countries the data on the incidence of congenital malformations is very limited. Most of them are observational studies in small number of pregnancies. The reported incidence of congenital malformation varied from 0.63% to 14.4%.[29,30,36-38] In the study from Kuwait by Shakir and Abdulwahab,[37] 17 mothers had 48 pregnancies before they developed epilepsy and 39 mothers who had epilepsy before motherhood had 131 pregnancies while on AEDs. The incidence of major congenital malformations in the babies born to 17 mothers before the onset epilepsy was 2.2% whereas it was 14.4% in the babies born to mothers who had epilepsy before motherhood and on AEDs. These observations suggest that the overall malformation rate in offspring of mother with epilepsy in developing countries is likely to be high. The likely risk factors in addition to AED therapy are maternal age, maternal malnutrition, maternal folate status, the high frequency of consanguineous marriage, and probably environmental factors. In addition, polypharmacy is highly prevalent in many developing countries.[39,40] The influence of these modifiable factors needs to be established in well-designed studies.

Developing Countries – Neural Tube Defects and Folate Status

Incidence of Neural Tube Defects

In the developing countries the reported incidence of neural tube defects (NTDs) is much high, 3 - 3.9 per 1000 births[41-44] when compared to developed countries, 1 per 1000 birth in the United States.[45]

Folate Status of Women of Childbearing Age

In developing countries the folate status of women of childbearing age is not optimal.[46-48] Pregnancy- and lactation-related folate deficiency up to 3 years after delivery remains a common cause of megaloblastic anemia in these countries.[49]

In a multicentric case-control study from Mexico folate deficiency was associated with NTDs (OR 11.1, CI 95% 1.2-106.2, $p < 0.04$).[50] Of the 85 pregnant WWE registered in the Kerala Registry of Epilepsy and Pregnancy in south India, 40% were not receiving folate supplementarion.[30]

Neural Tube Defects – Folic Acid Supplementation

The results of two randomized controlled trials showed that 50% or more of NTDs can be prevented if women consume a folic acid containing supplement (0.4 mg) before and during the early weeks of pregnancy in addition to the folate in their diet.[51,52] Medical Research Council study conclusively demonstrated that a daily dosage of 4 mg of folic acid, in addition to folate in the diet, before and during early pregnancy resulted in a 71% reduction of recurrence of NTDs in subsequent pregnancies among couples who have had a child with a NTD.[51] However no such studies have been conducted specifically in women taking AEDs.

WWE - Folic Acid Supplementation Recommendations

The United States Public Health Service (USPHS) recommends that all women of childbearing age who are capable of becoming pregnant take 400 mug of folic acid daily.[53] American Academy of Pediatrics (APA)[54] endorses the USPHS recommendation. Implementing of this recommendation may provide the opportunity for primary prevention of 50% or more of these serious disabling birth defects. For women who have had a previous NTD affected pregnancy AAP recommends 4000 μg of folic acid per day starting 1 month before the time they plan to become pregnant and throughout the first 3 months of pregnancy, unless contraindicated.[54] The amount of folic acid supplementation recommended for women receiving AEDs is largely extrapolated from these experiences with the general population. In view of sub-optimal folate status of women in childbearing age in developing countries, a higher dose of folate per day may be recommended in these countries.

Developmental Delay

Infants of WWE are reported to have higher rates of intra uterine and psychomotor retardation. This risk is increased by a factor of two to seven according to various authors.[55,56] The frequency of growth retardation is higher in infants exposed to AEDs than in control infants.[33] A large prospective study confirmed that phenobarbital and possibly phenytoin caused intrauterine growth retardation, in particular of the fetal head size.[57] The study by Holmes et al (2001) was controlled for cigarette and alcohol use, substance abuse, severity of seizures, and head circumference and height of the infant. None of these studies however were controlled for parental intelligence. In developing countries maternal nutrition is a confounding factor for intrauterine growth retardation. Chronic undernutrition throughout pregnancy affects birth weights of newborns. Poor nutrition causes intra-uterine growth retardation.[58]

Pregnancy Outcomes

A variety of obstetric complications have been reported to occur more commonly in WWE. Some studies from developing countries reported higher rates of preeclampsia, maternal hemorrhage, and cesarean delivery.[30] However no definitive conclusions can be generated regarding the absolute incidence of obstetric complication. Well-designed studies, which include correction for the confounding variables, need to be conducted to determine the exact incidence of various obstetric complications in WWE. In the developing countries maternal age, unattended deliveries, maternal malnutrition, poor health care infrastructure are some of the factors likely to be associated with increased risk of obstetric complications.

Neonatal Hemorrhagic Complications

Hemorrhagic phenomena in infants of mothers with epilepsy, hemorrhagic disease of the newborn (HDNB), tend to occur internally between 2 and 7 days of age. This complication occurs in children exposed to conventional AEDs.[59] Risk of HDNB may be a consequence of maternal deficiency of the vitamin. In developing countries chronic maternal malnutrition may be a contributing factor for the deficiency. The practice of prenatal supplementation for WWE should not supplant the recommendation of the American Academy of Pediatrics that all neonates receive vitamin K_1 (1 mg) at birth.

Breast Feeding

Breast feeding is strongly recommended by most health organizations to promote mother-child bonding and reduce the risk of infection and later-life immunological disorders.[60,61] For conventional AEDs like PHT, CBZ, and VPA, the concentration in breast milk is negligible because of their high protein binding. Maternal nutrition may be a confounding factor for drug metabolism and protein binding. For mothers with poor nutritional status, the best advice is to seriously consider breastfeeding and the infant can be observed for sleep cycles.

Managing Women with Epilepsy – Recommendations

Using current methodological standards for developing clinical practice guidelines, two independent groups in the United Kingdom[4] and the United States.[59,62] have assembled, wide ranging guidelines for managing WWE. Each group's recommendations are remarkably similar in direction and strength.

Management of WWE – Special Considerations in the Developing Countries

In view of certain special management issues for WWE in developing countries discussed above, the following recommendations are proposed as practice options in addition to the recommendations by American Academy of Neurology.

- High prevalence of maternal malnutrition - Due consideration should be given to maternal nutrition in the preconception period and during pregnancy.
- Ricketts and osteomalacia of nutritional origin is not uncommon in women in childbearing age – Calcium and vitamin D supplementation.
- High rate of contraceptive pill discontinuation - A barrier method of contraception can be considered if the contraception is considered especially important.

- Sub-optimal folate status of women of child bearing age and high incidence of NTD - Folic acid supplementation should be no less than 4 mg per day and possible preconceptional recommendation of folic acid supplementation.
- Poor maternal malnutrition – Preconceptional recommendation of vitamin K supplementation during the last month of the pregnancy.
- High rate of home deliveries by traditional birth-attendants - Emphasis should be made for attended delivery, preferably in the hospital.
- Poor practicing parameters – Equipping the practicing physicians and obstetricians with the knowledge of the special issues related to WWE.

Conclusion

Epilepsy is one of the most common chronic disorders affecting women of childbearing age. Women with epilepsy have many concerns regarding the effects of their condition and use of AEDs on their reproductive health and unborn children. In addition to these issues, WWE in developing countries face many social and cultural taboos related to the diversity in ethnic, racial, religious, economic, educational, and cultural spheres. In many developing countries objection to marry people with epilepsy still persists and a sizeable number of WWE with epilepsy are divorced. Childbearing for WWE in developing countries has not always been acceptable. The incidence of congenital malformations in infants of mother with epilepsy in developing countries is likely to be higher than the reported incidence in developed countries. In addition to AED therapy, the other likely risk factors include maternal age, maternal malnutrition, maternal folate status, the high frequency of consanguineous marriage, high prevalence of polypharmacy, and probably environmental factors. In addition to these risk factors unattended deliveries, and poor health care infrastructure may be associated with increased risk of obstetric complications. Further more primary care physicians and practicing obstetricians are not well informed with the special issues related to WWE. All these issues need consideration while managing WWE in developing countries.

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Chapter 18

Pharmacological Treatment of Epilepsy: Cost Effective Approaches

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Goals of Epilepsy Treatment

The ultimate goal of epilepsy treatment is to eliminate the adverse impact of the disease on the patient's quality of life. Since seizure freedom is the most important determinant of quality of life in these patients, this should also be the usual primary goal.[1-3] Currently available antiepileptic drugs (AEDs) allow to achieve complete seizure suppression in up to two thirds of an unselected epilepsy population, allowing these patients to lead a virtually normal life. Achieving seizure freedom, however, may not be feasible in severe epilepsies, when the price in terms of side effects becomes too high, or when the most appropriate AED is unavailable or unaffordable.

Most AEDs have a narrow therapeutic index, and the dosages that produce seizure control are close or even overlapping with those that produce tolerability problems. The sensitivity to different types of side effects may differ from patient to patient, and skilful management is required to identify the drug and dosage that are best suited to the characteristics of an individual.[4] Patients' well being should not be jeopardized by too aggressive therapeutic approaches which lead to unacceptable toxicity, and both acute and long-term side effects should be considered in the risk-benefit analysis.[5] For most patients living in tropical countries, the price of a drug is also a major side effect, and this has obviously to be considered in the therapeutic algorithm.[6]

In addition to the above mentioned objectives (seizure control and minimization of side effects), other goals should be actively pursued whenever feasible.[2] Reduction of morbidity (e.g., due to seizure-related injuries) and seizure-related mortality may be achieved not only by mere reduction of seizure counts,[5] but also by shifting the patient's seizures to a less severe pattern, as it may be seen when secondary generalization is suppressed or when complex partial seizures are turned into simple partial seizures. In symptomatic epilepsies, reduction of mortality and morbidity can be also achieved by treatments aimed at the underlying disease, for example in patients with brain tumours, parasites, viral and bacterial infections, or metabolic disorders.

In some forms of epilepsy, particularly some pediatric epilepsies (e.g., ESES or West syndrome), there is a need to improve not only seizure frequency but also interictal subclinical activity, since frequent paroxysmal discharges may lead to significant functional impairment. While in these patients improvement of electroencephalographic (EEG) discharges may become a main objective, in most forms of epilepsy treatment should be used at preventing clinical seizures rather than at "normalizing" the EEG.

Epilepsy in the Tropics, edited by J.M.K. Murthy and Nimal Senanayake.

Avoidance of adverse drug interactions is a further goal in the drug therapy of epilepsy. Care should be taken when treatment for an intercurrent disease needs to be given: for example, certain chemotherapeutic agents, including macrolide antibiotics, isoniazid or certain antifungal agents, may inhibit AED metabolism and increase serum AED concentrations leading to clinical toxicity, whereas other agents such as rifampicin may stimulate drug metabolism and lead to a fall in serum AED concentrations and consequent breakthrough seizures.[2] Many AEDs, most notably barbiturates, carbamazepine and phenytoin are also potent enzyme inducers and may decrease the effectiveness of concomitantly given drugs, including steroid oral contraceptives and some calcium antagonists. AEDs with a low interaction profile do offer distinct advantages.

In general, AED therapy should interfere as little as possible with daily living activities. Taking medicines in a working environment or at school at certain times may be a social embarrassment, particularly in the cultural environment present in emerging countries, and AEDs that can be taken once or twice daily, when patients are at home, offer clear advantages and ensure better compliance as well. Activities of daily living can also be affected by the adverse effects of some AEDs on alertness, mood, cognition or sexual functions, and these side effects can add considerably to the burden of epilepsy itself.

Although in West syndrome and some other childhood encephalopathies associated with progressive cognitive decline early achievement of seizure control may improve long-term intellectual outcome, in most forms of epilepsy there is no evidence that currently available AEDs interfere with the natural history of the disease,[7-9] as also confirmed by studies in tropical countries.[10-12] Although some AEDs do seem to antagonise the process of epileptogenesis in animal models, clinical evidence for a disease modifying effect of these drugs remains totally missing.

Specific Aspects of Epilepsy Management in Developing Countries

A wide gap in epilepsy treatment continues to exist between highly industrialized countries and the rest of the world, particularly the tropical countries in Latin America, Africa and Asia, where up to 94% of patients receive no adequate pharmacological therapy.[13-15] The reasons for this are manifold and include difficulties in access to medical care, economic constraints and factors related to local culture and tradition. In Europe and North America, drug therapy has long been considered the mainstay of epilepsy management, and only in recent times has attention been focused on alternative measures such as psychosocial support interventions and nonpharmacological treatments such as vagal nerve stimulation and epilepsy surgery. By contrast, in many tropical countries, epilepsies have been traditionally managed according to ethnic beliefs, leading to application of esoteric treatments and indigenous medications for which a Western-style rationale or "proof-of-efficacy" studies are generally unavailable. Taking the Indian subcontinent as an example, different levels of healing activities such as popular and folk-based practices coexist with professional medicine. Folk medicine, provided by healers, tends to come into play when self-treatment according to family traditions (popular practice) is ineffective: indigenous healer activities tend to conform to the patient's beliefs, while modern epilepsy treatment based on administration of pills that produce side effects does not. Availability of physicians and medical facilities, including EEG and neuroimaging instruments, may be severely restricted in the tropics, particularly in

rural areas.[16] Even when access to medical services is readily available, patients may still rely heavily on traditional or alternative medicine: in a recent survey, of 152 Indian patients with chronic epilepsy attending an outpatient clinic in the Lucknow area 58 were found to use homeopathy, 30 religious ceremonies, 18 piercing, 18 Ayurvedic medicines and 6 various other alternative treatments. Many of these patients had stopped AEDs in favour of other treatments, usually without informing the treating physician.[17] According to information collected from the national chapters of the International League against Epilepsy in eight Latin American countries,[18] up to one half of all epilepsy patients receiving AEDs have had or are having concomitant alternative treatments.

To allow wider application of evidence-based drug therapy in these cultural environments, major educational activities need to be implemented and directed not only to the patients themselves, but also to their families, local doctors, nurses, social workers, those healers who are willing to cooperate, and persons with political responsibilities at all levels. Education should include information about what AED therapy can achieve and alternative medicines cannot, the need to prescribe adequate doses, and the need to avoid stretching supplies by under-dosing or sharing AEDs with other patients. A popular practice in some developing countries involves combining low doses of various medicines based on the assumption that this leads to therapeutic synergism, a strategy that has not been proven to be successful in epilepsy. The importance of regular compliance also needs to be stressed. For some patients and families in rural areas it may be preferable to tolerate continued seizures than to endure daylong travel, wait in never ending queues and finally be faced with indifferent attitudes of clinic personnel, in addition to the costs of travel, medicine and lost work. In a survey of a 2 x 2 km area in the city of Mumbai closely connected to the local hospital, the prevalence of poor compliance with intake of antiepileptic medication was found to be as high as 54% even among patients who had no need to travel for consultation and could obtain adequate drug supplies.[19]

Unlike the situation in Western countries with well-structured health care and reimbursement systems, in tropical countries only direct costs of treatment can be reliably assessed. Therefore, cost-effectiveness of different treatments cannot be defined in the same way as in North America, Europe or Australia. For example, how can loss of labor hours for persons with epilepsy and caretakers be valued in South Africa´s Gauteng province, where unemployment rates among persons with epilepsy is 79%, but almost every second person in the area is unemployed anyway?[20] Cost-effective approaches in the tropics should take into account not only the prices of individual AEDs, but also the possibility of avoiding unnecessary polypharmacy, which is quite prevalent in some countries. For example, in a survey of patients seen at a comprehensive epilepsy care program in South India from 1993 to 1995, the average annual cost of AED therapy per patient in U.S. dollars (USD) decreased from 64 USD at entry to 48 USD at last follow up, and reduction of polypharmacy in particular resulted in net annual savings of 17 USD per patient (over 5% of the per capita gross national product).[21] More importantly, the proportion of patients seizure-free increased from 29% to 45%, and side effects were also reduced in the surveyed population.

Those supportive and educational measures that lead to better understanding of the disease and improve compliance with a rational treatment regimen need to be carefully identified in the local environment. In many areas, the most cost-effective approach is to prevent epilepsy wherever possible, as successfully done in Reunion

Island through the setting up of campaigns to reduce the prevalence of neurocysticercosis-related epilepsy.[22]

When Should Pharmacological Treatment Be Initiated?

Before embarking on AED treatment, a diagnosis of epilepsy and seizure types should be established. Any type of nonepileptic attack, e.g., psychogenic seizures or syncopal events, should be differentiated from epileptic seizure activity. Initiation of AED therapy is based on a positive risk/benefit evaluation in each individual patient, taking into account sex, age, type, severity and chronicity of the epilepsy, number and types of seizures, any associated neurological or mental handicaps, concomitant medical conditions, and the expected impact of treatment on patient's life, including psychosocial and financial matters.[5,23] In most cases, the indication for initiating AED therapy is clear, but there are situations where this is dubious. Reasons for starting or deferring pharmacological treatment and related implications should be clearly discussed with the patient and caregivers in a way that can be easily understood, respecting the patient's own perspective on this matter. Some situations that require special consideration are listed below.

Single Seizures

Epilepsy is defined as a condition characterized by unprovoked, recurrent seizures. Diagnostic and therapeutic uncertainties occur when a first single tonic-clonic seizure has occurred, particularly when no witnesses are available. A single seizure may have been provoked by external stimuli or an acute medical condition, e.g., an infection. A considerable number of these patients will not experience a recurrence and therefore AED therapy is usually deferred until a second seizure occurs. If specific prognostic factors such as interictal paroxysmal EEG abnormalities, focal lesions in imaging techniques or an otherwise identifiable persisting cause for seizures are present which indicate a high risk of recurrence, then AED treatment may already be considered after one seizure.[3] The same is true when the medical or psychosocial consequences of seizure recurrence outweigh the overall risks associated with long-term pharmacological treatment.

Infrequent Seizures

In patients with infrequent seizures or mild seizure types, which cause little or no interference with daily living activities (e.g., seizures occurring only during sleep), treatment may be withheld. The decision to treat or not to treat should again be taken on a case-by-case basis, taking into consideration the patient's age, attitude towards seizures, and need to maintain a driving licence. In some forms of epilepsy, such as photosensitive epilepsy, seizures may only occur after exposure to precipitating stimuli and avoidance of exposure to such stimuli may be sufficient to prevent seizures completely.[2]

Childhood Idiopathic Epilepsies

Idiopathic partial epilepsy with centrotemporal spikes (rolandic epilepsy) is a benign self-remitting disorder, which occurs in childhood and generally requires no AED treatment because seizures tend to be mild, infrequent and often nocturnal. When seizures are more frequent and occur during daytime, treatment may be indicated to avoid the psychosocial consequences of the disorder, even though AEDs have no impact on the overall favourable therapeutic outcome.[2] Although

childhood absence epilepsy is also a self-remitting condition, frequent absence seizures are disrupting and functionally impairing, and adequate AED treatment is indicated in these children. Febrile seizures in children older than one year generally do not warrant pharmacological treatment, except for intermittent prophylaxis with a benzodiazepine in selected cases.[24,25]

Poor Compliance

When there are reasons to believe that the patient will not comply with the prescribed drug regimen, treatment may be withheld, particularly when seizures are mild or infrequent. Irregular intake of medicines may do more harm than good, because abrupt discontinuation of AED therapy may lead to withdrawal seizures and status epilepticus. To prevent or minimise poor compliance, the patient should be clearly informed about the need and implications of treatment, reassured about potential side effects, and stabilised on a treatment schedule as simple as possible. In a five-year follow-up study conducted in South India, compliance with regular intake of medication was found to raise from 67% to 84% thanks to implementation of rational treatment schedules, improved patient's awareness, and supervision by doctors and paramedical workers.[26]

Epilepsy Prophylaxis

There is an ongoing debate on the value of prophylactic treatment in neurological disorders associated with a high risk of epilepsy, such as tuberous sclerosis, severe head trauma and supratentorial surgery.[5] Early AED therapy may be considered in infants with tuberous sclerosis to prevent occurrence of spasms and associated cognitive deterioration. With the possible exception of short-term phenytoin to reduce the risk of early (acute) post-traumatic seizures, AED prophylaxis has not been found to be effective in preventing the development of epilepsy after head trauma or neurosurgical interventions.[5] Therefore, administration of AEDs in these patients before occurrence of seizures is not indicated.

Choosing the Initial Drug

Treatment should be started with a single drug, and dosage should be adjusted gradually to achieve maximum seizure control with minimal side effects.[21,23,27] Up to 60-70% of patients with partial seizures and up to 80% of patients with primarily generalized tonic-clonic seizures can be completely controlled on the initially prescribed AED. The probability of seizure freedom may be even higher in childhood absence epilepsy, whereas symptomatic generalized epilepsies carry a much poorer prognosis. No single drug can be proposed as best for all patients, and a number of factors need to be considered in trying to tailor drug choice to the characteristics of a particular patient.

First, the spectrum of efficacy of the selected AED must be adequate to cover the seizure types presented by the individual.[2] If a syndromic diagnosis has been made, drug choice should be also influenced by prediction of additional seizure types that may occur in the future during the course of the disease. AEDs differ in their efficacy spectrum (Table 1), with valproic acid having the broadest activity in different seizure types while ethosuximide, which is active only against absence seizures, has the narrowest. Since tonic-clonic seizures may develop later in life in children with childhood absence epilepsy, a drug effective against both seizure types, such as valproate, may be preferred even in children who present only with absences.

Table 1. *Efficacy spectrum of available antiepileptic drugs against different types of seizures. Modified from Gatti et al.*[41]

All Seizure Types	All Seizure Types Except Absences	Partial and Generalized Tonic-Clonic Seizures	Absence Seizures
Valproic acid	Phenobarbital	Carbamazepine[1]	Ethosuximide[2]
Lamotrigine[3]	Primidone	Phenytoin[1]	
Benzodiazepines[4]		Oxcarbazepine[1]	
Topiramate[5]		Gabapentin[1]	
Zonisamide[6]		Pregabalin[1]	
Levetiracetam[7] (?)		Tiagabine[1]	
Felbamate[6]		Vigabatrin[1,8]	

[1]Carbamazepine, oxcarbazepine, phenytoin, vigabatrin and tiagabine may precipitate or aggravate myoclonic and absence seizures. Gabapentin and pregabalin may precipitate myoclonic seizures. Carbamazepine may be efficacious against tonic seizures associated with the Lennox-Gastaut syndrome. [2]Myoclonic seizures may also be ameliorated by ethosuximide. Ethosuximide is also a drug of choice in continuous spike wave during slow sleep (CSWS). [3]Lamotrigine efficacy is best documented against partial seizures, generalized tonic-clonic seizures, absence seizures, and drop attacks. Severe myoclonic epilepsy may be aggravated by lamotrigine. [4]Benzodiazepines, particularly when given of infancy intravenously, have been occasionally reported to precipitate tonic seizures, especially in patients with Lennox-Gastaut syndrome. [5]The efficacy of topiramate against absence seizures has not been established. Topiramate efficacy is best documented against partial seizures, generalized tonic-clonic seizures, and drop attacks. [6]The efficacy of zonisamide and felbamate against some generalized seizure types is suggested only by preliminary evidence. Efficacy is best documented for partial and secondarily generalized tonic-clonic seizures and, in the case of felbamate, also drop attacks associated with the Lennox-Gastaut syndrome. [7]For levetiracetam, broad-spectrum activity is expected based on findings in animal models but clinical evidence of efficacy from controlled trials is available only against partial and secondarily generalized tonic-clonic seizures. [8]Vigabatrin is also efficacious in West syndrome (infantile spasms).

Certain AEDs are known to worsen specific seizure types, for example carbamazepine, tiagabine and vigabatrin may aggravate or even precipitate absences and myoclonic seizures, gabapentin may precipitate myoclonic jerks, barbiturates may worsen absences and lamotrigine may aggravate severe myoclonic epilepsy of infancy.[28,29] When syndromic diagnosis is in doubt, a broad spectrum agent will be more likely to achieve and to maintain seizure control compared with a drug having a narrow activity spectrum.

At the present state of knowledge, information on a drug's mechanism of action is of little or no value in selecting the initial AED to be used in an individual patient, but this may change in the future with advances in knowledge of the pathophysiology of different syndromes. Based on the results of large comparative monotherapy trials, no major differences in efficacy have been found among older generation AEDs,[31-37] or between older and newer generation AEDs,[39] provided of course that

Table 2. A commonly used algorithm for the treatment of epilepsy*

	Generalized Epilepsies	**Partial Seizures**
First choice	Valproic acid	Carbamazepine
Second choice	Carbamazepine (PGTC seizures only)	Valproic acid
	Phenytoin (PGTC seizures only)	Phenytoin
	Ethosuximide (absence seizures only)	A new drug
	Lamotrigine	
	Topiramate	
	Levetiracetam	
	Phenobarbital	

*In this algorithm, valproic acid is preferred for the initial treatment of generalized epilepsies, while carbamazepine is preferred for partial epilepsies. Some physicians may prefer phenytoin or oxcarbazepine over carbamazepine. Carbamazepine, oxcarbazepine and, to a lesser extent, phenytoin may precipitate or aggravate myoclonic and absence seizures in patients with primarily generalized tonic-clonic (PGTC) seizures, particularly in idiopathic generalized epilepsies. Topiramate and phenobarbital are not a recommended second choice in patients with absence seizures. Different treatments may be indicated in special syndromes (e.g., vigabatrin or ACTH for West syndrome) or when there are conditions contraindicating specific drugs.

the investigated seizure types were consistent with the activity spectrum of the various drugs. There are, however, wide and important differences between drugs in terms of side effect profiles and cost, and it is precisely these factors that determine primarily AED choice.[1-3] In the case of phenobarbital, adverse effects like sedation, cognitive dysfunction and, in children, behaviour disorders need to be discussed, together with other potentially serious non-CNS effects. With phenytoin, acne, hirsutism and gingival hyperplasia are likely to represent a greater problem for a young girl than for an elderly man. When using carbamazepine, the potential for allergic reactions needs consideration, particularly in a patient with a known history of hypersensitivity. For patients who have tremor or tend to gain weight, valproate may not be the optimal choice. All of the old-generation AEDs may increase the risk of foetal malformations if taken in the early trimester of pregnancy, although valproic acid, particularly at high dosages, appears to carry a greater risk.[39,39a,b] Some studies suggest that valproic acid exposure during pregnancy may also be associated with an increased risk of neurodevelopmental delay in the offspring.[39a,b] Preliminary data suggest that the rates of congenital malformations after exposure to lamotrigine and oxcarbazepine in the first trimester of pregnancy may not differ significantly from that observed after exposure to carbamazepine.[39a,b] Teratogenicity risks associated with other newer generation AEDs, on the other hand, are unknown In women of childbearing potential, counselling about these issues is mandatory.

Factors that contribute to ease of use of an AED include a broad spectrum of efficacy, good tolerability, no idiosyncratic reactions, low liability for drug interactions, feasibility of rapid titration to the effective dose, once or twice daily dosing, linear pharmacokinetics, availability of convenient pediatric dose forms, and availability of a parenteral form that could be used when, due to intercurrent conditions like surgery, oral treatment is not an option for a limited time.

Table 3. The "one-drug" approach to the treatment of epilepsy*

	Absence Seizures	Partial Seizures (With or Without Secondary Generalization)	Other Seizure Types
First choice	Valproic acid	Valproic acid	Valproic acid
Second choice	Ethosuximide	Carbamazepine	Carbamazepine (PGTC seizures only)
	Lamotrigine	Phenytoin	Phenytoin (PGTC seizures only)
		A new drug	Lamotrigine Topiramate Levetiracetam

*This algorithm exploits the broad spectrum activity of valproic acid, which can be utilized as the treatment of choice irrespective of seizure type. In women of childbearing potential, however, valproic acid may not be the preferable choice, particularly in epilepsy syndromes (e.g., partial epilepsies) where equally effective AEDs are available. Some physicians may prefer oxcarbazepine over carbamazepine in this therapeutic algorithm. Carbamazepine, oxcarbazepine and, to a lesser extent, phenytoin may precipitate or aggravate myoclonic and absence seizures in patients with primarily generalized tonic-clonic (PGTC) seizures, particularly in idiopathic generalized epilepsies. Different treatments may be indicated in special syndromes (e.g., vigabatrin or ACTH for West syndrome) or when there are conditions contraindicating specific drugs.

In Western countries, when all the above factors are taken into consideration, valproic acid is generally regarded as the drug of first choice for generalized epilepsies, while carbamazepine or, in some countries, phenytoin or valproate itself are preferred for partial epilepsies (Tables 2 and 3).[2,3,23] In individual patients, however, choice may be different, primarily because of preexisting conditions, which may affect susceptibility to specific side effects.[5] Because of risks to the unborn baby, valproic acid, in particular, is probably best avoided as first line therapy in women of childbearing potential, at least in forms of epilepsy (e.g., partial epilepsy) when equally effective AEDs are available. Newer AEDs are rarely used as first line,[40-41] but there may be exceptions, with vigabatrin being a feasible choice for infantile spasms[42] and lamotrigine being a reasonable option against partial or tonic-clonic seizures with onset in old age.[43] Treatment guidelines for epilepsy management at the primary health care level, which are especially relevant for emerging countries, tend to advocate the use of a similar set of drugs: for example, the South African Epilepsy Working Group's guidelines[44] recommend using valproic acid for generalized epilepsies and carbamazepine, valproate, phenytoin or phenobarbital for partial epilepsies. Since primary care physicians are likely to be less skilful than specialists in making a correct syndromic diagnosis, an argument could be made for the preferential use of a broad-spectrum drug when generalized epilepsy cannot be excluded.[1]

In practice, in most tropical countries drug selection depends mainly on the range of AEDs which are locally available and affordable. In 28 countries, which contribute 40% of the world population, the per capita annual gross national product is barely sufficient to buy a year's supply of carbamazepine or valproate for one or two patients.[6] Phenobarbital is still recommended by the World Health

Table 4. The "low-budget" algorithm for the treatment of epilepsy*

	Absence Seizures Only	Partial Seizures (With or Without Secondary Generalization)	Other Seizure Types
First choice	Ethosuximide	Phenytoin or phenobarbital	Phenobarbital
Second choice	Valproic acid	Carbamazepine	Valproic acid Carbamazepine (PGTC seizures only) Phenytoin (PGTC seizures only)

*In this algorithm, cost is the primary determinant in drug selection. In some countries, carbamazepine may be preferable to phenytoin and valproic acid may be preferable to ethosuximide on a cost basis. Carbamazepine and, to a lesser extent, phenytoin may precipitate or aggravate myoclonic and absence seizures in patients with primarily generalized tonic-clonic (PGTC) seizures, particularly in idiopathic generalized epilepsies. Different treatments may be indicated in special syndromes (e.g., vigabatrin or ACTH for West syndrome) or where there are conditions contraindicating specific drugs.

Organization[45] and the Commission on Tropical Diseases of the International League against Epilepsy[46] as a reasonable first-line drug for the treatment of partial and generalized tonic-clonic seizures in emerging countries, because of its low price in the range of 10-30 US dollars per year, and a recent randomised trial in India did support its acceptability as a treatment of choice even in children.[47] Although phenytoin costs slightly more than phenobarbital, it may be a valuable cheap alternative for the first line treatment of partial seizures (Table 4), particularly those associated with neurocysticercosis and, possibly, the majority of other tropical diseases.[46] On the other hand, carbamazepine and valproate are 5 to 20 times as expensive as phenobarbital.

Driven by market interests, new AEDs are usually launched first in the U.S. and in Europe, and they may take time to become available in Africa, South Asia and Latin America due to delayed filing for approval, slow turnaround times, and extended periods for pricing discussions with governmental authorities. The price of these agents is such that in most tropical countries only a tiny fraction of the epilepsy population can afford them; however, approaches are being explored, in collaboration with the pharmaceutical industry, to secure in individual countries a small supply of such drugs to be made available at small cost to those patients' subgroups who are likely to be mostly in need, one example being vigabatrin for refractory infantile spasms.

Some tropical countries do manufacture generic versions of older AEDs, and in certain nations with loose patent regulations even generic formulations of new drugs may reach early the market at relatively low prices. This may improve treatment affordability, but care should be taken to ensure that these formulations have adequate quality.[48] Serious problems can arise when patients are switched from one product to another which is not equivalent in terms of bioavailability.[49]

Herbal Remedies

Although this chapter focuses primarily on evidence-based drug therapy, the situation in the tropics requires that consideration be also given to the implications of alternative treatments, particularly herbal remedies, which are widely used in traditional medicine.[50] Although herbal products in any part of the world are perceived by the lay public as safe, some of them contain pharmacologically active ingredients in sufficient quantities not only to produce undesirable effects, but also to exacerbate seizures. In the U.S., for example, a series of natural herb supplements was investigated and found to contain anthroquinone derivatives and ephedrine, leading to hospitalization due to increased partial and generalized seizures among patients treated at the MINCEP Epilepsy Care unit in Minneapolis.[51]

When CNS signs of toxicity develop after intake of herbal products in patients already receiving AEDs, consideration should be given to the possibility that such products contain anticonvulsants such as phenobarbital or phenytoin to enhance their efficacy as anti-seizure medications. In addition, interactions between herbal remedies and AEDs should not be discounted: for example, piperine, one of the active ingredients of *Piper nigrum*, an herb used for its putative antiepileptic properties in Chinese and Ayurvedic preparations, has been shown to increase serum phenytoin concentrations in human subjects.[50] Contrary to common belief, opting for a long-term poorly effective herbal treatment without seeing a specialist may be turn out to be more expensive than receiving adequate medical diagnostic and therapeutic assistance, as clearly demonstrated by an investigation in Columbian epilepsy patients surveyed over a 10-year period.[18]

Although overall there is little or no evidence that herbal remedies employed in different parts of the world as anti-epilepsy medications are clinically effective, the possibility that some of these medicines could actually contain useful active ingredients should not be discounted.[50] For example, some naturally occurring pyrones have been found to be active in electroconvulsive and chemical seizure models. As a result of this, kava pyrones from *Piper methysticum* originally collected from the Samoa Islands have been structurally modified and investigated as potential anticonvulsants in randomized placebo-controlled trials in Europe and the U.S.[52]

Route of Administration

When rapid loading is required, as in status epilepticus, intravenous formulations are available for benzodiazepine drugs, phenobarbital, phenytoin (and phosphenytoin), and valproate. With most AEDs, intramuscular injections are generally not recommended because of slow and variable absorption from muscle tissue. Diazepam can be given orally as solution, gel or capsules, suitable for use by nonmedical personnel as well, including application to children and infants. For long-term treatment, the oral route is invariably used.

Choosing the Right Dose

Dosage requirements vary considerably between patients, not only due to differences in type and severity of the disease, but also due to marked interindividual variability in pharmacokinetics and pharmacodynamics.

In newly diagnosed patients, it is usually appropriate to aim initially for a target dosage in the lower to middle range of the daily maintenance dosages indicated in the package insert, and further adjustments should be made according to clinical response.[4] For some drugs, particularly primidone, lamotrigine, topiramate and

tiagabine, starting dosage should be very low and escalated slowly over a period of several weeks to minimise the risk of adverse effects. If a tolerable CNS side effect develops, it may be advisable to wait for some time until it disappears (which is often the case), rather than to reduce the dose immediately and potentially lose out on efficacy. On the other hand, if seizures are not fully controlled and no or only mild side effects occur, doses should be increased stepwise until optimal effectiveness is achieved or side effects cannot be tolerated. The interval required to evaluate the response at any given dosage is dependent on baseline seizure frequency and on the time to reach a new steady-state after dose escalation, usually four half-lives of the drug. An AED with a long half-life such as phenobarbital can be given conveniently once daily. Drug with short half-lives need to be administered more frequently in order to avoid excessive plasma level fluctuations and consequent risk of intermittent side effects or breakthrough seizures: for carbamazepine and valproate, however, sustained-release formulations suitable for twice (and, sometimes, once) daily dosing have been developed.[53]

When seizures persist or relapse, compliance needs to be checked first, and the possibility of insufficient dosage, for example due to poor absorption or a drug interaction, should be considered. Monitoring serum drug levels can be of value in this process, particularly with phenytoin.[54,55] Because phenytoin exhibits nonlinear kinetics, small increments in dosage can result in disproportionately large increases in serum drug concentration with the attendant risk of toxicity. Decisions about need for dosage adjustments, in any case, should be made primarily on clinical grounds and not solely on the basis of plasma drug level measurements, since many patients exhibit their best response at blood concentrations below or above the optimal ranges quoted in the literature.[56-58] Measuring serum drug concentrations in an individual may be especially useful when there is an otherwise unexplained lack of efficacy, or when toxicity is suspected.

Treatment Strategies in Nonresponders

Poor compliance, misdiagnosis of seizures or epilepsy, inappropriate drug choice, inappropriate dosing, or the presence of a drug refractory form of epilepsy are the main causes for lack of response to the initially prescribed drug.[59] In a recent survey from a specialized epilepsy centre in Scotland, overall 47% of all patients with newly diagnosed epilepsy became seizure free on the first AED chosen by the treating physician.[60] If seizures continue at the highest tolerated dosage of the initially selected AED, the best strategy is to switch to an alternative monotherapy with a different drug.[2,59,62] Switching must be done carefully by adding the second drug at increasing dosages, and slowly discontinuing the initially prescribed agent. Adverse pharmacokinetic and pharmacodynamic interactions may be observed during the interval in which the two drugs are simultaneously given, but the advantage of a gradual discontinuation of the initial agent is that the danger of provoking withdrawal seizures can be minimized.[2]

In patients with difficult-to-treat epilepsies, at least two sequential monotherapies should be tried before embarking on a combination therapy regimen. The more AEDs are combined, the greater is the risk of interactions and side effects including teratogenicity. Monitoring of AED concentrations in plasma can be of value in guiding dosage adjustments when pharmacokinetic interactions are expected,[63] but drug concentration measurements in this situation should be interpreted flexibly because the optimal range of individual AEDs may be altered in the presence of comedication.

When polytherapy is indicated, it is generally preferable to combine AEDs with different side effect profiles, to minimize the risk of producing additive adverse effects.[64] Theoretically, it also makes sense to try to combine AEDs with different mechanisms of action, though the advantages of this strategy have not been adequately tested in formal studies.[65] There is no doubt that some AED combinations work better than others, for example valproate plus ethosuximide seems to be particularly effective in absence seizures refractory to either drug given alone,[66] and good results have also been reported with the combination of valproate and lamotrigine in a number of refractory seizure types.[67,68] The latter combination also has inherent economic advantages because valproate increases plasma lamotrigine concentration and reduces lamotrigine dose requirements, often resulting in reduced costs of therapy.[68]

Some patients do well on combination therapy, but there are also patients in whom addition of a second or third drug only produces an increased burden of side effects without appreciable improvement in seizure control.[65] In the latter case, restoration of monotherapy will lead to relief from side effects without deterioration of seizures.[21] Nonpharmacological approaches such as epilepsy surgery are not discussed in this chapter, but should be considered early in patients with drug resistant epilepsies.

Discontinuation of Pharmacological Treatment

Especially in children, where there is a higher proportion of self-remitting epilepsies and in whom seizure relapse entails less psychosocial consequences than in adults, patients who have been seizure free for at least two years should be considered as potential candidates for AED discontinuation.[69,70] If a decision to discontinue AED therapy is made, the drug(s) should be tapered down slowly and in small steps, the last step of withdrawal being often the most difficult. Obtaining EEG recordings during the taper phase may be valuable to identify reemergence of epileptiform activity before clinical seizures actually occur, but the overall prognostic value of these recordings remains controversial. Depending on the type of epilepsy and population, relapse rates after two years of seizure freedom vary from close to zero to over 90%. Information about the epilepsy syndrome provides the most valuable predictor of seizure relapse. Relapse rates are lowest (10% or less) in rolandic epilepsy, 5-25% in childhood absence epilepsy, 25-75% in cryptogenic or symptomatic partial epilepsies and 85-95% in juvenile myoclonic epilepsy.[3] Generally, the risk of relapses increases with increasing age, and is also higher when an underlying neurological disorder is present, when the interictal EEG is abnormal and when there was a long-lasting period of seizure activity before seizure freedom could be achieved. In counselling patients regarding the possibility of withdrawing AED therapy, the probability of relapse, the expected relief from side effects and the related psychosocial consequences need to be carefully discussed.

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Chapter 19

The Challenge Represented by Epilepsy Surgery in Developing Countries

André Palmini, Jaderson Costa da Costa and Jerome Engel, Jr.

Epilepsy, the most common neurologic disorder, affects approximately 1% of the world population with higher reported incidence rates in developing countries. The incidence of epilepsy in the developed world is around 50 new cases per 100,000 people per year whereas it is around 120 new cases per 100,000 people per year in the developing world.[1] Over four-fifth of the 50 million people with epilepsy are thought to be in developing countries.[2] Of the people with epilepsy about 30% are intractable to the presently available antiepileptic drugs (AEDs),[3] and about 80% of these patients live in developing countries.[2] Significant proportion of these patients may be candidates for epilepsy surgery. However, globally 85% of people with epilepsy are either inappropriately treated or not treated at all, most of them in developing countries.[4] Thus the likely treatment gap for patients with surgically remediable epilepsy are very high in developing countries and only few epilepsy surgeries are done in these countries.[5-8]

Surgically Remediable Syndromes

The concept of surgically remediable epilepsies refers to those epilepsy syndromes, which are highly refractory to AEDs, but respond extremely well to surgical treatment (Table 1).[9] Epilepsy surgeries can be cost-effective and cost saving with certain types of epilepsies, surgically remediable epilepsies. Fortunately, the preoperative workup and the surgical management of patients with many of these conditions can be performed without excessive technological sophistication, provided skilful personnel are available to identify, evaluate, and operate on these epilepsy syndromes.

Surgery for temporal lobe epilepsy, one of the most common surgically remediable epilepsy syndromes,[10] may not only control seizures but also prevent untimely death.[11-12] Of 11,680 operations for epilepsy reported by developed countries through 1990, 7766 (66%) were anterior temporal lobectomies or amygdalohippocampectomies performed for refractory temporal lobe epilepsies.[13] The diagnostic and therapeutic procedures required in these cases are technically least demanding. Satisfactory surgical results are much more dependent on the clinical skills of relevant specialists than on cutting-edge advances in neuroimaging or clinical neurophysiology. The most effective approach, therefore, would be to focus on patients with surgically remediable syndromes who can be identified, evaluated and operated on by a skilled team of professionals which should include epileptologists, neuroradiologists, neuropsychologists, and neurosurgeons, with a minimum of high technology-driven procedures. Epileptologists will need to confidently distinguish between simple and complicated refractory epilepsies, and recommend mesial temporal resections or neocortical lesionectomies on the basis of scalp EEG, clinical seizure semiology, magnetic resonance imaging (MRI), and neuropsychological

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Table 1. Surgically remediable epilepsies

Mesial temporal lobe epilepsy	
Benign neoplasms	
	Ganglioglioma
	Dysembryoplastic neuroepithelial tumor
	Low-grade astrocytoma
	Oligodendroglioma
Developmental lesions	
	Glioneuronal hamartoma
	Focal cortical dysplasias
	Hemimegalencephaly
	Sturge-Weber syndrome
	Tuberous sclerosis
Other focal lesions	
	Cavernous hemangioma and other vascular malformations
	Hemiconvulsions, hemiplegia, epilepsy (HHE) syndrome
	Congenital porencephalic cyst
	Atrophic scars
	Rasmussen's encephalitis

testing. In addition, there is the obvious need to optimize the allocation of limited technological resources. In practice, this means that potential candidates for epilepsy surgery must have access to MRI and video EEG monitoring, in countries where inequalities of medical care may tend to restrict availability of costly procedures to certain strata of the population.

Epilepsy Surgery Centers

The Need and the Challenge

The establishment of specialized epilepsy centers with surgery program in developing countries makes sense epidemiologically. A few specialized epilepsy centers could break the cycle of their intellectual and technological dependence on the industrialized world. This is a necessary first step to generate knowledge and begin a process of good quality training locally. Once these centers begin to produce good epileptologists, the 'set point' of the quality of care of epilepsy in that society will change favorably. Furthermore, when it becomes apparent that developing countries can generate credible original research in epilepsy, epileptologists from these regions will gain the confidence to create reliable and socially acceptable protocols to investigate and treat patients in a manner relevant to their environment. Cost-effective, high quality care, within the (realistically) available means of each society, can only be achieved by locally generated knowledge and experience. The establishment of such centers will allow access to surgical treatment for a significant number of patients with surgically remediable epilepsy syndromes.

The challenge is to reconcile the need for careful presurgical evaluation with the need to make epilepsy surgery widely available. To make epilepsy surgery more cost-effective and widely available to design simpler but effective strategies to evaluate patients for surgery in these countries. The best model will involve a creative partnership between specialists trained abroad and their local colleagues, to develop regional epilepsy surgery programs. The next step will be to train people locally, and legitimize the concept of regionally relevant approaches.

Ethical and Economic Issues

The most important ethical argument for epilepsy surgery in developing countries is the fact that most patients who will benefit from these procedures live in these poorer regions.[2] A treatment modality exists which can significantly alleviate the suffering of large numbers of people with refractory epileptic seizures; therefore, there is an ethical obligation for those involved in the care of these patients to pursue all possible avenues to make this treatment modality available where it is most needed. In developing countries, it is counterproductive to confuse the minimum with the ideal requirements for an epilepsy surgery program and, thereby, postpone the benefit for those who can be helped now. Well-trained personnel can do a qualified job without the latest, expensive technological advances.

The economic feasibility of surgical treatment in countries with limited resources is readily apparent. Data from Colombia show that epilepsy surgery can be performed at 5.5% of the cost of that in Zurich.[14] Countries like Brazil and India have reported a similar experience.[5-7] Epilepsy centers in developing countries should not be prevented from performing surgical treatment because they are not as well equipped as centers in developed countries, provided adequate expertise exists. Faced with the choice of (a) establishing an epilepsy surgery program with limited technological resources that must turn down the occasional temporal lobectomy or lesionectomy candidate with a more complicated presentation, but will help many other patients, or (b) not establishing the surgical program because technology to fully investigate the more complicated cases is not available or affordable, the more ethical approach would be to choose the first approach.

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It is important to consider the fact that AEDs are often unavailable, unaffordable, or irregularly distributed in the developing world (see Chapter 18). Eighty percent of the pharmaceutical market is focused on the 20% of persons with epilepsy living in developed countries.[15,16] It is clear that most of the governments in developing countries are not able to purchase and supply adequate amounts of AEDs to patients with epilepsy, and it is also a fact that most of their patients with epilepsy cannot afford to buy them. For those patients with medically refractory seizures - the ones taking more than one AED, and the ones in greatest need of regular supplies - the situation is even worse. To operate successfully on some of those with medically refractory epilepsy would have an enormous, far-reaching, impact on this aspect of medical care. The realistic goal to reduce or eliminate the need of AEDs in many patients should be critically considered in both the ethical and economic arguments for epilepsy surgery in developing countries. The view that one can never be sure whether patients are medically refractory because of the irregular supplies of AEDs, and therefore surgery should not be done, is, in our opinion, an excessively theoretical approach to a serious situation of real life suffering.

Quality of Life Issues

Because opportunities for education and work are considerably more limited in developing countries, the handicap imposed by uncontrolled epilepsy is almost certainly greater than in areas where schooling and employment are easier to obtain. Recent data have shown that about half the people unemployed before epilepsy surgery can find a job after operation, providing the patient is not mentally retarded and seizures are satisfactorily controlled by the procedure.[17] Psychological and social rehabilitation, however, is dependent on the preoperative educational and vocational status of the patients, indicating the need for an earlier and more aggressive

Table 2. Challenges to the development of epilepsy surgery in developing countries

*	Reconcile the need for careful assessment with increasing social pressure
*	Have epileptologists, neuropsychologists, and neur-osurgeons well trained
*	Optimize utilization of local resources
*	Espouse a critical view on the minimum required
*	Organize training programs
*	Build on the experience through a stepwise approach

approach to surgical intervention.[17-20] For nonwelfare states, losing a job, or not obtaining one in the first place, can be catastrophic for the lifetime of the individual. The data regarding these aspects is very limited from developing countries.

Epilepsy Surgery Program - Minimum Requirements

Minimum requirements depend on the types of medically refractory epileptic syndromes to be treated surgically in a given center. The ILAE working group in surgery suggested a two-tired structure for the surgical management of epilepsy.[21]The pragmatic approach would be, to focus as a first step on the surgical treatment of mesial temporal lobe epilepsy and certain types of neocortical lesional epilepsies. They form the largest proportion of surgically remediable epilepsies. A stepwise approach (Table 2) to more complex epileptic disorders would then be matched by an increase in the technological capabilities at selected regional and national centers.[21,22] The literature suggests that many candidates for temporal lobe surgery might be operated on with excellent results on the basis of interictal EEG epileptiform abnormalities, neuropsychology, and MRI.[23-28] When all are concordant for the same antero-basal temporal lobe region, surgery is usually successful, irrespective of the data provided by scalp ictal EEG. Presurgical evaluation without ictal EEG recordings, however, will demand even greater experience on the part of the diagnostic team, which is why 'skilled personnel' are an essential feature of the minimum requirements. In any event, a 16-channel EEG machine with a split-screen video system, plus 1.5T MRI and very good neuropsychology is all that is required to operate on many surgical candidates with mesial temporal lobe epilepsy (as well as certain types of neocortical lesional epilepsies and surgically remediable catastrophic epilepsies of infancy and early childhood). For the majority of poor countries we would propose that well trained and highly committed epileptologists, neuropsychologists, and surgeons can make do even without digital EEG. Thus, there is a clear challenge for specialized epileptologists in these countries: to develop realistic protocols, and to be open to continuously discuss the surgical results and the ways to improve presurgical and operative approaches.

The Porto Alegre Experience

The experience of the Porto Alegre Epilepsy Surgery Program demonstrates the above discussed concepts, During the first phase, in addition to clinical evaluation the presurgical protocol designed for the surgery program was based on 16-channel analogic video-EEG recording, 0.5 T MRI, and neuropsychology.[5] In the second phase, after the preoperative workup began to be performed with a 32- channel computerized video-EEG system with capabilities for intracranial recordings, 1.5 T MRI, and interictal and ictal single photon emission computerized tomography

(SPECT). In the first phase, from January 1992 to August 1993, 35 patients were operated, and in the second, from September 1993 to August 1996, 89 patients were evaluated and operated. This latter analysis allows for a minimum of 4 years of follow up.

Of the 35 patients evaluated and operated during the earlier period, 21 (60%) had temporal lobe epilepsy, 13 associated with MRI-identified hippocampal atrophy and 8 with slowly growing neoplasms or cavernous angiomas. The remaining 14 patients had extratemporal epilepsies characterized on the basis of semiology, ictal and interictal scalp EEG, and imaging all except one had MRI-identified lesions, sparing (n = 9) or encroaching upon (n = 4) eloquent (motor/language) cortex. The updated results of this earlier series shows that 27 patients (77%) are seizure free (Class I), 2 have only rare seizures (Class II) and the remaining 6 did not improve significantly and are in outcome Class IV (13). Before fully achieving a seizure free status, 5 of the 27 patients currently in outcome Class I had a few seizures over the years, which were resolved through either AED adjustments (2 patients had abruptly stopped their medications after a few years) or further resection of temporal lobe structures. In the end, all 21 patients with temporal lobe epilepsy were Classes I or II as were 8 of the 14 patients (57%) with extratemporal epilepsies.

The medication profile of this group deserves a closer analysis. Before operation, 14 of the 35 patients (40%) took 3 different types of AEDs, while after operation only 2 patients (6%) still needed 3 drugs. Of the other 21 patients (60%) were on 2 AEDs preoperatively, while at last follow up only 11 (31%) still needed 2 medications. While no patient was on monotherapy preoperatively, there are 6 patients now receiving only one AED. Furthermore, with a minimum of 7 years of postoperative follow up, 16 of the 35 patients (46%) are not taking any AEDs.

In comparison, of the 89 patients evaluated and operated between 1993 and 1996, after the technological upgrade, a similar proportion had temporal lobe epilepsy (52/89; 58%). Thirty-six of these had MRI-identified mesial temporal sclerosis (MTS), 13 had foreign tissue lesions in the temporal lobe, and 3 had normal MRI. Thirty-two of the 36 (88%) with MTS, 12 of the 13 (92%) with foreign tissue lesions, and none of the 3 with normal imaging are seizure free. Thus, 84% of patients with TLE in this series are Class I. Similar freedom from seizures was observed for 16 of 37 patients (43%) with extratemporal epilepsies operated during this period. As expected, the best results in this group were seen in those patients in whom an identified lesion was present in noneloquent cortex (9 of 14 [64%] seizure free), and progressively poorer results were observed in those in whom no lesion was present or the lesion involved eloquent cortex.

Therefore, results achieved with the less technologically advanced presurgical evaluation were by no means worse than those obtained later, with better diagnostic technology. Of course, a bias of patient selection may have occurred in the earlier series, but that is precisely the point: if patients are well selected, very good results can be obtained even with nonsophisticated technology. The data reviewed above show that advanced technology has not improved our ability to effectively operate on patients with surgically remediable syndromes. Rather, it has increased the number of patients who are now candidates for surgery. Although this is a desirable goal, it is not necessary where there are more than enough patients with surgically remediable syndromes to keep an epilepsy surgery program fully occupied well into the foreseeable future.

Experience in Other Developing Countries

Several centers in developing countries started epilepsy surgery programs with encouraging results.[14,29-34] The experience in Colombia has been reviewed elsewhere in this book (Chapter 23). In India at Sree Chitra Tirunal Institute of Medical Sciences and Technology, Tiruvananthapuram, 394 epilepsy surgeries were performed over a period of seven years, 370 of them were anterior temporal lobectomy with amygdalohippocampectomy (ATL) for refractory temporal lobe epilepsy.[7] Patients were selected for surgery based on noninvasive protocol comprising history, interictal scalp EEG, MRI, ictal video-scalp EEG, and neuropsychological data.[6] Among the 213 patients, who completed two or more years of post ATL follow-up, 166 (77.9%) were practically seizure free.[8] The out of pocket payment for ATL (including presurgical evaluation) in Indian set-up in this center is Indian National Rupees (INR) 50,000 (US$ 1,200). The direct total cost for caring a patient with intractable temporal lobe epilepsy from age 26 to 60 years has been calculated to be INR 200,000 (US$ 5,000).[6] However these costs do not account for the various in built subsidies of the charging systems of the institute The experience in the other center, All India Institute of Medical Sciences, New Delhi, using similar noninvasive presurgical protocol has shown similar encouraging results.[30]

In Chile of the 17 patients with intractable temporal lobe epilepsy whom had ATL based on data derived from noninvasive studies 15 patients were seizure free at the mean follow-up period of 29.1 months. The histopathological findings showed a low-grade tumor in six patients, MTS in five, neuronal migration disorder in four, and cavernous angioma in two patients. The total cost, including presurgical evaluation and surgery, was equivalent to US$ 5,020.[34]

Surgical Treatment of Epilepsy in Developing Countries—The Feature

Despite all the difficulties and the challenges that still need to be faced by those who wish to perform epilepsy surgery in developing countries, the last few years have already indicated that a transformation is in progress. Successful epilepsy surgery is already a reality in several developing countries, and there is a need to build upon this recent experience. Based on the papers presented at the 23rd International Epilepsy Congress in Prague in September 1999, there were 20 epilepsy surgery centers from Latin American, African, and Asian countries other than Japan, presenting surgical material (in addition to 14 centers from Eastern European countries).[35] This compared to 45 centers from developed countries presenting surgical material at the same meeting. The future, therefore, looks promising. In some countries, epilepsy surgery programs have promoted a virtual revolution in epileptology, leading to a significant increase in research and educational programs as well. In Brazil and in India, this effort resulted in two comprehensive textbooks,[5,36] which have set a new level of medical, educational and scientific standards in these highly populated countries.

Some of the challenges for those committed to the establishment of epilepsy surgery centers in developing countries are: (a) to optimize the use of presurgical investigative tools already available in each center; (b) to carefully select cost-effective technological advances in which to invest the limited budget of these centers; and (c) to encourage appropriate training of personnel.

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Chapter 20

Treatment of Epilepsy in India: Traditional Systems

Manjari Tripathi, Moolchand Maheshwari and Satish Jain

Traditional medicine may be defined as the sum of all knowledge and practices used in the prevention, diagnosis, and therapy of physical or mental illnesses and relying exclusively on practical experience and observations handed down from generation to generation, whether orally or written.[1] These systems of medicine encompass a large array of different systems and therapies. In India these include *ayurveda*, yoga, meditation, homeopathy, *siddha*, *unani,* and spiritual therapy. The utilization of these systems in a vast country like India probably far surpasses the availability, acceptability and affordability of allopathic medicine. Majority of the Indian population live in the rural and semi urban areas. The hold of these systems is much more in these settings and it takes little to convince this population to practice these systems. In a recent survey on practice of epilepsy in Kerala, a state with high literacy and health awareness, 27% of the respondents thought epilepsy is a form of insanity and 31% felt that epilepsy is a hereditary disorder. As many as 64% of respondents felt, that *ayurvedic* therapy is beneficial for epilepsy.[2] This is also true with meso-American culture where traditional indigenous medicine involves herbal remedies, rituals, spiritual cures or combination of all these. In developing countries, more than 80% of patients with epilepsy use only these remedies.[3] Patients who chose alternative medicine as their first level of care are probably influenced to do so by relatives, friends or neighbors. Probably socio-cultural factors may also influence the choice of a particular health facility. This preference for traditional medicine has been documented to cause delay of several years before many patients reach centers where they can be better treated.[4] This chapter will discuss some of the alternative systems of medicine practiced in India.

Ayurveda and Epilepsy

Atharveda a vedic text, describes *ayurveda* ('the science of life') as a philosophy of long and healthy living. *Ayurveda* emphasizes on prevention rather than treatment of disease. Healthy living implies that the *tridoshas* of *vata* (physical movement and sensory perceptions), *kapha* (moisture in body tissues), and *pitta* (metabolism and digestive) processes stay in harmony with each other and with the five basic elements of the universe namely water, earth, fire, air and ether. Any imbalance in this system incapacitates the otherwise strong human being.[5] In *ayurveda* epilepsy is designated as *apasmara, apa* meaning negation or loss of, and *smara* meaning recollection or consciousness. The ancient Indian texts by Charaka and Sushruta, record the etiopathogenesis, symptomatology, classification and management of *apasmar* around 1000 BC. This was much before the western documentation of epilepsy by Hippocrates around 400 BC.[6,7]

Epilepsy in the Tropics, edited by J.M.K. Murthy and Nimal Senanayake.

The treatise on treatment in the Charaka-Samhita mentions epilepsy to be caused by an imbalance "which the wise physicians treat the curable ones cautiously with strong evacuative and pacificatory measures". In this system of medicine when the presumed cause is thought to be an exogenous factor in addition to a disturbance of a *dosha*, "the physician prescribes a general treatment to alleviate the exogenous cause". Treatment is directed at correcting the whole body, physical, mental and spiritual and not just a symptom. Care is also taken while trying to pacify one disorder (epilepsy), no new disorder occurs due to the therapeutic intervention (side effect). The physician is directed as a first step to "awaken the heart" (waking the patient from unconsciousness), by clearing the *dosha*s that block the channels of the mind. That is the *vatika* (disturbance of *vata*) is treated with enema, the *pattika* with purgation, the *kaphaja* with emesis. The *sannipatika* (a combination of the above) remains the most difficult to treat.[8] Different plant parts - root, bark, stem, leaves, flowers and seeds have been advocated for therapy.[9,10] Blood letting, from the veins of temples, surprisingly a drastic measure, has been mentioned for therapy as first-aid measures. An unusual prescription consists of fermented liquor prepared from half digested contents of pig's stomach, the pig having been previously fed with a specially prepared diet of boiled rice and milky juice of the *bhagri* plant (*Clerodendron siphonanthus*) after a prolonged period of fasting. The contents of the pig's stomach are taken out surgically, dried and powdered and suspended in an aqueous decoction of the plant. Fermentation is induced in this decoction by adding sediments of wine and maturing it to a specific color and consistency.[11] Another relatively benign preparation described in Charaka is *mahapancagvgaghrt*a. Blends of local formulations such as *pancamulas* and *triphala*, both types of *haridra*, *kutaja* bark, *saptaparna*, *apamarga nilini*, *katurohini*, *aragvadha*, *phalgu* (root), *pusharamula*, and *duralabha* are used. Eighty grams of each is boiled with 10.24 liters water until it is reduced to one-fourth. Ten grams each of *bhargi, patha, triaktu, trivrt, nicula, gajapippali, adhaki, murva, danti, kiratatikta, citraka*, two types of *sariva, rohini, bhutika* and *madayantika*, should be powdered and added as paste. To this (decoction and paste) 640gm of ghee is added and the mixture is cooked with equal quantity of cow dung juice, sour curd, milk, and urine. This is like ambrosia and is efficacious in epilepsy and should be taken daily.

There are several similar formulations described in *chikitsasthanam*. Epilepsy is considered as chronic disorder and difficult to treat and medicines should be used regularly. Hence one should treat it mostly with *rasayana* measures. Patients with epilepsy should also be kept aloof from risky situations like water, fire, tree and hills because they take away the life immediately. One should use oil and garlic, *satavari* with milk, *brahmi* juice, *kustha* juice or *vaca* with honey. Other authors state in what is taken as a cleansing concept of the disorder - after the patient was cleansed by all means; drug formulations to alleviate epilepsy are administered. Several formulations, including the amount of each ingredient and method of preparation, are included *gandhaka* (sulfur), aged ghee (butterfat), and many herbs such as *Achyranthes aspena*, *Holanthena antidysenterica, Alstona scholaris,* and *Ficus carica*. Blends of herbal formations such as *Pancamula* and *Triphala* were also named. Pharmaceutical processes and preparations involving fermenting, extracting, preparing inhalable substances, filtrating, heating in a closed cavity, purifying, and pill making are described.[12,13] General measures to correct exogenous factors such as proper hygiene and balanced diet are recommended. In a recent study, an *ayurvedic* drug for epilepsy (*apasmara*), *ayush 56* has not been shown to have any significant effect on the

seizure frequency.[14] Other drugs *ayushman 12, 14, dhanvantaram 101* and *ayushman 18* have also been studied. Preliminary studies indicated that the Ayurvedic drugs are marginally effective in resistant epilepsy today. Commonly used plants in epilepsy are *Bramhi (Indian pennywort), satawari (Asparagus recemosus), vaca* (sweet flag), *mulethi* (*Glycyrrhiza alba*), *agastya* leaves (*Sesabania gtrandiflora*), garlic ginger, asafetida, pumpkin, *Uncaria rhycophylla*, and *Gastrodia elata*. These substances of are also used in other disorders suggesting a very broad spectrum of action. However, in the era where evidence based medicine is the gold standard, to date there are not many scientifically based studies on the use of *ayurvedic* medicine in epilepsy. Widespread use of these drugs without scientific evidence may be hazardous.[15] Also exists the menace of practicing traditional medicine but prescribing anticonvulsants in guise of *ayurvedic* preparations, which results in complex drug interactions and side effects.

Ayurveda or the science of healthy living steers clear of superstitions and the concept of supernatural beliefs on epilepsy. It is remarkable that this ancient system of medicine has so closely evaluated and categorized this disorder- resembling what we know of it now.[16,17] Therapeutically much needs to be done but it would probably do to say that we have lagged in our research rather than that the science being primitive.

Yoga Meditation and Epilepsy

Stress is considered an important precipitating factor for seizures. Yoga induces relaxation and reduces stress. The attractive feature of yoga as a therapeutic option for epilepsy is its nonpharmacological nature, minimal side effects and international acceptance. There is a mystique that surrounds the practice of yoga which is derived from the word *yug* meaning 'to join or bind'/ 'to attach' i.e., yoking of all powers of body, mind and soul together, in other words a balanced mind-brain system. It is a system of physical exercises, *asanas*, the practice of which maintains a healthy body, cures various diseases, and also leads to the achievement of some remarkable feats of endurance and control of one's autonomic activities.[18,19] The fundamental teachings of yoga are based on philosophical and spiritual principals. Yoga consists of external and internal meditative practice. Yoga probably works as a complementary and cotherapy measure in association with medicinal therapy. It is a must that this therapy is carried out only with adequate work plan and related knowledge. The components of therapy are: 1) *Shatkriyas* - which are effective eliminative and purification measures, 2) *Asana* - which help relax and tone the muscles and give a message to the internal organs. 3) *Pranayama* - which regulates the treating and inflow of *prana*, 4) Meditation - which brings about calm and peace and purifies the emotion and upgrades the internal spirit to heal. When a combination of these is performed in a planned manner with a specific purpose these prove to be much more effective. There have been limited documented studies in the scientific literature where meditation techniques have actually altered the seizure frequency and cumulative duration as seen as enhanced intensities of the sensor motor rhythms (SMR, 12-16Hz) in patients with epilepsy which increments during the continued practice of meditation.[20] Yoga probably contributes by producing a pro-neural regulatory (normalization) effect on brain rhythms. Other mechanisms could be mediation through the parasympathetic-adrenocortical axis, counteracting and balancing inter hemispheric activity, improvement of psycho physiological variables such as attention, deautomatization etc.[21] The anti-seizure effect of meditation may be by enhancing

the alpha activity or by inhibiting the low frequency high amplitude discharges (spikes, slow waves and interictal showing of EEG) or by both.[22] The effect of *sahaja* yoga was studied on the seizure control and EEG changes, on stress, and also on auditory evoked potentials (AEP) and visual contrast sensitivity (VCS) in patients with epilepsy. In patients practicing *sahaja* yoga there was a reduction in the seizure frequency by 86% at six months.[22] Patients who practiced the yoga experienced less stress and probably this effect on stress could explain the clinical improvement.[23] This yogic meditation had also some effect on the AEP and VCS.[24] Recently Ramaratnam and Sridharan[25] did a meta-analysis of all the randomized controlled trials and the controlled clinical trials of effect of yoga in patents with epilepsy was treatment of epilepsy with yoga was done. For inclusions studies with outcome measures like seizure freedom or 50% reduction in the seizure frequency or seizure duration and also studies with intention to treat analysis were considered. Only one study fulfilled the inclusion criteria. The meta-analysis concluded that as of now the number of studies done in a systematic manner are limited and further scientific evidence based trials are much needed to establish the efficacy of yoga as a treatment for epilepsy. Various other techniques like self-control-psychological approach,[26,27] behavior modification,[28] biofeedback,[29] and relaxation[30] have been tried. The common denominator of all these procedures seems to be an anxiety alleviating or relaxation-inducing factor, with little or no specific adherent procedures. These procedures need rigorous clinical trials before being vouched as definitive measures as adjuvant therapy in epilepsy. However, a new kind of polytherapy can be envisaged consisting of a combination of pharmacological and self control therapy.

Other Systems

The *unani* system of medicine came to India with the Islamic religion.[32] As the native medicine, *Ayurveda* is highly advanced the new system was not easily accepted. The physicians who practice *unani* are known as *Hakims*. Not much is known about the use of this system for treatment of epilepsy in a scientific way. Homeopathy, *siddha*, and acupressure are evolved from different areas of the world and are based on different principles. These again lack evidence of scientific trials endorsing their usefulness.

Conclusions

An atmosphere of fear, shame and mysticism surrounds epilepsy even in the present day. Traditionally, epilepsy was presumed to be possession by spirits by some systems and by abnormal brain function (hyperactivity) by others. The mythical concept of the disease is the basis of origin of traditional medicine in epilepsy. Various nonpharmacological interventional techniques may help in difficult to treat cases. However, more trials and validation of techniques of traditional based systems is required to scientifically prove them to be effective and an adjuvant in the management of epilepsy. As of now the psychological benefit obtained from the traditional therapeutic model has made this necessary and complementary to western-style treatment. The widespread use of these systems also suggests that alternative-medicine, cannot be considered irrelevant in management of epilepsy in India.

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Chapter 21

Treatment of Epilepsy in Africa: Traditional Systems

Amadou Gallo Diop and Mamadou Habib Thiam

Conditions and Management of Epilepsy in Africa

It is now well recognized that despite the availability of efficient means of treatment for epilepsy, the majority of people suffering from this disorder in Africa and many other developing countries are not treated. Also a large proportion of the population, who can geographically and financially reach the modern medical health care structures, are discontinually treated. It is either because their poverty does not allow them to afford the cheapest drugs or they have not been well informed about the necessity of a long-term treatment. Treatment gap, the difference between the number of people with active epilepsy and the number whose seizures are being appropriately treated in a given population at a given point of time, expressed as percentage, is highly prevalent in developing countries.[1] It is estimated that about 80% of people with active epilepsy in developing countries are not appropriately being treated with antiepileptic drugs (AEDs). In a prospective study in Ethiopia, of the 139 people with previously undiagnosed epilepsy, only 39% of patients were receiving AEDs (mainly phenobarbital), 19% were using only traditional treatments, and 42% were not on any treatment, either modern medicine or traditional treatment.[2]

In most of the African countries, people with epilepsy and their families often move from one healer to another to their complete dissatisfaction. Only then some of them may seek help from modern medical center and "test" the modern medicine. This preference to traditional medicine can cause delay of several years, 2 to 20 years, before they seek modern medicine. "*As it did not work in the African side, let us try the white men's medicine"* is the often heard phrase in Africa. When the patients reach centers where they can be better treated, they and their families realize the huge economic disparity between the two systems of medicine. The treatment of epilepsy in Africa is tightly related to the variable human and technical resources.[3]

Procedures

Traditional treatment of epilepsy practiced in Africa has socio-cultural basis. It generally utilizes a holistic approach. Classically traditional healers proceed to a diagnostic strategy before therapeutic intervention. Basically traditional healer's recommendations are based on their interpretation of the phenomena of epilepsy and their understanding of the presumed "mechanisms".

The diagnosis is based on the history of the illness and "complementary exploration" via search with cowries, sand, stones, animal sacrifices, interpretation of dreams, contact and dialogue with supernatural personages and forces. The treatment

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basically utilizes the different life elements: animal, vegetable, mineral and liquid. Following indications, these natural means will be utilized, transformed or forbidden, depending on their benefit or their disadvantages for the patient. If they are diagnosed as positive forces for the patient, they will be worn in different forms such as amulets for example, eaten, utilized for bath, drink, or breathed. Supernatural forces will be "invited" during special mystical celebrations, to visit the patient if they are protective, or withdrawn from his body and soul, if they are negative. These celebrations are public and crowded, accompanied with religious songs and dances. The themes of these evocations are generally dedicated towards the patient's family and ancestors. The blood got from sacrificed animals is often needed to satisfy evils or to calm the devils (named *cheytan* or *jiin*).[4]

In the cohort followed in Ethiopia, 17% were receiving herbs; 7.9% holy water; 19% emulates and 0.7% made animals sacrifices.[2] There were also many dietary restrictions, such as fresh meat, eggs, some type of vegetables, alcoholic drinks. Some periods were considered bad and potentially provocative for seizure. They included the full moon, the crepuscular, and the early afternoon. Some of these prescriptions in Africa are very similar to those described in Inca, Indians and Aztecs.[5]

As in modern medicine, traditional healers also specialize in certain domains of action and treatment. Everyone utilizes specific means for diagnosis and treatment. Often these means are derived either from the African culture or Holy texts, Bible or Quran. The honest healers are able to direct their patient to medical doctors at the very early stage, if they are convinced that the case is not relevant for their abilities. Others, for financial reasons, persist in saying to the family to only follow their prescription and not to mix with "western medicines". The family expenses are often higher than the annual cost of modern AEDs. Some traditional healers are reticent to manage people with epilepsy because they are afraid to vehicle that "contagious epilepsy" into their own family or next descendants.[6] People with epilepsy who have not been directed to modern medicine, often resign to their fate and consequently "*accept the decisions of God*".

Management of the Socio-Familial Environment

In Africa, epilepsy is often equated with mental illness. Similar attitude was found in the study in a province with high literacy and high human developmental indices, in south India.[7] In this study 27% of respondents thought epilepsy is a form of insanity. The stigma and discrimination associated with epilepsy affects several domains of affected individual's life: familial, social and economic.[8-10] Epilepsy is considered as contagious disease and people with epilepsy are often not helped during seizures. People are afraid of contamination by the sweat, urine, saliva and breath. Wind is often evoked as a factor. The whirlwind is considered the way the devil enters the body, especially the body of pregnant woman whose next newborn could be affected by this epileptogenic factor.[11] This is one of the local cultural explanations for newborn and infants' epilepsy. All these negative attitudes have a profound effect on the quality of life of the affected individual and also on the disease burden. In Africa, management of a chronic illness like epilepsy is not entirely in the domain of the affected individuals or the family. Community gets involved in the treatment. In most of the African societies family and community support is very high. Family and community members are often very much concerned and share the good and bad of the disease. For example, as a part of treatment the family members and/or members of some specific groups of the community will share the meal prepared

with the sacrificed animal. These rituals are the ways to atone the angry spirits and/or ancestors. Any health initiative in developing countries should consider all these aspects and involve the community and social groups.[6,11,12]

Advantages and Dangers of Traditional Medicine

Some means of the traditional treatment prescribed by the healers could be dangerous to the individual as well as to public health in general. For instance, dietary restrictions prescribed could lead to nutritional deficiency. Furthermore, certain preparations and/or the dosages used may be very toxic. Many things remain unknown about the interactions between the plants used and modern medication. This assertion is available for the large part of patients who consult both modern and traditional medicines. But it is very important not to oppose these attitudes and choices. People with epilepsy in Africa need the psychological security given by the traditional healer with his cultural interpretation of the disorder.[12]

The modern treatment even when efficient does not seem to be sufficient for the patient. Furthermore, most of the doctors trained in modern medicine may not spend enough time in talking to the patient taking into account the patient's psychology and cultural background. This aspect is well illustrated by the case reported by Martino et al[8] from Senegal. A young lady was presumed to be "oppressed" by the ancestral spirits and her episodic behavioral phenomena was attributed to the ancestral spirits. This went on for nearly 18 years, only when electroencephalographic recording revealed the epileptic nature of the behavior. She became seizure free with phenobarbital. However, she remained presenting a persistent delirium with the same initial theme. In such patients combined approach with both modern and traditional medicine is likely to achieve complete mental and physical health. Use of both modern medicine and traditional medicine has also been reported in many other tribes such as the *Bamilekes* in Cameroon.[13] The knowledge of the cultural background of people with epilepsy in Africa is essential for comprehensive care of the patient. This mysterious disease, which is sudden, severe and unpredictable, leading to burns, drowning, death, is a leading cause of personal and collective psychodrama. The psychological tension associated with epileptic event is a burden for the individual, the family and the group. It is often better managed by the traditional healers than the modern doctors, even if these practitioners share the same cultural background. The time and quality of listening for the patient and relatives are generally better in the mysterious traditional healers' huts than in the crowded modern hospitals. This factor could constitute a great advantage to consider, especially in psychogenic seizures. This approach also avoids unnecessary long-term drug therapy for patients with psychogenic seizures.

Conclusion

In Africa, epilepsy is not considered as a common disease. Epilepsy leads to stigmatization, rejection, and discrimination in several domains of the affected individual. Most of it is based on cultural beliefs. The causality of these attitudes and cultural beliefs is the quality of life of people with epilepsy. The major problem is lack of adequate knowledge traditional medicine and absence of bridge between the traditional and modern worlds. The patient is culturally limited to open his opportunities to modern sector. Preference to traditional medicine cause a delay of several years, 2 to 20 years before people with epilepsy approach the doctors trained in modern medicine. Even then, it is not in the interest of patient with epilepsy and

the family to oppose the practice of either system. While seizure remission can be achieved by antiepileptic drug treatment, traditional healers with knowledge of the cultural background of the patient can better manage the problems related to psychosocial issues. It is useful for modern professionals to respect these capabilities and encourage people to take the time to realize the efforts and benefits of the extraordinary development of modern epilepsy treatments made within the last few years.

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Chapter 22

Antiepileptic Drug Prescription and Economic Burden

J.M.K. Murthy

Epilepsy, one of the most common neurologic disorders, affects approximately 1% of the world population. Over four-fifth of the 50 million people with epilepsy are thought to be in developing countries.[1] Epilepsy care varies widely from country to country and also from one region to another within the country. In developed countries with well-structured health care and reimbursement systems, antiepileptic drug (AED) prescription is evidence-based, whereas in developing countries cultural attitudes, a lack of prioritisation, poor health care infrastructure, and inadequate supplies of AEDs all conspire to hinder appropriate treatment.[1]

Natural History of Epilepsy

Conventional AEDs allow achieving complete seizure control in up to two thirds of unselected population. Except in certain types of childhood epileptic syndromes, in most forms of epilepsy there is no good evidence to suggest that the currently available conventional AEDs will influence the natural history of the disease.[2] Studies from the developing countries have also confirmed, that the natural history of untreated epilepsy is not influenced by late institution of drug treatment.[3-5]

Treatment Gap

Treatment gap, the difference between the number of people with active epilepsy and the number whose seizures are being appropriately treated in a given population at a given point of time, expressed as percentage, is alarmingly high in developing countries.[6] Globally 85% of people with epilepsy are either inappropriately treated or not treated at all, most of them in developing countries.[6-9] In Ecuador, 85% of people with active epilepsy were not and 71% of them had never taken AEDs.[9] Some studies have reported differences in treatment gap between urban and rural areas. In the studies from rural India, 74 to 78% of patients with epilepsy were not receiving AEDs on the prevalence assessment day and it was 17% in the urban population.[10] The reasons for this wide treatment gap are manifold and include difficulties in access to medical care, economic constraints, distribution of drugs, factors related to local culture and tradition, and lack of prioritisation.[6]

Consequences of Untreated Epilepsy

The consequences of untreated epilepsy extend far beyond social issues. Untreated epilepsy is associated with productive losses from unemployment, decreased educational attainment, and increased mortality among other factors. Unemployment represents the largest proportion of these costs. Estimated total disability adjusted-life-years (DALY) for epilepsy in developed countries have been 7,100.

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Comparable data from developing countries are lacking. Years-lived-with-disability (YLDs) from epilepsy, a measure of duration of disability caused by disease, were high in developing countries when compared to developed countries and ranged between 593000-1,438,000 years.[11] Indirect costs related to productivity loss are enormous. In the UK study indirect costs accounted for approximately 70% of the total costs.[12] There is no data on this in developing countries.

Seizure-related death and sudden unexpected death in epilepsy (SUDEP) are common in people with recurrent seizures. In the year 1999, the estimated epilepsy deaths in developing countries were 1,025,000, whereas 127,000 deaths occurred in developed countries.[13]

Perception of Epilepsy

Studies of public perception of epilepsy from the developed world show an emergence of positive attitude towards epilepsy. When compared to this, epilepsy still continues to be a highly stigmatising disease in most developing countries (see Chapter 5). The negative attitudes of the highly literate population of Kerala, south India,[14] towards epilepsy were not much different from the less literate Chinese[15] population. This negative attitude may be a major factor why in many developing countries epilepsy is managed according to ethnic and cultural beliefs, leading to application of esoteric treatments and indigenous medication.

Studies from some of the developing countries suggest that significant number of patients with epilepsy receive traditional therapy even when access to medical services is readily available.[16,17] Folk medicine, provided by spiritual healers, tends to come into play when self-treatment according to family traditions (popular practice) is ineffective. This preference for traditional medicine has been documented to cause delay of several years before many patients reach centers where they can be better treated.[17] According to information collected from the national chapters of the International League Against Epilepsy in eight Latin American countries,[18] up to one half of all epilepsy patients receiving AEDs have had or are having concomitant alternative treatments. One of the reasons of pharmacoresistance is cultural beliefs and is linked with the absence of notion of chronic disease necessitating long and regular treatment in most of traditional societies.[19]

Physician Demographics

In developing countries patient with epilepsy is often cared for by the primary care physicians with least experience with epilepsy. The ideal neurologist-to-population ratio is 1 per 100, 000[20] and this ratio is not optimal in developing countries.[6] In sub Saharan Africa, there is one neurologist for four million people and in India there is one neurologist for 2.44 million people. Most of the specialists, principally work in the urban areas.[16,17,21]

Care Settings

In developing countries extremely limited medical resources exist to address the needs of epilepsy patients, particularly in rural areas.[6,22] When compared to well-structured health care and reimbursement systems in developed countries, in developing countries the loci of health care delivery vary widely. In a developing capitalist economy like Honduras, there is little government-sponsored health. In a country like India with a mixed economy, there is both government-sponsored health as well as well developed private health care system. In most countries a mix is found.[23] Loci of health care delivery include elite private hospitals, university

centers, individual practitioners, single speciality groups, polyclinics, multi-speciality clinics, and government-sponsored hospital based care.[24] In addition, particularly in rural areas, different levels of healing activities such as popular and folk-based practices coexist with professional medicine. Availability of investigative facilities, EEG and neuroimaging instruments may be severely restricted, particularly in rural areas.[8,16,17,22,25]

Antiepileptic Drug Therapy in Developing Countries

Antiepileptic Drug Availability

Unavailability and the lack of sustained supply of AEDs are probably the most important obstacles to the effective primary care of epilepsy in developing countries. Further more availability of a drug is not a guarantee for its quality.[6] Study conducted by ILAE in 35 developing countries between 1979 and 1983 concluded that the availability of AEDs is limited to less expensive, such as phenobarbital, conventional AEDs.[26] The scenario since then has changed to some extent; today the availability and distribution of conventional AEDs appears to have improved in most developing countries.[6] However, phenobarbital still is the only available drug in many sub Saharan African countries.[23,27] Newer AEDs have also been introduced into the market in certain countries.[6,27,28] However, in most developing countries the market is still oriented towards comparatively cheaper drugs. In Latin America the market share of barbiturates and phenytoin remains high, and their absolute sales are increasing at a faster pace than that of the more expensive drugs.[23]

Prescription Patterns

There is wide variability in therapeutic practices between and within developing countries. Drug choice is often largely dependent on the experience of the individual primary care physician. In most of the Mediterranean countries carbamazepine and valproate are preferred drugs.[29] Phenobarbital is the most frequently prescribed drug in sub Saharan Africa.[23] In French-speaking Africa, phenobarbital is prescribed in 65-85% of treated cases. In English speaking countries, phenytoin is also frequently prescribed drug.[6] In India phenytoin is the frequently used AED.[30,31]

Dosage of AEDs prescribed by the primary care physician may be suboptimal. In one study in northern India the dose was inappropriate in 49% of patients[30] and in the other study in southern India majority of patients received less than one Defined Daily Dose (DDD).[28] A popular practice in some developing countries involves combining low doses of various medicines based on the assumption that this leads to therapeutic synergism, a strategy that has not been proven to be successful in epilepsy. In a recent survey in south India of patients attending tertiary care epilepsy centre, among patients receiving polypharmacy at entry, in 94.5% of patients the ratio between Prescribed Daily Dose (PDD) and DDD was < 1.0 per day.[28]

There is unnecessary reliance on excessive polypharmacy. In a survey in south India in a tertiary hospital 58% of patients were receiving polypharmacy at entry and at last follow-up only 23% of subjects needed more than one AED.[28] In our survey 36% of prescriptions by primary care physician had more than one AED.[31]

AED Prescription – Appropriateness

In developing countries primary care physician is not well equipped with the knowledge about the classification of seizures, epilepsies, epilepsy syndromes and

specific efficacy of various AEDs. Failure to define properly the epilepsy or epilepsy syndrome can result in inappropriate AED selection. In a study in north India the choice of AED was wrong in 32% of patients.[30] The typical example in this case is juvenile myoclonic epilepsy (JME).[32] In our study, of the 61 patients with JME only 8 (13%) were receiving valproate at the time of registration.[32]

Antiepileptic Drug Therapy-Community-Based Studies

In the Nakuru, Ecuador, and Yelandur, studies treatment was carried out by health visitors and monitored by local doctors and/or specialists. Patients were treated with simple drug protocols. Most patients had several years of delay before starting appropriate therapy for epilepsy. All the three studies showed that in rural areas of less developed countries epilepsy control can be practical and effective with existing resources.[3,4,33] In these studies phenobarbital has been found to be the most cost effective drug protocol for partial or generalized tonic-clonic seizures. A recent randomized study in India had shown its acceptability as a treatment of choice even in children.[34]

Antiepileptic Drug Prescription: Suggested Recommendations for Developing Countries

Phenobarbital is still recommended by World Health Organization and the Commission on Tropical Diseases of the ILAE[23] as a reasonable first-line drug for the treatment of partial and generalized tonic-clonic seizures in the developing countries because of its low price. South African Epilepsy Working Group's[35] recommendations are similar to the treatment practices in developed countries.

In emerging countries cost is one issue, which clearly determines AED selection. Because of this cost differential, it seems reasonable to recommend one of the traditional medications as first line therapy. Phenobarbital seems to be the most cost-effective drug protocol particularly for partial and generalized tonic-clonic seizures.[33,34,36] Phenytoin may be a preferable cheap alternative. However, cost is of only limited interest unless related to outcome. There are no studies that have looked at the total medical costs and outcome differences of prescribing various conventional drugs. Drug therapy should not adversely affect the quality of life. In developing countries the appropriate choice of drug in an individual patient is a balance of efficacy, tolerability, and cost and should be tailored to the individual's affordability. Also in developing countries, the low socio-economic conditions of patients, which limit the choice of the most adapted drug in each case, is one of the important reasons of the pharmacoresistance.[19]

Economic Burden

Epilepsy represents a significant proportion of the treatable burden of disease. Developing countries carry more than 90% of financial burden of epilepsy.[37,38] But developing world with population five times the size of the developed world has at its disposal only 25% of the global total Gross Domestic Product (GDP) and 5% of the global per capita GDP.[39-41]

Estimated per patient lifetime costs, including productive losses, are enormous.[12,42] The per capita estimates of the costs of epilepsy in developed countries vary greatly from country to country reflecting partly differences in the list of cost components included in the direct cost estimations. The proportion of national health care expenditure on epilepsy estimated from studies performed from the societal perspective shows a range of 0.12-1.12% (percent of national expenditure on health, in

thousand 1996 US$) or 0.12-1.05% (percent of national expenditure on health converted to Gross Domestic Product Purchasing Power Parity - GDP PPPs) depending on the type of the conversion factor.[43] International comparisons between national cost-of-illness estimates should be interpreted with caution. The wide variations suggest that prices do not reflect the true cost of providing some of the aspects of epilepsy treatment.[44]

There are not many studies of estimates of costs of epilepsy in developing countries. Only direct costs of treatment can be reliably assessed. Any estimation of indirect costs will have significant limitations, mainly because of methodological issues. The calculated cost for chronic drug treatment of epilepsy is ~1-2% of the average individual Gross National Productivity (GNP).[23] In the study in Indonesia, the estimated total expenditure, for a patient with epilepsy per year, was US$ 303.75.This includes medication costs, productive losses, and mortality losses.[45] A cost-of-illness study performed on a retrospective cohort of medically treated patients form a regional hospital in Hong Kong estimated direct costs at US$ 0.98 million and indirect cost at US$ 1.32 million.[46] In this study lost productivity was used as a proxy for estimating the indirect costs. A recent cross-sectional study from India estimated the economic burden, due to epilepsy to the nation would be to the tune of US$ 1.7 billion. The proportion of national health care expenditure on epilepsy would be 0.5% of GDP. The calculated costs included only some of the indirect costs.[47] These calculations were made on the data available for 285 patients seen in six of the university or tertiary care hospitals. The other limiting aspects of this study were the heterogeneous nature of the patient population and referral pattern. Cost of managing a patient of epilepsy, in addition to other factors, is influenced by modality of referral to the center for epilepsy.[48] Recently Krishnan et al[49] studied the cost of epilepsy in patients attending a secondary-level hospital in India. The average annual cost of outpatient treatment of epilepsy was found to be US$ 47 per patient and the annual cost incurred in emergency and inpatient management was estimated at US$ 810.50. The total annual treatment cost for patients attending the hospital was US$ 11,470. The annual productivity loss for the same patients estimated at US$ 20,475. Applying these to the 5 million epilepsy patients in India, it comes to about 0.2% of the GNP of the country.

Medication costs are significant and account for a significant proportion of health budget. Commission on Epilepsy in Tropics estimated theoretic cost of AED treatment at a national level in three countries with different economies, France, India and Honduras.[23] In India with mixed economy, AED treatment costs when calculated on the assumption that 8% of patients receive phenobarbital or phenytoin and 2% receive more expensive drugs would be US$12.8 million. The costs would be US$ 185 million when calculated on the assumption that 45% receive phenobarbital or phenytoin and 45% receive more expensive drugs. The estimated costs for France, with similar assumptions, would be US$ 3.9 million and US$ 42 millions respectively. The calculations were made considering 1993 pharmacy prices, monotherapy at average daily doses, assuming a prevalence of active epilepsy of 0.5% and 90% of patients in the developing world and 10% in the developed world may receive no adequate pharmacological therapy.[23] The estimated medication cost in Indonesia, per individual per year was US$ 164.25.[45]

Unnecessary reliance on excessive polypharmacy is quite prevalent in most developing countries. This is likely to escalate the costs of managing epilepsy. In a recent survey of patients seen in a tertiary teaching hospital in south India from

1993 to 1995, the average annual cost of AED therapy per patient at entry was US$ 64. Of the 972 patients surveyed in the study, 58% were receiving polypharmacy at entry. Reduction in polypharmacy resulted in net annual savings of US$ 17 per patient, over 5% of the per capita GNP.[28]

Epilepsy-related direct medical costs (ERDMC) account for 25-30% of the total epilepsy-related costs in patients with medically intractable epilepsy.[11] Recent studies have reported cost-efficacy of epilepsy surgery[50] and cost-efficacy of vagus nerve stimulation (VSN).[59] In a recent study Boon et al[52] compared ERDMC of ongoing daily treatment of patients with medically intractable epilepsy who underwent resective surgery, VSN, and conservative treatment. Differences of ERDMCs in conservatively treated patients were significant when compared to patients treated with the other two modalities. There is hardly any data on economics of medically refractory epilepsy in developing countries. In the only study of patients with intractable temporal lobe epilepsy seen in a tertiary teaching hospital in south India, the direct costs of care of a patient was US$ 150 per year.[53]

Neurocysticercosis is the most common cause of epileptic seizures in developing countries and represents a significant proportion of the treatable burden of disease. Economic burden resulting from the cost of medical treatment and loss of productivity is enormous and can be significantly reduced by appropriate public health measures. A minimum of estimates of the cost of admissions to hospital and wage loss for neurocysticercosis in the United States (a nonendemic country) was 8.8 million US$ annually, whereas estimated treatment costs in Mexico were 89 million US$, and Brazil 85 million US$.[54] In a recent study in India, the estimated treatment costs of seizures associated with solitary cysticercus granuloma was 531.23 international dollars (costs in India were adjusted for purchasing power parity PPP). The relative cost was 266.6% of per-capita income of inhabitant of Andhra Pradesh, a province in south India.[55]

Conclusion

Epilepsy care varies widely from country to country and also from one region to another within the country, more so in developing countries. There is a large difference between the number of people with epilepsy in developing countries and the number of these people who are actually being treated for their epilepsy. Cultural attitudes, lack of prioritisation, poor health care infrastructure, and inadequate supplies of AEDs all conspire to hinder appropriate treatment. Furthermore the primary care physicians who most often treats majority of patients with epilepsy, is not well equipped with the knowledge about the classification of seizures, epilepsies, epilepsy syndromes and specific efficacy of various AEDs. Also epilepsy represents a significant proportion of the treatable burden of disease in developing countries. There is hardly any data on the economic evaluation of antiepileptic drug therapy in developing countries. Estimates of per patient lifetime costs are likely to be enormous and account for a significant proportion of GNP.

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Chapter 23

Economics of Epilepsy Surgery in Developing Countries

Jaime Fandiño-Franky

First epilepsy surgery was performed one hundred and fourteen years back by Victor Horsely on a patient with scar in the motor cortex and epilepsy, referred to him by Huglings Jockson, neurologist at National Hospital, Queen Square, London.[1] Interestingly the first patient was evaluated for surgery only clinically. No radiological and electroencephalographic studies were done. Thus epilepsy surgery began with careful clinical evaluation and a close cooperation between neurologist and neurosurgeon. Since then surgery has been accepted as a form of treatment for epilepsy. However, until recently epilepsy surgery has been a luxury, accessible only to patients in countries with established market economies and in countries with very high economic growth.

Developing countries in the tropical zone, of which there are nearly one hundred, have similar climatic characteristics due to their equatorial location. Almost all the countries, with the exception of the Arab countries, are multiethnic. The Gross National Product (GNP) per capita is considerably low. Disease patterns are often similar and also the neurological pathologies that produce brain lesions. The putative risk factors for epilepsy are also likely to be similar because of similar disease spectrum. The reported prevalence rates of epilepsy are high in these countries and range between 12 and 30 per 1000.[2] The proportion of people with epilepsy requiring surgery is likely to be high. The cost of treatment both medical and surgical, are proportionally higher than the per capita GNP.

Epilepsy in Developing Countries

In developed countries, with the structured healthcare systems, the burden of epilepsy related to preventable causes such as prenatal and perinatal pathologies and infections of central nervous system has been reduced considerably. However, much of epilepsy in developing countries results from preventable and treatable causes[3] (Table 1). The disease burden can be reduced to some extent by sound public health measures. Governments in developing countries must be made aware of the enormous economic burden associated with epilepsy so that the governments spend more money for permanent preventive campaigns at all levels.

In developing countries both direct and indirect costs related to epilepsy care are likely to be high for many reasons. The raw material for antiepileptic drugs (AEDs) is usually imported. Similarly the technology needed for diagnostic evaluation and also for epilepsy surgery is also imported. Considerable devaluation of the currencies in these countries against the US-dollar (US$) has resulted in rising costs. These aspects will have cascading effect on the economy of patients' families as well as the budgetary allocation to health by the governments. Consequently, in many

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Table 1. Etiology of epilepsy in the developing world (in order of frequency)

1. Prenatal and perinatal birth trauma
2. Infections of the central nervous system
3. Parasitic diseases - neurocysticercosis
4. Traumatic brain injuries
5. Cerebral vascular diseases
6. Metabolic and genetic diseases

developing countries epilepsy is not only common, but is an expensive disease that should be considered "economically intractable". If this economic criteria, is applied for intractability, the number of patients with intractable epilepsy will be much higher when compared to the number of patients with medically intractable epilepsy in developed countries.

Epilepsy Surgery

Even after the introduction of newer AEDs, approximately 20 to 30% of patients with epilepsy continue to have disabling seizures that are refractory to medical therapy.[4] These figures are based on the data gathered in developed countries. No reliable data are available in developing countries. This is made much more difficult by the fact that the reported causes of epilepsy vary widely and also the patient selection might differ due to changing biopsychosocial conditions of the patients.

In developing countries, hospitals are overburdened with patients affected by communicable diseases like malaria[5] or measles[6] and much of the financial resources are diverted to tackle the common highly prevalent diseases. Hardly any money is left for other health care facilities, like epilepsy surgery program. In many developing countries, most of the hospitals do not have the basic infrastructure essential for epilepsy surgery and the possibility of acquiring such facilities remains remote. The medical team needs to be highly trained.

A larger number of epilepsy surgery procedures are needed in developing countries than in developed countries. The cost of epilepsy surgery is so high that it often overwhelms the public health care system and even private health care providers. In some countries epilepsy surgery is not recognized as a social service and the cost has to be covered by the patients themselves or by their families, which in the majority of cases is simply impossible. On the other hand, government budgets are severely strained by the cost of basic health care, making it impossible to assign resources for any sophisticated treatments. Consequently, the system tends to leave such patients to their own resources.

The cost (direct cost in US dollars (US$) comparison for treating three common diseases in Columbia, malaria, new onset generalized tonic-clonic seizure, and status epilepticus, can provide some insight into the cost differentials (Table 2). Because of the high incidence of malaria, the government prefers to spend money to treat malaria rather than the other two conditions even though the initial drug treatment (injection diazepam) for the other two conditions is inexpensive. Because of lack of prioritization, there are no evidence-based treatment protocols for new onset generalized tonic-clonic seizure or status epilepticus. Often the cause of new onset seizure and status epilepticus is not established because of the prohibitive high costs involved. However, in a developed country, like in Australia, patients with new onset generalized tonic-clonic seizure and status epilepticus will leave the hospital with

Table 2. Comparison of costs of three frequent emergencies in Colombia

Costs (in US $)	Malaria	New Onset Single Generalized Seizure	Status Epilepticus
Laboratory workup	2	100	100
Drugs	2	4	40
Hospital admission	5	5	15
Total	9	109	155

a sound diagnosis and with a good chance of complete recovery, even when the difference in the cost of care is 10 times between the two conditions.

The criterion of intractability of epilepsies does not have the same significance in developing countries as in developed countries. In developed countries with the application of clear and precise treatment standards, the burden of intractable epilepsy is well established. In the agreement reached by Latin American International League Against Epilepsy (ILAE) (Workshop, Buenos Aires, May 2000) the term "economic intractability" formulated by Brazilian colleagues, emerged as a reality in developing countries. If economic criteria are applied, the number of patients evaluated for possible epilepsy surgery will be much higher than the number in developed countries. In such a scenario the protocols should be completely different, focussing on short preventive treatments and early surgery. Such an approach would reduce the overall costs considerably. For example, let's take a look at a patient with mesial temporal sclerosis (MTS) and intractable complex partial seizures in spite of maximal tolerable dose of carbamazepine for six months fulfilling the criteria (clear convergence – seizure semiology, neuropsychology, video-EEG, MRI) for standard temporal lobe resection. Such a patient is likely to have recurrent disabling seizures in spite of adequate dosage of AEDs, including newer drugs. The direct and indirect costs are likely to be high and the quality of life is likely to be poor. The best option for such a patient is early surgery to reduce the costs and also to improve the quality of life.[7,8] However, such treatment algorithms require high initial investment. In developing countries, this raises the question of government involvement and also definite political commitment.

Costs of Epilepsy Surgery in Developing Countries – An Approach

In developed countries a patient with epilepsy is considered medically intractable if he continues to experience disabling seizures in spite of having used two or three drugs in a maximal tolerable dose for an appropriate period. The costs of epilepsy surgery in these countries are similar and range from US$ 30,000 to 100,000. Nevertheless, this may vary in the case of an epilepsy with easy surgical diagnosis, such as unilateral MTS in the non dominant hemisphere with clear convergence or an extratemporal surgery with a difficult presentation, which might require subdural electrodes, prolonged video-telemetry and perhaps intraoperative recording. The Epilepsy Monitoring Units (EMU) and the continuous development of new technologies contribute to the high cost of epilepsy surgery and raise serious questions about the approval by health insurance companies of the requirements specified by

Table 3. Anterior temporal lobectomy - direct costs*

Costs	USA	LCE-Colombia**
CT scan with and without contrast	600	200
MRI with Gadolinium and Flair	700	300
Scalp EEG	100	30
Neuropsychological study		
Pre- and post-operative	300	20
Video-Telemetry (average 72 hours)	3000	350
Surgical procedure (operating room)	6000	300
Hospitalization (10 days)	2000	250
Intensive Care Unit (2 days)	2000	150
Laboratory	5000	91
Drugs	3000	125
Neurologist, neurosurgeon, Anaesthesiologist fee	10000	130#
Subtotal	**32700**	**1946**
If the application of subdural electrodes is required:		
6 electrodes of 6 contacts	3000	3000
Surgical procedure (operating room)6000	300	
Neurosurgeon, anaesthesiologist fees	6000	130
Hospitalization (three days more)	600	25
Video-Telemetry (three days)	3000	350
Subtotal	**18600**	**3850**
Total	**51300**	**5796**

*Approximate data collected through direct information from personnel working in different hospitals in U S A (no data has been published recently). **In the neurological hospital belonging to the Colombian League Against Epilepsy (LCE); # physicians work on a salary. Experience in epilepsy surgery - 11 years.[10-13]

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physicians and medical institutions. Besides, salaries and fees for doctors are substantial, and the need for maintaining and using the services of scientific personnel and technical staff increase the costs even further.

For the cost analysis of epilepsy surgery in developing countries, the cost in Colombia[9] (Table 3) can be considered as standard reference, 100% (US$5,796 for one epilepsy surgery, GNP US$70,263 billion) and the following formula can be applied to arrive at the cost of epilepsy surgery for comparison purposes. The cost of epilepsy surgery varies according to the GNP of the country.

$$\frac{100 \times a}{b} = x$$

a = GNP, b = GNP of Colombia, x = hypothetical cost of epilepsy surgery as compared to Colombia

Example: Singapore - GNP US$79,831 billion

$$\frac{100 \times 79{,}831}{70{,}263} = 114$$

The cost of epilepsy surgery in Singapore will be 14% more expensive than in Colombia.

Table 4. Expected hypothetical costs of epilepsy surgery for several equatorial (developing) countries, calculated in relation to a pre-determined country and based on GNP (in US$)

Country	GNP*	Cost of Epilepsy Surgery	%**
India	319660	26144	455
Mexico	304596	24938	434
Thailand	159630	13043	227
Saudi Arabia	310000	10802	188
Singapore	79831	6550	114
Malaysia	78321	6378	111
Colombia	**70263**	**5796**	**100% (ref.)**
Venezuela	65382	5343	93
Pakistan	59991	4884	85
Egypt	45507	3735	65***
Libya	32000	2634	46
Cuba	17000	1379	24
Ecuador	5997	1321	23
Jordan	6354	517	9
Nicaragua	1659	114	2

* in million US$; ** With Colombia taken as a point of reference; *** Provided that the necessary infrastructure exists, this is the minimum amount required to meet the cost of the imported subdural electrodes ($3000)

The hypothetical cost of epilepsy surgery, calculated by this formula, depends on the cost of epilepsy surgery in the predetermined country and the GNP of the country in reference (Table 4). Countries with a very low GNP would not be likely to introduce this kind of surgery at the present time and should therefore create specific resources for the government to consider. For example in Jordan with GNP of US$6,36 billion,[10] the amount available for epilepsy surgery (US$508) would be only 9% of the calculated cost in Colombia. Considering the single cost of subdural electrodes that amount would escalate to US$3,000, this means that epilepsy surgery program cannot be implemented even if there were enough qualified doctors. All these data suggest that countries with a GNP above 45 billion US$ only can start epilepsy surgery program, provided that the appropriate organization has been established. Countries below this benchmark (approximately 90% of the countries in the equatorial area) would need to implement or plan this expensive surgery under great sacrifices or simply delay such a program.

Proposals for Starting a Program of Epilepsy Surgery in Developing Countries

In some countries epilepsy surgery could be introduced gradually, provided that their economic organization is appropriate, basically to make sure that the program is not abandoned in the middle of implementation. The requirements include both human and technical aspects. Epilepsy surgery team should consist of two neurologists trained in epilepsy, an electroencephalographer (who may be a neurologist if he

Table 5. Equipment requirements for epilepsy surgery program

- EEG with a minimum of 16 channels
- Video-telemetry
- MRI (0.5 Tesla)
- CT-scan
- Laboratory for serum levels of AED
- Subdural electrodes
- Neurostimulator
- Intraoperative EEG equipment
- Rehabilitation centre attached to the hospital

is trained in video-telemetry), two neurosurgeons with sufficient experience and training in the surgical procedures related to epilepsy surgery, a neuropsychologist and a neuroradiologist familiar with the field. Such a team should be able to meet as often as is deemed necessary to discuss individual patients. If possible, the team members should be full-time employees. Besides, there should be provisions to establish an Epilepsy Monitoring Unit (EMU). All other technical facilities (Table 5) needed for epilepsy surgery, including intensive care unit, should be under one roof, a tertiary care hospital. The costs of these facilities have been calculated based on minimum prices in the U.S. (FOB), and do not include tariffs and duties applicable in each country (Table 6).

Infrastructure is a fundamental requirement for positive results in an epilepsy surgery program. Without the necessary equipment and infrastructure it will be hazardous to start epilepsy surgery. Epilepsy surgery program should be started in a phased manner. We believe that in the first phase palliative procedures, such as callosotomy,[11] that works fairly well in nonfocal epilepsies with bilateral discharges and nonprogressive encephalopathies (Drop attacks in Lennox-Gastaut syndrome) should be the surgical procedure to be started. In the next phase, with more experience and better technology, epilepsy surgery for MTS can be performed. In the final phase more complex surgeries like surgery of lesional and non lesional extratemporal epilepsy may be carried out, as these operations very often need the application of subdural electrodes.

In Colombia, we have built a hospital in Cartagena where epilepsy surgery is performed under the responsibility of the Colombian League Against Epilepsy.[12-14] This has proved to be an excellent modality providing unity in any proposal. We would like to point out that in developing countries this kind of surgery has to be performed on a nonprofit basis, with doctors working on a salary. If doctors raise personal fees and the hospital owners seek to make a profit, the program is likely to fail.

Conclusion

The costs for an epilepsy surgery program are substantial. Since the performance of this kind of surgery is indispensable, the political will of the government is necessary to acquire equipment and to train the scientific personnel. A first-rate hospital with epilepsy monitoring, intensive care and annexed rehabilitation units must be accessible. It is important to initiate the program step by step and to gain sufficient experience in patient and family care. On the other hand, a medical corps highly committed to this program is also essential for its continuation.

Table 6. Cost facilities for epilepsy surgery

Equipment	**Costs (US$)**
EEG, l6 channels	50,000
EEG, 8 channels (intra-operative cortical recording)	20,000
Video-telemetry	60,000
MRI	1,500,000*
CT-scan	800,000*
AED blood level equipment	20,000
Cortical brain stimulator	10,000
Subdural electrodes (for one surgery)	3,000
Total	**2,463,000**

* To be deducted if already available in major hospitals

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Chapter 24

Organization of Epilepsy Care: Developing Countries in Asia

K.S. Mani and Geeta Rangan

"What disease affects 40 million people worldwide, yet three quarters are untreated? Paradoxically the same disease, with early diagnosis and treatment can be effectively controlled in about three quarters of those affected. The disease is epilepsy, the commonest serious brain disorder in every country in the world".[1]

Ground Realities

In developing countries of Asia (Japan, Singapore, South Korea and Taiwan are excluded from this group) a vast majority of the population is rural. Poverty, ignorance and illiteracy combined with misguided allocation of scant resources and poor organization from lack of political will and bureaucratic tangles act as big obstacles for overall development. In countries with developing economies health expenditure averages 1% of Gross Domestic Product (GDP) as against 6% in countries with established economies. In India 70% of the population is rural, while 70% of the medical manpower, 100% of neurologists and facilities for investigations are urban. Because of this skewed distribution, a vast majority of the country's population has little or no access to fruits of modern development for quality health care. Forty percent of the population in India is below the poverty line. Health (medical) insurance in developing countries of this continent is practically nonexistent. In India health insurance excludes certain chronic diseases like asthma, diabetes and epilepsy from their ambit. Thus private health care is hard to afford and out of reach for the poor both rural and urban.[2] Critical care medicine is unknown except in metropolitan and large cities with resultant heavy toll in rural areas from acute illnesses and their complications, status epilepticus being a classical example. "The National Health Systems are not cost effective because 70% are siphoned off to big hospitals in lieu of immunization and basic preventive health care. This is a silent disaster waiting to strike".[2] However, some realization in recent years of this inequity offers a ray of hope.

Epilepsy Scenario

The prevalence of active epilepsy in developing counties of Asia ranges from 2.5 to 9.9 per 1000 population.[3] Meta-analysis of the prevalence data from community-based studies in India by Sridharan and Murthy[4] estimated overall prevalence rate at 5.59 per 1000. Prevalence rates for urban areas was 6.34 and for rural areas 4.94. These prevalence rates are similar to the reported prevalence rates from developing countries[5] and do not support the traditional view that prevalence of epilepsy is more in developing countries.

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In advanced countries, a patient with epilepsy has a ready access to quality medical care and social rehabilitation, thanks to national wealth, excellent organization, infrastructure, and health insurance. Except for the affluent class in developing countries, the scenario is totally bleak. The rural folk used to avail of the services of the readily available traditional healer, besides harmless pursuits like talisman, fasting, prayers or visits to places of worship. They can and do recognize tonic-clonic seizures, but may not know the cause. Faith in "English medicine" is a reality in parts of rural India and they opt for it from a primary care physician. Unfortunately, often the latter fails to deliver the goods owing to the archaic therapeutic nihilism and a negative approach from inadequate knowledge of practical epileptology. In addition, there is also the question of not having enough time to talk to the patient about the illness, a feature also shared by few specialist colleagues! The latter with a heavy patient load and located hundreds of miles away is, an expensive and impractical proposition since epilepsy care, at least in the early stages, requires frequent follow up evaluations. The villager expects a quick cure like anyone else and is not aware that such is impossible in epilepsy. None have explained about it and even if so, is reluctant to accept it. The result is frustration and resignation to fate with occasional brief visits to yet another "famous" specialist, institution or alternate systems of medicine, if not charlatans advertised in the media. Properly planned peripheral decentralized management of epilepsy in its early stages can avoid much of this tragedy, more so if chronic/intractable epilepsy is to be reduced.

Rural Epilepsy Control

In nearly two-thirds, especially in those without mental/neurological handicap, epilepsy is a self-limiting condition requiring medication only for 3 or 4 years with a possibility of permanent remission in more than 50% of such instances.[6] However, treatment has to be started early along with strict drug and life style compliance. Drugs can act only if taken properly and regularly. This utopian ideal cannot be attained especially for rural epilepsy control with urbanized, specialist / investigation oriented care as practiced today. The Mountain must go to Mohammed. The emphasis has to be on effective, peripheral, decentralized management by easily accessible, trained and *local* primary care physicians and health workers emphasizing the role of frequent follow up visits for adjustment of drug dosage. This requires a simplified practical clinical epileptology course for both the primary care physician and the Para Medical (health) Worker (PMW), which can also be initiated at the under-graduate level for the medical student. A plea for this has already been made[7-9] and a curriculum suggested,[10] which is detailed in appendix 1. This peripheral approach is extremely valuable for continuing health education of the patient and the family. Repeated and persistent stress on strict drug and life style compliance can be effectively carried out only by a local easily accessible physician and /or health worker and not by a remote urban specialist or Institute of excellence hundreds of miles away.

The most common seizure type in epilepsy is tonic-clonic seizure (GTCS) - primarily or secondarily generalized, which accounts for nearly 80-85% of all epilepsies. This poses a potential danger to life or limb from status epilepticus, drowning, burns, falls, head injuries and others. There is also a human element of apprehension of a next seizure, thus leading to impaired self-confidence and poor quality of life. Recent studies have shown that as far as control of partial with or without secondary generalization is concerned, there is little to choose between the

four front line anti-epileptic drugs (AEDs); phenobarbital (PB), phynetoin (PHT), carbamazepine (CBZ), and valproate (VPA), but the side effect profile, however, varies.[11-15] The perception of an adverse effect varies from one person to another and dependent on socio-economic-cultural ethos of the population and the type of occupation. The impact on the quality of life of an adverse effect cannot be uniform in a student, housewife, agricultural laborer, trader, factory worker, subordinate/managerial staff, professional, industrialist, executive, administrator or others. What is unacceptable in one need not be so in another. We must learn to individualize and not generalize. The drug for use in rural epilepsy control in the third world has to be inexpensive, stable with a long shelf life in tropical climate, effective even with one daily dose to enable long-term compliance and any adverse effect must be acceptable in that cultural ethos and has to be tailored to individual needs. Viewed against this background PB would appear to be a front line and PHT a second line drug for rural epilepsy control program in developing countries. Monotherapy in minimum effective dose and given once a day must be the mantra. The PMW must monitor the seizure calendar, ensure distribution of drugs once a month at nodal points in every village—(home delivery)—if provided for, strict drug and life style compliance (adequate sleep for 6-7 hours at the same time) and enquire for any adverse effects. Home delivery of AEDs once a month can be effectively combined with a similar approach to peripheral, decentralized management of other common treatable ailments like leprosy, tuberculosis and certain mental illnesses so as to make the effort cost effective. The three diseases mentioned above are like epilepsy in that with early diagnosis, strict drug compliance and health education, they are also capable of being managed at the doorstep as it were of the rural population.

It is important for a primary care physician to know when to refer a patient to a secondary and/or tertiary center. Referral is mandatory, if, in spite of strict drug and life style compliance, the response to first line AEDs in adequate dosage for at least 2 years, is poor and/or patients show clinical evidence of progressive neurological disease at entry or follow-up. It can also be considered for subjects with other seizure types and/or mental and neurological handicap, though the returns in such cases are unlikely to be good, barring occasional instances. Reduction of caseload in a tertiary center from unnecessary overcrowding can then lead to improvement in the quality of its services.

Are these flights of fancy or backed up by any reliable data? The role of PB in rural epilepsy control in developing countries is now a well-established fact from studies in Malawi[17] and Kenya[18] in Africa, Ecuador[19] in South America and in West Bengal in India.[20] As far as efficacy was concerned, no significant difference emerged between PB and CBZ[18,19] or PB and PHT[20] and adverse effects were not common, but follow up was limited to 1-2 years. It is interesting that PB as a primary drug for epilepsy control in rural areas was recommended to the Government of India as early as 1975, i.e., nearly a quarter century ago.[21]

Now reference must be made to the 5 year follow-up study started in 1990 at Yelandur in southwest part of Karnataka, a province in south India. The epidemiological aspects have already been published elsewhere.[3] Trained PMWs, health workers, made a door-to-door survey of a population of 64,963 in Yelandur taluk and unearthed 254 cases of active epilepsy. The study was based on clinical findings alone with a follow up for over 5 years. Support for investigations and critical care just did not exist, a reality, which cannot be wished away.

Antiepileptic drug therapy with PB or PHT was advised as monotherapy and 135 patients with partial and/or GTCS accepted it. The cases were all evaluated by a team of specialists (three of them neurologists) who offered their services "*gratis*" and commuted from Bangalore to Yelandur, 150 Km, 4 hours drive away - at least 40 times over 5 years. A team of doctors and PMWs—staff of Karuna Trust—a local nongovernmental organization (NGO) dealing not only with epilepsy but total rural health care, formed the bed rock of this 5-year project. This was cosponsored by the Indian Epilepsy Association (IEA) Bangalore chapter, who financed the cost of drug treatment throughout the study period. There was no research grant nor research officers. The total cost for this 5-year project was an astonishingly low, Rs.120,000 ($2,800) only, mainly for AEDs, which were supplied *gratis* at each village once a month without any break in the drug chain. The PMWs were personally involved in this drug distribution along with those for leprosy, tuberculosis and mental health - to make the effort cost-effective. They also helped in maintenance of a seizure calendar and carried out health education of the family and public through flip charts, posters, slides / TV / video in local languages with repeated emphasis on what patients can achieve rather than what they cannot. They interacted with the patients, obtained data every month on their condition and persuaded them to attend the follow-up clinic at Yelandur for management of adverse effects and annual follow-up. The three neurologists also visited the homes of *all patients - treated or untreated* - in January 1995 and December 1996 to obtain first hand information about their condition, including deaths.

Amongst the AEDs, PB was used as monotherapy in 68 (50%), PHT in 60 (44%) and both as duotherapy in only 7 (5%). The daily dose of PB was seldom above 45-60 mg in children and 90-120 mg in adults, while the corresponding figures for PHT were 100-150 mg and 200-300 mg respectively. In general, the body build of these subjects was on the lower side - usually short and thin.

The results of follow-up of patients treated with PB or PHT in partial tonic clonic seizures with or without secondary generalization gave interesting findings. Seventy-five (56%) subjects had a lifetime total (LTT) of > 30 GTCS and 29 (22%) overt brain damage. These are potential candidates for difficult to manage epilepsy. Patients were divided into two groups - group I made up of those who were drug compliant at successive follow-up year and had a LTT of $\leq$ 30 GTCS at entry, while group II patients failed to satisfy both the criteria. Analysis of the results was by intention to treat. In group I the percentage figures for a terminal remission of at least two years at each successive follow-up year from II to V were 58, 63, 67 and 66 as against that of 6, 16, 8 and 8 respectively in group II. The differences are obvious. Stepwise multiple logistic regression analysis was used to arrive at the predictors for a terminal 2-year remission amongst the following eight variables - gender, age at onset, duration, brain damage, LTT of GTCS (cut off point 30), frequency, assigned drug and its compliance. Drug compliance and a LTT of $\leq$ 30 GTCS emerged as the predictors for a terminal 2-year remission.

Facilities for psychological evaluation were not available. Clinical adverse effects were few. Of the 75 subjects on PB alone or with PHT, 72 (96%) did not experience any adverse effect; only one each experienced dullness, hyperkinesis or somnolence, while the last withdrew from the study owing to somnolence at the time of preparation for the examination. All these four subjects were only on PB. "Phenobarbital is an important anti-epileptic agent that may be allowed to fade from use, at least in

affluent societies, not so much because of its limitations, but because its virtues are no longer promoted".[22]

On the other hand, adverse effects were much more frequent with PHT (n = 67) and noted in 29 (43%) subjects. These were gingival hyperplasia in 21 (31%), ataxia in 5 (8%) and both in 3 (4%); 4 persons withdrew from the study – 3 because of ataxia (the other 5 with ataxia remained with us enabling a reduction of dose) and one from gingival hyperplasia. The latter was reckoned as moderate in 22 (33%) and severe in another two (3%). This was related to per diem dose, length of exposure and poor oral hygiene. It is interesting that in a case control study of 66 subjects on PHT for over 2 years from our private practice material drawn mainly from the urban middle and upper classes, gingival hyperplasia was seen only in 6 (9%), 2 of them rural! Surprisingly the local populace did not appear to be unduly concerned about gingival hyperplasia. These emphasize the importance of dosage and sociocultural ethos in the assessment of adverse effects, individualization rather than generalization and assessment of toxicity-benefit ratio.

The most gratifying spin off from this project is that rural epilepsy control is being continued in Yelandur by the team of doctors and PMWs from the NGO Karuna Trust, even after the Indian Epilepsy Association, Bangalore chapter had withdrawn from the scene. An awareness that epilepsy can be controlled has been created in the local population and drug compliance found to be much more satisfactory than at onset of the study. The secret of "success" in this study was committed PMWs and NGO, regular follow up, unbroken drug chain, home distribution of drugs, minimum effective dose, health education and dedicated medical specialists. Since two years, patients come to the clinic for the monthly supply of drugs and on a small token payment.

"Does epilepsy need exclusive diagnosis and treatment facilities? Clearly not".[23] This opinion, also increasingly emphasized from other developed nations,[24] addresses succinctly the ground realities in epilepsy control in developing countries, which have been stressed earlier.[21,25-27] They also give some credence to our views based on the Yelandur experience over the last decade.

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Epilepsy Control in Urban Areas

The same principle of control of epilepsy in its early stages holds good irrespective of rural or urban, developed or developing countries. However, the approach may vary. Not all rural people are poor or all urban folk necessarily rich. In some respects the urban poor who live in squalid slums are much worse off compared to their rural cousins. Sanitation is abominable and life more tough. Support from a joint family is often absent. Migration of the population in search of better opportunities is a common feature and hence the follow up evaluation is more difficult. These call for urban peripheral epilepsy clinics managed by trained primary care physicians with support from health workers trained in urban slum social work. Handling a poor patient from an urban slum is much more difficult than in rural areas. Drug and life style compliance are poor, with the additional problem of easier access to alcohol. However, a minority can afford CBZ or VPA.

In India, 300 million people are urban with a large conglomerate of the middle and upper classes. The management strategy in these cases, especially the latter has to be more or less on the western model. Adverse effects should be weighed against the toxicity-benefit ratio. Ideally, monotherapy is best to ensure maximum drug compliance, a point of advantage as far as PB and PHT are concerned.

The urban middle class is more knowledgeable. They are very conscious of the social consequences of a diagnosis of epilepsy, but like the rural elite, would like to keep it a secret. They can afford CBZ or VPA and drug compliance and regular follow up are better than with the urban poor. If they have a tendency to change drugs or doctors for every recurrence, it is mainly from poor communication with the medical profession. They can afford less expensive investigations like EEG or CT scan, but MRI, the recent AEDs or epilepsy surgery can be managed, though with considerable difficulty. Patients and caregivers working in the organized sector are included in this group.

The organized sector is made up of employees working in state or federal governments and autonomous organizations funded by them. They and their families are eligible for free consultations, investigations and treatment in government hospitals. Drugs are either supplied free or the expenses incurred reimbursable. The same facility exists for large governmental and private industries and factories; these also have their own out patient services and in patient facilities (as if they are secondary centers), the latter with good general medical, surgical, obstetric, pediatric and trauma care, but, if required, refer their employees and families for tertiary care to pre selected hospitals. These are a privileged class amidst a large pool of general public in the nonorganized sector. The latter have a choice of opting for the nascent health (medical) insurance; unfortunately, epilepsy is specifically excluded from its ambit. They do attend the huge monolith of a government hospital, some of which offer excellent quality service, but many still prefer a private practitioner or a specialist in search of a personalized care.

There is a need for strengthening the infrastructure facilities at district hospital and medical college levels with availability of a general physician (internist), surgeon, pediatrician and other specialists, including neurologists, neurosurgeons, and psychiatrists. Facilities for basic specialist investigations like EEG and CT scan and a rehabilitation medicine unit should be created. Such hospitals can then act as secondary centers, capable of handling common neurological problems, including epilepsy, except complicated cases. Management of specialized problems in epilepsy like intractable epilepsy, epilepsy surgery, vascular surgery etc should be at a tertiary center. Well equipped and adequately staffed, these tertiary centers should be located in each state capital or metropolitan cities. Facilities for rehabilitation of associated mental and neurological handicap is a Cinderella of neurology and epileptology and needs to be organized at least at the level of the tertiary centers, with minimal facilities at the secondary center as well. What has been proposed is a systematic decentralized health care from primary through secondary to tertiary levels.

The upper classes are like their counterparts in the west. More sophisticated, they have a thirst for knowledge about epilepsy, its management, and a feature seen also in the middle class, though to a lesser extent. They ask searching questions and are not easy to convince; but, once the initial hurdle is crossed, they tend to stick to the same doctor making subsequent management easier. If it is a case of intractable epilepsy, they will flit from one doctor to another, if not alternate systems of medicine, which is quite understandable. They can afford the recent AEDs on a long-term basis and epilepsy surgery. Since the last two decades both the middle and upper classes tend to visit a doctor, often a neurologist, even after the first seizure making early diagnosis, investigations, management and follow up much easier, especially with the latter. If requested to do so, patients in this group tend to keep in touch with their physician by either letter or telephone and may report regularly for a

follow-up assessment. In our private practice material catering mainly to the middle and upper classes and collected over 22 years, we had 3423 cases of epilepsy; 548 (16%) had a follow-up of 2 ≤ 5 years, 616 (18%) for 5 ≤ 10 years, 274 (8%) for 10 ≤ 15 years and 171 (5%) for 20 years and above.

Prevention of Epilepsy

We must emphasize that to some extent epilepsy is a preventable disorder. Better maternal nutrition and obstetric care should lead to safer deliveries with reduction of birth injuries and possibly some cases of mental retardation. Likewise, improved childhood nutrition and universal immunization would reduce the toll of childhood infections. Similarly, improved environmental sanitation and hygiene ought to diminish the scourge of malaria and tapeworm infestations. Basic education is an essential prerequisite to achieving this ambitious target. "Educate or Die".[28] Compulsory wearing of a crash helmet by both the drivers and pillion riders, as in hot humid Sri Lanka, will go a long way in reducing head injuries and their sequelae. Scrupulous control of diabetes, hypertension and obesity, all much easier said than done, will reduce the prevalence of cerebrovascular disease, a common cause of epilepsy past middle age. Brain tumors and degenerative diseases will have to await advances in molecular genetics and gene therapy!

Health Education

Management of epilepsy does not consist of history, examination, EEG, CT, MRI and drugs alone. The all important health education is of paramount importance. A good physician must be prepared to spend at least half an hour, if not more at the initial consultation and 15 minutes or more at each subsequent follow up visit. This may appear impractical or a counsel of perfection but needs to be followed if quality service has to be provided. A social worker in either a hospital setting or a group practice can be of inestimable value and save a physician much of his time. Health education is the inalienable right of not only the rich, but also the poor, rural or urban, literate or illiterate, which may also lead to a better compliance. Bereft of this basic concept, epilepsy care becomes a farce. This should be an area of urgent concern and remedial measures for large institutions and popular specialists to address themselves what with their enormous patient load. The role of lay epilepsy associations, school parent associations and other similar organizations in public education of epilepsy deserve special mention. We should specially target the pliable minds of the high school students in health education. They are not yet rigid or fossilized like their older counterparts! The patient has a right to know about his epilepsy, seizure type, possible cause, prognosis, duration of drug treatment, their adverse effects and life style. Many demand information on the relationship between epilepsy on the one hand and diet, studies, memory, work, driving, marriage, sex, pregnancy, heredity, children, recreation, travel, television, alcohol or brain damage from seizures on the other. This is where printed booklets, pamphlets, lay associations, self-help groups, TV / video programs in the form of skits, dramas or street plays are important. The style and content of the material to be communicated will have to vary dependent on the type of clientele and their level of education and sophistication. Yet, man is a creature of his heredity and culture. Questions on alternate systems of medicine are becoming common, especially in intractable epilepsy. Rehabilitation centers for management of associated mental/neurological handicaps are coming up, albeit, slowly in India and can be profitably utilized, some

also as day-care centers for such patients. We need to din into the public psyche repeatedly that epilepsy is not a chronic recurrent disorder belonging to the category of a mental illness and requiring life long medication.

Can the results from the Yelandur study for rural epilepsy control be replicated in other parts of the developing world, if not in India? Why not?[9] There are over 160 medical colleges in India. Can't they make a start and follow this procedure of using locally available talent with a supervisory or advisory role in a specified area or taluk (sub-district) and shift from there to another area after 3 or 4 years? The Departments of Medicine, Pediatrics or Neurology can be actively involved in these visits once a month after an initial training period. Cost of drugs - free or subsidized - can be met from philanthropic organizations like Rotary or Lions. Cannot these be combined with similar home distribution of drugs for leprosy, tuberculosis and mental health - a classical instance of cost effective peripheral decentralized management, but under supervision, for common treatable disorders?

All it needs is a sense of commitment, dedication and missionary zeal. The various medical associations and societies in the country must learn to accept their obligations and responsibilities to the public, especially the under privileged, rather than devote their attention only to conferences and seminars - national or international - no doubt important, but not the end all. A sense of accountability has to become part of our ethos. The time has come for more action and less talk. Pious resolutions without implementation will not suffice. This is a challenge. We should accept it, and do it. We ought to. We must. It is here that the WHO, ILAE, IBE - the troika of "*Epilepsy Out of the Shadows*" - has a great role to play. Developing countries require urgent practical attention towards rural epilepsy control, which can be carried out with better organization of the existing resources.

Appendix 1: A Course Curriculum on Practical Epileptology

1. Applied neuroanatomy
   Primary motor and sensory cortexes – partial motor and sensory seizures with march.
   Temporal lobe cortex, especially hippocampus and amygdala - partial seizures with visceral and autonomic phenomena
2. Complementary imaging studies
   Anatomical localization and the common pathological substrates - examples in CT and MRI
3. Applied neurophysiology
   Elementary and classical EEG findings with examples
4. Applied clinical neuropharmacology
   Pharmacokinetics / Pharmacodynamics of common AEDs - PB, PHT, CBZ, VPA
   Common drug interactions
5. Clinical epileptology – Diagnosis
   Definition of seizures and epilepsy
   Conditions mistaken for epilepsy - syncope, pseudo seizures, breath-holding attacks bodily jerks while falling asleep.
   Common seizure types and epilepsy syndromes; frontal lobe seizures
   Importance of proper history
   Associated "other" neurological symptoms
   "Quick" neurological examination
6. Clinical epileptology – Management
   Principles of drug treatment

Monotherapy first
Trial and error method for arriving at correct drug and its dosage
Importance of diary of attacks (seizure calendar)
Strict drug and life style compliance especially with regard to sleep
No need to change drug or dosage for every seizure recurrence
Duration of drug treatment
When and how to reduce drug therapy
Chances of relapse and their predictors

7. Clinical epileptology – Health Education
Epilepsy and life style – Quality of Life
Education, play, work, dietary restrictions
Marriage, sex, children
Recreation, driving

8. Special situations
Prevention of epilepsy
Febrile seizures
First aid for a single tonic – clonic seizure.
Cluster or serial seizures - role of oral / buccal / rectal DZP
Ground realities in management of status epilepticus
Heredity and epilepsy
Epilepsy, pregnancy and the child
Surgical treatment of epilepsy

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Chapter 25

Organization of Epilepsy Care: Latin America

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Socio-Economic Background

Latin America is part of American continent colonized by population of Latin origin, mainly Spanish or Portuguese. Geographically, it extends from northern Mexican border down to Tierra del Fuego, including the meridional part of North America, the Central American isthmus, Antilles islands and whole of South America. The British or the Dutch colonized some areas of Antilles islands and Guiana. There are strong cultural and ethnic diversities among these countries and the people. These countries share a colonial past, which has led to underdeveloped social and economic structures. Social and economic indicators are low in great majority of population in Latin America including industrialized nations, Mexico, Brazil, and Argentina. There is great regional diversity and inequality in terms of income distribution.

The Latin American countries are densely populated. In the year 1999, the population was 507,306,000. Poverty is still highly prevalent. In the year 2000, over 36% of Latin American homes and over 220 million people were living below poverty line. These figures are similar to the ones in 1994 and slightly higher than the figures for the year 1980. Income distribution has not changed much over the past decade. High levels of inequality still exist. In Argentina and Uruguay, less than 15% of households are below poverty line. In Brazil, Chile, Costa Rica and Panama, it is 15% to 30% and in the third group, which includes Colombia, El Salvador, Mexico, Paraguay, Peru, Dominican Republic and Venezuela, 31% to 50% of the households. Bolivia, Ecuador, Honduras and Nicaragua have the highest poverty levels, over 50% of households. This study also revealed that having a formal job in the public sector or in a private company was no guarantee for being above the poverty line. One of the main factors regarding rural poverty was land access. In terms of income distribution, the study indicates that resistance to change and unequal distribution of income have become notorious during critical times. Analysis of the changes in distribution in nine countries, from 1986 to 1997 showed that four significant setbacks were experienced in terms of distribution in Argentina, Mexico, Panama and Venezuela, there was practically no change in Brazil, Chile, Costa Rica and Paraguay- and only in Uruguay inequality decreased significantly. (The data cited is from the Economic Commission for Latin America and the Caribbean (ECLAC) and Social Development World Summit, United Nations, 1999: www.un.org).

Health Systems

Some of the South American countries have a well-structured and modern federal constitution, which provides every citizen the right to health and also states that

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it is the responsibility of the state to provide health to the citizen. However, in reality this does not exist. A very good example is Brazilian Unified Health System (Sistema Único de Saúde - SUS). Sistema Único de Saúde coordinates the combined health programs and services provided by municipal, state, federal organizations and institutions and it also permits private health care systems. Despite this legislation, a number of problems exist in the implementation of the Brazilian health program. These include social policies practiced by the federal government, management of responsibility at different levels, and an effective management of services rendered. Theoretically SUS covers whole of the population, but in reality only 77% of the population is covered. Of the 77% population covered, only 55% (86 million) receive some kind of assistance and the remaining (34 million) go unassisted. The population uncovered seek assistance from private sector: medical insurance, health medical organizations (HMOs), private medicine, and others.[1] A large portion of this private clientele ultimately ends up seeking or being sent to public health services. This happens especially in case of chronic and terminal diseases, and those diseases that involve complex and costly procedures, without any reimbursement on the part of public health services.

In general, investment in the health system is precarious and a great majority of the Latin American countries do not even recognize epilepsy as an important public health problem. A study published by World Health Organization (WHO) shows that in Brazil per capita annual health investment had fallen from U.S dollars (US$) 63.40 in 1990 to US$ 58.00 in 1993.[1]

Epilepsy in Latin America

Epidemiology

Epilepsy is a major health problem in Latin American countries. Epidemiological data on epilepsy in these countries are relatively few and some of the studies are not done according to the accepted methodology. Epidemiology of epilepsy in tropical countries has been comprehensively reviewed by Bittencourt et al,[2] in the International League Against Epilepsy Commission (ILAE) report. In developed countries the incidence of epilepsy is around 50 per 100,000 populations, whereas in the Latin American countries the estimated incidence rates are almost double. In Ecuador[3] the reported incidence was 122-190 per 100,00 per year and in Chile[4] it was 113 per 100,000. Similarly higher prevalence rates have been reported in the Latin American countries. In Colombia[5] the reported prevalence rate was 19.5/1000 and in Chile it was 17.7/1000. In Brazil, the prevalence of active epilepsy in Greater São Paulo was 11.9/1000,[6] whereas in Porto Alegre,[7] the reported prevalence rate for active epilepsy was 16.5/1000 and for inactive epilepsy the prevalence was 20.3/1000. Recently, a survey in 360,000 inhabitants city in Sao Paulo state revealed a prevalence of 1.8 per 1000 population and showed a clear-cut socio-economic distribution according to the adopted criteria, 3.6 per 1000 in economic class A and 26.3 per 1000 in economic class D. The study has also shown a higher rate of prevalence in the elderly above the age 65 years.[8] Another study a door-to-door survey in Bolivia reported a prevalence of 11.1/1000 for active epilepsy.[9] The reported prevalence of epilepsy is much lower in developed countries. For example, in the United States of America (USA) the prevalence is 6.8/1000.[10] In Latin American countries, there is consistent significant discrepancy between reported prevalence rates and incidence rates for active epilepsy. This discrepancy is partially due to premature death, recall bias, and stigma associated with epilepsy[11] but these

presumptions need to be verified by well-designed studies. There appears to be no significant difference in the incidence of various types of epileptic seizures and syndromes in Latin American countries.[12,13]

Etiology

One of the attributed factors for high prevalence of epilepsy in Latin America is high incidence of parasitic diseases. Neurocysticercosis is the most prevalent parasitic disease.[9,14-18] It is the most often diagnosed cause of epilepsy and epileptic seizures in adults in these areas. Seizure disorders related to neurocysticercosis are also frequent in childhood[19,20] and there are some specific clinical and tomographic findings.[21] The socioeconomic impact of neurocysticercosis in Latin America is widespread. Still there is lack of information on the natural history, treatment, and prognosis of the disease.[18]

Small-calcified lesion or lesions is a common finding in CT brain of patients with epilepsy. Some times these lesions are also seen in CT brain of patients with primary generalized epilepsies and mesial temporal sclerosis. The relation between the calcified lesion(s) and these specific epilepsy syndromes is not clear. We reported a patient with recent onset epilepsy with mesial temporal sclerosis (MTS) and calcified lesion. We suggested possible etiological relation between MTS and cysticercosis.[22] Jorge[23] in a review of surgical outcome of 71 patients with refractory temporal lobe epilepsy found no difference in the prognosis between patients with and without calcifications.[24]

Epileptic seizures are frequent in cerebral malaria. Malaria is a common cause of febrile seizures in children in tropical regions.[25]

Perinatal brain damage is another risk factor suggested for the high incidence of epilepsy. This is probably true for regions with inadequate antenatal and perinatal care. However, Sakamoto[26] in a study of etiology of epilepsy found perinatal brain damage as a risk factor for epilepsy in 14%. This observation is similar to the data collected by the Collaborative Perinatal Project.[27,28] Incidence of motor vehicle accidents is high in Latin America and traumatic brain injury is one of the important risk factor for epilepsy.[29] Sakamoto[26] while studying children and adolescents found traumatic brain injury as etiology of epilepsy in 3%. In a study of adolescents and adults, Gorz et al[30] found cerebral trauma as etiology of epilepsy in 13%.

Of the 312 patients studied by Carpio et al[31] a putative etiology was documented in 36.5%. In a study in Ecuador by Carpio,[32] perinatal brain damage accounted for 9% of the etiologies, neurocysticercosis for 8% and traumatic brain injury and cerebrovascular diseases for 4% each. We evaluated[97] patients with refractory localization-related epilepsy: 72 (74.2%) had temporal lobe epilepsy, 8 (8.2%) had extra-temporal lobe epilepsy and in 17 (17.6%), the epilepsy syndrome could not be ascertained. Electroencephalogram showed epileptiform abnormalities in 95.8% of the patients. Magnetic resonance imaging (MRI) findings are given in Table 1. No imaging abnormalities were found in 12 (12.3%) patients (Carlos A. M. Guerreiro, Marilisa M. Guerreiro, Campinas, Brazil, unpublished data).

We believe that the seizure types, epilepsies, and epilepsy syndromes in Latin America are no different to the rest of the world and present similar outcome and natural history of epilepsy. The only possible exception will be epileptic seizures and epilepsy associated with neurocyticercosis. Most often, in these patients seizure control is good and refractory epilepsy is rare. In our experience seizure recurrence is high in patients with neurocysticercosis when medication is discontinued when compared to patients with cryptogenic or idiopathic epilepsy.[33]

Table 1. Etiology of partial refractory epilepsy in a tertiary center based on MRI findings in 97 patients in Campinas, Brazil

MRI Findings	Number of Patients
Unilateral hippocampal atrophy	61 (62.8%)
Bilateral hippocampal atrophy	6 (6.2%)
Gliosis	4 (4.1%)
Focal cortical dysplasia	5 (5.1%)
Periventricular nodular heterotopia	2 (2.1%)
Cerebrovascular disease	2 (2.1%)
Pachigyria	1 (1.0%)
Polymicrogyria	1 (1.0%)
Vascular malformation	1 (1.0%)
Tumor	1 (1.0%)
Cysticercosis	1 (1.0%)
Unknown	12 (12.3%)
Total	97 (100%)

The basic strategy for the prevention of epilepsy, in Latin America, should include good prenatal care, safe delivery, control of infectious and parasitic diseases, enforcement of laws to prevent road traffic accident related brain damage, and preventive care of risk factors for stroke.[34,35]

Psychosocial Aspects

The laymen's knowledge about epilepsy is clearly unsatisfactory.[20,36-39] Prejudices against epilepsy continue to perpetuate in developing countries because of low literacy rate and cultural beliefs. A comprehensive effort to educate patients, family members, and the society is a basic step in successfully managing epilepsy.[40,41]

In southeast Brazil, Guerreiro et al[42] evaluated the impact of epilepsy on the quality of life of children with newly diagnosed epilepsy and found a great change in the relationship between parents and children. However, the interactions at school did not show significant changes after the onset of epilepsy.[43]

Neurologists

Based on the data provided by Novartis and the Brazilian League of Epilepsy, there were 3,255 neurologists in Brazil in the year 2000, but the actual number may be 20% higher. This number may include neurosurgeons practicing clinical neurology. In Brazil, from 1996 to 2000, the number of neurologists increased by 868 (36%), mainly in the more affluent areas.[44] In a previous analysis we found a positive relationship between the gross internal product (GIP) of the federation unit and the number of accessible neurologists.[1] Areas inhabited by people with higher income like Federal District and Rio de Janeiro, São Paulo, and Rio Grande do Sul States have more neurologists. Neurologists practice mainly in the private sector (52%), in specialized outpatient clinics or HMO's (22%), in hospitals (23%), and in the federal health system (3%). In Bolivia[39] there are 45 neurologists, in Ecuador[32] 70 neurologists, and in Peru[37] 170 neurologists. Because of this low number of neurologists and unequal distribution, most patients with epilepsy are treated by general practitioners, internists, pediatricians, psychiatrists and other professionals or may go unassisted.

Antiepileptic Drug Prescription Patterns and Compliance

In Campinas, Brazil, in the year 1994 the most commonly prescribed antiepileptic drug (AED) was carbamazepine (33%) followed by Phenobarbital (23%). The frequency of other AED prescription was phenytoin (13%), valproate (9%), lamotrigine (0.2%), and vigabatrin (0.1%) (Carlos A. M. Guerreiro, Marilisa M. Guerreiro, Campinas, Brazil, Unpublished data). In the year 1999, between January and October, the most commonly prescribed AEDs in Brazil were carbamazepine (29%) and clonazepam (22%). Phenobarbital was the AED in 17% of prescriptions, phenytoin in 11%, and valproate in 8%. Forty five percent prescriptions were issued by neurologists, 21% by general practitioners, 12% by psychiatrists, 8% by pediatricians, and the rest by others.[44] There was a change in the prescription pattern of AEDs in Brazil from 1979s and1980s.[45] There is a trend towards a decrease in sedative AEDs, such as benzodiazepines and Phenobarbital, and an increase in prescriptions of carbamazepine or valproate.

There are small data on drug compliance of patients with epilepsy in Brazil.[40,44,45] We followed 78 patients with newly diagnosed epilepsy for a mean period of 12.8 months to evaluate drug efficacy, tolerance, and compliance of the initial AED. Eleven (14%) patients had very poor drug compliance and 14 (18%) patients did not tolerate the initial drug and AED was changed of AED. At the end of 8 weeks, 66% of the patients were seizure free and at 56 weeks 63.8% were seizure free.[47] Our observations were in keeping with to the data from developed countries.[48-50]

Epilepsy Centers

In most Latin American countries there are neither Epilepsy Centers nor sophisticated technologies such as video-EEG, MRI, and single photon emission computerized tomography (SPECT) to investigate patients with refractory epilepsy. Such facilities are available only in few private and public hospitals, located in major cities. To our knowledge positron emission tomography (PET) is not available in Latin American countries. Facilities for epilepsy surgery are available in Argentina, Brazil, Chile,[51] Colombia,[38] and Mexico.

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The Brazilian Epilepsy Surgery Program

In Brazil eight centers, have been approved by the Ministry of Health for epilepsy surgery. These centers are in São Paulo (5), Goiás (1), Paraná (1), and Rio Grande do Sul (1). However, many more centers are emerging as centers for surgical treatment. The Ministry of Health officially approved the surgical procedure and supports epilepsy surgery economically in these approved centers. There has been an increase in the number of surgical procedures conducted at several private centers, but these centers are mostly in areas inhabited by people with higher income.

In the National Epilepsy Surgery Program, 329 patients underwent video-EEG monitoring and 197 had surgery for epilepsy (Silvado, Brazil, Unpublished Data, 2001). Of the patients evaluated for localization-related epilepsy, 4% had idiopathic epilepsy, 85% had symptomatic epilepsy, and 1% had cryptogenic epilepsy. Of the patients evaluated for generalized epilepsy, 1% had idiopathic epilepsy, 5% had cryptogenic/symptomatic epilepsy, and 4% had symptomatic epilepsy. Eighty- three percent of the patients had neuropsychological evaluation (48% normal IQ, 49% boarderline IQ, and 3% lower IQ profile). Intracarotid amytal sodium was performed in 47 patients. MRI was performed in 97% of the patients. MRI abnormalities

Table 2. Type of surgical procedures in the first 197 patients who underwent epilepsy surgery

Selective amygdalo-hypocampectomy	7	3.5%
Anterior temporal lobectomy	122	62%
Extra-temporal	9	4.5%
Lesionectomy	12	6%
Lesionectomy + corticectomy	21	10.5%
Calosotomy	20	10%
Multiple subpial transection	6	3%
Total	197	

included MTS (45%), localized atrophy (11%), diffuse atrophy (2%), cortical dysplasia (11%), tumors (5%), and other pathology (8%). In 15% of the patients the MRI was normal (Table 1). The surgical procedures, surgical complications, outcome, and pathology are listed in Tables 2 to 5.

Role of Societies

There are official chapters of the ILAE in Argentina, Brazil, Chile, Colombia, Cuba, Dominican Republic, Ecuador, Guatemala, Mexico, Panama, Peru, Uruguay, and Venezuela. In Colombia, the Colombian League has a special task to attend up to 23% of the patients with epilepsy in the country. They have been performing epilepsy surgeries very efficiently at a League Hospital in Cartagena.[38] The Brazilian League of Epilepsy (BEL) advises the Ministry of Health in formulating various projects related to epilepsy care in the country. BLE plays a major role in providing medical education on epilepsy. There is an Education Project, which distributes videos, booklets, and books on epilepsy to the members and to medical schools. BLE organizes scientific meetings and courses in the regional chapters and also an annual national scientific meeting. In the year 2000 the League has a membership of 1500, second largest ILAE chapter after USA.

Latin American Epileptology

Scientific research in epileptology is restricted to very few centers in Latin America. Approximately 5% of abstracts presented at the International Symposia in 1980s were from Latin America.[29] There was an increase to 10% in the number of papers presented at the International Epilepsy Congress in Prague, 1999.[52]

Table 3. Surgical complications in the first 197 patients who underwent epilepsy surgery

No complication	88%
Complications	12%
Functional deficit	5%
CSF fistula	1%
Hemorrhage	1%
Meningitis	2%
Others	3%

Table 4. Temporal lobe surgical-outcome in the first 197 patients who underwent epilepsy surgery

Anterior temporal lobe + Amygdalo-hypocampectomy				
Mean follow-up		146.5 ± 101.6 (7- 446) days		
Mean age		28.6 ± 13 years		
Engel scale	IA- 73%	IB-11%	IC-1.5%	ID-3%
	IIA-6%	IIB-6%		
	IIIA-3%			
	IVB-3%			
	VB-3%			

Conclusion

1. Government should value the social agenda, ensure full operation of democratic institutions, ensure an integrated approach to the economic, social and environmental dimensions of development and find external resources for appropriate development (Consensus of São Paulo World Summit for Social Development, 1997).
2. The organization of Latin American medical system for epilepsy care reflects the low socioeconomic development of this large and diverse continent of the world.
3. Some factors that cause or contribute to the high rate of epilepsy in Latin America are high incidence of infectious diseases, mainly parasitic (especially neurocysticercosis), poor quality of maternal-infant care in the poorer regions and high incidence of traffic accidents with traumatic brain injury. Improved health care, basic education, and sanitation can greatly change the scenario.
4. The role of nongovernmental agencies in the area of health welfare and education through public information has produced encouraging results in some countries, although at present, only a few segments of these societies are benefited.
5. Basic measures should be taken to bring about a more efficient health care system which includes: the remaking of governmental hierarchical policies related to epilepsy with referential and counter referential centers, and free dispensation of antiepileptic drugs to the low income patient population.
6. According to our experience an official recognition of epilepsy surgery by health, which is at the top of the medical system pyramid, can help to organize an algorithm in this increasingly complex medical care field.

Table 5. Pathological findings in the first 187 patients who underwent epilepsy surgery

Not done	20%
Mesial temporal sclerosis	49%
Dysgenia	7%
Tumor	5%
Calcification	1%
Vascular	2%
Nonspecific gliosis	3%
Without report	4%
Normal	3%
Others	6%

7. It is urgently required that the health organization includes epilepsy as a public health priority. Achieving this objective is crucial to the role of international health agencies in influencing local governments, the development of lay people organizations as well as the education of persons with epilepsy and their families.

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Chapter 26

Organization of Epilepsy Care: Africa

Bola Adamolekun

Africa comprises about 22% of the world's total land area, covering about 30,330,000 sq. km. About 12% of world's population (1990 census) lives in Africa, making it the world's second-most populous continent after Asia. Epilepsy is a common neurological problem in developing countries of Africa. Incidence of epilepsy in African countries is 2-3 times more when compared to the incidence in developed countries. A study in Tanzania[1] reported an incidence rate of 77/100,000. There are also important differences in the prevalence of epilepsy within the individual countries in Africa. Epidemiological studies in Nigeria, using a standardized protocol to define the prevalence of epilepsy, reported prevalence rates, in urban areas with well organized primary healthcare facilities similar to the reported prevalence rates in developed countries,[3] while the prevalence rates in areas without well-organized health care systems are seven times higher.[4] Peak age-specific prevalence rates for epilepsy occur in the first and second decades of life. Children under 15 years of age constitute about 45% of the total African population. In most African countries the standard of living is very low and health care systems are poorly organized. Populations are younger and are thus likely to be exposed to more risk factors for epilepsy. The putative risk factors identified in the case-control studies in African countries include febrile seizures, traumatic brain injury, and lack of immunization against common childhood infections.[2]

Health Care Financing in African Countries

Government Expenditure

One of the major obstacles to an effective health care system in Africa is the low governmental budgetary allocation to health (hardly exceeding 6% of the overall public budget). Per-capita expenditure for health care ranges from 3-300 US dollars (US$) per year. Total health expenditure as a percentage of Gross Domestic Product (GDP) in African countries is shown in Table 1. There is a wide variation in the scale of health care spending between African countries. This variation has important practical implications: African countries that spend more on health care tend to do better in terms of health services and outcomes than those who spend less.[6]

External Aid

In 1990s, external assistance made up only 2.9% of total health expenditure in developing countries as a whole.[7] External aid was about 3% of the total health expenditure in North African countries (Algeria, Tunisia, and Morocco), whereas larger percent of health expenditure in sub-Saharan Africa was by the external aid (as high as 52.9% of the total health expenditure in the case of Mozambique).

Epilepsy in the Tropics, edited by J.M.K. Murthy and Nimal Senanayake.

Table 1. Data on availability of medical personnel and health care financing in some African countries (1988-1992)[5]

	Medical Personnel		Health Care Financing	
Country	Doctors per 1000	Nurse:Doctor Ratio	Health Expenditure as a Percentage of GDP	Aid Flow as Percentage of Total Health Expenditure
Algeria	0.26	4.7	7.0	0.1
Tunisia	0.53	2.7	4.9	3.0
Morocco	0.21	4.5	2.6	3.0
Malawi	0.02	2.8	5.0	23.3
Mozambique	0.02	13.1	5.9	52.9
Tanzania	0.03	7.3	4.7	48.3
Nigeria	0.15	6.0	2.7	6.4
Cameroon	0.08	6.4	2.6	13.4
Benin	0.07	5.8	4.3	41.8
Burundi	0.06	4.3	3.3	42.7
Chad	0.03	0.9	6.3	43.0
Ethiopia	0.03	2.4	3.8	18.8
Zimbabwe	0.16	6.1	6.2	10.0
Kenya	0.14	3.2	4.3	22.5

This high dependence on external funding is potentially problematic. External funding tends to be targeted at diseases of interest to the donor.[7] The sub-Saharan countries with heavy dependence on external aid end up implementing vertical programs that promote donor-driven health priorities, policies, and programs. The donor community ends up usurping the leadership role of government in defining health priorities and in allocating funds for implementing health sector programs. In such scenarios, noncommunicable diseases like epilepsy end up being comparatively under financed.

Health Insurance

International agencies such as the World Bank have advocated the use of health insurance as a way of improving health sector efficiency and equity in developing countries. If those who, together with their employers can pay for health services are made to do so by insurance, the limited government funds can then be concentrated on providing service for fewer people, with improved coverage and standards.[8] One immediate difficulty in the implementation of a health insurance scheme is the fact that the majority of Africans are self-employed or work for small enterprises. For instance, in Tanzania only 3% of the population were employed in the formal sector and could be covered by compulsory health insurance.[9] Obtaining regular contributions from the informal sector may be quite difficult, given the administrative and organizational infrastructure currently available in most African countries. Because of these limitations, the number of Africans covered by health insurance is relatively low.

Health Expenditure by Companies and Corporations

Companies and corporations often enter into contracts with selected private hospital groups as health care providers, or provide limited cash reimbursements for

medical expenses incurred by employees in the private health sector. The contribution to health care by this private sector financing of health is quite substantial, given the number of companies that offer this facility and also the large number of workers and relatives covered. In Tanzania, private sector employers were spending an average of 11% of payroll on health care for their employees.[9]

Health Expenditure by Individuals

In many African countries, the majority of individuals purchase care as needed in private-for-profit clinics and hospitals. In many countries without a health insurance safety net, many families have to pay more than a 100% of their income for health care when faced with sudden emergencies. Acutely ill patients receive substantial financial support from the immediate and extended families, which mitigates considerably the overall costs of health care to the patient and makes it possible for such patients to have access to health care that may otherwise be out of reach from pecuniary constraints. However, this family support tends to wane over time in patients with illnesses requiring chronic therapy, such as epilepsy.[10]

Revenue

User Fees

Having patients pay part or all of their health care costs is a way to mobilize more resources for health, improve equity by selectively charging the wealthy and increase efficiency by encouraging reinvestment of fee revenues into cost-effective primary care. Access to government health services for the poor can also be maintained by well-targeted exemption procedures.[11] The Bamako Initiative in the African region of the WHO was designed to ensure regular availability of drugs. Seed drugs are provided to the health institutions either by the national government or through external aid. These are sold to patients at a small profit margin. The proceeds are then used to replenish stocks and the small profit used to improve services in the health center.[12] In Benin and Guinea, the Bamako initiative is in implementation since 1986. In these countries, a user-fee system generates community-financed revenue with the aim of covering local operating costs including drugs. Village health committees manage resources and revenue. Community user-fee revenue in Benin in 1993 amounted to about US$ 0.6 per capita, enough to cover recurrent nonsalary costs.[13] In Nigeria, cost recovery through revolving funds is consistent with the national health policy, which states that users shall pay for curative services but preventive services shall be subsidized.[14] A seed fund is provided to purchase a stock of drugs and other consumables employed in medical care. Subsequent replenishment of stocks is provided for by sales. Provision is made for losses, exemptions, inflation and overheads by adding 5-20% of the actual cost to the amount charged to the patient. The revolving fund scheme has been quite successful in many Nigerian teaching hospitals.

Experience with user fees in Kenya is, however, less impressive. The revenue generated by user fees covered only 2.4% of the recurrent health budget. Attendance in public clinics dropped by 50% during the period of cost sharing, prompting its suspension.[15]

Numerical Strength and Distribution of Health Care Personnel

Doctors

There are wide disparities in the doctor: population ratios in African countries, with North African countries and South Africa having much higher ratios than countries in sub-Saharan Africa (Table 1). For instance, as at 1992 Libya had 1.04 doctors per 1000 people, Tunisia had 0.53 doctors per 1000 and Algeria had 0.26/1000. South Africa had 0.61/1000. This contrasts with Malawi's 0.02 doctors/1000, Senegal's 0.05/1000, Cameroon's 0.08/1000 and Zimbabwe's 0.16/1000. By comparison, Australia has 2.29 doctors per 1000 and The Netherlands has 2.43 doctors per 1000. There are wide variations in doctor: population ratios within individual countries. For instance in Nigeria the 1991 doctor: population ratio varied from 1:1614 in urban and affluent Lagos state to 1:235,827 in Jigawa state with a low level of urbanization and weak economic infrastructure. In general doctors tend to cluster in urban areas, avoiding rural and economically depressed areas. In sub-Saharan Africa, there is a dearth of neurologists. Nigeria, Africa's most populous country has about 25 neurologists, ten of them are in cities Ile-Ife, Ibadan and Lagos, all within a 200-kilometer radius.

Nurses

Nurses and midwives constitute the largest trained workforce in the health care system in all African countries. There are no big differences in the nurse to doctor ratio in African countries (Table 1). As at 1992, Tunisia had a nurse-to doctor ratio of 2.7, Malawi had a nurse: doctor ratio of 2.8, Senegal 2.6, Cameroon 6.4 and Zimbabwe 6.1. Nurses are also much more evenly spread within the states than doctors and are more likely to be available in rural areas.

Organization of Health Care Delivery Systems for Epilepsy

Traditional Health Care Systems

Traditional medicine may be defined as the sum total of all knowledge and practices used in the prevention, diagnosis and therapy of physical or mental illnesses and relying exclusively on practical experience and observations handed down from generation to generation, whether orally or written.[18] Common to all the variants of traditional medicine are dualist explanations of the etiology of illness in natural and supernatural terms and the therapeutic use of herbs and magicoreligious rituals.

Herbal Therapy

The traditional mode of treatment of seizures commonly involves consultations with traditional deities in the supernatural world by the rendition of incantations or metaphors, combined with the administration of herbal remedies. The herbal remedies are commonly mixtures of plants with anticonvulsant, antipyretic or antibacterial activity.

One traditional herbal remedy for generalized convulsions in Western Nigeria includes the fruits of *Tetrapleura Tetraptera* Taub and the leaves of *Nicotiana Tabacum* Linn. These plants contain *Scopoletin* and its methyl derivative, *Scoparone* that have been shown to protect against leptazol-induced convulsions.[17]

The health-seeking behavior of patients with epilepsy suggests a strong preference for traditional herbal medicine over conventional medicine. For instance, all of

101 freshly - screened patients with epilepsy in a community - based survey in Igbo-Ora, Western Nigeria had been treated with herbal remedies, while only four (3.9%) were receiving conventional antiepileptic drug therapy.[3]

Spiritual Therapy

Epilepsy is often regarded as a manifestation of visitation of the devil, the effect of witchcraft, or the revenge of an aggrieved ancestral spirit.[18] The management of epilepsy is therefore commonly assumed to be in the domain of spiritual healers who hold out the attractive promise of a complete cure of epilepsy by magicospiritual therapies. These elaborate therapies include ritual dances, incantations, propitiatory rites and exorcism. They may take up considerable time, effort and money, but are of considerable psychotherapeutic value to the patients in view of the deep-rooted beliefs about the supernatural etiology of epilepsy.

Traditional herbal medicine appears to be more popular for epilepsy care than spiritual therapy. Of 265 patients with epilepsy who have used alternative forms of therapy prior to seeking hospital treatment in one study,[19] 47% had used traditional medicine, 20.4% had used spiritual healing, while the rest had combined both treatments. However, after initiation of drug therapy in hospitals, more than two-thirds of patients who had earlier used spiritual therapy tended to continue such therapy, compared with 14.6% of patients who had used traditional herbal medicine. This implies a stronger perception of continuing psychological benefit from spiritual therapy.

Conventional Health Care Systems

Developed countries practice a hierarchical model of epilepsy care with increasing levels of specialization and clear lines of referral from a primary care facility through secondary care to special epilepsy centers. In the Netherlands for instance, general practitioners provide primary care and refer cases to pediatricians and neurologists with follow up visits to the specialists at least once a year.[20] There are special epilepsy centers for therapy-resistant cases and those with complicated diagnostic or psychosocial problems. In U.K drug therapy for epilepsy will not solely be initiated by general practitioner, neurologists initiate drug therapy in 66% of adult cases.[21] Inequitable distribution of medical personnel, scarcity of specialists, and pecuniary constraints make this model impracticable in Africa. African countries must instead strive to organize health service delivery in a manner that provides adequate quality and coverage of health care to their populations despite the huge constraint of limited financial and manpower resources.

Primary Health Care

Role of Non Doctors in Primary Health Care

World Health Organization has recommended an integrated primary health care approach as the most efficient and cost-effective solution to the multiple problems of epilepsy care in developing countries. The objective of this approach is to make the primary health care clinics the main entry point and channel of health care delivery for patients with epilepsy.[21] The tasks of an effective primary health care delivery system for epilepsy should include the diagnosis, therapy, long-term follow-up and vocational and psychosocial rehabilitation of patients with epilepsy.

Diagnosis and Therapy of Epilepsy

One of the reasons for the epilepsy treatment gap of 80-90% in Africa is the numerical inadequacy and uneven distribution of medical manpower available for the management of epilepsy. As a solution WHO had advocated the use of nondoctor primary health care personnel to identify cases of epilepsy, apply simple treatment protocols, monitor therapy and provide referrals within a framework of an integrated primary health care program for epilepsy.[22]

In most sub Saharan African countries, primary health care workers are not trained or required to make a diagnosis of epilepsy or to initiate drug therapy in patients with epilepsy. Africans have been shown to demonstrate a pragmatic, efficacy-testing health-seeking behavior for any particular complaint,[23] decisions on choice of care depending among other things on whether the health care facility in question has a reputation for alleviating such complaints. In order to demonstrate the efficacy of conventional anti-epileptic drug therapy in the rural areas, there is a need to provide standing orders or practice guidelines for the primary health care management of epilepsy.

In Zimbabwe, a patient with suspected epilepsy is referred to the district hospital where a doctor is expected to make the diagnosis of epilepsy and initiate drug treatment. In a recent study,[24] primary health care nurses in a health district of Zimbabwe were trained to diagnose and manage epilepsy. Government permission was obtained for those nurses to diagnose and treat patients with generalized tonic-clonic seizures (GTCS) in their health centers, using phenobarbitone and dosing criteria suggested by the WHO.[22] This intervention led to a 74% district-wide increase in epilepsy patient enrollment over a six-month period. This increase was attributed to the active seeking out of patients by primary health care workers coupled with the awareness by patients that they can receive epilepsy care in the nearby health center, without the inconvenience and expense of travel to the district hospital.

Reports from Kenya[25] has shown that primary health care nurses, using a protocol to determine drug maintenance doses were effective in the monitoring of drug therapy in epilepsy patients. A recent report from Zimbabwe[26] has confirmed that primary health care nurses can manage epilepsy drug therapy effectively. Of 114 patients managed by nurses, 40.3% had been seizure free for at least 6 months. Sixty-eight patients (59.6%) were on monotherapy, 52 (76.5%) of these on phenobarbitone. Overall, 82 patients (71.9%) were on phenobarbitone either as monotherapy or in combination with carbamazepine or phenytoin. No physician intervention to drug therapy was required in 43% of patients. The most important physician intervention in patients with inadequate seizure control was an increase in drug dose, required in 29% of consultations. The tendency to subtherapeutic dosing with antiepileptic drugs amongst nurses suggested that written guidelines for epilepsy management at the primary health care level would be beneficial to the primary health care nurse management of epilepsy. In South Africa, a guideline for the primary health care management of epilepsy was recently published.[27]

Psychosocial and Vocational Rehabilitation

In Africa, the cultural perception of epilepsy as a stigmatizing disease creates significant psychosocial disability, which produces a profound impact on the social, cognitive and vocational functioning of individuals with epilepsy.[28]

An important problem of epilepsy management in African countries is the lack of vocational rehabilitation. Ideally, social and vocational rehabilitation should be

started as soon as the diagnosis of epilepsy is established, and should be available at the primary health care level. A report from Zimbabwe suggests that it is possible to develop and integrate vocational therapy into community-based epilepsy care in Africa.[26] In that report, an epilepsy support group (ESG) consisting of epilepsy patients, their parents and relatives was formed under the auspices of the Epilepsy Support Foundation (ESF), (a nonprofit, nongovernmental organization). The group had an elected committee chaired by a parent, an administrative office provided by the town Council and ran its own finances.

The ESG meetings occurred immediately after the monthly epilepsy clinics. The meetings encouraged patient and parental understanding of, and participation in the care of epileptic patients, with a particular focus on drug compliance and emergency management of seizures. Time was also devoted to the sharing of information and personal experiences between patients, parents and social workers.

A skills training program for income - generation was organized for the group by the hospital social worker, hospital occupational therapist and the ESF coordinators. These activities included crocheting, sewing, knitting, floral arrangement and small-scale trading. The ESG also had an active outreach program, involving group members making personal contacts with epileptic patients not actively receiving therapy.

The vocational training program, apart from providing much needed vocational skill also provided an extra incentive for compliance with clinic attendance.

Role of Doctors in Primary Health Care

Physicians in private health facilities as well as those in the government district or general hospitals may provide primary health care for patients with epilepsy within their catchment areas. Private health care facilities are most often concentrated in the urban areas, and are often retained by companies and corporations for the care of their staff and dependents. However, most workers will not disclose their epilepsy to their employers because of fears about job discrimination and will therefore tend to avoid utilizing health services provided by their employers.[29] Most cases of epilepsy in urban areas are probably diagnosed and treated by physicians, particularly partial seizures and absences that are often poorly recognized by nondoctor healthcare workers.[10]

Specialist Services

The organization of specialist health care varies in different African countries and depends on several factors including economic, cultural and political determinants. There is a dearth of specialists in the neurosciences in Africa. There is also a scarcity of neuro-radiological and neurophysiological diagnostic facilities as well as drug level monitoring facilities, which are often considered essential for the tertiary care of epilepsy. Tertiary care for epilepsy is not well developed, particularly in sub-Saharan Africa and is often available only in university hospitals. For similar reasons, facilities for epilepsy surgery are not routinely available in most African countries. There are no special centers for epilepsy care in Africa.

Conclusion

The scarcity of medical doctors in most African countries creates an imperative for nondoctor primary health care workers to treat epilepsy at the primary care level. Studies have shown that these health care workers can be trained to identify cases of generalized tonic-clonic epilepsy, apply simple treatment protocols, monitor therapy

and provide referrals as appropriate. Such training, if adopted by African countries can significantly enhance epilepsy care. It should be reinforced by the provision of written national guidelines for the primary health care management of epilepsy. The district health system should be strengthened to provide epilepsy education to primary health care workers on a regular basis, and to improve patient referral within the system. Drug treatment of epilepsy should be made available at all health care levels and should be subsidized to improve compliance. Lastly, the etiological risk factors for epilepsy in the different countries should be identified[30] and preventive measures promoted.

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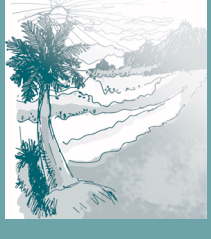

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