James Vincent Byrne

Tutorials in Endovascular Neurosurgery and Interventional Neuroradiology

Second Edition

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Writing a second edition of this book has been a chance to update and amend the text in view of developments in the field since 2012. This process has taken place in tandem to changes in the curriculum and teaching on the Oxford University M.Sc. Course in Endovascular Neurosurgery and Interventional Neuroradiology. During the 5-year interval since the first edition, the course has expanded to include a clinical attachment at the University Hospital of Southampton, supervised by Dr. John Millar. As a result, I have to acknowledge eight former students who have completed the course since 2012, in addition to all the prior graduates whose work has shaped the course's tutorial teaching and thereby the content of this book.

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Oxford, UK James Vincent Byrne

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Preamble

From whence we come…

What is the value of studying embryology when variant and anomalous vessels are so uncommon? Surely we always rely on a detailed analysis of each patient's vascular anatomy to guide endovascular treatments.

For me, anatomy is like a city street map. To be more precise, it is like the streets and roads of London, where I grew up. As a child I learnt to navigate those within walking distance of home and knew only main routes taken by car or bus to visit friends, shopping and other excursions. This familiarity of use fundamentally changed when I learnt to drive and was no longer a passive observer. Now, consider the role of chauffeur extended to showing visitors around my city. My priority changed, from learning shortcuts, good parking places and congestion avoidance (though all very useful to the city guide), to pointing out the sites and important historic places.

We should learn the history of the routes we travel to deliver our therapy with the intimacy of the London cab driver and be prepared for the obscure address which few but they would know. In embryology we have a chance to marvel at the compressed evolution of foetal development. By learning about those processes, we are delighted when recognising throwbacks and anomalies, which, like historic sites, provide evidence of 'from whence we come'.

In this tutorial the embryology of cranial vascular development is presented in a simplified

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overview. Unlike other tutorials, the text contains few citations, since the descriptions are largely based on the classic works of D. H. Padget which are listed with other source texts, at the end of the tutorial. Readers may find it useful to read this tutorial in conjunction with Tutorials 2 and 7 because it represents the precursor vascular anatomy covered in the subsequent chapters.

1.1 Definitions of Terms Used in Embryology

Embryonic period: The embryonic period is defined as the first 8 weeks after fertilisation or the first 10 weeks after the last menstrual period which is the gestational age. It is the time when tissues differentiate to form the principle organs (i.e. organogenesis).

- Phylogeny: This term refers to the sequence of events involved in the evolutionary development of a species or taxonomic group of organisms.
- Ontogeny: Refers to the development of an individual organism.
- Foetal period: The time from the end of the embryonic period until birth.

Anomaly and malformation: An anomaly is a deviation from the common or normal, whilst malformation means badly formed and implies a defective structure. Both should be distinguished from abnormality which refers to a given anatomical configuration that is pathological.

Variation: Is a modification or different form of something and is used to describe divergence from the usual or expected growth pattern. It does not imply that the result is harmful to the individual.

1.1.1 Timelines in the Embryonic Period

The first 4 weeks of the embryonic period precedes the development of the heart and circulation, so our interest in the development of cranial vessels begins at about 22 days, i.e. the start of the fourth week after fertilisation. The relevant milestones in the remaining embryonic period are shown in Table 1.1.

Table 1.1 Events expected during the second half of the embryonic period

Embryonic period: 4th–8th week
4th week (22–28 days from fertilisation = 4 mm CRL)
Heartbeat begins
Branchial arches form
The neural tube closes (day 24)
The ears begin to form as otic pits
5th week (29–35 days from fertilisation = 9 mm CRL)
Optic cups form
Nasal pits form
The brain divides into five vesicles
Rudimentary blood flow starts
6th week (36–42 days from fertilisation = 13 mm CRL)
Brain grows
Lymphatic system appears
7th week (43–49 days from fertilisation = 18 mm CRL)
Foetal heartbeat detectable
Spontaneous limb movements seen on ultrasound scan
Foundation of all essential organs in place
8th week (49–56 days from fertilisation = 40 mm CRL)
Adult pattern of cranial arteries established

CRL crown rump length: This measure is variable and given only a guide to the size of the foetus at each stage.

1.1.2 General Concepts in Vessel Development

Before reviewing the recognised stages of embryonic cranial vessel development, it is worth first considering how blood vessels grow and adapt to supply tissues. Where no blood vessels exist, as in the embryo, their growth is termed vasculogenesis. Growth of existing blood vessels is by angiogenesis:

(a) Vasculogenesis occurs from clusters of endothelial cells, which develop from precursor cells, called angioblasts. Endothelial cells form vessels that grow and differentiate under the influence of growth factors and the extracellular matrix. These local clues include signal proteins, adventitial fibroblasts, pericytes and smooth muscle cells. A primary network forms, by a combination of apoptosis and proliferation. Once blood flow is established, it stimulates selective remodelling of vessels by angiogenesis in response

to the tissue need. Once complete vasculogenesis does not occur again under normal conditions, but certain steps may be reactivated under pathological conditions, such as tumour growth.

(b) Angiogenesis refers to the growth of new vessels in response to tissue growth, wound healing and the formation of granulation tissue. There are two types: sprouting and non-sprouting or splitting angiogenesis.

Sprouting angiogenesis is the growth of new vessel from parent vessels, similar to the growth of branches on a plant. It occurs in a well-described series of events initiated by the activation of endothelial cell receptors and the release of proteases that degrade the basement membrane allowing endothelial cells into the adjacent matrix. These cells then 'spout' through the matrix towards the source of the angiogenic stimulus. They migrate in tandem because of adhesion molecules called integrins and form new vessels linking adjacent vessels. Vascular endothelial growth factor (VEGF) is the principle driver of angiogenesis and the Notch receptor pathway for its control.

Non-sprouting or splitting angiogenesis is the development of a new vessel by the splitting of existing ones. This involves the formation of a core of pericytes and myofibroblasts between two vessels. These tissues form the extracellular matrix for growth of a new vessel lumen. The process is more economic than sprouting angiogenesis in the number of endothelial cells required, which is an advantage during embryonic development. It is important in the growth of capillary networks throughout life.

1.2 Closure of the Neural Tube and Development of the Head Arteries

In the embryonic period, massive changes in the distribution of newly formed vessels take place in a recognisable series of events. D. H. Padget divided the development of the cranial vessels into seven stages (see below) after which the adult configuration of arteries is established. The development of veins and dural sinuses takes longer and continues up to and beyond birth.

First we need to review the steps in the development of the head and in particular how the brain and facial structures appear.

1.2.1 Pre-choroidal Stage

Closure of the neural tube occurs at about 24 days after the start of the embryonic period. Blood vessels develop from a mesh of primitive cells (meninx primitiva) on its surface. Initially, arteries and veins are indistinguishable amongst these vessels, arranged as a network of vascular channels (Fig. 1.1). Longitudinal arterial channels

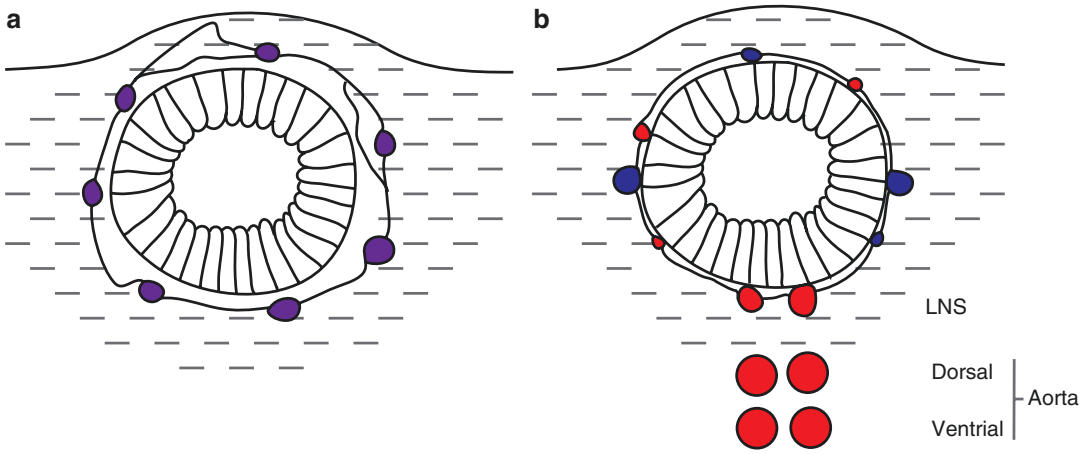

Fig. 1.1 (**a**) Neural tube and meninx primitiva. (**b**) Development of the longitudinal neural system (LNS) (Published with kind permission of © Henry Byrne, 2012. All rights reserved)

develop ventral to the neural tube within the meninx primitiva. These comprise the longitudinal neural system (LNS). This process is preceded by the development of the heart and paired ventral and dorsal aortae from the truncus arteriosus.

During the fourth week, the cranial neural tube develops three expansions termed primary brain vesicles. These are called prosencephalon (forebrain), mesencephalon (midbrain) and rhombencephalon (hindbrain). The ventricles form within these expansions.

1.2.2 Choroidal Stage

The increasing metabolic demand of the neural tube prompts invaginations of choroid from the meninx primitiva into ventricles within the vesicles so that blood supply occurs from both inner (ependymal) and outer (pial) surfaces.

During the fifth week, the primary vesicles develop secondary vesicles. These involve division of the prosencephalon into telencephalon and diencephalon and the rhombencephalon into metencephalon and myelencephalon. Thus, there are now five vesicles. At the same time, the branchial pouches are maturing.

1.2.3 Branchial Stage

The head develops around the rostral end of the neural tube with the face and neck forming ventral to the developing brain. These structures are derived from a series of branchial pouches with intervening arches (called pharyngeal arches in humans) and appear in the fourth week. They represent an evolutionary period when the organism depended on gills.

The head and neck structures are formed from the cranial three branchial arches and develop from neural crest cells together with contributions from paraxial mesoderm, ectoderm and endoderm.

The patterning information is provided by the cranial neural crest cells and can be traced to a transient period of hindbrain segmentation in seven subdivisions called rhombomeres. Each rhombomere has a unique identity provided by Hox gene expression. The gene products are Hox proteins (i.e. transcription factors) which dictate the ordered development of facial structures and the migration and differentiation of neural crest tissue into the first three branchial arches. They control the orientation of nerves, ganglia, bone, cartilage and connective tissue [1].

Paired connections between the ventral and dorsal aortae form between the pharyngeal arches. There are six arch arteries, separated by the transient pharyngeal pouches. The formation of the heart and great vessels is well described in general texts and will not be covered here. It should be understood that the six aortic arch arteries arising between the dorsal aorta and the ventral aortic sac are not present simultaneously. The three rostral arches concern us since the carotid arterial system develops from them. The posterior cerebral circulation develops as the meninx coalescences to form segmental and longitudinal arteries. The longitudinal intersegmental arteries form a system of vessels termed the longitudinal neural system (LNS) with the adult pattern emerging after the carotid system (Fig. 1.1).

1.2.4 Development of the Carotid and Vertebrobasilar System

This section will describe the stages in the development of the carotid artery. Our understanding of the cranial artery developments in the embryo comes from studies of post-mortem tissue. E. D. Congdon in 1922 [2] described the aortic arch system and the origins of the major cerebral arteries, i.e. carotid, vertebral and basilar. The details of how the cranial vasculature changes during the embryonic period were described by D. H. Padget [3] in a study of 22 embryos held in the Carnegie Collection, Washington.

She identified the seven stages in this process and related these to the size of the embryos at each stage:

Stage 1 = 4–5 mm CRL
Stage 2 = 5–6 mm CRL
Stage 3 = 7–12 mm CRL

Stage 4 = 12–14 mm CRL
Stage 5 = 16–18 mm CRL
Stage 6 = 20–24 mm CRL
Stage 7 = 40 mm CRL

The internal carotid artery is established in the first three stages and the vertebrobasilar arteries by the fourth stage. These will be described chronologically. Other developments are easier to describe as systems because they develop in parallel streams.

1.2.4.1 Stage 1

Six aortic arch arteries connect the dorsal and ventral aorta, of which the upper three develop into the carotid system. The adult pattern results from a process of regression of various components of the three rostral connections (Fig.1.2a).

The dorsal aorta caudal to the third arch involutes and its rostral portion forms the first section of the primitive internal carotid artery. Its connection with the ventral aorta remains and the caudal portion of the ventral aorta becomes the

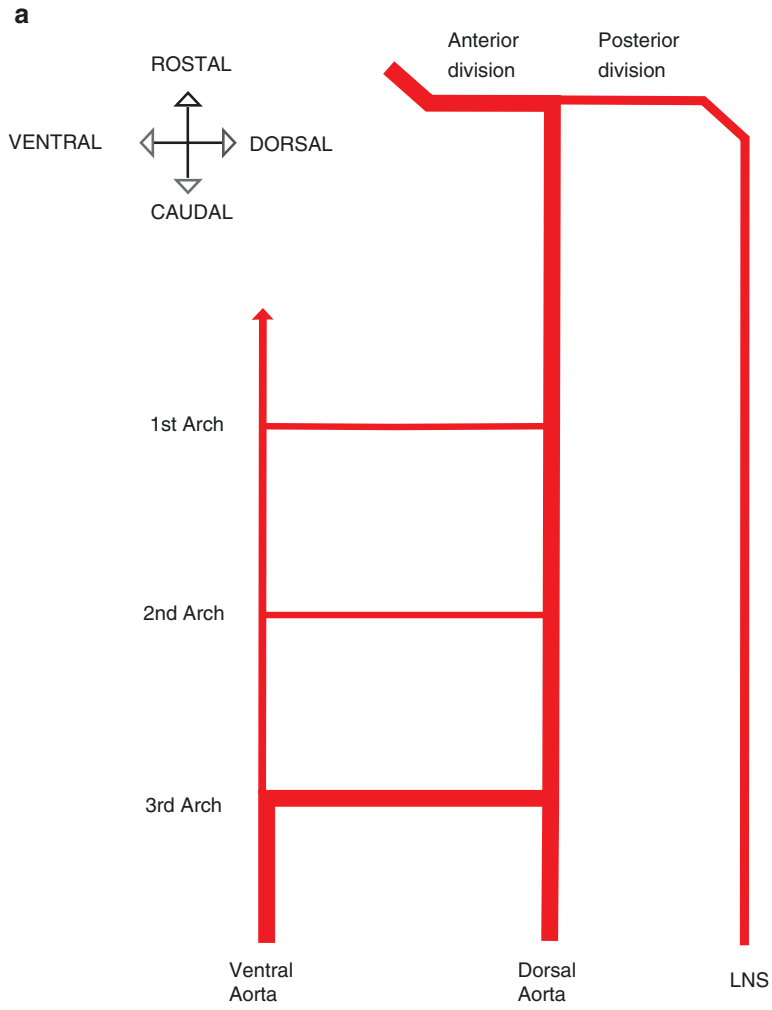

Fig. 1.2 Stage 1, development of carotid arteries. The three rostral aortic arches connect the ventral and dorsal aorta (**a**). Regressions result in the arrangement shown in (**b**). Interconnecting arteries between the first and second arches and with the longitudinal neural system (LNS) are now evident. In (**c**) parts of the first and second arch arteries have regressed and branches arising from the dorsal aorta rostral to the first arch artery developed. (Published with kind permission of © Henry Byrne, 2017. All rights reserved)

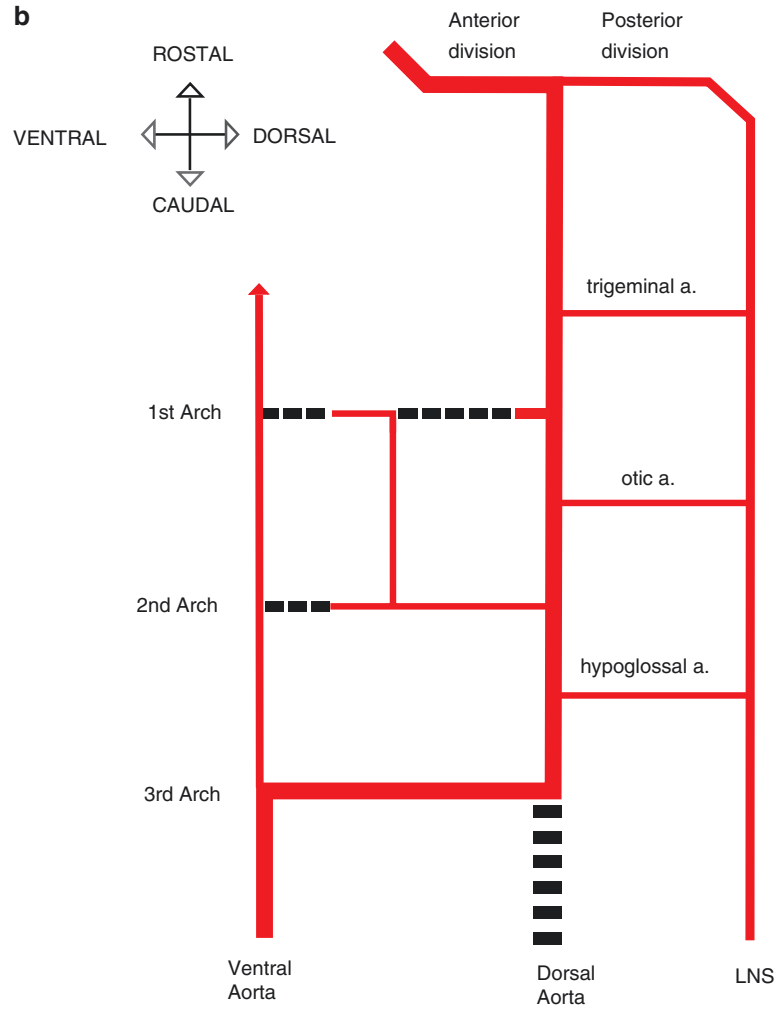

Fig. 1.2 (continued)

common carotid artery. The ventral portions of the first and second arches and the dorsal part of the first arch also regress leaving an interconnecting vessel between the first and second arches and the dorsal portion of the second arch (Fig. 1.2b, c).

The most rostral extent of the dorsal aorta, now the primitive internal carotid artery, divides into a ventral branch or anterior division which forms the anterior cerebral artery and a dorsal or posterior division which is the precursor of the posterior communicating artery. These vessels supply the developing prosencephalon (subsequently the telencephalon) and mesencephalon, respectively. The internal carotid artery (ICA) also supplies the rhombencephalon and the emerging LNS by the transient primitive trigeminal, otic and hypoglossal arteries (Fig. 1.3).

The dorsal aorta gives three branches rostral to the first arch – the ventral ophthalmic artery (VOA), the dorsal ophthalmic artery (DOA) and

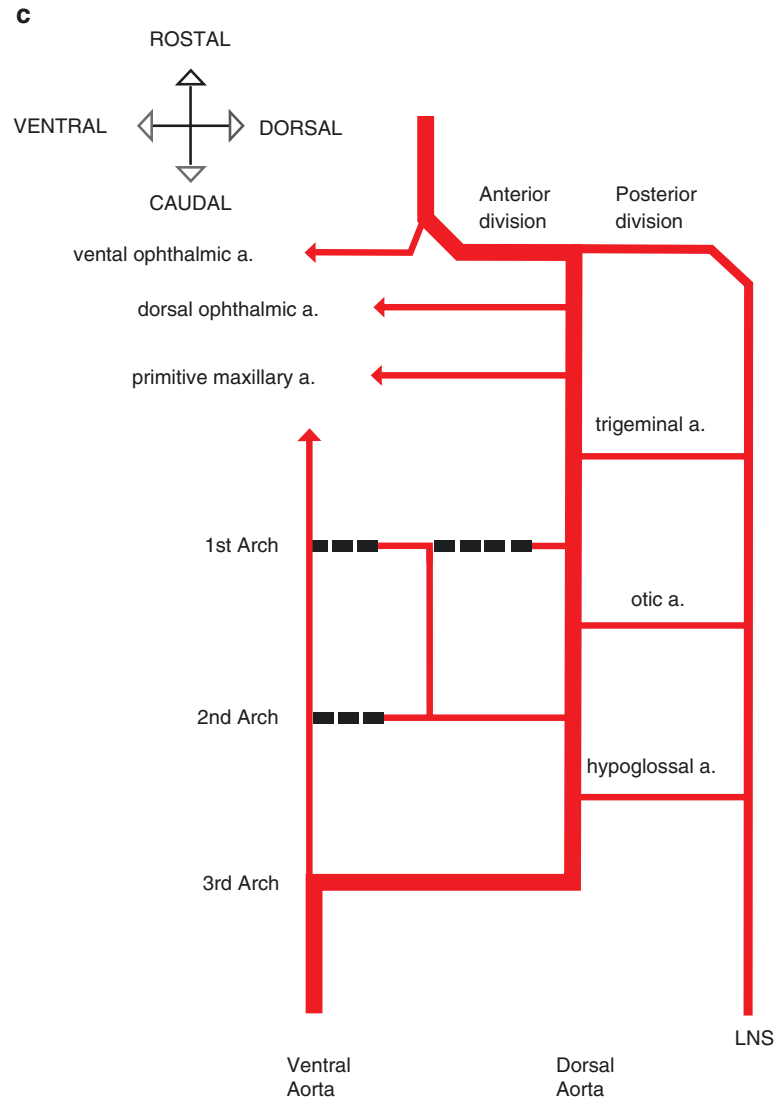

Fig. 1.2 (continued)

most caudally the primitive maxillary artery. The primitive maxillary artery supplies Rathke's pouch,[1] from which the anterior pituitary develops. It appears before the optic vesicle (Fig. 1.2c).

[1]Martin Heinrich Rathke (1793–1860), professor of zoology and anatomy at Königsberg who first described the pouch and the arches.

1.2.4.2 Stage 2

The internal carotid artery is thus formed from the dorsal aorta and the third arch artery with part of the ventral aorta. The second arch artery becomes the hyoid trunk but maintains a connection with the first arch. This connection with the first arch is destined to become the stapedial artery, whilst the remnant of the first arch artery becomes the mandibular artery.

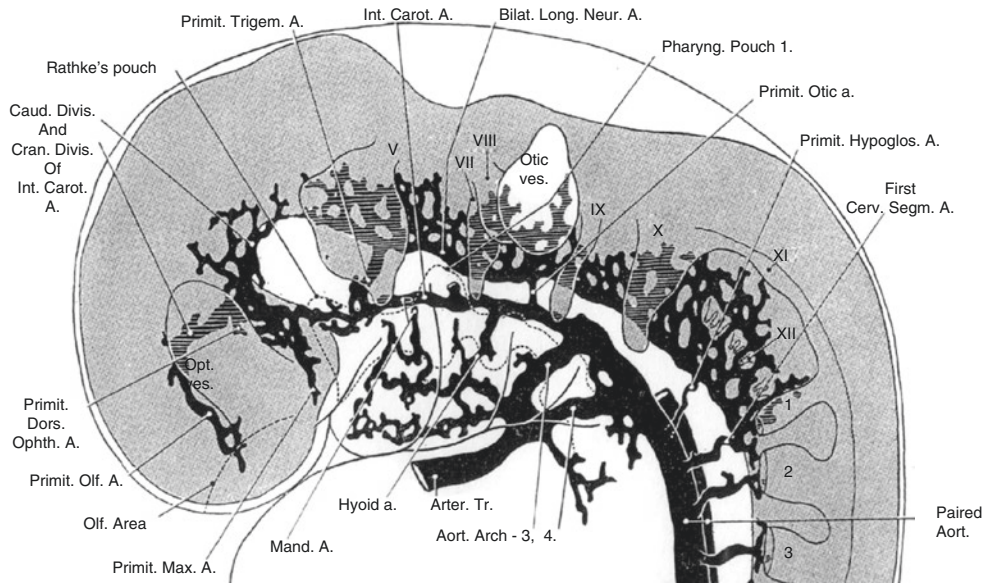

Fig. 1.3 Graphic reconstruction of cranial arteries in a 4 mm embryo by Padget [3]. Note the rostral division of the internal carotid arteries, the prominence of the branchial hyoid artery and the LNS emerging from a network of vessels and supplied from the internal carotid by trigeminal, otic and hypoglossal arteries (Reproduced with permission)

At this time (about 6 mm CRL), paired ventral pharyngeal arteries develop from the third arch. The ventral pharyngeal artery is destined to form the proximal part of the external carotid artery but it maintains a connection with the second arch (marked * on Fig. 1.4). It will form the lingo-facial system with lingual and thyroid branches.

The connection to the second arch provides a link to the hyoid/stapedial system and is the key to understanding the development of the internal maxillary artery (second arch) and the middle meningeal artery (first arch).

Also in this stage, we see initial signs of the two primitive ophthalmic arteries (VOA and DOA) as the eye starts to develop. These will eventually regress leaving a single ophthalmic artery that follows the course of the VOA, whilst the DOA regresses and forms the precursor of the inferolateral trunk (ILT). The last of these three rostral branches of the dorsal aorta is the primitive maxillary artery, which is destined to survive in the adult pattern as the posteroinferior hypophyseal artery (PIHA).

Finally, because the posterior division of the internal carotid artery, i.e. the posterior communicating artery, consolidates its connection to the LNS, the primitive trigeminal, otic and hypoglossal arteries regress.

1.2.4.3 Stages 3 and 4

These stages encompass the transition from the branchial to post-branchial stages. The cranial divisions of the internal carotid artery (i.e. ventral and dorsal branches) develop. The ventral division forms the primitive olfactory artery from which the VOA arises. It also gives the anterior choroidal artery and small branches, which will coalesce into the middle cerebral artery as the telencephalon grows. The dorsal or posterior division forms the posterior communicating artery, which gives the posterior choroidal artery and supplies the mesencephalon and emerging basilar artery. The paired posterior choroidal arteries supply the diencephalon together with the anterior choroidal arteries.

The formation of the internal maxillary artery and middle meningeal artery is complex. This is

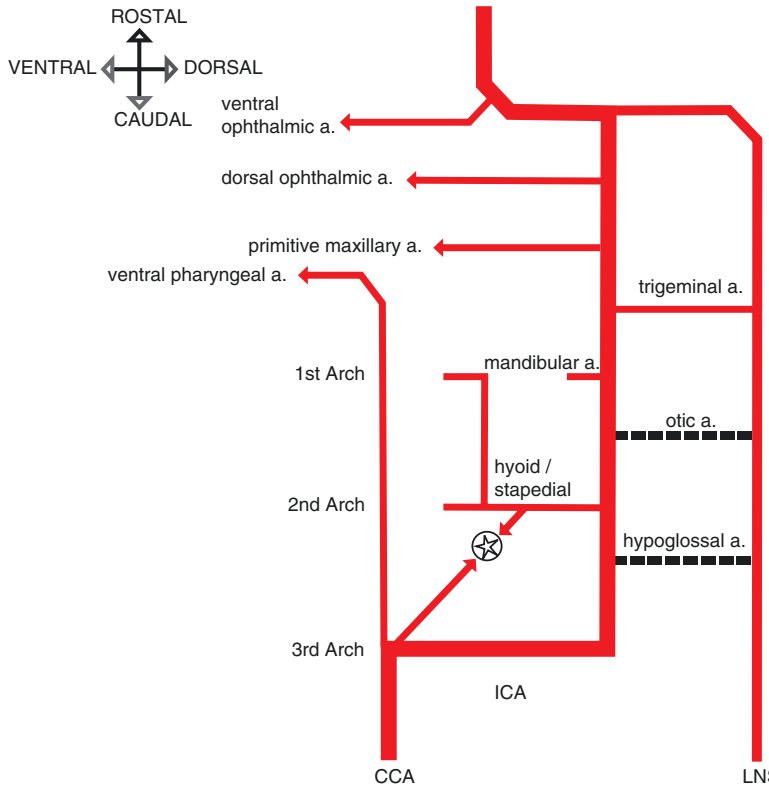

Fig. 1.4 Stage 2. The stapedial artery links the first and second arch arteries and the ventral pharyngeal artery develops from the third arch. *ICA* internal carotid artery, *CCA* common carotid artery (Published with kind permission of © Henry Byrne, 2012. All rights reserved)

because of the development of the face after completion of the branchial stage causes arteries (and arterial territories) to establish and then partially or completely regress as new patterns of blood supply develop. At the beginning of the fourth stage, the stapedial artery is formed as the continuation of the second arch's hyoid artery trunk and an arterial link to the first arch. It divides into dorsal or supraorbital and ventral maxillomandibular divisions. The supraorbital branch is taken over by the ophthalmic system and the maxillomandibular trunk annexed by the developing internal maxillary artery (Fig. 1.5). These processes will be described in more detail below.

The basilar artery is formed by fusion of the parallel LNS on the midline surface of the developing hindbrain. Initially its caudal supply is from the first segmental artery of the aorta and the primitive hypoglossal artery. At this stage, lateral to the LNS and the developing basilar artery longitudinal channels are prominent. These transient arteries are called the primitive lateral vertebrobasilar anastomoses. They regress as the more medial basilar and vertebral arteries mature. The vertebral arteries are formed from longitudinal channels between the upper six spinal segments. Other connections between these segments and the aorta regress as the vertebral arteries grow. With growth of the hindbrain vesicles, symmetrical branches of the basilar artery appear.

1.2.5 Embryological Basis of Variations in the Carotid Artery

Before considering potential arterial anomalies, it is worth revisiting the primitive pattern in

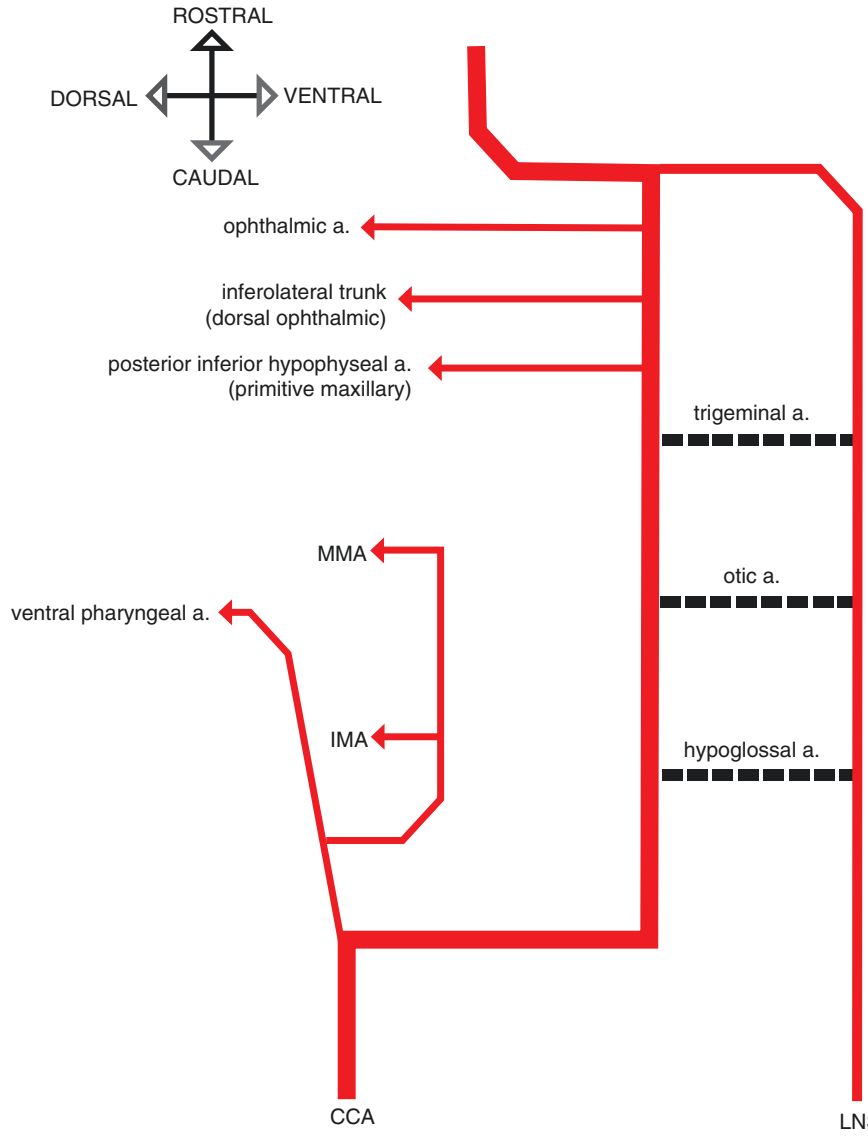

Fig. 1.5 Stage 3: Regression of the stapedial artery and annexation of its territory by the ventral pharyngeal system. *MMA* middle meningeal artery, *IMA* internal maxillary artery. See Figs. 1.2 and 1.4 for other abbreviations (Published with kind permission of © Henry Byrne, 2017. All rights reserved)

which the dorsal aorta and LNS develop from segmental centres. The LNS supplies the developing hindbrain comprising the mesencephalon, metencephalon and myelencephalon secondary vesicles and the primitive carotid artery the forebrain comprising the telencephalon and diencephalon secondary vesicles (Fig. 1.6).

Anastomoses develop and regress between the carotid system and the LNS. The rostral (and persisting) anastomosis is the dorsal or posterior division of the carotid system which connects the rostral LNS with segmental cervical arteries. Prior to development of the basilar and vertebral arteries, the LNS is supported by additional transient arterial connections with the carotid system via otic, hypoglossal and trigeminal arteries and by the dorsal aorta via the first cervical segmental artery, i.e. proatlantal arteries. Thus, the posterior communicating artery is the remnant of the posterior division, and the posterior cerebral arteries

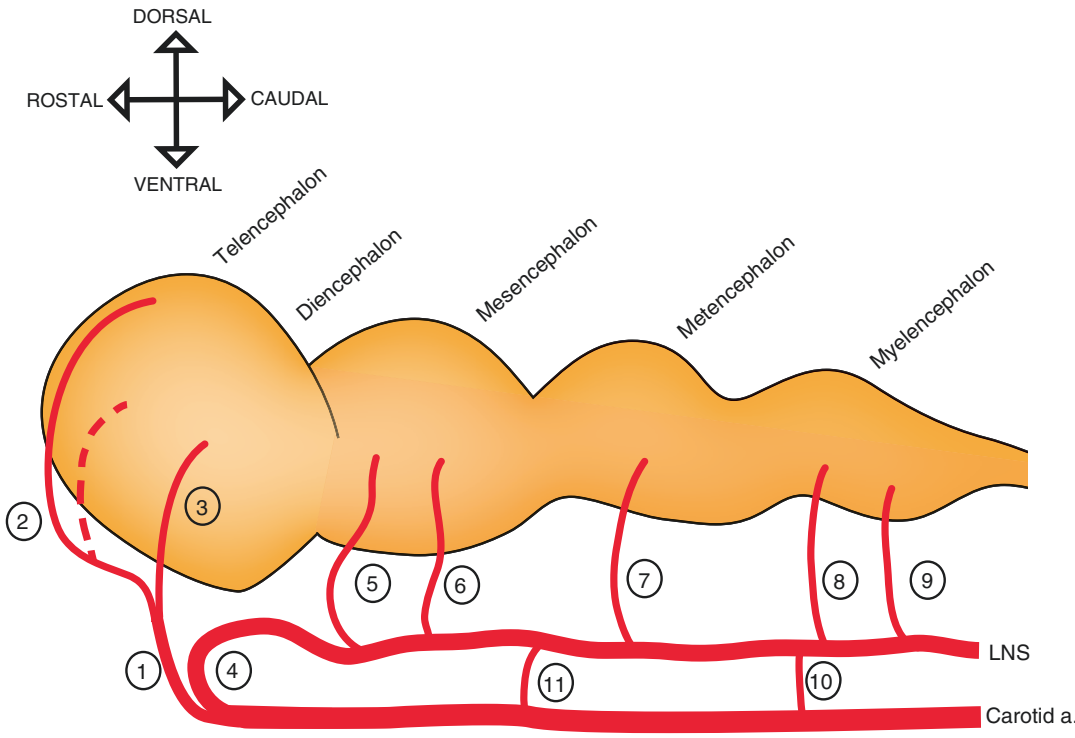

Fig. 1.6 Development of secondary brain vesicles (5 weeks). The arterial supply to the secondary vesicles are numbered; *1* anterior division of ICA, *2* anterior cerebral artery (from which the middle cerebral artery arises – *dotted line*), *3* anterior choroidal artery, *4* posterior communicating artery, *5* posterior choroidal arteries, *6* collicular arteries, *7* superior cerebellar artery, *8* anterior inferior cerebellar artery, *9* posterior inferior cerebellar artery, *10* proatlantal artery, *11* primitive trigeminal artery (Published with kind permission of © Henry Byrne, 2012. All rights reserved)

represent the supply of this carotid division to the diencephalon. As the posterior division develops, the primitive trigeminal artery regresses. The otic and hypoglossal arteries normally are present only at the 4–6 mm stage.

The branches, which develop from the LNS (and subsequently the basilar artery), are the future posterior choroidal arteries (assumed by the posterior cerebral arteries), collicular arteries, the superior cerebellar arteries, anterior inferior cerebellar arteries and posterior inferior cerebellar arteries.

1.2.5.1 Variants to the Adult Pattern of the Carotid System

(a) Anterior cerebral artery variants

Multiple cortical branches arise from the anterior cerebral artery to supply the expanding cortical mantle of the telencephalon and all potentially supply branches to the striatum. These regress leaving the middle cerebral as the dominant vessel but the process is subject to variations. Similarly, the paired anterior cerebral arteries, which communicate across the midline via a plexus of vessels, are liable to variations. Regression of the midline anastomotic systems usually leaves a solitary anterior communication artery, but duplications are common and the proximity of the anterior cerebral arteries creates the potential for fusion (see below). The patterns, resulting from embryological variations, most commonly involve:

1. Duplication(s) of the anterior communicating artery.
2. Dominance of the recurrent artery of Heubner.
3. Duplication of the middle cerebral artery, i.e. persistence of a sister branch of the

anterior division of the primitive internal carotid artery.
4. A single midline (azygos) anterior cerebral artery.
5. Bi-hemispheric patterns of the anterior cerebral artery complex, with one side supplying parts of both hemispheres.

(b) Agenesis of internal carotid artery segments

The branchial arch arteries and branches of the primitive internal carotid artery provide potential routes for the carotid system to be reconstitute if sections fail to develop. To understand these potential variants of the internal carotid artery (ICA), we return to Fig. 1.4 which is updated in Fig. 1.5. Potential persistent connections between the LNS and the carotid system (i.e. primitive trigeminal, otic and hypoglossal arteries) and the definitive ophthalmic artery are shown. Also shown is the annexation of the internal maxillary and middle meningeal arteries by the ventral pharyngeal artery and regression of the hyoid artery (its remnant being the caroticotympanic artery) and mandibular arteries. This process is described below. The described patterns of agenesis are as follows:

1. Absence of the proximal ICA derived from the third arch and dorsal aorta caudal to the second arch. In this variant the distal artery is supplied by the ascending pharyngeal artery (via its inferior tympanic branch) to the caroticotympanic branch of the internal carotid artery within the skull base.
2. Absence of the dorsal aorta section below the first arch. The distal internal carotid artery is reconstituted by the distal internal maxillary artery (pterygovaginal artery) via the mandibular artery.
3. Absence of the section above the first arch and below the primitive maxillary artery. The distal internal carotid artery is reconstituted either by a persistent trigeminal artery or from transclival arteries at the level of the posterior inferior hypophyseal artery (PIHA).
4. Absence of the section distal to the primitive maxillary artery. The distal internal carotid artery is supplied via collaterals through the DOA remnant, i.e. the ILT.
5. Absence of the cavernous section distal to DOA. The distal internal carotid artery is reconstituted by the ophthalmic artery (via branches of the middle meningeal or internal maxillary arteries).

(c) Anomalous carotid-vertebrobasilar anastomoses

The pre-segmental branches of the dorsal aorta supplying the LNS are usually temporary and have disappeared at around the 15 mm CRL stage. The most common persistent artery is the trigeminal artery (Fig. 1.7). The five recognised bridging arteries are:

1. Trigeminal artery
2. Otic artery
3. Hypoglossal artery
4. Proatlantal artery type 1
5. Proatlantal artery type 2

If present these persistent embryonic arteries connect the internal carotid artery to the basilar artery (trigeminal and otic) or the vertebral artery (hypoglossal, proatlantal type 1) or the external carotid artery (proatlantal type 2). The otic artery is so rare that its existence as a persistent vessel has been disputed. It is described as arising from the petrous internal carotid artery, running through the internal acoustic canal, to anastomose with the basilar artery. The others will be described below.

1.2.6 The Role of the Stapedial Artery

The stapedial artery arises as a branch of the hyoid artery within the rudimentary middle ear. The hyoid artery, which developed at the 9 mm CRL stage, is the second arch artery. It regresses after the embryological period, and only its origin remains as the precursors of the caroticotympanic trunk.

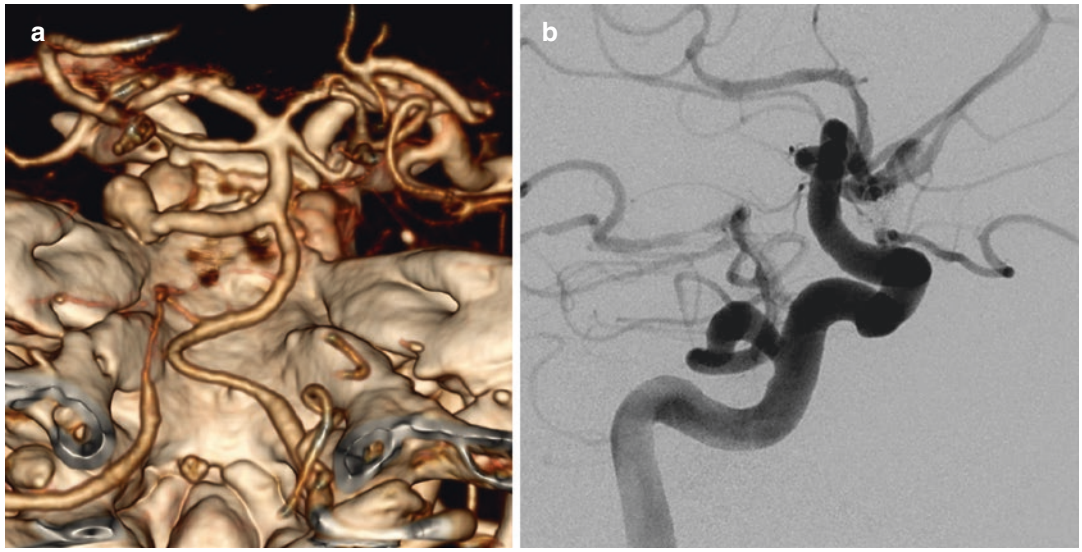

Fig. 1.7 Persistent trigeminal artery. Reconstructed frontal CTA (**a**) and lateral DSA (**b**) showing a persistent trigeminal artery between internal carotid artery and the mid portion of the basilar artery

The stapedial artery grows to supply the non-neural structures of the developing face and orbit. It passes between the crura of the primitive stapes and divides within the middle ear cleft into a dorsal or supraorbital division to supply primitive dura and orbital structures and a ventral or maxillomandibular division to supply the developing face (Fig. 1.8).

The supraorbital division of the stapedial artery gives a branch to supply primitive dura (which will become part of the distal territory of the middle meningeal artery) and an orbital branch which accompanies the ophthalmic division of the trigeminal nerve through the superior orbital fissure to supply the adnexa of the orbit (see below). The ventral maxillomandibular division establishes a connection with the internal maxillary artery as this develops from the emerging external carotid artery. The external carotid artery, formed at the remnant of the dorsal aorta distal to the third arch, will eventually replace both the ventral pharyngeal and stapedial artery systems. But, at Stage 5 the stapedial artery system is dominant.

In the next stage (Stage 6), the stapedial artery regresses and the superior part of the mandibullomaxillary division becomes the proximal part of the middle meningeal artery. The stapedial stem remains only as its tympanic branch (superior tympanic artery). Thus, the stapedial system is at its maximum extent during Stage 5 (16–18 mm CRL) when the definitive ophthalmic artery develops (see Fig. 1.9). The development of the adult ophthalmic artery and the orbital branches arising from the supraorbital branch of the stapedial artery are intimately related and will be considered together in the next section.

1.2.7 Development of the Ophthalmic Artery

The stem of the adult ophthalmic artery at the 18 mm CRL stage arises from the internal carotid artery as the primitive VOA and DOA regress. The process by which a single adult stem replaces these precursor arteries with very separate origins is uncertain. Since in the preceding stages, the primitive VOA originated as a branch of the anterior cerebral artery and the primitive DOA arises from the internal carotid artery, one or both presumably migrates to the adult position. It is likely, as suggested by Fig. 1.9, that the primitive

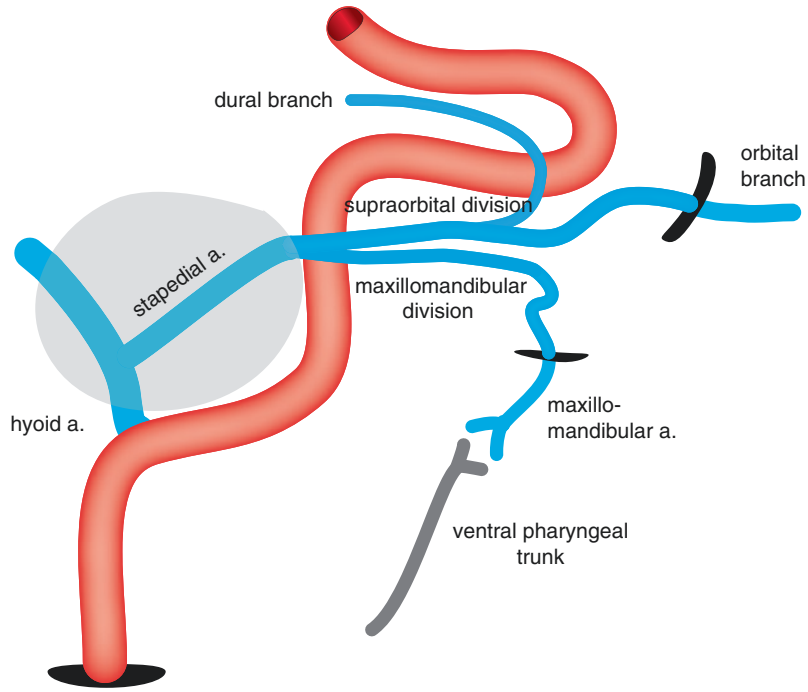

Fig. 1.8 Hyoid/stapedial system: The stapedial artery divides into a supraorbital division to supply dura and non-neural orbital structures and a maxillomandibular division which supplies tissue in the infra-temporal region

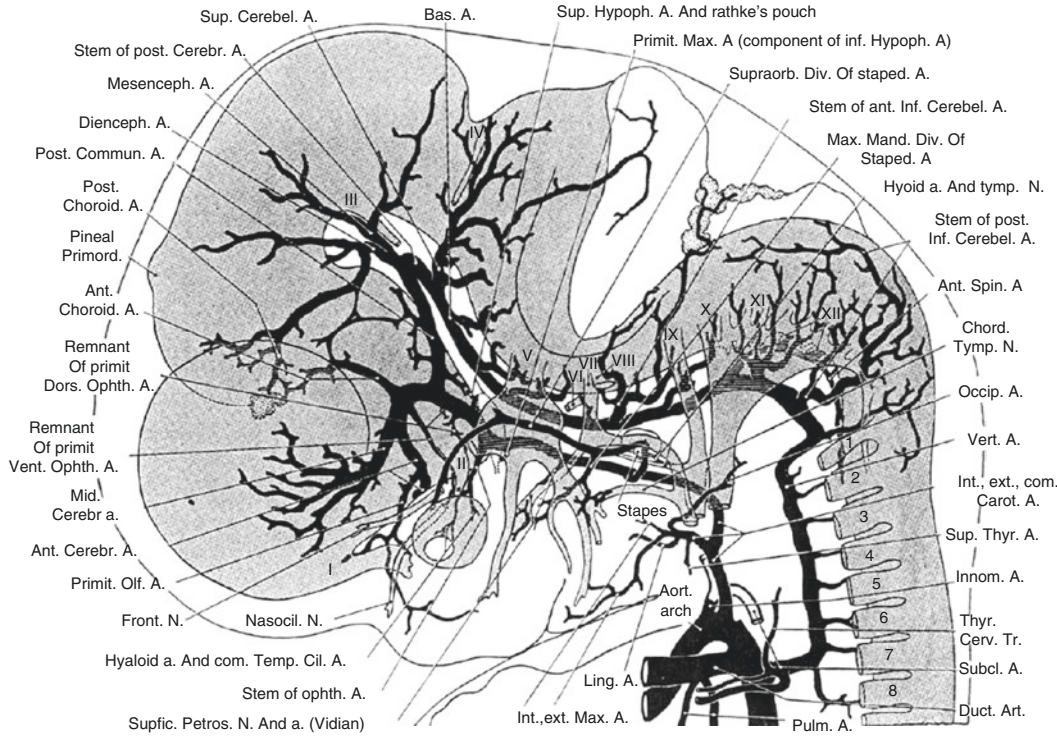

Fig. 1.9 Stage 5. An 18-mm embryo from Padget [3], showing the divisions of the stapedial artery and the adult origin of the ophthalmic artery (Reproduced with permission)

DOA regresses and the definitive ophthalmic artery annexes the primitive VOA as part of an anastomotic ring of arteries around the developing optic nerve. This arterial ring, to which both VOA and DOA originally contributed, has by now started to regress. The definitive ophthalmic artery contributes three branches to the developing eye and orbit: The common temporal ciliary artery, the hyaloid artery and the common nasal ciliary artery. The hyaloid artery (which will become the central artery of the retina) and temporal ciliary artery being derived from the DOA and the common nasal ciliary artery from the VOA. It passes into the orbit (through the future optic canal) around the optic nerve (a remnant of the anastomotic ring) and anastomoses with the supraorbital division of the stapedial artery.

The DOA takes part in the anastomotic ring around the optic nerve from its caudal position (i.e. via the future superior orbital fissure) along with the orbital branch of the supraorbital division of the stapedial artery. Its anastomosis with the VOA around the optic nerve is a potential source of anatomical variations (see below). It regresses leaving only a stem which is represented in the adult pattern by the ILT and a recurrent branch of the ophthalmic artery which connects to the ILT through the superior orbital fissure (Fig. 1.10).

The orbital branch of the supraorbital division of the stapedial artery system divides into medial and lateral branches. The medial nasociliary branch anastomoses with the definitive ophthalmic artery as part of the anastomotic ring. The lateral branch is independent of this anastomosis and contributes to the lacrimal artery in the lateral part of the orbit.

Thus, the normal pattern of the ophthalmic artery involves migrations of the VOA origin to the ICA and regression of the proximal portion of the DOA (Fig. 1.11a). Failure of this complex development results in variations due to failure of connections and regressions between the VOA and DOA around the orbital optic nerve and with the stapedial system.

The more common variants are:

1. No anastomosis between the stapedial system and the primitive ophthalmic artery so that the occulosensory supply comes from the ophthalmic artery and the middle meningeal

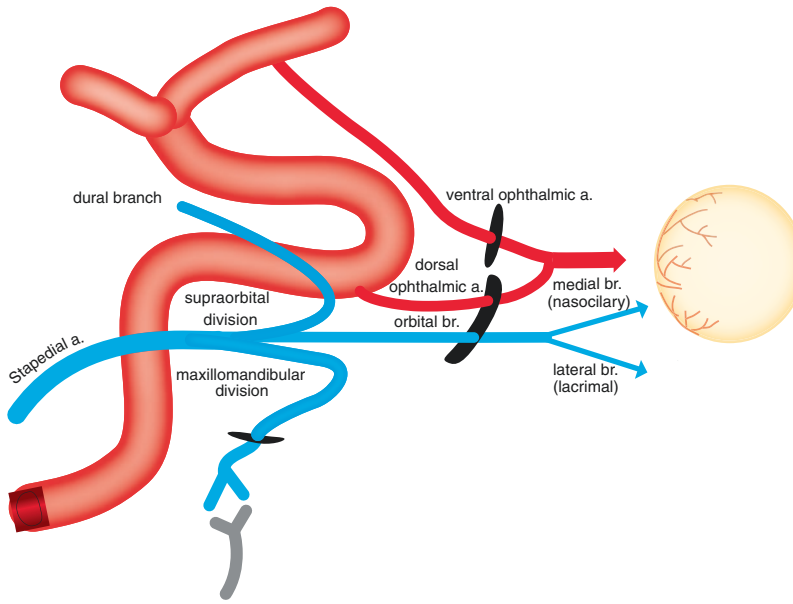

Fig. 1.10 The developing eye: Ventral and dorsal ophthalmic arteries anastomose around the optic nerve (Published with kind permission of © Henry Byrne, 2017. All rights reserved)

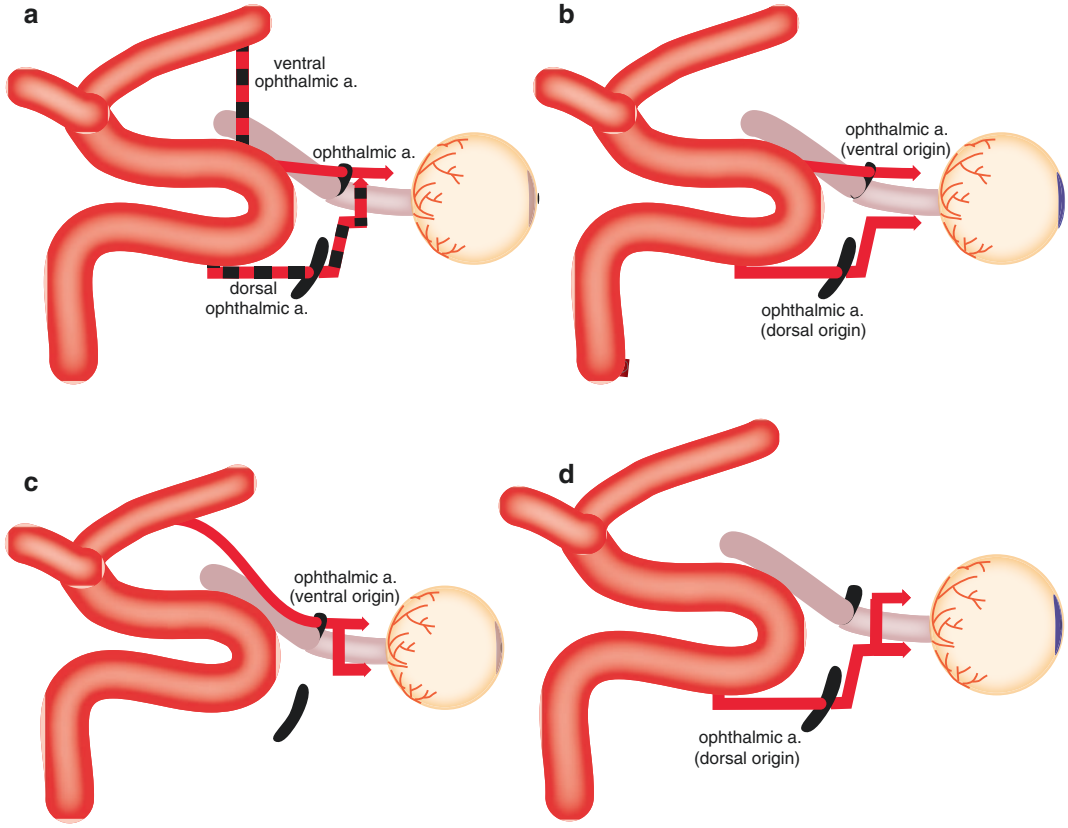

Fig. 1.11 Variations in the ophthalmic artery origin. (**a**) Normal pattern: The dorsal ophthalmic artery joins the ventral ophthalmic artery to form the primitive ophthalmic artery and then regresses. (**b**) Double ophthalmic arteries: The dorsal ophthalmic artery fails to regress. (**c**) Dominant ventral ophthalmic artery: The ophthalmic artery arises from the anterior cerebral artery. (**d**) Dominant dorsal ophthalmic artery origin: The ophthalmic artery arises from the cavernous internal carotid artery (Published with kind permission of © Henry Byrne, 2017. All rights reserved)

artery supplies orbital muscles, the lacrimal gland and the ethmoid/nasal territory.

2. All three embryonic vessels persist so the VOA maintains an anterior cerebral artery origin, the DOA arises from ILT and the orbital branch of the stapedial artery persists and takes origin from the internal carotid artery or the middle meningeal artery. This results in two ophthalmic arteries, one passing into the orbit through the optic canal and the other the superior orbital fissure (Fig. 1.11b).
3. Dominance of either VOA (Fig. 1.11c) or DOA origins (Fig. 1.11d).
4. Ring variants. This term refers to variants in the anatomical relationship of the ophthalmic artery with the optic nerve. In the majority of adults, the lateral half of the anastomotic ring formed by the VOA and DOA persists so the ophthalmic artery crosses above the nerve sheath to the lateral side and the central artery of the retina arises lateral to the nerve. In a minority (estimated up to 15%), the artery curves around the medial side and the central artery of the retina arises more medially.
5. Middle meningeal artery origin of the ophthalmic artery. In this variant, the primitive ophthalmic artery regresses and the orbital branch of the stapedial system persists so that the ophthalmic artery arises from the middle meningeal artery and enters the orbit through the superior orbital fissure.

6. Early regression of the proximal supraorbital division. Since the dural territory of the stapedial artery is annexed by the middle meningeal artery, variations in the separation of the orbital and dural branches of the supraorbital division may cause the middle meningeal artery to arise in the orbit and pass through the superior orbital fissure to the middle fossa (Fig. 1.12). Alternatively, the middle meningeal may give a branch to supply the lateral orbit. This meningo-lacrimal artery may pass through the superior orbital fissure or enter the orbit through Hyrtl's canal (or the meningo-orbital foramen).

1.2.8 Development of the Cavernous Sinus Region

The embryology of the cavernous sinus region involves four embryological arterial systems, namely, DOA, stapedial (supraorbital artery),

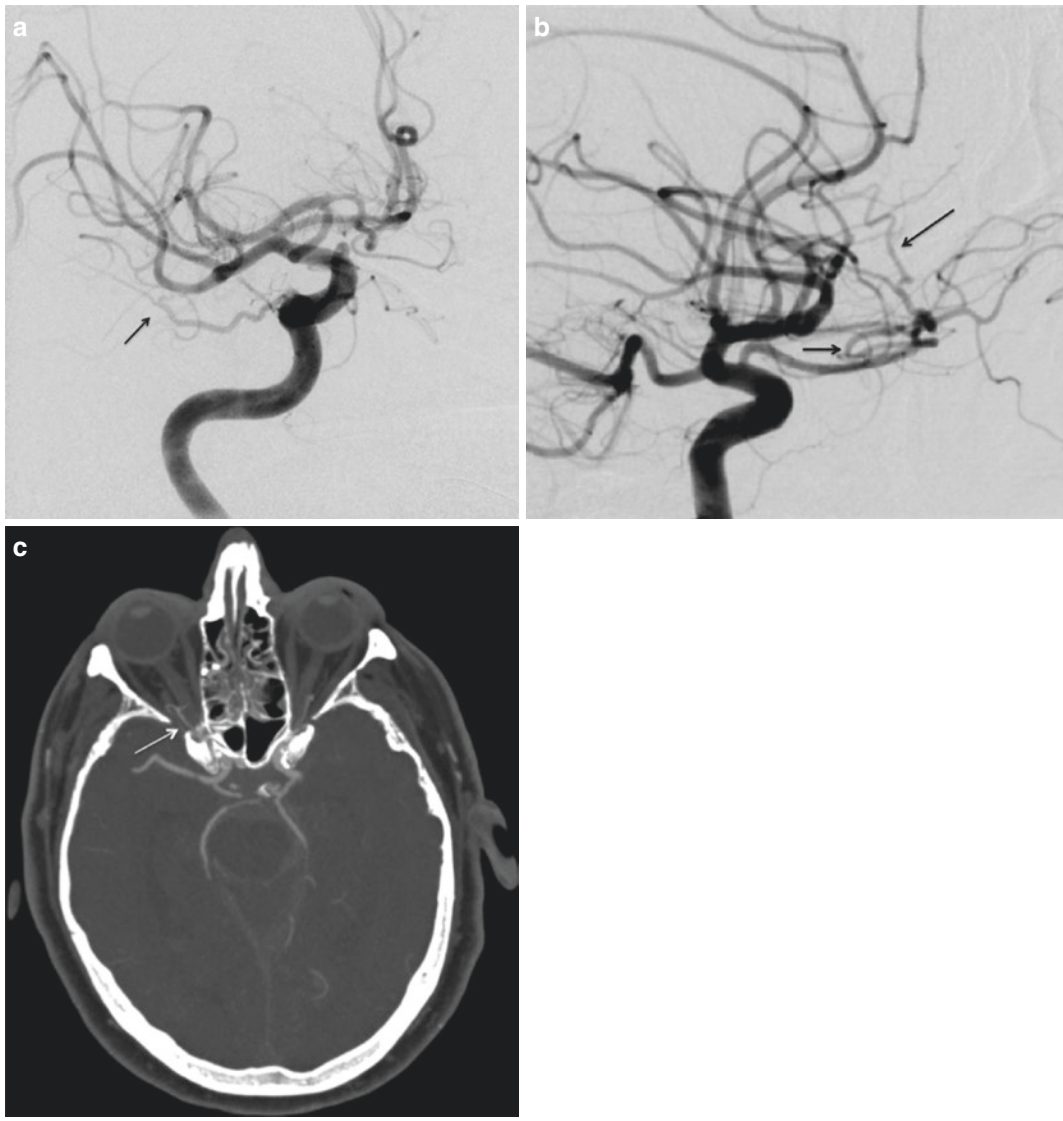

Fig. 1.12 Ophthalmic origin of middle meningeal artery. DSA (**a** and **b**) and CTA (**c**) showing the middle meningeal artery arising from a recurrent branch of the ophthalmic artery (*arrows*)

primitive maxillary artery and trigeminal artery. Their embryological origins as branches of the ICA are described above and their importance lies in the potential for their arterial derivatives to act as collateral routes to the cavernous ICA. In this section the embryology described above is used to explain the complex connections between arteries in this region. It will use the adult pattern to describe how these embryological systems interconnect and the value of understanding their contributions to the region's arteries.

Foremost is the inferolateral trunk (ILT), which originates as the proximal remnant of the dorsal ophthalmic artery (Fig. 1.13). The anterior branch of the ILT divides into antero-medial and antero-lateral branches. The antero-medial passes through the superior orbital fissure to unit with the ophthalmic artery. This anastomosis may persist as a branch of the ophthalmic artery, termed the deep recurrent ophthalmic artery. The antero-lateral branch passes to the foramen rotundum (with the maxillary branch of the trigeminal nerve) and anastomoses with the internal maxillary artery via the artery of the foramen rotundum.

The posterior branch of the ILT divides and creates anastomoses with the internal maxillary artery that can be traced back to the hyoid/stapedial system. One branch anastomoses with the accessory meningeal artery via the foramen ovale and others with dural branches of the middle meningeal artery. These arteries create potential routes to the orbit and via the middle ear to the caroticotympanic trunk. The more posterior recurrent artery of the foramen lacerum may arise from either ILT or the meningohypophyseal trunk (see below). Its pedigree is difficult to fit with the above since it anastomoses with the ascending pharyngeal artery through the carotid branch of the superior pharyngeal artery.

The primitive maxillary artery is derived from the proximal remnant of the first branchial arch and is represented in the adult pattern as the posterior inferior hypophyseal artery

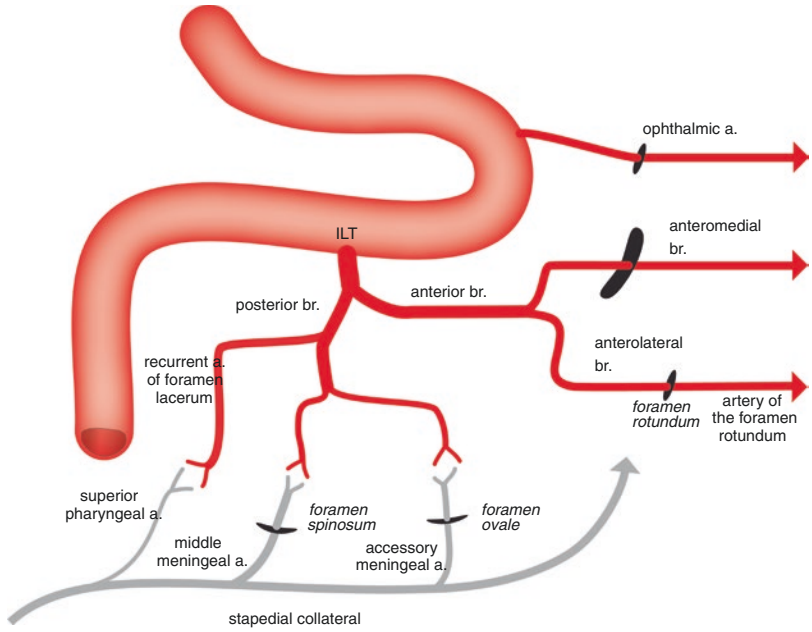

Fig. 1.13 Cavernous sinus region. The branches of the inferolateral trunk (ILT) are shown. The anterior branch supplies the orbit, together with the ophthalmic artery and a contribution from the remnant of the hyoid/stapedial system, designated in the diagram as the stapedial collateral. The stapedial collateral gives branches of the internal maxillary artery and the ascending pharyngeal artery due to the annexation of the hyoid/stapedial territory by the ventral pharyngeal artery (Published with kind permission of © Henry Byrne, 2017. All rights reserved)

(PIHA). This is a branch of the meningohypophyseal trunk which arises from the cavernous internal carotid artery posterior to the ILT (Fig. 1.14). Though a persistent primitive maxillary artery has been described, it simulates the PIHA. The PIHA gives the medial clival artery and branches, which anastomose with the contra-lateral PIHA. These trans-clival anastomoses provide a route to the internal carotid artery from the opposite side when occlusion of the internal carotid country occurs below the cavernous segment. Additionally, from this trunk arise a group of dural vessels to the tentorium (marginal and basal tentorial arteries), the lateral clival artery and variably the recurrent artery of the foramen lacerum. The lateral clival artery represents the remnant of the primitive trigeminal artery (with a medial branch passing posteriorly under the petroclinoid ligament in Dorello's canal with the sixth cranial nerve).

The transient primitive trigeminal artery connects the LNS with the primitive internal carotid artery. It develops during Stage 1 (4–5 mm CRL) and starts to regress as the definitive posterior communicating artery develops during Stages 3 and 4 (7–14 mm CRL). It is represented in the adult form by the lateral clival artery. Since it was a cavernous region branch, it may take part in anastomoses with the DOA/ITL and stapedial systems. Failure to regress results in the persistent trigeminal artery, which connects the basilar artery to the internal carotid artery. A persistent trigeminal artery is the commonest carotid to basilar connection (after the posterior communication artery) found in about 0.2% of angiograms. Two patterns are recognised in its posterior configuration. The first supplies both posterior cerebral arteries and the superior cerebellar artery territories, and the second joins the basilar artery below a functional posterior communicating artery and is then the principal supply to the superior cerebellar arteries only (see Fig. 1.7).

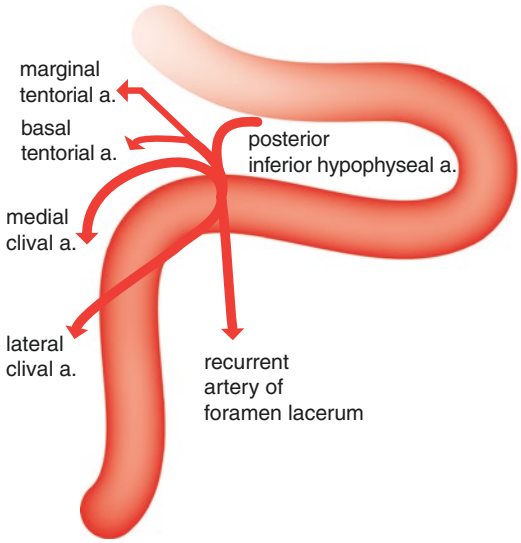

Fig. 1.14 Meningohypophyseal trunk. The adult pattern of branches arising from the meningohypophyseal trunk of which the posterior inferior hypophyseal artery is the remnant of the primitive maxillary artery (Published with kind permission of © Henry Byrne, 2012. All rights reserved)

1.2.9 The Inner and Middle Ear Arteries and Their Variants

The blood supply to the inner ear is derived from the acoustic branch of the anterior inferior cerebellar artery (AICA) whilst the middle ear derives its blood supply from the carotid system.

In the adult pattern, the following arteries supply the middle ear:

1. The superior tympanic artery which arises from the middle meningeal artery and represents a remnant of the stapedial artery.
2. The caroticotympanic artery which arise from the petrous ICA and is the remnant of the hyoid artery (second branchial arch artery).
3. The inferior tympanic artery which is a branch of the ascending pharyngeal (third brachial arch artery).
4. The artery of the stylomastoid foramen arising from the posterior auricular artery (or superficial temporal artery) and the anterior tympanic artery from the internal maxillary artery.

The arterial variants that may occur in the middle ear are:

1. Persistent stapedial artery replacing the middle meningeal artery and arising from the ICA and following the course of the stapedial artery through the middle ear to the middle and infra-temporal cranial fossae. Thus, the foramen spinosum is small or absent and an origin of the middle meningeal artery from the internal maxillary artery is absent.
2. Segmental agenesis of the internal carotid artery below the second branchial arch (C1 or C2). This variant leads to a pseudo-ICA or aberrant ICA reconstituted via the ascending pharyngeal artery and its branch, the inferior tympanic artery, to the middle ear. The ICA is reconstituted at the level of the caroticotympanic trunk via the caroticotympanic artery. Persistence of the stapedial artery may also occur with this variant. The variant artery therefore does not pass through the foramen lacerum and the carotid canal is absent.
3. A pharyngotympanostapedial artery results from the tympanic branch of the ascending pharyngeal artery replacing the middle meningeal artery. It is rare but its existence demonstrates an anastomosis between the inferior tympanic artery and the superior tympanic branch of the middle meningeal artery and thus a route to the internal maxillary artery. It thus replaces the origin of the middle meningeal artery from the internal maxillary artery.

1.2.10 Vertebral and Vertebrobasilar Anomalies and Persistence

The LNS comprises bilateral median longitudinal arteries which differentiate along the ventral surface of the neural tube. At about the 10 mm CRL stage, the LNS on the mesencephalon and rhombencephalon connect cranially with the posterior division of the internal carotid system (i.e. posterior communication artery) and caudally with the developing vertebral arteries. The vertebral arteries are formed by differentiation of more lateral longitudinal channels between the segmental arteries of the cervical embryonic somites. Fusion of the LNS in the midline to form the basilar artery and anterior spinal artery occurs over a relatively long period, extending up to the 40 mm CRL stage. Since these arteries are formed by their fusion in the midline, incomplete fusion can occur leading to duplications and fenestrations. It should also be borne in mind that parallel, more lateral longitudinal arteries may arise and regress which also may result in duplications and fenestrations. The transitory pre-segmental connecting arteries between the dorsal aorta and the developing basilar and vertebral arteries have been described previously.

1.2.10.1 Common Anomalies of the Vertebral Arteries

In the adult pattern, the vertebral arteries run in vertebral canals formed in the transverse processes of vertebrae C6–C2, but since they are constituted from cervical segmental arteries, level variations in their origins are not uncommonly encountered. Their proximal origin is usually described as being from the C6 segmental artery because they normally enter the foramen transversarium of the C6 vertebra.

It is important to understand the convention used in numbering segmental arteries in the cervical region. The segmental artery is in fact better termed the intersegmental artery because, with differentiation of the bony vertebrae, the segmental artery is displaced between the vertebrae and by convention numbered with the vertebra above. Thus, the sixth intersegmental artery lies between C6 and C7 vertebrae. The adult subclavian arteries develop from the C7 intersegmental arteries, i.e. the next caudal level. Since the first intersegmental artery arises below C1, the artery above is designated the proatlantal intersegmental artery.[2]

[2]Not to be confused with numbering of the cervical nerve roots and their arteries in which the nerve root is numbered by the vertebra above which they emerges, i.e. C2 root between C1 and C2 vertebrae and C8 root between C7 and D1 vertebrae.

1. Variations in the vertebral level where the artery enters the vertebral canal. The frequency of entry at different levels has been estimated as 10% at C5, 90% at C6 and 5% at C7.
2. Direct origin from the aortic arch. This is attributed to dominance of the fourth intersegmental artery and is most often seen on the left side. The vertebral artery arising from the aorta, thus usually enters the vertebral foramen under the C4 vertebra.
3. Rarely the vertebral artery arises from the thyrocervical trunk alone or with a dural origin directly from the aorta.
4. Fenestrations and duplications. The distinction between these terms is at times difficult to understand. Fusion of the LNS that causes the emergence of the basilar artery is the best example of an incomplete embryological process causing fenestration. It results in the fenestrated basilar arteries seen as a variant of the adult pattern. In the vertebral artery, when two channels are seen within the vertebral canal, it is also termed fenestration and attributed to a fusion failure. Whereas, the vertebral artery is duplicated when one channel runs within the vertebral canal and the other alongside but outside the canal. This situation is due to a regression failure and the persistence of an embryonic vessel.

1.2.10.2 Variants at the Vertebrobasilar Junction

Adapted from Lasjaunias and Berenstein [4], the template shown in Fig. 1.15 attempts to illustrate the potential for variants to the adult pattern that result from the development of the vertebral arterial system from the LNS. The horizontal lines represent segmental levels and the numbered vertical line intrasegmental longitudinal connections. Thus, (1) represents the midline longitudinal neural system which gives the basilar artery and the anterior spinal artery; (2) a para-medial longitudinal system, exemplified by the lateral spinal arteries; and (3) a more lateral longitudinal intrasegmental anastomoses which constitute the vertebral arteries.

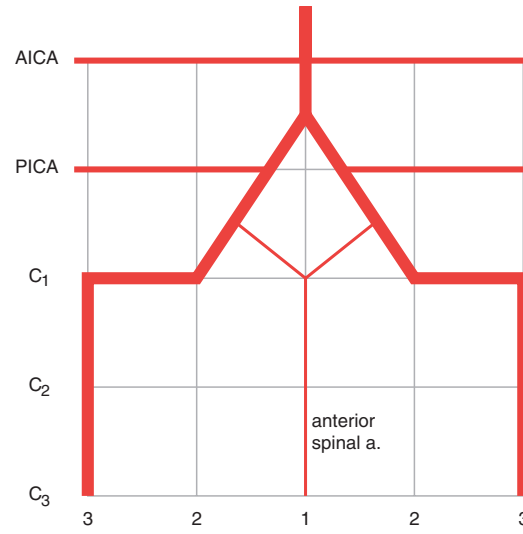

Fig. 1.15 Development of the vertebrobasilar junction. This diagram and Figs. 1.16 and 1.17 are based on a template adapted from [4] (see text). It emphasises the vertebral and basilar arteries development from longitudinal connections between segmental levels. *AICA* anterior inferior cerebellar artery, *PICA* posterior inferior cerebellar artery, *C1, C2, C3* cervical spinal levels (Published with kind permission of © Henry Byrne, 2017. All rights reserved)

This template will be used to illustrate the more common arterial variations at the vertebrobasilar junction.

The template also helps to illustrate the three caudal anomalous carotid to vertebrobasilar anastomoses (Fig. 1.17a–c).

1. Persistent hypoglossal artery (Figs. 1.17a and 1.18).

   This vessel runs from the internal carotid artery to the vertebrobasilar system through the hypoglossal canal. The intracranial ipsilateral vertebral artery inferior to the junction is absent and the contralateral vertebral often hypoplastic (Fig. 1.18). A 'forme fruste' of this variant exists when PICA arises from the ascending pharyngeal artery. This is possible because the hypoglossal artery normally arises as a branch

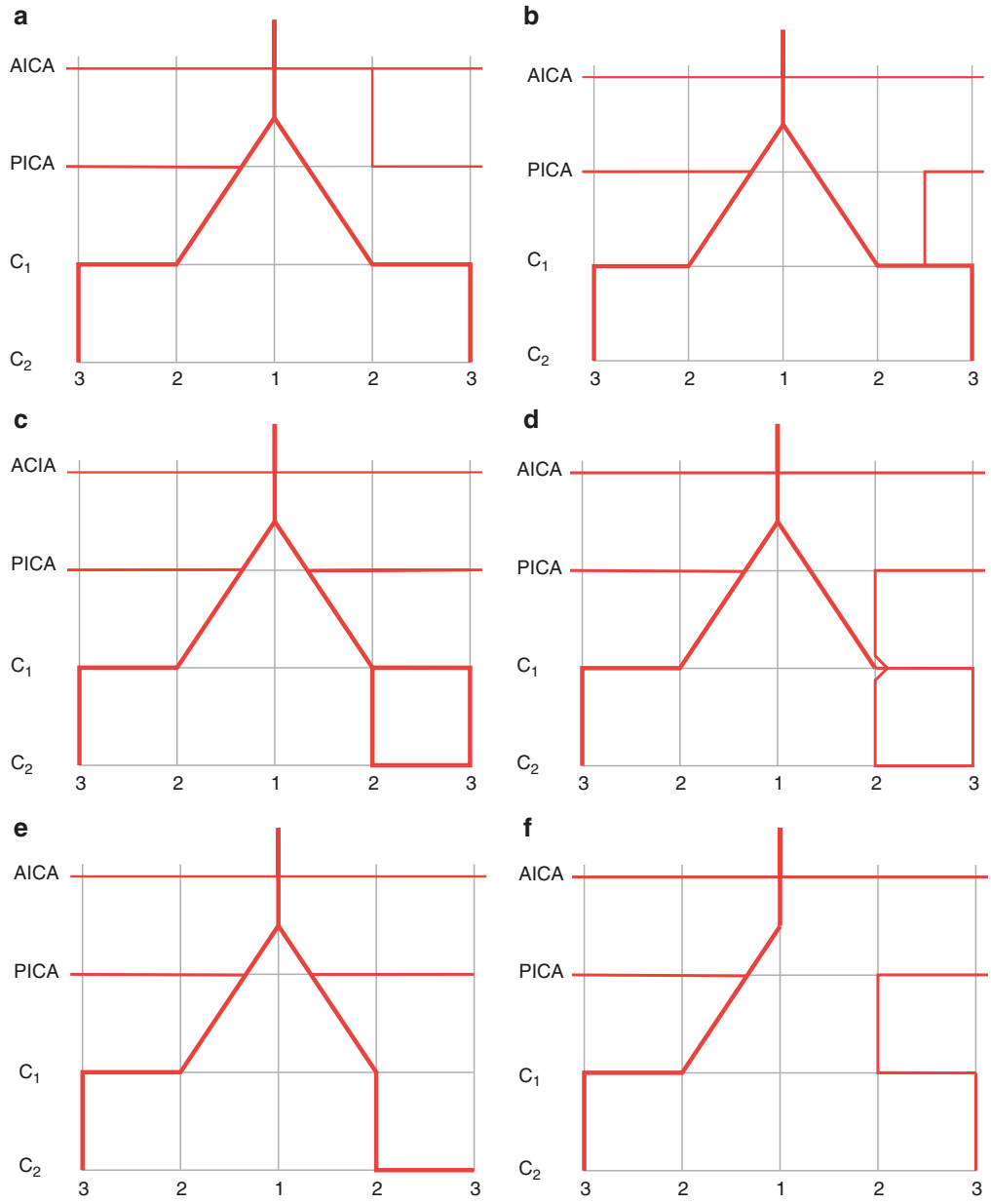

Fig. 1.16 (**a**) Dominant AICA (*left side*), the PICA territory has been subsumed by the ipsilateral AICA on the left side. (**b**) Proximal PICA origin from C1 Level, PICA arises from the intersegmental C1 arterial branch of the vertebral artery. (**c**) Para-medial duplication of the vertebral artery at C1/C2. (**d**) C2 origin of PICA. (**e**) Intradural spinal course of the vertebral artery medial to C1. (**f**) Vertebral artery origin of PICA with absent distal vertebral artery (Published with kind permission of © Henry Byrne, 2017. All rights reserved)

of the ascending pharyngeal artery. The PICA origin from the ascending pharyngeal artery is thus attributed to a partial persistence of the embryonic hypoglossal artery.

2. Persistent proatlantal artery type I (Fig. 1.17b).

The internal carotid artery anastomoses with the vertebral artery via this persistent intersegmental artery branch at C1, which passes through the first intervertebral space

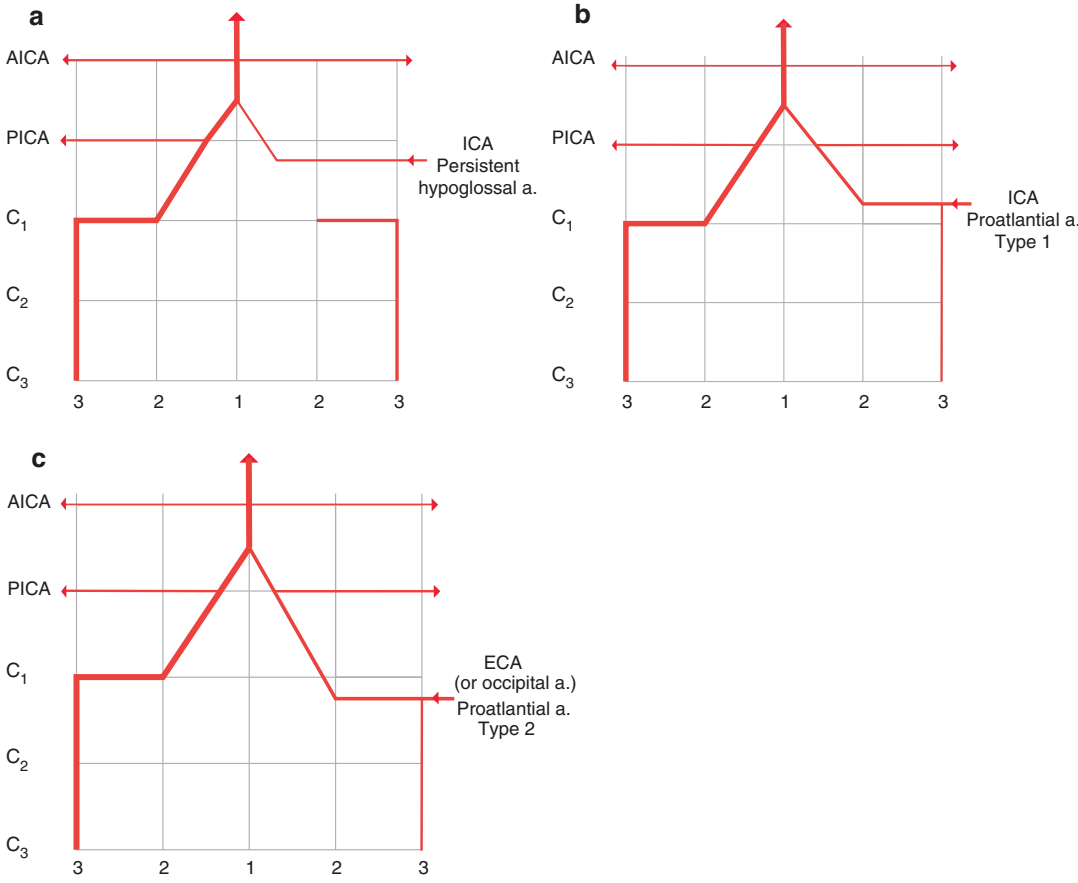

Fig. 1.17 (**a**) Persistent hypoglossal artery with hypoplastic ipsilateral vertebral artery. (**b**) Persistent proatlantal intersegmental artery type 1. (**c**) Persistent proatlantal intersegmental artery type 2 (Published with kind permission of © Henry Byrne, 2017. All rights reserved)

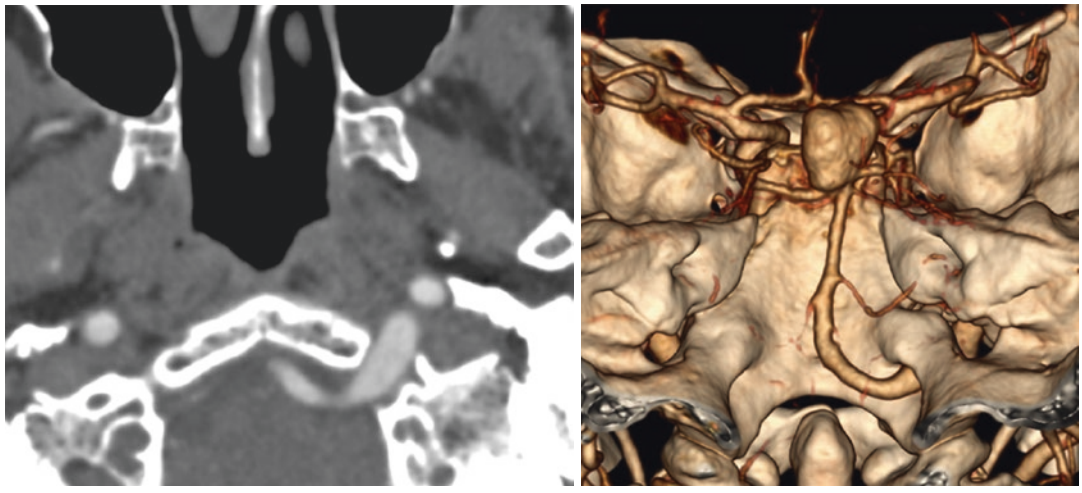

Fig. 1.18 Persistent hypoglossal artery. CTA showing the basilar artery arises from the hypoglossal artery, in this patient with an aneurysm. The artery passes through the left hypoglossal canal

(above the lateral ring of C1). A 'forme fruste' involves the PICA arising from the occipital artery. This reflects the common anastomoses between the C1 and C2 vertebral artery and the occipital artery.

3. Persistent proatlantal artery type 2 (Fig. 1.17c).

   This differs from type 1 because the connecting artery arises from the external carotid artery (but usually in conjunction with the occipital artery) and passes under the C1 ring to anastomose with the vertebral artery. A similar 'forme fruste' is described with the PICA arising from the occipital artery via this inferior route. There is a degree of ambiguity in the descriptions of the origins of the persistent proatlantal arteries, which probably reflects their intimacy with the occipital artery.

1.3 Development of Cerebral Veins

The earliest venous system consists of a network of primitive collecting veins that drain into a superficial venous network on the surface of the neural tube. This primitive network is superficial to the arterial network and drains centrifugally (outward). Later as the cerebral hemispheres develop, this early pattern of flow changes. Medullary veins develop, and once a deep cerebral venous system is established, drainage is both centrifugal and centripetal, i.e. superficial drainage is centrifugal and drainage of the deep white matter and basal ganglia is centripetal to subependymal veins of the lateral ventricles and thence to the deep veins. The cerebral veins develop later than the arteries [5].

The dural sinuses and superficial venous networks develop together from a matrix of vessels, which become concentrated as plexuses as the vesicles develop. The initial matrix pattern is retained during their development and larger channels are formed by the coalescence of vessels without the longitudinal and lateral orientations seen in the segmental LNS. The development of the dural venous sinuses continues after birth.

1.3.1 Superficial Veins and Dural Sinuses

The superficial network of pial veins on the developing cerebral vesicles drains to the venous plexus of the dura which drains to the primary head vein. The primary head vein appears in the region of the midbrain at 5 weeks, run caudally on either side of the neural tube to the precardinal veins and sinus venosus (Fig. 1.19). It initially drains three plexi of capillaries. The anterior (draining prosencephalon and mesencephalon) enters rostral to the trigeminal ganglion. The middle (draining metencephalon) enters caudal to the trigeminal ganglion, and a posterior dural plexus (draining myelencephalon) enters at the start of the precardinal vein (Fig. 1.19 – 14 mm).

At around the 6-week stage, growth of the middle ear requires a change in its course. To make the necessary adjustment, an anastomosis is established dorsal to the otic capsule between the middle dural plexus and the posterior dural plexus (Fig. 1.19 – 18 mm). The superior petrosal sinus is a derivative of a remnant ventral to the otic capsule. Next the anterior plexus fuses with the middle plexus and both drain through this new channel, dorsal to the otic capsule, to the posterior plexus and the cardinal veins.

The cavernous sinuses form from a secondary plexus of the primary head vein lying medial to the otic capsule. The primary head vein also receives the primitive maxillary vein, which drains the maxillary prominence and the optic vesicle. The primitive maxillary vein is the precursor of the superior orbital vein. The rostral portion of the primary head vein forms the future internal jugular vein but its primary connection to the cavernous sinus regresses and its remnant in the adult is the inferior petrosal sinus. The principle drainage from the paired cavernous sinuses is through the original trunk of the middle plexus, which are now the superior petrosal sinuses, into the newly established dorsal channels. These become the transverse sinuses (Fig. 1.19 – 21 mm).

From the anterior plexus, a pair of marginal sinuses extends along both sides of the cranial

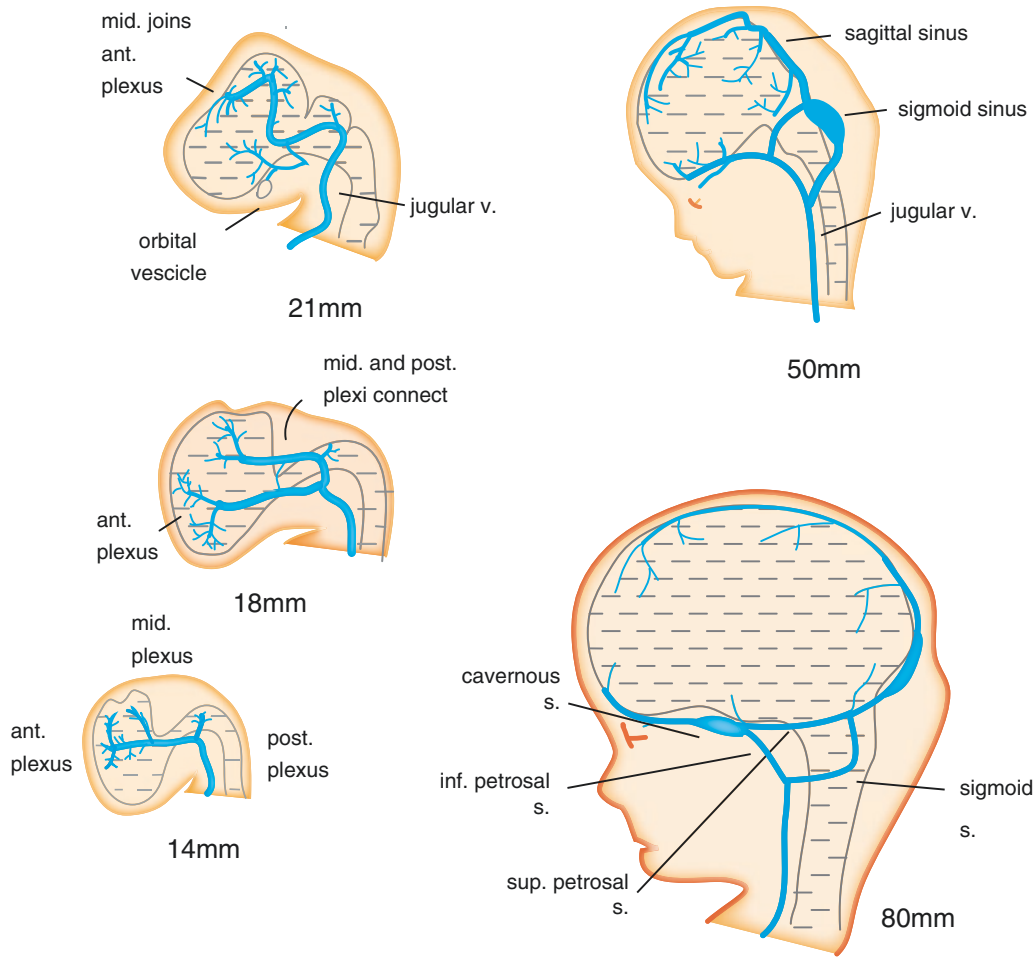

Fig. 1.19 Stages in development of the dural sinuses (Published with kind permission of © Henry Byrne, 2017. All rights reserved)

cerebral vesicles. These embryonic sinuses extend forward and fuse in the midline to form the superior sagittal sinus (Fig. 1.19 – 50 mm). The straight sinus is formed in the ventral part of the sagittal plexus from reorganisation and fusion of the embryonic territorial plexus, and the transverse sinuses are displaced laterally by the expanding cerebellum (Fig. 1.19 – 80 mm).

The external jugular vein at first drains the scalp and enters the primitive jugular vein as a lateral tributary. A group of veins from the face and lingual region converged to form a common vein, the lingo-facial vein, which also terminates in the primitive jugular vein. Later, cross communications develop between the external jugular and lingo-facial veins, with the result that the posterior group of facial veins is transferred to the external jugular vein.

1.3.2 Deep Veins

The precursor of the deep veins is a single transitory midline vein, the median prosencephalic vein. This drains the choroid plexi and runs backwards towards the developing dorsal interhemispheric dural plexus, termed the falcine sinus. As the basal ganglia and choroid plexi induce the development of the internal cerebral veins, the median prosencephalic vein regresses. This

occurs about the tenth week of gestation, and the caudal remnant of this vein unites with the internal cerebral veins to form the vein of Galen. The basal vein of Rosenthal develops from a transitory dural sinus called the tentorial sinus. This drains the ventral surface of the diencephalon to the newly formed transverse sinus. As the hemispheres expand and the temporal lobes develop, it regresses and its territory reverts to the pial plexus connecting to the vein of Galen.

The infra-tentorial, i.e. metencephalic and mylencephalic, veins have a very variable pattern of development and have proved too difficult for our tutorials. They are therefore left to the more industrious student to explore alone.

Variants to cerebral veins and sinuses:

1. Cerebral veins may not develop to the adult pattern until the 80 mm CRL stage. Even so, the lateral mesencephalic veins are not present at birth, and in infants, occipital and tentorial sinuses are often present though both are rarely evident in adults.
2. When persistent, the median prosencephalic vein continues to serve as the drainage pathway of the diencephalic and choroidal veins. This results in an atretic straight sinus and aneurysmal enlargement of the vein of Galen (i.e. vein of Galen malformation, see Tutorial 12).
3. The basal vein of Rosenthal may drain to a tentorial sinus reflecting its initial drain laterally and infra-tentorially to a 'trigeminal vein' which is described as corresponding to the superior petrosal sinus in the adult pattern.
4. The torcular often shows duplication of channels with asymmetry and dominance to the right when the straight sinus goes to the left. These reflect its derivation from a series of venous channels. Right side dom inance has been suggested as being a reflection of the right dominance of the large central veins.
5. The sphenoparietal sinus may not drain to the cavernous sinus; it may be directed posteriorly via a tentorial sinus (termed the sphenobasal sinus) to either the superior petrosal sinus or the transverse sinus.

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Cranial Arterial Anatomy

2

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Preamble

The purpose of this tutorial is to outline cranial arterial anatomy for the student endovascular therapist. These details are reproduced widely in text books, so why include them in the tutorials of the Oxford Course? The answer is to give guidance by providing context and suggesting priorities in this core knowledge. The tutorial therefore intends to equip the reader with an understanding of the detail that they need to master in order to practice. Like other tutorials, the attempt is to be both comprehensive and selective. By emphasising areas important to the performance of endovascular treatments, it aims to avoid simply reproducing a standard anatomical text.

The blood supply of the cranium is traditionally described separately as cerebral and craniofacial circulations. The two systems are obviously not isolated from each other, and understanding and recognition of actual and potential connections between them are fundamental practical skills in endovascular neurosurgery. Anastomoses between extra- and intracranial blood supplies are potential dangers and their recognition underpins safe interventions in the head and neck. They will be outlined here but considered again in Tutorial 7. The student needs to realise that if an artery is rarely seen on angiography, it doesn't mean that it is not there or a potential route that may cause a complication during embolisation. Familiarity with small arteries not normally seen on angiography is important for this reason

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because they need to be identified if a disease causes their enlargement. If you don't know where to look, you won't find them.

2.1 Internal Carotid Artery (ICA)

The internal carotid artery originates in the neck as a terminal branch of the common carotid artery (CCA) at the level of the thyroid cartilage, i.e. C3 or C4 vertebrae (but varying between extremes at D1 and C1). It terminates intracranially at the inferior surface of the brain by dividing into anterior and middle cerebral arteries.

No single system for identifying different sections of the large cerebral arteries has been generally adopted. This is particularly the case for the ICA. Fischer in 1938 [4] used a simple code (A1, A2, M1, M2, P1, P3, etc.) to describe sequential arterial sections in the direction of blood flow at and above the circle of Willis[1] based on branch points. This is intuitive and is generally consistently applied in the literature. However, for ICA he used five sections (C1–C5) but applied them in reverse (i.e. from distal to proximal and against the direction of blood flow). Subsequent authors misinterpreted or ignored this convention, and there is now confusion in the literature over the naming of sections of the ICA. So, simple anatomical descriptors will be used for this artery and Fischer's convention for the arteries comprising the circle of Willis. Thus, the ICA will be discussed in four sections: cervical, petrous, cavernous and supraclinoid portions from proximal to distal.

2.1.1 The ICA Cervical Portion

This extends from the bifurcation of the CCA to the skull base. In this section, the artery lies in the carotid sheath with the internal jugular vein laterally and the vagus cranial nerve (tenth) and the cranial root of the accessory nerve (eleventh) that travel with the tenth, lying posteriorly and between these vessels. The sheath, which is comprised of all three layers of the deep cervical fascia, also contains lymph nodes and sympathetic postganglionic fibres from the superior cervical ganglion.

The internal diameter is about 4–5 mm throughout, except at the carotid sinus (often called the carotid bulb by angiographers) where the artery is 7.5 mm wide for a distance of 15–25 mm. The wall of the carotid sinus contains baroreceptors to monitor systemic blood pressure and the carotid body. The carotid body houses chemoreceptor cells that monitor blood oxygen, CO_2 and pH levels and stimulate respiration and heart rate in response to detected hypoxia. These receptors are connected via nerve fibres of Xth and XIth cranial nerves to the cardiovascular centre in the medulla oblongata and nerve endings in the carotid sinus connected to the inferior ganglion of the vagus. The parasympathetic nervous system modulates systemic blood pressure, and endovascular stimulation of the sinus may simulate its physiological response to increases in pressure by signalling to reduce heart rate and, by inhibiting the vasoconstrictor centre of the medulla oblongata, causing peripheral vasodilatation.

The ICA normally (in 80% of individuals) lies initially behind and lateral to the external carotid artery (ECA) but as these arteries run cranially, the ECA inclines superficially to lie lateral to the ICA on a frontal angiogram. With the exception of anatomical variants, no named branches arise from the cervical portion of the ICA. The most common variant is that the ascending pharyngeal artery (APA) arises from the proximal ICA. Other ECA branches may arise from the ICA and agenesis or hypoplasia may occur, as discussed in Tutorial 1.

2.1.2 The ICA Petrous Portion

During its intrapetrous course, the ICA is initially situated within the bony carotid canal before entering the cartilaginous foramen lacerum. It makes a right angle turn in the canal after an initial short vertical section and then runs anteromedially in the horizontal plane where the bony

[1]Thomas Wills (1621–1675) English physician who worked most of his life in Oxford. He described the basal anastomotic ring in 'Cerebri anatome cui accesit nervorum descriptio et usus' published in 1664.

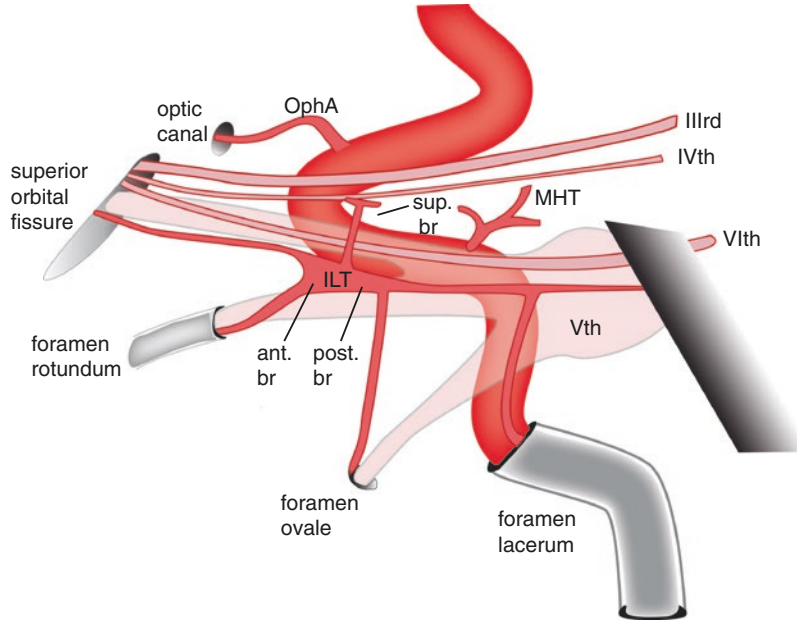

Fig. 2.1 Inferolateral trunk. Diagram showing the three branches of the inferolateral trunk. *ILT* inferolateral trunk, *OphA* ophthalmic artery, *MHT* meningohypophyseal trunk (Published with kind permission of © Henry Byrne, 2017. All rights reserved)

canal is continuous with the foramen lacerum. Its anatomical limit is the petroclinoid ligament where it turns upwards into the cavernous sinus. Sympathetic postganglionic fibres continue into the carotid canal with the ICA where in the horizontal section it is accompanied by a venous plexus. The sympathetic plexus, derived from the superior cervical ganglion, is vulnerable in cases of arterial wall dissection, and its damage causes ipsilateral Horner's syndrome. It leaves the artery in the horizontal section to join the Vidian[2] nerve (with the greater superficial petrosal nerve) in the pterygoid canal and runs anteromedially to the pterygopalatine fossa.

Branches: From the horizontal segment of the petrous ICA arise the caroticotympanic artery and the mandibulo-Vidian trunk (MVT). The former gives the tympanic artery to supply the middle ear. The MVT arises from the ICA in the foramen lacerum. It gives the artery of the pterygoid canal (or Vidian artery) which supplies the sphenoid sinus and anastomoses with the Vidian artery arising from the proximal portion of the internal maxillary artery (IMA) and the mandibular artery. The mandibular artery takes part in the anastomoses around the Eustachian[3] tube.

2.1.3 The ICA Cavernous Portion

Following its petrous passage, the ICA enters the cavernous sinus and lies medial to the Gasserian ganglion, the ophthalmic division of the trigeminal nerve (Vth) and the oculomotor (IIIrd), trochlear (IVth) and abducens (VIth) cranial nerves. It runs horizontally forwards and then turns superiorly and medial to the anterior clinoid process, passing through the dural ring to its final intradural course (Fig. 2.1). The branches that arise in this portion of the ICA are small and difficult to identify individually on angiography but nevertheless as important to the endovascular therapist as to a pituitary surgeon.

2.1.3.1 Branches of the Cavernous ICA

These will be described in three groups.

Group 1: The meningohypophyseal trunk (MHT)

[2]Vidus Vidius (1509–1569) Italian surgeon and anatomist who worked in Florence and Paris and taught at the University of Pisa.

[3]Bartolomeo Eustachi (1514–1574) Italian anatomist whose anatomical drawings were published posthumously because he feared excommunication from the Catholic Church.

The MHT and posterior inferior hypophyseal artery are remnants of the first branchial arch artery and arise from the proximal section of the cavernous ICA (Fig. 1.14). These small vessels may arise from a common trunk or separately as three arteries:

(a) Marginal tentorial and basal tentorial arteries. These dural arteries usually arise as a common trunk (called the dorsal meningeal artery). The marginal (or medial) tentorial artery is memorable because of its wonderfully musical eponymous label as the artery of Bernasconi and Cassinari [1]. It follows the free edge of the tentorium posteriorly and therefore runs medial to the basal artery. The basal tentorial artery runs laterally and divides over the tentorium posterior to its attachment to the petrous ridge. It anastomoses with the posterior branch of the middle meningeal artery (MMA).
(b) Lateral clival artery. This vessel supplies the dura of the clivus dividing into lateral and inferolateral branches, which follow the superior and inferior petrosal sinuses, respectively. They anastomose with the contralateral artery, with dural branches of the MMA and jugular branch of the (APA).
(c) Posterior inferior hypophyseal artery (PIHA). The PIHA supplies the posterior lobe of the pituitary and anastomoses with the capsular arteries of McConnell as well as its contralateral counterpart. It gives a medial clival branch (also, in my view confusingly, called the dorsal meningeal artery by some authors) which anastomosis with the clival meningeal branches of the hypoglossal artery (another APA branch).

Group 2: The inferolateral trunk (ILT)

The ILT was known as the inferior cavernous sinus artery, until renamed by Wickborn and Stattin in 1958 [2] after they identified it on angiograms performed to investigate a meningioma.

It arises on the lateral side of the midsection of the cavernous ICA and crosses over the VIth cranial nerve to divide into three principal branches (Fig. 2.1). These are:

(a) A superior branch which returns medially towards the roof of the cavernous sinus, which it supplies together with the IIIrd and IVth cranial nerves as they lie in the wall of the sinus.
(b) An anterior branch which runs forwards in the cavernous sinus and supplies the IIIrd, IVth and VIth cranial nerves. It gives branches, which traverse the foramen rotundum and the superior ophthalmic fissure to anastomose, respectively, with the artery of the foramen rotundum (a branch of the internal maxillary artery (IMA)) and the deep recurrent ophthalmic artery (i.e. the remnant of the embryonic dorsal ophthalmic artery). A further branch to the foramen ovale anastomoses with the accessory meningeal artery, which, if the ILT is small, may become the dominant vessel supplying its territory.
(c) A posterior branch which follows the VIth nerve posteriorly, which it supplies as well as the maxillary division of the trigeminal nerve and the Gasserian ganglion. It gives dural branches which anastomoses with the marginal tentorial artery and with the MMA laterally in the middle cranial fossa and the recurrent artery of the foramen lacerum. The recurrent artery of foramen lacerum is a small artery, which returns along the carotid canal to the foramen lacerum.

It is usually a branch of ILT that may arise from the MHT. Its importance is because of a potential anastomosis with the superior pharyngeal branch of the APA in the foramen lacerum.

Group 3: The capsular arteries of McConnell

These are a series of small arteries providing a systemic (rather than portal) supply to the anterior lobe of the pituitary and the sella dura. They are of little relevance to the endovascular

therapist though they have been implicated in the formation of the uncommon medially directed aneurysm of the cavernous ICA.

If the ILT is absent, the MHT will supply most of its territory, and if a persistent trigeminal artery is present, its carotid connection is at the level of the MHT.

2.1.4 The ICA Intradural Portion

The supraclinoid portion of the ICA is intradural, the artery having entered the subarachnoid space through the dural ring medial to the anterior clinoid process. It turns posteriorly and runs lateral to the optic nerve to terminate by dividing into the anterior and middle cerebral arteries. From this portion arise successively the ophthalmic artery (OphA), the superior hypophyseal artery or arteries, the posterior communicating artery (PComA) and the anterior choroidal artery (AchA). The level of the OphA origin varies, and it may arise in an 'extradural' location below the ring, but this distinction is usually impossible to make from a standard catheter angiogram (DSA) but may be possible on rotational 3D images.

2.1.4.1 Branches

1. Ophthalmic artery (OphA) (Fig. 2.2)

The OphA originates from the anterior surface of ICA and runs forwards into the orbit through the optic canal. In the canal, it is initially lateral

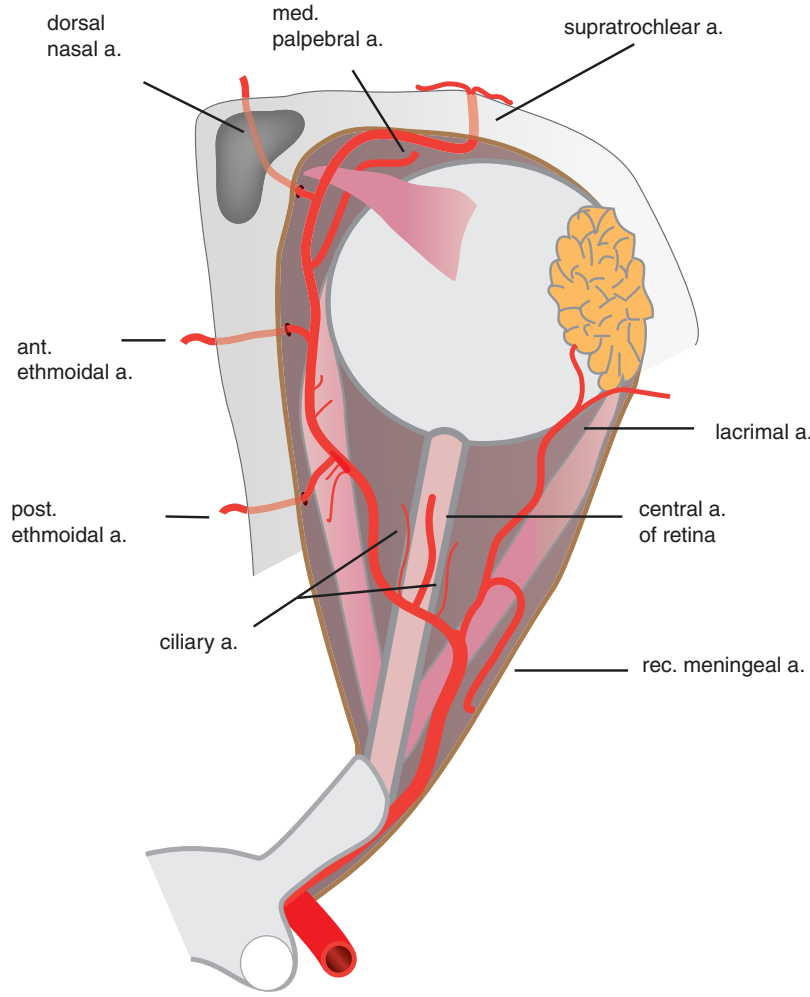

Fig. 2.2 Arteries of the orbit. Superior view of the ophthalmic artery crossing over the optic nerve and running above the medial rectus muscle (Published with kind permission of © Henry Byrne, 2017. All rights reserved)

and then above the optic nerve. Once in the orbit, it runs medially along the upper border of the medial rectus muscle and terminates by dividing into the dorsal nasal artery (or dorsal artery of the nose) and supratrochlear artery. Its major branches are the central artery of the retina (which arises within the optic canal and penetrates the dural sheath of the optic nerve to supply the retina), ciliary arteries (responsible for the choroidal blush), the lacrimal artery (which gives the recurrent meningeal artery and distributes to the lacrimal gland, lateral extraocular muscles and lateral eyelids), the posterior and anterior ethmoidal arteries, the supratrochlear artery and the dorsal nasal artery. The supratrochlear artery runs forwards to the supraorbital notch and is distributed as the supraorbital artery to the skin of the forehead, whilst the dorsal nasal artery supplies superficial structures of the medial orbit and upper nose. The anterior ethmoidal artery gives off anterior meningeal branches (as the anterior artery of the falx) and supplies the mucosa of the superior nasal septum. The posterior ethmoidal artery supplies the posterior ethmoid sinus and part of the posterosuperior aspect of the nasal mucosa. The proximity of the territories of these branches and those of the IMA (in particular the sphenopalatine artery and MMA) makes the study of the vascular anatomy of this region so important (see Tutorial 7). Other small arteries are distributed to the extraocular and palpebrae muscles.

2. Superior hypophyseal artery

The superior hypophyseal artery is infrequently identified on angiograms since it is small and may arise as a single branch or as several small branches. It supplies the pituitary gland and part of the optic chiasm and intracranial optic nerve.

3. Posterior communicating artery (PComA)

The PComA is an anastomotic artery with the vertebrobasilar network and part of the circle of Willis. It joins the posterior cerebral artery between the P1 and P2 segments of that artery. It runs posteromedially above the oculomotor cranial nerve to reach the posterior cerebral artery (PCA).

It gives small perforator arteries from its superior surface that supply the pituitary stalk, optic tract, chiasm and the floor of the third ventricle. A group of small arteries supplying the thalamus and hypothalamus and internal capsule are called the anterior thalamoperforating arteries, but most branches arise from its anterior portion and run medially between the mammillary body and tuber cinereum. Perforating arteries, which share the territory of branches of either PComA or the anterior choroidal artery, may arise from the ICA between the two vessels.

4. Anterior choroidal artery (AchA) (Figs. 2.3 and 2.4)

The AchA arises from the lateral surface of ICA and is applied immediately to the under surface of the brain. It runs posteriorly, passing inferior to the optic tract (from lateral to medial). It then runs around the cerebral peduncle (which it supplies) and recrosses the tract (from medial to lateral) at the level of the lateral geniculate body before passing into the middle part of the choroidal fissure to reach the choroid plexus of the lateral ventricle. Prior to entering the choroid fissure, it gives a series of perforator arteries, which supply the posterior limb of the internal capsule, in particular its inferior level and part of the retrolenticular segment. It gives small branches to the optic radiation, the lateral geniculate body, the angle of the hippocampus and the amygdala as well as part of the globus pallidum and thalamus. The intraventricular terminal branches anastomose with the lateral posterior choroidal artery and follow the choroid plexus from the temporal horn to the trigone area [3]. It may, in addition, supply part of the inferior cortex of the adjacent temporal lobe.

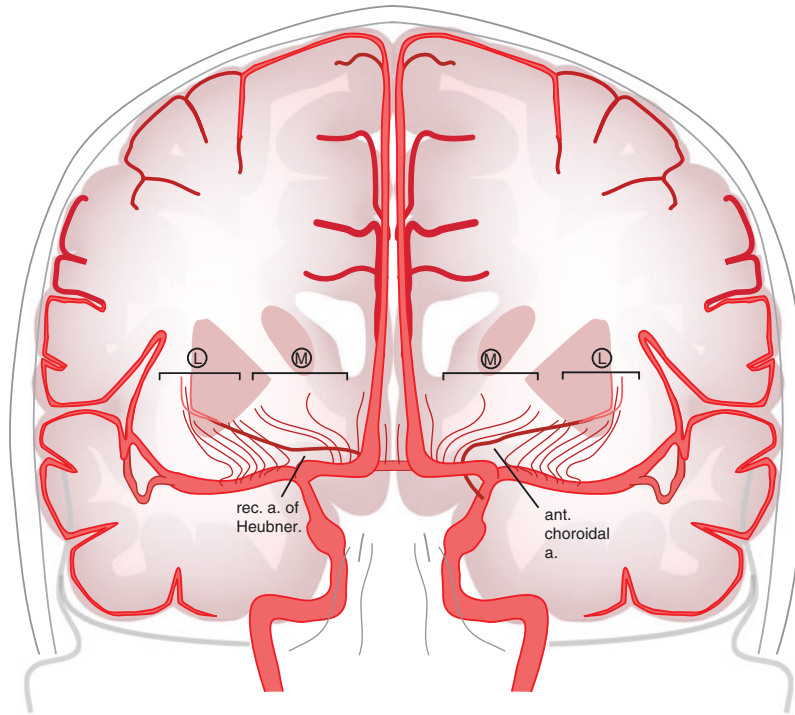

Fig. 2.3 Artist's impression of the anterior circle of Willis showing lenticulostriate arteries arising from the anterior cerebral arteries (*M* medial group) and middle cerebral artery (*L* lateral group). On the left, the anterior choroidal artery (AChA), and on the right, the recurrent artery of Heubner (RaH) is shown (see Fig. 2.4). Note that anterior perforating arteries also arise from the anterior communicating artery (Published with kind permission of © Henry Byrne, 2017. All rights reserved)

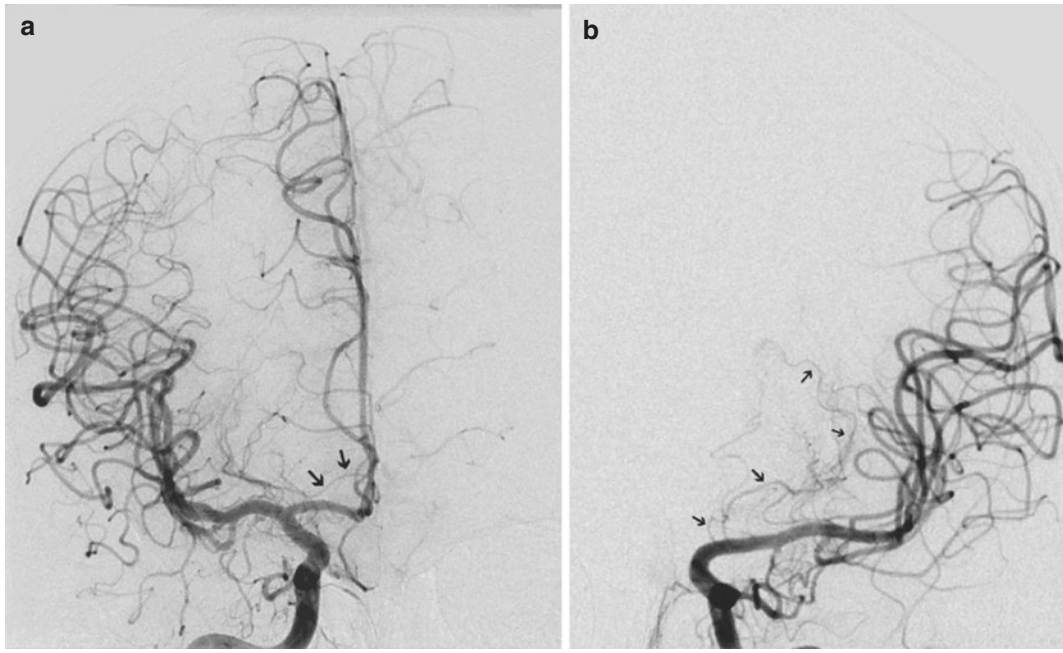

Fig. 2.4 Internal carotid angiograms in the frontal projections. Right (**a**) shows the recurrent artery of Heubner arising from the A2 (*2 arrows*) and left (**b**) with absent anterior cerebral artery shows the anterior choroidal artery (*arrows*)

2.2 The Terminal Branches of the Internal Carotid Artery

2.2.1 Anterior Cerebral Artery (ACA)

The ACA originates below the anterior perforating substance, lateral to the optic chiasm (Fig. 2.3). The convention proposed by Fischer [4] will be used to describe sections of the larger arteries. Thus, the A1 section runs horizontally forwards and medially, crossing above the optic nerve to the anterior inter-hemispheric fissure, where it communicates with its counterpart via the anterior communicating artery (AComA). The ACA then changes direction, and the A2 section runs upwards and forwards in the fissure to reach the genu of the corpus callosum. The definition of the junction of A2 and A3 sections is anatomically difficult because the Fischer convention is based on the numbering of arterial sections up to the next major branch point or bifurcation. In the case of the distal ACA, the next major branch point is the origin of the callosomarginal artery, but its branch pattern is more varied than is usual in the arterial tree. A solution is to define the junction as the point at which the ACA turns to run over the genu of the corpus callosum and so the A3 section starts at the genu and the A4 when the artery reaches the body of the corpus callosum. Confusingly Fischer added an A5 section to designate the artery posterior to the coronal suture (but since we now use bone-subtracted angiograms, this is a less useful landmark). In practice, because of the high level of individual variability, it is sensible to learn an ideal pattern using whatever convention one likes and expects to have to adapt it on a case-by-case basis.

After passing superior to the genu, the A4 section follows the corpus callosum posteriorly either on its surface or in the cingulate sulcus convexity. It terminates as the posterior pericallosal artery passes along the body of the corpus callosum to the splenium for a variable distance which may extend to the region of the pineal body.

2.2.1.1 Branches: A1 Section (Pre-communicating Artery)

1. Lenticulostriate arteries. The medial group of lenticulostriate arteries arise from the A1 section. The majority are short central or diencephalic arteries which arise from the superior surface close to the origin of ACA and run into the anterior perforating substance to supply the anterior basal ganglion and anterior commissure. Medial branches piece the lamina terminals to supply the anterior aspect of the lateral wall of the third ventricle, the anterior hypothalamus and septum pellucidum. Inferiorly directed branches supply the optic nerve and chiasm.
2. Recurrent artery of Heubner. This vessel represents a long central artery which arises either from A1 or A2 sections of ACA (rarely from the AComA) and terminates by supplying part of the head of the caudate nucleus, the anterior portion of the lentiform nucleus and the neighbouring portion of the internal capsule. It usually runs parallel and above the A1 section, directed medially if arising from A1 or laterally if recurrent from an A2 origin. Lateral to the ICA bifurcation, it enters the anterior perforating substance (Fig. 2.4).
3. Anterior communicating artery (AComA). This short anastomotic artery gives perforating arteries, which parallel those of the A1 section to supply the septum pellucidum, corpus callosum and lamina terminalis. It gives posterior directed branches to the chiasm and hypothalamus.

It is estimated that only 30–40% of adults have a single communicating artery, and two or more connections are present in the majority. This is well known to operating neurosurgeons, but multiple channels may be overlooked during diagnostic angiography because they are small and don't always fill because the flow of radiographic contrast media is distorted by blood flow from the contralateral A1. There is a substantial literature describing a plethora of possible variations and asymmetric arterial dispositions which are consequence on the coalescence of the cranial division of the embryonic carotid artery (primitive olfactory artery) in the midline. These variations will not be discussed here, but the student should recognise the possibility of an azygos (i.e. single) A2 vessel (Baptista type 1) and the presence of a third A2 artery arising from the anterior communicating artery following the

course of a pericallosal artery. The reader is directed to the works of Rhoton [5] and Baptiste [6] for an idea of the described variation in the communication complex and the distal anterior cerebral arteries.

2.2.1.2 Branches: A2 Section

The A2 section of the ACA thus runs superiorly to the genu of the corpus callosum (Fig. 2.5). The callosomarginal artery may arise from this section but the main branches are:

1. Orbitofrontal artery. This cortical artery runs forwards in the inferior inter-hemispheric fissure and supplies the gyrus rectus, olfactory bulb and the medial inferior frontal lobe.
2. Frontopolar artery. This artery arises at some point below the genu of the corpus callosum to supply frontal cortex. It may arise as more than one vessel.

2.2.1.3 Branches: A3 Section (Distal to the Origin of the Callosomarginal Artery or the Genu)

The ACA distal to the genu of the corpus callosum is called the pericallosal artery, a term that includes the A3 and distal sections. The callosomarginal artery typically arises at the level of the genu of the corpus callosum and runs parallel to the pericallosal artery in the cingulated sulcus. Its size is inversely related to the size of the pericallosal artery and it is frequently larger [7].

The callosomarginal artery gives a group of four branches:

(a) Anterior internal frontal
(b) Middle internal frontal
(c) Posterior internal frontal
(d) Paracentral artery

These divide into a network of sulcal vessels to supply the medial frontal lobe, classically as far as the central sulcus, but the arterial pattern that delivers this supply varies depending on whether the stem artery arises from pericallosal or callosomarginal arteries.

2.2.1.4 Branches: A4 and A5 Sections

In its A4 and A5 final sections, the pericallosal artery runs posteriorly over the body of the corpus callosum in the cistern of that name. It terminates and anastomoses with the posterior pericallosal artery which arises from the PCA.

It gives:

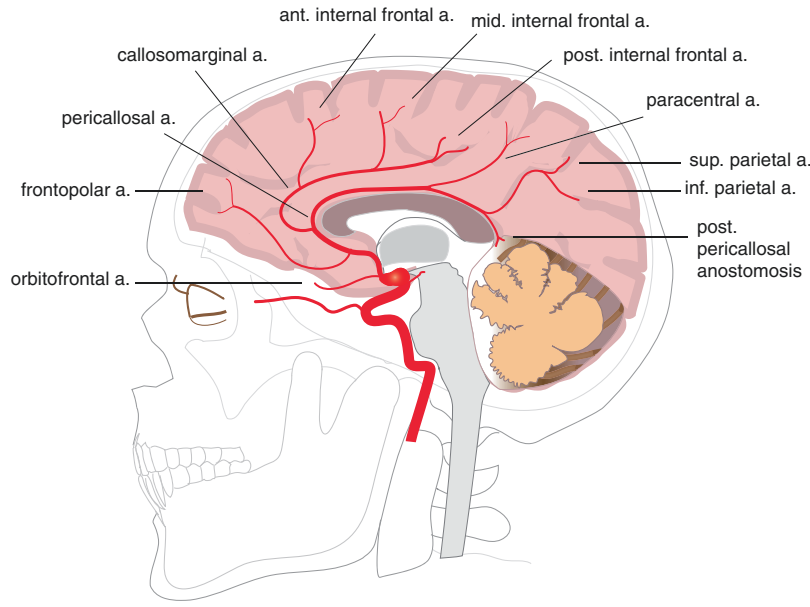

Fig. 2.5 Distal branches of the anterior cerebral artery (Published with kind permission of © Henry Byrne, 2017. All rights reserved)

(a) Short callosal perforating arteries that piece the corpus callosum and supply the pillars of the fornix and anterior commissure.
(b) Long callosal arteries that run parallel to the main trunk for a variable distance, supplying the adjacent cortex and may participate in the anastomoses at the splenium.
(c) Dural branches to the adjacent falx.
(d) Parietal arteries. These are the terminal cortical branches to the medial parietal lobe. They may be separable as a superior parietal artery and an inferior parietal artery which arise posterior to the callosomarginal artery and distribute to the cortex via their respective sulci.

Anatomical variants in the ACA pattern are not infrequent and occur in 20% of patients according to various authors. Common variants include absence or hypoplasia of the AComA and asymmetry of the proximal ACAs cerebral arteries with the entire territory supplied from one ICA. In addition to the collateral blood flow to the contralateral hemisphere provided by the AComA, cortical branches of the ACA border the middle cerebral and the posterior cerebral arterial territories. These can provide efficient collateral support in cases of proximal carotid occlusion when the AComA is ineffective or only partially effective or in cases of occlusion of the A2 and more distal ACA.

2.2.2 Middle Cerebral Artery (MCA)

The MCA arises as the lateral terminal branch of the ICA (Fig. 2.6). It runs horizontally and laterally to its primary bifurcation at the limen insulae (M1 segment). The upper and lower trunk arteries thus formed turn upwards and run in the Sylvian fissure lateral to the insular cortex (M2 segment), before they turn laterally in the horizontal portion of the fissure above the temporal and below the frontal lobe opercular surfaces (M3 segment). They emerge from the fissure in a series of branches (M4 segment). These turn inferiorly or superiorly to respectively supply the cortex of the temporal and frontal lobes.

The angular artery is often described as the continuation of the MCA because it lies at the centre of this candelabrum of branches when viewed on lateral angiography. It exits from the

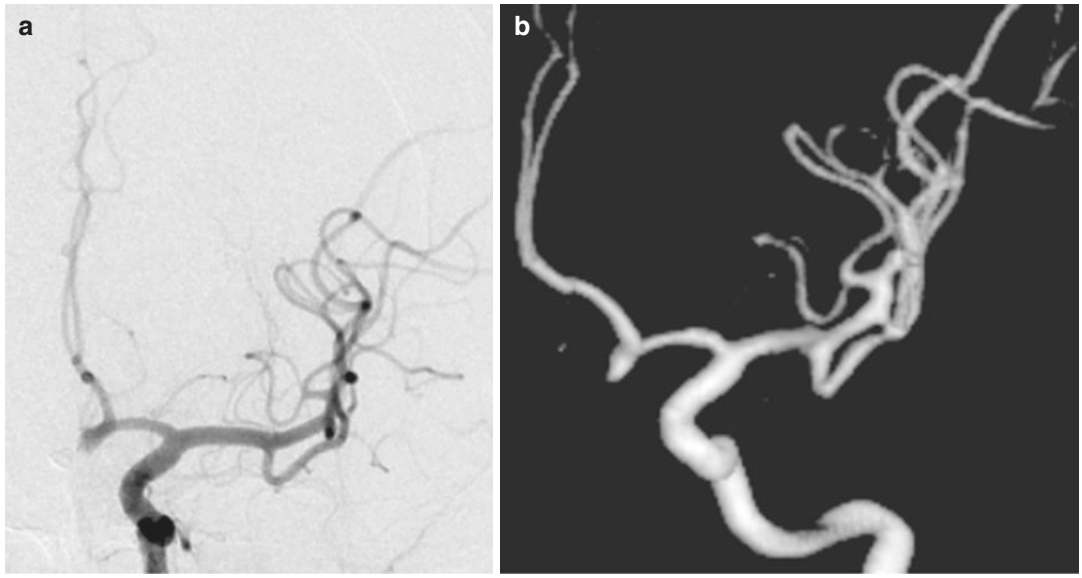

Fig. 2.6 Frontal DSA of the middle cerebral artery bifurcation in a patient with a dominant upper trunk shown in 2D (**a**) and 3D reconstruction (**b**). The upper trunk supplies the anterior (frontal lobe) and the lower trunk the posterior (posterior temporal and parietal lobe, including the central sulcus) portions of the middle cerebral artery territory, though parietal branches may arise from either trunk

posterior limit of the Sylvian fissure and is therefore a landmark for mapping the 'Sylvian triangle' of vessels (a useful 'tool' used by pre-CT neuroradiologists to decide if a mass originated in the temporal or frontal lobe).

Descriptions of the configuration of the primary MCA bifurcation vary. It is usually described as a bifurcation with variant trifurcations or 'quadrifications'. What is clear is that the majority of anatomical dissections show a bifurcation. I suggest it is easiest to consider this as the standard and the trifurcation appearance due to early rebranching of one of two primary trunks (i.e. the upper and lower MCA trunks).

The relative positions of the upper and lower trunks can be difficult to distinguish on two-dimensional imaging, but it is important to recognise that the lower trunk branches contribute to the posterior part of the territory (and therefore it is the usual origin of the angular artery). Since the upper trunk supplies the anterior part of the territory (i.e. frontal lobe and a variable amount of the temporal lobe), the presence of a pre-bifurcation (M1) branch directed to the frontal or anterior temporal lobe may result in it being smaller than the lower trunk.

2.2.2.1 Branches

These should be considered as deep (perforator) and superficial (cortical) arteries.

1. Lenticulostriate arteries. These arise from the superior surface of the M1 section. They are grouped as the medial and lateral lenticulostriate arteries which piece the anterior perforating substance to supply the globus pallidum and lentiform nucleus (medial group) and passing through the globus pallidum supply, the superior part of the internal capsule and the upper part of the head and body of the caudate nucleus (lateral group). The territory of the medial group overlaps with those arising from A1.
2. Cortical arteries. The superficial or cortical branches supply a considerable proportion of the superficial hemispheric cortex. They follow the sulci of the brain, and their description (and relative size of each stem artery) depends on the distances between branch points. For those who like to memorise lists, they are shown in Fig. 2.7. However, I prefer to identify only the lobe to which they are directed and their relationship to the Rolandic fissure and the Sylvian point. The last being the site at which the angular artery emerges from the posterior Sylvian fissure.
   (a) Arteries to the temporal lobe. These run inferiorly after leaving the lateral sulcus of the Sylvian fissure and are arranged from anterior to posterior:
      (i) Temporal polar artery
      (ii) Anterior temporal artery
      (iii) Middle temporal artery
      (iv) Posterior temporal artery
   (b) Arteries to the frontal lobe. These run superiorly after leaving the fissure, from anterior to posterior:
      (i) Orbitofrontal artery of the middle cerebral artery
      (ii) Prefrontal artery (supplies Broca's area)
      (iii) Precentral artery (or pre-Rolandic[4] artery of Sillon)
      (iv) Central artery (or artery of the Rolandic fissure)
   (c) Arteries to the parietal and occipital lobes. These run posterior to the Sylvian fissure, from superior to inferior:
(i) Anterior parietal
(ii) Posterior parietal
(iii) Angular artery
(iv) Occipitotemporal artery

Cortical arteriolar-arteriolar anastomoses exist between branches of the anterior and posterior cerebral arteries and between the distal branches of the MCA. They are often seen in patients with occlusion of the proximal MCA and become more reliable, as collateral support to the cortex, if occlusions are made distal to the first branch point (i.e. MCA bifurcation), though there is

[4] Luigi Rolando (1773–1831) Italian anatomist and physiologist who worked in Turin and Sardinia.

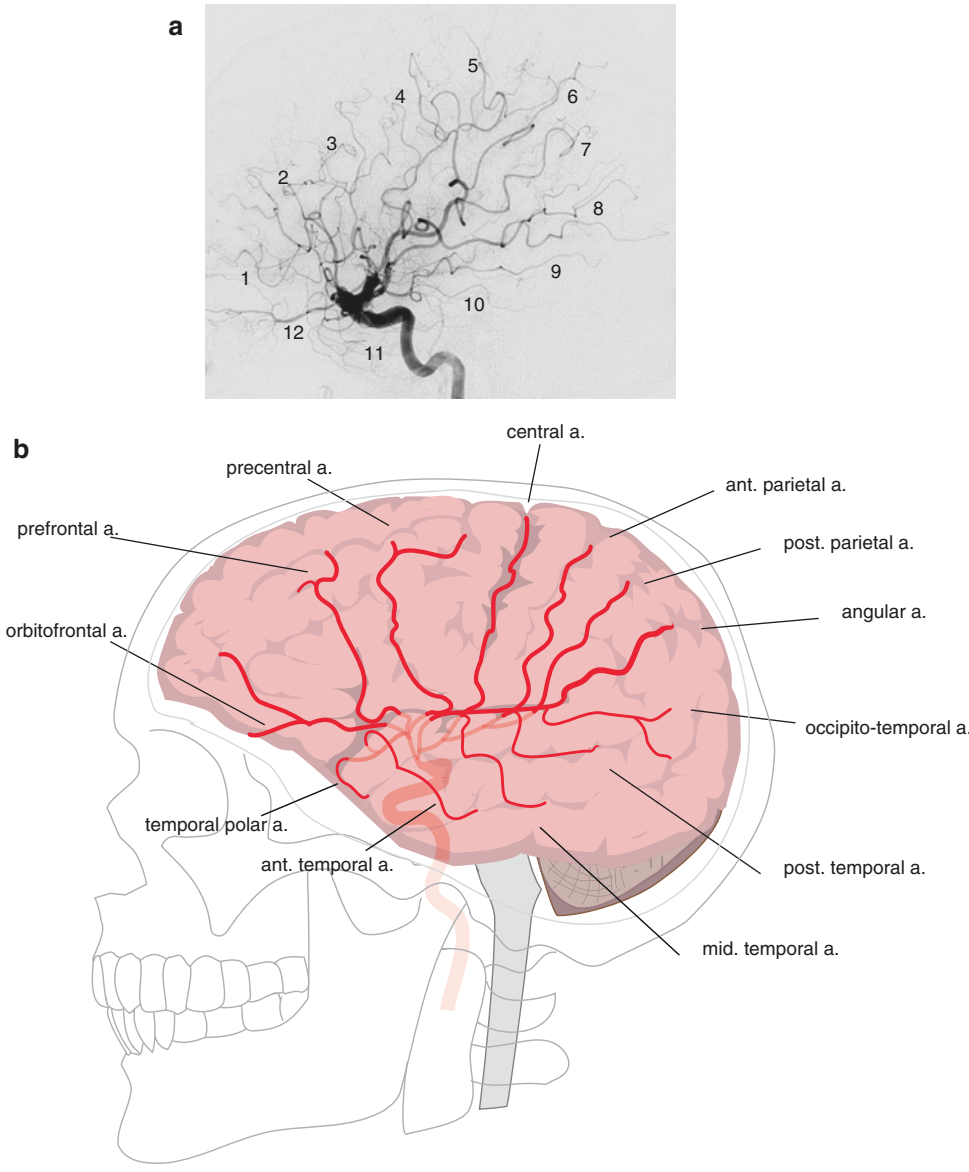

Fig. 2.7 Cortical branches of the MCA, shown on lateral carotid DSA (**a**) and illustrated in (**b**) and in a patient with an absent A1 artery showing the cortical branches of the left MCA. Legends (**a**) Key: *1* orbitofrontal a. *2* prefrontal a. *3* precentral a. *4* central a. *5* ant. parietal a. *6* post. parietal a. *7* angular a. *8* occipito-temporal a. *9* post. temporal a. *10* mid. temporal a. *11* ant. temporal a. *12* temporal polar a (Published with kind permission of © Henry Byrne, 2017. All rights reserved)

obviously a limit to how distal embolisation can be tolerated in any tree.

2.3 The Vertebrobasilar System

The vertebrobasilar or posterior cerebral circulation supplies the posterior part of the brain,

namely, the occipital lobes, parts of the temporal and parietal lobes, thalamus and cerebral peduncles, the brain stem, cerebellum and the superior portion of the cervical cord. It supplies cranial nerves and contributes to the blood supply of dura and extracerebral structures of the skull base and upper spine. It comprises the vertebral, basilar and posterior cerebral arteries and their branches. It is normally connected to the carotid territory by the posterior communicating arteries.

2.3.1 Vertebral Artery (VA)

The vertebral arteries are paired and have variable calibres of about 3–4 mm with the left usual larger (dominant). They are the first branch of the subclavian arteries that arise from its superior aspect and run vertically and posteriorly to the level of C6 where they enter the foramen in the transverse process. The VA then runs superiorly in the vertebral canal passing through foramina in the transverse processes of all the upper cervical vertebrae. After leaving the superior border of the foramen of the atlas (C2), it runs horizontally and posteriorly to pass through the more laterally positioned foramen of the axis (C1) and then turns medially to the foramen magnum. There, it penetrates the atlanto-occipital membrane and dura to enter the cranial cavity through the foramen magnum and then runs upwards and medially to terminate as the basilar artery, formed by joining its contralateral counterpart anterior to the upper border of the medulla oblongata.

2.3.1.1 Extracranial Branches

In its extracranial course, the VA gives branches, which supply the spinal cord and its dura, cervical vertebrae and muscles, as well as the dura of the inferior posterior fossa (Fig. 2.8). These include (from proximal to distal):

1. Branches to the superior cervical ganglion (stellate ganglion).
2. Spinal arteries: C6–C1. The spinal arteries supply the nerve roots, root sheaths and bone structures of these vertebrae, together with the

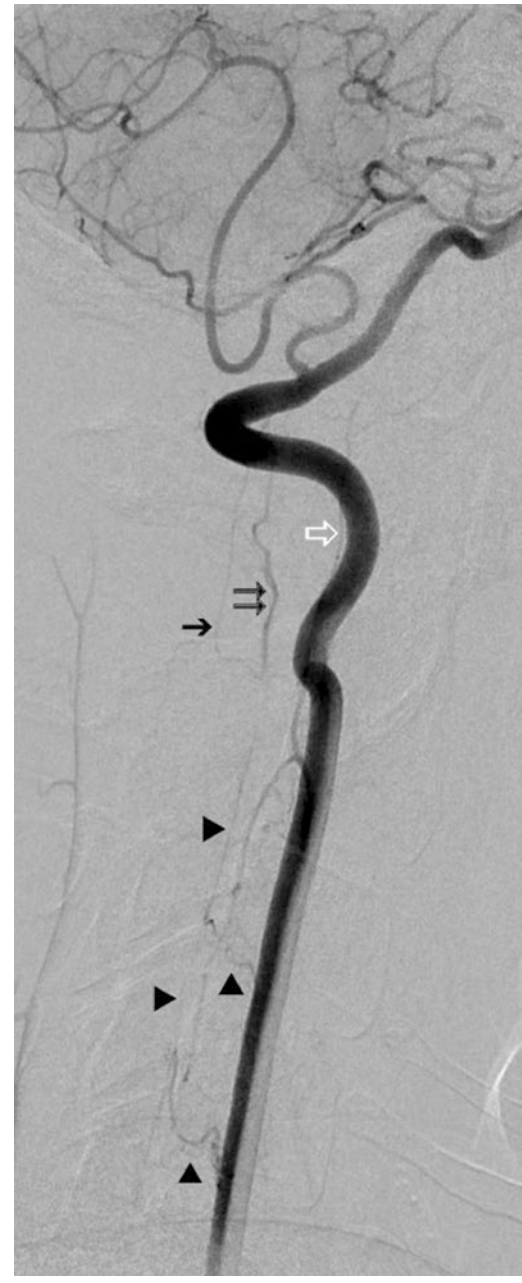

Fig. 2.8 Vertebral artery DSA (lateral view of the *right* side). At C3, a spinal artery branch is seen running cranially to the odontoid arcade (*white arrow*). The anterior spinal artery is seen in the mid-cervical spine with contributing segmental spinal arteries at C4 and C5 (*arrowheads*). The posterior-lateral spinal artery fills in the upper spine (*black arrow*) via a contribution from the lateral spinal artery (*double black arrows*). The lateral spinal artery is a descending branch of the intracranial vertebral artery

deep cervical artery (costocervical trunk) and ascending cervical artery. From C3 to C1 levels, spinal branches of the VA contribute to the odontoid arterial arcade together with collaterals from the ascending pharyngeal artery and occipital artery.

3. Arteries of the cervical expansion. Spinal radiculomedullary arteries support the anterior spinal and posterolateral spinal arteries in the lower cervical spine (i.e. the cervical expansion) and arise between C6 and C4. They are usually bilateral and may arise from the thyrocervical trunk or the ascending or deep cervical arteries.
4. Muscular branches to the paraspinal muscles. These anastomose with branches of the deep cervical and occipital arteries.
5. Anterior meningeal artery. This very small artery arises from the distal VA and supplies the dura of the anterior foramen magnum and the inferior clivus. It also takes part in the anastomoses forming the odontoid arterial arcade (Fig. 2.9).

2.3.1.2 Intracranial Branches

In its intracranial portion, the VA gives branches that supply dura and the upper cervical cord, medulla oblongata and cerebellum. These are:

1. Posterior meningeal artery and artery of the falx cerebelli. The VA may be the dominant source of the artery of the falx cerebelli. This easy-to-recognise vessel may arise from the extracranial VA or from the occipital artery or PICA.
2. Medial group of perforator branches. These supply the medulla oblongata and pyramids. An artery to the foramen caecum is described which is one of this medial group of perforators. It ascends to the pontomedullary junction, where a concentration of perforator arteries congregates in the midline to pass deep into the brain stem, and supplies nuclei of the floor of the fourth ventricle and long tracts.
3. Anterior spinal artery. The rostral origin of the anterior spinal artery is usually bilateral arteries, but one side is often larger. They descend to unite and form a single median artery at the C2/C3 level.
4. Posterolateral spinal arteries. The cranial origins of these paired longitudinal arteries arise from the VA or PICA. They are reinforced by spinal branches of the extracranial VA arteries.
5. Lateral spinal artery. This small branch of VA supplies the IXth cranial nerve and runs caudally supplying the lateral spinal cord to join the ipsilateral posterolateral spinal artery at C4. It may arise from PICA.
6. Posterior inferior cerebellar artery (PICA). The PICA arises 15 mm proximal to the termination of the VA. It is of variable calibre being reciprocal in size to that of the ipsilateral anterior inferior cerebellar artery. Classically, the PICA course is separated into five sections: anterior medullary, lateral medullary, tonsillomedullary, telovelotonsillar and cortical (Fig. 2.10).

The anterior medullary section is intimately related to the hypoglossal nerve (which lies anterior and between PICA and its parent VA). The lateral medullary section runs around the inferior surface of the olive to the XIth cranial nerve. The tonsillomedullary section carries the artery between the spinal and cranial roots of the XIth cranial nerve and then behind the Xth and IXth cranial nerves to the telovelotonsillar section where it runs medial to the cerebellar tonsil. It enters the telovelotonsillar section at the midpoint of the tonsil. Then, it runs medial to the tonsil and lateral to the vermis to reach the cortical surface of the cerebellar hemisphere and its last (cortical) section. This complicated description highlights the difficulty of surgical dissection needed when clipping aneurysms at the PICA origin and reflects its importance (in the past) for determining the position of the cerebellar tonsils relative to the foramen magnum.

It comprises branches:

(a) Perforators to the lateral and posterior aspect of the medullar oblongata from the proximal three sections. These are small branches that supply the lateral medulla and olive. They are sometimes described as circumferential arteries depending on their length.

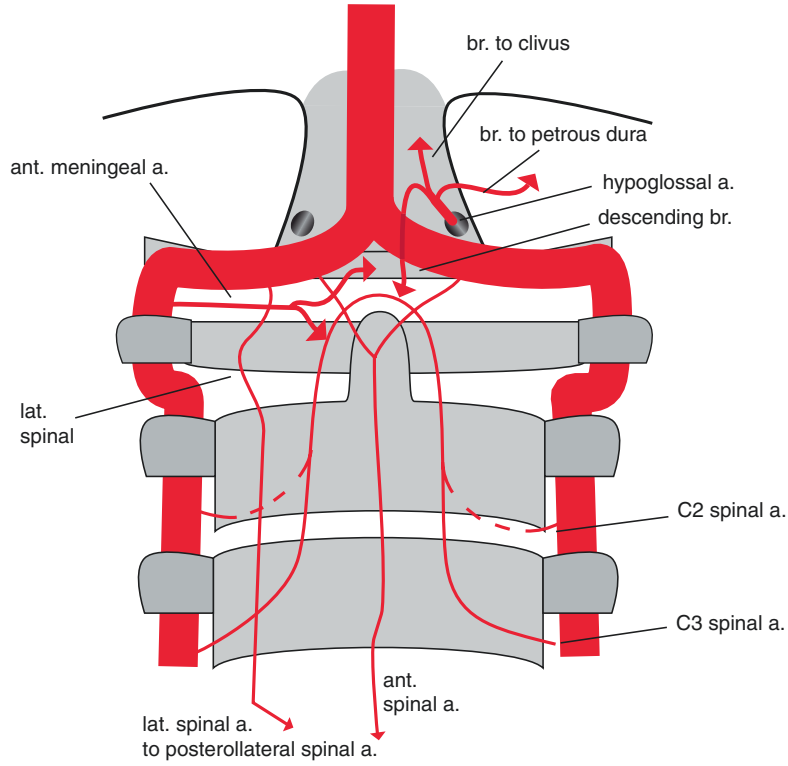

Fig. 2.9 Arteries of the odontoid arcade (Published with kind permission of © Henry Byrne, 2017. All rights reserved)

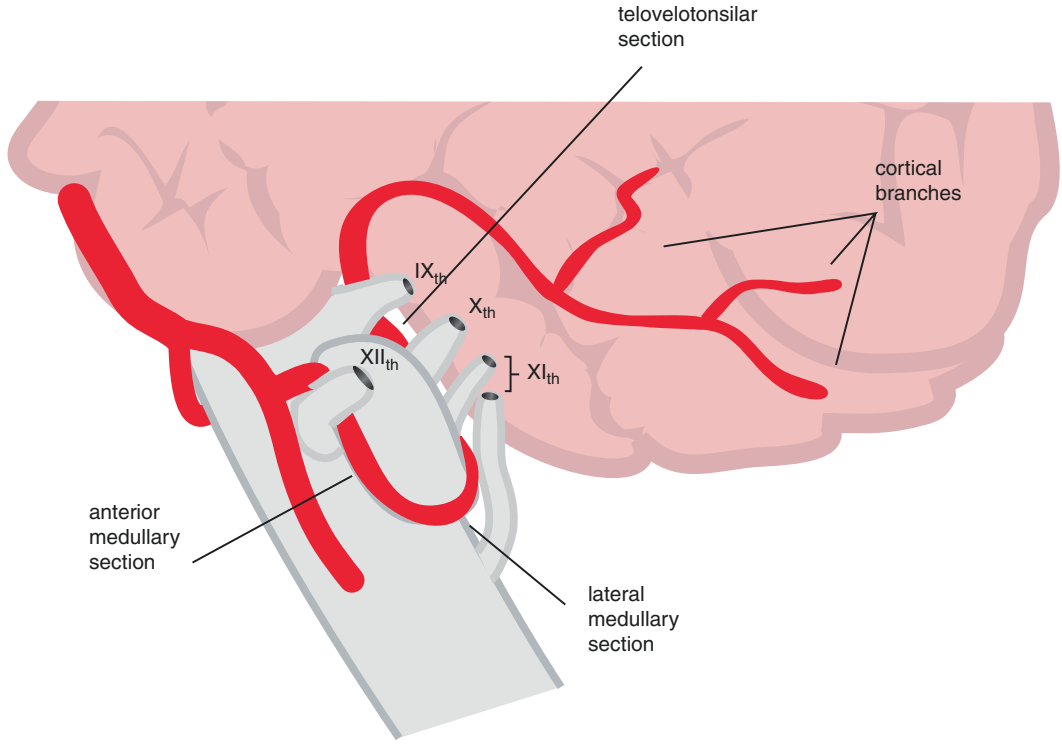

Fig. 2.10 Proximal sections of the posterior inferior cerebellar artery (Published with kind permission of © Henry Byrne, 2017. All rights reserved)

(b) Choroidal arteries. These arise from the tonsillomedullary and telovelotonsillar sections. The apex of the cranial loop (telovelotonsillar sections) is described as the choroidal point, which marks the roof of the fourth ventricle on the lateral angiogram. It is the distal limit for perforator arteries to arise from the PICA trunk.
(c) Terminal cortical branches supply the posteroinferior aspect of the cerebellar hemispheres and a median branch to supply the vermis, the choroid plexus and the fourth ventricle.
(d) The lateral spinal artery and posterior meningeal arteries may arise from the PICA rather than the VA.

2.3.2 Basilar Artery (BA)

The BA arises just below the pontomedullary junction between the emerging VIth cranial nerves and runs superiorly on the anterior surface of the pons to terminate at the pontomesencephalic junction. The level of the basilar bifurcation is variable. It is usually within 1 cm of the superior surface of the dorsum sella, but in 30% of individuals, it is above and in 20% below this range. Relative to the brain stem, the termination can be as far caudal as 1 cm below the pontomesencephalic junction and as far rostral as the mammillary bodies.

2.3.2.1 Branches

Its branches can be divided into two groups: the perforating arteries and the long circumferential arteries. The perforating arteries are paramedian and circumferential in distribution. They supply the corticospinal tracts, other connecting white matter tracts and the vital deep nuclei of the pons and midbrain. In the physiological state, they are rarely visible on angiography and do not cross the midline.

The long circumferential arteries consist of three paired vessels:

1. The internal auditory artery (labyrinthine artery) which arises from the basilar artery or AICA and runs laterally to the internal auditory canal where it gives cochlear and vestibular branches. A small branch, the subarcuate artery, supplies meninges of the subarcuate fossa and the bone of the semicircular canals.
2. The anterior inferior cerebellar artery (AICA) arises at the junction of lower one-third and upper two-third of the basilar artery and runs laterally on the anterolateral surface of the pons to the flocculus. It supplies the inferior cerebellar peduncle, the middle cerebellar peduncle and the inferior portion of the flocculus and the adjacent cerebellar hemisphere. The choroid plexus of the lateral recess of the fourth ventricle is also supplied by this artery. It anastomoses on the surface of the cerebellar hemispheres with branches of PICA and the superior cerebellar arteries.
3. The superior cerebellar artery (SCA) arises 1–3 mm below the termination of BA and parallels the course of the PCA around the cerebral peduncle in the ambient cistern. It is separated from the PCA by the oculomotor nerve cranial nerve medially and the trochlear nerve cranial nerve laterally. Lying below the free edge of the tentorium, it gives the medial dural-tentorial artery [11]. Posterolateral to the midbrain it gives the superior vermian artery and then terminates in cortical branches to the superior cerebellar hemisphere. It supplies the superior cerebellar peduncle and part of the middle cerebellar peduncle, the dentate nucleus, roof of the fourth ventricle, as well as the superior portion of the cerebellar hemispheres.

2.3.3 Posterior Cerebral Artery (PCA)

The paired posterior cerebral arteries are the terminal branches of the basilar artery and complete the posterior circle of Willis (Fig. 2.11). The PCA can be described in three main sections: P1, from the origin to PComA; P2, running around the cerebral peduncle; and P3, posterior to the midbrain to the anterior limit of the calcarine fissure. The main trunk continues posteriorly and terminates by dividing into parieto-occipital and

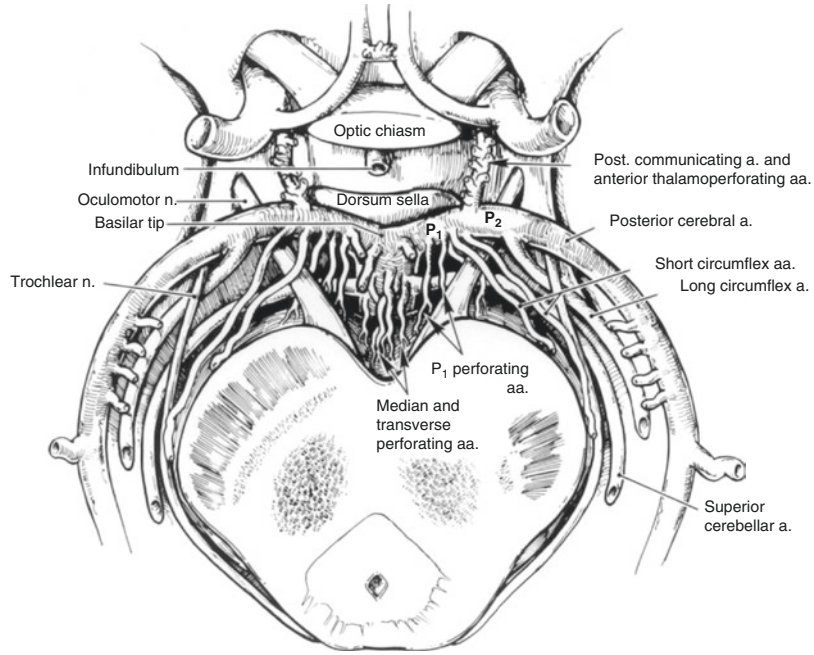

Fig. 2.11 Artists impression of the basilar artery termination and proximal posterior cerebral arteries (Reproduced with permission from Wascher TM, Spetzler RF. Saccular aneurysms of the basilar bifurcation. In: Carter LH, Spetzler RF, editors. Neurovascular neurosurgery. New York: McGraw-Hill; 1994. p. 730)

occipital branches, with the calcarine artery usually arising from the latter.

The P1 section passes around the front of the cerebral peduncle, above the IIIrd and IVth cranial nerves, and receives the PComA at the level of the IIIrd nerve.

The P2 section then runs laterally and posteriorly (parallel to the SCA) to reach the inferior surface of the temporal lobe. It runs in the ambient cistern, whose anterior portion is sometimes called the crural cistern (i.e. the portion extending from the uncus to the cerebral peduncle).

The P3 section continues in the ambient cistern and then in the lateral part of the quadrigeminal cistern. As it runs posteriorly, the PCA turns towards the midline, under the splenium of the corpus callosum.

From this short arterial segment, a large number of small arteries arise which supply mesencephalon and diencephalon structures and the choroid plexus. They are described in anatomical texts as groups of perforators or arterial stems with frequent multiple origins and variations in sites of origin from the PCA parent, but in this plethora of data, it is important for the student to realise that the proximity of their origins and target territories means that overlaps are inevitable. With this in mind, a standard description of the PCA branches follows.

2.3.3.1 Branches: P1 Section

1. Posterior thalamoperforating arteries (Fig. 2.12). The thalamoperforating arteries enter the posterior perforating substance and supply the posterior part of a territory shared with the anterior thalamoperforating arteries (which arise from PComA). These vessels between them (i.e. anterior and posterior thalamoperforating arteries) supply the anterior and posterior parts of the thalamus, posterior optic chiasm and tracts, the posterior limb of the internal capsule, hypothalamus, subthalamus, substantia nigra, red nucleus and the oculomotor and trochlear nuclei, as well as parts of the rostral mesencephalon including part of the cerebral peduncles. They may arise from the terminal BA or from the SCA. An azygos posterior thalamoperforator trunk artery that supplies both thalami is well described and is generally known as the artery of Percheron [8].

There are complex descriptions of the distribution of the thalamoperforating arteries of the PCA

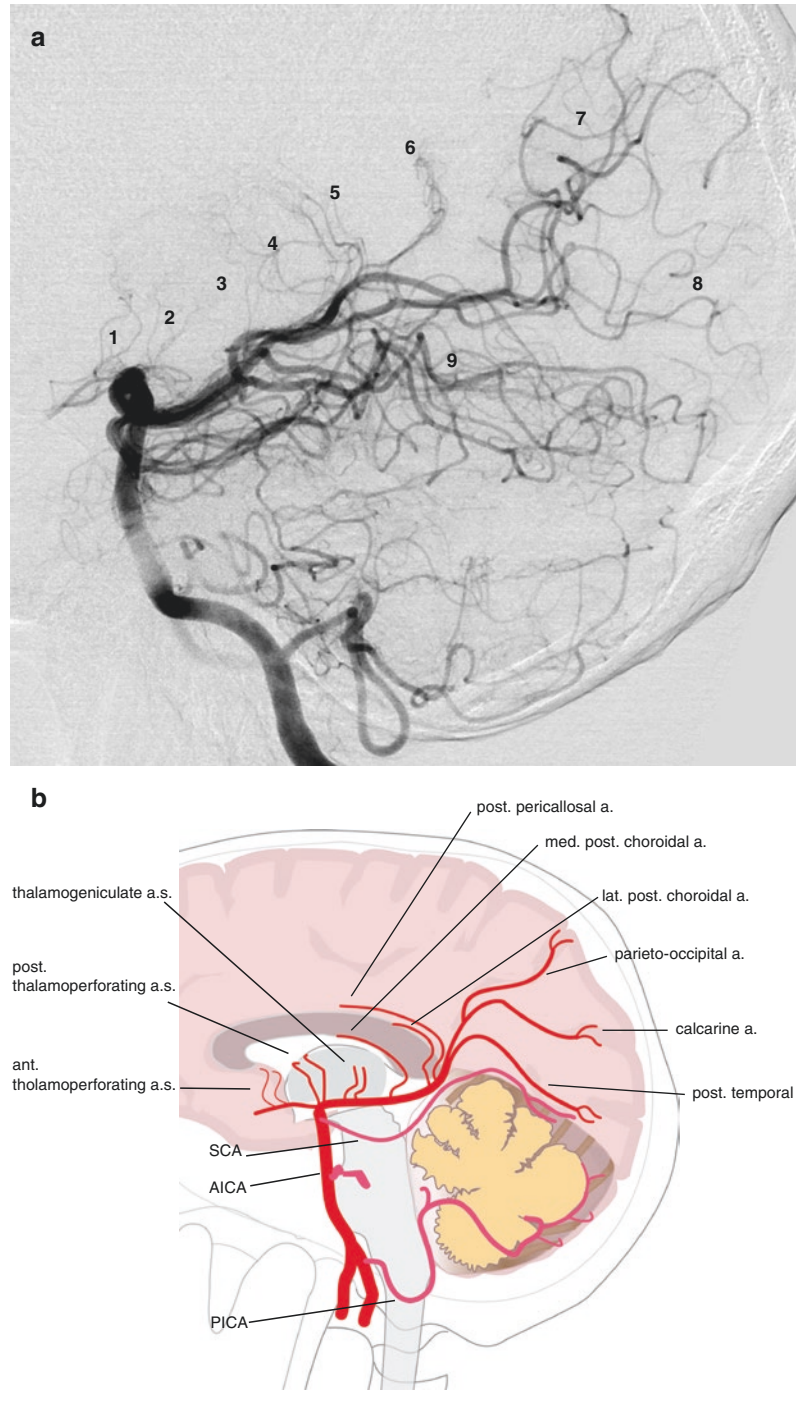

Fig. 2.12 Branches of the posterior cerebral artery, shown on vertebral angiography (**a**) and illustrated in (**b**). In (**a**), the branches have been numbered according to the following keys: *1* ant. thalamoperforating a. *2* post. thalamoperforating a. *3* thalamogeniculate a. *4* med. post. choroidal a. *5* lat. post. choroidal a. *6* post pericallosal a. *7* parieto-occipital a. *8* calcarine a. *9* post. temporal a (Published with kind permission of © Henry Byrne, 2017. All rights reserved)

in the neurosurgical literature. An example of this potential difficulty for the student is the descriptions by Yasargil [9] who divided them into groups: an interpeduncular group, a peri-infundibular group, a perimammillary group and a retro-optic group and a 'simpler' scheme proposed by Pedroza et al. [10] who described perforators that enter the anterior and posterior parts of the posterior perforating substance as paramedian thalamic and superior paramedian mesencephalic arteries, respectively, and the perforators that supply the brain stem posterior to the posterior substance as

the inferior paramedian mesencephalic arteries. These descriptions of vessels, which are largely invisible to the endovascular therapist, reflect the complexity of extravascular surgery in this region. For us, their separation into so many different groups is unnecessary, but it remains important to remember that this is an area where embolisation has to be conducted with great caution.

2. Circumflex arteries (short and long). The circumflex arteries (two or more arteries) arise from the distal P1 or proximal P2 and parallel the course of P2 in the ambient cistern (Fig. 2.11). They follow the main trunk around the midbrain and give small branches to the cerebral peduncles and tectum. The long circumflex artery extends to the colliculi and supplies the tectum, tegmentum, cerebral peduncle and geniculate body; the short circumflex artery supplies just the geniculate body, the peduncle and part of the tegmental area. Some authors describe a separate quadrigeminal artery to this territory. The tectum and quadrigeminal plate is also supplied by branches of the SCA.

2.3.3.2 Branches: P2 Section

3. Thalamogeniculate arteries. This group of perforator arteries (usually 8–10) arise distal to the PComA confluence and supply the medial and lateral geniculate bodies, the lateral and inferior part of the thalamus and the posterior internal capsule.
4. Medial posterior choroidal arteries. The medial posterior choroidal artery arises from the medial side of the PCA as 1–3 vessels and run medially to enter the roof of the third ventricle in the velum interpositum. It gives branches in its proximal 'cisternal' course (in the ambient, quadrigeminal and pineal cisterns) to adjacent structures, i.e. the tectum, pineal gland, habenula and medial geniculate body and posterior thalamus.

Within the velum interpositum, it runs forwards to the foramen of Monro,[5] supplying choroid plexus and anastomoses with terminal branches of the lateral posterior choroidal arteries, which have come 'the other way' through the lateral ventricle.

5. Lateral posterior choroidal arteries. The lateral posterior choroidal arteries are a group of arteries that arise from the lateral surface of the PCA, usually distal to the medial posterior choroidal arteries and run superior and anteriorly to enter the choroidal fissure and the lateral ventricle. In their 'cisternal' course (in the ambient cistern), they give branches to supply the cerebral peduncle, the pineal gland, the splenium of the corpus callosum, posterior commissure, tail of the caudate nucleus, lateral geniculate body and thalamus (dorsomedial nucleus and pulvinar). In the ventricle, the arteries pass around the pulvinar and forwards to the foramen of Monro. They supply the choroid plexus and give additional branches to the thalamus.
6. Temporal branches.

The temporal lobe supply from the PCA is normally arranged as:

(a) Hippocampal artery
(b) Anterior temporal artery
(c) Middle temporal artery
(d) Posterior temporal artery

These supply the brain in partnership with the middle cerebral artery cortical branches. The hippocampal artery is found in only two-third of dissections. It arises most proximally and supplies the uncus, hippocampus and dentate gyrus. The middle temporal branch is usually smaller than the anterior and posterior arteries.

7. Meningeal branch or artery of Davidoff and Schechter. A small dural branch that arises from the choroidal or distal cortical branches of the PCA that is, like the medial dural-tentorial artery, only seen on angiography when pathologically enlarged [11]. It supplies the tentorium and posterior falx, but its important relevance to this tutorial is the charming story that the eponymous titles are those of the mentors of the authors who first described it [12], an act of generosity that gives credit to all concerned.

[5] Alexander Monro (1733–1817) Scottish physician who was professor of anatomy in Edinburgh.

8. Posterior pericallosal or splenial arteries. These are usually a group of small arteries rather than solitary bilateral arteries, whose origin varies between the parieto-occipital artery, the calcarine and the posterior temporal branches of the PCA. They initially run posteriorly and then anteriorly and superior to the splenium of the corpus callosum. They anastomose with the terminal branches of the pericallosal artery, and can form an effective collateral supply to the ACA territory.
9. Calcarine artery. This is the artery of supply to the visual cortex. It usually arises from the PCA trunk but may arise from the parieto-occipital artery or posterior temporal artery. Typically, its origin appears inferior to the parieto-occipital artery on a lateral angiogram, and because it runs deep in the calcarine fissure, it appears lateral to the larger parieto-occipital artery on the frontal view. It also supplies part of the cuneus and lingual gyrus as well as the calcarine cortex.
10. Parietal-occipital artery. This is the largest and most superior of the terminal branches of the PCA. It runs in the parieto-occipital fissure and is a cortical branch supplying the cuneus, precuneus and superior occipital gyrus. It may also supply the precentral region (medial surface of the hemisphere) and superior parietal lobule. It often gives an accessory calcarine branch to the visual cortex.

2.4 External Carotid Artery (ECA)

The ECA supplies the tissues of the scalp, skull, face and neck. These include the skin and superficial soft tissues of the head, facial adnexa, dura, cranial nerves and the support structures associated with the special senses, upper airway and alimentary systems. It arises at the level of the superior border of the thyroid cartilage and terminates deep to the neck of the mandible by dividing into superficial temporal and internal maxillary arteries. At its origin, it is situated anterior to the ICA, but as it ascends, it lies more posteriorly and finally lateral to ICA. Thus, on frontal angiography, its origin is medial to the ICA origin and the vessels reverse their relative positions as they run superiorly, but on the lateral view, the ICA is always posterior.

The ECA lies lateral to the pharynx and medial to the sternocleidomastoid muscle. At the angle of the mandible, it lies deep to the posterior belly of digastric and stylohyoid muscles before entering the parotid gland. It divides into the superficial temporal and internal maxillary arteries within the parotid gland. It has eight branches which will be described in their usual sequence from proximal to distal. These are (a) superior thyroid artery, (b) lingual artery (LA), (c) ascending pharyngeal artery (APA), (d) facial artery (FA), (e) occipital artery (OA), (f) posterior auricular artery (PA), (g) superficial temporal artery (STA) (terminal) and (h) internal maxillary artery (IMA) (terminal).

The anterior branches of ECA supply the face and its adnexa, i.e. the FA and the IMA (supported by the superior thyroid and LA). The principal arteries to the superficial structures of the skull, i.e. scalp, and bone are the STA anteriorly (supported by the FA) and the OA posteriorly (supported by the PA). The IMA supplies the anterior deeper structures, i.e. the meninges (via the middle meningeal artery) with the OA supported by the PA and VA, supplying the posterior meninges. In these descriptions, the contributions of the APA have been omitted because its branches supply both anterior and posterior deep structures.

The APA territory is the key to understanding the blood supply to the skull base since it supplies the intermediate zone bordered anteriorly by the IMA territory and posteriorly by the OA and VA. Its embryological heritage from the third branchial arch artery links it to the ICA and so its importance bears no relation to its apparently insignificant size.

2.4.1 Superior Thyroid Artery

The STA arises from the anterior surface of the ECA, just below the greater cornu of the hyoid bone. It describes an inferior concave curve as it runs infero-medially deep to the omohyoid, sternothyroid and sternohyoid muscles to gain the superior apex of the thyroid gland.

2.4.1.1 Branches

1. Infrahyoid artery. A small artery which parallels the hyoid bone medially to supply the thyrohyoid muscle and anastomoses across the midline and with the suprahyoid branch of LA.
2. Branch to the sternocleidomastoid muscle.
3. Superior laryngeal artery. This is the largest branch and supplies the strap muscles above the cricoid ring before it penetrates the cricothyroid membrane and supplies the mucosa of the larynx.
4. Cricothyroid artery. A small branch that runs along the inferior border of the thyroid cartilage and anastomoses across the midline.
5. Terminal branches. The superior thyroid artery terminates by dividing into anterior and posterior branches to supply the thyroid gland.

2.4.2 Lingual Artery

This artery arises from the anterolateral border of the ECA at the level of the greater cornu of the hyoid bone or from a common linguofacial trunk with the FA. It runs forwards and initially loops upwards, where it crosses the hypoglossal nerve and then downwards and forwards on the middle constrictor muscle, deep to the hyoglossus muscle. Finally, it ascends, between the genioglossus muscle and the anterior border of hyoglossus muscle, and runs forwards into the base of the tongue. It gives small branches before terminating in the dorsal artery of the tongue which gives a series of characteristic parallel end arteries.

2.4.2.1 Branches

1. Suprahyoid artery. Posterior to the hyoglossus muscle, it gives this small branch which anastomoses with the infrahyoid artery.
2. Sublingual artery. This branch arises from LA anterior to the hyoglossus muscle and supplies the sublingual gland, adjacent mucosa and anterior mandible.
3. Dorsal artery of the tongue. The dorsal artery of the tongue (or dorsal lingual artery) arises from the horizontal portion of the main trunk and may comprise two or more branches. It runs upwards to vascularise the mucosa at the base of the tongue and sends small branches posteriorly as far as the palatine tonsil.
4. Deep lingual artery. This term (or ranine artery) is used for the most anterior portion of LA which runs parallel to the frenulum, supplying the muscle and mucosa of the tongue.

Though there is a rich anastomosis with proximal branches of the FA at the base of the tongue, there are no anastomoses between the muscular arterial networks and the two halves of the tongue. Embolisation of this section of the lingual artery is thus not advised because of the risk of causing necrosis.

2.4.3 Ascending Pharyngeal Artery (APA)

The APA arises from the posteromedial surface of the ECA (or occasionally from the ICA) at a variable distance after its origin but usually at the same level as the lingual artery. Its trajectory is vertical, lying on the longus capitis muscle, between the carotid sheath and the lateral wall of the pharynx. It supplies the mucosa and muscles of the pharynx, prevertebral muscles and dura of the posterior fossa and craniocervical junction. The trunk divides into anterior and posterior divisions.

2.4.3.1 Anterior Division (Pharyngeal Trunk)

The anterior division or pharyngeal trunk supplies the muscles and mucosa of pharynx in a series of branches:

1. Inferior pharyngeal artery. This supplies the hypopharynx.
2. Middle pharyngeal artery. Supplies the oropharynx and soft palate and takes part in the pharyngeal anastomoses.
3. Superior pharyngeal artery. This is the terminal branch which supplies the nasopharynx and is the major contributor to the pharyngeal anastomosis. Branches anastomose with the accessory meningeal artery in the region of

the foramen spinosum. This is one of several potential anastomotic routes to branches of the ILT. Another is via a branch to the foramen lacerum which is an anastomotic route to the ILT via the recurrent artery of the foramen lacerum. Branches of the superior pharyngeal artery also anastomose with branches of the IMA around the Eustachian tube, i.e. the pterygovaginal and Vidian arteries.

4. Palatine branches are small branches which pass medially on the superior pharyngeal constrictor muscle and supply the soft palate and tonsil and take part in an anastomosis with the descending palatine artery of the IMA and the branches around the Eustachian tube. They may take the place of the ascending palatine artery (from the FA), if it is small.
5. Prevertebral branches are small branches which supply the longus capitis and colli muscles, the sympathetic trunk, the Xth cranial nerve and the lymph node chain as the trunk ascends. They anastomose with branches of the ascending cervical artery.

2.4.3.2 Posterior Division (Neuromeningeal Trunk)

The posterior division or neuromeningeal trunk supplies dura and the lower cranial nerves. It gives two main branches:

1. Hypoglossal artery. This artery is important because of the variety of zones to which it contributes branches. It supplies the hypoglossal cranial nerve in the hypoglossal canal and dura of the anterior posterior fossa and foramen magnum region and contributes to the odontoid arcade [13].

Branches after passing through the hypoglossal canal (Fig. 2.9):

(a) Clival branches which run superiorly onto the clivus and anastomose with the medial clival branch of the MHT.
(b) Branches to the meninges of the posterior fossa which reciprocate their territory with the jugular artery. It anastomoses with the small anterior meningeal artery which is a branch of the VA.
(c) Descending branches which enter the spinal canal through the foramen magnum. They give dural branches to the odontoid arcade. These are best called prevertebral arteries, though this term is sometimes confusingly used for intraspinal arteries that anastomose with the C3 spinal artery of the VA.

2. Jugular artery arises lateral to the neuromeningeal trunk and is the larger of the two main posterior division branches. It runs upwards and medially to enter the cranium through the jugular foramen. In the foramen, it supplies the IXth, Xth and XIth cranial nerves before continuing to supply dura in the posterior fossa (it reciprocates this territory with the hypoglossal artery).

After leaving the foramen, it gives a small medial branch which runs superiorly on the clivus to supply the sixth cranial nerve and continues posterolaterally giving dural branches to supply dura over a variable but usually wider area than branches of the hypoglossal artery. It branches to the dura of the lateral clivus anastomose with the lateral clival artery (meningohypophyseal trunk) and with the dural territories of the middle meningeal, posterior auricular and occipital arteries. From these may arise the artery of the falx cerebelli or the posterior meningeal artery. The meningeal distribution of the neuromeningeal trunk in the posterior fossa varies in extent and can be virtually negligible.

2.4.3.3 Other Branches of the Ascending Pharyngeal Artery

1. Musculospinal arteries arise from the main trunk or the posterior division (i.e. neuromeningeal trunk) in the neck and run posteriorly and upwards. They supply paraspinal muscles (with branches of the ascending cervical artery, in the C3 and C4 regions), the superior sympathetic ganglion and the XIth cranial nerve. These may be evident as a single branch

at the C3 level which some authors term the musculospinal artery and can be seen running posterior to the APA trunks [14]. They take part in the supply of the upper paraspinal muscles and thus potentially anastomose with branches of the deep cervical artery, spinal branches of VA and the ascending cervical artery.

2. The inferior tympanic artery is a small but important artery. It is classically described as a branch that arises from the anterior division (or superior pharyngeal branch) but may arise from the APA trunk or its posterior division. It reaches the middle ear via the inferior tympanic canal (i.e. canal of Jacobson) to supply the cochlear and vestibule, thereby contributing to the anastomotic network of the middle ear cavity.

2.4.4 Facial Artery (FA)

This artery arises from the anterolateral surface of the ECA, above the LA (or from a common trunk with the LA) and medial to the stylohyoid and the posterior belly of digastric muscles. Initially, it lies deep to the mandible and runs alongside the submandibular gland, first upwards and then downwards on its medial and lateral surfaces. It then turns under the inferior border of the mandible (where it is palpable against bone) to climb obliquely across the face, running upwards and forwards. The FA may cross the cheek as a single artery or accompanied by the long facial artery, which arises from its superior surface proximally and runs above to it towards the inner canthus. The long facial artery represents one of several possible branching patterns of the FA on the cheek, sometimes described as jugal pedicles. If multiple, these run a parallel course across the cheek, one above the other.

It terminates at the medial angle of the orbit by forming the angular artery. Branches of the FA are numerous. They arise successively as follows.

2.4.4.1 Branches

1. Ascending palatine artery. This branch arises close to the origin of the FA and supplies the pharynx, soft palate, tonsil and Eustachian tube.
2. Tonsillar artery. The tonsillar artery may be a single artery or represented by two or more small branches. It is usually the dominant supply to the palatine tonsil.
3. Submandibular branches. These arteries are short branches arising as the FA passes around the gland.
4. Submental artery. This branch arises deep to the inferior border of the mandible and gives branches to the submandibular gland, to the mylohyoid and digastric muscles and to the mandible, including a mental branch. It anastomoses across the midline with its counterpart and with the inferior labial branch. A glandular branch may arise as a separate trunk of the FA, proximal to the submental artery origin. During embolisation of the FA, in the context of epistaxis, it is recommended that superselective catheterisation should be performed distal to the origin of this branch artery to avoid damaging the gland.
5. Inferior and superior labial arteries. These run forwards to supply the skin and subcutaneous tissues of the lips. They anastomose across the midline. There is a risk of labial necrosis when embolisation is performed with very small particles in these vessels.
6. Branches to the muscles of the face and the buccinator and masseter muscles. This arterial territory may be configured with a long facial artery so that these branches arise from one of the FA pedicles running superomedially across the cheek towards the inner canthus.
7. Lateral nasal artery. This arises after the superior labial artery to supply the lateral nose. It divides into two (superior and inferior alar arteries) to supply the alar of the nose, i.e. alar cartilages and soft tissue around the nostrils. It anastomoses across the midline with its counterpart.
8. Angular artery. This is the terminal branch of FA and runs superiorly in the angle between the nasion and the medial orbit. It supplies medial cheek and lateral nasal tissues and anastomoses with the dorsal nasal artery (branch of the OphA).

2.4.5 Occipital Artery (OA)

The OA arises from the posterior aspect of the ECA at the level of the FA. It passes upwards, laterally and posteriorly. It crosses lateral to the internal jugular vein and then passes between the mastoid process and the transverse process of the atlas. It gives muscular branches, the transmastoid artery and the stylomastoid artery. These supply muscles at the craniocervical junction, the meninges of the posterior cranial fossa and the middle ear, respectively. The occipital artery passes through the fascia between sternomastoid and trapezius and divides into two superficial branches, one lateral and one medial, to supply the scalp of the posterior cranium. It is a potent route for anastomoses with the vertebrobasilar system.

2.4.5.1 Branches

1. Muscular branches which represent segmental arteries supplying the upper cervical muscles (and nerves and bone). They contribute to the territory of the VA branches at C1 and C2 and anastomose with the spinal arteries of these levels. The muscular branches run posteriorly from their origins with a characteristic proximal section directed superiorly and a longer distal section directed inferiorly. What makes this most striking is that they run parallel to each other. They supply the sternocleidomastoid and other paraspinal muscles in conjunction with branches of the vertebral artery and the deep cervical artery. At C3 and C4 levels, this may include an overlap with the muscular territory of the musculospinal arteries of the APA and at C2, C3 and C4 with the deep cervical artery. A prominent descending muscular branch may be evident arising at the C1 level which runs inferiorly to anastomose with the deep cervical artery at the C3 and C4 levels.
2. Stylomastoid artery. This branch more frequently arises from the posterior auricular artery. See below.
3. Transmastoid artery or artery of the mastoid foramen. This branch is usually identifiable as a single vessel which arises posterior to the stylomastoid process and gives small muscular branches before passing intracranially though its foramen just behind the sigmoid sinus. It supplies the meninges of the posterior fossa, giving branches to the jugular foramen, and dura around the posterior foramen magnum and adjacent posterior fossa. These branches thus reciprocate territory with branches of the jugular and, to a lesser extent, the hypoglossal branches of the APA and posterior meningeal arteries of VA. A small ascending branch to the internal auditory canal can anastomose with AICA through the subarcuate arcade.
4. Lateral meningeal arteries often arise from the OA as it passes posteriorly and upwards. These supply dura in the occipitoparietal region. They pass though small individual foramen and their territory borders on the territory of the posterior branch of the middle meningeal artery.
5. Terminal Scalp Branches. The OA terminates in a series of branches which supply the scalp of the posterior cranium and anastomose across the midline.

2.4.6 Posterior Auricular Artery (PA)

This smaller posterior artery usually arises from the posterior aspect of the ECA, distal to the OA or with it as a common trunk. It passes between the ear and the mastoid process and terminates in superficial auricular and occipital branches to the scalp. It provides branches to the parotid gland, adjacent muscles and is the usual source of the stylomastoid artery.

2.4.6.1 Branches

1. Muscular branches. These supply the adjacent muscles, i.e. sternocleidomastoid, digastric and stylohyoid muscles.
2. Parotid branches. These are usually small and ignored, but may supply the VIIth cranial nerve.

3. Stylomastoid artery. This branch runs upwards into the stylomastoid foramen and supplies the VIIth cranial nerve, the middle ear and the mastoid sinuses. It takes part in the anastomosis within the middle ear with branches of the middle meningeal artery, APA and ICA.
4. Auricular branches supply the posterior pinna.
5. Occipital branches supply the scalp posterior to the ear, in a reciprocal relationship with the OA.

2.5 Terminal Branches of the External Carotid Artery

The ECA divides just above the neck of the mandible and within the parotid gland into the superficial temporal artery (STA) and internal maxillary artery (IMA) (Fig. 2.13).

2.5.1 Superficial Temporal Artery (STA)

The STA is the smaller terminal branch. It supplies skin and superficial scalp muscles in an extensive ramification, anastomosing with the opposite side and the adjacent PA and OA territories (Fig. 2.13). It runs superiorly after emerging from the parotid gland over the posterior portion of the zygomatic arch. Above the arch, it divides into two main branches (frontal and parietal) which run over temporalis deep to the epicranial aponeurosis. These supply muscle, bone and scalp of their named regions. It provides small branches to supply the parotid gland and the temporomandibular joint, as well as the following named branches.

2.5.1.1 Branches

1. Transverse facial artery (or transverse artery of face). This branch varies in size because it reciprocates its territory with the FA. It arises within the parotid gland and runs horizontally anteriorly above the parotid duct to supply superficial facial structures via superior and inferior directed branches.
2. Anterior auricular artery. This small artery arises from the STA below the zygomatic arch and ramifies to supply the anterior external ear.
3. Posterior deep temporal artery supplies the temporalis muscle. It is the smallest of the three possible deep temporal arteries. The anterior and middle deep temporal arteries arise from the IMA.
4. Zygomatico-orbital artery arises above the zygomatic arch and runs anteriorly to supply scalp and the orbicularis oculi muscle. It takes part in the superficial anastomosis of arteries around the orbit.
5. Frontal and parietotemporal scalp arteries are distributed over the anterior scalp and anastomose with their counterparts across the midline. The territory of the frontal branches borders those of the OphA and FA on the forehead and the parietotemporal branches

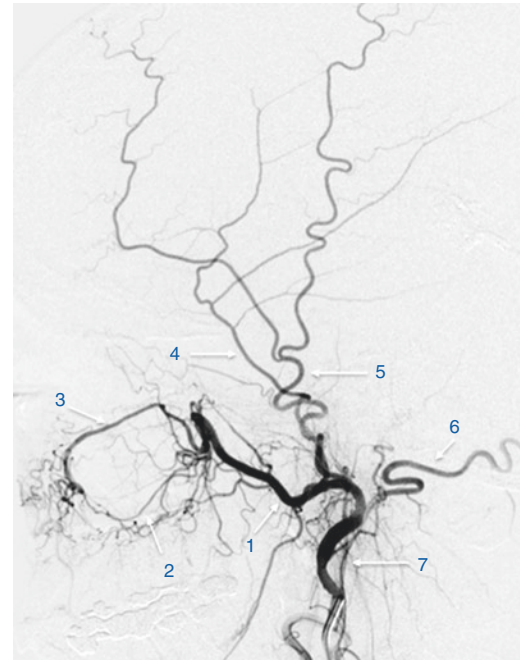

Fig. 2.13 Branches of the distal external carotid artery shown on a lateral angiogram. The numbered arrows mark the following: *1* int. maxillary a.*2* greater palatine a. *3* inf. orbital a. *4* mid. meningeal a. *5* sup. temporal a. *6* occipital a. *7* ascending pharyngeal a

border the PA and OA territories over the lateral cranium.

2.5.2 Internal Maxillary Artery (IMA)

This is the larger terminal branch of the ECA and arises with STA in the parotid gland (Fig. 2.13). It runs medially, deep to the mandible to lie either superficial or deep to the lateral pterygoid muscle before entering the pterygomaxillary fissure and passing into the pterygopalatine fossa (Fig. 2.14). It traverses the fossa and terminates as the sphenopalatine artery. It gives branches to the deep structures of the face, including muscles of mastication, the pharynx, orbit, nose as well as the bone and dura of the anterior skull.

Its 14 named branches, visible on angiography, will be described in the six groups (a–f) used by Djinjian and Merland [15].

(a) Ascending and intracranial arteries, destined to vascularise the meninges, ear and neurocranium
(b) Ascending extracranial arteries
(c) Descending branches which with (e) vascularise the viscerocranium (i.e. the face, mouth and jaw)
(d) Recurrent arteries, which supply structures at the skull base
(e) Anterior branches to the face
(f) The terminal branch, i.e. the sphenopalatine artery

2.5.2.1 The Ascending and Intracranial Arteries

1. Anterior tympanic artery. This arises from IMA close to its origin (but may arise from the ECA termination). It supplies the tympanic cavity, temporomandibular joint and external ear. It is difficult to identify on angiography and runs posteriorly and inferiorly. It gives the deep auricular artery which vascularises the external auditory meatus, as far medially as the tympanic membrane, and branches to the temporomandibular joint and then enters the squamotympanic fissure and supplies the malleus and mucosa of the middle ear.
2. Middle meningeal artery (MMA). The MMA enters the cranial cavity through the foramen spinosum and ends by dividing into frontal and parietal branches (Fig. 2.13). These supply the majority of the convexity meninges. After entering the middle cranial fossa through, it gives the following branches:
   (a) Petrous branch. This small artery supplies dura of the posterior cavernous sinus region and reciprocates with the territories of the petrosquamous branch and the basal tentorial artery of the MHT. It enters the middle ear as the superior tympanic

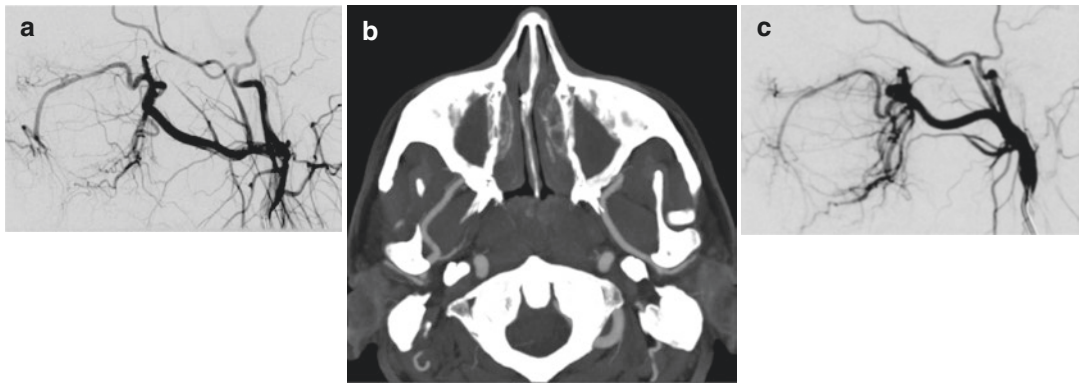

Fig. 2.14 Course of the internal maxillary artery relative to the lateral pterygoid muscle. The arteries are seen on the central MIP reconstructed image from CTA (**b**) and on lateral DSA images, running superficial to the muscle on the right (**a**) and deep to the muscle on the left (**c**)

artery which takes part in the middle ear anastomosis and the supply of the VIIth cranial nerve.

(b) Petrosquamous branches. These are small arteries which arise after the petrous branch to supply dura of the middle fossa floor and part of the anterior tentorium and cavernous sinus. They anastomose with branches of the basal tentorial artery.

(c) Sphenoidal branch. This supplies dura of the anterior part of the middle fossa floor and extends medially to supply the planum sphenoidale as well as sending branches to the cribriform region and anterior falx. A branch may enter the orbit through the superior orbital fissure (meningo-ophthalmic artery).

(d) Meningolacrimal artery. This is an inconstant artery, which enters the lateral orbit via Hyrtl's canal to supply the lacrimal gland.

(e) Temporal branch which is often a large vessel that runs posteriorly on the squamous temporal bone to supply dura of the lateral middle fossa. It contributes to the supply of the tentorium and may supply the posterior falx.

Terminal Branches. The MMA grooves the inner table of the temporal bone to terminate at the pterion by dividing into frontal (anterior) and parietal (posterior) branches which supply bone and dura of the calvarium.

3. Accessory meningeal artery is a small artery which supplies the pharynx, Eustachian tube and a variable amount of the dura of the middle cranial fossa. It arises distal to MMA, but it may arise from MMA, depending on the relationship of the IMA to the lateral pterygoid muscle. The IMA most frequently runs medially, deep to the lateral pterygoid and in this case the accessory meningeal artery arises directly from IMA. If the IMA runs superficial to the muscle, the MMA and the accessory meningeal artery arise from a common trunk (hence the latter's name). The two patterns also correlate with the origins of the inferior alveolar and the middle deep temporal arteries which arise from a common temporodental trunk in the deep variant (Fig. 2.14).

Soon after its origin, the accessory meningeal artery divides into an anterior branch to the pharynx and Eustachian tube and a posterior branch which passes through foramen ovale (anterior to the mandibular nerve (V^3)) and supplies the lateral margin of the cavernous sinus and the Gasserian ganglion.

2.5.2.2 The Ascending and Extracranial Arteries

1. The anterior and middle deep temporal arteries. The anterior and middle deep temporal arteries arise from the IMA. The deep temporal arteries are described in anatomical texts as anterior, middle and posterior but all three are rarely identified on angiograms because the posterior deep temporal artery is small or arises from STA.

The anterior and middle (larger) deep temporal arteries run upwards beneath the temporalis muscle which they supply. The middle deep temporal artery arises from the temporodental trunk of the IMA in the deep variant, as described above. A branch of the anterior deep temporal artery contributes to supply the lateral orbit, anastomosing with the lacrimal branch of OphA.

2.5.2.3 The Descending Branches

1. The inferior alveolar artery (or inferior dental artery) arises from the inferior surface of the IMA, opposite the MMA origin (alone or with the middle deep temporal artery). It traverses the mandibular canal to the mental foramen where it gives the mental artery which terminates in the midline. It gives off dental branches and the mylohyoid artery.
2. Pterygoid branches which supply the pterygoid muscles.
3. Buccal arteries which supply the buccinator muscle, and skin and mucosa of the cheek.
4. Masseteric branches which supply the masseter muscle.

2.5.2.4 The Recurrent Arteries

1. The artery of the pterygoid canal or Vidian artery arises from the IMA in the pterygopalatine fossa and runs posteriorly around the sphenopalatine ganglion (producing a small curve) and then through the pterygoid canal to the nasopharynx. It supplies mucosa of the superior portion of the pharynx near the pharyngeal end of the Eustachian tube and takes part in the anastomosis around the tube. Confusingly, the Vidian artery, with the same territory of supply, can also arise from the MVT of the petrous ICA. It thus can arise from either ICA or IMA and serve as an anastomosis between these arteries.
2. Pterygopalatine artery arises close to the Vidian artery or with it as a common trunk. It is called the pterygovaginal artery by some authors [16] and pharyngeal branch of the internal maxillary artery by others [15]. It passes through the pharyngeal canal (or palatinovaginal canal) which connects the pterygopalatine fossa and the nasopharynx. It supplies mucosa of the pharyngeal roof and around the Eustachian tube and reciprocates its territory with the accessory meningeal and pharyngeal branches of APA.
3. Artery of the foramen rotundum passes backwards to supply the maxillary nerve and adjacent skull base. It runs above the level of the other recurrent arteries and at its origin shows a small bend. It accompanies the maxillary nerve (V^2) with an oblique posterosuperior trajectory on the lateral angiogram and anastomoses with the anterior branch of the ILT. It thus forms a potential collateral route to the ICA.

2.5.2.5 The Anterior Branches

1. The posterior superior alveolar artery (or alveolar-antral artery). This arises from IMA close to the origin of the infraorbital artery or from the proximal section of the infraorbital artery. It runs inferiorly over the tuberosity of the maxilla and gives small branches that supply the molar and premolar teeth, gums of the upper alveolus and mucosa of the maxillary sinus.
2. Infraorbital artery (Fig. 2.13). The infraorbital artery passes through the infraorbital fissure, along the infraorbital groove and canal to the infraorbital foramen. In the canal, it gives a branch to the orbit which supplies the inferior rectus and inferior oblique muscles and the lacrimal sac. Then, the anterior superior alveolar artery which descends to supply the incisor and canine teeth of the upper jaw. After emerging from the infraorbital foramen, it divides into numerous branches which supply the inferior eyelid, the side of the nose, eyelid and upper cheek. These take part in the superficial orbital anastomosis with the angular artery (branch of FA) transverse facial artery (branch of STA) and the dorsal nasal artery from the OphA.
3. The descending palatine arteries (or greater palatine arteries) which run inferiorly and give off lesser palatine arteries destined to supply the soft palate posteriorly and the greater palatine artery which runs forwards to supply the hard palate and terminates in the nasal septum.

2.5.2.6 The Terminal Branch

The sphenopalatine artery is the terminal branch of the IMA. At the medial extent of its course in the pterygopalatine fossa, the IMA enters the sphenopalatine foramen and becomes the sphenopalatine artery to supply the medial and lateral walls of the nasal cavity and adjacent paranasal sinuses.

The sphenopalatine artery gives a pharyngeal branch and then divides within the nasal cavity into lateral nasal and septal nasal arteries.

1. The lateral nasal artery (or posterior lateral nasal artery) divides into two main branches: the artery of the middle concha and artery of the inferior concha. They run forwards and downwards to supply the mucosa of the conchae, the middle and inferior meatuses and the maxillary sinuses.
2. The septal nasal artery is longer than the lateral branches of the sphenopalatine artery and supplies the nasal septum and roof of the nasal cavity. It usually gives branches to supply the superior concha and these anastomose with the anterior and posterior ethmoidal arteries.

An inferior branch runs forwards on the septum to the anterior palatine canal and anastomoses with a branch of the descending palatine artery to form the anterior palatine artery.

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Cranial Venous Anatomy

3

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Preamble

It is important to strike the right balance in this tutorial between the extremes of oversimplification and excessive detail. The venous system is difficult to interpret on an angiogram because of its notorious variability and the imaging challenge of timing the optimum period of data collection. Faced with these problems, how does the student of endovascular therapy decide which veins are important in practice?

If I revert to the analogy of city streets and roads, a temporary interruption to traffic flow (e.g. a vehicle collision or road repairs) induces individual drivers to vary their route to avoid the blockage. They use their knowledge of the available bypass roads and streets. This situation is similar to an embolus or occlusion in the arterial system. An experienced observer, knowing the city street map, is able to predict the new circulation. For the venous system, things are different, because the channels are now not consistently unidirectional. There are no valves in the intracranial veins or sinuses and the only valves in the head and neck are in the internal jugular veins. This makes the prediction of changes in flow patterns much more difficult because there are more route options. Its equivalent, in my road analogy, is for the city council to decide to abolish a one-way traffic system. In this situation, how the individual driver responds and the way they choose to reach their individual objective is far less predictable. The result may be traffic driver mayhem

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until a new stable pattern of traffic circulation is established. Thus, it is important to be able to recognise potential blood flow patterns in the cranial veins and sinuses, though more difficult to predict the effect of focal thrombosis and other pathologies such as raised intracranial pressure or compression by tumours.

This tutorial therefore aims to equip the student with an understanding of the major routes [territories] and normal directions of venous blood flow. Whilst reading these descriptions, remember the effect of gravity and that drainage varies with body position. Our patients are usually examined and treated in the supine position whilst for most of the day they are normally erect with very different venous blood flow patterns.

3.1 Extracranial Veins

The distal venous drainage of the head is through the jugular, vertebral and inferior thyroid veins which drain to the brachiocephalic or subclavian veins. They receive the venous drainage of the veins of the face and neck, which for description can be divided into deep and superficial drainage systems or into anterior-to-posterior territories. The following description is a mix, and the reader is invited to use the diagrams to mentally assemble the described pathways into their coherent reality of interconnecting valveless channels. They will be described in groups based on the main named veins. These do not fit easily into anatomical areas but collect definable tributaries before reaching the inferior neck. Their relative position will be described from proximal to distal in the most consistent direction of blood flow (i.e. towards the heart).

3.1.1 Scalp Veins

The drainage of the scalp, remote from the major dural sinuses, is arranged to follow the regional arteries, so the forehead drains to the supratrochlear and supraorbital veins and then to the facial vein, the temporal region to the superficial temporal vein and thence to the external jugular vein and the posterior scalp to posterior auricular and occipital veins which also drain to the external jugular vein.

They communicate (i.e. blood flow is two-way) with veins in the diploe of the skull, and via emissary veins with the dural sinuses and veins of the pericranium and meninges. The intracranial distribution of veins is described below, but it is worth remembering that in the region of the major dural sinuses, emissary veins are common and thus venous blood flow may be directed intracranially in the parasagittal, mastoid and the occipital regions. A series of venous plexuses at the base of the skull (cavernous, pterygoid, vertebral and suboccipital) drain deeper structures. They intercommunicate and are connected to dural sinuses draining to the extracranial veins. The ophthalmic veins of the orbit are a good example of this bidirectional flow.

3.1.2 Veins of the Face and Neck

3.1.2.1 Internal Jugular Vein (IJV)

This is the largest vein in the neck and drains venous blood from the brain, face, cranium and the majority of the neck. It commences as the continuation of the sigmoid sinus in the posterior portion of the jugular foramen. It descends, in the carotid sheath, and terminates by joining the ipsilateral subclavian vein to form the brachiocephalic vein (Fig. 3.1). Its calibre is approximately 10 mm, and there are dilatations at its origin (superior bulb) and at its termination (inferior bulb). Immediately above the inferior bulb, there is a bicuspid valve, the first valve in this venous pathway draining the brain. The surface marking of its course is a line passing from the medial end of the clavicle to the midpoint of a line between the mastoid process and the ramus of the mandible.

Contributors:

It is usually possible to recognise at least eight tributary veins. From cranial to caudal, these are: inferior petrosal sinus, anterior condylar vein (i.e.

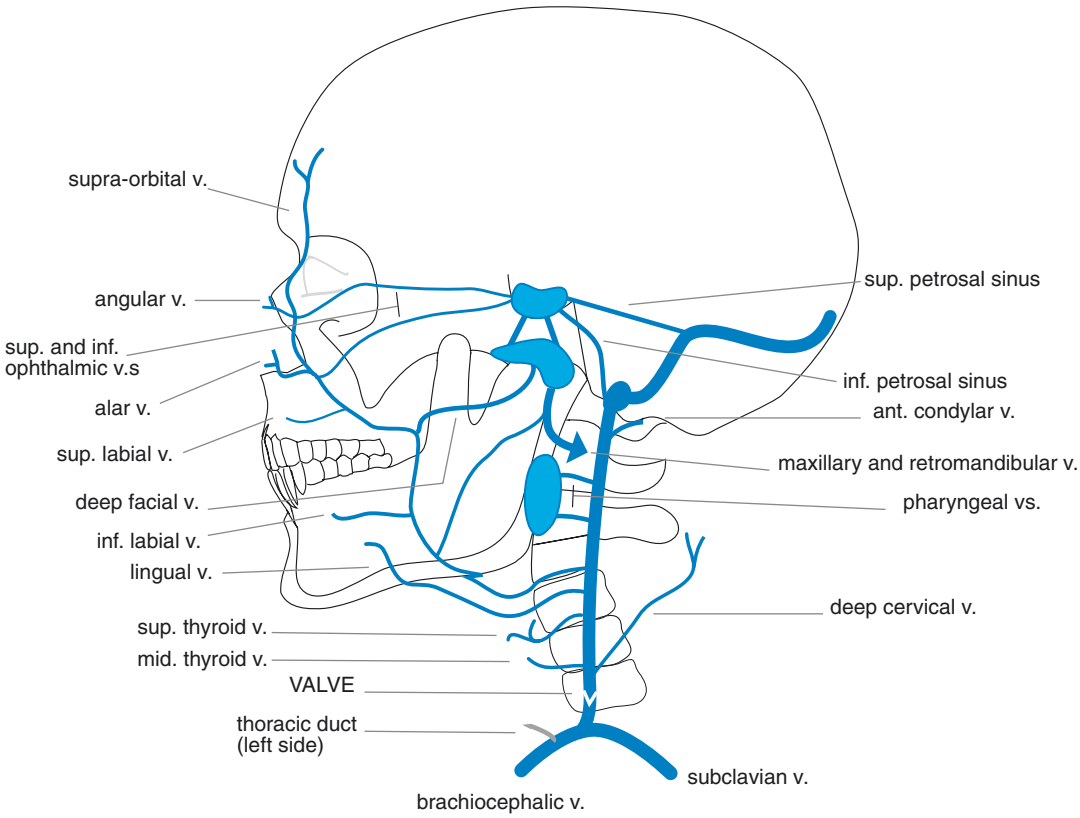

Fig. 3.1 Internal jugular vein and its tributaries (Published with kind permission of © Henry Byrne, 2017. All rights reserved)

vein of the hypoglossal canal), facial vein, lingual vein, pharyngeal veins, posterior external jugular vein, superior and middle thyroid veins.

1. The inferior petrosal sinuses: These originate from the posteroinferior portion of the cavernous sinuses and run posteriorly within the petrous-occipital fissure to cross the anterior portion of the jugular foramen and join the ipsilateral IJV below the level of the jugular canal. They may be single or multiple channels and receive labyrinthine veins, veins of the medulla oblongata and communicates with the clival (or basal) plexus of veins over the clivus.
2. The anterior condylar vein: This connects the IJV with the venous plexus of the hypoglossal canal. It collects blood from the plexus and acts as a communication channel between the IJV and the vertebral epidural venous system.
3. The facial vein: This concentrates the venous drainage from the anterior scalp, face, mouth and muscles of mastication. It originates at the medial angle of the orbit at the confluence of the supratrochlear and supraorbital veins (angular veins). It then runs across the cheek with an oblique trajectory to the ramus of the mandible where it turns medially to terminate by joining the internal jugular vein at the level of the greater cornu of the hyoid.

Facial vein tributaries are:

(a) From the face: The superior palpebral vein, external nasal vein, inferior palpebral vein, superior labial and inferior labial veins drain

the superficial structures of the face to the facial vein.

(b) From the scalp and temporal fossa: The supraorbital and supratrochlear veins drain the anterior scalp. In addition, the superficial temporal vein drains the temporal region. It drains to the external jugular vein but usually joins the maxillary vein (see below) within the parotid gland to form the retromandibular vein, which communicates with the facial vein through a connecting vein (or veins).

(c) From the orbit: The superior and inferior ophthalmic veins drain anteriorly from the orbit and create a direct communication between the facial vein and the cavernous sinus.

(d) From the pterygoid plexus: Deep facial veins drain from the pterygoid plexus to the facial vein. This plexus of the skull base is formed around the pterygoid and temporalis muscles. It acts as a collection area for the subtemporal region and receives drainage from the pharynx (nasopharynx and oropharynx), adjacent muscles of the skull base with direct connections through middle fossa foramen (e.g. ovale, spinosum and the foramen of Vesalius[1]) to the cavernous sinus and via the inferior ophthalmic vein to the orbit. It also drains laterally to the maxillary vein and hence to the external jugular vein (see below).

(e) From the submandibular region: The external palatine vein, submental vein (from the floor of the mouth) and branches from the parotid gland.

At its termination, the facial vein forms a trunk vessel called the common facial vein. This in turn may receive as tributaries the lingual vein and the superior thyroid vein, individually or as a combined vessel called the thyrolingual vein. The superficial section of the facial vein over the cheek is sometimes called the anterior facial vein and the retromandibular vein called the posterior facial vein, when they join before entering the internal jugular vein as the common facial vein. These additional nomenclatures can be confusing.

4. The lingual vein: This drains the tongue, the sublingual and submandibular glands. It joins the IJV at the level of the great cornu of the hyoid, sometimes together with the facial vein, as part of a common thyrolingual vein.
5. The pharyngeal veins: These are a series of two or three short veins which drain the pharyngeal plexus lying in the lateral pharynx to the IJV.
6. The superior thyroid vein: This originates at the superior aspect of the lateral lobe of the thyroid. It accompanies its corresponding artery and joins the IJV directly or via a thyrolingual vein with the lingual vein. It receives the superior laryngeal veins.
7. The middle thyroid vein: This originates lateral to the thyroid gland and terminates in the IJV at the latter's midpoint.
8. The deep cervical vein: This vein arises from suboccipital plexus and the occipital veins (see below). It drains the deep structures of the posterior neck and accompanies the deep cervical artery running inferiorly to join either the distal IJV or the vertebral vein.

3.1.2.2 External Jugular Vein (EJV)

This vein drains the deep regions of the face, the mid and posterior scalp and the posterolateral aspect of the neck (Fig. 3.2). It arises at the level of the angle of the mandible from the confluence of the retromandibular vein and the posterior auricular vein and/or the superficial temporal vein. It runs inferiorly superficial to the sternocleidomastoid muscle to join the subclavian vein. A one-way valve, similar to the IJV, is usually sited just proximal to its termination.

Contributors:

1. The superficial temporal vein: The superficial temporal vein drains the temporal region of scalp. It accompanies the superficial temporal

[1]Andreas Vesalius (1514–1564) born in Brussels, he became a court physician to Charles VI and wrote 'De humani corporis fabrica', which contained a detailed but confusing (it does not always differentiate correctly arteries and veins) account of blood supply.

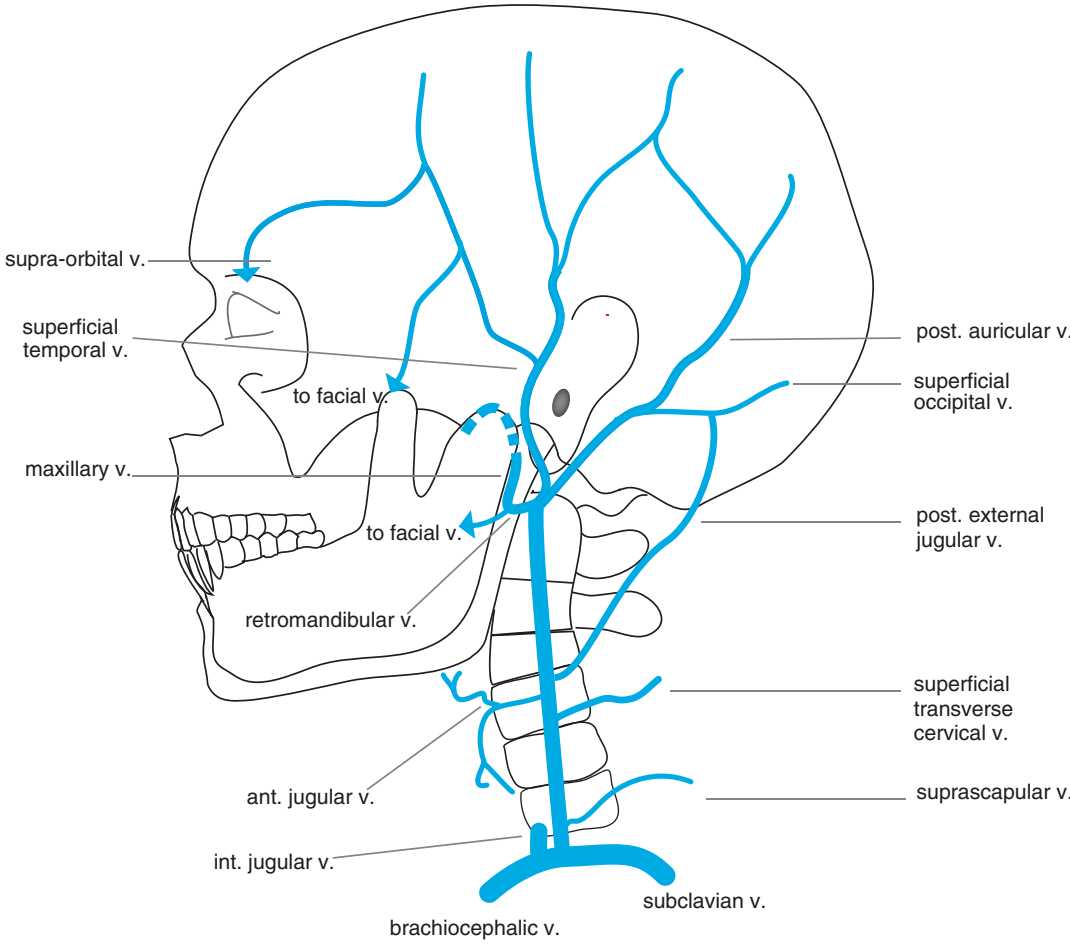

Fig. 3.2 External jugular vein and its tributaries (Published with kind permission of © Henry Byrne, 2017. All rights reserved)

artery and descends vertically in front of the tragus of the ear and posterior to the temporomandibular joint. It receives the middle temporal veins, the transverse vein of face, veins of the temporomandibular joint and the anterior auricular veins before crossing the zygomatic arch and entering the parotid gland. Within the parotid gland, it unites with the maxillary vein to form the retromandibular vein. It may join the posterior auricular vein rather than the retromandibular vein. Either way it ends at the commencement of the EJV.

2. The posterior auricular vein: This vein drains the scalp posterior to the territory of the superficial temporal vein. It runs posterior to the tragus and joins the retromandibular vein to form the EJV. It communicates with the superficial occipital veins.
3. The maxillary vein: This arises from the pterygoid venous plexus and accompanies the internal maxillary artery. The pterygoid venous plexus receives veins that accompany branches of the internal maxillary artery, i.e. the middle meningeal veins, deep temporal veins, the pterygoid canal vein and through the sphenopalatine vein, the drainage of the internal nasal veins. It also receives drainage from the cavernous sinus through emissary veins and communicates with the inferior ophthalmic vein. It forms the retromandibular vein with the superficial temporal vein. The retromandibular vein runs inferiorly in the

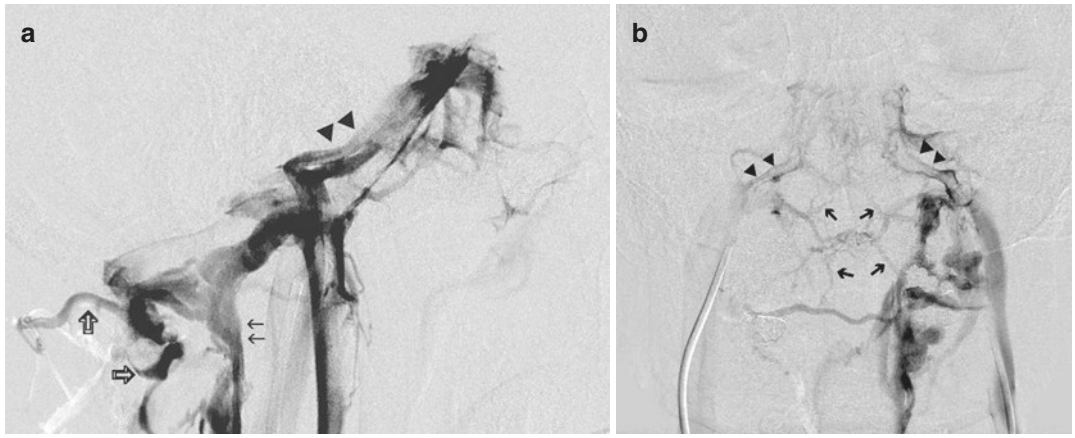

Fig. 3.3 Lateral (**a**) and frontal (**b**) projection of a venogram performed by injection of the proximal internal jugular veins. Retrograde filling of the inferior petrosal sinuses (*arrowheads*) is seen, and contrast fills the veins of the suboccipital plexus (*white open arrows*) and vertebral venous plexus (*small arrows*)

parotid gland and gives an anterior branch to the facial vein before joining the posterior auricular vein to form the EJV.

4. The posterior external jugular vein: Arises from the occipital vein, which carries the superficial drainage of the suboccipital plexus (see below). The posterior external jugular vein additionally drains the superficial structures of the posterior neck and joins the EJV at its mid-point. Its equivalent in the anterior neck is the anterior jugular vein.
5. The terminal tributaries to the distal EJV: These are the superior scapula vein, the transverse cervical vein and muscular branches which it receives before draining into the subclavian vein.

3.1.2.3 Anterior Jugular Vein

This smaller neck vein arises from superficial submental veins. It descends on the anterior aspect of the neck as a network of subcutaneous veins, receiving muscular and cutaneous branches and forms a venous arcade that then communicates across the midline with the contralateral anterior jugular vein. It terminates by joining either the subclavian vein or the EJV and is a hazard when performing tracheostomy.

3.1.2.4 Suboccipital Plexus

The suboccipital plexus is a collection of veins in the posterior neck with extensive connections to superficial occipital veins and the vertebral artery venous plexus (Fig. 3.3). They receive mastoid and occipital emissary veins, as well as draining the muscles of the suboccipital triangle. Its drainage is to the EJV via the occipital vein, which pierces the trapezius and drains to the superficial occipital veins and the posterior external jugular vein. The deep drainage of the plexus is to the vertebral venous system (see below) and so to IJV via the deep cervical vein and the vertebral vein.

3.1.2.5 The Vertebral Venous System and Vertebral Vein

The direction of venous drainage from the cranium is positional. In the erect position, it is probable that the majority is directed to the vertebral venous system. The vertebral venous system comprises veins surrounding the spinal cord that can be separated into internal and external vertebral plexuses. The internal vertebral plexus comprises a series of epidural veins, which run caudally in the cervical canal (both anterior and posterior to the spinal theca) and connect with veins of the external vertebral plexus via the intervertebral foramen. The external vertebral plexus comprises two groups of veins centred on the vertebral artery venous plexus and the deep cervical vein.

The vertebral artery venous plexus forms around the vertebral arteries in the vertebral canal at the C2 level. It has numerous interconnections with the veins around the foramen magnum and

the suboccipital plexus. Tributaries to the vertebral artery plexus include the lateral condylar vein, the anterior condylar veins of the hypoglossal plexus and the posterior condylar vein. It accompanies the vertebral arteries through the vertebral canal and distally consolidates into a solitary trunk – the vertebral vein. In the vertebral canal, it receives spinal radicular veins from the internal vertebral plexus and muscular branches. The vertebral vein exits the vertebral canal at the foramen transversarium of C6 to join the brachiocephalic vein.

The deep cervical vein drains from the suboccipital venous plexus and runs posterior to the transverse process of the cervical vertebrae and either joins the vertebral vein or drains separately into the IJV or brachiocephalic vein. Its course accompanies the deep cervical artery.

The venous outflow from the posterior fossa (in the erect position) to the vertebral venous system involves three condylar veins and the mastoid emissary vein. The anterior condylar vein (or vein of the hypoglossal canal) participates in a venous hub at the anterior craniocervical junction. It connects the internal vertebral veins with the hypoglossal venous plexus situated anterior to the hypoglossal canal. The lateral condylar vein arises from the plexus and connects it with the IJV, inferior petrosal sinus and the laterally situated vertebral artery venous plexus (vertebral vein). The posterior condylar vein arises from the distal sigmoid sinus, at or near to its junction with the jugular bulb, and runs through the posterior condylar canal to the vertebral artery venous plexus. Since angiography is usually performed on people in the supine position, radiographic contrast drains preferentially via the IJV and these vessels are under filled.

3.2 Intracranial Veins

There are five types of intracranial veins:

- Diploic
- Emissary
- Meningeal
- Dural sinus
- Cerebral
  - Superficial
  - Deep

3.2.1 Diploic Veins

These are relatively large thin-walled endothelial lined channels, which run between the inner and outer table of the skull, i.e. in the diploe (Fig. 3.4). They connect externally to scalp veins and internally to meningeal veins and dural sinuses.

They are most numerous in the calvarial (cancellous) bone of the skull. Their regional distribution can be separated into frontal (drain to the supraorbital vein and the superior sagittal sinus

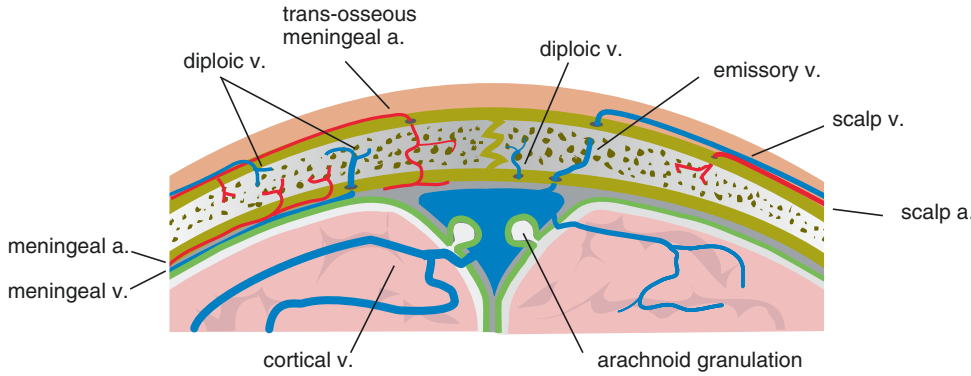

Fig. 3.4 Diagram showing the superior sagittal sinus (*coronal view*) with arachnoid granulations and scalp, meningeal and diploic vessels (Published with kind permission of © Henry Byrne, 2017. All rights reserved)

[SSS]), anterior temporal (drain to deep temporal veins and sphenoparietal sinus), posterior temporal (drain to posterior auricular veins and transverse sinus) and occipital (drain to superficial occipital veins or internally into the transverse sinus). They are difficult to image by catheter angiography.

3.2.2 Emissary Veins

These are connecting veins between extracranial veins, diploic veins and the intracranial meningeal veins and sinuses. They are concentrated around major dural sinuses, particularly parasagittal to the SSS and around the sigmoid sinus. Named emissary veins are parietal (connecting the superior sagittal sinus and scalp veins via parietal foramen), mastoid (connecting sigmoid sinus and superficial occipital veins or the posterior auricular vein) and condylar emissary veins (connecting distal sigmoid sinus with the vertebral venous and suboccipital plexuses). Emissary veins also traverse named foramen between the sinuses of the skull base and extra-cranial veins of the pterygoid, vertebral venous and suboccipital plexuses. These include foramen rotunda, foramen ovale the sphenoid emissary vein (via the foramen of Vesalius), foramen lacerum and the condylar veins. Evident less consistently are occipital emissary veins between the torcular sinuses and occipital scalp veins and veins in the cribriform region connecting the superior sagittal sinus and veins of the nasal mucosa. The condylar veins (see above) are generally considered large emissary veins but it then becomes a question of scale in distinguishing emissary veins from other veins and sinuses that traverse bone. Two-way blood flow means they function in response to the head position, and one can only speculate as to their physiological role, e.g. for cooling the head. They are potential portals for infection and collateral routes in the event of sinus blockage. These structures are best imaged by contrast-enhanced CT [1].

3.2.3 Meningeal Veins

The meningeal veins are a network of vessels in the outer layer of dura, between it and the periosteum of the inner table of the skull. Over the calvarium, the larger veins, which may groove the bone, accompany branches of the middle meningeal artery (MMA) to the foramen spinosum (or foramen ovale) through which they drain to the pterygoid plexus. More anterior (i.e. frontal) meningeal veins accompany anterior branches of MMA and join the sphenoparietal sinus, which usually drains to the cavernous sinus but may drain posteriorly to the lateral sinus. Other veins drain the falx, tentorium and more posterior convexity dura to the nearest intracranial sinus.

The meningeal veins of the skull base follow the same pattern. The anterior cranial fossa drains to the ophthalmic veins, anterior meningeal vein and the sphenoparietal sinus and thence to the cavernous sinus. Exceptions are the extreme anterior portion of the anterior cranial fossa, which drains to the anterior SSS or through the cribriform plate, and subfrontal meningeal veins, which may drain to the basal vein (of Rosenthal). In the central skull base, (i.e. body of the sphenoid bone and the clivus) drainage is to the inferior petrosal sinuses, clival plexus, anterior condylar veins and thence to the pterygoid plexus, vertebral venous plexus. From the posterior skull convexity, drainage is to the transverse, sigmoid, occipital and marginal sinuses or vertebral veins with emissary veins connecting to the scalp veins.

3.2.4 The Dural Sinuses

Sinuses are formed within two layers of dura and drain the veins of the brain, the meninges and the cranium principally to the IJV. They are usually triangular-shaped, endothelium-lined trabeculated chambers formed by meningeal or endosteal layers of dura mater. They are valveless, and their walls are devoid of smooth muscle.

They function with one-way drainage to them from the calvarium, meninges and cerebral veins

and two-way connections between them and diploic and emissary veins. They comprise the following.

3.2.4.1 Superior Sagittal Sinus (SSS)

The SSS is situated within the superior attachment of the falx cerebri to the calvarium (Fig. 3.5). It extends from the foramen caecum of the crista galli along a longitudinal arc-like trajectory within a gutter on the internal surface of the frontal bone, the sagittal borders of the parietal bone and the occipital bone, to the confluence of sinuses, i.e. the torcular Herophili.[2] The sinus receives the superior cerebral veins which drain the cortex, diploic veins and meningeal veins. The cerebral veins enter the sinus obliquely, and together with fibrous bands known as *chordae Willisii* within the sinus, act as valves to reduce reflux and encourage flow through the sinus. At the torcular, it generally drains to the right transverse sinus, but the configuration is variable and duplications of the channels are common. The sinus contains arachnoid granulations (or Pacchionian[3] granulations). They are clumps of arachnoid villi. Arachnoid villi are a microscopic projection of arachnoid into the

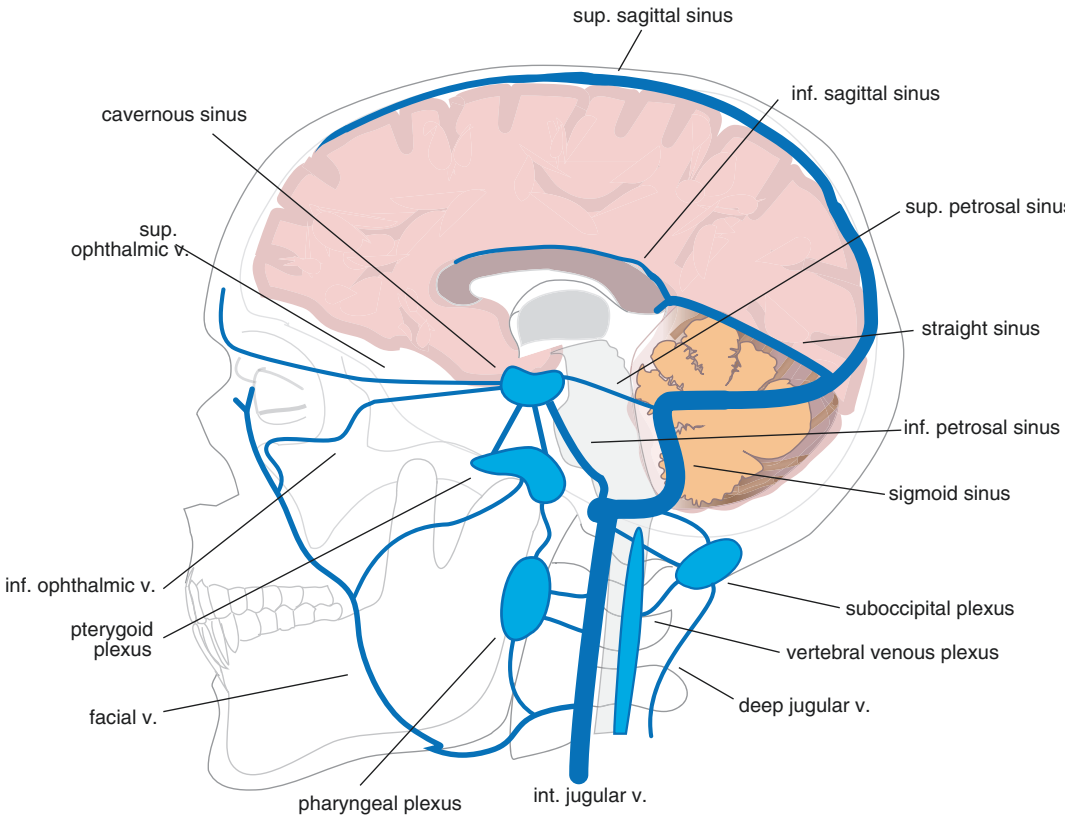

Fig. 3.5 Large intracranial sinuses and plexuses of the skull base and upper neck (Published with kind permission of © Henry Byrne, 2017. All rights reserved)

[2]Herophilus (335–280 BC) a physician who was born in Turkey and is regarded as a founder of the great medical school of Alexandria where he spent most of his life. He corrected Aristotle's idea that the heart was the source of thought and distinguished veins from arteries.

[3]Antonio Pacchioni (1665–1726) Italian physician who worked in Rome and wrote 'Dissertatio de epistolaris glandulis conglobatis durae meningis Humanae, indeque ortis lymphaticis to piam meningem productis' describing dural arachnoid granulations in 1705.

walls of the dural sinus, which drain cerebrospinal fluid into the venous system. They are present in all the dural sinuses but most obvious in the SSS where they protrude into its inferolateral margin (Fig. 3.4). Blood in the SSS drains posteriorly and normally not anteriorly to small veins in the region of the cribriform plate.

3.2.4.2 Inferior Sagittal Sinus

The inferior sagittal sinus runs along the inferior border of the falx cerebri. Its trajectory is parallel to the superior sagittal sinus. It arises at the junction of the anterior and middle one-third of the falx cerebri above the genu of the corpus callosum and receives meningeal veins from the falx and veins from the anterior corpus callosum, cingulate gyrus and the medial surface of the hemisphere. It drains posteriorly into the straight sinus which it joins in conjunction with the vein of Galen (VOG).

3.2.4.3 Straight Sinus

The straight sinus is situated at the junction of the falx cerebri and the tentorium cerebelli. It runs posteriorly to the torcular where it usually drains to the left transverse sinus. It is essentially a connecting vessel and the main channel for the brain's deep venous drainage but may be duplicated in approximately 15% of individuals and receives tentorial and cerebellar veins.

3.2.4.4 Transverse Sinus

The transverse sinuses (or lateral sinuses) are paired and arise at the confluence of the sinuses (torcular Herophili) in continuity with one or both of the superior sagittal or straight sinuses. They pass laterally forwards and then downwards in a groove in the inner table confined by the peripheral margin of the tentorium. Anteriorly they continue below the level of the tentorial attachment as the sigmoid sinuses. In a significant minority (5%) of individuals, angiography shows narrowed or atretic sections caused by arachnoid granulations. They receive cerebral veins from the temporal and occipital lobes (in particular the inferior anastomotic vein or vein of Labbé[4]), cerebellar veins, the superior petrosal sinuses (at the junction with the sigmoid sinus) and accessory sinuses (e.g. a lateral tentorial sinus).

3.2.4.5 Superior Petrosal Sinus

The paired superior petrosal sinuses connect the posterosuperior aspect of the cavernous sinus with the sigmoid sinus at its junction with the transverse sinus. They run posteriorly and laterally within the attached margin of the tentorium cerebelli, along the superior border of the petrous portion of the temporal bone and terminate at the junction of the transverse and sigmoid sinuses. They receive veins draining the midbrain, pons, medulla oblongata and cerebellum via the petrosal vein and veins from the middle ear.

3.2.4.6 Sigmoid Sinus

The sigmoid sinuses are the continuations of the transverse sinuses. Each sinus grooves the mastoid portion of the temporal bone and ends by crossing the jugular process of the occipital bone where they turn anteriorly into the jugular foramen to become the superior bulb of the IJV. They receive the superior petrosal sinuses and drain to the internal jugular veins. They receive no direct cerebellar venous drainage. They give rise to mastoid and condylar emissary veins. The anterior condylar vein and confluence connect then with the marginal sinuses and, via the posterior condylar vein, to the internal vertebral venous plexus.

3.2.4.7 Occipital Sinus and Marginal Sinuses

The occipital sinus is the smallest and most variable of the major sinuses (Fig. 3.6). It runs along the attached border of the falx cerebelli from the confluence of the sinuses (i.e. torcula Herophili) along the internal occipital crest to the posterior

[4]Charles Labbé (1851–1889) French surgeon who worked in Paris.

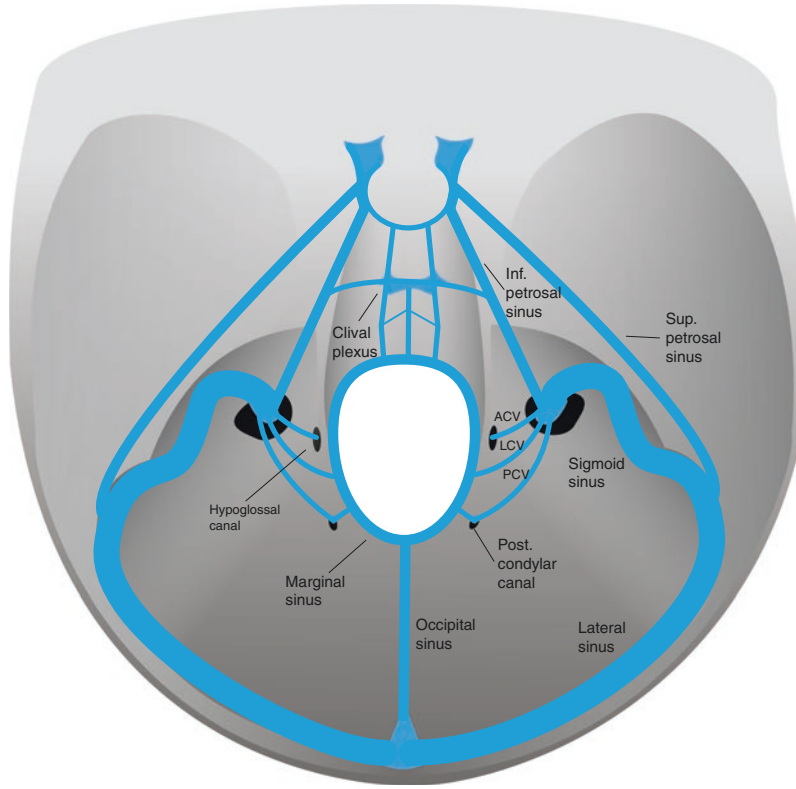

Fig. 3.6 Marginal sinus and dural veins of the foramen magnum region. (Published with kind permission of © Henry Byrne, 2017. All rights reserved)

margin of the foramen magnum where it usually continues as the paired marginal sinuses. The marginal sinuses circle the foramen magnum and are connected to the clival (or basal) venous plexus anteriorly, to the vertebral venous plexus inferiorly and to the sigmoid sinuses and internal jugular veins laterally by small veins. Veins connecting the marginal sinus to the jugular bulb comprise the anterior condylar vein which passes through the hypoglossal canal, the lateral condylar vein from the lateral portion of the marginal sinus, and the posterior condylar vein which may connect to the jugular bulb as well as the suboccipital plexus and internal vertebral venous plexus through the posterior condylar canal. The anterior condylar vein, tributaries of the clival plexus and lateral condylar veins form the anterior condylar confluence along the medial margin of the jugular bulb. Occipital sinuses are most evident in children and presumably regress with age or persist in adults as large tentorial veins or sinuses. The pattern of emissary and condylar veins is also variable, and it is unusual for all the vessels described above to be present in the same individual.

3.2.4.8 Inferior Petrosal Sinus (IPS)

The inferior petrosal sinuses drain the posterior cavernous sinus to the internal jugular vein. They run backwards, downwards and laterally along the petroclival suture to the anterior portion of the jugular bulb and join the IJV just below its exit from the jugular canal. They receive cerebellar veins, pontine veins and the labyrinthine vein. They communicate with the clival and anterior vertebral (hypoglossal) venous plexuses, as described above.

3.2.4.9 Cavernous Sinuses

The cavernous sinuses are situated on either side of the body of the sphenoid bone and are partitioned by numerous fibrous strands, which give

the appearance of cavernous tissue. These strands are important to the endovascular therapists because the resulting partitioning of the sinuses impede catheter navigation when using the transvenous route to treat arteriovenous shunts. Its inferior wall is continuous with the dura of the temporal fossa, and the superior wall is formed by a triangular layer of dura limited by the free margin of the tentorium and the anterior and posterior clinoid processes. The lateral wall forms the medial boundary of the middle cranial fossa and extends between the free edge of the tentorium and the dura of the fossa floor. The medial wall conforms to the body of the sphenoid bone and forms the lateral boundary of the pituitary fossa (see Tutorial 11 and Fig. 11.1).

The internal carotid artery traverses the sinus with its sympathetic plexus as well as the abducens nerve (VIth), which runs immediately lateral to the artery. Embedded within the lateral wall (from superior to inferior) are the oculomotor (IIIrd), trochlear (IVth) and the maxillary (V^2) division of the trigeminal nerve (Vth) cranial nerves. The terminal portion of the sphenoparietal sinus runs for a short distance in the sinus roof. The cavum trigeminale (Meckel's cave), containing the trigeminal ganglion and its branches, lies in the posteroinferior margin. All the structures which traverse the sinus are surrounded by the endothelium to isolate them from the venous circulation.

The cavernous sinuses, because of their strategic position, connect the anterior and posterior parts of the venous system of the skull base (Fig. 3.5). They drain to the superior and inferior petrosal sinuses, the pterygoid plexus and the facial veins via the orbital veins. Inferiorly, they are connected to the pterygoid plexus via emissary veins passing through the middle fossa foramen (e.g. ovale, lacerum and spinosum). Their tributaries are as follows:

- Superior and inferior ophthalmic veins. These are principal veins of the orbit and drain via the superior orbital fissure into the anterior portion of the cavernous sinus. They also communicate anteriorly with superficial periorbital veins and thus form part of a communication route between the proximal IJV (via the inferior petrosal sinus) and the facial vein. The inferior ophthalmic vein also communicates directly with the pterygoid plexus via a branch, which passes through the inferior orbital fissure.
- The sphenoparietal sinus and meningeal veins. The sphenoparietal sinus, though classically described as a single structure (see below), which drains the Sylvian or superficial middle cerebral vein and meningeal veins of the parietal region, is often comprised of two or more channels, which congregate at the anterolateral cavernous sinus.
- Intercavernous sinuses and hypophyseal veins. A plexus of veins communicates across the midline via the intercavernous sinuses. These are sometimes called the circular or coronary sinuses and comprise a series of connecting veins in the diaphragma sellae which pass over the pituitary gland and fossa connecting the two cavernous sinuses. These midline connections are reinforced by the veins of the clival (i.e. basilar) plexus. This plexus of meningeal veins, situated anterior to the clivus, connects the cavernous sinuses, the inferior petrosal sinuses and the internal vertebral venous plexus. These extensive communications across the midline are the reason for some patients with caroticocavernous fistula developing contralateral exophthalmos.
- Veins of the medial temporal lobe. Uncal veins and sometimes the deep middle cerebral vein drain to the posterior part of the cavernous sinus.
- Superior and Inferior petrosal sinuses. Posterior drainage is to the transverse sinuses via the superior petrosal sinuses and to the inferior jugular veins via the inferior petrosal sinuses.

3.2.4.10 Sphenoparietal Sinus

The sphenoparietal sinus is a dural sinus running along the lesser sphenoid wing, which collects meningeal and cortical veins. Short anterior meningeal veins drain to its distal section. Its posterior parietal portion arises in meninges and drains middle meningeal veins. However, there may be separate (parallel) meningeal veins which run directly into the cavernous sinus.

The superficial middle cerebral vein (or Sylvian[5] vein) is classically described as draining into the sphenoparietal sinus but it probably usually runs as an independent parallel vein feeding directly to the cavernous sinus [5]. It collects the superficial venous (cortical) outflow of the brain bordering the Sylvian fissure via a series of insular veins or deep middle cerebral veins. Arising in the fissure, it runs forwards and inferiorly to the pterion where the sphenoparietal sinus forms. It is at this point that superficial cortical veins from the adjacent frontal and medial (uncal) temporal lobes collect and join the sinus or the independent middle cerebral vein. It thus competes with the anterior territory draining to the basal vein of Rosenthal[6] (BVR).

The sphenoparietal sinus also receives diploic veins and, before it enters the wall of the cavernous sinus, the orbital veins.

The sphenoparietal sinus usually drains into the anterolateral part of the cavernous sinus but rarely, turns posteriorly, and does not connect with the cavernous sinus. In this variant, the sinus either runs posteriorly to the lateral sinus or runs under the temporal lobe on the floor of the middle cranial fossa. In the latter case, it is termed the sphenopetrosal sinus and drains to the superior petrosal sinus or a tentorial sinus.

3.3 The Cerebral Veins

The description that follows is intended to take the reader through the cerebral venous system from proximal to distal, i.e. from venule to the major collecting veins in the upper neck. It will distinguish superficial and deep veins in the description because of their functional differences. The cortical mantle drains centrifugally to superficial veins and the deeper white matter centrally to the deep system of veins.

3.3.1 The Supratentorial Superficial (Cortical) Veins

The superficial cerebral veins form in the convexity sulci and collect over the surface of the brain draining cortical grey matter and subcortical white matter. They are distributed over the hemispheres in an even network in which the principal vein follows a sulcus and grows larger as it collects tributaries and runs towards a dural sinus.

3.3.1.1 Convexity Hemisphere Veins

The pattern these veins make over the lateral surface of the hemispheres is easy to appreciate and appears like the radiating spokes of a wheel, with its hub centred on the Sylvian point, i.e. the posterior Sylvian fissure. Three larger veins, into which small- and medium-sized veins drain, are recognised as the superior anastomotic vein (of Trolard[7]) running superiorly to the superior sagittal sinus, the posterior anastomotic vein (of Labbé) running posteriorly to the transverse sinus and the superficial middle cerebral (Sylvian) vein running anteriorly to the sphenoparietal sinus. There is a good deal of variability in the course, size and number of these veins, and seldom are all three anastomotic veins evident in the same hemisphere.

3.3.1.2 Medial Hemisphere Veins

The periphery or margins of the medial surfaces of the cerebral hemispheres drain to tributaries of the superior sagittal sinus. These veins run onto the convexity surface before joining convexity veins, prior to their entry into the superior sagittal sinus.

In the more central portions of the medial surfaces, the frontal and parietal cortex drains to the inferior sagittal sinus or posterior pericallosal vein. The cingulate gyrus and paraterminal gyrus drain to the anterior pericallosal, paraterminal and anterior cerebral veins. The medial occipital cortex drains to the straight sinus, the vein of Galen[8] (VOG) and to tentorial veins.

[5] Sylvian: It is not certain which of two famous European anatomists to ascribe this epithet. Jacques Dubois (1478–1555), known as Jacobus Sylvius in Latin, was a French anatomist in Paris or François de le Böe (1614–1672), known as Franciscus Sylvius though born in Germany, taught at the University of Leiden.

[6] Friedrich Christian Rosenthal (1780–1829) German anatomist whose name is linked to the basal vein and the spiral canal of the cochlear.

[7] Jean Baptiste Paulin Trolard (1842–1910) Algerian anatomist.

[8] Aelius Galenus or Claudius Galenus (129–c. 200/c. 216 AD), also known as Galen of Pergamon, was a Greek physician and philosopher. His writings were the foundation of mediaeval medicine.

3.3.1.3 Inferior Hemisphere Veins

The veins of the inferior surfaces drain either to dural sinuses or the BVR. The veins of the inferior surfaces of the frontal lobes drain anteriorly via anterior orbitofrontal veins to the superior sagittal sinus or posteriorly via the posterior orbitofrontal and olfactory vein to the middle cerebral vein and the cavernous sinus. The temporal lobes drain either medially to the BVR or laterally to the transverse sinus. The occipital lobes drain via short veins to the transverse sinus or BVR.

Generally, the superficial veins do not communicate with those of the deep venous system. The exceptions are the inferior part of the occipital lobe and the medial part of the temporal lobe. The latter may drain to the BVR via the uncal, olfactory and deep middle cerebral veins or to the cavernous sinus via short uncal veins and the deep middle cerebral vein (either directly to the sinus or via the sphenoparietal sinus).

3.3.2 The Medullary Veins

The medullary veins drain white matter (Fig. 3.7a–c). Huang and Wolf [2] used this term for them describing short and long venous channels draining white matter to the cortex and the deep venous system, respectively. The boundary zone for these two groups is approximately 2 cm below the cortex. Though this distinction is not absolute, and interconnecting vessels between superficial and deep draining medullary veins have been described, the short superficial veins run through the cortex and drain both the white and grey matter. The long deep medullary veins run with a straight trajectory perpendicular to the

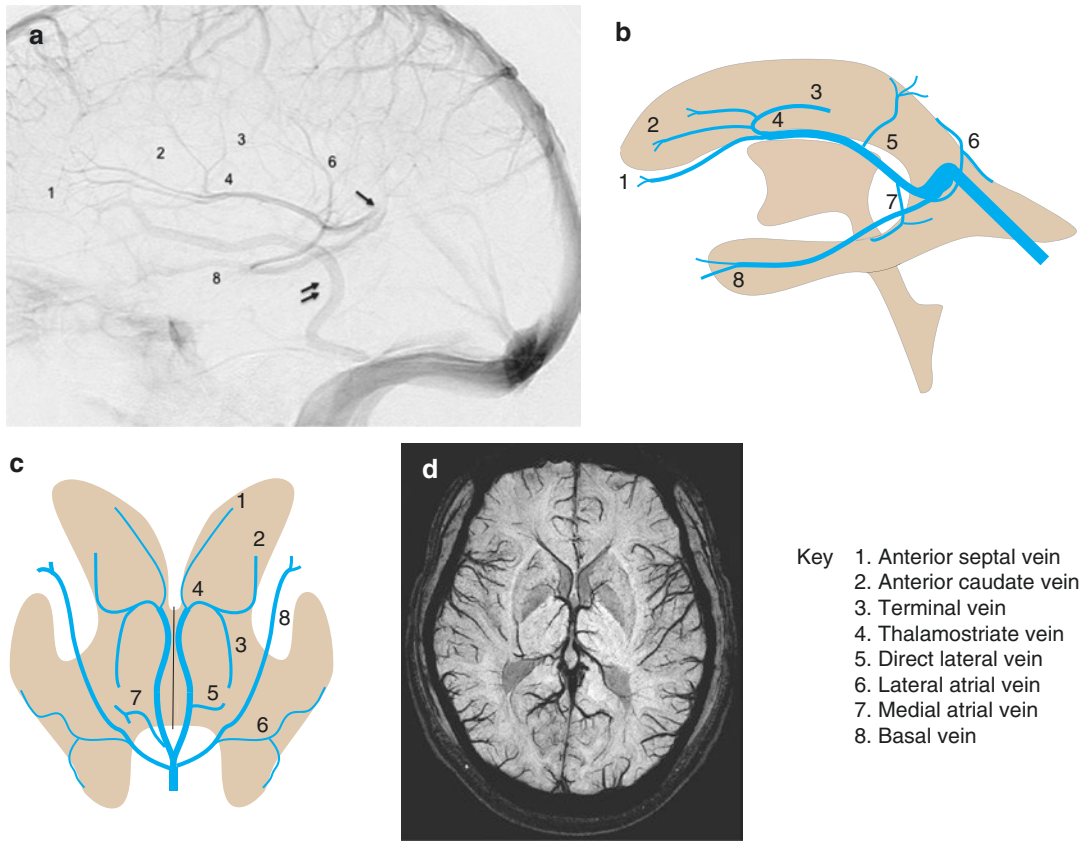

Fig. 3.7 (**a**) Lateral DSA venogram, (**b**, **c**) diagrams showing the tributaries of the internal cerebral veins. (Published with kind permission of © Henry Byrne, 2012. All rights reserved.) (**d**) Axial susceptibility-weighted MRI performed after a subject was given caffeine to slow blood flow and increase its deoxyhaemoglobin content (Courtesy of Dr. J. Neelavalli and Dr. M. Haake)

cerebral surface to subependymal veins along the medial walls of the lateral ventricles or to the BVR. They drain the hemispheric white matter, basal ganglia, corpus callosum, limbic system, thalamus, midbrain and pineal region via to the deep venous system. The ventricular group of subependymal veins converges into tributaries that drain to the internal cerebral veins. Tributaries of the BVR can be considered separately as a cisternal group of veins (see below). The origins of the ventricular group can be divided into medial and lateral subependymal veins [2].

3.3.2.1 Medial Subependymal Veins

These comprise the veins of the septum pellucidum, i.e. the anterior, middle and posterior septal veins and the atrial veins. The anterior septal vein arises in the frontal horn of the lateral ventricle as a confluence of the deep medullary veins of the anterior frontal lobe. It runs posteriorly along the septum pellucidum to join the thalamostriate vein and form the venous angle at the foramen of Munro. The confluence marks the site of the foramen on angiography, but it may occur posterior to the foramen (see below) [3]. The posterior and middle septal veins are a variable group of veins, which drain the posterior frontal lobe, corpus callosum and parietal lobe directly into the internal cerebral veins or via subependymal veins running along the medial surface of the lateral ventricle. The latter comprise the medial atrial vein which is formed by the more posterior median medullary veins draining the posterior parietal and occipital lobes to the internal cerebral vein and small direct tributaries to the internal cerebral vein. The medial atrial vein may drain to a common atrial vein, posterior to the pulvinar, formed by combining with the lateral atrial vein (see below). This enters the posterior portion of the internal cerebral vein.

3.3.2.2 Lateral Subependymal Veins

The principal vein draining the lateral subependymal veins is the thalamostriate vein. This drains the medullary veins of the posterior frontal and anterior parietal lobes, the caudate nucleus and the internal capsule. It receives the superior choroidal vein and, despite its name, drains little of the thalamus. It is the main contributor to the origin of the internal cerebral vein. It arises from the confluence of the anterior caudate vein and the terminal vein. The anterior caudate vein is a group of veins draining the medial surface of the caudate nucleus, which congregates in the sulcus between caudate and thalamus. The terminal vein may be considered the originating tributary of the thalamostriate vein. It begins in the atrium and runs anteriorly in the thalamocaudate groove to join the anterior caudate vein and form the thalamostriate vein.

The other named lateral subependymal vein is the lateral atrial vein which runs anteroinferiorly along the lateral wall of the atrium, exits the choroidal fissure and joins the BVR or turns medially over the thalamus to join the medial atrial vein to form the common atrial vein and drain to the internal cerebral vein. It drains the posterior temporal and parietal lobes. The last to be considered is the inferior ventricular vein, which drains the temporal lobe and receives the inferior choroidal vein. It begins in the posterior body of the lateral ventricle and runs along the anterior wall of the atrium and then anteriorly along the roof of the temporal horn before turning medially exiting the choroidal fissure and draining into the BVR.

3.3.2.3 Internal Cerebral Vein

The internal cerebral veins are paired and formed by the junction of the anterior septal vein and thalamostriate vein (Figs. 3.7 and 3.8). They run posteriorly in the roof of the third ventricle and velum interpositum, receiving numerous small tributaries. They run side-by-side on either side of the midline initially, and when they reach the pineal recess, they deviate laterally, following the superolateral surface of the pineal body, to converge below the splenium and form the vein of Galen. Just before this convergence, they are usually joined by the BVR.

Thus, the internal cerebral veins originate at the foramen of Munro, and this usually corresponds to the venous angle. The venous angle is an angiographic definition of the junction of the thalamostriate vein and the anterior septal vein (on a lateral view). However, the anterior septal vein may join the internal cerebral veins posterior to its origin at the foramen of Munro, shifting the angle posteriorly by as much as 13 mm [3]. The angle and its position relative to the thalamostriate vein need to be carefully defined when read-

ing venogram so as not to be confounded by the notorious posterior 'false angle'.

3.3.2.4 Basal Vein of Rosenthal (BVR)

The basal veins of Rosenthal originate in the chiasmatic cistern, medial to the uncus, and runs posteriorly in basal cisterns to the internal cerebral vein. It receives both superficial and deep (medullary) veins. These drain the orbital surface of the frontal lobe, insular, medial temporal lobe, hypothalamus, basal ganglia, thalamus and midbrain. Its course is best described in three sections (Figs. 3.7 and 3.8).

The first (anterior) section runs from its origin under the anterior perforating substance in the chiasmatic cistern to the anterior margin of the cerebral peduncle. The origin is typically a confluence of anterior cerebral vein and deep middle cerebral vein. The anterior cerebral vein receives the olfactory veins, posterior orbitofrontal veins and the anterior pericallosal vein. The deep middle cerebral vein is formed from insular veins and inferior striate veins. It originates as a confluence of these veins at the linen insulae and thus drains the medial temporal lobe and basal ganglia. The anterior cerebral vein drains the inferior frontal lobe and may connect across the midline with its counterpart via an anterior communicating vein or fail to connect to the middle cerebral vein and then drain to the cavernous sinus.

The second section runs around the cerebral peduncle and is closely related to the optic tract. It receives peduncular veins from the midbrain, the inferior thalamic vein from the basal ganglia and hippocampal veins from the medial temporal lobe. It also receives ventricular veins. In the ambient cistern, it receives the inferior ventricular vein, the inferior choroidal vein and may receive the lateral atrial vein. It may connect across the midline via a posterior communicating vein and receive the midline anterior pontomesencephalic vein (see below).

The third posterior section lies posterior to the midbrain and receives veins of the posterior

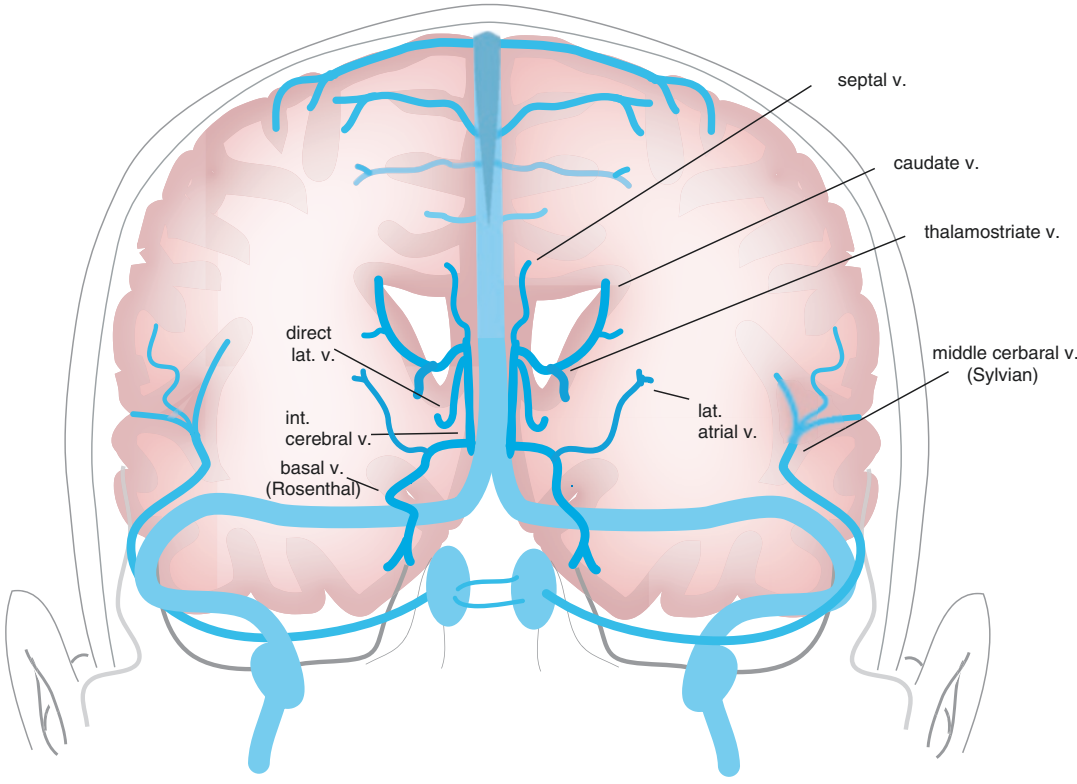

Fig. 3.8 Diagram showing the deep cerebral veins in a frontal projection (Published with kind permission of © Henry Byrne, 2017. All rights reserved)

fossa, namely, the lateral mesencephalic vein and the precentral and vermian veins. Through the lateral mesencephalic vein, the BVR potentially connects to the superior petrosal sinus. The entry point with the internal cerebral veins may vary, and a variant, typically associated with the vein of Galen malformation, involves the basal veins draining to a tentorial sinus.

3.3.2.5 Vein of Galen (VOG)

The vein of Galen is a short midline vessel formed by the confluence of the internal cerebral veins. It is between 5 and 20 mm in length and terminates by joining the inferior sagittal sinus to form the straight sinus at the apex of the tentorial hiatus. It receives in addition to the inferior sagittal sinus, the posterior pericallosal veins, the internal occipital veins and posterior fossa veins.

3.3.3 Veins of the Posterior Fossa

The different feature of the veins draining the brain stem and cerebellum is that they have functionally important connections to the veins of the supratentorial compartment and spinal cord. For description, they will be discussed separately though they communicate freely and functionally should be considered a single group.

3.3.3.1 Veins of the Brainstem

These are best considered as either draining longitudinally (i.e. craniocaudal) or transversely around the brainstem. They are named after their anatomical location.

The longitudinal group comprises a midline axis of veins and a lateral group of veins. The midline group runs on the front of the pons, medulla oblongata and midbrain. It comprises peduncular veins, the anterior pontomesencephalic vein and the anterior medullary vein. The peduncular veins run on the cerebral peduncles and drain to the BVR and the posterior mesencephalic vein. The anterior pontomesencephalic vein drains the pons and lower midbrain. It connects superiorly with the peduncular veins and caudally with the anterior medullary vein. The anterior medullary vein continues inferiorly as the anterior spinal vein (Fig. 3.9).

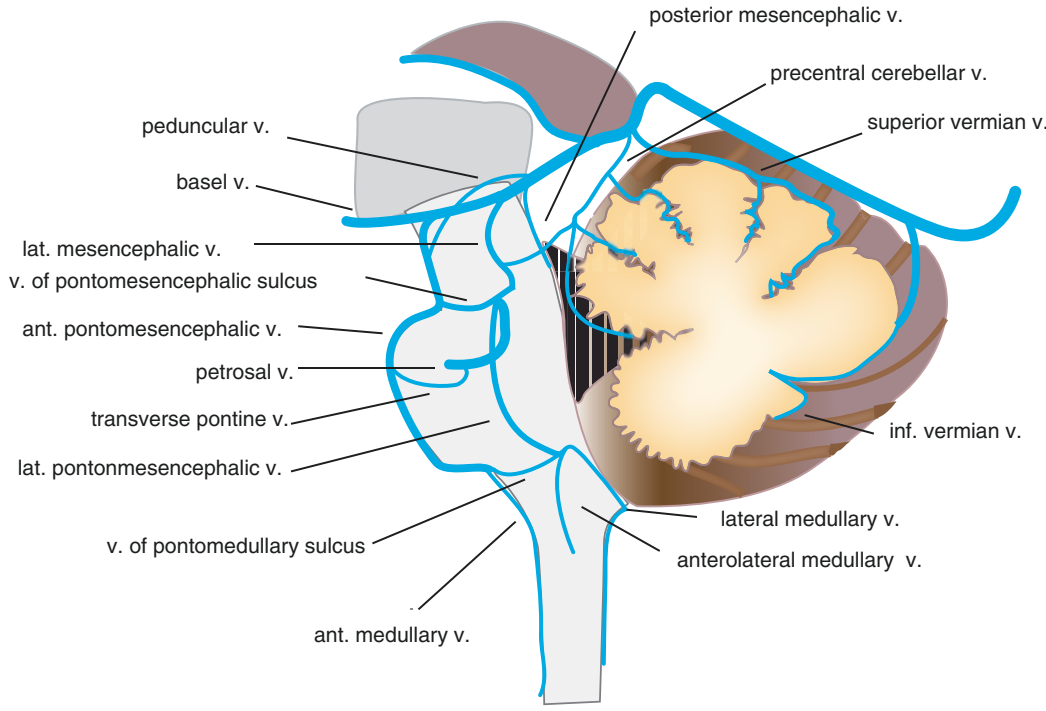

Fig. 3.9 Veins of the brain stem and vermis (Published with kind permission of © Henry Byrne, 2017. All rights reserved)

The lateral longitudinal group runs on the lateral surface of the midbrain and brain stem. The most important is the lateral mesencephalic vein, which lies in the lateral mesencephalic sulcus. It also drains cranially to the BVR or posterior mesencephalic vein and communicates inferiorly with the inferior members of this group. These are the lateral pontomesencephalic vein, which connects superiorly with the lateral mesencephalic vein and inferiorly with the anterolateral medullary and lateral medullary veins. The anterolateral medullary vein and its companion, the lateral medullary vein, run in the craniocaudal direction on the lateral side of the medulla. These veins are separated by the olive and connect cranially with the transverse vein of the pontomesencephalic sulcus and vein of the pontomedullary sulcus, respectively. Inferiorly, they drain to spinal veins and the internal vertebral venous plexus.

The transverse group comprises two main connecting veins (vein of the pontomesencephalic sulcus and vein of the pontomedullary sulcus) which run in the pontomesencephalic sulcus at the cranial margin of the pons and the pontomedullary sulcus at its caudal margin, respectively. They thus connect the longitudinal veins. Additional transverse connections are the paired petrosal veins. The vein of the pontomesencephalic sulcus (and thus anterior pontomesencephalic vein) may drain preferentially to the petrosal vein which runs anterolaterally to join the superior petrosal sinus.

3.3.3.2 Cerebellar Veins

The cerebellar hemispheres and vermis drain centrifugally to surface veins, and their description classically involves considering these structures from the prospective of three cerebellar surfaces: anterior, posterosuperior and posteroinferior.

1. Veins of the anterior cerebellar surface. The anterior surface of the cerebellum is divided into superior and inferior parts by the horizontal fissure. It lies behind the petrous bone and is separated from the brainstem by the cerebellomesencephalic fissure (above the pons) and the cerebellomedullary fissure (below the pons). The latter separates the cerebellar tonsil from the medulla oblongata. Within these fissures run veins of the same name, i.e. vein of the cerebellomesencephalic fissure and vein of the cerebellomedullary fissure. The superior cerebellomesencephalic fissure crosses the superior and inferior cerebellar peduncles, and separating these is a shallow sulcus containing a transverse vein, which is continuous with the more anterior vein of the pontomesencephalic sulcus and superiorly with the lateral mesencephalic vein. It thus sits at the centre of a confluence of veins, which drain superiorly to the BVR or posterior mesencephalic vein and anteriorly to the petrosal vein. The posterior mesencephalic vein arises in the interpeduncular fossa and runs parallel, but medial, to the BVR in the ambient cistern to join the VOG or the internal cerebral vein. An additional player is the brachial vein which is a vessel connecting the confluence of vein of the pontomesencephalic sulcus and the lateral mesencephalic vein with the petrosal vein and thus to the superior petrosal sinus.

   Posteriorly the vein of the cerebellomesencephalic sulcus extends to the midline and collects the venous drainage of the vermis. Draining the medial, i.e. superior part of the cerebellum and vermis, is the precentral vein. This originates in the fissure between the lingual and central lobule of the vermis. It runs upwards parallel to the roof of the IVth ventricle to pass over the colliculi and terminates in the VOG. It drains medial part of the superior cerebellum and superior vermis via the superior hemispheric veins and superior vermian veins and is a ‘landmark’ for the midline on angiograms.

2. Superior or tentorial surface. The venous drainage of the cerebellar hemispheres is peripherally to adjacent sinuses or medially to the superior vermian veins. Thus, superior cerebellar veins drain to the lateral sinus, torcular or superior petrosal sinuses and anterosuperiorly to the precentral vein. The superior vermian veins drain the vermis to the precentral vein or may drain directly to the straight sinus or torcular.
3. Inferior or occipital surface. A similar pattern of drainage occurs on the inferior surface of the cerebellum, with inferior hemispheric veins

Table 3.1 Veins of the posterior fossa grouped by their drainage destinations

Destination	Veins
Superior (VOG, BVR, straight sinus posterior mesencephalic vein)	Anterior pontomesencephalic vein
	Lateral mesencephalic vein
	Vein of the cerebellomesencephalic fissure
	Precentral vein
	Superior vermian veins
Anterior (superior petrosal sinuses)	Petrosal vein (anterior pontomesencephalic and vein of the pontomesencephalic sulcus)
	Brachial vein (vein of the cerebellomesenceephalic sulcus)
Posterior (straight, transverse sinus, tentorial veins)	Inferior cerebellar hemispheric veins
	Inferior vermian vein

collecting over the surface and running to the lateral sinus, veins in the tentorium and medially or to the vein of the cerebellomedullary fissure and thus to the petrosal vein. The inferior hemispheric veins drain part of the inferior vermis. The rest of the inferior vermian and tonsils are drained by inferior vermian veins, which are formed by the confluence of the superior and inferior tonsillar veins. They drain the inferior vermis and adjacent medial hemispheres usually to the straight sinus but may drain to the lateral sinus or tentorial veins [4].

The subject of veins in the posterior fossa is daunting to the student because different authors use different techniques for their description and nomenclature, and they are notoriously variable in appearance. Thus, the above system relies on breaking down what is obviously a unitary process of collecting the venous outflow of the cerebellum into three parts based on the surface appearances. An alternative is to consider the destinations of the veins. In this way, the drainage comprises a group of veins that drain to the VOG, a group that drains to the superior petrosal sinus and a posterior group draining to the tentorium and transverse sinus. This system is summarised in Table 3.1.

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Spinal Vascular Anatomy

4

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Preamble

The spinal blood supply is based on multiple arterial pedicles since the primitive spine develops from somites arranged alongside the neural tube. Each somite receives a primitive segmental arterial blood supply from the dorsal aorta. These paired segmental or metameric arteries supply the neural tube, as well as all the constituent tissues of the metamere, i.e. tissue which will differentiate into bone, skin, nerves etc. The paired arteries persist in the adult pattern as spinal arteries, which supply the bone and muscle of the spine and at selective vertebral levels the neural tissues of the spinal cord.

To understand this anatomy, the tutorial first considers the embryological development of the spinal blood supply with an emphasis on the arteries. It then describes the adult arterial pattern and finally the venous supply. The principal teaching objective is for a student to learn the sites of arterial pedicles that potentially supply spinal pathology and to be able to distinguish normal from pathological vessels on spinal angiography.

4.1 Embryology of Spinal Arteries

4.1.1 Primitive Segmental Arteries

Cell differentiation starts with the formation of three germ cell layers (endoderm, mesoderm and ectoderm) during the very early embryonic phase

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called gastrulation. The neural plate appears as a thickening in the ectoderm layer. It undergoes a folding process termed neurulation. The neural tube is formed by this process, which is controlled by growth factors from the notochord. At the margins of the neural tube, cells of the neural crest are formed. The spinal cord and brain develop from the neural tube. Closure of the neural tube occurs at about 3 weeks. At which stage the cells of the neural crest are at its lateral margins and the notochord ventrally.

The notochord is formed from endoderm. It precedes the formation of the neural tube and modulates its development. It extends the length of the neural tube and acts as a scaffold for the spinal support structures, which develop from surrounding (paraxial) mesoderm and then regresses. The cells of the neural crest contribute to the formation of bone, meninges and the dorsal root ganglia of the spinal cord. The structures of the spine form segmentally from blocks of mesoderm on either side of the notochord arranged as repeating somites. This pattern of repeated segments is known as metamerism and the individual blocks metameres. The post-embryonic remnant of notochord is represented by the nucleus pulposus (Fig. 4.1).

During the 3–6 week stage, up to 44 somites form but then regression leaves 31 somites, each receiving a pair of primitive arteries from the dorsal aorta. These segmental arteries thus supply tissues derived from the neural tube, neural crest and somite that together constitute the metamere, i.e. the precursors of the spinal cord, spinal nerves and paraspinal muscle, skin and bone.

The primitive segmental artery, for each metamere, makes a primary division into dorsomedial and dorsolateral branches. The dorsomedial division supplies the neural tube, neural crest and dorsal epimere (i.e. that part of the somite which contributes to the vertebral column and paraxial muscles). The dorsolateral division supplies all the other structures of the metamere. At its cranial extent, the dorsal aorta contributes to the carotid arteries and at its caudal extent becomes the median sacral artery.

4.1.2 The Vasa Corona and Longitudinal Neural Arteries

The blood supply to the neural tube develops from a primitive vascular plexus on its surface called the vasa corona supported by dorsomedial segmental arteries. On the ventral surface of the neural tube, longitudinal channels form on either side of the midline from longitudinal connections within the vasa corona. In Tutorial 1, when they developed anterior to the hindbrain, we called these the longitudinal neural system (LNS), though in the spine they are often called ventral longitudinal arteries. They run on either side of the developing median sulcus. As the cord develops, they give branches that enter the sulcus and branches to the vasa corona (Fig. 4.2).

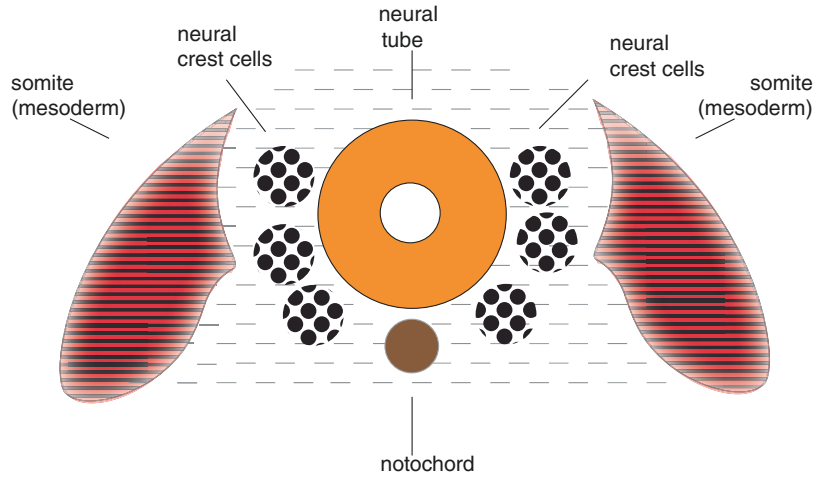

Fig. 4.1 Closure of the neural tube and differentiation of somites (Published with kind permission of © Henry Byrne, 2017. All rights reserved)

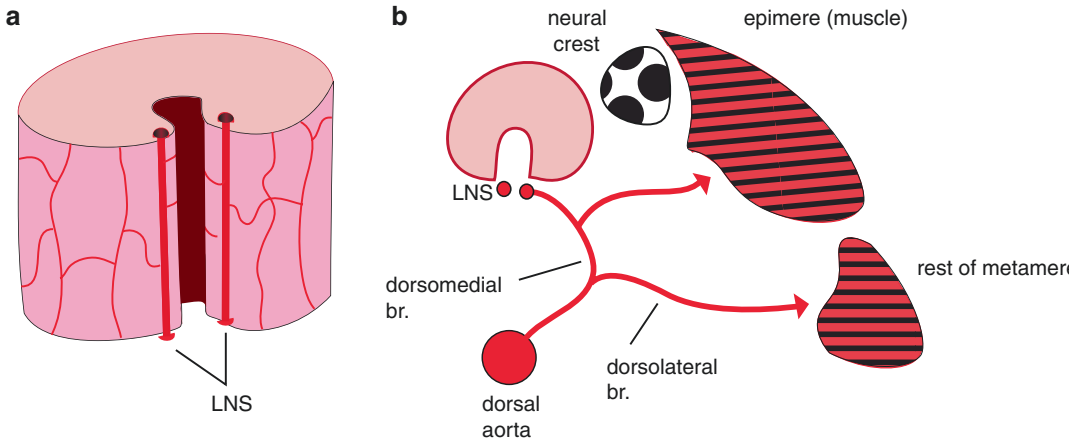

Fig. 4.2 (**a**, **b**) Development of the spinal arteries after closure of the neural tube. (**a**) Shows the longitudinal neural system (LNS) or ventral longitudinal arteries, which are the first inter-somite channels to develop. (**b**) Shows the division of the segmental artery to the somite into dorsomedial and dorsolateral branches. The dorsomedial branch supplies the neural tube and nerves, muscle and bone of the developing spinal segment (Published with kind permission of © Henry Byrne, 2017. All rights reserved)

The dorsomedial branches of the segmental artery to the developing spinal cord supply the anterior spinal roots and the ventral longitudinal arteries, i.e. future anterior spinal artery. They also give branches to the dorsal neural tube to supply the dorsal vasa corona and the posterior roots. Posterior longitudinal channels on the dorsolateral surface of the neural tube form later from the plexus of vessels forming the vasa corona and subsequently develop into the posterior spinal arteries. The delay is because the ventral longitudinal arteries supply most of the grey matter within the cord, which precedes the formation of white matter tracts [1].

4.1.3 Formation of Multimetameric Arteries and Desegmentation

The formation of longitudinal arteries supplying multiple metameres changes the segmental pattern of blood supply and leads to the development of the adult system of spinal arteries. On the neural tube, craniocaudal midline fusion of the ventral longitudinal arteries occurs after 6 weeks and creates the anterior spinal artery (ASA). Failures of fusion are more often evident in the cervical spinal cord and represent a failure of maturation of this system. They are evident as apparent duplications of the anterior spinal artery in the adult pattern.

At the same time (6–12 weeks), desegmentation occurs. This is a process in which most of the primitive segmental arteries supplying the neural tube regress. Completed, this process leaves only 4–8 ventral spinal arteries supplying the ASA and 10–20 dorsal spinal arteries supplying the vasa corona. The rest of the dorsomedial segmental artery supply is to the other metameric tissues of the spine, i.e. the nerve root, dura and bone. Each spinal artery is named after the nerve it accompanies into the neural foramen.

Concurrently, longitudinal anastomoses between the segmental arteries of each metamere develop around the developing spine. These longitudinal arteries are identified by their position relative to the transverse processes of vertebra, i.e. pre-transverse, transverse, post-transverse. The vertebral artery (VA) in its canal is the most developed transverse longitudinal artery connecting segments.

4.1.4 Development of Craniocervical Arteries

At this point, we need to consider the development of the arterial supply of the cervical spine

and craniocervical junction together to understand the numerical labels used for the cervical vertebrae. There are eight radiculospinal arteries (like the eight cervical spinal nerves) supplying the seven cervical vertebrae. In Fig. 4.3, the somite and vertebral level of the craniocervical region and upper spine are presented in diagram form. The longitudinal multimetameric arteries in the neck are shown (i.e. VA, ascending cervical artery and deep cervical artery) and the proatlantal artery.

Eight cervical segmental arteries develop for the eight cervical somites, and the first cervical somitic artery is the proatlantal artery, which lies above the C1 vertebra. This is because the vertebral bodies develop between somite levels with the intervertebral disc as the centre of the metamere. Thus, the embryonic vertebral body is supplied by two adjacent pairs of somitic (segmental) arteries, and its numbered radiculospinal artery actually arises between vertebrae. The adult pattern of seven cervical vertebral bodies arising from eight cervical somites creates the need for the proatlantal artery nomenclature, as was explained in Tutorial 1.

The intracranial VA gives the C1 spinal artery. The continuation of the cranial vertebral artery represents an ascending branch of its ventral radiculomedullary branch. This takes a medial course to the ventral surface of the future medulla oblongata. A descending ventral radiculomedullary branch runs to the midline surface of the spinal cord to form the cranial origin of the ASA. The other branches of intracranial vertebral artery are derived from the posterior radiculomedullary branch of the first cervical spinal artery, i.e. posterior inferior cerebellar artery (PICA) and the posterolateral spinal artery [2].

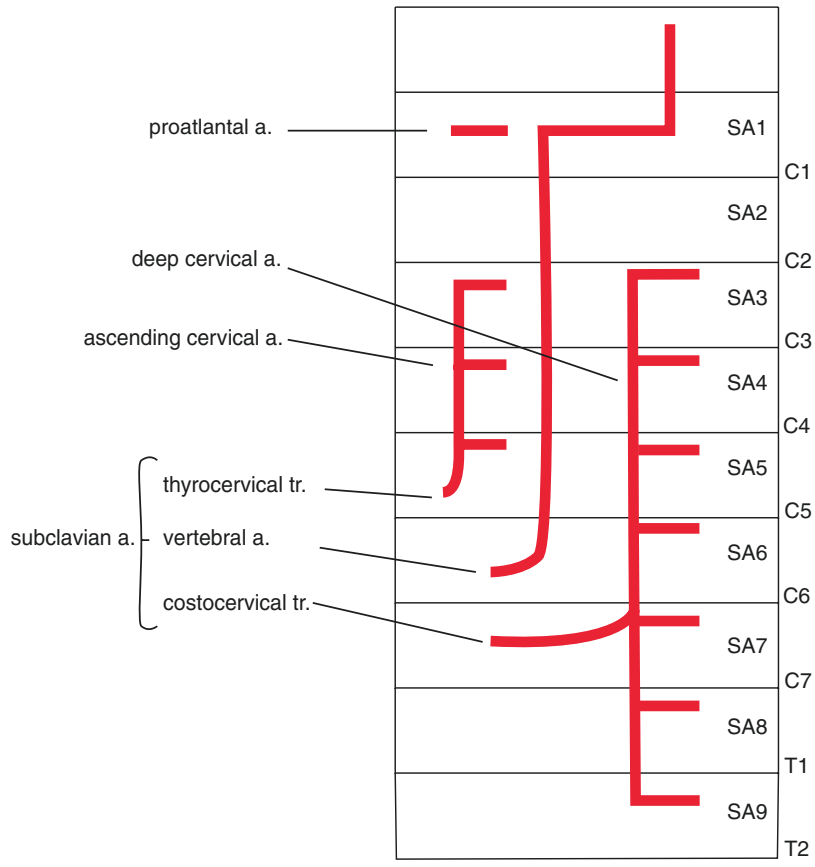

Fig. 4.3 Segmental pattern of blood supply to the upper spine and craniocervical junction. *SA* somite level, *C* cervical level, *T* thoracic level (Published with kind permission of © Henry Byrne, 2017. All rights reserved)

4.2 The Spinal Arteries

4.2.1 The Basic Adult Pattern of Extradural Arteries

A standard adult pattern of spinal arteries is based on this embryonic development with variations at both cranial (cervical) and caudal (lumbosacral) ends. Regional variations will be described later, but first it is worth considering a standard vertebra of the thoracic and lumbar spine with its arterial blood supply arising from the descending aorta. Figure 4.4 shows posterior intercostal arteries running posteriorly on either side of a vertebral body. They give short osseous branches to the vertebral body before dividing into ventral and dorsal branches. An anterior longitudinal anastomosis between segments is shown before the division. The ventral branch becomes an intercostal or lumbar artery. These are numbered by the rib or transverse process under which they run. The dorsal branch connects to a pre-transverse longitudinal anastomosis before giving a radiculospinal branch to the intervertebral foramen. It then passes under the transverse process of it numbered vertebra to supply the posterior muscles and bone of the lamina and spinous process and connect to a posterior-transverse longitudinal anastomosis.

The radiculospinal artery enters the spinal foramen and gives an anterior epidural branch to take part in the retrocorporeal anastomosis. This supplies the bone and dura and anastomoses with its counterpart at the midline. These midline anastomoses occur at disc level and are easily recognised by a hexagon pattern (created by longitudinal and horizontal arteries) on angiography. It reflects the developmental origin of the vertebral body and its blood supply from two pairs of intersegmental arteries. The spinal artery also gives a posterior epidural branch to the prelaminar anastomosis and supplies the dura and bone of the lamina. The prelaminar anastomosis is usually smaller than the retrocorporeal anastomoses with fewer longitudinal anastomoses, but any longitudinal component lies close to the midline and should not be mistaken for the anterior spinal artery. The radiculospinal artery usually then terminates in radicular spinal branches.

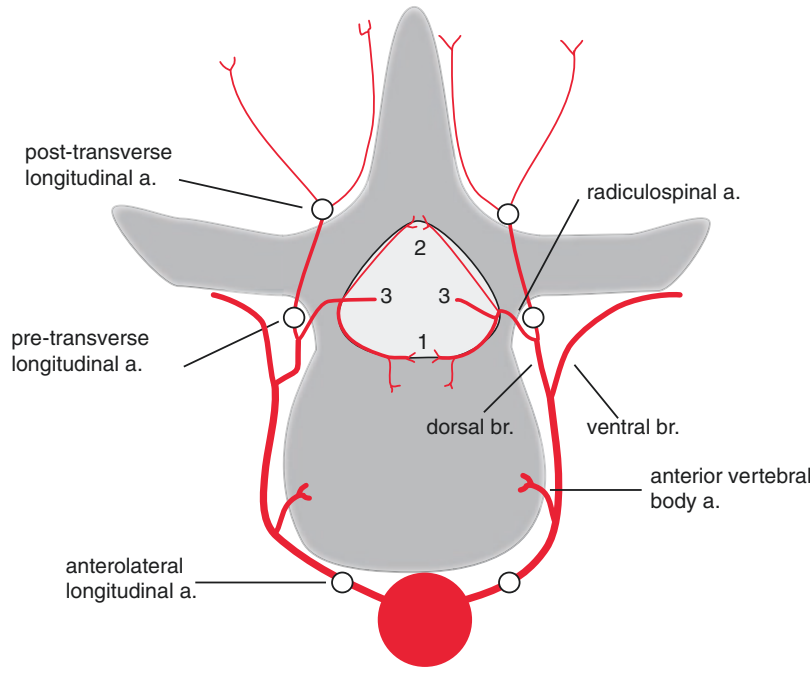

Fig. 4.4 Basic adult pattern of blood supply to a vertebra from posterior intercostal or lumbar arteries of the descending aorta (see text). *1* anterior epidural branches and retrocorporal anastomosis, *2* posterior epidural branches, *3* radiculospinal a (Published with kind permission of © Henry Byrne, 2017. All rights reserved)

4.3 Arterial Supply to the Spinal Cord

The radiculospinal arteries supply the spinal cord and its nerve roots. These arteries were termed 'radicular', 'radiculopial' and 'radiculomedullary' by Tanon [3] because they individually provide one of three types of supply to the neural tissue. The radicular artery supplies nerve roots only; the radiculopial artery supplies nerve root and pial plexus (white matter), and the radiculomedullary artery supplies roots, pial plexus and cord medulla (grey matter).

4.3.1 Radicular Arteries

These represent the minimum contribution to the neural crest of the embryonic segmental system (Fig. 4.5a). They branch to both anterior and posterior nerve roots and are usually too small to be imaged on angiography. On each side, all 31 segmental (intersegmental) arteries give a radicular artery except at C1. They run with the nerve roots medially to the surface of the cord, and their trajectory reflects that of the roots, i.e. near horizontal in the upper cervical spine and with an increasing upwards direction in the lower thoracic and lumbar spines.

4.3.2 Radiculopial Arteries

The radiculopial arteries arise from 10 to 20 spinal arteries (Fig. 4.5b). They divide to follow the anterior and posterior nerve roots onto the spinal cord. The posterior radiculopial artery is the larger and supplies the posterior pial plexus, which is usually more developed than the ventral plexus. The plexus has longitudinal connections

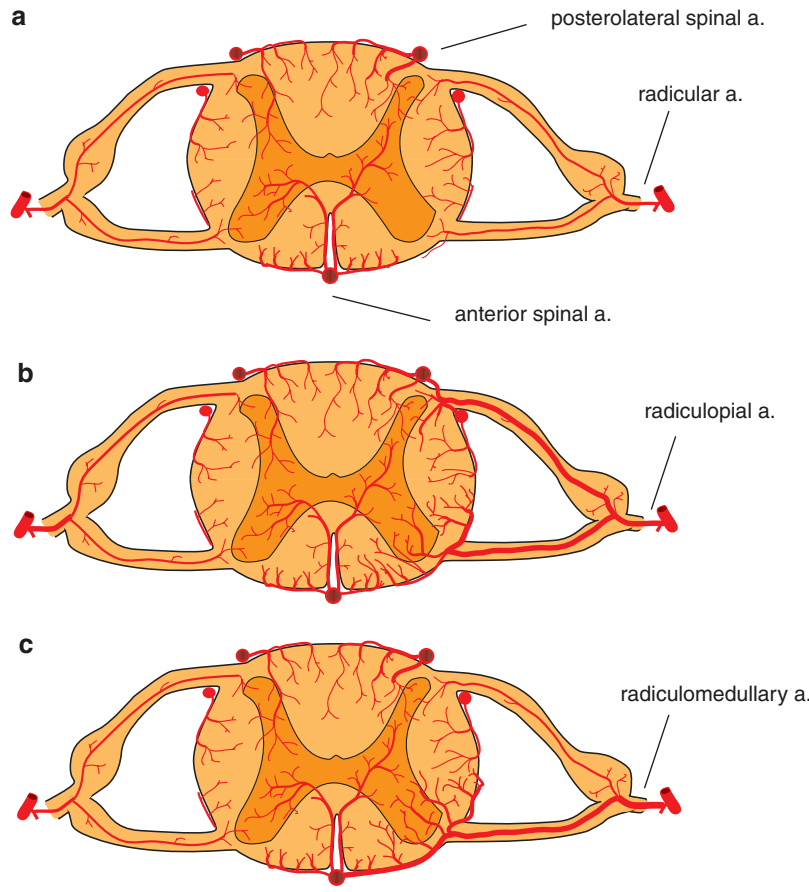

Fig. 4.5 Distribution of arteries to the spinal cord. (**a**) Radicular artery supply. (**b**) Radiculopial artery supply on left side. (**c**) Radiculomedullary artery supply on left side (Published with kind permission of © Henry Byrne, 2017. All rights reserved)

but is functionally monosegmental. The posterolateral longitudinal arteries are usually the most lateral and dominant of the longitudinal channels that constitute the PSA. In the upper thoracic spine (where white matter predominates), a posterior median longitudinal channel may occur, and in the upper cervical cord, a far lateral longitudinal channel arising from the VA or PICA and running caudally with the spinal accessory nerve is described as the lateral spinal artery.

4.3.3 Radiculomedullary Arteries

These arteries are the segmental supply to the ASA (Fig. 4.5c). They occur at 4–8 levels (mostly in the cervical spine) with the largest at the lumbosacral enlargement and termed 'the artery of Adamkiewicz' [8] (usually arising from a posterior intercostal artery between T9 and T12, and more often on the left side than on the right side) [4]. They give radicular branches and contribute to the anterior (ventral) pial network before joining the ASA with a distinctive hairpin course evident on angiograms.

4.3.4 The Anterior Spinal Artery (ASA)

This artery represents the result of fusion of the embryonic ventral longitudinal arteries in the midline (Fig. 4.6). It runs from the vertebrobasilar junction to the filum terminale. Cranially, it arises from bilateral small branches of the intracranial VA (i.e. the descending ventral radiculomedullary branch), which join in the midline on the surface of the medulla oblongata at the level of the olives. It then runs on the ventral surface of the spinal cord to the conus where it continues as the artery of the filum terminale. It lies at the entrance of the anterior median sulcus and deep to the anterior median vein. It supplies the anterior two-thirds of the spinal cord and the majority of its grey matter.

It is often only partially fused in the cervical region, where it receives collateral support from radiculomedullary arteries. It may appear discontinuous in the upper thoracic region, and longitudinal anastomoses between two or more spinal levels may parallel the ASA. These arteries (if present) run deep to the ASA at the entrance of the median sulcus [2]. The ASA reaches its largest calibre in the lower thoracic canal before contributing to extramedullary circumferential anastomoses around the conus with the posterior spinal arteries (arcade of the conus or rami anastomotici arcuati). This anastomotic ring is the spinal equivalent of the circle of Willis.

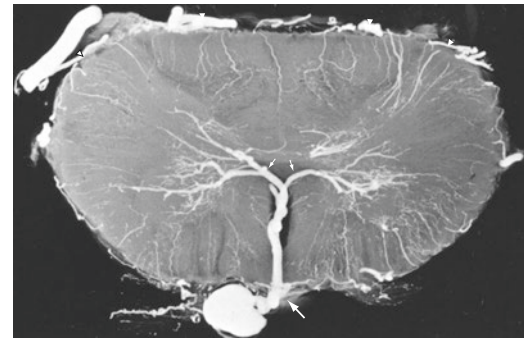

Fig. 4.6 Microangiogram of a post-mortem section of the lumbar spinal cord showing superficial and intrinsic spinal arteries. The anterior spinal artery (*large arrow*) lies at the entrance of the median sulcus and the posterior and posterolateral spinal arteries are seen on either side of the posterior root entry zone (*arrow heads*). The sulcal arteries run in the central sulcus to supply the two sides of the cord in a centrifugal distribution (*small arrows*) (Reproduced from Thron A., Vascular Anatomy of the Spine, Interventional Neuroradiology, Byrne JV. (Ed). Oxford University Press, 2002 p24, with permission)

4.4 Intrinsic (Medullary) Arteries of the Spinal Cord

In this section, the distribution of arterial branches within the spinal cord is described. These can be separated into a group arising from the ASA and radiating in a centrifugal direction from within the median sulcus and a group arising from the pial network on the surface of the cord and running in a centripetal direction. The former are sometimes called internal and the latter external. I think this is confusing and suggest considering them both together as the intrinsic cord arteries.

4.4.1 Sulcal Arteries

These paired arteries arise from the ASA. They run in the median sulcus and each supplies one-half of the spinal cord. They measure 100–250 μm, run to the depth of the sulcus on one side and then branch within the ipsilateral grey matter. Their lateralisation represents the embryonic separation of the bilateral ventral longitudinal arteries, which is maintained despite their fusion to form the ASA. The sulcal arteries branch within grey matter with a centrifugal radiation pattern and supply the anterior horn, base of the posterior grey matter column (including the dorsal nucleus) and adjacent white matter (including the corticospinal tracts). They are said to give longitudinal channels between cord levels within the median sulcus, but once they penetrate pia, they probably don't take part in any substantial longitudinal anastomosis. The cord is vulnerable to their occlusion because they are end arteries and because they supply areas of high metabolic demand.

4.4.2 Perforator Arteries of the Surface Pial Network

The network of arteries on the surface of the cord give branches that penetrate the pial surface to supply the underlying white matter. They supply the cord in a centripetal pattern and behave as end arteries. They are smaller (about 50 μm) than sulcal arteries with a short straight course.

The network has longitudinal and circumferential pial arteries. The posterolateral spinal arteries are the most conspicuous elements of the former and the conus anastomotic ring of the latter. The plexus is supported by the radiculopial arteries and branches of the ASA.

Anastomoses between the sulcal (central) and these radial perforating (peripheral) arteries have been demonstrated. These are described as being directed in centro-posterolateral and centro-anterolateral directions, but they are rarely evident in practice.

4.5 The Extradural Multimetameric Spinal Arteries

This section describes the arteries that contribute to the blood supply in different regions of the spine. Its content repeats some of the previous sections, but this repetition is justified on the basis that it attempts to cover the practical question of which arterial pedicles need to be studied during selective catheter spinal angiography. It is separated into the major spinal regions for convenience.

4.5.1 Arteries Supplying the Cervical Spine

The cervical spine is supplied by three longitudinal multimetameric arteries with additional contributions from arteries at the craniocervical junction (Fig. 4.7).

1. Vertebral artery (VA). In the neck, the VA represents the longitudinal anastomosis of the arteries of the transverse processes between C6 and C1. It arises from the subclavian artery at the level of the C7 metamere and ascends to enter the transverse foramen of C6. Its course and branches have been described above and in Tutorial 2.
2. Ascending cervical artery. Arising from the inferior thyroid artery soon after its origin from the thyrocervical trunk, the ascending cervical artery passes anterior to the VA and runs superiorly between the scalenus anterior and longus capitis muscles. It represents the segmental arteries of the C3–C4 metameres and gives branches to the segmental anastomoses at these levels.
3. Deep cervical artery. This arises from the costocervical trunk and corresponds to the segmental arteries of the C5–C6 metameres. The costocervical trunk arises from the subclavian artery distal to the thyrocervical trunk and runs posteriorly to divide into the deep cervical artery and the highest or supreme intercostal artery anterior to the neck of the first rib. The deep cervical artery usually supplies spinal levels from C7 to C3.

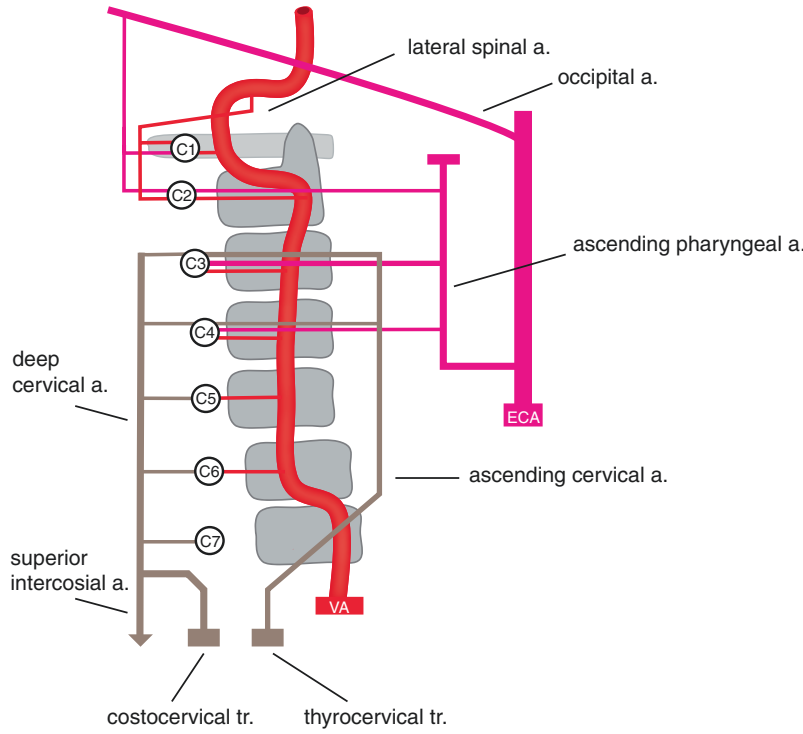

Fig. 4.7 Diagram of the adult pattern of arteries supplying the cervical spine (Published with kind permission of © Henry Byrne, 2017. All rights reserved)

4. The occipital and ascending pharyngeal arteries. The spinal cord supply cranial to C3 can be considered as cephalic rather than spinal, though contributions from the ascending pharyngeal artery (C2–C4) and occipital artery (C1–C2) are partial remnants of the segmental system. The ascending pharyngeal artery gives musculospinal branches in the midcervical region (C4 and C3) and additionally contributes via the hypoglossal artery and the odontoid arcade.
5. Lateral spinal artery. This small branch of the cranial VA or PICA contributes with the posterior spinal artery to the pial plexus. It runs on the lateral surface of the upper spinal cord and supplies the posterolateral axis between C1 and C3 and joins the posterior spinal artery at C4 [9].

4.5.2 Arteries Supplying the Thoracic Spine

In the upper thoracic spine, the highest or supreme intercostal artery, which arises from the costocervical trunk, supplies a variable number of vertebrae from T1 to T4. The T4 level is usually supplied from the aorta, but several variations may occur, with the highest intercostal artery arising from (or some of its branches from) VA, the subclavian artery, thyrocervical trunk or from segmental trunks of the bronchial or phrenic arteries. The caudal thoracic spine is supplied by eight or nine pairs of posterior intercostal arteries. In both thoracic and lumbar spines, pre-transverse and post-transverse longitudinal arteries are usually evident connecting adjacent posterior intercostal and lumbar arteries.

4.5.3 Arteries Supplying the Lumbar Spine

The cranial four lumbar arteries arise from the aorta, and the L5 level is supplied by the iliolumbar artery and the median sacral artery. The iliolumbar artery arises from the internal iliac artery and runs cranially anterior to the sacroiliac joint, supplying muscle and giving the lumbar branch

to L5. The medial sacral contribution consists of small branches to the L5 roots. The L1–L4 lumbar spinal arteries are arranged in a similar manner to the thoracic spinal arteries.

4.5.4 Arteries Supplying the Sacral Spine

The median sacral artery is a small branch of the abdominal aorta that arises from its posterior surface at the level of the terminal division. It runs in the midline over L4 and L5 and the sacrum, to the coccyx and anastomosis with branches of the superior and inferior lateral sacral arteries.

The lateral sacral arteries are the principal supply to the sacral spine. They arise from the internal iliac artery. The superior lateral sacral artery runs cranially to the S2 pelvic foramen and the inferior artery caudally as a trunk anterior to the lateral sacrum (i.e. a pre-transverse anastomotic artery) contributing branches that enter the S3–S5 pelvic foramen. It terminates at the coccyx.

4.6 Venous Drainage of the Spinal Cord

The venous drainage will be described from proximal to distal and divided into the veins of the spinal cord and those of the vertebral column [5].

4.6.1 Veins of the Spinal Cord

These veins will be described in three groups: internal cord veins, longitudinal cord veins and radiculomedullary veins. These distinctions are on the basis of anatomical location rather than physiological differences.

4.6.1.1 Internal Cord Veins

The internal medullary venous drainage of the cord is centrifugal with a radiating pattern of intrinsic veins draining from centre to periphery. They are distributed symmetrically, on transverse sections, and drain to a venous pial plexus on the surface of the cord. Short and long veins are evident and both run independent of the penetrating arteries. However, in the lower thoracic cord at the lumbar enlargement, this symmetry varies with a modest dominance of drainage to central veins in the median sulcus. The pattern suggests that drainage is largely horizontal with little vertical flow through the parenchyma.

In addition to these small symmetrical medullary veins, larger veins traverse the parenchyma at various levels. These are termed transmedullary veins or transparenchymal anastomotic channels and usually make anterior to posterior anastomoses between the anterior and posterior surface veins in the midline but may run obliquely. Two types are described: centro-dorsal anatsomoses and midline anastomoses [3]. The former are small connections between peripherally sited and central intrinsic veins and the latter between the midline longitudinal veins. The second type are not collecting vessels and are thought to conduct blood in either direction in response to intradural pressure changes (i.e. cough veins). They are more numerous in the cervical and upper thoracic cord than in the lower (caudal) cord.

The intrinsic medullary veins drain to a pial network of veins on the surface that are vertically and circumferential in orientation. The vertical longitudinal veins are of varying length and present around the cord with larger consistent veins running the length of the spinal cord in the midline. These two longitudinal midline veins, namely, the anterior and posterior median spinal veins are the principal veins of the cord surface (see below). The pattern therefore differs from the distribution of intrinsic medullary arteries, since the veins don't follow medullary arteries. In the past, authors have described a system of central veins and peripheral veins but to avoid confusion, I suggest it is better to think of the previously described central veins as those that congregate to the anterior and posterior median veins.

4.6.1.2 Longitudinal Cord Veins

The anterior and posterior median spinal veins drain to the internal and external vertebral plexus

of veins via veins that follow the anterior and posterior spinal roots. These have been called radicular veins, but in this tutorial, the term radiculomedullary veins will be used. The anterior median vein is continuous with the anterior medullary vein and thus connects cranially with the veins of the posterior fossa. In the cervical and most of the thoracic spine, both are usually single vessels, but over the thoracolumbar enlargement, the posterior median vein forms a series of parallel veins (the posterior venous plexus), and the anterior median vein reaches its maximum calibre (up to 1.5 mm) (Fig. 4.8). The anterior median spinal vein continues as the vein of the filum terminale at the conus and drains to sacral epidural veins, though may run with a sacral root to the sacral plexus. This pattern of midline veins represents the dominant veins of a pial plexus of veins with more lateral vertically orientated longitudinal veins (most commonly on the anterolateral surface) and connecting smaller transverse veins present at several levels.

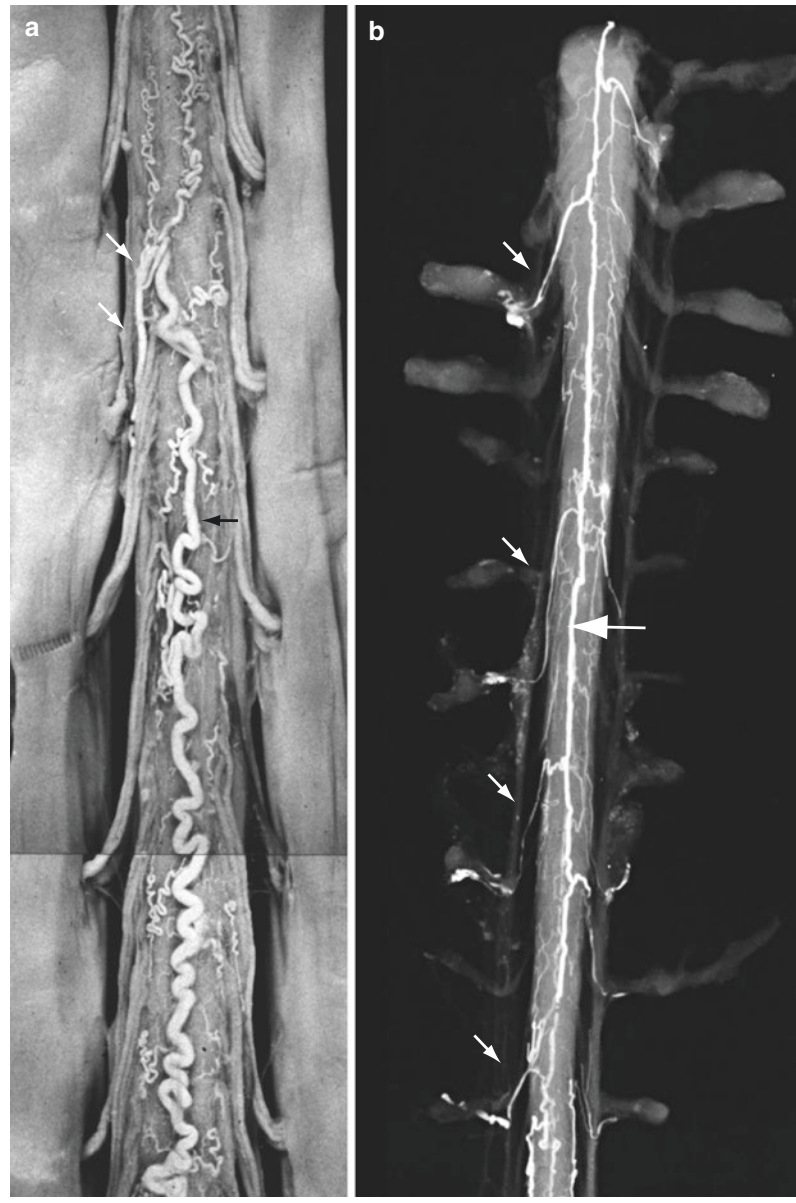

Fig. 4.8 (**a**) Injected post-mortem specimen of the posterior surface of the spinal cord showing veins of the lower dorsal and conus region. The posterior midline vein (*black arrow*) is discontinuous, and the radicular veins are shown making a hairpin course, similar to the spinal arteries to follow spinal roots (*white arrows*). (**b**) Radiograph in the venous phase showing the continuous anterior median spinal vein (*large arrow*) and multi-segmental radicular veins (*small arrows*) (Reproduced from Thron A., Vascular Anatomy of the Spine, Interventional Neuroradiology, Byrne J.V. (Ed). Oxford University Press, 2002 p26, with permission)

4.6.1.3 Radiculomedullary Veins

These occur at most but not all spinal levels. They run in either anterior or posterior spinal root sheaths. They connect the longitudinal cord veins to the internal vertebral plexus. The numbers of radiculomedullary veins have been reported as varying from 50 to 15. The latter is probably closer to the number identifiable on imaging. An estimate for the student who likes numbers is 5–8 in cervical, ten in the upper thoracic and 1–2 in the lumbar regions. Most radiculomedullary veins follow the anterior spinal nerve to piece the dura, but about 30% exit independently of the nerve root [6]. They don't occur in association with segmental arteries, and a larger vein, from the lumbar expansion, is said never to travel with the artery of Adamkiewicz.

Two important things to remember are that the system is valveless, and their transdural course may be up to 1 cm in length, which is thought to act as a one-way valve. The connection between the median spinal and radiculomedullary veins has a 'hairpin' tortuosity, again probably design to act as a one-way valve (anti-reflux) valve, and this configuration should not be mistaken for a radiculomedullary artery. The second important feature is that there is a 'watershed' in the longitudinal cord drainage at midthoracic level; above which drainage is cranial and below caudal. How this is engineered is not completely understood.

4.6.2 Epidural Venous Plexus (Internal Vertebral Plexus)

The vertebral venous plexus of veins can be considered as two interconnected systems of veins comprising the epidural or internal vertebral venous plexus lie between the thecal lining of the spinal cord and the bony canal and an external plexus surrounding the vertebrae [7]. The internal plexus receives the radiculomedullary veins and veins from the vertebral bodies (basivertebral veins). It comprises epidural venous channels with descriptive terms, such as venous lakes, lacunae and fissures, rather than discrete veins. The plexus is the largest anterior (retrocorporeal) to the theca and extends from the skull base to the sacrum. It therefore connects cranial sinuses to pelvic veins. On angiography, the channels of the plexus have a characteristic hexagonal pattern. The plexus drains to the external vertebral plexus through the intervertebral foramen.

4.6.3 External Vertebral Plexus

The veins form the external plexus, also extend from the base of skull to the sacrum and are valveless. They run on the anterior surface of the vertebral bodies with posterior veins arranged posterolateral to the canal running over the lamina. It connects with the azygos and hemiazygos veins via intercostal and lumbar veins. In the neck, the plexus drains to the vertebral vein and deep cervical veins.

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Control of Cerebral Blood Flow

5

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Preamble

This tutorial has been written by Dr. Piers Nye, a physiologist who teaches this topic on the Oxford course. It aims to provide an overview of the physiological mechanisms that control cerebral blood flow and explain the brain's ability to regulate its own blood supply. It is intended to remind students of the basic mechanisms controlling the blood supply to an organ and to cover those that are unique to the cerebral circulation in the healthy individual. An understanding of the factors that control cerebral perfusion is essential for the interpretation of functional imaging studies, such as magnetic resonance images (f-MRI) of the brain and for the development of treatments for neurological disorders such as stroke and Alzheimer's disease [1]. But the focus of this tutorial is the physiological control of cerebral blood flow, and the effects of pathological interruptions in flow will not be considered further here. It has recently become apparent that, although CO_2 (or the associated fall in pH) is an exceptionally powerful determinant of CBF, it is not normally responsible for the tight coupling of flow to neuronal activity. This is done by feedforward mechanisms that depend primarily upon the secretion of neurotransmitters such as glutamate.

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5.1 Cerebral Intolerance of Hypoperfusion

Of all the tissues in the body, the brain is the most vulnerable to hypoperfusion. Ischaemic changes and infarction (cell death due to low oxygen) occur within minutes of an interruption of blood flow. This fragility is due to its exclusive aerobic metabolism and the very high metabolic rate required to restore the ionic gradients that are altered by the constant activity of synapses and action potentials. One expression of the remarkable intensity of cerebral metabolism is that though the brain represents only 2% of total body weight, it uses 20% of the oxygen supply. The cerebral blood flow (CBF) that supplies this demand for oxygen comprises 18% of cardiac output or about 50 ml/100 g of brain/min. The brain's fragility is evident by the loss of synaptic transmission within minutes of flow falling to one-third of its normal value. At one-fifth normal flow (10 ml/100 g/min), membrane pumps fail and neurons and glia die. However, irreversible damage by infarction is not immediate; it takes 10 min to develop at zero flow and about 2 h at 12 ml/100 g/min [2].

5.1.1 Cerebral Protection of Blood Flow

Several mechanisms protect the brain from hypoperfusion injury. The first level of protection is anatomical and is provided by the multiplicity of supply arteries. The paired internal carotid and vertebral arteries anastomose at the circle of Willis to which 80% of CBF comes from the carotid arteries, while anastomoses by some cortical arteries also provide collateral blood flow. The second level of protection is physiological, matching local perfusion to local metabolism by changing the resistance of vessels. The combined effect of these local control mechanisms is to hold CBF stable over a wide range of arterial blood pressure values (Fig. 5.1).

5.1.2 Vascular Resistance

There are only two factors that could possibly determine the rate of flow through the brain and these are the pressure gradient from arteries to veins, i.e. arterial blood pressure (ABP) – venous

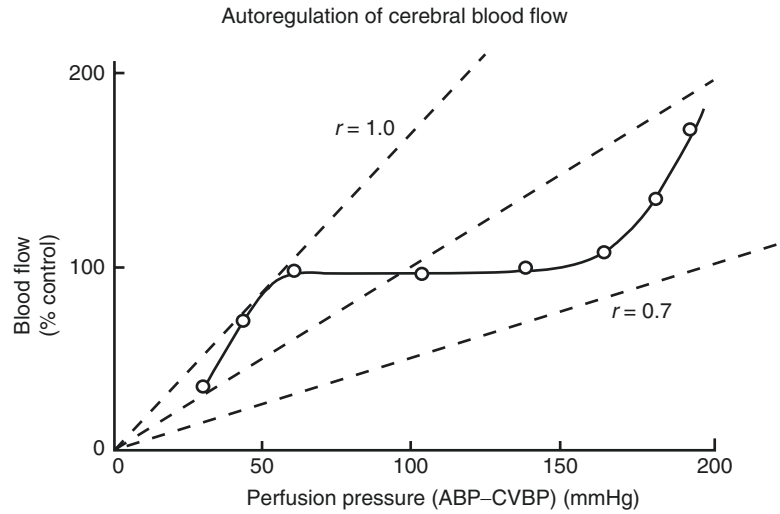

Fig. 5.1 Cerebral blood flow is almost completely independent of perfusion pressure (arterial–venous pressure) between 60 and 150 mmHg. This is shown here by a vascularly isolated brain in which the arterial reservoir is raised to take perfusion pressure from 30 to 200 mmHg. The almost constant blood flow in the normal range of pressures, termed autoregulation, is an intrinsic property of the blood vessels that is independent of the innervation of vascular smooth muscle (*VSM*) by autonomic nerves

blood pressure (VBP) and the resistance to flow provided by the brain's blood vessels, i.e. cerebrovascular resistance (CVR).

$$\mathrm{CBF} = \left(\mathrm{ABP} - \mathrm{VBP}\right) / \mathrm{CVR}$$

ABP − VBP may be abbreviated to cerebral perfusion pressure (CPP) and CVR may be expanded to reveal its components (η = blood viscosity, l = vessel length and r = vessel radius). This relationship was first formulated by Jean Louis Marie Poiseuille[1] in 1840 and is therefore known as Poiseuille's Law [3]. It is directly analogous to Ohm's Law (I = V/R):

$$\mathrm{Flow} = \mathrm{CPP} / \left(8\eta l / \Pi r^4\right)$$

CPP is generally held fairly constant by the arterial baroreflex and it affects all parts of the brain equally, so vascular resistance, which is highly variable and which can increase in one place while it decreases in another, is by far the most important determinant of flow. Furthermore, among the three factors that contribute to resistance, only vessel radius is adjusted physiologically, and because it is raised to the fourth power, a modest change in radius has a very large effect on resistance. A vessel's smooth muscle need only constrict to half its radius to increase resistance by 2 × 2 × 2 × 2 = 16-fold and, if a vessel were to double its radius, flow through it would increase by 16-fold. If such an increase in flow were to be achieved by changing perfusion pressure, ABP would have to rise from 100 to 1600 mmHg.

5.2 The Blood–Brain Barrier

The blood–brain barrier (BBB) is composed of endothelial cells (ECs), pericytes, astrocyte end-feet and neurons which together make up the 'capillary neurovascular unit' [4] (Fig. 5.2). In pre- and post-capillary vessels, pericytes are replaced by vascular smooth muscle [5].

The BBB differs radically from the blood–tissue barriers found elsewhere. Its ECs, which form the primary barrier, are surrounded by complex tight junctions that prevent the passage of all charged solutes. The formation and maintenance

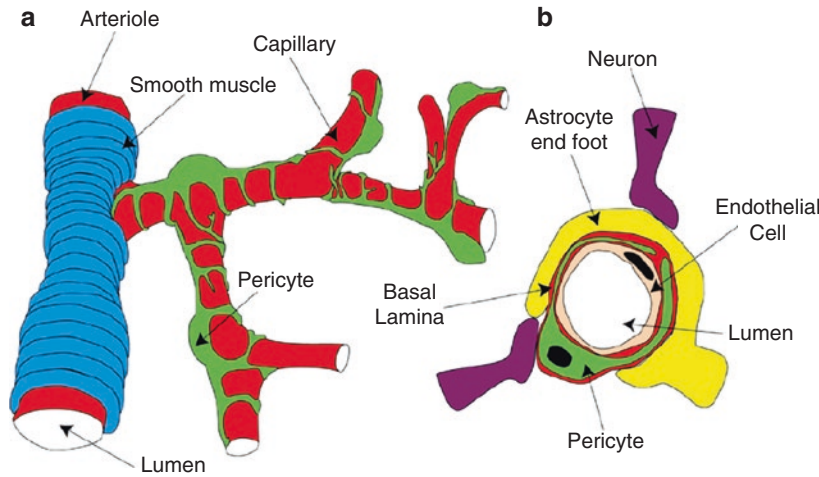

Fig. 5.2 Organisation of the capillary neurovascular unit. (**a**) Rings of smooth muscle encircle arterioles, while pericytes send processes along and around capillaries, without fully covering them. (**b**) Pericytes are located outside the endothelial cells and are separated from them and the parenchyma by a layer of basal lamina. In the parenchyma, astrocyte end-feet and neuronal terminals are closely associated with the capillary (From [5] with permission)

[1]Jean Louis Marie Poiseuille (1797–1869) was a French physician and physiologist.

of these is mediated by the release of factors from pericytes and the astrocytic end-feet as shown by mutant mice which are deficient in pericytes [6, 7]. Experiments in which human ECs were co-cultured with pericytes and astrocytes [8] demonstrated that the formation of connections between ECs require the presence of both astrocytes and pericytes. Cerebral ECs also possess very few pinocytic vesicles. Thus, the BBB isolates its vascular smooth muscle, and the brain parenchyma, from the effects of circulating humoral stimuli and ions such as catecholamines and protons [9]. Only small, uncharged lipid-soluble molecules such as O_2, CO_2 and glucose, and those transported across the membrane by specific carrier systems, pass through the endothelium with any rapidity [10]. In addition, high levels of monoamine oxidase within endothelial cells (ECs) degrade catecholamines, forming an additional 'enzymatic' BBB. As a result, CBF is almost completely unaffected by the circulating humoral stimuli that so powerfully influence other vascular beds. In essence the cerebral circulation is 'selfish' in that, unlike, for example, the renal and splanchnic circulations, it does not participate in the redistribution of blood flow during emergencies such as haemorrhage and exercise. This very different behaviour of cerebral blood vessels may be related to the fact that the smooth muscle cells and pericytes of the cerebral circulation (and thymus) are derived from the neural crest rather that the mesothelium as in all other tissues [11].

5.2.1 Other Distinguishing Physiological Responses of Cerebral Vessels

Blood flow through cerebral vessels, like that in other tissues, e.g. renal and splanchnic circulations, is increased by raising the partial pressure of carbon dioxide (PCO_2), by lowering the partial pressure of oxygen (PO_2) and by lowering pH. The mechanisms responsible for these responses are similar to those seen in other tissues, but generally cerebral vessels are more responsive than others to raised PCO_2 and lowered PO_2. Another widespread link between metabolism and vascular resistance in excitable tissues is the local concentration of extracellular potassium that rises each time an action potential is repolarised (a greater intensity of action potential discharge giving rise to a proportional increase in extracellular potassium). However, there is one key link between metabolic rate and vascular diameter that is used exclusively by the brain and this is the local concentration of the excitatory neurotransmitter glutamate. It appears that evolution has made use of *any* signal that provides a good index of metabolic rate and that while raised PCO_2 [and the protons (H^+) formed when it reacts with water] and lowered PO_2 are available to all, the brain also makes use of glutamate, a signal peculiar to itself.

The responses of cerebral vessels to the innervation of their vascular smooth muscle (VSM) also differ from those in other vascular beds. For example, within the normal range of arterial blood pressures (60–140 mmHg), sympathetic activation of an intensity that might close down blood flow to the kidney or severely reduce flow to the skin or skeletal muscle has no effect on cerebral blood flow. It does, however, extend the range of autoregulation when ABP is high, protecting the cerebral microcirculation from excessive pressures and flows. Conversely, abolishing sympathetic discharge by cervical sympathectomy or by alpha-receptor blockade extends the range of autoregulation at low levels of ABP (Fig. 5.3).

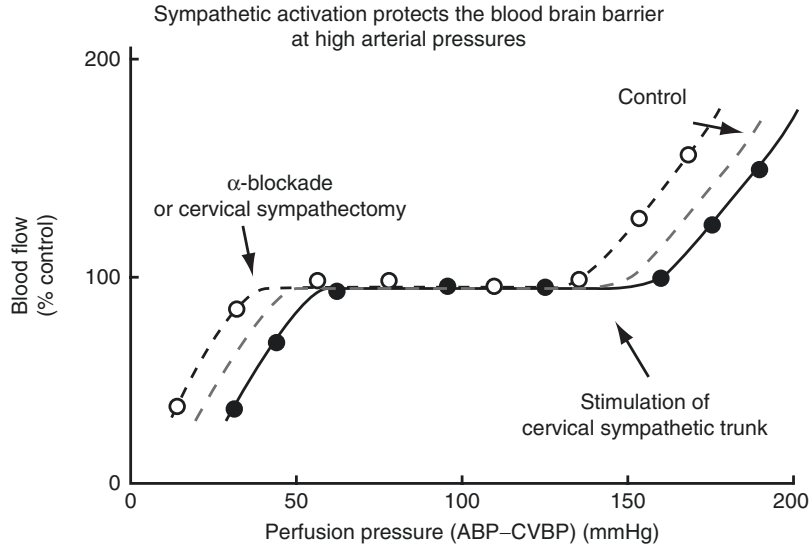

Fig. 5.3 Electrically stimulating the sympathetic innervation of the cerebral vasculature raises the upper limit of autoregulation, and interfering with it, either by pharmacological blockade or by cutting nerves, reduces the lower limit, but in the normal range of pressures neither stimulation nor blockade affects cerebral blood flow [12]

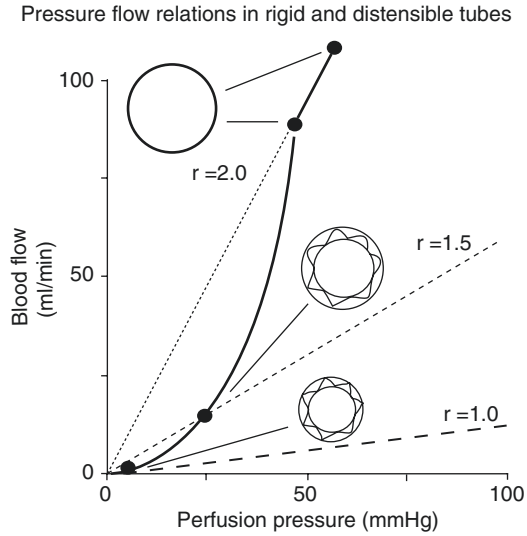

Fig. 5.4 Pressure-flow relations through lifeless tubes. Rigid tubes have linear relations in which a doubling of radius increases flow by 16-fold (Poiseuille's r^4 relation) and they pass through the origin. In distensible tubes, the relation is upwardly bending and tangents to the curve pass through the x-axis. A tangent can only pass through the y-axis if the vessel is alive and showing some degree of autoregulation

5.3 Autoregulation

Most organs, such as the kidney, heart and skeletal muscle, match local blood flow to local metabolism. This *autoregulation* of blood flow reflects the intrinsic ability of an organ's vessels to determine its own blood flow without any contribution from the autonomic nervous system. It is most simply demonstrated by removing an organ from the body, to isolate it from the influence of autonomic nerves, and perfusing it from an arterial reservoir that can be raised or lowered. Flow through a lifeless system of *rigid* vessels treated in this way would increase linearly, and in a lifeless system of *compliant* vessels, such as thin, rubber tubes or dead blood vessels, the line would curve upwards as the rising arterial pressure distends them, reducing their resistance (Fig. 5.4).

In both these cases, all tangents to the pressure–flow relation pass through the origin or through the x-axis. It is only when the vessels are alive, and actively constricting in response to rising arterial pressure, that a tangent can pass

through the y-axis, as it does in Fig. 5.4. An experiment such as this is a straightforward way to demonstrate that the vessels of most tissues possess the intrinsic ability to hold blood flow at an appropriate level and has come to define autoregulation. However, the constriction of resistance vessels, when an arterial reservoir is raised, is due to two distinct processes, each of which elicits its own constricting effect. The first is the washout of vasodilating by-products of metabolism and the second is mechanical stretch of vessel walls. These processes are referred to, respectively, as metabolic and myogenic influences. More revealing, but harder to perform, experiments along these lines would look at metabolic and myogenic influences separately by (a) altering the metabolism of an isolated organ, at constant perfusion pressure, by stimulating its neural input or (b) raising transmural pressure of the vessels, at constant metabolism, by raising both the arterial and venous reservoirs by the same amount. Although one cannot denervate a brain as one can a kidney or a heart, similar autoregulation appears to occur in the cerebral circulation.

Autoregulation of cerebral vessels was first observed in pial vessels viewed through a cranial window [13] by Fog in 1937 [14], and this was later quantified by the Kety-Schmidt [15] method of measuring cerebral blood flow using low concentrations of inspired nitrous oxide. More recently the use of transcranial Doppler ultrasound to measure blood flow velocities non-invasively and continuously has revealed the dynamics of the response, demonstrating that flow can recover within 5–10 s of the onset of a hypotensive challenge [16].

An obvious question now is 'which vessels contribute most to the change in resistance?' In most tissues, measurements of the pressure drops across various parts of a vascular bed show that the greatest, and most variable, resistance comes from the small arterioles of about 50–100 μm diameter. However, Kontos et al. [17], who observed changes in diameter directly by looking at those vessels they could see through a microscope, found that the larger pial arteries of the cat (those with a diameter of 200 μm) responded most to changes of perfusion pressure within the physiological range. The smaller, precapillary pial arterioles (diameter < 100 μm) dilated only when ABP fell below 90 mmHg, and below 70 mmHg they were more responsive than the larger ones. When ABP was taken to very high levels (>170–200 mmHg), the larger vessels remained constricted but the smaller arterioles failed to sustain their constriction and dilated, accounting for the upward curve on the right hand side of Fig. 5.1. Kontos estimated that extracranial vessels account for 17% of total cerebral vascular resistance, while the surface pial arteries and precapillary arterioles account for 26% and 32%, respectively. This relative importance of larger vessels contrasts with the situation in most vascular beds where smaller arterioles are responsible for almost all resistance changes. However, in these experiments the blood vessels that are buried in the brain tissue were not observed. Indeed, recent work [1, 5, 18] strongly suggests that cerebral *capillaries* make an important contribution to cerebral vascular resistance and that capillary diameter is controlled by contractile pericytes as described in Sect. 5.4.4.

5.3.1 The Myogenic Response

VSM cells contract when they are stretched by a rise in transmural pressure. This intrinsic response, first described by Bayliss in 1902 [19], usually returns vessel diameter to its control value, but it can, especially in small arterioles, be so pronounced that the final diameter of a vessel is smaller than that before pressure was increased. Figure 5.5a shows an experimental setup that can be used to demonstrate this and Fig. 5.5b represents results obtained. It is as if the sensor is *in series* with the muscle cells, encoding tension rather than circumference where, according to the LaPlace relation, $T \propto P \times$ radius. So if pressure (P) is raised and held high then tension (T) will not return to its original value until the vessel's radius is smaller than it was before the test. It is thought that this myogenic response provides a background basal tone against which other vasoactive influences play. It contributes to the autoregulation

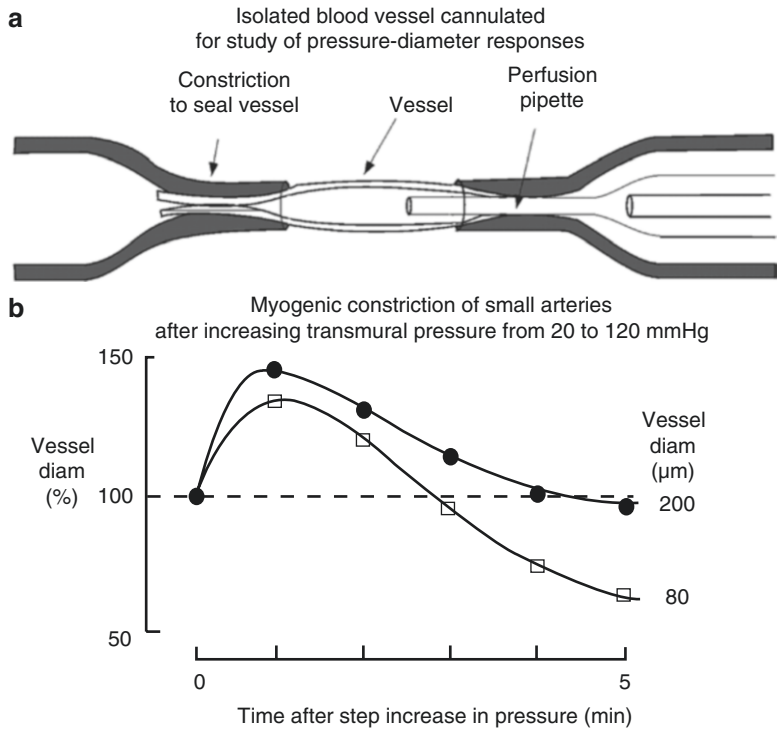

Fig. 5.5 (**a**) Apparatus for recording the diameter of a small blood vessel as transmural pressure is changed. (**b**) Changes of diameter observed in two sizes of vessel after a step change of transmural pressure from 20 to 120 mmHg. After an initial distension in response to the rise in pressure, both vessels constrict. The larger (200 μm) vessel returns to its initial diameter but the smaller (80 μm) vessel constricts so forcefully that it ends with a diameter that is less than it started with [20]

of blood flow by helping to couple the behaviour of larger feed vessels to that of small ones embedded in active tissue (see Sect. 5.5), but its main role is probably in limiting the changes of capillary pressure, and the resulting fluid shifts between blood and interstitium, which occur during changes of posture. It is therefore concerned with protection against cerebral oedema.

There are several broad hypotheses concerning the sequence of events that couples changes in intravascular pressure or stretch with alterations in VSM activity or tone. These include stretch-activated sarcolemmal Transient Receptor Potential, Melastatin-type (TRPM) ion channels, which depolarise the VSM by allowing the entry of Na^+ ions, and the classical transient receptor potential ion channels TRPC6 which primarily conduct Ca^{2+} ions [21]. Also involved is the modulation of biochemical signalling pathways within VSM, length-dependent contractile protein function and endothelial-dependent modulation of smooth muscle tone. Increased intravascular pressure stimulates the production of cytochrome P-450 4A which catalyses the formation of 20-hydroxyeicosatetraenoic acid (20-HETE) from arachadonic acid. 20-HETE is a powerful vasoconstrictor which activates protein kinase C which depolarises vascular smooth muscle cells by closing Ca^{2+}-activated K^+ channels thereby opening L-type, voltage-gated, Ca^{2+} channels. The resulting rise in intracellular Ca^{2+} constricts the vessel [22].

5.3.2 Metabolic Responses

Whereas the pressure-induced myogenic response dominates in medium-sized intrinsic (parenchymal) arterioles (20–30 μm), metabolic control mechanisms exert their primary effect on the smallest arterioles (less than 20 μm) that are surrounded by metabolising tissue. In the cerebral circulation, as in other vascular beds (e.g. coronary, skeletal muscle) local changes in metabolism are tightly coupled to local blood flow. Several substances have been proposed to link perfusion to cerebral metabolism. These include oxygen, and carbon dioxide levels, and extracellular concentrations of protons, potassium

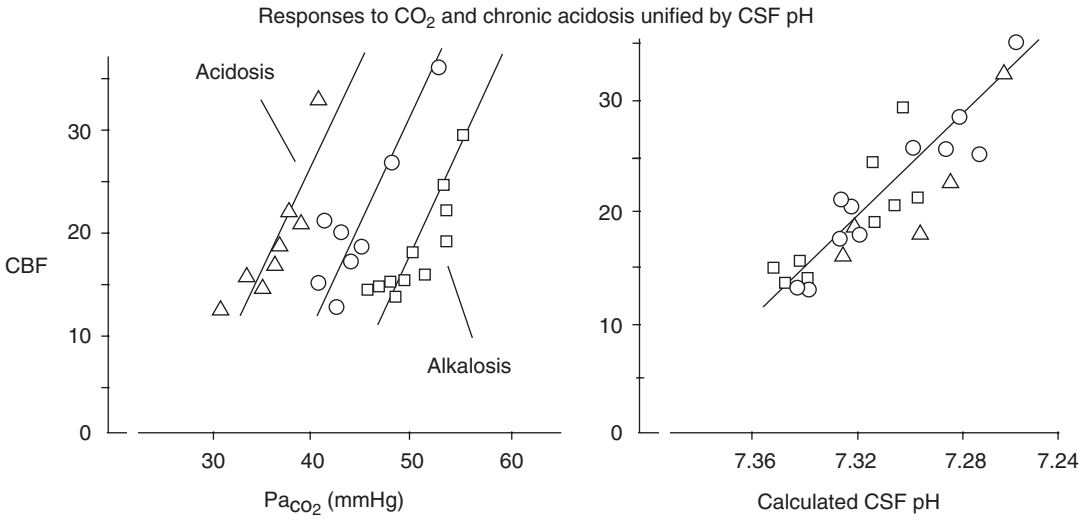

Fig. 5.6 Experiments suggesting that CO_2 acts, not as molecular CO_2, but by reacting with water to form protons [23]. When Cerebral Blood Flow (CBF), calculated from the difference between arterial and venous O_2 contents, is plotted against calculated CSF pH rather than Pa_{CO2}, the three sensitivity lines coincide

ion, adenosine and lactate. However, the brain has its own mediator that provides the vasculature with an index of neuronal activity. This is the local concentration of the excitatory neurotransmitter glutamate.

5.3.2.1 Inspired PCO_2 and pH

CBF is greatly increased when inspired PCO_2 is raised. This shows up as a steep, linear rise in CBF within a $PaCO_2$ range of 25–60 mmHg which Fencl et al. [23] showed to be a simple function of calculated CSF pH. So, while protons cannot diffuse through the BBB at any significant rate, CO_2 does so freely and then reacts with water to form protons (Fig. 5.6). The system behaves as if arterial CO_2 is the primary stimulus, but in fact it is the pH at the receptor site that is transduced into a response by VSM.

The above experiments show that protons are responsible for the powerful effects of CO_2 but they do not show whether the critical changes are extracellular or intracellular. The answer to this was provided by Apkon and Boron [24] who used a pH-sensitive fluorescent dye to follow the intracellular acidity of small cerebral blood vessels while they separately altered intracellular and extracellular pH. They found that vessel diameter responded only to changes in extracellular pH – an arrangement that 'makes sense' because it is the job of these vessels to ignore their own metabolism and to respond to the metabolic activity of the nerve cells that surround them.

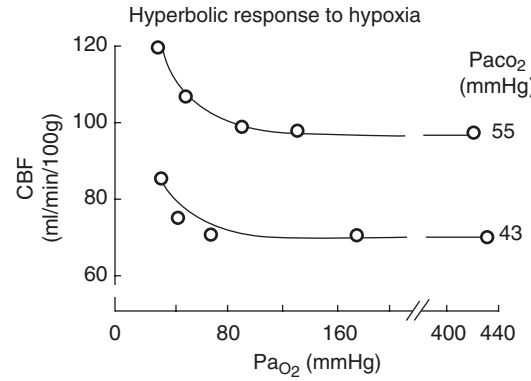

Fig. 5.7 Cerebral blood flow is virtually insensitive to the reduction of arterial oxygen until Pa_{O_2} falls to dangerously low levels. The response to carbon dioxide is much more powerful [25]

5.3.2.2 Oxygen

Reductions in blood levels of O_2 have little effect on CBF until the partial pressure of arterial oxygen (PaO_2) falls below 50–60 mmHg (Fig. 5.7). At lower PaO_2, the CBF rises markedly and flow

is almost doubled when levels reach the very low value of 30 mmHg. The hyperbolic shape of this curve suggests that the response to hypoxia may be an emergency mechanism activated when other stimuli fail.

Several mechanisms have been proposed to account for the vasodilating effect of hypoxia. One is that it may be largely due to the opening of VSM potassium channels (K_{ATP} channels) that are held shut at normal ATP levels. This occurs if hypoxia becomes intense enough to slow down the rate of ATP synthesis by electron transport. Evidence for this comes from experiments on rats where tolbutamide reverses relaxation by hypoxia but not that caused by raised CO_2. The tolbutamide mimics the effect of raised intracellular ATP levels that would close these channels [26].

Other likely links between hypoxia and vasodilation are lactate (from anaerobic metabolism) and adenosine, both of which relax VSM, the former by lowering extracellular pH (see Sect. 5.3.2.1) while the latter activates vasodilatory A_{2A} adenosine receptors on VSM. The importance of adenosine is emphasised by the observation that blocking adenosine receptors with theophylline can roughly halve cerebral hyperaemia [27]. Another factor that can vasodilate by opening K_{ATP} channels is hydrogen sulphide (H_2S) which is described in Sect. 5.5.2.

The great sensitivity to inspired CO_2 does not, however, mean that CO_2 is necessarily the dominant factor that determines CBF. Indeed when natural stimuli, such as the stimulation of sensory nerves, are used, most studies show that CO_2 falls and PO_2 rises in excited parts of the brain.

5.3.2.3 Potassium

Raised extracellular potassium increases CBF by dilating vessels. The cell membrane potential is stabilised by the presence of inward-rectifier potassium channels which maintain resting membrane potential when they are opened. They also contribute to vasodilation in response to increased neuronal activation because the repolarisation of every action potential involves the release of some potassium into the extracellular medium which are not removed by sodium pumps with sufficient rapidity to prevent the buildup of extracellular potassium. Raised interstitial potassium relaxes VSM in two ways. Firstly, it stimulates the hyperpolarising electrogenic activity of VSM sodium pumps, the rate of which is normally limited by the relatively low resting level of extracellular potassium. Secondly, the inward-rectifier potassium channels of VSM are activated by modest rises in extracellular potassium. They are potassium-activated potassium channels that hyperpolarise the VSM membrane when opened [28] and relax the vessels by closing voltage-gated calcium channels.

5.3.2.4 Glutamate

Glutamate is the most widespread excitatory neurotransmitter in the brain and, in contrast to acetylcholine at the neuromuscular junction, it is not instantaneously destroyed by an enzyme upon release. Its concentration in the interstitium therefore rises and falls as the mean activity of excitatory neurons waxes and wanes – i.e. it is a good index of cerebral metabolism. Glutamate excites metaboreceptors (mGluRs) on astrocytes and NMDA receptors on postsynaptic neurons and both of these ultimately generate powerful vasodilators that relax cerebral VSM (Fig. 5.8). In astrocytes, two processes contribute to this link between local metabolism and local perfusion. First, the activated mGluRs raise $Ca^{2+}i$ and this leads to a cascade that releases a vasodilatory prostaglandin (PG). The raised $Ca^{2+}i$ also opens large conductance calcium-activated K^+ channels, allowing potassium to diffuse down its electrochemical gradient into the interstitium. This relaxes VSM, by opening delayed rectifier K^+ channels on the smooth muscle cell membrane.

The activation of NMDA receptors on postsynaptic neurons raises $Ca^{2+}i$, resulting in a cascade that releases vasodilatory PG; however, a more powerful vasodilatory influence is also initiated by the raised $Ca^{2+}i$, and this involves the activation of neuronal nitric oxide synthase (NOS). The gaseous nitric oxide (NO) that is released diffuses directly to VSM where it activates cyclic guanosine monophosphate (cGMP) which sequesters cytoplasmic Ca^{2+}.

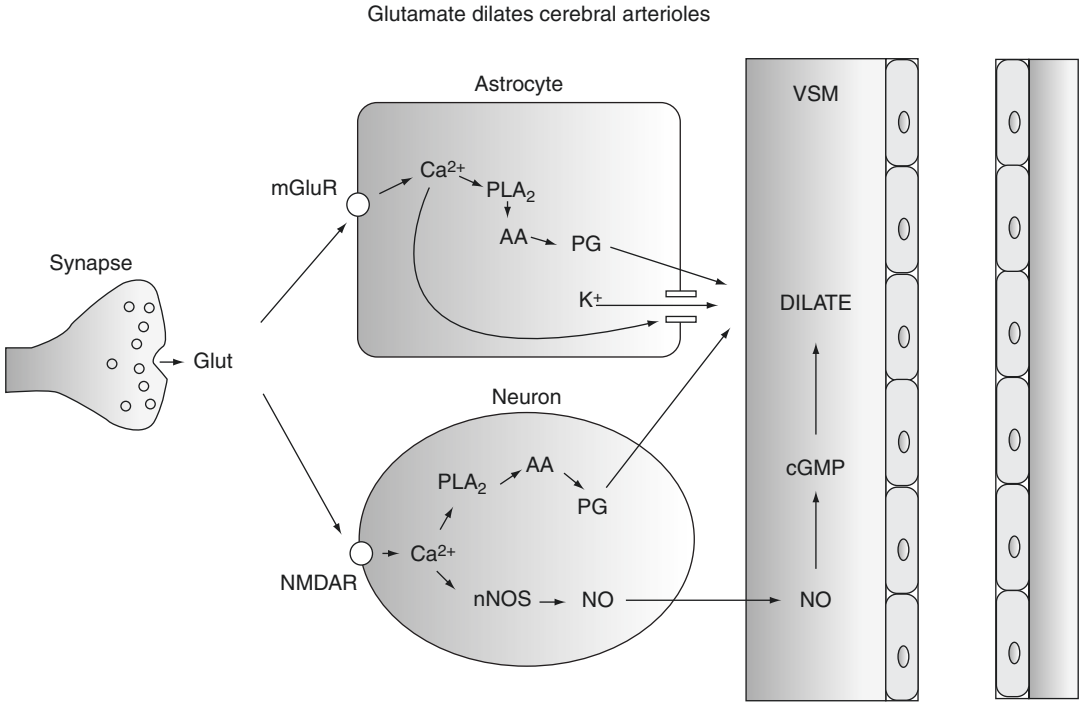

Fig. 5.8 Glutamate, released by excitatory presynaptic nerve endings, dilates cerebrovascular smooth muscle (*VSM*) by several mechanisms, four of which are shown here. It activates metabotropic receptors (*mGlut*) on astrocytes and NMDA receptors (*NMDAR*) on postsynaptic neurons. The first step of the response is the same in both cell types: intracellular Ca^{2+} rises and activates phospholipase A2 to generate arachidonic acid (*AA*) and, from that, a vasodilating prostaglandin (*PG*). In astrocytes, the rise in Ca^{2+} also opens Ca^{2+}-activated K^+ channels, allowing modest amounts of K^+ to leave the cell and dilate VSM by opening K^+-activated K^+ channels that hyperpolarise it [28]. In neurons, the rise in Ca^{2+} triggers the synthesis of neuronal nitric oxide synthase (*nNOS*) with the resulting formation of NO. The NO diffuses to the VSM where it activates cyclic GMP (*cGMP*) which relaxes the VSM by reducing cytoplasmic Ca^{2+}. Section 5.5.2 describes yet another link between glutamate and vasodilation – the sensitising of hyperpolarising BK_{Ca} channels on VSM by carbon monoxide (CO) released by astrocytes

5.4 Neurogenic Influences

Cerebral blood vessels are innervated by both the peripheral and central nervous systems. In addition to sympathetic and parasympathetic innervation (extrinsic nerves), cerebral blood vessels are influenced by neurotransmitters that have been identified in perivascular nerves within the brain (intrinsic nerves).

5.4.1 Sympathetic Innervation

Post-ganglionic sympathetic nerves from the superior cervical ganglion release noradrenaline and neuropeptide Y which are vasoconstrictors. Sympathetic nerve fibres most densely innervate the large cerebral arteries at the base of the skull. They are more abundant in the carotid arteries than the arteries of the posterior circulation. Neuropeptide Y has been demonstrated around cerebral vessels particularly the major arteries of the circle of Willis. *In vitro*, it elicits strong concentration-dependent contraction of cerebral arteries.

However, in spite of this rich innervation, stimulation has little effect on CBF when arterial blood pressures are in the normal range. The effects are confined to arterial blood pressure either well above or well below the normal range. This is shown by the observation that electrical stimulation of cervical sympathetic

nerves has no effect on cerebral blood flow between about 50 and 150 mmHg. It appears that the sympathetic constriction of large inflow vessels is countered by metabolic dilation of smaller distal vessels. Sympathetic stimulation does, however, shift the autoregulatory curve to the right, protecting the brain from breakthrough vasodilation during acute hypertension (Fig. 5.3).

5.4.2 Parasympathetic Innervation

Post-ganglionic parasympathetic nerves from the sphenopalatine and otic ganglia are vasodilators. They release a range of neurotransmitters including nitric oxide (NO), acetylcholine, vasoactive intestinal peptide (VIP) and peptide histidine isoleucine (PHI-27) neurotransmitters. The NO is synthesised *de novo* from L-arginine by the activity of nitric oxide synthase (NOS, termed nNOS in nitrergic nerves to distinguish it from endothelial eNOS). The parasympathetic nerves play a role in pain-mediated vasodilatory responses and they may contribute to the dilatory response to hypercapnia. However, as is the case with sympathetic nerves, surgical division of parasympathetic nerves does not affect CBF under normal conditions. In contrast to other neurotransmitters which are ineffective when injected systemically because their effects are prevented from reaching cerebral VSM by the blood–brain barrier, the injection of acetylcholine (ACh) does increase cerebral blood flow. However, it does this not by passing through the barrier itself but by activating endothelial muscarinic receptors that lead to the release of NO. VIP and PHI-27 which have been found in the walls of cerebral arteries vasodilate *in vitro* probably act on a specific receptor since their effect is not endothelium-dependent [29].

5.4.3 Sensory Innervation

Somatosensory nerve fibres, originating in the trigeminal ganglion, release substance P, calcitonin gene related peptide (CGRP) and neurokinin A. The trigeminal nerves appear important only under special circumstances, such as during seizures, when their stimulation causes increases in CBF. There is evidence that kinins and substance P in particular are involved in the transmission of nociceptive information. Substance P relaxes contracted arteries *in vitro* and the trigemino-cerebral system is thought to be involved in the restoration of normal vessel diameters in conditions of pronounced vasoconstriction. CGRP is the most likely candidate for mediating this function.

5.4.4 Pericytes and Astrocytes

Cerebral capillaries are not like capillaries in other tissues and the differences go beyond the existence of the blood–brain barrier's distinctive endothelial cells with their tight junctions and paucity of cytoplasmic vesicles. There is one cell type in particular that is in intimate contact with cerebral endothelium and, although it is found in association with all capillaries, it is most abundant in the cerebral circulation. This is the pericyte, which secretes growth factors that govern the formation and maintenance of the blood–brain barrier [6]. They also possess contractile cytoplasmic processes that grasp capillaries at 50 μm intervals (Fig. 5.2) and which are relaxed by application of the neurotransmitter glutamate [18], NO [30] or adenosine [31] and constricted by ATP [32], dopamine [33] and noradrenaline [18]. Pericytes are thus well positioned to contribute to the control of cerebral blood flow [34], all the more so because the capillaries they constrict contain red blood cells that are frequently compressed as they pass through. Human red blood cells are 6.2–8.2 μm in diameter while capillaries range from 5 to 10 μm, so only a small reduction in radius would be expected to cause a large increase in resistance. However, the relative importance of pericytes and arterioles in the matching of local blood flow to metabolism is hotly disputed. Some claim to be able to show that pericytes do little or nothing [35–39] while Attwell's group insist they are very significant, that they respond *in vivo* to sensory activity before arterioles, and that they account for over

80% of the increase in blood flow [1, 5, 18, 38, 39]. Pericytes are coupled by gap junctions that allow the spread of excitation from one to another.

Astrocytes (star-like cells) are non-neuronal glial cells which make up roughly 15% of the mass of the brain and spinal cord. They have end-feet that are in close contact with pericytes and endothelial cells (see Fig. 5.2) and they work alongside pericytes in promoting the formation and maintenance of the blood–brain barrier by secreting growth factors. Furthermore, they are thought by some to release the transmitters glutamate, ATP and D-serine [40, 41]. They are also apposed to cerebrovascular smooth muscle cells and release vasodilatory carbon monoxide (cf. Sect. 5.5.2).

5.5 Gaseous Vasodilators

Three gases, all of them highly toxic at surprisingly low concentrations, have been discovered to be produced endogenously and all three have powerful vasodilating effects. The story started with Furchgott's discovery in 1980 [42] that acetylcholine relaxes blood vessels if their endothelium is intact but constricts them if it is removed. Clearly something, an endothelial relaxing factor (EDRF) was being released. In 1988, Furchgott proposed that EDRF might be nitric oxide (NO) [43]. This was based on the observations that superoxide dismutase (SOD, which removes O_2^-) protected EDRF from rapid inactivation and that haemoglobin selectively inhibited it. The idea that an endogenous gas could be responsible for a physiological effect was completely new and met with considerable resistance. However, in 1987, Palmer made an aqueous solution of NO and, using a bioassay, compared its actions with those of the effluent from Moncada's cultured vascular endothelial cells [44]. EDRF and NO closely resembled one another in terms of half-life, stabilisation by SOD and inhibition by haemoglobin [44] and NO was quickly accepted as an important physiological substance – indeed, by 2006, only 25 years after Furchgott's first account of EDRF, 31,000 papers with nitric oxide in their title had been published [45].

Carbon monoxide (CO), previously known exclusively to be a poison which excludes O_2 from haemoglobin by binding to it with 250 times the affinity, was then found to be both produced endogenously and vasoactive. And finally hydrogen sulphide (H_2S), which is even more toxic than CO, being lethal if breathed at only 100 ppm, was also shown to be an endogenous vasodilator [46, 47].

5.5.1 Nitric Oxide: Ascending Vasodilation and Limiting Intracerebral Steal

A question that for many years taxed physiologists was how arterioles upstream of active tissue respond appropriately to distal metabolic changes that they cannot 'see'. One answer to this conundrum is offered by shear stress-induced release of nitric oxide (NO) (Fig. 5.9). The smallest arterioles (micro-vessels) are embedded in active tissue so they dilate when metabolism increases and when they dilate, resistance falls and blood flow through them, *and through the feed vessels upstream of them*, increases. Increased flow in the feed vessels 'tugs' on the endothelium increasing shear stress which stimulates the release of endothelial NO. This NO diffuses through the BBB to immediately adjacent VSM which it relaxes by increasing cyclic GMP (cGMP) which, in turn, sequesters Ca^{2+}. Thus, the nitric oxide mechanism amplifies the relatively small reduction in resistance that starts in micro-vessels by spreading it to the larger feed vessels [48, 49]. The myogenic responses of larger vessels contribute to this ascending vasodilation because when the downstream resistance of micro-vessels is reduced, the pressure in feed vessels also falls and this elicits myogenic relaxation. A third mechanism that may contribute to ascending vasodilation is the upstream conduction, through gap junctions, of electrical changes that start in the micro-vessels.

Another physiological role for ascending vasodilation is in the limitation of intracerebral steal in which blood flow to a healthy part of the brain with constant metabolism (part A) decreases when an area adjacent to it (part B) dilates. This occurs

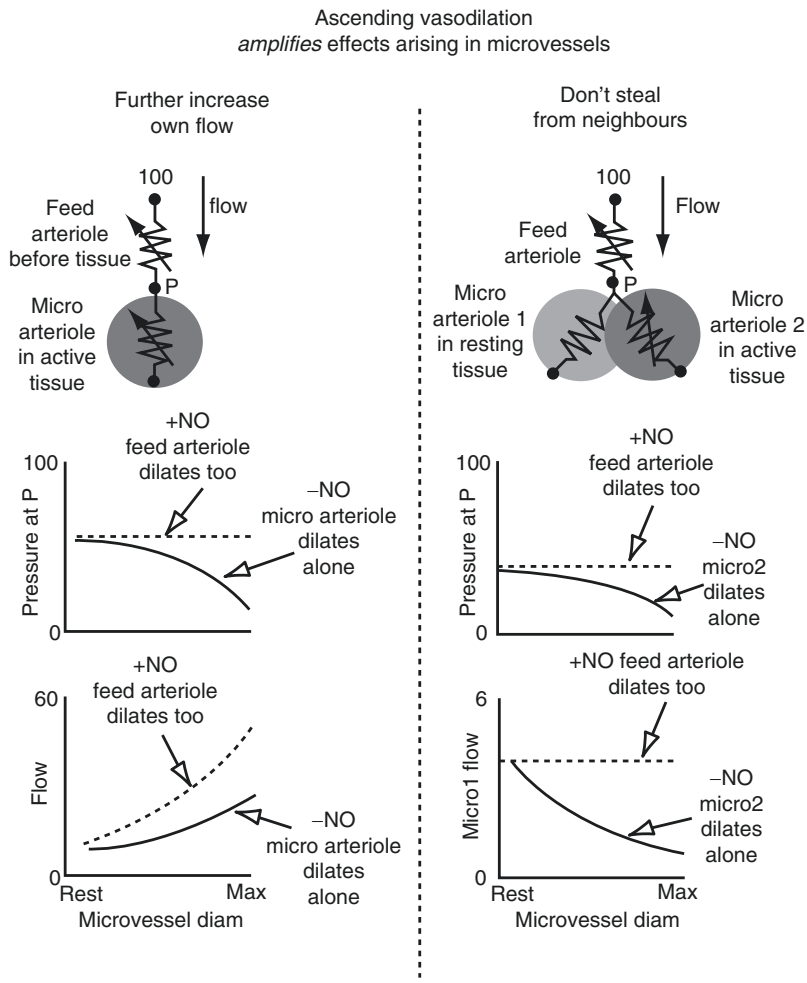

Fig. 5.9 Coupling of the behaviour of upstream vessels to those embedded in active tissue. *Left panel*: a micro-arteriole dilates when there is metabolism of the tissue immediately adjacent to it. Dilation increases flow through all vessels that are in series with the micro-arteriole and this includes the upstream feed arteriole where the increased shear stress releases NO. The pressure at P initially falls because the resistance that holds it above venous pressure has fallen. However, when the feed arteriole dilates, pressure P rises back towards its control value because the resistance that holds it below arterial pressure has now fallen. *Right panel*: if micro-arteriole 2 dilated in response to raised metabolism and if (as one would expect) pressure P fell because of this, then the flow through micro-arteriole 1 would fall. However, ascending vasodilation limits this intracerebral steal by holding pressure P relatively constant (After Segal [48])

because when the metabolic rate of part B increases, the pressure in the feed arteriole, which serves both parts, falls. Thus, the perfusion pressure, and therefore flow, through Part A would fall as Part B stole it. The coupling of the activity of feed arterioles to that of micro-arterioles by the three mechanisms that contribute to ascending dilation tends to reduce the pressure fall in the feed arteriole, thereby reducing intracerebral steal.

5.5.2 Carbon Monoxide and Hydrogen Sulphide

NO is the best known and best understood gaseous paracrine substance, but at least two other freely diffusible endogenous gases, carbon monoxide (CO) and hydrogen sulphide (H_2S) have been implicated in cerebrovascular control. Low levels of endogenous carbon monoxide (CO),

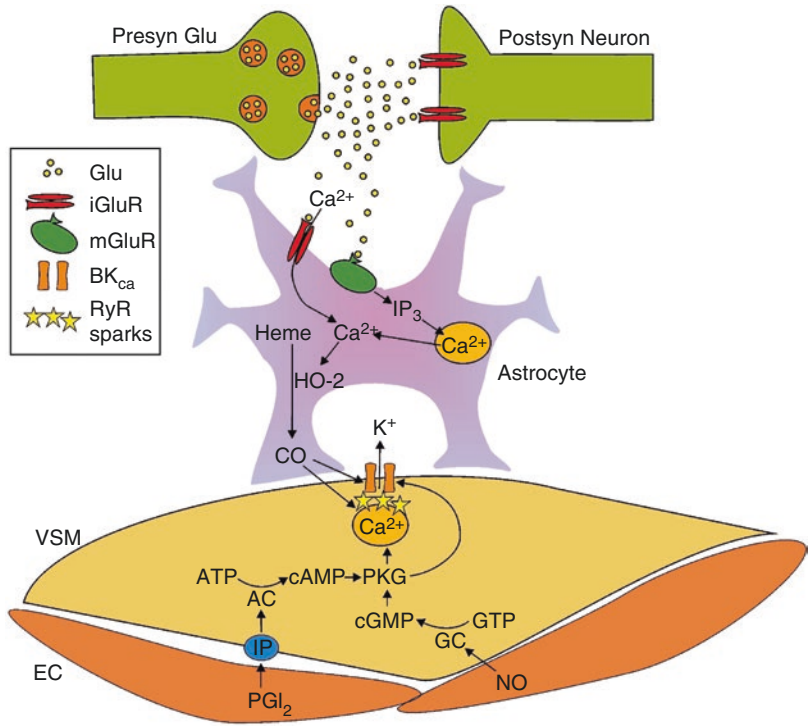

Fig. 5.10 Vasodilation by carbon monoxide (CO). Glutamate (Glu) released by presynaptic glutaminergic neurones (Presyn Glu) raises astrocytic Ca^{2+} by (1) opening Ca^{2+} channels (iGluR) and (2) by exciting metaboreceptors (mGluR) which raise intracellular inositol 1,4,5 trisphosphate (IP_3) which releases Ca^{2+} from intracellular stores. CO production from heme, catalysed by heme oxygenase 2 (HO-2) is activated by raised Ca^{2+}. CO diffuses into nearby vascular smooth muscle (VSM) where it opens sarcoplasmic reticulum ryanodyne receptors (RyR), generating Ca^{2+} sparks that open BK_{Ca} channels. Sparks are also generated by raised protein kinase G (PKG) which is stimulated by two pathways: (1) endothelial cell (EC) NO activates guanylate cyclase (GC) which increases cGMP and (2) endothelial prostaglandin-I_2 (PGI_2) which acts on its recetor (IP) to activate adenylyl cyclase (AC) thus increasing cAMP. CO increases the calcium-sensitivity of BK_{Ca} channels as well as the frequency of the sparks themselves. Finally, PKG also acts directly to open BK_{Ca} channels (After Leffler et al. [30]). The postsynaptic neuron (Postsyn Neuron) is excited by the opening of Ca^{2+} channels that are similar to those on astrocytes

which passes unimpeded through all cell membranes, including the blood-brain barrier, are produced continuously by the action of heme oxygenase (HO). HO is found in the endothelial cells of cerebral blood vessels, in cerebrovascular smooth muscle and in nearby glial cells and neurones [11]. There are two isoforms of HO, HO-1 which is inducible and HO-2 which is constitutive. The highest concentrations of HO are found in the brain and its blood vessels where HO-2 is most abundant. HO-1 is found primarily in the liver and spleen where it contributes to the degradation of red blood cells, but it can be induced in other tissues, including the vasculature of the brain, by oxidative stress (an imbalance between the production of free radicals and their removal by antioxidants). The HO-2 activity of astrocytes is increased by glutamate that leaks from excitatory glutaminergic synapses (see Fig. 5.10). Glutamate acts on both ionotropic and metabotropic receptors on astrocytes, raising intracellular Ca^{2+} which activates HO-2 to break down heme from hemoproteins such as cytochrome, catalase, heme peroxidase and endothelial nitric oxide synthase. The resulting CO diffuses into adjacent smooth muscle cells where it activates large-conductance calcium-activated K^+ (BK_{Ca}) channels by binding to an associated heme. The Ca^{2+} sparks that open BK_{Ca} channels, thereby relaxing the smooth muscle

cells by hyperpolarising them, are also increased in frequency by CO.

Hydrogen sulphide (H_2S), the third endogenous gaseous vasodilator, is formed by the action of cystathionine gamma-lyase on L-cysteine, an effect enhanced by NO. H_2S opens K_{ATP} channels hyperpolarising VSM thereby closing voltage-gated Ca^{2+} channels with the resulting fall in intracellular Ca^{2+} relaxing the vessel [27]. Thus, H_2S reinforces NO-induced vasodilation, but because the physiological factors that determine the rate of H_2S synthesis have not been fully elucidated, its significance has not been established.

5.6 Posture and Its Effects on Cerebral Blood Flow

On standing, the cerebral arterial, venous and intracranial pressures fall because a few 100 ml of blood are lost from the thorax and abdomen to become pooled in the compliant leg veins. The fall in ABP would be about 30 mmHg were it not for the rapid activation of the arterial baroreflex. This involves a reduction in the discharge of the carotid sinus baroreceptors which, within a heartbeat, reflexly reduces the parasympathetic, vagal innervation of the heart and, more slowly, activates the sympathetic nervous system. These complementary autonomic responses increase heart rate, ventricular contractility and the constriction of extracranial arterioles with the result that cerebral perfusion pressure falls by only perhaps 4 or 5 mmHg. At the same time, intracranial venous pressure drops by 5–8 mmHg, but venous collapse, even at subatmospheric pressures, is prevented by the rigidity of the dural sinuses. There may be a small fall in CBF, but the delivery of oxygen and glucose is soon brought back to normal by autoregulation. Figure 5.11 shows blood pressure and heart rate responding to a postural change similar to, but more pronounced than, that seen upon standing in which the leg veins are compressed, thereby reducing the pooling of blood within them.

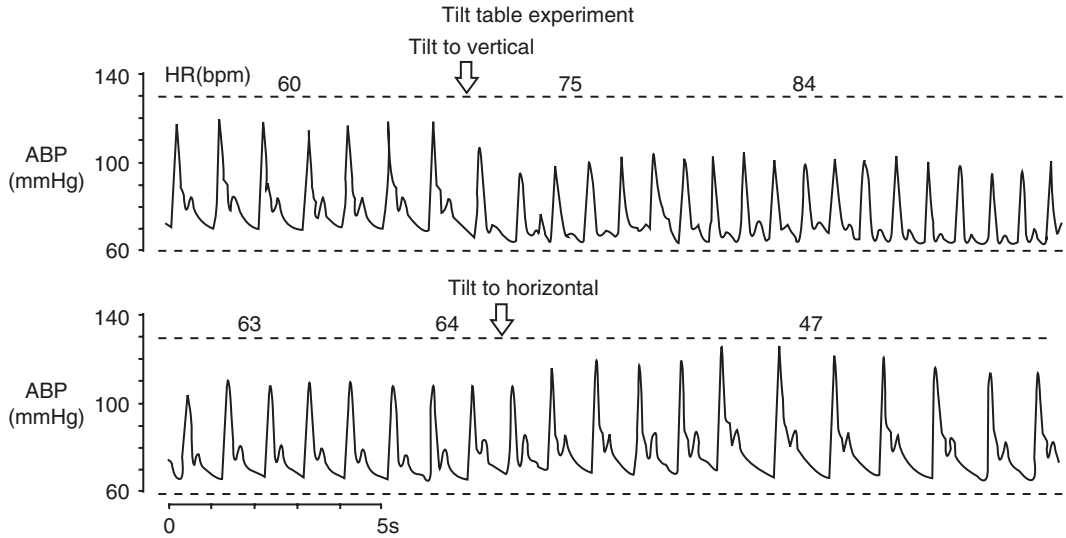

Fig. 5.11 Passive tilt of a completely relaxed subject from the horizontal to vertical exaggerates the effects of standing up because more blood pools in the valved leg veins which are not squeezed by contracting muscle, as they are upon standing. But even here, there is only a 10 mmHg fall in arterial pressure measured at the level of the carotid sinus. This is a much smaller change than would have occurred if the baroreflex had not excited the heart and constricted extracranial arterioles. The two traces are continuous; note how the baroreflex almost immediately increases heart rate from 60 to 75 beats per minute. Tilting the subject back to the horizontal raises ABP, and reflexly slows heart rate, as blood from the leg veins is poured back into the thorax. The pressure trace, which is measured at the level of carotid sinus, is a good approximation to cerebral perfusion pressure. The baroreflex has held mean pressure (diastolic P + 1/3rd pulse P) within 10–15 mmHg of control

5.7 Results Depend upon the Experimental Technique Used

The literature on the cerebral circulation contains many conflicting statements. For example, the main stimuli involved in metabolic autoregulation are not agreed upon, and the size of the vessels that play the dominant role is disputed. This lack of consensus can probably be explained by the many different approaches used to study the cerebral circulation. Each approach gives its own set of results and each has its own limitations. The main approaches and their limitations include:

- Adding CO_2 to the inspired air to dam up its outflow from brain tissue into cerebral capillaries. It is unlikely that a system would behave normally when its output is blocked.
- Reducing the oxygen in the inspired air, throttling off its input with little effect on other factors. Pure hypoxia is very rarely seen in nature. When it is caused by a reduction in either ventilation or perfusion, it invariably comes with raised CO_2 and inadequate perfusion also reduces the supply of glucose.
- Raising cerebral perfusion pressure is akin to force-feeding the brain as if it was a foie gras goose, it is the approach that gave rise to the definition of autoregulation as in Fig. 5.1. This simultaneously washes metabolites out of the brain and threatens the cerebral interstitium with oedema. In fact perfusion pressure (ABP − VBP) rarely changes in life because arterial pressure is held constant in the short term by the baroreflex and postural changes tend to influence ABP and VBP to the same extent, so even here, perfusion pressure changes little.
- Looking at surface pial vessels in vivo through a cranial window gives no information about the vital small vessels that are buried in metabolising tissue.
- Studying isolated vessels in a bath of stagnant, plasma-free, Ringer solution where there is no contact between vessel and living, functioning nerve cells is thoroughly unphysiological.

It is therefore perhaps unsurprising that when a natural stimulus, such as exciting a sensory input, is used while blood gas tensions within discrete parts of the brain are studied by fMRI, the results are utterly at odds with those obtained by the above means. In fact, fMRI shows that during the natural excitation of local metabolism blood oxygen and pH rise, while CO_2 falls! This is most easily explained by the suggestion that the control of cerebral blood flow depends more upon feed forward stimuli such as glutamate and potassium than it does upon feedback from the waste products of metabolism.

It could, however, also be that the measurement of blood oxygen and pH does not represent these stimuli *at their site of sensation*. The important site could be within tissue where O_2 is lowest and CO_2 highest, i.e. at the downstream end of capillaries and off to the side, halfway between one capillary and its parallel neighbour. This, in Krogh's *lethal corner*, is where the delivery of nutrients is most critically needed and changes here would not be properly represented in blood, even in venous blood.

5.8 Summary of Cerebral Blood Flow Control

It is intuitive that the systems that control cerebral blood flow are functionally integrated and that the arterial network responds in a coordinated fashion. This hypothesis integrates the myogenic, metabolic and flow mediated controls, though different elements of the microvasculature are governed by different regulatory mechanisms. Thus, metabolic control exerts a dominant effect on the smallest arterioles which wanes in the upstream vessels because they are distant from the initiating metabolic change and ascending vasodilation brought about by the myogenic response and the release of nitric oxide dominates in medium-sized arterioles [39].

In practice, the system functions in the following manner:

(a) Increase in demand:
    1. Increased neuronal activity results in the dilation of small vessels, capillaries and small arterioles that respond, primarily to a local rise in glutamate.
    2. Vasodilation of the smallest vessels lowers pressure in the larger, upstream feed arterioles (which possess a strong myogenic response) causing them to dilate.
    3. This dilation further decreases vascular resistance, increasing blood flow which initiates shear stress-induced release of NO and the further dilation of feed arterioles. The net effect of ascending dilation is to amplify the resistance changes initiated by the smallest vessels.

(b) Recovery:
    1. When metabolic demand has been met, the smallest vessels constrict, raising upstream pressure and eliciting the myogenic constriction of medium-sized arteries.
    2. The reduction in flow reduces the shear stress-induced release of NO so, once again, the behaviour of the larger feed arterioles is coupled to that of the smallest vessels which can sense metabolism directly because they are buried in active tissue.

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6

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Preamble

This tutorial, as Chap. 5, has been written by a specialist tutor. In this case, Dr. Paul Giangrande has been a consistent teacher of students taking the Oxford, MSc course. The tutorial is intended to provide the student with a broad understanding of haematology and how drugs are used in general medical practice to modulate clotting. It intentionally covers areas outside the usual reference of interventional neuroradiology and endovascular surgery. Specific drugs and haematological modulations used in our treatments are covered in later tutorials.

6.1 Blood Coagulation

The fundamental step in blood coagulation is the formation of insoluble fibrin strands at the site of tissue injury. The cleavage of small polypeptide chains from the soluble parent fibrinogen molecule is sufficient to achieve this transformation. However, this is only the last step in a series of enzymatic reactions that take place during coagulation (Fig. 6.1). It is now recognised that the coagulation cascade is triggered by the interaction of factor VII with tissue factor, a protein released from damaged tissues. The conversion of circulating soluble fibrinogen into insoluble strands of fibrin is achieved by thrombin, which is itself formed by the enzymatic action of a complex of factor X, factor V and calcium on

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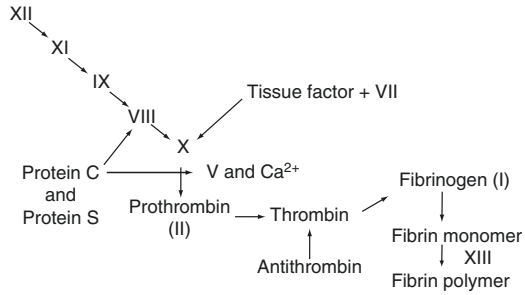

Fig. 6.1 The coagulation cascade

prothrombin (factor II). The initial fibrin clot is relatively unstable as adjacent strands are merely linked by hydrophobic bonds. Factor XIII subsequently stabilises the fibrin by promoting the formation of firm covalent bonds between the fibrin monomers. The coagulation cascade is counterbalanced by natural anticoagulants. Antithrombin inhibits the action of thrombin, whilst proteins C and S destroy coagulation factors V and VIII by cleavage at specific sites.

6.2 Anticoagulation Therapy

Anticoagulants and thrombolytic agents are widely used in many branches of medicine. These agents can be truly life-saving but there is a narrow therapeutic margin and they can cause serious haemorrhagic complications. Some knowledge of their basic pharmacology is therefore essential for their optimal and safe use in interventional neuroradiology. Haemorrhage is the most important complication of anticoagulant therapy. Bleeding complications may range from bruising and oozing from the gums to epistaxis, haematuria or intracerebral haemorrhage. Anticoagulation should not automatically be embarked upon in all patients as some patients are at particular risk of bleeding whilst on treatment and may not be suitable for anticoagulation. Recent haemorrhagic stroke should be regarded as a contraindication. Elderly or confused patients may also not cope with the demands of anticoagulation, particularly if they are already taking several other drugs. Patients with peptic ulceration, pre-existing haemorrhagic diathesis, hepatic cirrhosis, disseminated malignancy, uncontrolled hypertension or proliferative retinopathy may not be suitable for long-term anticoagulation. Pregnancy is not a contraindication, but does pose special management problems (see below). Patients receiving anticoagulants should never receive intramuscular injections as they are likely to develop a large haematoma at the site of injection.

6.2.1 Warfarin

Vitamin K is required for the synthesis of coagulation factors II (prothrombin), VII, IX and X. Warfarin and other similar oral anticoagulants such as nicoumalone are competitive antagonists of vitamin K and reduce the synthesis of these coagulation factors, resulting in prolongation of the prothrombin time. The drugs are well absorbed from the gastrointestinal tract, but their effect on coagulation is delayed for up to 24 h. Unlike heparin, these anticoagulants are not active in vitro.

The prothrombin time is the laboratory test used to monitor warfarin therapy. The patient sample is compared with a normal sample and the result is expressed as the international normalised ratio (INR). The therapeutic range of INR for a patient on warfarin is between 2.0 and 4.5, but target values for specific conditions have been recommended. A target INR of 2.5 is appropriate for venous thromboembolism, atrial fibrillation, cardiac mural thrombosis, cardiomyopathy and prior to cardioversion. A higher target INR of 3.5 is suitable for subjects with a mechanical heart valve (long-term anticoagulation is not required with a biological valve) and patients who have experienced recurrent venous thromboembolism.

The delay in onset of its anticoagulation effect means heparin should be given at the start of treatment with warfarin. The usual induction dose for adults is 10 mg warfarin daily for two successive days. Treatment with heparin should continue in parallel with oral anticoagulation for 5 days or until the patient's INR is more than 2.0 for two consecutive days, whichever is longer. The daily maintenance dose of warfarin in adults

is usually in the range from 3 to 9 mg daily. The INR should be checked daily or on alternate days initially, but the interval can then be extended to a maximum of 12 weeks for patients who are stable on long-term warfarin. Many drugs interact with warfarin through a variety of pharmacodynamic mechanisms. It is prudent to check the INR again 1 week after starting any new medication.

6.2.2 Reversal of Warfarin

The treatment of over-anticoagulated patients depends upon the INR and the clinical circumstances. Temporary suspension is often all that is required for minor bleeding problems. If the INR is eight or more and there are no significant bleeding complications, a small dose of 0.5–2.0 mg vitamin K may be given to reduce the INR. Correction of anticoagulation is not immediate and may be delayed for up to 24 h.

In the case of a major bleeding episode, such as intracranial haemorrhage or gastrointestinal bleeding, rapid and complete reversal is required. In such cases, coagulation factor concentrates known as prothrombin complex concentrates are the most effective treatment. These plasma-derived blood products contain coagulation factors II (prothrombin), VII, IX and X and can be given by rapid intravenous injection without regard to blood group. If they are not available, fresh frozen plasma should be infused. A reason for a prolonged INR should be sought (e.g. interaction with a new medication or confusion over the number of warfarin tablets to take). Haemorrhagic problems when the INR is in the therapeutic range may deserve investigation, particularly in the elderly, in order to exclude latent pathology. For example, haematuria may be associated with a tumour of the bladder and melaena may be the first manifestation of a peptic ulcer.

6.2.3 Direct-Acting Oral Anticoagulants (DOACs)

Although warfarin is still widely used, newer oral anticoagulant agents are increasingly being adopted for many clinical indications. Such drugs are referred to generically as direct-acting oral anticoagulants (DOACs) since they directly inhibit either thrombin in the case of dabigatran (‘Pradaxa’) or factor Xa in the case of rivaroxaban (‘Xarelto’) and apixaban (‘Eliquis’). The principal advantage of these drugs is that patients received a fixed daily dose and there is generally no need for any blood tests for monitoring. There are also far fewer drug interactions which have to be taken into consideration, by contrast with warfarin. These agents are widely used for the treatment and prevention of venous thromboembolism as well as in atrial fibrillation. They have not replaced warfarin for anticoagulation in children and subjects with valvular heart disease.

None of these new agents has been shown to be better than the others in head-to-head clinical trials. The dose of each DOAC is product specific, e.g. 20 mg rivaroxaban once daily is the usual maintenance dose for adults with venous thromboembolism whilst 5 mg twice daily is the usual dose of apixaban. All DOACs depend to a variable degree on renal excretion and dose adjustment will be required in patients with renal impairment. DOACs should not be used during pregnancy.

The half-lives of these drugs are all significantly shorter than warfarin: 12 h in the case of apixaban and 5–9 h in the case of rivaroxaban. Thus, mild bleeding episodes can usually be managed by suspending further treatment and applying pressure to the bleeding site. Idarucizumab (‘Praxbind’) is a humanised monoclonal antibody which is now licenced for reversal of the effect of dabigatran. At the time of writing, there is no licenced antidote for factor Xa inhibitors like apixaban and rivaroxaban, However, a specific antidote for these agents is at an advanced stage of clinical development. Andexanet alfa (‘AndexXa’) is a recombinant factor Xa inactive decoy protein which binds factor Xa inhibitors with a high affinity. The infusion of fresh frozen plasma or cryoprecipitate will not reverse the anticoagulant effect of any of these new agents. In the case of severe bleeds with factor Xa inhibitors, FEIBA (an activated prothrombin complex concentrate) and recombinant activated factor VII have been used ‘off label’.

6.2.4 Heparin

Heparin is a polymeric glycosaminoglycan, consisting of alternating chains of uronic acid and glucosamine. Originally identified in liver extracts (hence the name), it is extracted for commercial production from porcine mucosa. The anticoagulant properties of heparin reside in a pentasaccharide sequence, which binds avidly to antithrombin. This antithrombin–heparin complex behaves as a serine protease inhibitor, inactivating both thrombin and factor X. Heparin is highly negatively charged and has to be given by intravenous or subcutaneous injection as it is not absorbed effectively from the gastrointestinal tract. Unlike warfarin, it exerts an immediate anticoagulant effect and so it is also effective in vitro. It may be used as an anticoagulant for renal dialysis and in cardiopulmonary bypass machines. The anticoagulant effect of standard, unfractionated heparin may be monitored in the laboratory by measuring the activated partial thromboplastin time (APTT). The APTT should be maintained between 1.5 and 2.5 times the value of normal control plasma for full therapeutic anticoagulation with standard heparin.

Standard, unfractionated heparin consists of molecules with a molecular weight varying between 3000 and 35,000 Da (mean approximately 15,000 Da). Low-molecular-weight heparins (LMWH) are produced by the chemical degradation of standard, unfractionated heparin to produce smaller molecules with a mean molecular weight of approximately 5000 Da. These smaller molecules are more readily and predictably absorbed from sites of injection and have pharmacokinetic profiles, which offer almost complete bioavailability as well as a longer plasma half-life. By contrast, the bioavailability of standard heparin is only approximately 50%. Full anticoagulation can thus be easily achieved with once-daily subcutaneous injection, which a patient can be trained to give, so that they can be discharged from hospital to the community more quickly. Furthermore, the greater predictability of response means that it is generally not necessary to monitor treatment with laboratory tests, and the dose is based merely on the weight of the patient.

LMWHs have relatively little inhibitory effect against thrombin and so the APPT cannot be used for laboratory monitoring. Monitoring, if necessary, is by anti-factor Xa assay because they inactivate factor X. The dosage of these preparations is expressed in anti-Xa units. Examples of when anti-Xa monitoring may be indicated include monitoring of treatment in children, pregnancy, renal failure, obesity and patients with active bleeding. Samples for anti-Xa assays should be drawn 4 h after the last subcutaneous injection. As a rough guideline, the therapeutic range for full anticoagulation is 0.5–1.0 anti-Xa units/ml. A lower range of 0.2–0.4 anti-Xa units/ml is suitable for prophylactic treatment.

The various LMWHs available commercially should not be considered to be identical. The doses are based upon body weight, and many preparations come in prefilled syringes both to facilitate treatment and also to minimise errors in dosage. LMWHs cost considerably more than standard heparin but are becoming increasingly adopted for the initial treatment of venous thromboembolism where full anticoagulation is required. By contrast, the cheaper standard heparin preparations are still widely used for prophylaxis of venous thromboembolism in the setting of surgery, where full anticoagulation is not necessary.

6.2.5 Complications of Heparin Therapy

Most patients who require anticoagulation will only be exposed to heparin for a few days because it is used as short-term prophylaxis during an intervention or until full anticoagulation with warfarin is established. However, there are circumstances where prolonged anticoagulation with heparin may be required (e.g. prophylaxis against thromboembolism during pregnancy). Heparin-induced thrombocytopenia (HIT) is seen in approximately 5% of subjects who receive unfractionated heparin and around 0.5% of those who receive LMWH. This is due to the development of antibodies directed against a complex of heparin and platelet factor 4, which results in

platelet activation. HIT typically develops within 5–10 days of starting treatment with heparin, but it can develop much more quickly in individuals who have been previously exposed. Once the problem has been identified, heparin treatment should be suspended and argatroban, fondaparinux or bivalirudin used as alternative anticoagulants if systemic anticoagulation is still required. Platelets should not be transfused as this can trigger intravascular thrombosis due to explosive activation of the transfused platelets by the circulating antibodies. Patients with a history of heparin-induced thrombocytopenia should never be re-exposed to this anticoagulant. Osteoporosis is a recognised complication of long-term heparin administration, and this can result in vertebral fractures.

6.2.6 Reversal of Heparin

Protamine sulphate can be used to reverse the anticoagulant effect of heparin when bleeding occurs. Titration in vitro may be useful to determine the required dose: 1 mg of protamine will neutralise approximately 100 units of heparin: Protamine is given by slow intravenous infusion as rapid administration can result in hypotension, bradycardia and dyspnoea. Protamine does not inactivate LMWH as effectively as it does unfractionated heparin.

6.2.7 Thrombophilia

Haematologists generally place considerable importance on whether an episode of thromboembolism was provoked or unprovoked when deciding whether long-term anticoagulation is required. Where there is a clear underlying cause, such as surgery or a long-haul flight, patients will generally only receive anticoagulation for few months. By contrast, a patient who has an unprovoked episode of thromboembolism will be considered for long-term treatment and in certain circumstances, screening for abnormalities in blood, which predispose to venous thromboembolism (thrombophilia).

Congenital conditions associated with thrombophilia include deficiencies of antithrombin, protein C and protein S. Deficiencies of these three natural anticoagulants are relatively rare, each affecting perhaps 1 in 10,000 of the general population. Deficiency of any of these three natural anticoagulants is associated with a markedly increased risk of venous thromboembolism: approximately 60% of subjects with antithrombin deficiency will have experienced at least one episode by the age 60. Two other common mutations, which have been linked to thrombophilia, are the factor V Leiden mutation and G20210A mutation within the prothrombin gene. These are encountered in approximately 4% and 2% of the European population, respectively, but they are fortunately associated with a relatively low risk of thromboembolism. It is important to emphasise that none of these thrombophilic mutations is associated with an increased risk of arterial thrombosis, stroke or myocardial infarction.

By contrast, the ‘lupus anticoagulant’ is an acquired disorder, which is associated with both venous and arterial thrombosis, as well as placental infarction which can lead to recurrent foetal loss. It is associated with the appearance of antiphospholipid antibodies which interfere with the coagulation cascade.

It is not possible to carry out a full thrombophilia screen whilst a patient is anticoagulated and testing is best deferred until a patient comes off warfarin. Even then, it is not feasible to screen all patients with thromboses, but the following categories should be considered for screening:

- First thrombosis under the age of 40
- Recurrent venous thromboembolism
- Thrombosis at an unusual site
- Family history of venous thrombosis
- Recurrent foetal loss
- Unexplained prolongation of APTT

If an inherited abnormality is detected, relatives should also be screened. Asymptomatic individuals with a thrombophilic abnormality do not require long-term anticoagulation, but they will certainly require some form of prophylaxis to cover surgery or pregnancy. Most haematologists

would recommend long-term anticoagulation for an individual with an inherited thrombophilic defect who has experienced one or more thrombotic episodes.

Consideration should also be given to screening patients who present with an unprovoked deep vein thrombosis for occult cancer. This is a recommendation of the UK National Institute for Health and Care Excellence (NICE).

6.2.8 Anticoagulation in Special Situations

6.2.8.1 Pregnancy

Anticoagulation during pregnancy is not contraindicated, but does pose special risks. Examples where anticoagulation may be required in pregnancy include the treatment and prophylaxis of venous thromboembolic disease, prevention of foetal loss in patients with antiphospholipid antibodies ('lupus anticoagulant') and continued anticoagulation because of a mechanical prosthetic heart valve. The risks of anticoagulation in pregnancy include teratogenic effects of warfarin, risk of bleeding in the foetus (as warfarin crosses the placenta) and risk of formation of spinal canal haematoma with epidural anaesthesia. Administration of warfarin during the first 12 weeks of gestation is associated with a well-defined constellation of foetal abnormalities, including nasal hypoplasia and epiphyseal damage. All women patients of childbearing age must be counselled about these side effects.

The development of low-molecular-weight heparins has simplified the treatment of pregnant women. Women with prosthetic heart valves who are on long-term warfarin may switch to subcutaneous heparin during pregnancy. Unlike warfarin, heparin does not cross the placenta, but prolonged treatment with heparin can also be associated with loss of bone density and even vertebral fracture. There is general consensus that an acute deep vein thrombosis during pregnancy should be treated by full anticoagulation with heparin in the conventional way, and the introduction of low-molecular-weight heparin has certainly made this easier. Anticoagulation should also be extended for 6 weeks into the postpartum period, which is also associated with a high risk of thromboembolism.

6.2.8.2 Caval Filters

Inferior vena caval filters have an important role in selected patients where anticoagulation is contraindicated or when pulmonary embolism has occurred despite full anticoagulation. Suitable cases, for example, might include a patient recovering from neurosurgery who develops pulmonary embolism or a patient already on warfarin who experiences recurrent pulmonary embolism. Filters are small cones, which resemble miniature umbrellas with a tangle of fine mesh wire. Most filters are inserted on a temporary basis for a few days, but occasionally older types of filter models have been left permanently in place. The filter is usually inserted under local anaesthesia via the right femoral vein, as the alignment with the inferior vena cava is better on this side. Where thrombosis has extended proximally into the abdomen, insertion is carried out via neck veins and the filter is placed in the inferior vena cava above the level of the renal veins. This site is also recommended in pregnant women, to avoid compression of the filter by the gravid uterus, which could lead to damage or even penetration of the vessel wall.

6.2.9 Precautions Prior to Interventions in Anticoagulated Patients

A common problem is what precautions should be taken if patients on long-term anticoagulation require relatively simple intervention such as percutaneous arterial puncture for catheter angiography or lumbar puncture. An example of this situation is epidural or spinal anaesthesia during labour. In the past, some physicians were reluctant to offer this to patients receiving subcutaneous heparin because of concerns about subsequent haematoma formation in the spinal canal. In fact, the incidence of this complication is very low indeed: a European study estimated an incidence of 1 in 2,250,000.

Recommended guidelines for epidural analgesia in patients receiving heparin for thromboprophylaxis are as follows:

- Eight to twelve hours should elapse between a dose of LMWH and the sitting of an epidural catheter.
- No LMWH should be given for 2 h following the sitting of an epidural catheter.
- This interval should be increased to 8 h if the catheter placement was traumatic or involved multiple attempts.
- Catheter removal should be 8 h after the most recent dose of LMWH, or 2 h before the next dose is scheduled.
- Awareness of the significance of a change in neurological status should be maintained for 3 days after catheter removal.

These precautions could be considered prior to arterial puncture for elective catheter angiography.

6.3 Antiplatelet Therapy

Platelets are intimately involved in the development of arterial thrombosis. It has long been recognised that arterial thrombi are rich in platelets ('red thrombi'), whilst relatively few are seen in venous thrombi, which are typically paler ('white thrombi'). The pathophysiology of venous thromboembolism is primarily dependent upon activation of the coagulation cascade.

Arterial thrombosis occurs after injury to the vessel wall and leads to the formation of a 'platelet plug'. The process involves three stages: initial platelet adhesion at the site of injury, their activation and then resulting aggregation of additional platelets to form a platelet rich thrombus. Wall injury exposes von Willebrand factor and collagen to circulating blood to which some platelets adhere. These release thromboxane A2 and adenosine diphosphate (ADP), which recruits other platelets to join the forming clot. Once activated these in turn, initiate aggregation of the collection of platelets by linking fibrinogen receptors their membranes (i.e. glycoprotein IIb/IIIa receptors). These processes can be inhibited by aspirin, which inhibits thromboxane A2 synthesis in platelets and thienopyridine agents, which inhibit activation of the surface $P2Y_{12}$ receptor by ADP (Fig. 6.2).

6.3.1 Aspirin

Aspirin is the most widely used and least expensive antithrombotic agent. It is effective in all forms of occlusive arterial disease, including acute myocardial infarction and ischaemic stroke. By contrast, aspirin is of very limited benefit in preventing venous thrombosis. Aspirin (like other conventional nonsteroidal anti-inflammatory agents such as indomethacin and ibuprofen) inhibits both cyclooxygenase isoenzymes 1 and 2 (COX-1 and COX-2). COX-1 is responsible for the production of thromboxane A_2 in platelets as well as maintenance of the integrity of gastric mucosa. COX-2 is involved in the synthesis of prostacyclin by endothelial cells as well as mediators of inflammation (Fig. 6.2).

Antiplatelet agents are effective in preventing arterial thrombosis. Early trials of thrombolytic therapy in the setting of myocardial infarction showed that aspirin alone significantly reduces mortality. Aspirin also reduces the reinfarction rate after acute myocardial infarction and is effective in unstable angina. It is also of benefit in transient cerebral ischaemia, where symptoms are improved and the incidence of completed strokes reduced. It is generally not advisable to combine aspirin with oral anticoagulant therapy. Although the incidence of repeat thrombotic events may be reduced, this is at the expense of a significantly increased risk of haemorrhagic problems. Similarly, aspirin is contraindicated even as a simple analgesic in subjects with congenital bleeding disorders such as haemophilia, as the bleeding tendency is exacerbated. Specific inhibitors of COX-2 such as etoricoxib may be used as anti-inflammatory agents in patients receiving anticoagulants as these do not inhibit thromboxane A_2 synthesis by platelets. Paracetamol (acetaminophen) is also a safe and effective alternative in such cases, although it is less potent as an anti-inflammatory agent.

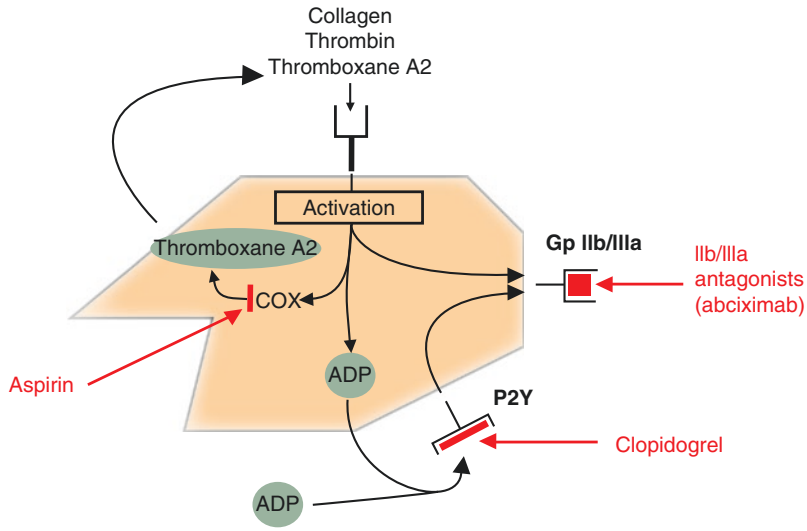

Fig. 6.2 Sites of action of antiplatelet drugs. Platelet activation is initiated by collagen, thrombin and thromboxane A2. Synthesis of thromboxane A2 by the enzyme cyclooxygenase is inhibited by aspirin. The action of ADP on the $P2Y_{12}$ receptor is blocked by clopidogrel, which prevents activation of the Gp IIb/IIIa surface receptor. This receptor initiates and maintains platelet aggregation. Abciximab is one of several drugs that can block this receptor to prevent aggregation. *COX* cyclooxygenase, *ADP* adenosine diphosphate, *Gp* cycloprotein receptor (Published with kind permission of © Henry Byrne, 2012. All rights reserved)

6.3.2 Thienopyridine Agents

Aspirin inhibits only one of the pathways of platelet activation and is a relatively weak antiplatelet agent. Clopidogrel ('Plavix') is an alternative and more powerful antiplatelet agent, which irreversibly inhibits the binding of ADP to the platelet $P2Y_{12}$ receptor. As platelets contain no nucleus and thus no DNA, platelet function is inhibited for the whole of its lifespan (which is around 10 days). Clopidogrel is widely used in cardiology for the treatment of acute coronary syndrome and prevention of thrombosis after placement of an endovascular stent. Dual antiplatelet therapy with aspirin and a PY_{12} inhibitor is standard after acute coronary syndromes. Clopidogrel may also be used in other indications as an alternative antiplatelet drug for patients who are intolerant of aspirin.

Clopidogrel is a prodrug, which is activated in the liver by cytochrome P450 enzymes, including CYP2C19. The concomitant administration of drugs which inhibit this enzyme (such as omeprazole, fluoxetine, fluconazole and carbamazepine) should be avoided. The active metabolite has an elimination half-life of about 8 h and acts by forming a disulphide bridge with the platelet ADP receptor. Platelet inhibition can be demonstrated as early as 2 h after a single dose of oral clopidogrel, but the onset of action is slow, so that a loading dose is usually administered at least 1 days prior to elective endovascular procedures in which platelet inhibition is needed, e.g. stent placement. The antiplatelet activity is even slower to wear off, so treatment should ideally be suspended at least 5 days before elective surgery or other invasive procedures.

The usual loading dose of clopidogrel is 300–600 mg and 75 mg once daily is the typical maintenance dose. The inhibitory effect on platelets is evident within 2–8 h of treatment. However, polymorphisms within the cytochrome enzymes, which metabolise clopidogrel, result in considerable variability in response. Approximately 14% of the population are poor metabolisers, at high risk of treatment failure and recurrence of

cardiovascular events. Special platelet function tests have been developed to identify patients who would benefit from higher dosing but these are not widely available in hospital laboratories. This phenomenon has led to the adoption of alternative thienopyridine drugs like prasugrel ('Efient'), dabigatran ('Pradaxa'), apixaban ('Eliquis') and ticagrelor ('Brilinta'). Prasugrel is metabolised more efficiently and has a faster onset of action than clopidogrel. Like clopidogrel, it binds irreversibly to $P2Y_{12}$ receptors but is more potent. A loading dose of 60 mg results in platelet inhibition after 30 min and the full inhibitory effect is seen after 2–4 h. Ticagrelor has the advantages of not requiring metabolic action and of binds reversibly to $P2Y_{12}$ receptors. The usual loading dose is 180 mg, followed by 90 mg twice daily. Its elimination time is 3–5 h, which is considerably shorter than the elimination time of 7–10 days seen with both clopidogrel and prasugrel. On the negative side, dyspnoea is experienced by 10–20% of patients who receive ticagrelor. Arrhythmias have also been associated with the use of this drug.

If a patient on antiplatelet therapy requires surgery or other invasive procedures, an assessment of both the thrombotic risk associated with stopping therapy and the bleeding risk associated with the procedure is required. A patient with a history of an ischaemic event such as myocardial infarction or occlusive stroke in the previous 4 months should be regarded as being at high risk. The six months after insertion of a coronary artery stent are also regarded as a high-risk period. If it is considered that the bleeding risk associated with the procedure is high, the procedure should be deferred for 5 days in the case of clopidogrel and ticagrelor and 7 days in the case of prasugrel. Guidelines permit neuraxial and peripheral nerve blocks whilst on aspirin but not in patients taking inhibitors. There is no specific antidote for these antiplatelet agents, though antidotes to ticagrelor (MEDI2452) and apixaban (andexanet alfa) are currently under test. General measures, which may help to stop excessive bleeding, include infusion of platelet concentrates or tranexamic acid.

6.3.3 Glycoprotein IIb/IIIa Receptor Inhibitors

The most potent inhibitors of platelet function are those which inhibit the binding of fibrinogen to glycoprotein IIb/IIIa receptors on platelets. These require intravenous injection and are not intended for use as long-term therapy:

- Abciximab ('ReoPro') is a chimeric human–murine monoclonal antibody Fab fragment, usually used together with aspirin and heparin in a number of interventions. It is particularly valuable for preventing cardiac ischaemia in patients undergoing percutaneous interventions (including angioplasty, atherectomy and stent placement or in subjects with unstable angina). The various major clinical trials in which it has been evaluated include EPIC, EPILOG, ADMIRAL and CAPTURE. It is the most widely used drug in this category. Abciximab has a plasma half-life of about 10 min and is usually given by intravenous infusion. The suggested initial bolus dose is 0.25 mg/kg by intravenous infusion, followed by 0.125 μg/kg/min thereafter for 12–24 h. No dose adjustment is required in cases of renal insufficiency. The bleeding time usually returns to normal some 12 h after discontinuation of an infusion, although some abnormality of platelet aggregation may be evident in the laboratory for up to 72 h after a stopping treatment. The principal adverse events seen after treatment are haemorrhagic and directly attributable to its antiplatelet effects. The most common type of bleeding due to abciximab is gastrointestinal haemorrhage. Thrombocytopenia is a rare but recognised side effect, observed in around 1–2% of treated patients. This may persist for 7–10 days after initial drug administration, and transfusion of platelets may be required.
- Eptifibatide ('Integrilin') is a synthetic cyclic heptapeptide, which also inhibits platelet glycoprotein IIb/IIIa receptors. It was specifically designed with an Arg-Gly-Asp (RGD)

sequence, which binds reversibly to platelets. The suggested loading bolus dose is 180 μg/kg, followed by 2 μg/kg/min thereafter for 72–96 h. Clearance is predominantly renal so dose adjustment will be required when the creatinine level is elevated. It has been evaluated in several major clinical trials, including PRIDE, PURSUIT and ESPRIT. A significant advantage of this agent is its short duration of action; platelet function will be restored 3–4 h after stopping treatment.

- Tirofiban ('Aggrastat') also belongs to this class. It is a synthetic non-peptide molecule. The suggested initial bolus dose is 0.4 μg/kg/min by infusion over 30 min, followed by 0.1 μg/kg/min thereafter for 48–96 h. The dose will need to be reduced if there is renal insufficiency. The major clinical trials in which this product was evaluated include RESTORE, TARGET and PRISM.

6.4 Thrombolytic Therapy

Anticoagulation with heparin serves merely to prevent extension of thrombus caused by sludging of the circulation. A number of agents are available which dissolve clots through activation of the fibrinolytic system. Thrombolytic agents are agents which promote the conversion of circulating, inert plasminogen to plasmin, which has a high affinity for fibrin and which degrades it to small fibrin degradation products (FDPs). The ideal thrombolytic agent would specifically target fibrin-bound plasminogen, but none is entirely fibrin-specific. Administration of all thrombolytic agents invariably results in consumption of plasma fibrinogen to a variable degree, which results in hypocoagulability. Clinical contraindications for thrombolytic therapy are largely self-evident and include disorders such as active peptic ulceration, severe hypertension, pre-existing bleeding disorder, previous history of haemorrhagic stroke and trauma and surgery in the previous 2 weeks. Thrombolytic agents should not be used during pregnancy, but normal menstrual bleeding is not a contraindication.

The most widely used thrombolytic agents are streptokinase, alteplase, reteplase and tenecteplase.

- Streptokinase is a bacterial protein which forms a complex with plasminogen, which in turn activates other plasminogen molecules. Streptokinase was the first agent to be used for thrombolysis after its value was demonstrated in a major study of myocardial infarction in 1986. Streptokinase infusion is associated with transient hypotension or allergic reactions in a significant minority of patients. Administration is often followed by the appearance of antistreptokinase antibodies, which may persist for some months and significantly limit efficacy with repeat administration. Despite these limitations, streptokinase is still widely used for thrombolysis due to its low cost.
- Alteplase is a recombinant version of naturally occurring tissue plasminogen activator (t-PA). It binds more specifically to fibrin than streptokinase and has a shorter half-life of around 5 min. It is now the most widely used agent for thrombolysis and is the only thrombolytic agent currently licenced for use in acute ischaemic stroke. It does not generate antibody formation and so treatment can be repeated, if necessary. Allergic-type reactions to alteplase are very rare. Reteplase is a second-generation recombinant t-PA composed of 355 of the 527 amino acids of native t-PA. It does not bind to fibrin as tightly as native t-PA or alteplase, which allows it to penetrate a clot better. It is claimed that this product is therefore able to dissolve clots faster than other agents. Reteplase has a half-life of around 15 min and is easier to administer than alteplase as continuous infusion is not required. In the setting of myocardial infarction, reteplase is administered as two boluses of 10 U given 30 min apart. Like alteplase, reteplase can be used repeatedly.
- Tenecteplase is a recombinant fibrin-specific plasminogen activator that is derived from native t-PA by modifications at three sites of the protein structure. It binds to the fibrin component of the thrombus and selectively

converts thrombus-bound plasminogen to plasmin, which in turn degrades the fibrin matrix of the thrombus. Tenecteplase has a higher fibrin specificity and greater resistance to inactivation by its endogenous inhibitor (PAI-1) compared to native t-PA.

6.4.1 Clinical Applications of Thrombolytic Therapy

The clinical indications for thrombolytic therapy include myocardial infarction, acute ischaemic stroke, pulmonary embolism and extensive proximal deep vein thrombosis. In the setting of myocardial infarction and acute ischaemic stroke, the choice of thrombolytic agent is of secondary importance and the speed with which treatment is given is what matters. Thrombolytic drugs should be given within 6 h of the onset of symptoms, although the best results are seen when treatment is initiated within 1 h. There is no evidence that catheter-directed administration of thrombolytic therapy after myocardial infarction offers any advantage over intravenous infusion. Indeed, intravenous infusion offers the prospect of faster treatment and also avoids the risks of bleeding at the site of catheter insertion. Aspirin has an important place as adjunctive therapy. It should be given to all patients with suspected myocardial infarction (unless there is a clear contraindication), preferably before administration of the thrombolytic agent. After the acute event, aspirin should be continued for life at a daily dose of at least 75 mg.

Systemic thrombolysis is a widely accepted treatment for pulmonary embolism in patients with persistent hypotension (e.g. systolic blood pressure < 90 mmHg for 15 min) and who are not at high risk of bleeding. Catheter-directed thrombolysis may be used in patients at increased risk of bleeding as a lower dose of a thrombolytic agent is infused directly into the pulmonary artery via a catheter. Catheter-directed thrombolysis is also effective in lowering pulmonary arterial pressure and improving right ventricular function. However, several randomised controlled clinical trials have failed to show that thrombolysis for pulmonary embolism is followed by a sustained improvement in either morbidity or mortality.

The great majority of patients with deep vein thrombosis in the lower limb will benefit from treatment with conventional anticoagulants. Selected patients may benefit from catheter-directed thrombolysis, and a recent Cochrane review concluded that this reduces the risk of development of post-phlebitic syndrome by approximately one-third.

Catheter-directed lysis is also suitable for restoration of patency after peripheral arterial occlusion. However, this can be a challenge as a clot has often been present for some time before clinical presentation. The clot may be partially organised and thus relatively resistant to dissolution. Local intra-arterial administration achieves a higher local level of thrombolytic agent and permits angiography to monitor dissolution of the thrombi. A typical regimen would involve the administration of a 5-mg bolus of alteplase directly into the thrombus, followed by continued intra-arterial infusion at 0.5–1 mg/h for up to 24 h.

The use of thrombolysis in acute ischaemic stroke has grown considerably in recent years: Almost 90% of all strokes are ischaemic in origin. Alteplase is the only drug approved for use in acute ischaemic stroke and the usual dose is 0.9 mg/kg infused over 60 min. Clinical outcome is best in patients who receive treatment within 3 h of onset of symptoms but stroke units aim for a maximum ‘door-to-needle’ time of 60 min. Advanced age and hypertension are poor prognostic indicators.

Thrombolysis is also used to treat cerebral venous sinus thrombosis but only after anticoagulation therapy (i.e. heparin) has failed to control or arrest symptoms. Catheter-directed lysis is performed to restore patency of major intracranial sinuses and usually delivered as an infusion. As for peripheral arterial thrombosis, alteplase is infused at 0.5–1 mg/h to dissolve clot and the effect is monitored by repeated angiography. Local instillation of thrombolytic agents may also be used to dissolve clots in occluded venous access devices.

6.4.2 Complications of Thrombolytic Therapy

Haemorrhage is the major specific complication of thrombolytic therapy. The most common problem is bleeding at the site of infusion, and it is important to monitor the site periodically. Pressure at the site will often be sufficient to control bleeding. Arterial or venous puncture should be avoided if possible. If puncture of a major vein is considered essential (e.g. for insertion of a pacemaker or Swan–Ganz catheter), an antecubital, femoral or even jugular vein should be used in preference to a subclavian vein. Profuse melaena may be the first symptom of an unsuspected peptic ulcer or other lesion in the gastrointestinal tract. The incidence of intracranial haemorrhage after thrombolytic therapy for myocardial infarction is approximately 0.5–1.0% but significantly higher at around 6% in cases of ischaemic stroke. In the setting of myocardial infarction, reperfusion arrhythmias may be observed soon after thrombolysis and rupture of the heart or other organs may occur due to vigorous resuscitation.

6.4.3 Reversal of Fibrinolysis

There is no specific antagonist or antidote for thrombolytic agents. The basic principles for reversal of thrombolytic agents include:

- Stop infusion of the thrombolytic agent.
- Interrupt administration of other anticoagulants (e.g. heparin).
- Inhibit plasmin activity.
- Replenish levels of fibrinogen and other coagulation factors.

The half-life of streptokinase is approximately 20–30 min whilst that of t-PA is shorter at only 5 min. However, plasminogen activators such as alteplase which are more effectively bound to fibrin may still continue to exert a local lytic effect. Replenishing levels of fibrinogen can be performed with tranexamic acid, which contains a high level of fibrinogen and inhibits fibrinolysis by inhibiting the binding of plasminogen to fibrin. Fresh frozen plasma (15–25 ml/kg) is also a source of both fibrinogen and other coagulation factors. It also contains plasminogen, and so it is prudent to give the tranexamic acid first. Protamine may be given to neutralise the effect of any circulating heparin. Laboratory monitoring of thrombolytic therapy is generally not required, but the advice of a haematologist is recommended if bleeding occurs.

6.5 Prevention of Venous Thromboembolism

Deep vein thrombosis is a well-recognised postoperative complication of many types of surgery, as well as medical conditions associated with prolonged immobility. Thrombosis in the proximal veins of the leg (popliteal and femoral veins) may result in pulmonary embolism. Deep vein thrombosis may also result in chronic venous insufficiency and ulceration in the longer term. Venous thromboembolism is an important cause of death in hospital. All inpatients (and especially those scheduled for surgery) should be assessed for clinical risk factors, as preventive measures may be taken:

Risk factors for venous thromboembolism in hospital inpatients:

- Age > 60 years
- Previous venous thromboembolism
- Malignant disease
- Hip or knee replacement or hip fracture
- Surgery involving pelvis or lower limb
- Pregnancy
- Hormone replacement therapy or oestrogen-containing oral contraceptive
- Obesity (BMI > 30 kg/m^2)
- Thrombophilia
- Significantly reduced mobility for 3 days or more
- Varicose veins with phlebitis

A number of agents may be used for prophylaxis in high-risk patients, including established agents like LMWH or newer drugs such as dabigatran and rivaroxaban. In patients at lower risk, or high-risk patients where the risk of bleeding is felt to be high, mechanical options such as compression hosiery or foot pumps may be used. Early mobilisation after surgery should be encouraged.

Cranial Anastomoses and Dangerous Vascular Connections

7

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Preamble

Dangerous vessels can be defined as vessels unsafe to embolise because their loss risks causing unwanted tissue damage. In previous tutorials, the cranial arterial anatomy has been described in terms of which structures a particular artery supplies. Leaving aside the question of individual anatomical variability for a moment, this means that we can precisely plan embolisation procedures knowing which tissue will be devascularised when a particular artery is occluded. Unfortunately, we all know that this is not the reality. Our ability to predict the consequences of embolisation is imprecise and may fail, because some tissues are supplied by two or more pedicles (i.e. dual supply) or are able to recruit collateral blood supply sufficiently quickly to survive. We therefore have to include an assessment of possible sources of collateral blood supply in our treatment planning.

If we extend this uncertainty to include unwanted tissue damage to nontarget tissue because embolisation agents can spread, we then have to additionally consider the potential effects of embolisation on adjacent structures and their blood supply. This makes the analysis more complex and increases our reliance on an understanding of vascular anatomy. In the head and neck, the

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particular challenge is to anticipate extracranial (EC) to intracranial (IC) anastomoses in order to identify neural tissues 'at risk' when an arterial pedicle is embolised.

Anastomosis, between the occipital artery (OA) and the vertebral artery (VA), following internal carotid artery (ICA) thrombosis was described in 1952 by Richter [1], but the circulation's ability to support tissues after occlusion of large arteries by expanding collateral vessels has been known since the eighteenth century when John Hunter[1] [2] developed an operation to ligate the popliteal artery to treat syphilitic aneurysms. In the cerebral circulation, the principle was exploited by neurosurgeons in the nineteenth and twentieth centuries to treat cranial aneurysms by carotid ligation [3]. It has since been recognised that some of the vessels involved represent embryonic supplies to the neural crest (external carotid artery (ECA) to ICA) or metameric remnants (ECA to VA). Some of these connections exist without an apparent purpose. In other words, they can be demonstrated in the absence of a causative pathology, and the frequency of their demonstration depends on the sophistication of the imaging technique employed.

External to internal cranial anastomoses can therefore be considered as pathological or nonpathological. In the pathological situation, increased blood flow to a tumour or arteriovenous shunt may recruit collateral blood supply via an EC–IC (or IC–EC) anastomosis. In the nonpathological situation (i.e. anastomosis in the absence of an inducing pathology), they usually represent anatomical variants or persistent primitive vessels. These may be connections which embolisation, by altering blood flow patterns, appears to reveal. In either case, they are potentially routes for the spread of embolisation particles or liquids to nontarget structures. Knowing their sites and being able to recognise them on angiograms is therefore a skill needed to avoid complications caused by unwanted infarction of tissues in adjacent territories [4].

[1]John Hunter (1728–1793) a Scottish surgeon and anatomist who worked in London and was an early advocate of careful observation and scientific method in surgery. He is considered the 'father' of modern surgery in the UK.

This tutorial aims to consolidate the anatomical knowledge of the first four chapters and prepare the student for performing embolisation procedures in the head and neck region. It will use the same abbreviations for the major head and neck arteries used in previous tutorials. At first, the plethora of transcranial potential connections appears daunting to the novice, but remember embolisation is commonly performed in the extracranial circulation and complications are relatively rare. Knowledge remains our shield.

7.1 Anterior External Carotid Artery: Superficial Connections

The classic anatomical sequential description of ECA branches (from proximal to distal) is not helpful in identifying their territorial borders because branches directed posteriorly may arise adjacent to an anterior directed branch and that is the limit of their proximity. The face receives a superficial blood supply from the facial artery (FA) and a deep supply from the internal maxillary artery (IMA). The boundary tissues between these two arterial territories are the sites of anastomoses and duplication of supply. Therefore, the territories will be considered as superficial and deep groups, though the reader will appreciate that the distinction is arbitrary. Furthermore, for description the territories and their supplying arteries will be separated into those supplying anterior or posterior tissues. To separate them into anterior or posterior groups, the ECA branch arteries will be described as running either anterior or posterior to an arbitrary line extending from the ECA origin to the proximal portion of the superficial temporal artery (STA). This is a purely descriptive division, which the paths of some branches straddle (e.g. STA and ascending pharyngeal artery (APA)) and others cross (e.g. middle meningeal artery (MMA)). The superficial groups are less likely to involve dangerous EC–IC anastomoses, but the extensive anastomoses between arteries supplying the face need to be interpreted for treatment planning to avoid collateral tissue damage. EC–IC connections dominate when considering treatments in arteries of the deep anterior group of ECA branches.

7.1.1 Anastomotic Branches of the Face and Pharynx

Anastomoses in these regions involve the superficial anterior branches of ECA. The major component of the system is the FA. The anterior branches involved are:

(a) Superior thyroid artery: This artery supplies the larynx and thyroid gland. A branch (inferior hyoid artery) contributes to the sublingual anastomosis and gives a branch to anastomose with the suprahyoid artery (br. of lingual artery) around the hyoid. It also anastomoses with the opposite side via another branch (cricothyroid artery). Its terminal branches to the thyroid gland anastomose with the inferior thyroid artery. The infrahyoid artery is thus a potential bypass route between FA and lingual artery.
(b) Lingual artery: The lingual artery territory lies between the vascular territories of the FA and superior thyroid arteries. Its proximal branches take part in anastomoses with these vessels in the sublingual and suprahyoid regions. It supplies the sublingual gland, floor of mouth and the tongue. It gives the suprahyoid artery, which anastomoses with the superior thyroid artery and the sublingual artery which takes part in the sublingual anastomosis around the sublingual gland.
(c) Facial artery (FA): The long course of the FA, from its origin medial to the stylohyoid muscle and the posterior belly of digastric muscle to its termination medial to the orbit, borders several territories of ECA and ophthalmic artery (OphA) branches.

Its named branches that border and anastomose with adjacent arterial territories are:

1. Ascending palatine artery to the pharyngeal anastomosis.
2. Submental and smaller submandibular arteries to the sublingual anastomosis.
3. Middle mental artery, which anastomoses with the mental artery over the chin. The mental artery is a terminal branch of the inferior alveolar artery (br. of IMA).
4. Branches to masseter and buccinator muscles, which anastomose with their counterparts arising from the IMA over a wide area of the cheek region in the jugal anastomosis.
5. Cutaneous branches, which anastomose with the inferior orbital artery (br. of IMA) and branches of the transverse facial artery (br. of the superficial temporal artery (STA)) on the cheek and the zygomatico-orbital artery (br. of STA) as part of the superficial orbital anastomosis.
6. Angular artery, which anastomoses with the dorsal nasal artery and supratrochlear artery (extra-orbital terminal branches of OphA) in the periorbital anastomosis. It may also anastomose with the inferior palpebral artery (br. of OphA) though the latter usually anastomoses with the infraorbital artery (br. of IMA).
7. Alar artery, which supplies the nostrils, anastomoses with the contralateral FA and an extensive network of arteries over the nose. It can take part in the nasal (mucosal) anastomosis with terminal branches of the sphenopalatine artery (br. of IMA).

(d) Internal maxillary artery (IMA): The IMA supplies the temporal and pterygoid regions of the face, paranasal sinuses, jaw and nose as well as giving transosseous intracranial branches to supply dura of the anterior cranium. It is the larger terminal branch of the ECA. Its territory of supply can be divided into an extracranial territory (which borders the territories of the FA, ascending pharyngeal artery (APA), STA and OphA) and an intracranial territory (which is the site of potentially dangerous anastomoses with the ICA).

The branches of the IMA that take part in anastomoses with adjacent anterior arterial territories will be described. These boundary connections are potential routes for collateral support in the event of a proximal arterial occlusion and pathways for inadvertent spread of embolic agents during endovascular treatments.

1. Inferior alveolar artery anastomoses, via its mental branch, with the FA territory over the chin.

2. Masseter and buccal arteries to the muscles and deep soft tissue of the cheek take part in the jugal anastomosis with FA branches to these muscles and with branches of the transverse facial artery (br. of STA).
3. Lesser descending palatine artery takes part in the pharyngeal anastomosis. It supplies the soft palate and oropharynx and anastomoses principally with the middle pharyngeal artery (br. of APA).
4. Infraorbital artery takes part in the cutaneous periorbital anastomosis with cutaneous branches of FA, the transverse facial artery (br. of STA) and extra-orbital branches of the OphA (as part of the superficial orbital anastomosis).
5. Sphenopalatine artery and greater descending palatine artery are distal branches of IMA that supply the nasal mucosa and take part in the nasal anastomosis with the alar and superior labial arteries (br. of FA).

(e) Ascending pharyngeal artery (APA): The APA contribute to the pharyngeal anastomosis via the middle and superior pharyngeal arteries. These also take part in anastomoses with deep branches of the IMA, which will be described in more detail below.

(f) Superficial temporal artery (STA): The smaller terminal branch of the ECA, it supplies skin and superficial muscles of the face and anterior scalp. It anastomoses with its counterpart across the midline and borders the territory of FA anteriorly and posterior auricular artery (PA) and OA posteriorly. It provides a route for collateral supply to the distal IMA and FA if either of these vessels is occluded.

Its anastomoses are:

1. Transverse facial artery or transverse artery of face, which supplies a large area of the upper face. It anastomoses with terminal branches of the infraorbital artery (br. of IMA) and with the adjacent zygomatico-orbital artery, taking part in the superficial orbital anastomosis. Inferiorly it anastomoses with branches of FA, over the cheek and with the buccal and masseter branches in the jugal anastomosis (brs. of FA and IMA).
2. Zygomatico-orbital artery supplies the lateral margin of the orbit and contributes to the superficial orbital anastomosis.
3. Posterior deep temporal artery supplies the temporalis muscle and anastomoses with the middle deep temporal artery (br. of IMA).
4. Anterior auricular artery supplies the superficial tissue of the anterior pinna and anastomoses with PA.
5. Frontal temporal and parietal temporal arteries supply the anterior scalp and anastomose anteriorly with the superficial orbital anastomosis (OphA, FA, IMA) and posteriorly with OA and PA. They also anastomose across the midline.

7.2 Anastomotic Zones of the Face and Pharynx

In Fig. 7.1, five areas of extracranial anastomosis are shown with the arteries that contribute to them. These anastomotic zones are:

7.2.1 Sublingual Anastomosis

The sublingual anastomosis is centred at the base of tongue and around the sublingual gland. Its dominant components are the submental artery (br. of FA), the sublingual artery (br. of lingual artery) and short submandibular arteries (br. of FA). The anastomosis links the submental artery with the infrahyoid artery (br. of superior thyroid artery) and a more anterior anastomosis between its mental branch and branches of the inferior alveolar artery.

7.2.2 Pharyngeal Anastomosis

There is an extensive potential anastomotic network in the mucosa of the pharynx which involves the ascending palatine artery (br. of FA), the middle pharyngeal artery (br. of APA) and lesser descending palatine artery (br. of IMA) in the oro-

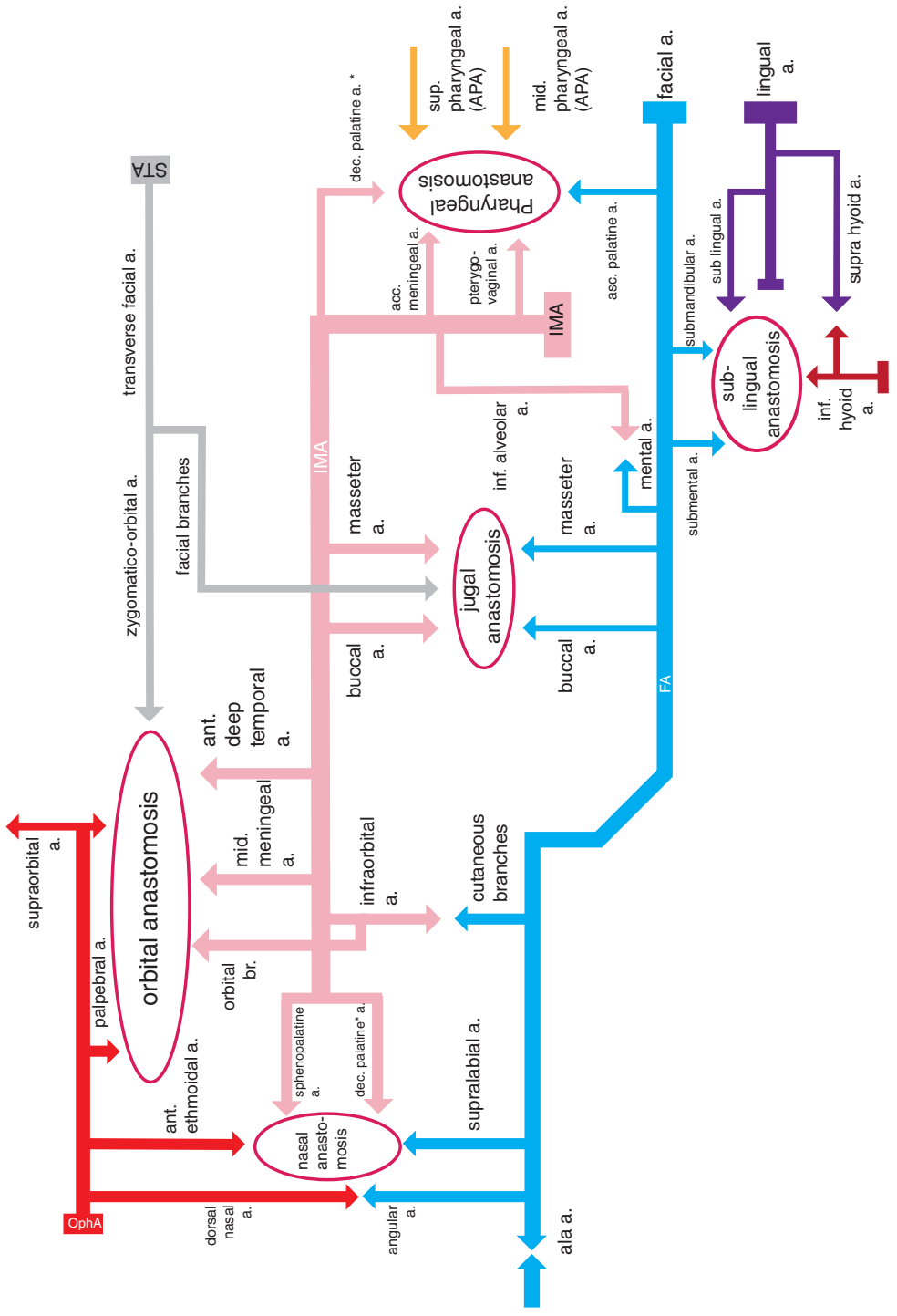

Fig. 7.1 Diagram of anastomoses involving branches of the facial artery. *Branches of the descending palatine artery (Published with kind permission of © Henry Byrne, 2017. All rights reserved)

pharynx, and the superior pharyngeal artery (br. of APA), accessory meningeal artery (br. of IMA) and the pterygovaginal artery (br. of IMA) in the nasopharynx. It reflects the rich blood supply to the mucosa, particularly of the soft palate and uvula. Thus, this region is a potential site of EC–IC anastomosis since the accessory meningeal artery has branches that anastomose with the ICA.

7.2.3 Jugal Anastomosis

The branches of FA to masseter and buccinator muscles reciprocate their territory of supply with the branches of the IMA to the same muscles. Thus, masseter branches of the FA anastomose with masseter branches of the IMA and the transverse facial artery (br. of STA). More superficial, and anterior to these vessels on the lateral angiogram, are anastomoses between the buccal arteries of the IMA and muscular branches of the FA. This is a potential route for collaterals to develop in the event of occlusion of IMA, FA and ECA.

7.2.4 Orbital (Superficial) Anastomosis

The orbit is a point where several cutaneous arterial territories come together. The FA supplies the medial orbital margin, via the angular artery and borders the territories of the supratrochlear and dorsal nasal arteries (branches of OphA). These two arteries supply the superomedial orbital margin. The superior orbital margin is supplied by the supratrochlear and supraorbital arteries. The latter usually arises as a separate branch of the distal OphA to supply scalp of the forehead in a shared territory with the supratrochlear artery. This borders the territory of the frontal branch of the STA. The inferior orbital margin is supplied by the inferior orbital artery (br. of IMA) and borders the cutaneous territory of the FA on the cheek and the lateral margin by the zygomaticoorbital artery (br. of STA). The inferior and superior palpebral arteries are branches of the OphA and anastomose with the infraorbital artery (br. of IMA), frontal branch of the STA and the angular artery (br. of FA) at the margins of the orbit.

7.2.5 Nasal Anastomosis

The principal source of blood supply to the nasal mucosa is from the sphenopalatine artery (br. of IMA) and descending palatine artery (br. of IMA). These arteries anastomose with nasal branches of the alar artery and the superior labial artery (brs. of FA) inferiorly and with the anterior and posterior ethmoidal arteries (br. of OphA) superiorly. The anterior ethmoidal artery supplies the upper nasal septum.

7.3 Anterior External Carotid Artery: Deep Connections

The deeper structures supplied by the anterior branches of ECA involve branches arising from the IMA and APA. Since the majority of the APA branches are directed posteriorly, the connections described in this section involve principally branches of IMA. Arteries that supply dura, cranial nerves and the organs of the special senses are sites of anastomoses between the ECA and ICA, and therefore particularly dangerous EC–IC connections. They generally enter the cranium through foramen in the skull base (though blood flow in both directions occurs). As above, the description will concentrate on areas where groups of vessels anastomose.

7.3.1 Anastomotic Branches of the Anterior Skull Base

The anterior ECA branches supplying the deep structures of the face and anterior skull base are:

(a) Internal maxillary artery (IMA): The branches of the IMA that take part in ECA–ICA anastomoses are those with an intracranial territory or which border arteries with an intracranial territory. These are the anterior tympanic artery, MMA, accessory meningeal artery, artery of the Vidian canal, pterygovaginal artery, artery of the foramen rotundum, infraorbital artery, anterior deep temporal artery and sphenopalatine artery:

1. Anterior tympanic artery supplies the middle ear, which it reaches through the petrotympanic fissure accompanied by the chorda tympani. It takes part in the anastomosis of the middle ear with a potential EC–IC connection via the caroticotympanic trunk (CCT) of the ICA.
2. Middle meningeal artery (MMA) is a major route for several real and potential anastomoses with OphA and ICA. Its territory of supply borders that of the OphA via several branches. Sphenoid branches run along the greater wing of the sphenoid to supply dura and may enter the orbit via the superior orbital fissure to anastomose with a recurrent branch of the OphA. The terminal territory of its frontal branch supplies the anterior falx and may anastomose with the anterior ethmoidal artery (br. of OphA). In addition, a not infrequent variant is the branch to the lacrimal gland (that enters the lateral orbit through Hyrtl's[2] canal) termed the meningo-orbital or meningolacrimal artery (depending on the extent of its territory) and creates a potential collateral route to the OphA. Anastomoses to ICA involve its parasellar and petrous dural branches. Soon after MMA passes through the foramen spinosum, it gives the superior tympanic artery to supply the middle ear, which will be considered with posterior anastomoses below. In addition to this important branch, the proximal intracranial MMA gives a cavernous branch to supply dura in the parasellar and petrosal regions which potentially anastomose with branches of the inferolateral trunk (ILT) (br. of ICA) and the lateral clival artery (br. of meningohypophyseal trunk (MHT)).
3. Accessory meningeal artery gives dural branches in the middle cranial fossa which contribute to the parasellar dural anastomosis with branches of the ILT (br. of ICA) and to the anastomosis around the Eustachian tube with the mandibular artery (br. of mandibulo-Vidian trunk (MVT)), the pterygovaginal artery (br. of IMA) and the Eustachian branch of the APA.
4. Artery of the pterygoid canal or Vidian artery connects the IMA with the mandibular artery and takes part in the Eustachian anastomosis. It may supply mucosa of the oropharynx. Its origin is variable either arising from the IMA or from the mandibular artery and therefore the MVT of ICA. As a result, its dominant direction of supply varies between EC–IC and IC–EC.
5. Artery of the foramen rotundum runs through the foramen rotundum with the maxillary division of the trigeminal nerve (V^2) and takes part in the parasellar anastomosis with branches of the ILT (br. of ICA), MMA, accessory meningeal artery and recurrent ophthalmic artery (br. of OphA).
6. Pterygovaginal artery supplies the Eustachian tube and takes part in the Eustachian anastomosis.
7. Infraorbital artery anastomoses with the recurrent ophthalmic artery (OphA) which returns through the inferior orbital fissure and takes part in the parasellar dural anastomosis with MMA, accessory meningeal artery and artery of the foramen rotundum (brs. of IMA) and the ILT (br. of ICA). It also gives the inferomedial muscular artery or a series of small branches which supply the lacrimal sac, nasolacrimal duct and extraocular muscles and anastomose with branches of the OphA. After emerging from the infraorbital foramen, it anastomoses with the inferior palpebral artery and dorsal nasal artery (brs. of OphA) and cutaneous branches of FA in the inferior part of the periorbital anastomosis.
8. Anterior deep temporal artery runs on the surface of the skull, under the temporalis muscle in parallel with the middle deep temporal artery (br. of IMA) and posterior deep temporal artery (br. of STA). Unlike them, it gives a branch (the lateral

[2]Josef Hyrtl (1810–1894) an Austrian anatomist and renowned teacher at the University of Vienna.

muscular artery) that enters the lateral orbit and anastomoses with the lacrimal artery (OphA). This branch either enters the orbit via the inferior orbital fissure or directly through the lateral orbital wall. In the latter case, it is then called the transmalar branch.

9. Sphenopalatine artery supplies most of the nasal mucosa and anastomoses with branches of the anterior ethmoidal artery (br. of OphA) in the roof of the nose, with the septal branch of the descending palatine (br. of IMA) and branches of FA at the nostrils.

(b) Ascending pharyngeal artery (APA): The APA is the smallest and usually first branch of ECA. It divides early in its course into anterior and posterior divisions. The latter with the inferior tympanic artery will be considered in the next section. The anterior division gives the inferior (a small artery usually unrecognised on angiography), middle and superior pharyngeal arteries. These supply the mucosa of the pharynx and soft palate, and the middle and superior constrictor muscles. Both middle pharyngeal artery and superior pharyngeal artery take part in the pharyngeal anastomoses with branches of the ascending palatine artery (br. of FA). In the superior pharynx, the superior pharyngeal artery anastomoses with the accessory meningeal artery (br. of IMA) and both take part in the Eustachian anastomosis with the pterygovaginal artery (br. of IMA) and mandibular artery (br. of MVT). These proximities are potential EC–IC connections via the accessory meningeal artery and branches of ILT and Eustachian branches via the mandibular artery and MVT.

7.4 Anastomotic Zones of the Anterior Skull Base

There are three main anterior zones of extracranial anastomosis between the deep branches of the IMA and ICA or OphA. They comprise the Eustachian, orbital and cavernous (parasellar) anastomoses (Fig. 7.2). The source of arteries supplying these regions has been described above but the regional arterial supply to each anastomosis will be covered again to emphasise potential routes of dangerous vascular connections in each zone.

7.4.1 Eustachian Anastomosis

The Eustachian or pharyngotympanic tube is a remnant of the 1st pharyngeal (branchial) pouch. It lies in the angle between the petrous and tympanic parts of the temporal bone. Its anterior cartilaginous portion pieces the pharyngobasilar fascia above the superior constrictor and opens into the nasopharynx. It is the focus for an anastomotic network between IMA, APA branches and the mandibular artery.

The arteries involved are:

1. The accessory meningeal artery (br. of IMA) and a Eustachian branch of the superior pharyngeal artery (br. of APA) supply the Eustachian mucosa at its pharyngeal opening.
2. The pterygovaginal artery arises from the distal IMA and anastomoses with the inferomedial branch of the accessory meningeal artery at the meatus of the Eustachian tube.
3. Artery of the pterygoid canal (Vidian artery) (br. of IMA or ICA) supplies the cartilaginous part of the pharyngotympanic tube and may give branches to mucosa at its opening.
4. The mandibular artery (1st pharyngeal arch artery) arises from the MVT of the ICA but does not always persist after birth. If present, it arises from the MVT in the petrous portion of the ICA, divides in the foramen lacerum into a branch, which enters the pterygoid canal and anastomoses with the artery of the pterygoid canal (Vidian artery) and gives an inferior branch (termed the mandibular artery) which takes part in the anastomoses around the Eustachian tube opening.

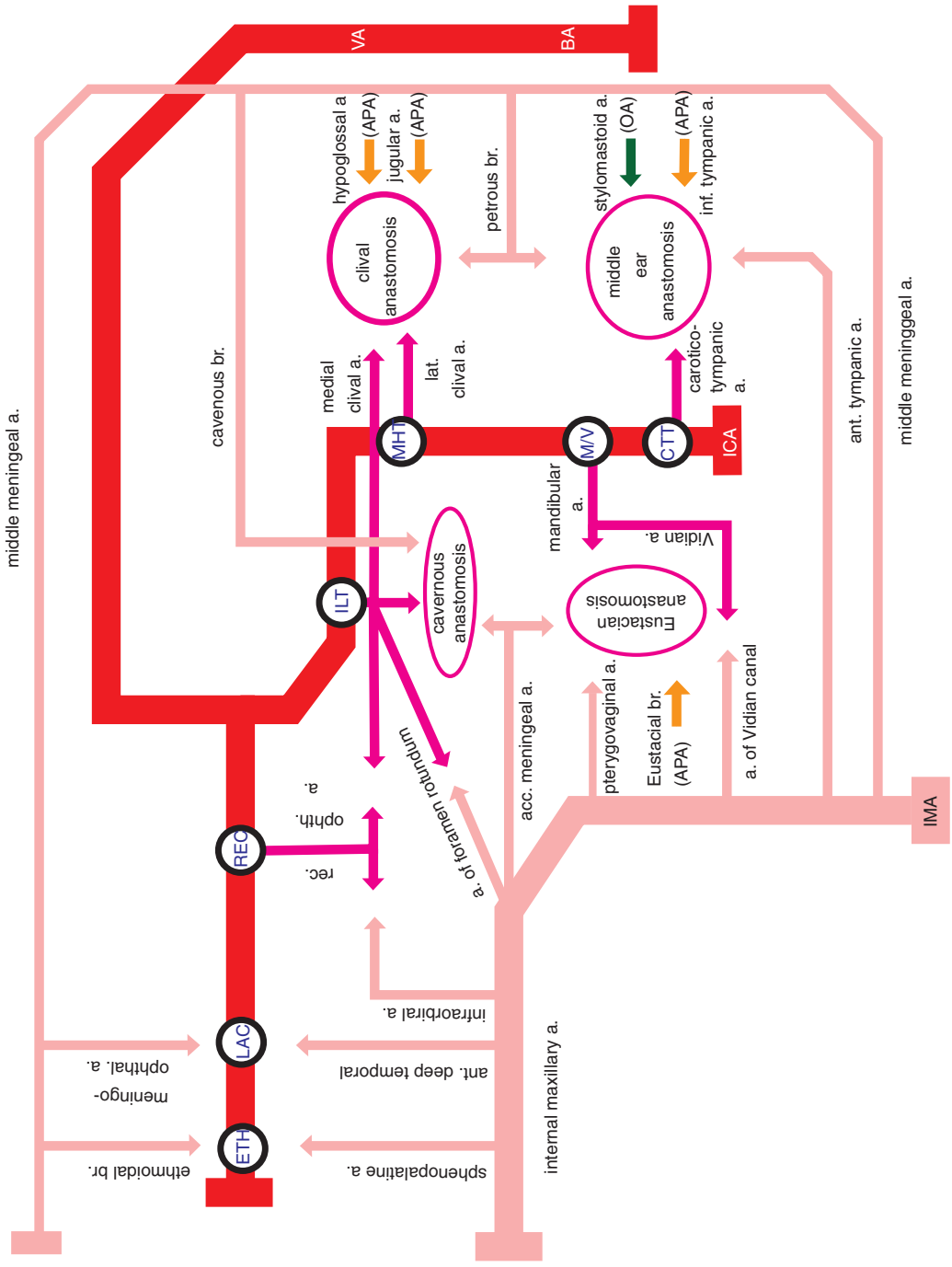

Fig. 7.2 Diagram of EC–IC anastomoses involving branches of the IMA (Published with kind permission of © Henry Byrne, 2017. All rights reserved)

7.4.2 Orbital Anastomosis

The principal artery supplying structures found within the orbit is the OphA. Additional marginal supply arteries or anatomical variants are potential routes for collateral supply, EC–IC connections and the inadvertent spread of embolic agents to the retina.

The arteries involved are:

1. The inferomedial muscular artery (br. of infraorbital artery) and the lateral muscular artery (br. of anterior deep temporal artery) supply structures of the medial and lateral orbit, respectively, and anastomose with the OphA territory. In the event of ICA or OphA narrowing or occlusion, a collateral blood supply is more likely to involve the anterior deep temporal artery (lateral) route than the infraorbital artery route.
2. The anterior branch of the ILT passes through the superior orbital fissure to anastomose with the recurrent ophthalmic artery (br. of OphA).
3. The MMA may contribute to the orbital anastomosis via the meningo-orbital artery (or meningolacrimal artery). This artery, if present, passes through Hyrtl's canal and subsumes the territory of the lacrimal branch of OphA. It is the most common of the possible anatomical variants that reflect the embryonic origin of the MMA territory from the hyoid/stapedial system and a dangerous connection between the OphA and the IMA. The existence of a possible intraorbital supply when embolising in the MMA should always be anticipated.
4. The anterior and posterior ethmoidal arteries (brs. of OphA) supply the ethmoid sinuses. The anterior ethmoidal artery gives a branch to the falx cerebri through the foramen caecum and both supply the roof of the nasal cavity and may give branches through the cribriform plate to the anterior fossa dura. Their territories thus border the sphenopalatine artery (br. of IMA) territory and the anterior territory of MMA. These anastomoses via the ethmoidal arteries thus constitute potential routes for ECA–OphA–ICA connections. Rarely, the frontopolar artery (br. of ACA) supplies the anterior falx via a transpial branch and thus creates an additional ECA–ICA connection.

7.4.3 Cavernous (Parasellar) Anastomosis

In the parasellar region, the ILT and meningohypophyseal trunk (MHT) arise from the ICA (see Tutorial 2, Fig. 2.1). They give branches, which anastomose with branches of IMA and APA. The posterior branches of the ILT are closely related to the dural branches of the MHT. The ILT is the key to understanding the real and potential anastomoses that exist in the cavernous region.

The arteries involved are:

1. The anterior branch of the ILT, which anastomoses with the recurrent ophthalmic artery (br. of OphA), the artery of the foramen rotundum (br. of IMA) and the accessory meningeal artery (br. of IMA). The accessory meningeal artery may be directed to the posterior branch of the ILT. The anastomosis with the artery of the foramen rotundum is a common collateral route when the ICA is occluded proximal to the ILT.
2. The posterior branch of the ILT anastomoses with the cavernous branch of the MMA and gives the recurrent artery of the foramen lacerum. The recurrent artery of the foramen lacerum usually arises from ILT but may arise from the MHT. It anastomoses with the superior pharyngeal artery (br. of APA) around the foramen lacerum.

7.5 Posterior External Carotid Artery: Connections

The central position of the APA is the key to understanding the blood supply to the skull base and the territorial boundaries in this region. The posterior ECA branches involved are the APA, PA and OA. Their territories border each other and those of the VA and upper spinal arteries. Crossing the arbitrary anterior–posterior separation, used to describe the distribution and connections of ECA branches in this tutorial, are posterior branches of STA, which supply scalp and posterior branches of the MMA, which supply cranial nerves and dura.

7.5.1 Anastomotic Branches of the Posterior Cranium

The major components of this system are the APA and OA and their territories border those of the cervical branches of the subclavian and vertebral arteries in the neck. Thus EC–IC connections may involve both ICA and VA. The latter connections will be considered in more detail in the next section.

(a) Ascending pharyngeal artery (APA)

The importance of the anatomy and relationships of APA branches to understanding cranial vascular connections has been emphasised previously. This is evident in their participation in so many anastomotic zones of the skull base. Its course typically divides into two main divisions in the neck with additional branches from the pre-division main trunk (Fig.7.3).

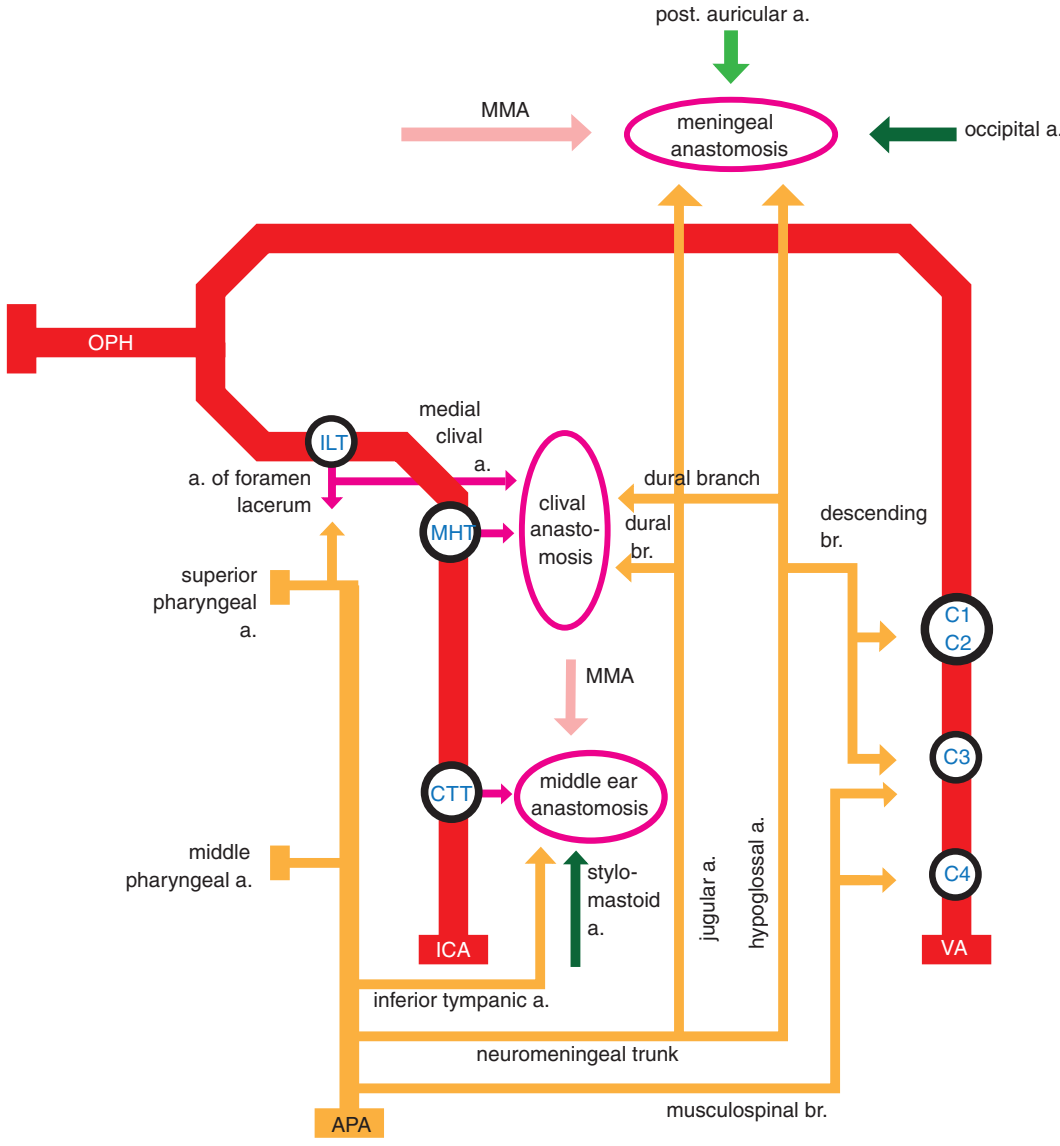

Fig. 7.3 Anastomoses involving branches of the ascending pharyngeal artery (Published with kind permission of © Henry Byrne, 2017. All rights reserved)

1. Anterior division gives small (inferior pharyngeal branches) to the hypopharynx and to prevertebral muscles in the neck. Its main branches are the middle pharyngeal and superior pharyngeal arteries which take part in the pharyngeal anastomoses with the ascending palatine artery (br. of FA) lesser descending palatine artery (br. of IMA), pterygovaginal artery (br. of IMA) and accessory meningeal artery (br. of IMA).
2. Musculospinal arteries arise from the main trunk or posterior division and anastomose with branches of the VA directly or via branches of the ascending cervical artery at the C2 and C3 levels. Direct muscular branches of the ECA or ICA (rarely) may take part in this anastomosis.
3. Posterior division or neuromeningeal trunk gives the hypoglossal artery and jugular arteries and is important for this tutorial because it supplies inferior cranial nerves, dura of the posterior fossa and is a potential route of EC–ICs connections.
   - Hypoglossal artery supplies the XIIth cranial nerve and gives dural branches to the posterior fossa meninges and the upper spine. Dural branches may include the posterior meningeal artery and the artery to the falx cerebelli. It anastomoses with medial clival artery (br. of ICA) and takes part in the clival anastomosis. The prevertebral artery (i.e. descending branch) contributes to the odontoid arcade at the C1/C2 levels and anastomose with the C3 branch of the vertebral artery.
   - Jugular artery supplies the dura and cranial nerves VIth, IXth, Xth and XIth. It anastomoses with the lateral clival artery (br. of ICA) and also takes part in the clival anastomosis. It reciprocates its meningeal territory with the hypoglossal artery and branches of the OA, PA and MMA.
4. Inferior tympanic artery

This branch of the APA trunk or its posterior division takes part in the middle ear anastomosis along with the stylomastoid artery (br. of OA), superior tympanic artery (br. of MMA), anterior tympanic artery (br. of IMA) and caroticotympanic artery arising from the caroticotympanic trunk (CTT) (br. of ICA).

(b) Occipital artery (OA)

The OA is the principal artery of the posterior cranium (Fig. 7.6). It supplies a mix of intracranial, spinal and extracranial territories. Its branches supply the scalp, parts of the occipital and temporal bones, intracranial dura, VIIth cranial nerve, upper cervical muscles and spinal nerves. Its territory borders those of the APA, VA, MMA, STA, PA and the contralateral OA. It anastomoses with branches of these arteries and with the deep cervical artery and the anterior inferior cerebellar artery (AICA) (br. of VA).

Its proximal portion, with muscular and transmastoid intracranial branches, should always be regarded as particularly dangerous sites of EC–IC anastomoses which connect the OA to the VA, spinal arteries and ICA. They are potential collateral routes in the event of occlusion of the VA.

Its branches are:

1. Stylomastoid artery supplies the VIIth cranial nerve and takes part in the middle ear anastomosis. It can arise from the OA or PA.
2. Muscular branches take part in upper cervical anastomoses from C1 to C4 with the muscular branches of VA, musculospinal branches of the APA and the deep cervical artery. They also participate in the odontoid arcade with the hypoglossal artery (br. of APA) and VA and give spinal radicular branches at C1 and C2, which anastomose with spinal branches of VA (see below).
3. Transmastoid artery is usually a single large branch, which enters the cranium through a transmastoid foramen and takes part in anastomoses with the jugular artery (br. of APA) around the jugular foramen and with AICA (br. of VA) in the subarcuate arcade at the internal acoustic meatus. It anastomoses with the adjacent dural arterial territories of the posterior meningeal artery (br. of VA or OA or PICA) and the artery of the falx cerebelli (br. of VA or OA or PICA). There may be multiple smaller branches which penetrate the mastoid bone to supply dura.

4. The terminal cutaneous branches anastomose with branches of the STA, PA and contralateral OA. The scalp territory borders are not rigid and their extent is reciprocal with these 'neighbours'.

(c) Posterior auricular artery (PA)

This artery is primarily a scalp vessel whose territory lies between those of the OA and STA. It supplies muscular branches to sternocleidomastoid muscle along with OA, but these are not a recognised focus for a connecting anastomosis. The site where it does take part in anastomoses with potential consequences during embolisation procedures are:

1. Stylomastoid artery arises slightly more commonly from the PA than OA. It contributes to the middle ear anastomosis with the petrous branch of the middle meningeal artery, inferior tympanic artery (br. of APA), anterior tympanic artery (br. of IMA) and caroticotympanic artery (br. of CTT).
2. Cutaneous anastomoses with the OA and STA. On the scalp, there are extensive anastomoses between the lateral branch of the OA and distal branches of the PA. The territories of these vessels are related and in balance with those of the anterior auricular branch(es) of the STA. The OA and PA are so intimately related that they may arise from the external carotid artery as a common trunk.
3. Superficial temporal artery supplies the skin and superficial muscles of the anterior scalp and borders the territory of PA and OA; this is a potential site of anastomosis and collateral supply.

7.6 Anastomotic Zones of the Posterior Skull Base

There are two main posterior zones of anastomosis in the skull base, which involve the posterior branches of ECA and are potential sites for EC–IC anastomoses. These comprise the clival and middle ear anastomoses. Additional connections between the posterior ECA branches occur in dura and scalp of the posterior cranium. These will be described in the next section.

7.6.1 Clival Anastomosis (Fig. 7.4)

A series of dural arteries anastomoses occur over the clivus reflecting its central position in the skull base. These anastomoses connect arteries of the parasellar region (brs. ICA and ECA) with arteries entering the cranium through the hypoglossal foramen, jugular foramen and foramen magnum (brs, of APA and VA).

The arteries involved are:

(a) Meningohypophyseal Trunk (MHT) is a trunk vessel arising from the proximal section of the cavernous portion of the ICA. It supplies the pituitary via the posterior inferior hypophyseal artery (PIHA), the tentorium (marginal and basal tentorial arteries) and dura over the clivus and petrous margin of the posterior fossa. Its branches involved in the clival anastomosis are:
   1. Basal tentorial artery supplies tentorial dura. It runs along the petrous attachment and borders the territory of the petrosquamous artery (br. of MMA).
   2. Lateral clival artery whose inferomedial branch anastomoses with the jugular artery (br. of APA) in the jugular fossa.
   3. Medial clival artery usual arises from PIHA, rather than directly from MHT. It is a dural artery with a territory medial to the lateral clival artery and is sometimes called the dorsal meningeal artery. It descends along the clivus and anastomoses with the clival branches of the hypoglossal artery (br. of APA) and with branches of the small anterior meningeal artery (br. of VA). This is a particularly dangerous EC–IC route that should be considered when performing embolisation in the APA.

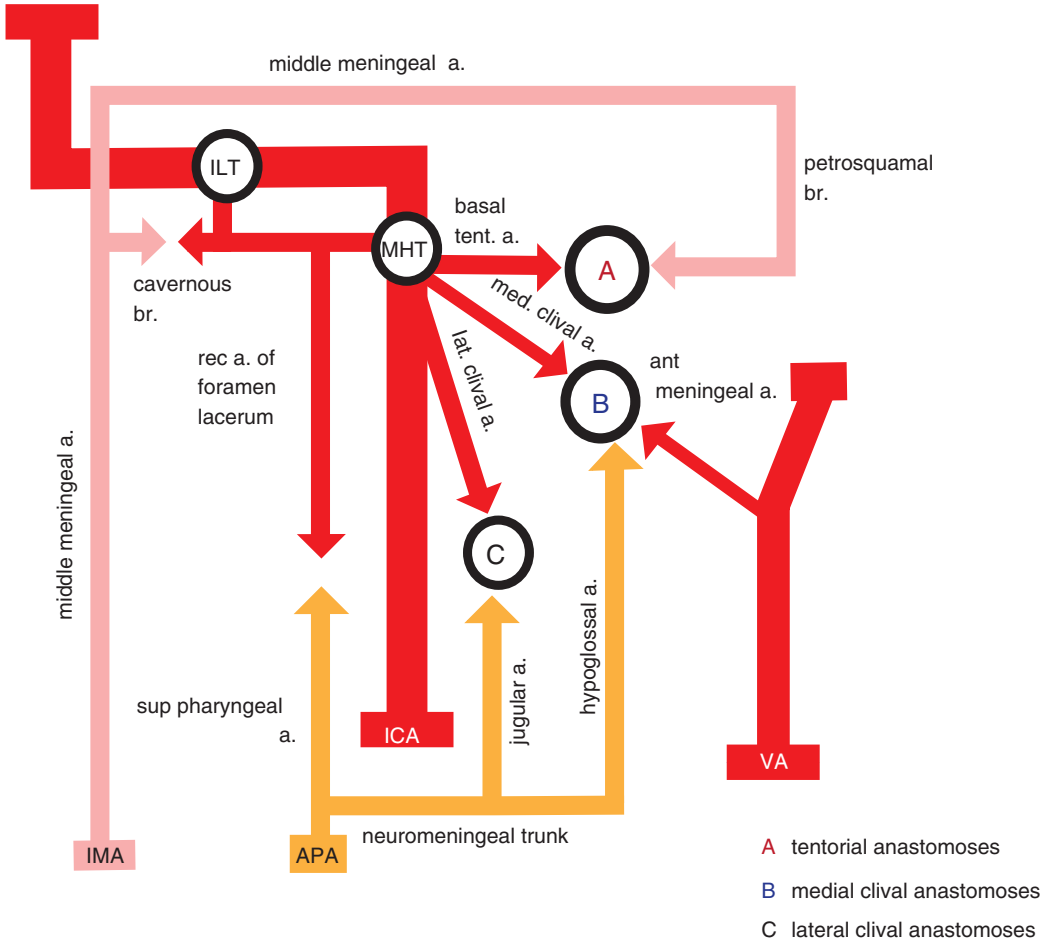

Fig. 7.4 Clival anastomosis (Published with kind permission of © Henry Byrne, 2017. All rights reserved)

(b) Anterior meningeal artery supplies the inferior clivus and also takes part in the anastomoses forming the odontoid arterial arcade.
(c) Petrosquamous and petrosal branches of MMA arise soon after it passes through the foramen spinosum and supply dura of the medial middle temporal fossa and petrous apex. Their territories border that of the basal tentorial artery and may extend to the margins of clivus.
(d) Hypoglossal and jugular arteries (brs. of APA), as described above.

7.6.2 Middle Ear Anastomosis (Fig. 7.5)

The inner ear is supplied by intracranial branches of ICA, IMA, APA and OA. Anastomoses, within the middle ear cavity, are potential collateral routes that link branches of the IMA, ICA and distal ECA. The arterial arcade that follows the facial nerve (VIIth) cranial nerve links the stylomastoid artery (br. of OA or PA) with the anterior tympanic artery (br. of IMA) and the superior tympanic artery (br. of MMA). The superior tympanic artery and the inferior tympanic artery (br.

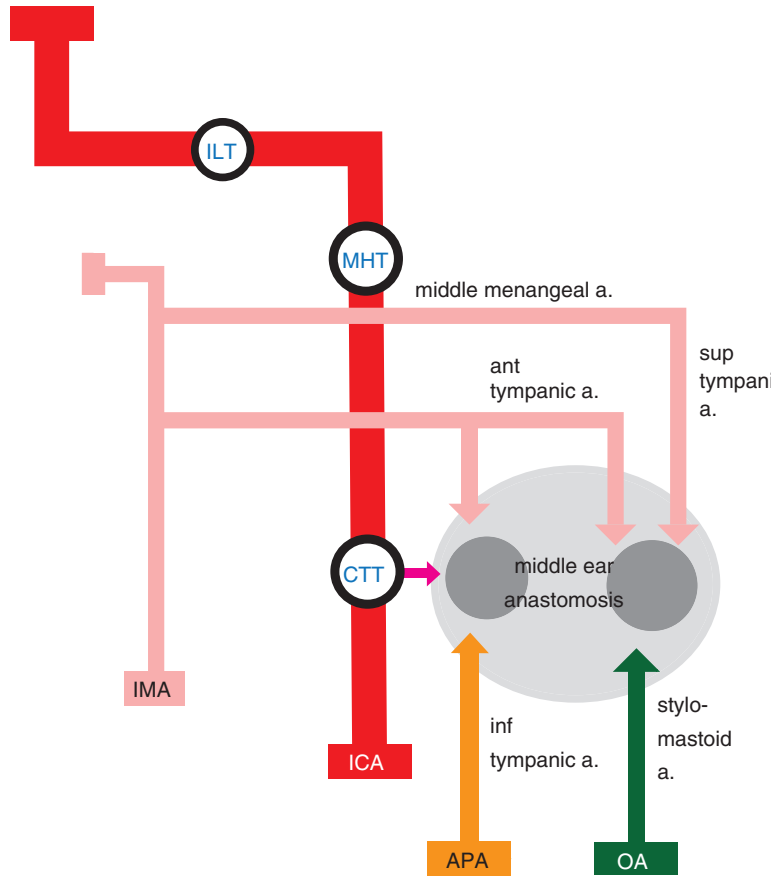

Fig. 7.5 Middle ear anastomosis (Published with kind permission of © Henry Byrne, 2017. All rights reserved)

of APA) anastomose and the inferior tympanic artery also anastomoses with branches of the CCT.

The arteries involved are:

(a) Stylomastoid artery, which may arise from either OA or PA and enter the middle ear via the stylomastoid foramen to run alongside the postganglionic VIIth cranial nerve.
(b) Superior tympanic artery, which arises from the petrous branch of the MMA in the middle fossa. It enters the tympanic cavity with the greater superficial petrosal nerve, supplies the geniculate ganglion of the VIIth nerve and anastomoses with the stylomastoid artery.
(c) Anterior tympanic artery, which arises from the first section of IMA and runs posteriorly from its origin to enter the inner ear cavity with the chorda tympani (parasympathetic to salivary glands) through the petrotympanic fissure. It anastomoses with the stylomastoid artery around the VIIth nerve and with the caroticotympanic artery (br. of CCT).
(d) The inferior tympanic artery (br. of APA) enters the middle ear from below, via the inferior tympanic canaliculus accompanied by Jacobson's nerve (tympanic branch of IXth cranial nerve), and it branches to anastomose with branches of the superior tympanic artery (br. of MMA) and those arising from the CCT (brs. of ICA). The CCT lies at the junction of the ascending and horizontal petrous ICA, i.e. proximal to the foramen lacerum. It gives the caroticotympanic artery but this may exist as small branches, which are described as running posteriorly into the middle ear but, in my experience, are invisible on angiography.

(e) The labyrinthine artery (br. of basilar artery or the anterior inferior cerebellar artery) supplies the internal acoustic canal and contributes to the subarcuate dural anastomosis. It does not normally contribute to the anastomosis in the tympanic cavity but collateral flow between branches of the labyrinthine artery and the arteries supplying the tympanic cavity has been described.

7.7 Anastomotic Zones of the Craniocervical Junction and Cervical Spine

Anastomoses between ECA branches, the VA and upper cervical spinal arteries in the craniocervical junction region are to be expected because of its embryological development from somites around the rostral neural tube. These occur in the upper cervical spine and posterior cranium and involve OA, APA, the vertebrobasilar system and cervical spinal arteries. The OA is most prominent of ECA branches contributing to these potentially dangerous EC–IC anastomoses (see Fig. 7.6). Its distal branches contribute to anastomoses between scalp arteries of the posterior cranium, i.e. with PA and across the midline. These extra-cranial anastomoses have been described above.

The anastomoses are:

7.7.1 The Odontoid Arcade

This is a dural anastomosis in the anterior upper cervical canal at the C1/C2 level. The development of APA occurred as part of the C3 metamere. A reflection of this ancestry is a descending branch of the hypoglossal artery (br. of APA), which anastomoses with the C3 spinal artery (br. of VA) (see Tutorial 2, Fig. 2.9). It gives a series of prevertebral branch arteries that ramify around the dens forming an arcade of vessels, before anastomosing with an ascending branch of the C3 spinal artery (see below). The C1 and C2 spinal arteries (brs. of VA) and muscular branches of the OA also contribute to this system and thus a connection is established at C1 and C2 between the VA, OA and APA. The term odontoid arcade is loosely used for these anastomoses (see Tutorial 2, Fig. 2.4).

7.7.2 C3 and C4 Anastomoses

At the C3 level, the descending branch of the hypoglossal artery and musculospinal artery branches of the APA anastomose with the C3 spinal arteries. This anastomosis includes radicular branches from the deep cervical artery (br. of costocervical trunk) and descending muscular branches of the OA. The muscular branches of OA can anastomose with the deep cervical artery at any level between C1 and C4. This represents a potential posterior (post-transverse) collateral route to the ECA if the common carotid artery is occluded. The ascending cervical artery and a musculospinal artery (br. of APA) supply the C4 space. Thus, this also represents a potential collateral route anterior to the spine (pre-transverse) to the ECA from the subclavian artery.

7.7.3 Posterior Fossa Dural Anastomoses

The dura of the posterior fossa, remote from the clivus, is supplied by branches of the jugular artery (br. of APA), transmastoid branch(es) of OA, petrossal branch of MMA, subarcuate artery (br. of AICA), posterior meningeal artery (br. of VA or OA or hypoglossal artery) and the artery of the falx cerebelli (br. of VA or OA or PICA). The boundaries of the dural territories of these arteries are sites of anastomosis and create connections between ECA and VA branches. They are particularly dangerous connections during embolisation of extra-cranial lesions supplied by APA or OA.

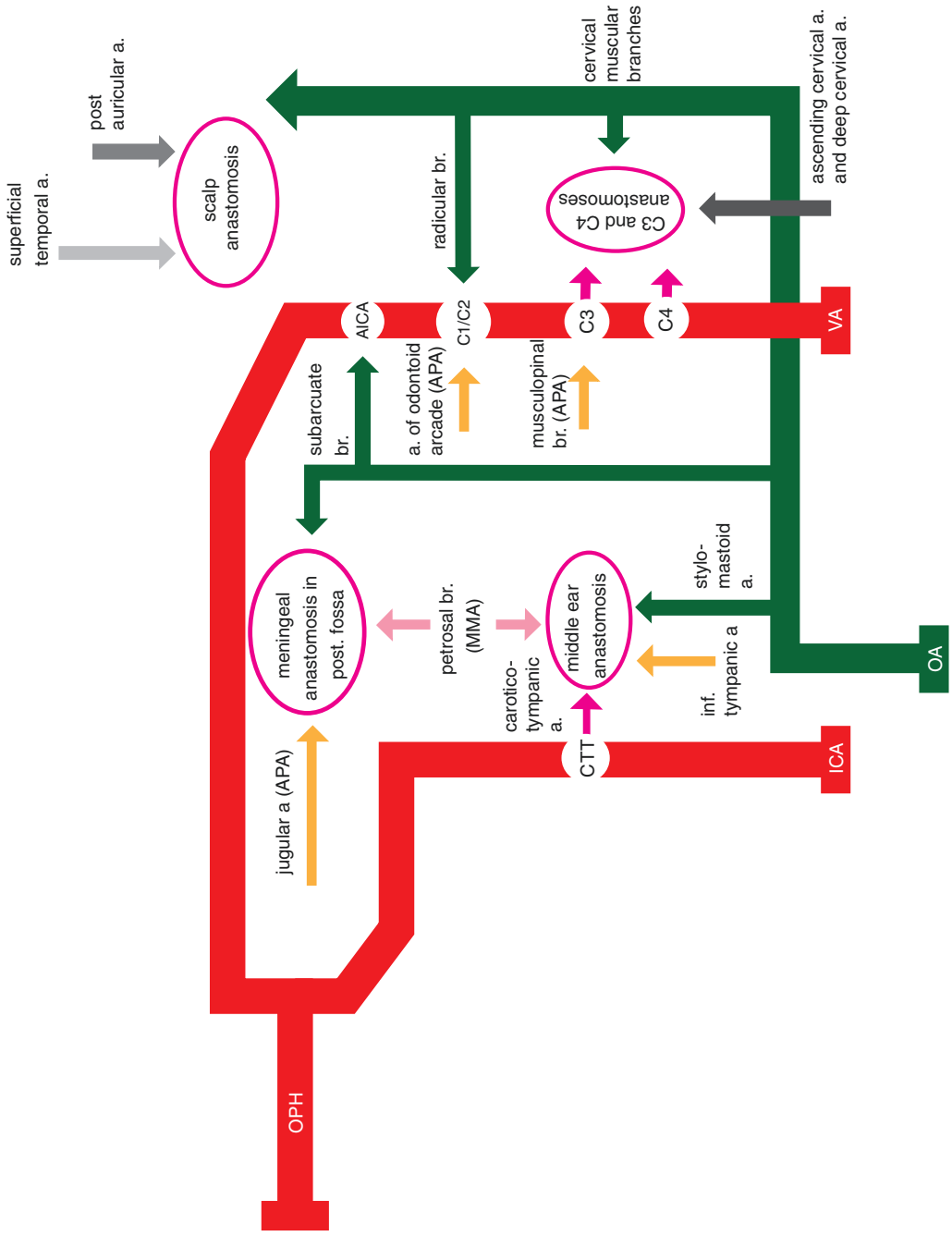

Fig. 7.6 Anastomoses involving branches of the occipital artery (Published with kind permission of © Henry Byrne, 2017. All rights reserved)

7.8 Arterial Supply to the Cranial Nerves

The cranial nerves are clearly included in the definition of tissues 'at risk' during embolisation in the branches of the ECA. Their blood supply is worth considering separately, partially to provide a referable resource to use when planning a procedure and partially to encourage the student to think beyond the reciprocal nature of arterial territories to the tissues they supply (Table 7.1).

In practice, the cranial nerves most vulnerable to damage during embolisations are the optic nerve, the oculomotor nerve, the facial nerve and the bulbar nerves (IXth, Xth, XIth) [5]. The arteries supplying cranial nerves have been discussed above. Thus, embolisation in MMA and APA are more likely to lead to cranial nerve palsies due to inadvertent migration of particles or liquid agents than embolisation in FA. The use of n-butyl cyanoacrylate has long been regarded as increasing the risk of cranial nerve damage since its relatively low viscosity combined with injections under pressure (i.e. wedged-catheter technique) makes spread to the small arterioles of the vasa nervorum more likely. This may or may not be true of higher viscosity liquid agents, such as cellulose acetate polymers. Similarly, very small particles are liable to penetrate to smaller vessels than larger particles, i.e. >150 μm, and their use is not advised in arteries whose branches are likely to supply cranial nerves.

Table 7.1 Cranial nerves and their arterial blood supply

Cranial nerve	Major source	Branch artery	Sub-branches
Ist	ICA	ACA	
IInd	ICA	OphA	
IIIrd	BA/ICA/ECA	MHT/ILT/OphA/IMA	Superior cerebellar
			Thalamoperforating a.
			Marginal tentorial a.
			Acc. meningeal a.
IVth	BA/ICA/ECA	ILT/MHT	Marginal tentorial a.
Vth	BA/ICA/ECA	ILT/MHT/APA/IMA	MMA (ganglion)
			Carotid br. APA (ganglion)
			a. foramen rotundum (V^2)
			Infraorbital a. (V^2)
			Acc meningeal a. (V^3)
			Inf. alveolar (V^3)
VIth	BA/ICA/ECA	ILT/MHT/APA	Acc meningeal a.
			Jugular br.
VIIth	BA/ECA	PA or OA/APA/IMA	MMA (petrous br.)
			Inf. tympanic a.
			Stylomastoid artery
VIIIth	BA/ECA	AICA	Internal auditory a.
IXth	ECA	APA	Jugular br.
Xth	ECA	APA	Jugular br.
XIth	ECA	APA	Jugular br. (cranial part)
			m. spinal br. (spinal part)
			C3 spinal br. (spinal part)
XIIth	ECA	APA/IMA	Hypoglossal br.
			Lingual a.

ICA internal carotid artery, *ACA* anterior cerebral artery, *OphA* Ophthalmic artery, *BA* basilar artery, *MHT* Meningohypophyseal trunk, *ECA* external carotid artery, *ILT* inferolateral trunk, *APA* Ascending pharyngeal artery, *IMA* Internal maxillary artery, *OA* Occipital artery, *MMA* Middle meningeal artery, *AICA* anterior inferior cerebellar artery

Finally, it is worth emphasising that positioning catheters well distal to potentially dangerous branch arteries, such as the petrous branch of MMA which arises within 2–5 mm of the foramen spinosum, are simple precautions. A trained therapist with a knowledge of standard anatomy is able to plan embolisations accordingly. What has not been covered in the descriptions in this tutorial are the many described anatomical variants of the standard anatomy that usually can be traced back to the developmental embryology of the cranial vessels. The potential existence of such variants should always be in the mind of the endovascular therapist and sought during study of angiograms when planning treatments.

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Arterial Aneurysms

8

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Preamble

Treatment of intracranial aneurysms is still the biggest challenge in endovascular neurosurgery. In the last 20 years, it has become the major component of most services. The concept of preventing aneurysm growth and rupture by inducing sac thrombosis appears simple but can be extremely complex. The size of the subject means it is covered in two tutorials during the Oxford Course, the first discussing aetiology, histopathology and epidemiology and the second covering clinical symptoms, signs and treatments. They are combined in this chapter.

Intracranial aneurysms are very rarely found in animals and can be considered an evolutionary flaw in man's development. The brain, sitting in its bath of cerebrospinal fluid, receives its blood supply from vessels that have to cross the subarachnoid space. The frequency of aneurysms in this special environment is probably due to the lack of support from surrounding soft tissues and a relatively thin vessel wall together with the haemodynamic stress of the high blood flow demand of the brain. The liability to aneurysm formation in arteries of the circle of Willis

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due to this design is amplified by our longevity compared to other mammals. The implication of this theory is that we all will develop aneurysms given sufficient time. Clearly this is not the situation, so the question is why some people do and most don't.

Our understanding of their natural history is incomplete but we know that a substantial proportion of aneurysms will never rupture. We therefore have to balance our advice to people, with or at risk of developing aneurysms, knowing this and the fact that aneurysm rupture causes death and disability. We also need to remember that an individual may have multiple aneurysms and to distinguish symptomatic from asymptomatic aneurysms. Asymptomatic aneurysms may be solitary or coexist with other aneurysms, i.e. coincidentally. Confusingly, this term is sometimes used for aneurysms discovered 'coincidentally' during investigations for an unrelated disease or symptoms, and in this situation, I suggest the term 'incidental' is used.

Nevertheless, the majority of intracranial aneurysms are diagnosed after spontaneous haemorrhage and less often patients present with symptoms caused by pressure on local neural structures, dissection, or as an incidental diagnosis. The last part of the chapter describes clinical presenting features and their consequences in the first two situations, namely, ruptured and symptomatic unruptured aneurysms, and the selection process for intervention. The tutorial does not concentrate on interventions, and only endovascular treatments are described in terms of their indications and efficacy. Topics, such as complications, anticoagulation prophylaxis, etc., are dealt with in separate tutorials. The reader may feel that too much emphasis has been given to the background theory rather than practical tips on embolisation. This is because I think it is best if students are taught practical techniques in the traditional surgical method, as an apprentice to an experienced therapist. The intention of the tutorial is to provide theory because knowing as much as possible about your enemy precedes successful battle and learning about the disease process precedes successful treatment.

8.1 Arterial Aneurysms: Definitions and Descriptions

An aneurysm may be defined as a persistent dilation of the wall of a blood vessel or the heart. In this tutorial, we will be considering only intracranial arterial aneurysms. They are commonly described by their morphology, size, location and aetiology.

The word aneurysm comes from the Greek word 'aneurysma'. This is a composite of 'ana' meaning across and 'eurys' meaning broad. It was possibly first used to describe enlarged blood vessels by Galen[1] [1].

8.1.1 History of Intracranial Aneurysms

Descriptions of apoplexy, i.e. sudden loss of consciousness, can be found in ancient medical and nonmedical writings, a subject which was extensively reviewed by Walton [1]. He credited the first description of intracranial aneurysms to Morgagni[2] in 'De sedibus et causis morborum per anatomen indagatis' published in 1761 [2]. However, Bull [3] concluded that Morgagni speculated rather than conclusively demonstrated that intracranial aneurysms existed and that only two autopsy descriptions of intracranial aneurysms were made in the whole of the eighteenth century. The first description, by Biumi in 1765 [4], involved the case of a woman who died following the rupture of an intracavernous aneurysm. The second report concerned the autopsy of a 65-year-old woman performed by John Hunter in 1792, at which he discovered bilateral parasellar aneurysms of the internal carotid arteries (ICAs). The autopsy was reported by Blane in 1800 [5].

The first case of apoplexy, which autopsy showed to be caused by rupture of an intracranial aneurysm, was by Blackhall[3] in 1813 [6]. In the

[1] Galen of Pergamon (AD 129–199) was a Roman physician, surgeon and philosopher.

[2] Giovanni Battista Morgagni, 1682–1771, was an Italian anatomist (Padua).

[3] John Blackall (1771–1860) was an English physician who consulted at the Devon and Exeter Hospital.

nineteenth century, there were several clinicopathological reports, but the syndrome we now recognise as aneurysmal subarachnoid haemorrhage (SAH) was not defined until the twentieth century in papers by Collier in 1922 [7] and Symonds in 1924 [8]. The introduction of angiography by Egas Moniz[4] in 1927 allowed in vivo diagnosis of intracranial aneurysms and paved the way for the development of direct treatments [9]. Neurosurgical clipping was first performed in 1937, and as a result patient management transferred from physicians to surgeons [10].

8.1.2 Morphology

An arcane term, used for intracranial aneurysms in particular, is 'berry' aneurysm. This was purely descriptive and coined by Collier [11] who called them 'berry-like'. The only advantage to its use was that unlike terms, such as 'congenital', 'mycotic' and 'false', it does not presuppose aetiology. For the description of an aneurysm, it is now considered best to use only two morphological terms: saccular with a single entrance to the aneurysm sac or fusiform when there are two separate entrances to the sac. Other descriptive terms based on morphology, such as lobulated, cottage loaf, daughter, Murphy's tit, etc., are best avoided, except amongst colleagues who know what you are talking about. Exceptions are terms used for so-called atypical aneurysms based on their morphology such as blister, serpiginous and serpentine which have specific meanings.

There have been several attempts to distinguish ruptured aneurysms based on their shape. This has been aided by the increased sophistication of the analysis of individual aneurysm morphology, since the introduction of 3D imaging, improved image segmentation and computer fluid dynamics. However, it is difficult to separate cause from effect in retrospective comparisons of ruptured and unruptured aneurysm shapes. The parameters that have been related to rupture are:

1. Aspect ratio – calculated from the distance between the neck and the fundus divided by the maximum neck width (i.e. sac length/widest neck width). The larger the ratio value, the longer the aneurysm sac and the greater the likelihood of the aneurysm having ruptured. Ujiie et al. described the ratio and showed that ratios greater than 1.6 were characteristic of ruptured aneurysms [12]. They showed that the ratio distinguished aneurysms with slower blood flow at the fundus which supports the theory that proteolytic enzymes, such as metalloproteinases (MMPs) and elastase, generated by neutrophils to prevent thrombosis weaken the wall and initiate rupture [13].
2. Volume-to-ostium area ratio – calculated by dividing aneurysm volume by the area of its neck or ostium. It has been reported to be a better metric of aneurysm rupture status than aspect ratio [14]. It also links slow or stagnant blood flow in the sac with rupture
3. Size ratio – maximum sac dimension divided by parent artery diameter. It is a more recently described metric, which has also been correlated to rupture status, particularly for small aneurysms [15].

8.1.2.1 Size

The size of an aneurysm has implications for its likely behaviour and the treatment options. Several conventions based on size thresholds have been described to categorise aneurysm. The most widely adopted is a three-point scale of maximum sac diameter: small (<10 mm), large (>10 and <25 mm) and giant (>25 mm).

Alternatives are a five-point scale: baby (>2 mm), small (2–6 mm), medium (6–12 mm), large (12–25 mm) and giant (>25 mm) [16], to which some authors add a supergiant aneurysm >35 mm.

These thresholds were based on neurosurgical experience, but if I were to design a scale for the endosaccular therapist, it would be baby (<4 mm), small (4–10 mm), large (10–20 mm) and giant (>20 mm), since these sac sizes present different challenges for their endovascular treatment. For example, the coil choice and packing

[4]António Caetano de Abreu Freire Egas Moniz (or Egas Moniz), 1874–1955, was a Portuguese neurologist who first described cerebral angiography.

strategy is quite different for a baby aneurysm than for a 10-mm aneurysm. Another maximum sac dimension threshold to note is the use of 7 mm as the limit for small size used in the ISUIA [17] observational study of unruptured aneurysms (see below).

Other dimensions of intracranial aneurysms are useful for pre-embolisation assessments. These include:

1. Neck width: A 4-mm threshold has been established as defining the neck of saccular aneurysms as small or large based on the likelihood of recurrence after packing with coils [18]. A neck greater than 4 mm is also less likely to retain coils so the threshold affects both the complexity and reliability of endovascular treatment.
2. Neck to sac width ratio: This parameter (widest sac width/widest neck width) is also used to define the likely difficulty of endosaccular coil embolisation. If the ratio equals 1.0 or less, the aneurysm can be described as sessile in shape and unlikely to retain coils. If greater, the sac is broader than the neck and more favourable for endosaccular packing.
3. Size of the parent artery proximal and distal to the aneurysm neck and size and proximity of branch arteries are relevant to endovascular treatments employing stents or flow diverters. More detailed sizing of the sac and neck are required for treatments using flow disrupters and other implants and 3D imaging has become an essential component of size estimations and pre-embolisation assessments.

8.1.3 Location

The majority of intracranial aneurysms arise at branch points on the basal cerebral arteries; over 90% are found at just 14 locations and most (85%) develop on arteries of the anterior cerebral circulation. The exception to the general rule that aneurysms arise at branch points is the so-called blister aneurysm (see below).

Determining the frequency of aneurysms at specific locations from the literature is difficult because reports vary depending on how patient cohorts are collected. For example, because of selection bias the termination basilar artery location is usually under-represented in surgical series and relatively over-represented in endovascular treatment cohorts. The anterior communicating artery (AComA) complex is the commonest location for ruptured aneurysms, and the middle cerebral artery (MCA), the commonest for coincidental and unruptured aneurysms (see Table 8.1).

The aneurysm site determines its potential to cause pressure symptoms, influences the consequences of rupture and is important for treatment

Table 8.1 Variations in the frequency of aneurysms arising from different intracranial arteries reported in large series

	Coop. study	Int. Coop. study	Autopsy study	Community-based study		
				n = 2555 [22]		
	n = 2672 [19]	*n* = 3524 [20]	*n* = 205 [21]	RAs	URAs	All
				n = 1237	*n* = 1318	*n* = 2555
ACA	895 (33%)	1374 (39%)	46 (46%)	445 (36%)	239 (18%)	684 (27%)
ICA	1104 (41%)	1051 (30%)	13 (13%)	269 (22%)	313 (24%)	582 (23%)
MCA	529 (20%)	786 (22%)	33 (33%)	404 (33%)	651 (49%)	1055 (41%)
V/B	144 (6%)	266 (7.5%)	8 (8%)	102 (8%)	93 (7%)	195 (7%)

These studies were two surgical series (Co-operative Study (Coop. study) [19] and International Co-operative Study (Int. Coop. study) [20]), an autopsy series of patients after subarachnoid haemorrhage [21] and a community-based study [22].

RA ruptured aneurysms, *URA* unruptured aneurysms, *ACA* anterior cerebral artery, *ICA* internal cerebral artery, *MCA* middle cerebral artery, *V/B* vertebral and basilar arteries

planning. It may also suggest the aetiology of a particular aneurysm because unusual aneurysm locations should alert one to possible rarer causes. For example:

(a) Distal aneurysms (defined as those found at least one arterial branch point beyond the circle of Willis) are more likely to be caused by infection.
(b) Medially directed carotid cavernous aneurysm may be the result of arterial damage during paranasal sinus surgery or hypophysectomy.
(c) Petrous carotid aneurysm by a skull base fracture.
(d) Superior surface of the intra-dural ICA is the classic site for blister aneurysms.
(e) Distal vertebral fusiform aneurysms are likely to be due to dissection.
(f) Radiation-induced aneurysms occur on vessels included in the field of previous radiotherapy such as the cervical carotid artery after treatment of neck tumours.

8.1.4 Unruptured Aneurysms

The distinction between aneurysms that have ruptured and those that have not is fundamental to their management. The majority of aneurysms are diagnosed after SAH. Unruptured aneurysms (URAs) are diagnosed as the result of symptoms or incidentally during investigations for other reasons.

They can be divided into:

(a) Asymptomatic incidental. Discovered during investigation of an unrelated condition, i.e. truly incidental.
(b) Symptomatic. In patients presenting with symptoms, e.g. headaches, seizures, tinnitus, vertigo, syncope, memory loss, etc.
(c) Asymptomatic coincidental. Patients with multiple aneurysms, some of which are asymptomatic and discovered when a symptomatic (usually ruptured) aneurysm is diagnosed.

Multiple aneurysms are found in 19–25% of SAH patients [23]. When reading about URAs, it is worth remembering that observation studies usually recruit SAH patients with coincidental aneurysms. For the same reason, data on incidental aneurysms and symptomatic URAs comes from surgical series, which tends to be biased towards treatable lesions.

The relative frequency of symptomatic and asymptomatic URAs is difficult to estimate. In 130 patients with URAs diagnosed at the Mayo Clinic between 1955 and 1980 [24], angiography was performed for the following reasons: ischaemic cerebrovascular symptoms 32%, headache 15%, cranial nerve palsies 10%, seizures 8%, mass effects 5% and other symptoms unrelated to intracranial aneurysms 30%. Symptoms due to the discovered aneurysms were present in 31/130 (24%), and half of these were attributable to cranial nerve compression. The prevalence (see below) of URAs has been estimated at 0.6% (0.1–2.9%) [25, 26].

Symptoms may be vague, and the reasons for the initial investigation are sometimes forgotten or change once an aneurysm has been discovered. Table 8.2 attempts to capture this uncertainty. Symptoms generally depend on the aneurysm's location and size, with the possible exception of thromboembolism, which theoretically can arise from any size sac but is more likely to be generated in larger aneurysms. Presentation with symptoms of cerebral ischaemia (usually transient) is not related to a particular aneurysm location [27]. This presentation is generally considered to increase the risk of surgical morbidity [24].

Table 8.2 Symptoms caused by unruptured aneurysms

Symptoms due to unruptured intracranial aneurysms	Estimate (%)
Headache/pain	10
Cranial nerve palsies	15
Other compression symptoms (e.g. visual disturbances, motor or sensory loss)	15
Seizures	5
Cerebral ischaemia or infarction (e.g. TIAs, hemiparesis, dysphasia and hemianopsia)	10–30
Others	35–55

8.2 Causes of Intracranial Aneurysms

What causes intracranial aneurysms? The short answer is a focal weakness in the arterial wall, which is exploited by the gradient between intraluminal and ambient intracranial pressure to cause the wall to expand. Most aneurysms develop due to a combination of causes and where and how they develop is dictated by the strength of the arterial wall and local blood flow dynamics. Our current understanding of aneurysm aetiologies is that the following have been implicated as contributing causes.

8.2.1 Haemodynamic Causes

There is general consensus that most aneurysms are the result of haemodynamic factors acting with degenerative factors. Initial weakening of the wall combined with haemodynamic factors such as high wall shear stress, raised wall pressure, oscillations of the wall and changing wall shear stress gradients cause aneurysms to develop and grow. These factors are now the subjects of research using computational modelling of the mechanobiology of the arterial wall and aneurysm development [28]. These techniques use combinations of morphological characteristics, structural analysis, computational fluid dynamic analysis (CFD) and aneurysm evolution models to study the processes behind aneurysm development and growth [29].

The haemodynamic factors involve:

- Uneven pulsation pressures at the apex of bifurcations.
- Increased blood flow in the parent artery due to an arteriovenous shunt, asymmetry of the circle of Willis and variant arteries such as azygos A2 artery or a persistent primitive trigeminal artery and vessels providing collateral support after major artery occlusions (Fig. 8.1).
- Systemic hypertension. An association between systemic hypertension and aneurysmal SAH was established in the Asia Pacific Cohort Studies Collaboration [30]. This study showed that the risk of SAH doubled if the patient's systemic blood pressure was >140 mmHg, see below. The association is intuitive in conditions that cause increases in cerebral arterial blood pressure. In patients with coarctation of the aorta, aneurysms are frequent; prevalence rates of 2.5–10.6%

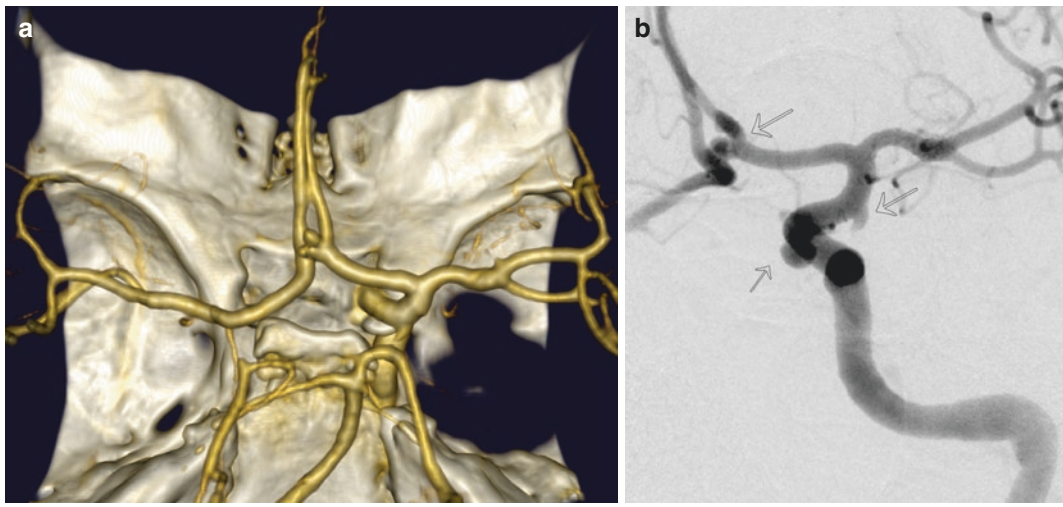

Fig. 8.1 Reconstructed CTA (**a**) and DSA (**b**) images showing multiple small flow aneurysms of the anterior communicating artery and *left* internal carotid artery (*arrows*) 10 years after spontaneous thrombosis of the right carotid artery (Note the large calibre of the anterior cerebral arteries (A1 sections))

have been reported and the incidence of SAH is increased. However, this incidence (risk) is reduced by effective treatment and normal if treatment is performed before 20 years of age [31].

8.2.2 Structural Causes

The large arteries in the subarachnoid space are thinner than peripheral arteries. Their walls are composed of three layers:

(a) Intima, comprising an endothelial cell layer, basement membrane and the internal elastic lamina separating it from the media.
(b) Media, consisting of a network of elastin fibres, smooth muscle cells and collagen fibres. It is thin relative to extracranial arteries and there is no external elastic lamina. The muscle fibres are arranged circumferentially and longitudinally. The longitudinal fibres separate at branch points to create 'medial defects'.
(c) Adventitia, which is a thin acellular outer sheath composed of bundles of collagen fibres arranged with a helical pitch around the artery. The collagen provides tensile strength. Normal intracranial arteries are devoid of vasa vasorum except for short segments of the carotid and vertebral arteries just after they enter the subarachnoid compartment [32]. Metabolic support probably occurs through the CSF, and so-called vasa vasorum only develop in response to disease [33].

These structural differences between extracranial and intracranial arteries are likely to make the latter more vulnerable to develop aneurysms but they apply to all arteries of the subarachnoid space. The 'medial defects' were described by Forbus [34], who suggested that they explained the frequency of aneurysms at arterial branch points. However, like most subsequent authors, he concluded that an additional initiating factor was needed since they are universal. Stehbens [35] argued that they were microraphes, i.e. the point at which diverging muscle fibres pull together and therefore in practice areas of structural strength.

Structural factors important to the development of cerebral aneurysms are apoptosis of medial smooth muscle cells, loss of elastin fibres and growth and remodelling of the collagen fabric. During aneurysm formation, the media layer disappears leaving only thinned intima and adventitia. Various molecular signalling pathways that cause apoptosis of vascular smooth muscle cells have been described. Five regulator substances in particular are implicated: monocyte chemoattractant protein-1 (which is associated with chronic inflammation), tumour necrosis factor-alpha (a cytokine causing smooth muscle apoptosis), NF-B (a transcription factor that regulates a variety of cellular responses via control of DNA transcription), nitric oxide and its generator inducible nitric oxide synthase (iNOS) (increased in cerebral aneurysm and implicated in smooth muscle apoptosis) and endothelin-1 (a vasoconstrictor, whose elevated expression in cerebral aneurysm has been associated with induced apoptosis) [36].

Ageing affects the wall structure with loss of elastic tissue in old age reducing the responsiveness of the wall to changes in pressure. Aneurysm walls are mostly composed of collagen, which may reflect a general reduction in elastin with increasing age or an inability to replace it. The process probably involves both haemodynamic stress and structural wall remodelling. Chronic inflammation has been proposed as a possible trigger for structural change involving loss of smooth muscle cells. Inflammatory cells have been found in unruptured aneurysm walls [37] and proposed as part of a process initiated by endothelial (haemodynamic) damage which causes smooth muscle cells to change from a contractile phenotype to a pro-modelling, pro-inflammatory synthetic phenotype and finally dedifferentiation phenotype [38]. This thesis and the contributions of age and atherosclerosis to structural weakening remain the subject of intense research and raise the possibility of preventative medical treatments in the future.

8.2.3 Genetic Causes

Familial aneurysms are found in individuals who give a positive family history and do not have a recognised hereditary disease. A positive family history (i.e. a first- or second-degree relative with aneurysms) has been reported in 7–20% of aneurysm patients as well as a three- to sevenfold increased risk of SAH. These patients generally present at a younger age (peak incidence 30–40 years) [37].

There have been several genetic studies of people with familial aneurysms but no single causative gene has been identified. However, genome studies have identified what appears to be an increasing number of risk loci. A review in 2008 of 10 studies reported 4 that were found in more than one study: 1p34.3-p36.13, 7q11, 19q13.3 and Xp22 [38]. A more recent meta-analysis of microarray gene expression studies identified 5 studies which analysed tissue from only 60 aneurysms and identified 507 genes with altered expression. It concluded that larger samples are needed [39]. Even so, they were able to show that only seven genes had altered expression in three or more studies. It is probable that this research will lead to genetic testing able to identify people at risk.

Several hereditary diseases have been described as being associated with the occurrence of aneurysms. These can be divided into those vascular diseases with an established linkage and others in which intracranial aneurysms have been reported but in which the link is unclear.

8.2.3.1 Hereditary Diseases with Established Increased Intracranial Aneurysm Frequency

(a) Autosomal dominant polycystic kidney disease (ADPKD): In this condition, an association with intracranial aneurysms has been firmly established. Those affected develop predominantly saccular aneurysms, though dissections and fusiform aneurysms have been reported. In a large review of patients with ADPKD, 40% gave a positive family history for SAH or aneurysms. Subarachnoid haemorrhage occurred at an earlier age than in patients without ADPKD, and they were more likely to be male. Aneurysms are observed in 25% at autopsy and were the cause of death in 20% of patients [40].

(b) Ehlers–Danlos syndrome: Is an autosomal dominant connective tissue disease with 10 described subtypes. Type IV causes a defect in type III collagen and generalised vascular wall abnormalities including aneurysms. It affects large- and medium-size arteries and causes both saccular and fusiform aneurysms. In the cranium, it most commonly involves the cavernous carotid artery, and patients present with caroticocavernous fistula rather than SAH [41].

(c) Loeys–Dietz syndrome: Is an autosomal dominant connective tissue disease caused by a mutation in either the TGFBR1 or TGFBR2 genes (transforming growth factor beta receptor 1 or 2). Those affected develop tortuous arteries and fusiform aneurysms of the large arteries (Fig. 8.2) [42].

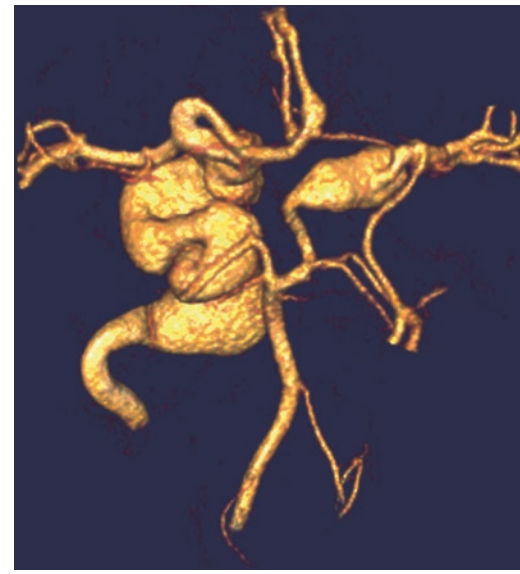

Fig. 8.2 Reconstructed MRA of a patient with Loeys–Dietz syndrome and bilateral carotid aneurysms. There is a large fusiform aneurysm of the right internal carotid artery and a remnant aneurysm on the left after the left internal carotid artery had been occluded to treat a more proximal aneurysm

8.2.3.2 Inherited Disease with Less Certain Increased Frequency

(a) Marfan syndrome: Is an autosomal dominant condition due to a mutation in the gene encoding for fibrillin-1, a protein component of the extracellular matrix. Those affected develop large artery dissections as well as other connective tissue abnormalities, but it remains uncertain whether the incidence of intracranial aneurysms is higher than the unaffected population [43].

(b) α_1-Antitrypsin deficiency: This causes vascular disorders including aneurysms, spontaneous dissections and fibromuscular dysplasia. Inheritance is described as autosomal dominant, and the affected gene is located on chromosome 14. Both heterozygous and homozygous patterns have been implicated.

(c) Fibromuscular dysplasia: Is an autosomal dominant condition which causes fibrous thickening of the arterial wall and carotid stenosis [44]. A slightly increased prevalence (7%) of intracranial aneurysms has been calculated for individuals with this condition [45].

(d) Neurofibromatosis type I: Is an autosomal disorder affecting connective tissue and has been suggested as a cause for intracranial aneurysms but no increased risk has been established.

(e) Pseudoxanthoma elasticum: One report of an association with intracranial aneurysms was made in the 1980s [46]. It has been recycled as a cause in textbooks.

(f) Rendu–Osler–Weber and Klippel–Trenaunay–Weber syndromes: These are vascular conditions in which intracranial aneurysms have been reported but not with sufficient frequency to confirm an above-chance association.

8.2.4 Specific Causes

1. Atherosclerosis: Atheroma affects the internal elastic lamina of arteries and reduces their ability to withstand intraluminal pressure. Atherosclerotic plaques are commonly found in the walls of intracranial aneurysms, but this disease is also common in aneurysm populations so its role has been difficult to define [36]. Kosierkiewicz et al. [47] found changes of atherosclerosis in all aneurysms they studied. Small aneurysms showed diffuse intimal thickening composed predominantly of proliferating smooth muscle cells (SMC) with a small number of macrophages and lymphocytes with large aneurysms showing changes of advanced atherosclerosis with cellular infiltrates composed mostly of macrophages and lymphocytes. Arterial wall degeneration with increasing age is likely a factor (as described above), and the frequency of atherosclerosis points to a combination effect of age-related degeneration and atherosclerosis in older patients [48].
2. Infection: Aneurysms caused by infections are the result of an arteritis caused by either septic emboli which infect the luminal surface or transmural extension of an extravascular infection. This cause should not be confused with the chronic inflammatory changes described in idiopathic aneurysms.

   Infectious aneurysms are classically due to subacute bacterial endocarditis and occur in 5–15% of patients. They are typically located on smaller arteries distal to the circle of Willis and about 20% are multiple (Fig. 8.3). Septic

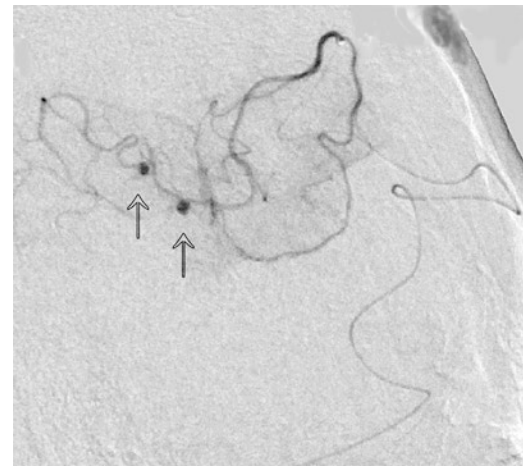

Fig. 8.3 Superselective DSA of a distal cortical artery showing two infectious aneurysms in a patient with subacute bacterial endocarditis

emboli lodge in these smaller arteries, often at branch points where they initiate a local arteritis which weaken the wall. Such aneurysms may resolve spontaneously or rupture. It is assumed that the embolus causes thrombosis and occlusion and that the aneurysm forms when the artery reopens.

The alternative process is for an extravascular infection to affect the adventitial surface and cause arteritis. Aneurysms that develop by this mechanism are typically caused by an adjacent focus of infection, such as meningitis, paranasal sinusitis or cavernous sinus infectious thrombophlebitis. It thus involves larger proximal arteries.

The infective agent is usually bacterial: streptococcus or staphylococcus, but fungal or nonbacterial aneurysms can also occur. The latter may occur in patients with an impaired immune system (e.g. AIDS) or fungal sinusitis due to aspergillus, candida or phycomycetes. Other infectious agents have been reported including amoebae.

3. Trauma: Traumatic aneurysms are due to closed head injury in 75% (with skull fractures), penetrating trauma in 15%, and surgery (e.g. craniotomy, transsphenoidal or other paranasal sinus surgical procedures) in 10% of patients [49]. The petrous and cavernous portions of the internal carotid artery are most at risk when fractures involve the skull base. Penetrating missile injuries usually affect the supratentorial vessels. The type of aneurysm that develops depends on the extent of wall injury. Thus, major disruption may cause fusiform dilations and/or pseudo aneurysms with (at least initially) little defined wall around a haematoma (Fig. 8.4).
4. Neoplastic aneurysms: This rare type of aneurysm is usually caused by intravascular metastasis rather than arterial wall invasion by tumour. The classic cause is cardiac myxoma, because this tumour usually involves the left atrium and tumour emboli are carried to cranial arteries. The commonest sites are branches of the MCA, and aneurysms are either fusiform or saccular in shape and often multiple. Metastatic choriocarcinoma may also invade intracranial arteries and cause arterial rupture, occlusion or aneurysms by disrupting the internal elastic laminar and media [50]. Rarely, local spread by tumours at the skull base and invasion of the arterial wall causes an aneurysm [51].
5. Drug abuse: Aneurysms and an increased incidence of spontaneous intracranial haemorrhage have been reported in abusers of drugs such as amphetamines, heroin and cocaine. It is difficult to identify a specific reason for intravenous injectors to develop intracranial aneurysms unless the individual has an abnormal left-to-right cardiac connection. Transient raised levels of systemic blood pressure caused by the use of vasoactive drugs are assumed to cause spontaneous haemorrhage and contribute to the formation of aneurysm.
6. Radiotherapy: Aneurysms of arteries included in the radiation field are a late complication of

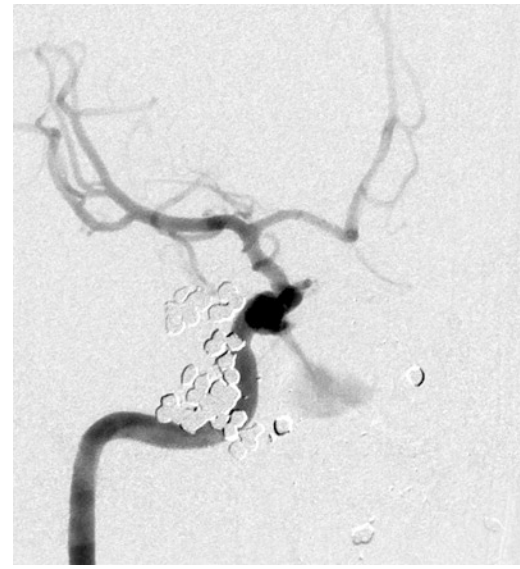

Fig. 8.4 Traumatic aneurysm of the cavernous internal carotid artery caused by a shotgun injury. Shotgun pellets are seen on the image with a 'jet' of contrast entering the traumatic aneurysm in the sphenoid sinus

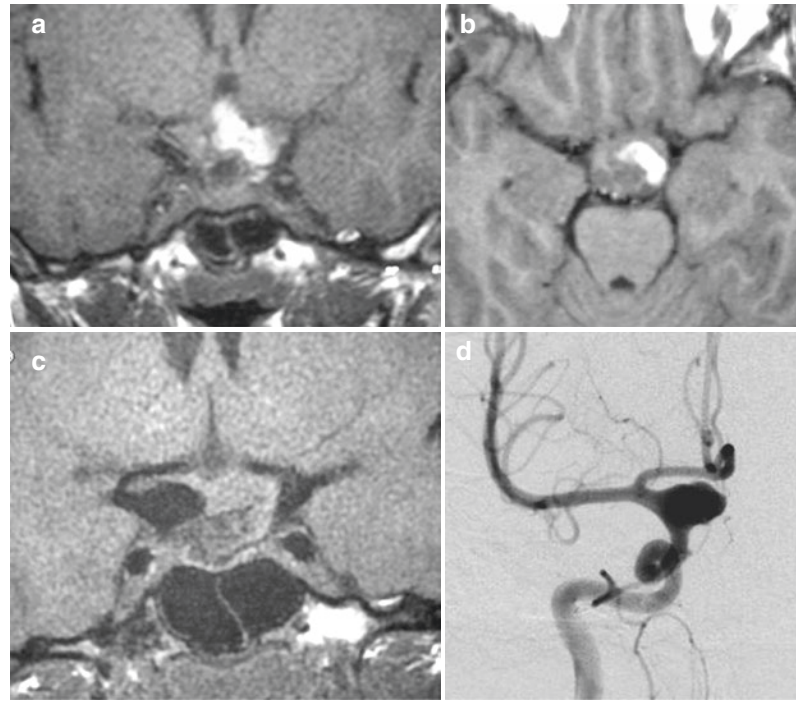

Fig. 8.5 MRI showing a pituitary tumour (**a** and **b**) before and 4 years after radiotherapy (**d** and **c**). A wide-necked radiation-induced aneurysm developed on a section of the right internal carotid artery which had been included in the radiation treatment field

radiotherapy. Ionising radiation weakens the arterial wall, and saccular and fusiform aneurysms are a long-term problem in oncology after treatment of head and neck tumours (Fig. 8.5).

8.3 Pathology of Intracranial Aneurysms

Descriptions of the histology of intracranial aneurysms are relatively few, presumably because most aneurysms are not examined after clipping and most data come from autopsies. The histological appearance of aneurysms varies depending on their size and rupture status.

8.3.1 Histopathology of Small Unruptured Aneurysms

The walls of small URAs aneurysms are typically thin and composed principally of acellular adventitia which is continuous with the parent artery. The muscle fibres of the parent artery media end abruptly at the junction of sac and parent vessel, but the internal elastic lamina extends a variable distance inside the sac. The endothelium continues on the sac wall, but it is often partially deficient and only extends continuously to the fundus in small aneurysms [52]. The fundus of small aneurysms contains fibroblasts, a few elastic fibres and an intact endothelial layer. This reflects their development, which is accompanied by a loss of arterial wall elastin and adaption of the collagen fabric.

8.3.2 Histopathology of Large and Giant Unruptured Aneurysms

The interior of an intracranial aneurysm is typically smooth, but in larger and fusiform aneurysms, it is irregular due to areas of intimal

thickening or organised thrombus. The wall consists of collagen (of variable thickness) with fibroblasts and laminated thrombus may be present. The dome (fundus) is irregular and composed of collagen with few cells and no endothelial layer. Thickening of the walls may be a reparative response involving local mechanical forces (e.g. wall shear stresses acting on the endothelial cells), mural haemorrhage or secondary to atherosclerosis. Layers of fibrous tissue, patches of haemosiderin and cholesterol deposits are present. In very large and giant aneurysms, calcification occurs. Such changes may be due to mural damage or intraluminal thrombosis. The latter is caused by the slower circulation of blood within a large sac. Its subsequent organisation results in a wall thickened by laminated thrombus which contains microvessels and cellular elements, principally macrophages. New vessels develop as part of the inflammatory reaction and organisation of intravascular thrombus. They are usually transient, disappearing when fibrosis of the clot is complete. The common finding of microvessels in the walls of giant aneurysms, incorrectly described as 'vasa vasorum' by some authors, probably reflects the chronic nature of thrombus formation in this situation.

8.3.3 Histopathology of Ruptured Aneurysms

The site of acute rupture may be identified by the presence of inflammatory cells, red blood cells and haemosiderin. Rupture occurs most commonly at the fundus (57–64%), at a portion of the body (17–33%) and rarely at the neck region (2–10%). A lobule or nipple-shaped protuberance at or near the fundus may be evident at the rupture site on angiograms. At this point, the wall is absent and the acute defect is closed by a clot. The formation of fibrin within the clot is followed by its subsequent organisation into sac wall. Stehbens [53] described this situation as a 'false' aneurysm. He considered that tearing of the wall, whether this resulting in minor leakage or severe haemorrhage, was the most likely cause of mural thrombus. The histological finding of haemosiderin-laden macrophages within the wall suggests that mural haemorrhage, with or without rupture, is part of the process of wall thickening associated with growth.

8.3.4 Histopathology of Fusiform Aneurysms

These are most commonly due to severe atheroma affecting larger arteries and causing ectatic enlargement due to loss of mural elasticity. Histological examination shows fibrous tissue without a smooth muscle layer and disruption of the elastic membrane with hyaline degeneration and deposition of cholesterol, inflammatory cells and internal haemorrhage in the wall [54]. Intraluminal thrombosis is common. In young adults, histology has demonstrated the loss of the internal elastic lamina and medial muscle layers without degenerative features [300].

8.3.5 Histopathology of Dissecting Aneurysms

Arterial dissection is characterised by the penetration of circulating blood into the substance of the wall and its sequence extension between layers of the wall. Dissection of intradural arteries

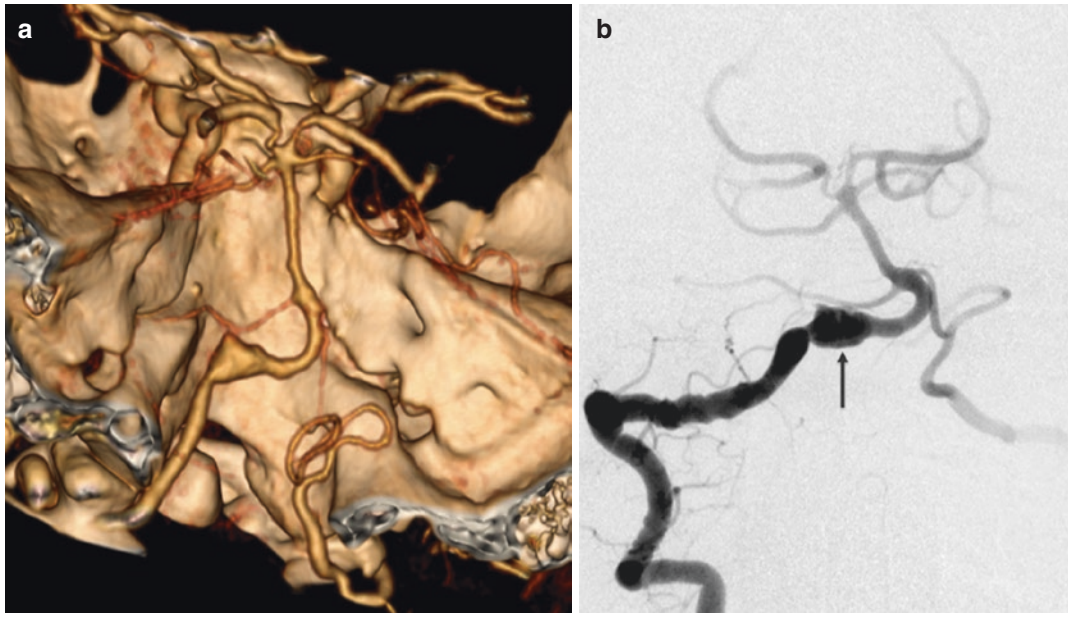

Fig. 8.6 Fusiform dissection of the vertebral artery. Right vertebral DSA with 3D reconstruction (**a**) and frontal radiograph (**b**) showing a fusiform aneurysm of the intracranial vertebral artery (*arrow*). The hypoplastic distal left vertebral artery precluded treatment by parent artery occlusion after acute subarachnoid haemorrhage, so endovascular treatment was performed with a flow diverter stent and coils

occurs deep to the internal elastic lamina rather than external to the media, as in extradural arteries. It may be related to an underlying arteriopathy [55]. The torn intima may act as an abstracting flap and occlude the true lumen or a distal tear develops and allows blood flow to re-enter the true lumen. On histology, the tear usually involves the majority of the vessel circumference. In the acute situation, thrombus is present in the wall, and the overlying intima is thickened and convoluted (Fig. 8.6). If the adventitia is penetrated, SAH occurs. Acutely, this is a particularly unstable situation, but if the victim survives, the weakened arterial section may dilate to form a fusiform aneurysm [56].

8.3.6 Histopathology of Blister Aneurysms

The term blister or blood-blister aneurysm has been applied to small aneurysms found at non-branch points of large intradural arteries because they look like a blister at surgery [57]. The wall is thin and extremely friable at operation, and they may enlarge over a few days which suggests that they are caused by dissection and/or mural haemorrhage [(Fig. 8.7). The few reports of histological examinations have found absence of the internal elastic lamina and smooth muscle with a wall consisting of adventitia and fibrous tissue only without changes suggesting dissec-

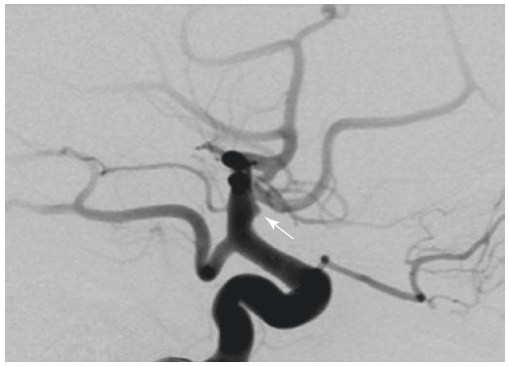

Fig. 8.7 Blister aneurysm of the internal carotid artery (*arrow*). This has a typical 'thorn-shape'

tion [58]. Since most are diagnosed after SAH, Abe et al. suggested it was the effect of an adjacent subarachnoid blood clot that causes rapid growth [59].

8.4 Epidemiology of Intracranial Aneurysms

The natural history of intracranial aneurysms is important to the interventional neuroradiologist because they have to advise asymptomatic patients in whom an aneurysm has been discovered, either incidentally after imaging for an unrelated reason or coincidentally to another symptomatic aneurysm. The crucial question in this situation is the risk of the asymptomatic aneurysm rupturing or causing symptoms in the future. Epidemiology which studies aneurysms at the population and public health levels helps to identify risk factors and determine guidance for preventative interventions.

Two important parameters that are used to measure the epidemiology of diseases are prevalence and incidence. These terms have specific meanings:

Prevalence is the number of people with the condition in the population at a given time. It is usually expressed as a percentage of the population, but the denominator value can vary.

Incidence is the number of people in a population who develop the condition during a given period of time. It is expressed as the number of cases diagnosed per year/100,000 of the population.

8.4.1 Prevalence of Intracranial Aneurysms

Prevalence rates are calculated from the number of people with aneurysms discovered at autopsy or on imaging. The rates (Table 8.3) reported in autopsy studies vary widely because they depend on how assiduously aneurysms are sort. This usually depends on whether the examination was performed by a general or specialist (neuro) pathologist. Imaging data originally came from audits of catheter angiograms, and the subjects are therefore preselected as those requiring investigations, but with MRA and CTA more widely used, these data are less influenced by selection bias and should more reliably reflect rates for asymptomatic aneurysms in the general population.

An educated guess is that aneurysms are present in 2–3% of the population at any time, but the risk for an individual developing an aneurysm at some time during their life is numerically greater. One should take care to distinguish study populations as ruptured or URAs aneurysms. In a recent meta-analysis of URA data, the prevalence was higher for people over 30 years, women (mainly over 50 years), patients with ADPKD and those with a positive family history of intracranial aneurysms or previous SAH [60].

8.4.2 Incidence of Subarachnoid Haemorrhage

This is an easier parameter to estimate than prevalence because the population draining to a hospital or group of hospitals can be more accurately

Table 8.3 Prevalence of intracranial aneurysms reported in autopsy and imaging studies

Study	Author	Rates
Autopsy (unselected)	Jellinger [49]	1.6%
Autopsy (selected)	Bannerman [50]	0.34% ruptured 1.09% unruptured
Autopsy (meta-analysis)	Rinkel [29]	0.4 and 3.6%[a]
Imaging (meta-analysis)	Rinkel [29]	3.7 and 6.0%[a]

[a]The lower rate was calculated from retrospective and the higher from prospective studies

Table 8.4 Incidences of subarachnoid haemorrhage, annual cases per 100,000 of the population reported in three decades

Author	Country	Incidence/ 100,000
1960–1970		
Brewis et al. [63]	UK	10.9
Pakarinen [64]	Finland	12.0
Joensen [65]	Denmark (Faroes)	7.0
Gudmunsson [62]	Iceland	8.0
1980–1990		
Philips et al. [66]	USA	11.6
Tanaka [67]	Japan	20.0
Fogelholm [68]	Finland	19.4
Kristensen [69]	Greenland	6.0
Bonita et al. [70]	New Zealand	14.3
Inagawara [71]	Japan	21.0
Kiyohara [61]	Japan	96.1
2000–2010		
Ingall [72]	Finland	22.5
	China	2.0
ACROSS [73]	Australia/New Zealand	8.1
	Japan	23
Inagawa [74]	Japan	32

calculated. Rates are generally underestimates because of incomplete case ascertainment, since a proportion of atypical headaches or nontraumatic sudden deaths are not diagnosed as aneurysmal SAH. Up to a third of patients die acutely after SAH; some never reach hospital medical care and are only diagnosed at autopsy [61]. For example, Gudmunnson [62] found an annual incidence of 10/100,000 in the urban but only 6/100,000 in the rural populations of Iceland. He attributed the difference to the greater availability of medical services (and in vivo diagnostics) in the urban situation.

Epidemiology studies have generally reported annual incidences for SAH, in the range of 8–16/100,000 population (Table 8.4) with some regional and racial variations. The incidence increases with age, though some earlier studies suggested the highest incidence was in the fifth and sixth decade of life (Table 8.5). Variations may be due to methodological differences, i.e. if patients without aneurysms are included, differences in the study populations and ascertainment levels. The extraordinarily high rate in the Kiyohara study [61] is attributed, by the authors, to improved ascertainment of study data and emphasises the importance of methodology in such studies. Thus, high incidence in Japan (e.g. 20/100,000) [67, 71] was assumed to be due to a racial propensity to develop aneurysms but their prevalence is paradoxically not increased compared to other regions [60]. It is speculated that this is due to a higher tendency to rupture or good medical services and high ascertainment levels but remains unexplained.

8.4.3 Risk of Aneurysm Rupture

The risk of an URA rupturing is low. A simple calculation based on prevalence and incidence date makes this clear. If the population prevalence is 5%, and the incidence of SAH 10/100,000, there are 5000 people with aneurysms per 100,000 and only 10 will suffer SAH in 1 year. The problem is that this assumes a constant, time-independent risk of rupture. Even so, it highlights the difficulty in balancing the risk of intervention against rupture risk and the need to identify people at relatively high risk for whom intervention is justified. So how can we assess the risk to a patient's health if an asymptomatic aneurysm is diagnosed in life? The answer is that we have to

Table 8.5 Annual incidences of subarachnoid haemorrhage per 100,000 of the population by patient age decade

Decade	Year	3rd	4th	5th	6th	7th	8th	9th+
Brewis et al. [53]	1966	3.4	12.7	22.1	23.1	13.7	11.4	12.5
Pakarinen [54]	1967	6.1	13.4	26.9	38.6	30.6	26.6	–
Fogelholm [57]	1981	8.0	16.0	38.0	35.0	41.0	49.0	–
Bonita and Thomson [59]	1985	7.0	18.9	23.8	24.4	29.9	14.9	–
Kiyohara [51]	1989	–	–	34.9	38.4	97.4	148.9	281.7

rely on observational studies and meta-analysis of amalgamated data to assess the risk.

8.4.3.1 Observational Studies

These studies recruit and follow up people known to harbour unruptured aneurysms. They may collect data retrospectively or prospectively and most cohorts include patients with coincidental aneurysms. Annual rupture rates are calculated from the numbers who experience SAH during the study period. These studies are presented in Table 8.6. The average annual rupture rates reported in studies of all aneurysms is 1–1.5% with ISUIA [17], an outlier with rates of 0.05–0.8.

The largest studies are the International Study of Unruptured Intracranial Aneurysms (ISUIA) and The Natural Course of Unruptured Cerebral Aneurysms in a Japanese Cohort (UCAS). ISUIA collected observational data on untreated and treated patients with URAs. It reported findings on a retrospective cohort of 1449 patients with untreated URAs in 1998 and a prospective cohort of 1692 patients in 2003 [17, 77]. The paper distinguished patients without (group 1) from those with (group 2) a history of previous SAH and stratified aneurysms according to size. In the last report, small aneurysms were defined as <7 mm, and rupture rates were reported as 5-year cumulative rates based on a mean follow-up period of 4.1 years (Table 8.7). Thus, large and posterior fossa aneurysms in group 2 patients had the highest rupture rates. The observation period has been extended and data presented to investigators, but this is as yet unpublished (Table 8.8).

UCAS recruited 5720 patients with newly diagnosed unruptured aneurysms and reported in 2012 [79]. This national study recruited this large number of people with minimal or no symptoms over a relatively short period and censured registrants when aneurysms were treated, ruptured or patients died. All aneurysms were <5 mm in size and 91% incidental. Rupture occurred during follow-up in 111 aneurysms giving an annual rupture rate of 0.95% (CI 0.79–1.15) which is considerably higher than the 0.05% rate for small group 1 aneurysms in ISUIA.

The methodology problems associated with observational studies explains some of their differences, for instance, the Juvela et al. [81] followed a small cohort for more than 20 years and UCAS a large cohort for only up to 3 years. Thus, the data need to be interpreted cautiously, and students should read these reports care-

Table 8.6 Annual rates of SAH in observational studies of patients with unruptured aneurysms

	N=	Mean obs (months)	No. SAH	Annual rate %
Graf [75]	52	60	2	1.0
Weibers et al. [24]	130	100	15	1.1
Juvela et al. [76]	181	166	27	1.4
ISUIA 1[a] [17]	1449	99	32	0.05–0.8
ISUIA 2 [77]	1692	49	51	Cum. rates
Ishibashi et al. [78]	419	30	19	1.4
Juvela et al. [77]	142	252	34	1.1
UCAS invest. [79]	5720	Up to 36	111	0.95
Sonobe et al.[b] [80]	384	41	7	0.54

[a]Retrospective cohort
[b]All small aneurysms (<5 mm)

Table 8.7 Five-year cumulative rupture rates calculated in the ISUIA[a]

Site of aneurysm	Gp1: <7 mm	Gp2: <7 mm	7–12 mm	13–24 mm	>25 mm
Cavernous carotid	0	0	0	3.0%	6.4%
ACA/MCA/ICA	0	1.5%	2.6%	14.5%	40%
PComA and posterior fossa	2.5%	3.4%	14.5%	18.4%	50%

[a] *ISUIA* International Study of Unruptured Intracranial Aneurysms [77]
ACA anterior cerebral artery, *MCA* middle cerebral artery, *ICA* internal cerebral artery, *PComA* posterior communication artery

Table 8.8 Ten-year cumulative rupture rates calculated in the ISUIA*

Site of aneurysm	Gp1: <7 mm	Gp2: <7 mm	7–12 mm	13–24 mm	>25 mm
Cavernous carotid	0	0	0	2.0%	4.7%
ACA/MCA/ICA	0	1.3%	2.7%	20.7%	46%
PComA	6.0%	5.2%	24%	14.8%	33%
Posterior fossa	4.4%	7.8%	8.5%	13.4%	53%

*Results presented at investigators' meeting and reported by A. Molyneux, ESMINT teaching course, Barcelona, 2010
ISUIA International Study of Unruptured Intracranial Aneurysms, *ACA* anterior cerebral artery, *MCA* middle cerebral artery, *ICA* internal cerebral artery, *PComA* posterior communication artery, *Gp1* without previous SAH, *Gp2* with previous SAH

fully. They suffer from a fundamental problem which is the natural reluctance of doctors to recruit patients they 'feel' are at high risk of rupture. Thus, biasing the cohort of patients with aneurysms judged to be of lower rupture risk.

8.4.3.2 Meta-Analysis of Amalgamated Data

An alternative approach to observational studies has been to critically amalgamate data from different studies, i.e. the systematic review. Using data from 19 studies, Wermer et al. [82] calculated overall rupture rates from reported studies with a mean observation period of less than 5 years as 1.2% and 0.6% between 5 and 10 years and 1.3% for those with greater than 10 years of follow-up. The surprising variation in rates may reflect differences in study populations or that the annual rupture changes over time. If the latter, then calculating an annual rupture risk from data from observational studies is substantially flawed. For example, it may be that aneurysms form and either rupture over a short time period or reach a stable state and can then be observed over a long period with a lower risk of rupture. The higher rupture rates observed in large aneurysms may reflect an unstable growth period. They must grow from a minority of small aneurysm (possibly in a stuttering manner), and the growth process makes them more liable to bleeding. The data presented in Tables 8.7 and 8.8 supports this hypothesis with rupture rates stabilising in the long term, and follow-up studies of rebleed rates in patients followed up after treatment of ruptured aneurysms tend to plateau after an initial period of 3–5 years [83, 84].

Recognising the need for data on which to base advice to patients diagnosed with unruptured aneurysms, Greving et al. [85] performed a systematic review of pooled data from five observational studies [77–81] and the meta-analysis of Wermer et al. [82] and calculated a 1-year rupture risk of 1.4% (CI 1–1–1.6) and a 5-year risk of 3.4% (CI 2.9–4.0). The risk between individuals varied considerably; for instance, they calculated a 5-year rupture risk of 0.25% for a person under 70 years with a small (<7 mm) aneurysm and no vascular risk factors and more than 15% for someone older with a giant aneurysm of the posterior circulation. Clearly, it is important to take this into account when advising patients since it is hard to justify any surgical intervention in the former given current treatment risks. They there-

fore proposed an algorithm for quantifying individual rupture risks as PHASES, with a scores based on (P) the population from which the person comes, (H) hypertension, (A) age, (S) size of aneurysm, (E) earlier SAH and (S) site of aneurysm. Based on these factors and the derived scores, they published a useful prediction chart based on these risk factors and an estimate of rupture risks over 5 years (Fig. 8.8).

8.4.3.3 Risk Factors for Aneurysmal Subarachnoid Haemorrhage

The risk factors associated with aneurysmal SAH provide an insight into the mechanisms of aneurysm rupture and have been the subject of many studies over the last 30 years. Taking systemic review to another level, Clarke [86] performed a review of reviews to study identify commonality amongst the possible associated

a Populations from North America and European countries other than Finland

Size	No hypertension, no history of SAH — Aneurysm location: ICA	MCA	ACA	Pcom/posterior	Age	Hypertension, no history of SAH — Aneurysm location: ICA	MCA	ACA	Pcom/posterior	Age	Both hypertension and history of SAH — Aneurysm location: ICA	MCA	ACA	Pcom/posterior
≥20 mm	7	13	>15	>15	≥70 years	10	>15	>15	>15	≥70 years	14	>15	>15	>15
10·0–19·9 mm	2	4	6	7		3	5	8	9		4	7	11	13
7·0–9·9 mm	1	1	3	3		1	2	3	4		2	3	5	6
<7 mm	0	1	1	1		0	1	1	2		1	1	2	3
≥20 mm	5	9	15	>15	<70 years	7	12	>15	>15	<70 years	10	>15	>15	>15
10·0–19·9 mm	1	2	4	5		2	3	6	7		3	5	8	9
7·0–9·9 mm	1	1	2	2		1	1	2	3		1	2	3	4
<7 mm	0	0	1	1		0	1	1	1		0	1	2	2

b Japanese population

Size	No hypertension, no history of SAH — Aneurysm location: ICA	MCA	ACA	Pcom/posterior	Age	Hypertension, no history of SAH — Aneurysm location: ICA	MCA	ACA	Pcom/posterior	Age	Both hypertension and history of SAH — Aneurysm location: ICA	MCA	ACA	Pcom/posterior
≥20 mm	>15	>15	>15	>15	≥70 years	>15	>15	>15	>15	≥70 years	>15	>15	>15	>15
10·0–19·9 mm	5	10	>15	>15		7	13	>15	>15		10	>15	>15	>15
7·0–9·9 mm	2	4	7	8		3	5	9	11		4	8	13	15
<7 mm	1	2	3	4		1	2	4	5		2	3	6	7
≥20 mm	13	>15	>15	>15	<70 years	>15	>15	>15	>15	<70 years	>15	>15	>15	>15
10·0–19·9 mm	4	7	11	13		5	9	15	>15		7	13	>15	>15
7·0–9·9 mm	2	3	5	6		2	4	6	8		3	5	9	11
<7 mm	1	1	2	3		1	2	3	3		1	2	4	5

High risk
Intermediate risk
Low risk
Very low risk

Fig. 8.8 Risk prediction charts for aneurysm rupture. (**a**) Populations from North America and European countries other than Finland. (**b**) Japanese population. The number in each cell refers to the predicted risk (%) for aneurysm rupture within the next 5 years. Colour coding refers to the risk of rupture, not to the trade-off between the risk of rupture and risk of treatment. *ICA* internal carotid artery, *MCA* middle cerebral artery, *ACA* anterior cerebral arteries (including the anterior cerebral artery, anterior communicating artery and pericallosal artery), *Pcom* posterior communicating artery, *posterior* posterior circulation (including the vertebral artery, basilar artery, cerebellar arteries and posterior cerebral artery), *SAH* subarachnoid haemorrhage (From Greving et al. [85], reproduced with permission)

features. These include patient factors (demographics, medical comorbidities, lifestyle, etc.), aneurysm characteristics (location, etc.) and events at the time of rupture onset (Table 8.9).

1. Patient factors
   (a) Age. There is a linear correlation between age and SAH. The majority of early reports demonstrated a maximum incidence in middle and late middle age (Table 8.5), but recent studies found maximum incidences in the oldest patients with a linear increase in incidence [61, 68]. This was probably masked in some studies because of under investigation of older patients. A meta-analysis of 20 studies found an annual incidence, over all age groups of 13.9/100,000 and calculated rates in people <25 years of 2.0/100,000 with a steady increase though the subsequent age groups to a maximum of 31.3/100,000 in people >85 years of age (Table 8.10) [87].
   (b) Gender. There is an increased incidence of SAH and the presence of an intracranial aneurysm in women. The rate in women increases with age. In older patients, female rates of SAH are generally 1.5–2.5 times higher than men, and the median age of presentation is later than men. This is largely due to the higher rates of aneurysms in young males with gender differences in rates of SAH less apparent amongst younger patients and those with familial aneurysms [22]. Bonita et al. found male SAH rates to be greater than female up to the end of the third decade [70].

      Clarke [86] calculated incidence of SAH for adult women as 11.5% (95% CI 10.6–12.6%) and men as 9.2% (95% CI 8.4–10.2%). Prevalence rates for intracranial aneurysm were calculated separately by Rinkel et al. [37] for woman as 4.6% (95% CI 3.5–5.9%) and men as 3.5% (95% CI 2.7–4.5%). This difference was age dependent as discussed above.
   (c) Ethnicity. Regional differences in the incidence of SAH have reported higher rates in Japan and Finland. Wermer et al. in their review calculated the relative risk of SAH as 3.4 (95% CI 2.6–4.4) in Japan or Finland compared to unity in other countries [82]. The prevalence of URAs in these countries, when adjusted for sex and age in a recent review was not increased compared to other countries. However, the rupture rate of URAs in a review of the Japanese literature was 2.7% (CI 2.2–3.3%) [88]. A paradox discussed above.
   (d) Previous SAH. Excluding early rebleeding, patients with URAs and a history of previous SAH were found to have higher rupture rates during observation in ISUIA and UCAS. This observation was confirmed in a review which calculated the increased relative risk of SAH in patients with a history of previous SAH at 1.3 (95% CI 0.85–2.0) [88]. There are several possible reasons, but the obvious

Table 8.9 Risk factors for subarachnoid haemorrhage

Positive	Negative	Neutral
Age (increasing)	Raised cholesterol	Body mass index
Female gender	Diabetes	
Japanese and Finnish		
Previous SAH		
Posterior fossa, AComA and PComA aneurysms		

[a]Data from a review of reviews [86]
AComA anterior communicating artery; *PComA* posterior communicating arttery

Table 8.10 Incidence of subarachnoid haemorrhage by age [87]

Age group (years)	Incidence per 100,000 (95% CI)
<25	2.0 (1.6–2.6)
25–35	7.7 (6.8–8.8)
35–45	10.5 (9.0–11.3)
45–55	19.5 (17.8–21.4)
55–65	24.8 (22.7–27.2)
65–75	25.4 (23.1–28.0)
75–85	26.2 (22.5–30.4)
>85	31.3 (24.6–39.8)

practical conclusion is that if some patients with URAs are more likely to suffer SAH than others and we can discover what causes this difference, we could be able to target preventative treatment to the higher-risk subgroup.

(e) Medical Comorbidities. Studies of coexisting medical conditions in victims of SAH have found several associations. These are:

(i) Raised systemic blood pressure. The evidence concerning an association between SAH and hypertension is contradictory, possibly because of the confounding effect of acute haemorrhage and complicating vasospasm. However, there have been four systematic reviews, all reporting a link between raised blood pressure and SAH [30, 89–91]. Reviews of data collected in the Asia Pacific Cohort Studies Collaboration (APCSC) [30] performed an individual patient data meta-analysis on 306,620 participants in 26 cohort studies, with nearly 1.9 million person years of follow-up [91, 92]. The calculated hazard ratio for SAH was 2.0 (95% CI 1.5–2.7) for people with systolic blood pressure >140 mmHg compared to those with lower blood pressure and for each 10 mmHg further increase in systolic blood pressure, the risk of SAH increased by 31% (95% CI 23–38). Both Feigin et al. [89] (in an update of the Teunissen et al. review [90]) and a review by Krishna and Kim [93] concluded that higher blood pressure is statistically associated with a higher risk of SAH.

(ii) Raised cholesterol levels. The relationship between cholesterol and SAH was investigated by APCSC [22], Teunissen et al. [90] and the Feigin et al. [89] update. The APCSC review found a hazard ratio for SAH of 0.9 (95% CI 0.7–1.3) when comparing people with cholesterol of 4.5 mmol/L or higher versus those with lower levels. The Feigin et al. review also concluded that hypercholesterolemia appears to be a risk-reducing factor for SAH [89].

(iii) Diabetes. In relation to diabetes, Feigin et al. wrote, 'an unexpected and new finding in this review was that diabetes mellitus was associated with substantial reduction of the risk of subarachnoid haemorrhage' [89]. This finding is counterintuitive given the association of diabetes with vascular disease but reminds us that the presence of an aneurysm does not inevitably lead to SAH.

(iv) Body mass index. The APCSC review [91] analysed body mass index (BMI) and reported a hazard ratio for SAH of 1.0 (95% CI 0.7–1.3) for body mass index of >22 kg/m^2 compared to a lower value. The same threshold was used in the review by Feigin et al. [89] and concluded that the evidence for an association with raised body mass index was inconsistent.

(f) Lifestyle factors. Other factors assessed as associated with SAH are:

(i) Smoking. Five systematic reviews have reported smoking as a risk factor for SAH. The individual participant data in the APCSC reported a hazard ratio for current smoking compared to not smoking patients of 2.4 (95% CI 1.8–3.4) [78]. This increased risk was independent of sex, age or whether the participants were in Asia or Australasia. This conclusion is supported by Krishna and Kim [93] who calculated an increased relative risk of SAH for current smoking versus nonsmoking of 3.2 (95% CI 2.4–4.3) in a meta-analysis of published data.

(ii) Alcohol. The APCSC review did not show an association and calculated a hazard ratio for SAH amongst people who currently drank alcohol compared to those who did not of 1.0 (95% CI 0.7–1.4) [78]. However, Krishna and Kim categorised alcohol consumption as none or low (<150 g/week) and high (>150 g/week) and found an increased risk of SAH amongst high-intake drinkers [93]. Similarly, the review by Feigin et al. [89] concluded that excessive alcohol intake had a statistically significant and consistent increased risk for SAH.

(iii) Physical activity. Raised blood pressure and increased cerebral blood flow during exercise theoretically increases the risk of aneurysm rupture. Physical activity, at the time of SAH, has been the source of interest and controversy. Locksley [19] found that SAH from all causes occurred during sleep in 27% and during coitus in 3% of patients. Fisher found ictus was related to exertion in 55% of patients and in only 8% did it occur during sleep, and then usually after coitus [94], but Sengupta RP and McAllister VL [95] reported that 73% of patients were awake and not involved in strenuous exertion at the time of ictus. Feigin et al. [89] assessed the evidence for a relationship between regular vigorous exercise and SAH. They reviewed three studies and concluded that any association was inconsistent [89]. Therefore, a link with physical exertion at the time of ictus or regular vigorous exercise has not been proved.

(iv) Time of day, day of the week and seasons of the year. This is an aspect of SAH that has received a surprising amount of attention. Two systematic reviews have reported on the onset of SAH at different times of day, on different days of the week, and during different seasons. Vermeer et al. combined data from 10 studies with a total of 2778 patients [96]. They found aneurysm rupture risk to be low during the night, start to rise in the early morning, remain high during the day with a small nadir around noon, and then to decrease in the evening. Feigin et al. [97] also found rupture more common during the day. They used midnight to 6 a.m. as a reference standard and calculated relative risks of 3.19 (95% CI 3.03–3.36) for 06.00–11.59 h, 2.63 (95% CI 2.47–2.80) for 12.00–17.59 h and 2.30 (95% CI 2.15–2.47) for 18.00–23.59 h. They also (unlike Vermeer et al.) found a higher rate on Sundays when compared to the other days of the week (relative risk 1.22, 95% CI 1.09–1.37, compared to the reference day which was Monday). The effect of season was assessed and relative risk for SAH in winter was 1.10 (95% CI 1.02–1.17) and in spring 1.07 (95% CI 1.01–1.13) compared to summer. The comparison of autumn to summer was not significant and was not reported as a relative risk [97].

2. Aneurysm Specific Factors

(a) Location. The anterior communicating artery (AComA) is the commonest site of a ruptured aneurysm in surgical and autopsy series (Table 8.1). Wermer et al. [82] calculated relative risks of rupture by site of aneurysm relative to ICA (including PComA) as follows: AComA 0.7 (95% CI 0.4–1.5), ICA (excluding PComA) 0.8 (95% CI 0.3–2.8), PComA 1.8 (95% CI 0.7–4.5), middle cerebral artery 0.4 (95% CI 0.2–1.0) and posterior circulation 0.8 (95% CI 0.3–2.8) (defined

as vertebral artery, basilar artery and posterior cerebral artery). This report thus supports the ISUIA finding that aneurysms of the posterior fossa have high rupture rates, though this was the same as AComA aneurysms in a recent report [98].

(b) Multiple aneurysms. The incidence of multiple aneurysms amongst patients presenting with SAH has been reported as between 15% and 33%. Patients with multiple aneurysms are more likely to be female (5:1 male to female ratio) [99]. Studies of patients with multiple aneurysms provide an insight into the relative rupture risks at different locations. Thus, the commonest locations for multiple aneurysms are the PComA and MCA locations, and the latter is the commonest location for a coincidental unruptured aneurysm to be identified in SAH patients [76]. This observation would suggest that the MCA is a 'safer' location.

(c) Size of aneurysms. Observational studies have shown a linear relationship with increasing aneurysm size and the occurrence of SAH as described above. Wermer et al. [82] in a data meta-analysis, calculated relative rupture risks for unruptured aneurysm by size with <5mm as references as: 5–10 mm 2.8 (CI 95% 0.9–8.4), >10 mm 5.2 (CI 95% 1.8–15.3) and >15 mm 15.5 (CI 95% 3.7–64.5). One conclusion which is generally accepted in practice is that the rupture rate for small URAs (<7 mm) is so low that it is probably lower that the complication rates of interventions. However, most SAH patients present with small ruptured aneurysms, i.e. less than 10 mm. The mean size of ruptured aneurysms was 8.6 mm and unruptured aneurysms 4.7 mm, in an autopsy study reported by Chason and Heidman [100]. This paradox may be explained if small aneurysms develop during an initial rapid period of growth and then either rupture or stabilise to a low rupture risk lesion. A scenario that makes it unlikely that surveillance imaging is likely to detect periods of short rapid growth prior to rupture, unless performed very frequently.

8.4.3.4 Screening for Intracranial Aneurysms

The advantages and disadvantages of screening for intracranial aneurysms are finely balanced. It is obviously better to avoid the potential morbidity of spontaneous rupture, but showing that screening is beneficial depends on showing that the chances and consequent morbidity of rupture are greater than the iatrogenic morbidity of preemptive treatment. Screening well people for intracranial aneurysms is bound to identify asymptomatic aneurysms in a sizable minority (i.e. 2–4%), and the majority of these aneurysms are statistically unlikely to rupture. So who do you screen and which aneurysm do you treat?

Central to these questions is the likelihood of rupture. The issue is made more difficult by our lack of understanding of the natural history of the growth and rupture process. If aneurysm rupture soon after they develop and before they can be detected, then screening is useless. Similarly, if a stable state develops, in which future rupture is unlikely, detecting and treating such lesion is a waste of resources.

1. *Who Should Be Screened?* It is now accepted that MRA is a safe and reliable method of detecting intracranial aneurysms since only very small lesions (which are unlikely to warrant treatment) are likely to be missed. To image the entire population is too expensive. Thus, screening has been proposed for people in high-risk groups:
   (a) Patients with ADPKD. In this condition, the prevalence of aneurysm has been estimated at 7–22% [101–104].
   (b) People with two first-degree relatives with aneurysms [105, 106]. The results of screening patients with one first-degree relative are not advocated because the yield is low (300 at-risk people need to be screened to prevent one fatal SAH [107].

But the detection rate of screening people with two or more first-degree relatives is 9% [108, 109].

(c) Patients with a history of previous aneurysmal SAH. They are clearly at greater risk than a person who has never had an aneurysm diagnosed, but the benefit has not been determined (see below).

2. *When Should People Be Screened?*
Screening before the age of 20 years is not recommended because aneurysms are so rare in children and a negative scan does not mean that individuals will not develop one when older. It is thus necessary to repeat screening. In one study, imaging repeated 5 years after a negative scan found new aneurysms in 7% of individuals [108]. Similarly, follow-up imaging in patients successfully treated for a ruptured aneurysm found a 20% incidence of de novo aneurysms as well as enlargement of coincidental aneurysms [110]. Bor et al. [109] modelled various intervals for repeat screening of at-risk individuals and concluded that the optimum interval was 7 years between scans in subjects between 20 and 80 years. Surveillance imaging after aneurysm treatments is initially intended to identify recurrences in treated lesions, but at some stage (currently undetermined), it is probable that recurrence is less likely than finding a de novo aneurysm and therefore the individual is effectively being screened.
3. *Determining at What Age to Cease Screening*
It must always be kept in mind that the point of screening is to improve the patient's health, and in older patients, the years of health gained by an intervention affect the decision to continue screening. Obuchowski et al. [111] reviewed the efficacy of screening individuals with a positive family history and concluded that non-invasive screening was only justified in young people (30 years old or younger). They estimated that a screening programme would actually reduce life expectancy if all patients with URAs were diagnosed and underwent surgery. Their recommendation assumed a constant risk rate of aneurysm rupture, which is not generally accepted, but it does highlight the need to consider the individual's life expectance when recommending treatment for an asymptomatic aneurysm and the potential consequences of offering screening.

8.5 Aneurysmal Subarachnoid Haemorrhage

Rupture of an intracranial aneurysm usually causes SAH and this event leads to the diagnosis in the majority of patients. Spontaneous SAH is an established clinical syndrome, which may occur without an aneurysm being identified as its cause. For practical purposes, it is assumed that acute spontaneous SAH is caused by an aneurysm until proven otherwise. In this section, the reader can assume that SAH is used to mean aneurysmal SAH, unless otherwise stated.

Acute SAH may occur with associated intracerebral haematoma in 20% and/or intraventricular haemorrhage in 40% of patients. Subdural haemorrhage is found in approximately 3% of patients [112]. Our understanding of the range of possible consequences of aneurysm rupture come from two large surgical observational studies in the 1960s and 1980s. The first, called the Cooperative Aneurysm Study, studied 5836 cases retrospectively and reported in a series of papers. It established most of the principles on which aneurysm surgery was based [113]. The second was the International Cooperative Study on the timing of aneurysm surgery [20], which recruited 3521 patients. It was designed to clarify the optimum timing for clipping and demonstrated that the best surgical results were obtained if operation was delayed for 10 days after SAH, but rebleeding during this time balanced the risk of surgery performed in the first 2 days.

8.5.1 Clinical Syndromes of Subarachnoid Haemorrhage

The consequence of SAH is a spectrum of symptoms and signs, which range from transient headache with minimal systemic disturbance to

sudden death. For description, this can be divided into the following groups:

(a) *Massive haemorrhage*: Patients rapidly loss consciousness and present in coma. They usually die within hours of ictus without regaining consciousness. This group represents about 20% [64] of all patients and about 12% die before reaching a specialist medical centre [114]. Rebleeding at anytime worsens the effects of SAH and is thought to be a common cause of deaths in the first few hours. Rebleeding within 24 h occurs in up to 15% of patients [115, 116].

The abnormal clinical signs are flaccid paralysis, which progresses to decerebrate limb movements. Hypertension and bradycardia may develop in response to raised intracranial pressure followed by unstable cardiovascular signs, pupillary irregularity and pyrexia due to loss of brain stem function, usually immediately prior to death. Autopsy examinations demonstrate intracerebral and intraventricular haemorrhage in the majority of victims [117].

(b) *Major haemorrhage*: This is the commonest presentation amongst patients admitted to specialist neurological centres. The symptoms and signs are headache, loss of consciousness, vomiting, seizure, confusion and focal neurological deficits. Headache and nausea are the commonest initial symptoms, present in 70–80% of patients [118, 119]. The headache is of sudden onset and typically of unusual type and severity. Vomiting is a nonspecific feature of spontaneous intracranial haemorrhage, which if accompanied by diarrhoea suggests bleeding in the posterior fossa. Loss of consciousness (usually transient) occurs in 30–40% of patients [120, 121]. Neck stiffness is present in 35% [122], and a seizure occurs in about 10% of patients [123]. Other symptoms include photophobia, blurring of vision, meningism and confusion. Focal neurological disturbances may be related to intracerebral extension of haemorrhage or direct involvement of a cranial nerve.

(c) *Minor haemorrhage*: Rapid cessation of bleeding following aneurysm rupture will limit the volume of SAH and the severity of the clinical syndrome. Leakage is a better description of this level of bleeding, which is presumably quickly tamponaded by the effects of a rise in pressure around the aneurysm sac together with the combined effects of reduced cerebral blood flow and local clot formation [124, 125]. The latter depends on several factors, i.e. blood coagulability, size of the rupture point, aneurysm location and effect of fibrous membranes within the subarachnoid space. Patients complain of unusual headache, which may be mild but usually of sudden onset, and photophobia. They may develop neck or back pains. Consciousness is not lost and signs of meningism may be minimal and transient. Higher mental functions are preserved and abnormal physical signs, including disturbances of autonomic functions, are absent. Patients with mild transient symptoms due to aneurysm rupture represent a diagnostic challenge for primary care physicians.

(d) *Warning leaks*: Some patients describe episode(s) of transient unusual headache prior to presentation with substantial SAH. These headaches are less severe, may be accompanied by nausea and last a few days. They have been reported to occur in the 2–4 weeks prior to SAH in 15–37% of patients [126–128]. Amongst SAH patients studied by Leblanc and Winfield [126], half had consulted physicians with symptoms such as hemicranial or periorbital pain and generalised headaches in the previous 4 weeks, but none were diagnosed as harbouring aneurysms. The headache is usually attributed to minor leaks, after which aneurysm bleeding rapidly ceases, because CT is negative for SAH.

(e) *Sentinel headache*: This term is sometimes used synonymously with 'warning leak', but I think it is best reserved for the patient who presents with a shorter history of usual headache of progressing intensity prior to SAH. A well-recognised syndrome is spontaneous onset painful ophthalmoplegia due to parasellar aneurysms, typically of the posterior communicating artery. In this instance, an alternative explanation is that the headaches are caused by aneurysm enlargement and/or mural haemorrhages during periods of rapid aneurysm growth preceding rupture.

8.5.2 Causes of Subarachnoid Haemorrhage

Spontaneous SAH is due to aneurysm rupture in approximately 80% of patients. A list of other possible causes is presented in Table 8.11. The commonest alternative vascular cause is a brain arteriovenous malformation, found in 6–10% of patients. There are also patients who present with spontaneous SAH, and no aneurysm or vascular cause is demonstrated on angiography. This syndrome is usually called angiographic negative subarachnoid haemorrhage (ANSAH). The incidence of ANSAH has fallen as the sensitivity of imaging for the detection of aneurysms has improved. Thus, the proportion of SAH patients with demonstrated aneurysms was 51% in the cooperative study [113], 75% in 1990 [129] and 85% in 2002 [125]. A perimesencephalic distribution of SAH on CT scans is common after ANSAH [130]. No explanation or underlying vascular cause has, so far, been discovered to explain this association.

Table 8.11 Causes of subarachnoid haemorrhage

Ruptured aneurysm
Trauma
Intracranial vascular malformations: brain AVM, dural AVF and cavernous malformation
Hypercoagulation states: iatrogenic, idiopathic or congenital
Pituitary apoplexy
Sickle cell disease
Vascular thrombosis
Vasculitis
Tumour, primary or secondary
Cocaine or amphetamine abuse

8.5.3 Acute Effects of Subarachnoid Haemorrhage

Haemorrhage into the subarachnoid space[5] irritates meningeal sensory fibres and causes a rise in intracranial pressure (ICP). The immediate results are:

(a) Pain, characterised by severe headache and neck stiffness.
(b) Fall in cerebral blood flow (CBF) and acute cerebral ischaemia, which is exacerbated by impaired cerebral autoregulation. The mechanisms involved are a combination of the rise in ICP, acute vasoconstriction, reduction in cerebral perfusion pressure, decrease in available nitric oxide and microvascular changes including an increase in platelet aggregation, decreased perfusion and increased endothelial permeability [131].
(c) Systemic release of a range of catecholamines causing cardiac and pulmonary effects.

Rises in intracranial pressure after SAH usually resolve rapidly within minutes or hours, but as with the severity of subsequent responses to

[5]The subarachnoid space is lined by arachnoid and pia mater and contains approximately 150 ml of CSF, arteries and veins, cranial nerves and fibrous bands between the meningeal layers. The space extends for a variable distance into cerebral sulci and around cerebral arteries and veins as they penetrate the cerebral substance. Cerebrospinal fluid percolates through the space; the prevailing extra ventricular flow is from posterior fossa through the basal cisterns to parasagittal arachnoid villi.

SAH, the rate and completeness of recovery depends on how well blood is cleared from the space and whether acute hydrocephalus develops. The overall severity of the resulting illness thus depends to a large extent on the volume of haemorrhage (i.e. blood load in the subarachnoid space).

Patients are usually initially assessed at non-specialist hospitals before being transferred to the neurological centre. At the severe end of the severity spectrum, they are often transferred to a specialist hospital after intubation and on mechanical ventilation, in which case, it is important to review the record of the initial examination. Abnormal findings on physical examination after SAH can be separated into nonlocalising and localising:

Nonlocalising Signs

(a) *Signs of meningeal irritation*: Headache is the commonest and may persist for 2–4 weeks. It may be accompanied by neck stiffness, backache (with a positive Kernig's sign), photophobia and pyrexia [94].
(b) *Irritability and confusion*: The restless or confused patient should be monitored carefully because if worsening, such symptoms may be signs of raised ICP and developing hydrocephalus or vasospasm.
(c) *Cardiac, respiratory and autonomic system dysfunctions*: The initial cardiovascular response to aneurysm rupture is systemic hypertension. Systemic blood pressure may fluctuate over the first few postictal days. Pre-existing hypertension may be difficult to exclude and secondary features of chronic hypertension, such as left ventricular enlargement, retinal artery changes and evidence of renal disease, should be sought.
(d) *Retinal, subhyaloid or vitreous haemorrhages*: This effect of aneurysm rupture should be excluded by examination, since patients may not be aware of subtotal visual loss. Intraocular bleeding probably results from transmission of raised intracranial pressure to the orbital optic nerve causing engorgement and rupture of retinal veins. It is known as Terson's syndrome [132] and is commonest after anterior communicating artery aneurysm rupture. It usually clears spontaneously over 3–12 months but may need surgical evacuation [133].
(e) *Ictal seizures*: A single seizure or occasionally 2–3 seizures occur in 10–17.5% of patients at the time of bleeding or soon afterwards [134, 135]. They are known as 'ictal seizures' and usually defined as occurring in the first 24 h after SAH. Importantly, they don't imply an increased risk of subsequent epilepsy.

Localising Signs

In the International Cooperative Study, focal abnormal findings on examinations at post-SAH day 3 were described as focal motor deficits (12% mild and 5.6% severe), including dysphasic speech (4.7%), cranial nerve deficits (12.2%) and hemianopsia (2.2%) [20].

(a) *Hemiparesis, hemianopsia or dysphasia*: Focal neurological deficits are caused by pressure of haematomas or vasospasm with ischaemia/infarction in the distal arterial territory. Classically, ACA aneurysms cause paraparesis [136] and MCA aneurysms hemiparesis with dysphasia if in the dominant hemisphere.
(b) *Memory disturbances and impaired higher mental functions*: These are common but difficult to assess in the acute period. Dementia and emotional liability occur after bifrontal damage due to rupture of ACA aneurysms [137], and Korsakoff's syndrome [138] has been described after infarction in the mammillary bodies, fornices and thalami.
(c) *Cranial nerve palsies*: These are caused by compression by an expanding aneurysm or nerve damage secondary to rupture (direct trauma or bleeding into the perineural sheath) [139]. Mass effect due to intracerebral

haematoma (ICH) or hydrocephalus may cause brain stem compression or distortion of cranial nerves around the tentorial hiatus. In the International Cooperative Study, cranial nerve deficits were reported in 428 patients, and in 277 (64.7%), it involved the IIIrd cranial nerve. Oculomotor nerve palsy occurs due to compression by PComA, basilar artery (BA) or intracavernous ICA aneurysms. Painful ophthalmoplegia occurs with some degree of pupillary dilation due to direct pressure or extravasation of blood into the nerve fascicles. The nerve is most often affected following PComA aneurysm rupture, and the pupil is usually involved because the preganglionic parasympathetic fibres to the ciliary ganglion are carried in the superficial nerve and are vulnerable to local pressure. Their interruption causes a dilated pupil, which fails to constrict to light or on attempts at the convergence–accommodation reflex [140].

Palsies of other cranial nerves are unusual after SAH, though any cranial nerve may be damaged by localised SAH. Anosmia and deafness or hyperacusis occasionally occur and usually recover. They are presumably a direct effect of blood in the subarachnoid space. The VIth nerve, because of its vertical course in the subarachnoid space, is liable to distortion by downward pressure on the brain stem and palsy has been described after brain stem infarction [141].

8.5.4 Grading of Patients After Subarachnoid Haemorrhage

The broad spectrum of symptoms and signs after SAH lead to the introduction of grading scales. These systems are widely used for research and in clinical practice to quickly communicate a patient's condition. The student should differentiate systems used for the assessment of a patient's neurological condition at presentation from those used to assess outcomes after SAH.

8.5.4.1 Assessment of Neurological Conditions at Presentation

The assessment of the patient's neurological condition when they first reach hospital is crucial since it correlates with the severity of the subsequent illness and its prognosis. The first grading system was modelled on a five-point scale described by Botterell et al. [142] and then adapted by Hunt and Hess [143]. In the 1980s, a plethora of scoring systems were in use, and in order to define a universally acceptable scale, a committee of the World Federation of Neurological Surgeons (WFNS) was set up [144]. This group concluded that the most important factors affecting outcome were the patient's level of consciousness (which predicted death and disability) and the presence or absence of hemiparesis and/or aphasia (which predicted disability but not mortality). The presence of headache and neck stiffness in conscious patients had no significance on outcome and therefore Hunt and Hess [143] Grades I and II were identical for outcome. They formulated a WFNS grading system on the basis that:

(i) A 5-grade system is retained and unruptured aneurysm could be classed Grade 0.
(ii) The Glasgow Coma Scale [145] is used for the evaluation of the level of consciousness.
(iii) The presence of a major focal deficit (aphasia and/or hemiparesis or hemiplegia) is used to differentiate Grades II and III.

The WFNS grading system is easier to use and less liable to the inter-observer errors associated with Hunt and Hess and Nishioka systems [146]. Its link to Glasgow Coma Scale is it main advantage (Table 8.12).

The Glasgow Coma Scale (GCS) was introduced to assess head injury patients in 1974 [145] and has stood the test of time. It is a practical scale which can be used in any patient with altered level of consciousness and is widely used for the assessment of SAH patients (Table 8.13). It is frequently called the Glasgow coma score [134].

Table 8.12 Grading systems used for patients after SAH

	Botterell et al. [128]	Hunt and Hess [129]	WFNS[a] [130]
Grade 1	Conscious patient with or without signs of blood in subarachnoid space	Asymptomatic, minimal headache or slight nuchal rigidity	GCS = 15, no hemiparesis or aphasia
Grade 2	Drowsy patient without significant neurological deficit	Moderate to severe headache, nuchal rigidity, neurological deficit confined to cranial nerve palsy	GCS = 14–13, no hemiparesis or aphasia
Grade 3	Drowsy patient with a neurological deficit and probably an intracerebral clot	Drowsiness, confusion or mild focal deficit	GCS = 14–13, with hemiparesis or aphasia
Grade 4	Major neurological deficit and deteriorating because of large intracerebral clots or older patients with less severe neurological deficit but pre-existing degenerative CVD	Stupor, moderate-severe hemiparesis, possibly early decerebrate rigidity, and vegetative disturbances	GCS = 12–7, with or without hemiparesis or aphasia
Grade 5	Moribund or near moribund patient with failing vital centres and extensor rigidity	Deep coma, decerebrate rigidity, moribund appearance	GCS = 6–3, with or without hemiparesis or aphasia

[a]Patients with unruptured aneurysm = Grade 0, *CVD* cerebrovascular disease, *GCS* Glasgow coma scale

Table 8.13 Glasgow coma scale for assessing level of consciousness. Assessment scores for each response are added together to give a scale value between 3 and 15

Glasgow coma scale		
Eye response	Verbal response	Motor response
1 – No eye opening	1 – No sounds	1 – No movements
2 – In response to pain	2 – Incomprehensible	2 – Extension to pain
3 – In response to speech	3 – Inappropriate	3 – Abnormal flexion to pain
4 – Spontaneous	4 – Confused	4 – Withdrawal to pain
	5 – Normal	5 – Localises to pain
		6 – Obeys commands

8.5.4.2 Assessment of Outcomes After Subarachnoid Haemorrhage

After the GCS was established, a 5-level scale was proposed by the same group to assess outcome in head injury patients [147]. This is now generally known as the Glasgow Outcome Scale (GOS) or outcome score. There is some confusion in the literature about how the scale should be presented. In the original proposal, five outcome categories were defined: (1) dead, (2) vegetative state, (3) severely disabled, (4) moderately disabled and (5) good recovery. A higher grade meant improvement. However, this has been variously interpreted as a 1–5 scale, with Grade 1 = dead or Grade 1 = good recovery. Since the original authors did not specify a numerical order, it has been left to editors to decide its correct use; thus, the literature is ambiguous. I prefer to use it as: Grade 1 = good recovery and Grade 5 = dead because it is more intuitive in the light of the other commonly used outcome-scoring system the modified Rankin scale [148]. This was developed to assess stroke patients and was modified for use in the UK-TIA trial [149] and is now known as the modified Rankin scale (mRs) [150]. The modified Rankin scale (Table 8.14) is a six-point scale with Grade 6 = dead. It was used in the International Subarachnoid Aneurysm Trial (ISAT) [151] in which patients or their carers completed a vali-

Table 8.14 Descriptive terms used in the Glasgow Outcome Scale (GOS) and modified Rankin Scale (mRS)

Glasgow Outcome Scale [147]		Modified Rankin scale [149]	
		0	No symptoms at all
1	Good recovery: Patient can lead a full and independent life with or without minimal neurological deficit	1	No significant disability despite symptoms and able to carry out all usual duties and activities
2	Moderately disabled: Patient has neurological or intellectual impairment but is independent	2	Slight disability: Unable to carry out all previous activities, but able to look after own affairs without assistance
3	Severely disabled: Patient is conscious but totally dependent on others to get through daily activities	3	Moderate disability: Requiring some help, but able to walk without assistance
4	Vegetative state: Patient is breathing spontaneously but remains unresponsive	4	Moderately severe disability: Unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Dead	5	Severe disability: Bedridden, incontinent and requiring constant nursing care and attention

Table 8.15 Complications after aneurysmal SAH

Complication	Frequency
Rebleeding	4–10% < 24 h
	1–1.5% per day < 30 days
	3% pa > 3 months
Hydrocephalus	15–20% < 15 days
	5–8% > 15 days
Vasospasm	60% angiographic
	20–30% symptomatic
Seizures	10% ictal
	6–10% postclipping
	2–4% postcoiling

dated questionnaire. Both systems have been shown to be reliable in interobserver studies [152, 153]. These outcome-scoring systems are used to evaluate the overall social impact of brain damage for survivors of SAH (Table 8.15).

8.5.5 Complications of Subarachnoid Haemorrhage

The mortality rate after SAH (up to 30 days) reported in the 1960s Cooperative Study was 50%; it has reduced and was recently calculated from in-hospital deaths statistics in the USA as 33% [154]. It is the nature of SAH that the only way to improve mortality and morbidity rates is to prevent or mitigate the effects of its associated complications. The complication of SAH and their frequency are listed in Table 8.15.

8.5.5.1 Aneurysm Rebleeding

Rebleeding after SAH is the most clearly preventable complication after SAH. It will be discussed in terms of its frequency, risk factors and means of prevention.

(a) *Incidence and timing of rebleeding*: Estimating the rates of rebleeding is difficult because ruptured aneurysms are now secured as soon as possible after SAH, leaving few patients for observation studies. An exception is the pre-CT Cooperative Study, which was able to observe untreated patients and reported an overall confirmed fatal rebleeding rate of 25% [155]. In the later International Cooperative Study, Kassel and Torner [156] estimated the rebleeding rates as 1–5%/day after the first 48 h with a cumulative rate of 26.5% by 14 days. This study suggested that the risk falls with time and is greatest in the first 24 h. It is generally agreed that by 3–6 months, the risk has fallen to the annual rebleeding rate of 3–4% [155, 157]. The overall incidence reported in more recent studies is in the range 6–10% [116, 158, 159]. An increase in mortality rates for SAH patients has been consistently reported if rebleeding occurs and estimates range from 50% to 90% [159–161].

(b) *Risk factors for Rebleeding:* Poor WFNS grades and delay in clipping or coiling are associated with increased rebleed rates [162]. Early angiography has been shown to be a

cause; Inagawa et al. [163] estimated that early angiography (within 6 h of rupture) doubled the risk of rerupture. It is likely that the introduction of CT angiography acutely after SAH will therefore reduce the risk of early rebleeding from this cause. Other reported risk factors are intracerebral haematoma [162], systemic hypertension [164], ventricular drainage [165, 166] and large aneurysm size [164].

(c) *Factors contributing to reducing rebleed rates*: Successful clipping was calculated to reduce the risk of rebleeding by 19% in a meta-analysis comparing clipping to conservative treatment [167]. Early surgical clipping halved the rate in the International Cooperative Study; rebleeding occurred in 13.9% of patients operated on Day 11–14 and 5.7% of patients operated on Day 0–3 post-SAH [168]. Similarly, the International Subarachnoid Aneurysm Trial (ISAT) showed that endovascular treatment is effective at reducing rebleeding rates, albeit at a rate less than after successful clipping, with annualised rates of 0.9% after clipping and 2.9% after coiling in 2143 randomised participants [169]. Medical treatment with antifibrinolytic drugs (i.e. tranexamic acid and epsilon aminocaproic acid), which stabilise perianeurysm clot, has been shown to reduce rebleed rates [170]. However, this treatment was found to increase the frequency and severity of delayed vasospasm and abandoned [171]. A recent study, which showed a benefit if used for bridging prior to early coiling or clipping, has renewed interest in their potential to reduce rebleeding [116].

8.5.5.2 Vasospasm

Acute vasospasm occurs immediately after aneurysm rupture, causes transient constriction of basal cerebral arteries and contributes to the presenting illness. Its cause is probably a combination of the sudden rise in intracranial pressure, mechanical disruption/compression of arteries and release of short-acting vasoconstrictors, such as adrenaline, thrombin and 5-hydroxytryptamine from platelets.

Delayed vasospasm occurs 6–10 days after SAH and is recognised as angiographic narrowing of cerebral arteries which causes symptoms if the collateral blood supply is inadequate. If ischaemic symptoms result, the term symptomatic vasospasm is used. This complication is another potentially preventable cause of additional morbidity after SAH and is caused by the adventitial exposure of cerebral arteries to the breakdown products of blood and subsequent changes in vascular smooth muscle function. There is currently no universally effective therapy.

Symptomatic vasospasm due to cerebral ischaemia is an inconsistent consequence of angiographic vasospasm. It was first described by Robertson [172] in 1949 and is characterised by the insidious onset of confusion, decreased conscious level and/or focal neurological deficits. Angiographic vasospasm after SAH was first described by Ecker and Riemenschneider in 1951 [173]. They reported finding focal narrowing of basal cerebral arteries, which usually involved arteries adjacent to the ruptured aneurysm, in patients examined within 23 days of SAH. They felt it was provoked by arterial disruption at the time of the ictus and that its role was protective, i.e. to limit the amount of haemorrhage. The time course of symptomatic vasospasm parallels that of angiographic vasospasm, the onset being rare before the third post-ictal day, with a peak incidence at about the seventh day [174]. It rarely persists for longer than 3 weeks after SAH [175].

(a) *Aetiology of delayed vasospasm*: It is caused by the adventitial exposure of cerebral arteries to the breakdown products of blood and subsequent changes in vascular smooth muscle function. Early researchers noted that vasospasm did not occur without a significant amount of blood in the subarachnoid space [176], and the locations of periarterial haematomas correlated with sites of arterial narrowing [177–179]. Components of whole blood have been suspected as acting as the putative spasmogen, most recently haemoglobin and oxyhaemoglobin, since its release from red blood cells and breakdown coincides with the delay in vasospasm onset.

Oxyhaemoglobin has a vasoconstriction action, possibly due to it acting as a generator of superoxides or inhibiting endogenous dilators such as nitric oxide either directly [180] or indirectly via smooth muscle cyclic guanosine monophosphate [181] or by stimulation of vasoconstrictors such as the endothelins produced by endothelial cells [182].

(b) *Incidence and effects of delayed vasospasm*: In an extensive survey of the literature, Dorsch and King [183] calculated the incidence of angiographic vasospasm as 43.3% (range 19–97% in 222 studies) and symptomatic vasospasm as 32.4% (range 5–90% in 296 studies). When they restricted the survey to reports of its diagnosis between 4 and 11 days after SAH, the incidence of angiographic vasospasm increased to 67.3% (range 40–97% in 38 studies) but was similar for symptomatic vasospasm at 32.6%. Thus, only about half the number of patients with evidence of angiographic vasospasm will develop neurological symptoms, but asymptomatic patients may show evidence of vasospasm on serial transcranial Doppler or perfusion CT [184, 185].

(c) *Consequences of delayed vasospasm*: Whether individual patients experience symptoms of cerebral ischaemia or not depends on the degree of arterial narrowing, its location and the adequacy of collateral blood flow as well as other factors, such as increased intracranial pressure or the presence of cerebral oedema. Delayed Mortality rates are increased amongst patients with symptomatic vasospasm; Dorsch [186] calculated that the odds of a fatal outcome were three times greater. He coined the term delayed ischaemic neurological deficit (DIND) for symptoms due to vasospasm and more recently delayed cerebral ischaemia (DCI) for symptoms accompanied by CT evidence of infarction. The morbidity (i.e. permanent neurological defict) and mortality rates of patients who develop DINDs are 34.7%, and 31.0% respectively [166].

(d) *Treatment of delayed vasospasm:* Preventative treatment using the calcium channel blocker, nimodipine, is the most universally applied therapy. A benefit in terms of reducing infarcts and improving outcomes has shown in a randomised trial [187]. But oral nimodipine does not reduce the frequency of angiographic vasospasm, and management of symptomatic patients has relied on the so-called triple-H therapy: hypertension, hypervolaemia and haemodilution [188]. The objective is to maintain the optimum cerebral perfusion, and intensive care management of symptomatic patients has adapted the technique (normovolaemia is now generally parcticed) since its original description in 1983. Various additional drugs have been trialled, such as magnesium, statins and the endothelin receptor antagonist clazosentan, but none have not proved entirely effective [189, 190]. Endovascular treatment by selective angioplasty is generally reserved for symptomatic patients refractory to supportive measures. Angioplasty can be performed by intra-arterial injections of vasodilators or by balloon inflation. These techniques and their results are described in Tutorial 9. However, overall supportive treatment has improved outcomes over the last two decades [191].

8.5.5.3 Hydrocephalus

The additional morbidity due to hydrocephalus can be avoided by expeditious treatment, which in turn depends on expeditious diagnosis. Thus, the patient after SAH requires monitoring of their level of consciousness and CT available at short notice.

(a) *Incidence*: Obstruction to the circulation of cerebrospinal fluid may occur acutely or days or weeks after SAH. The incidence of acute hydrocephalus following SAH is 15–20% [134, 192]. Ventriculomegaly evident on CT scan or MRI implies an impediment to normal CSF flow, but its clinical consequences are variable, and the severity of symptoms of raised intracranial pressure dictate the need for surgical intervention. It has been shown that in 50% of patients with enlarged ventricles at presentation, CSF flow can be normal within 24 h. Thus, emergency

treatment is usually provided by a temporary ventricular or lumbar drain [134].

(b) *Aetiology*: Acute ventriculomegaly is caused by blood cells and cellular debris obstructing CSF flow in the ventricles, basal cisterns or around the exit foramina of the fourth ventricle. Alternatively, ventricular enlargement occurs due to haematomas, particularly in the posterior fossa compressing CSF pathways. Chronic hydrocephalus is due to the development of fibrosis and adhesions within the leptomeninges which impede CSF flow and/or its absorption by arachnoid granulations.

The presence of intraventricular haemorrhage is obviously more likely to cause acute hydrocephalus. Mohr et al. [193] reported acute ventricular dilation in 85% of 91 patients with intraventricular haemorrhage. Other factors causing hydrocephalus are diffuse SAH, posterior circulation aneurysms, large aneurysm size, low GCS on admission, pre-existing systemic hypertension, increasing age and use of antifibrinolytic drugs [192].

(c) *Clinical consequences*: These vary from sudden death to mild reduction in the level of consciousness. In a cohort reported by Hasan et al. [134], 91 patients had hydrocephalus on their initial CT but their levels of consciousness were normal in 28%, slightly impaired in 14% and moderately or severely impaired in 58%. Ventricular drainage has been reported to increase the risk of rebleeding, but a recent report suggests the rebleeding risk is not increased [194]. Patients who develop subacute and chronic hydrocephalus complain of headache, drowsiness with fluctuating levels of consciousness, ataxia, dementia and incontinence. Onset of symptoms is typically insidious but a patient's condition may deteriorate rapidly and simulate rebleeding. A definitive CSF drainage procedure either ventricular–peritoneal or lumbar–peritoneal shunting is necessary in only 5–8% of SAH patients [195], and often symptoms can be managed during the subacute period by serial lumbar punctures and CSF drainage alone.

8.5.5.4 Medical Complications

Patients after SAH are now generally nursed in the neurosurgical ward or an intensive care unit. Intensive care specialists are expert in managing the medical complications associated with this illness, but endovascular therapist should be aware of the effects of SAH on patient's general condition and be able to participate in multidisciplinary team discussions with knowledge of potential medical complications. Furthermore, together they represent a large proportion of all complications after SAH. In a multicentre study, Solenski et al. [160] attributed the causes of death at 3 months to 19% initial haemorrhage, 22% rebleeding, 23% vasospasm and 23% to medical complications.

(a) *Pulmonary*: These affect 20–25% of patients and include aspiration pneumonia, adult respiratory distress syndrome (ARDS), pulmonary embolus and neurogenic pulmonary oedema (sometimes considered synonymous with ARDS) [196]. Pulmonary oedema (in the absence of left-sided cardiac failure) may occur after any cerebral insult associated with raised intracranial pressure and after SAH usually occurs in the first few days. It affects 23% of patients and severely in 6% [160]. The mechanism is uncertain but it is thought to be the result of a massive adrenergic discharge, which may act to decrease left ventricular compliance or directly on pulmonary adrenergic receptors to increase capillary permeability and leakage of protein-rich fluid [197].

(b) *Cardiovascular*: These complications include systemic hypertension and arrhythmias. Systemic hypertension may be reactive or predate SAH and occurs in 16–36% of patients [146]. Cardiac dysrhythmia and electrocardiogram abnormalities may be found in 35–50% of patients [160, 198]. The latter are prolongation of the Q–T interval, T wave abnormalities including inversion, ST segment changes and prominent U waves. A variety of arrhythmias

occur in the first few days and usually are not life threatening. The heart is affected by excessive sympathetic activity, which is thought to cause these effects seen after SAH [199]. A reversible cardiomyopathy affects up to 20% of poor-grade patients and includes abnormal levels of cardiac enzymes simulating myocardial infarction [200, 201].

(c) *Electrolyte disturbances*: These include hyponatraemia, hypokalaemia and diabetes insipidus. The commonest is hyponatraemia, which is defined as plasma sodium levels below 135 mEq/L for two consecutive days. It occurs in 27–35% of patients. In the past, it was thought to be due to inappropriate secretion of antidiuretic hormone, but it is now considered a primary natriuresis (or cerebral salt wasting syndrome) associated with cerebral injury [202]. Its severity is proportional to the severity of SAH. Diabetes insipidus is relatively rare except in poor-grade patients after severe and prolonged episodes of raised intracranial pressure.

The pathophysiological mechanisms for electrolyte and endocrine disturbance after SAH remain uncertain. It is postulated that hypothalamic damage is the cause since hyponatraemia has been linked with the presence of blood in the chiasmatic cistern, third ventricle and AComA aneurysm rupture [203]. Atrial natriuretic factor (a diuretic natriuretic hormone) may play a role in urinary salt loss particularly as both hypothalamic and myocardial lesions have been demonstrated at autopsy [204]. Iatrogenic factors contribute to electrolyte disturbances, particularly during diuretic and hypervolaemic treatments to control ICP and vasospasm, which makes medical management complex.

(d) *Seizures*: Seizures after SAH that occur at the time of aneurysm rupture, i.e. ictal seizures, have been discussed above. Delayed events are related to the occurrence of complications and whether craniotomy is performed. Delayed recurrent seizures constitute epilepsy. Older surgical series (i.e. treatment by clipping) reported late seizures occurring in as many as 20% of patients with the highest incidence after clipping of MCA aneurysms. In recent reports of patients treated by clipping, incidences of late seizures are 3–10% [135, 205]. In a single hospital study with 12 months follow-up, Claassen et al. [206] reported an incidence of 7% for late seizures with subdural hematoma and cerebral infarction as independent risk factors. They didn't distinguish between coiling and clipping treatments. An audit of coiled patients with 2 years follow-up reported an incidence of only 1.7% and treatment of hydrocephalus a risk factor [135]. Amongst patients randomised in ISAT (which included relatively few MCA aneurysms), the frequency of late seizures at 5 years was 6.4% and 9.6% for patients randomised to coiling and clipping, respectively [207]. The occurrence of ictal seizures is not associated with an increased incidence of delayed seizures [208] and doesn't warrant the use of prophylactic antiepileptic drugs.

8.6 Endovascular Treatments of Aneurysms

Endovascular treatments to occlude aneurysms can be divided into those that involve occlusion of the parent artery and those that preserve it. We are rapidly progressing to the point when the former is largely obsolete, but it is likely to retain a limited role for some time yet.

- Treatment with parent artery occlusion
  Proximal artery occlusion and/or trapping
  Flow reversal
- Treatments with parent artery preservation
  Endosaccular coil embolisation
  Balloon-assisted coiling
  Endosaccular liquid embolic agents
  Stent-assisted coiling
  Neck-bridge devices
  Flow diverter devices
  Endosaccular flow disruptor devices

8.6.1 Endovascular Treatments with Parent Artery Occlusion

Occlusion of the aneurysm parent artery is an effective method of inducing thrombosis and preventing aneurysm growth and rupture [209]. Surgical ligation of the common carotid artery was used to treat cavernous and larger aneurysms of the carotid artery prior to the introduction of endovascular occlusion by Serbinenko in 1974 [210]. Endovascular occlusion is safer than surgical ligation because it can be combined with a more accurate assessment of collateral blood flow to tissues supplied by the target artery [211]. Occlusion is generally performed at the level of the aneurysm neck or immediately proximal to the neck. Variations to this principle are to trap the aneurysm with occlusions proximal and distal to its neck, to reverse the direction of blood flow in the parent artery by remote embolisation or to combine endovascular ligation with a surgical by-pass operation. Balloons, coils or plugs (i.e. nitinol expandable mesh devices) can be detached in the artery to cause occlusion.

The indications include:

- Giant secular aneurysms with wide necks and heavily calcified walls
- Wide-necked and fusiform aneurysms
- Distal aneurysms above the level of the circle of Willis on small arteries
- Post-traumatic pseudoaneurysms and infectious aneurysms
- Failed endosaccular embolisation
- As a salvage procedure after dissection or implant malposition

(a) *Technique*: Preliminary test occlusion of the parent artery is generally performed with the patient awake and heparinised (with activated clotting time (ACT) increased to 3× baseline). A non-detachable balloon is inflated for 20–30 min at the site of proposed permanent occlusion. The patient's neurological status is assessed at intervals (typically at 5, 15 and 30 min) during the occlusion. Collateral blood flow is also assessed angiographically by comparing the time delay in the appearance of contrast in cortical veins of the two cerebral hemispheres. A delay of greater than 2 s indicates an inadequate collateral blood supply. Additional provocative testing can be performed using acetazolamide or induced systemic hypotension and quantitative assessments of cerebral blood flow with transcranial Doppler ultrasound, HMPAO or SPECT. If there is no change in the patient's neurological examination, the artery is usually occluded immediately with detachable implants (coils, balloons or plugs), and the patient is kept well hydrated and under careful observation for 2–4 days [212]. Adjuvant medical treatments with corticosteroids (to reduce the effect of aneurysm swelling) and/or antiplatelet drugs (to reduce risk of intravascular thrombosis) are often prescribed empirically. CT or MRI is adequate for documentation of aneurysm thrombosis and regression. For treatment of very distal aneurysms, particularly infectious aneurysms, balloon test occlusion may not be feasible because of the small size of the parent vessels and operators have to rely on angiographic assessment of collateral blood supply. In this situation aneurysm and artery occlusions are generally performed with a liquid agent such as cyanoacrylate.

(b) *Complications*: The causes of immediate neurological complications are device misplacement, procedural thromboembolism and cerebral ischaemia due to inadequate collateral blood flow (i.e. inaccurate test occlusion). Delayed symptoms may develop due to swelling of the thrombosed aneurysm, inadequate collateral blood flow or thromboemboli generated in redundant artery sections (so-called stump emboli). The reported morbidity of surgical ligation of the common carotid artery was 13–31% [156, 211] and mortality 3–24% [155, 213]. Complications occurred more frequently in patients in poor clinical condition after SAH, presumably because of vasospasm [155]. Complication rates for endovascular balloon occlusion of the ICA are reported

as transient neurological deficits in 7.25–10.3% and permanent deficits in 1.5–4.4% of patients in two series with no mortality [214, 215]. The reduced morbidity associated with endovascular balloon occlusion is due to the ability to test collateral support in the conscious patient and use periprocedural anticoagulants to protect against thromboembolic complications.

(c) *Results*: There have been several reports of the effectiveness of parent artery occlusion of the carotid [215, 216] and vertebral arteries [217, 218] for the treatment of inoperable intracranial aneurysms. This treatment is particularly effective for aneurysms of the proximal internal carotid artery. Occlusion usually relieves compression symptoms such as pain or cranial nerve palsies although aneurysm regression can take months or years [216].

There is little data concerning the protection afforded by parent artery occlusion against rebleeding and few series large enough for comparisons between endovascular and surgical techniques. Early rebleeding after carotid ligation has been reported in 4.4% of patients [219] and late rebleeding in 11% of patients [220]. There are no series reporting rebleeding after endovascular occlusions but most parent artery occlusions are now performed for giant aneurysms, which seldom present with SAH. Symptoms due to compression may recur months or years after initially successful aneurysm thrombosis [209] and enlargement of a completely thrombosed aneurysm has been described [221]. Follow-up of these patients is therefore important and can be performed noninvasively using MRA.

8.6.2 Endovascular Treatments with Parent Artery Preservations

8.6.2.1 Endosaccular Coil Embolisation

Endosaccular coil embolisation substantially replaced neurosurgical clipping for most aneurysms after the introduction of control release detachable coils by Guglielmi in 1991 [222, 223]. The basic technique has evolved with the introduction of improved coils, balloon-assisted coiling and stents flexible enough to use in the intracranial arteries. Soon after its introduction, the potential of a minimally invasive technique to prevent rebleeding after SAH was exploited [224] and the benefit confirmed in the ISAT randomised control trial (RCT), which reported in 2002 [151]. Coil embolisation after SAH is now generally accepted as the first-line treatment for ruptured aneurysms. However, its use in URAs has never been tested in an RCT [225, 226] and one should remember this when discussing the indications and results of endovascular aneurysm treatments [227].

The International Subarachnoid Aneurysm Trial (ISAT) randomised 2143 patients to either clipping or coiling on the basis of intention to treat aneurysms and judged equivalence of both methods [151]. The primary end point of the trial was the proportion of patients dependent or dead (modified Rankin scale 3–6) after 1 year. The trial reported in 2002 that 23.7% and 30.6% of patients allocated to coiling or clipping, respectively, were dependent or dead after 1 year: an absolute risk reduction for this outcome of 6.9% (CI 2.5–11.3). The pragmatic end point thus included the potential detrimental effects of complications resulting from either treatment or SAH. Since this publication, there has been a wholesale switch from clipping to coiling in most European centres. The trial has been criticised because only 22% of the available SAH patients were considered suitable for both treatments and offered randomisation at the participating centres. However, the outcome has been confirmed in a subsequent prospective multicentred study with complete ascertainment [228], and in a single centre randomised study which a clear benefit for treatment of posterior circulation aneurysms [229]. There have been several other prospective trials and registries, in particular two RCTs to test the benefits of modified coils, which reported an overall improvement in procedural safety since the ISAT [230, 231].

(a) *Technique*: A standard technique will be described. Local practices will vary particularly in regard to the use of anticoagulation and antiplatelet drugs to prevent thrombotic complications. Adjuvant techniques will be described below. Coil embolisation is performed under general anaesthesia so the patients can be adequately monitored and immobilised. Selective catheterisation of the aneurysm sac is performed using 1 or 2 (double catheter technique) microcatheters after systemic anticoagulation (by bolus injection or infusion of heparin), and packing is usually performed by placing large initial coils into which smaller coils are packed. The objective is to place as much metal within the sac as possible, which in practice means approximately 25% of the available space. Following embolisation, patients may be prescribed additional heparin and antiplatelet agents. Our practice is to make prescriptions based on the size of the aneurysm neck, using anticoagulants when the parent artery blood flow is exposed to a large surface of recently placed coils or if coils protrude into the parent artery [212]. Packing should be as dense as possible because subtotal treatment risks leaving the patient liable for delayed aneurysm rebleeding or recurrence.

(b) *Complications*: The reported procedural complication rate associated with coil embolisation is about 10%, and the commonest events are intra-arterial thrombosis and haemorrhage which occur in about 5% and 2% of procedures, respectively. The frequency of these two complications depends on whether treatment is for ruptured or unruptured aneurysms. Reported complication rates of thrombosis were 13.3% and 7.3% and of haemorrhage 3.7% and 2.0% for treatments of ruptured and unruptured aneurysms respectively in two large studies [228, 232].

The reported morbidity due to complication has reduced as the technique has matured. In a large retrospective Japanese study ($n = 5624$) of coil embolisation of ruptured aneurysms, the overall procedural morbidity was 2.9% and mortality 0.8% and attributed to haemorrhagic events (0.7% morbitity and 0.6% mortality), ischaemic events (2.0% morbitity and 0.3% mortality) and other events (0.2% morbitity) [233]. For this reason, anticoagulation during procedures is generally advised [211] and thrombolytis agents, such as IV aspirin and glycoprotein IIb/IIIa receptor inhibitors used to treat thromboembolism [301]. Other complications are technical due to device failures or those associated with endovascular navigation (e.g. arterial dissection, access site haematomas, etc.) with angiography (e.g. hypersensitivity reactions to administered drugs, cortical blindness) and general anaesthesia. Reported delayed complications include aneurysm bleeding or exacerbation of compression symptoms, hydrocephalus and a sterile meningitic reaction adjacent to the thrombosed aneurysm, transient ischaemic episodes, radiation-induced alopecia, seizures and coil compaction causing aneurysms recurrence [212, 234, 235].

(c) *Results:* Outcomes will be separated into anatomical and clinical. Obviously, the important end point is the clinical outcome, which in the long term depends on the risk of the treated aneurysm bleeding or becoming symptomatic. However, because coil embolisation is associated with a higher rate of anatomical aneurysm recurrence than clipping, coil compaction and recurrence has been closely studied (and reported). It is probable that a degree of coil compaction is an inevitable part of the maturation process of the thrombus around endosaccular coils and causes neck remnants. The two outcomes are nevertheless linked. Recurrent sac filling occurs in about 30% of aneurysms with major recurrences in 20% of aneurysms. Of all treated aneurysms, about 10% are retreated, and though rebleeding is uncommon it occurs three times as often in aneurysm that are unstable on follow-up imaging [83].

(i) Anatomical Outcomes: The morphological results of endovascular treatment have been based on an assessment of the occluded proportion of the sac. The reported occlusion rates vary considerably because they are

largely subjective. Attempts at numerical assessments of percentage occlusion and packing density (i.e. proportion of the sac occupied by platinum wire) have not been proved to be consistent because estimating the volume of the aneurysm sac is difficult. Aneurysm volumes are estimated either using a mathematical formula ($3/4\pi r^2$), which assumes all aneurysms are spherical in shape, or using a computer segmentation programme to calculate volumes from 3D imaging data. However, the reproducibility of aneurysm volume estimates is generally poor and these objective assessments of the degree of aneurysm packing have not been generally adopted.

Despite packing as densely as possible, the proportion of metal (coils) is generally only about 15–40%; several reports have suggested that if packing density is greater than 25%, recurrence rates are reduced [248–250]. This is intuitive but may be an oversimplification since the important element of embolisation is the obstruction of blood flow at the aneurysm neck (and in particular at the 'inflow' point). The value of packing density estimates was reviewed by Piotin et al. who concluded that the value of this metric was not proven [251].

The literature therefore relies on subjective assessments, and most authors use a three-point scale, often described as the Raymond or Montreal scale after papers published by Raymond and colleagues in 1997 [237, 252, 253] in which a four-point scale was proposed. One grade was subsequently dropped by these authors [242] because of difficulty differentiating a neck remnant from a neck remnant described as 'dog ear'. In Oxford, we have always used a three-point scale, treated aneurysms being graded as completely excluded (occlusion Grade 1 or 100% occlusion), as showing evidence of a neck remnant (occlusion Grade 2, 90–95% occlusion or neck remnant) and as showing substantial residual filling (occlusion Grade 3, <90% occlusion or incomplete occlusion) [254] (see Table 8.16). A recent meta-analysis of wide-necked aneurysms treated with coils alone or stent-assisted coiling calculated rates of complete or near complete occlusion at 57.4% (CI 48.1–66.8%) and on follow-up at 74.5% (CI 68.0%–81.0%) [255]. Results that suggest a benefit of adjuvant stenting

Table 8.16 Reported anatomical results in series of endosaccular coil embolisation

			OG 3	OG 2	OG 1
Study report	*n*	Type	<90%	>90–95%	100%
Vinuela [236]	403	All	25%	75%	25%
Raymond and Roy [237]	70	All	17%	40%	43%
Eskridge [238]	150	Basilar/nonsurgical	–	18%	82%
Murayama [239]	120	Incidental/nonsurgical	6%	28%	66%
Byrne [240]	317	Ruptured	2%	34%	64%
Cognard [256]	203	<15 mm	2%	11%	88%
Thornton [241]	196	All	15%	46%	39%
Raymond [242]	501	All	14%	46%	36%
Murayama [243]	916	All	3.5%	35.4%	55%
Henkes [244]	1811	All	5.5%	21%	66%
Gallas [245]	705	Ruptured	2.4%	25%	73%
Mejdoubi [246]	234	Ruptured	8%	11%	81%
Pierot [232][a]	622	Unruptured	14.6%	22.5%	63%
Plowman [83]	570	Ruptured	4.9%	28.5%	66.6%
Ferns [247][b]	6991	All	8.2%	29.5%	62.3%

n number of patients treated, *OG* occlusion grade
[a]Multicentre study with independent review of imaging
[b]Meta-analysis

Table 8.17 Recurrence rates after coil embolisation

Authors	% recurrence
Byrne [240]	15
Cognard [256]	15
Thornton [241]	18
Raymond [242]	33
Murayama [243]	26
Gallas [245]	15
Mejdoubi [246]	17
Pierot [232]	26.5
Ferns [247]	20.8
Zhoa [255]	9.4

and improvement in anatomical outcomes over the decade.

There is no agreed definition of what constitutes recurrence or recanalisation of a coiled aneurysm. It is generally taken to mean an increase in the size of patent sac compared to angiograms performed at the end of treatment. The reported recurrence rates from single centres ranged from 5% to 55% in the early literature, which reflected methodological variations, e.g. some centres performed control angiography at the end of treatment with the patient anticoagulated whilst others preferred to wait till the next day after stopping anticoagulation. What is probably more important is whether any remnant filling changes on serial imaging, i.e. whether a remnant filling is stable or unstable [219] (see Table 8.17).

A more objective end point is retreatment rate, since, though there are no defined criteria, retreatment implies that the degree of recurrence is of sufficient concern to recommend another procedure. Retreatments were performed in 9% of the ISAT endovascular cohort [254]. Similar rates have been reported by other authors [241, 242, 247, 257]. Stable small remnants are commonly seen and not necessarily associated with progression and aneurysm recurrence.

The assumption behind the use of a criteria such as packing density is that densely packed coils are better able to resist the continued haemodynamic 'pressure' generated in the parent artery which endosaccular packing does not alter. The factors that increased the risk of recurrence are:

- Neck width >4 mm [18]
- Large and giant sac size
- Intra-saccular thrombus lining large aneurysms

The factors that reduced the risk of recurrence are:

- Balloon-assisted coiling
- Coated coils (benefit shown in the HELPS trial [230])
- Stents
- Complex coil designs

(ii) Clinical Outcomes: The rebleeding rates after surgical clipping are less than 1%. It usually occurs within 1 year of clipping and is generally due to inadequate primary occlusion of the aneurysm. It has been reported as 0.38–0.75%/year [258, 259] for all patients and 0.79–1.9%/year if an aneurysm remnant is present [259, 260]. The more recent CARAT study reported no rebleeding after 1 year in 771 clipped patients [261].

The benchmark for clinical outcomes in patients treated by endosaccular coiling after SAH was set by ISAT, and the long-term follow-up of randomised patients has established that difference in outcomes between endovascular treatment and clipping are still evident up to 7 years after treatment [169]. Subsequent controlled trials have reported improvements in the safety of coil embolisation, with lower clinically consequential complication rates [228]. For example, the 2-month mortality after SAH was 4.1% in the HELPS trial [230] compared to 7% in ISAT.

An initial concern of the ISAT result was that late rebleeding, because of aneurysm recurrence, would negate the benefit of reduced death and disability at 12 months follow-up. The ISAT cohort of UK patients has been followed for a minimum of 10 years, and the cumulative risk of the target aneurysm rebleeding was 0.0216 (95% CI 0.0121–0.0383) in the endovascular group and 0.0064 (0.0024–0.0173) in the neurosurgery group [262]. Though 33 patients rebled later than

Table 8.18 Reported late rebleeding rates after endovascular treatment of aneurysms by coil endosaccular packing

Studies	Rebleeding rate	Number/size of cohort
Byrne[a] [240]	1.3%	4/317
Raymond [242]	1.1%	3/271
Murayama [243]	4.1% (early experience)	9/230
	0.5% (late experience)	3/488
Sluzewskia [263]	1.3% (0.32%/year)	5/393
CARAT [261]	0.11%	1/199
Plowmana [83]	0.2–0.4%/year	6/570

[a]Treatment of ruptured aneurysm only

1 year after treatment, only 17 (13 EVT and 4 neurosurgery) were from the treated aneurysm [262]. Similar rebleeding rates have been reported in single-centre and multicentre follow-up studies (Table 8.18). Late bleeding occurred in 3.4% of recurrent aneurysms and in 1.5% of aneurysms stable on follow-up in Oxford patients [83].

There is no reason to believe that the protection offered to patients with ruptured aneurysms will not apply to those with URAs, but in this situation, the risk-to-benefit equation is different. Naggara et al. reviewed the literature on endovascular treatments of URAs and calculated a late rebleeding risk of 0.2% [264]. In this meta-analysis, they also found that the retreatment rate was 9.1%, i.e. the same as after treatment of ruptured aneurysm, and treatment complications resulted in permanent morbidity in 4.8% and death in 1.9% of patients. In the absence of an RCT to determine the effectiveness of coil embolisation in URAs, their assessment is currently the best evidence available.

8.6.2.2 Balloon-Assisted Coiling

Balloon-assisted coiling (BAC), which is also known as 'the remodelling technique', involves placing a suitably sized compliant non-detachable balloon across the aneurysm neck during coil deployment. The balloon is used to retain coils within the aneurysm, to compress their profile at the neck (i.e. remodelling) and to be available to arrest blood flow should rupture occur during embolisation [265]. The popularity of BAC has steadily increased and is now employed in the majority of coiling procedures in some centres.

(a) *Technique*: The principle of this technique has changed little since it was first described by Moret et al. in 1997 [265]. A balloon is placed at the aneurysm's neck and inflated during the introduction of each coil. It is deflated whilst monitoring the coil position and, if the coil is seen to herniate into the parent artery, it is re-sited or replaced. With improved geometries and better interaction between coils, some operators leave the balloon inflated during the placement of several coils. Obviously, the length of time the balloon is inflated needs careful monitoring to prevent its inflation causing hypo-perfusion damage. Variations to this basic technique, which is intended for side-wall aneurysms, are to use two balloons or hyper-compliant balloons (to treat bifurcation aneurysms) or to place but not inflate the balloon (using it only in case of aneurysm rupture or if coil herniation occurs). Patients are anticoagulated and systemic blood pressure carefully controlled during inflations.

(b) *Complications:* There has been a controversy as to whether BAC increases the risk of complications because it increases the complexity of the procedure. An increased incidence of complications was reported by Sluzewski et al. [266], but a substantial difference has not been confirmed in multicentre studies [231]. Without a randomised study, it is difficult to compare BAC with non-BAC treatments because 'easy' aneurysms are those most often treated without BAC. The ability to rapidly inflate a balloon after procedural aneurysm rupture has been reported to reduce the resulting morbidity in the patients affected [267].

(c) *Results*: The efficacy of BAC in achieving better anatomical aneurysm occlusion has

surprisingly not been shown consistently. Both initial and follow-up occlusion rates were reported to be better by Sharpiro et al. [268] but the same in the multicentre ATENA study of URA treatments [269].

8.6.2.3 Endosaccular Liquid Agents

The potential of liquid agents to occlude the sac of aneurysms whilst preserving the parent artery was initially explored in experimental aneurysms [270], and in clinical trials after the introduction of a commercial preparation of ethylene vinyl alcohol copolymer as Onyx (Micro Therapeutics, Inc., Irvine, CA, USA). It has been generally reserved for the treatment of recurrent and high-risk aneurysms.

(a) *Technique:* The aneurysm sac is catheterised, and a balloon is placed across the neck so as to obstruct the neck and prevent the liquid (injected via the endosaccular microcatheter) from spilling into the parent artery. A high concentration of Onyx (20%) dissolved in dimethyl sulfoxide (DMSO) is slowly injected with the neck sealed by the inflated balloon. The amount injected is limited by the time it is considered safe to have the balloon inflated (usually about 5 min). The injection procedure is repeated until enough material has been injected to occlude the aneurysm sac. All material used have to be resistant to being dissolved by DMSO.

(b) *Complication:* The complications reported in the multicentre Cerebral Aneurysm Multicenter European Onyx (CAMEO) trial were due to aneurysm bleeding, thromboembolism and spillage of the material [271]. In this report, the rates of procedure related morbidity were 12% and mortality 4%. This experience emphasises the need to obtain a complete seal of the aneurysm sac during injections of the liquid agent.

(c) *Results:* The angiographic occlusion rates reported in CAMEO were excellent with only 2% of aneurysms incompletely occluded immediately after treatment. On follow-up at 12 months, 79% remained completely occluded, 13% were more than 90% occluded and 8% incompletely occluded [271]. In a more recent registry of treatments, complete or near complete occlusions were achieved in 93% of aneurysms [272]. At 6 months follow-up, this cohort of 113 patients, aneurysms occlusions were completely in 77%, near complete in 15% and incomplete in 7%. On follow-up, recanalisation occurs in 8% and 4.5% needed retreatments. Despite the initial enthusiasm, the technique has not been widely adopted, probably because of the relatively high complicated rate and competition from new adjuvant devices.

8.6.2.4 Stent-Assisted Coiling

Stent-assisted coiling (SAC) is indicated for some aneurysms. Placing a stent in the parent artery is a logical solution to the problem of retaining coils in sessile very wide-necked aneurysms. The introduction of stents (initially designed for use in the heart) sufficiently flexible for intracranial navigation in the 1990s allowed their deployment in cerebral arteries [273, 274] and led to the design and production of stents specifically for intracranial use [275, 276]. Stents can be used to protect blood flow in the parent artery lumen and to ensure coils are retained within wide-necked, larger and fusiform aneurysms, thus increasing the number of aneurysms in which endovascular treatments can be used. They can also be used as a salvage device to preserve the parent artery lumen and fix stray coil loops against distal migration. Other factors are the presence of comorbidities and whether the patient is to be treated acutely after SAH, since prophylactic antiplatelet drugs will be needed.

(a) *Technique*: There is a range of stents now available for intra-cranial navigation and deployment. Their description and perceived strengths and weaknesses will be covered in Tutorial 18. The main consideration is the risk of induced thrombosis and delayed artery stenosis. Preventing the former requires treatment with antiplatelet

drugs. Initially, the combined use of coils and stents was confined to treatments of URAs because of the need to place patients on antiplatelet drugs (in addition to periprocedural heparin) as prophylaxis against thrombosis within the stent [247]. The effects of dual antiplatelet treatment (e.g. aspirin and clopidogrel) are difficult to reverse if patients need emergency neurosurgery for hydrocephalus, and so the use of stents after SAH remains a balance of risks. For treatment of URAs, dual antiplatelet treatment is started a few days prior to the treatment. Stent placement is performed by either placing the stent and then introducing a microcatheter through the stent struts to deploy coils or positioning the microcatheter in the sac and then placing the stent (so-called jailing technique). There are various permutations of these procedures, and I particularly like coiling the aneurysm after positioning a stent delivery catheter and then placing the stent across the coiled aneurysm neck. The procedure can be combined with BAC, and at bifurcation two stents may be needed to effect a barrier at the aneurysm neck (e.g. Y-stenting).

(b) *Complications:* The use of any stent may result in complication because the device performs incorrectly. The latter events (described as technical complications) involve the stent failing to open, kinking or migration from the initial deployed position. A recent literature review calculated the incidence of such complication as 9%: comprising 4% failure of the stent to deploy and 5% malposition or migration [277]. In this reporting, the overall complication rate was 19% with 2.1% consequent mortality. The commonest complication was thromboembolism (10%) and then haemorrhage (2.2%). A meta-analysis of 17 reports of SAC treatments after SAH found that both anticoagulation and antiplatelet drugs were used in the majority of procedures (96%), and 10% of patients who required external ventricular drainage experienced intracranial bleeding as a result [278]. A delayed complication of SAC is stenosis within the stent on follow-up angiograms. This complication common to all types of stents remains an unpredictable occurrence in a small minority of patients; Shapiro et al. [277] reported a rate of 3.5% but Lee et al. reported a rate of 12.7% [279].

(c) *Results:* Complete occlusion rates reported after SAC vary between 59% [280], 63% [278] and 66% [281]. The retreatment rates in two large studies were 8.3% [280] and 14% [281]. In a literature review, King et al. estimated complete occlusion rates of 53% immediately after treatment and 69% on follow-up with a mean period of 14.1 months [282].

Thus, complication rates of SAC are higher than coil embolisation alone, and the value of SAC procedures is a reduction in rates of recurrence but this (as judge by retreatment rates) remains uncertain. The long-term benefits appear marginal. The absence of a randomised study and selection bias towards patients with more difficult aneurysms makes comparisons with coiling alone difficult [283].

8.6.2.5 Neck-Bridge Devices

Neck-bridge devices can be defined as implants that are positioned at the aneurysm neck (either in the parent artery or within the aneurysms) and function to improve the stability of coils in wide-necked aneurysms, assist coil packing and prevent coil migration. They vary in design and in the extent that the neck is covered. The original device of this type was called TriSpan (Target Therapeutics/Boston Scientific, Fremont, CA, USA) and consisted of three loops of nitinol wire partially covered with platinum, which could be placed within the aneurysm sac. A second microcatheter was then introduced through one of the loops and used to introduce coils into the sac. The loops became imbedded in the resulting coil ball, and once packing was complete, the device was detached from its delivery wire by electrolysis. It was withdrawn from the market in 2003. There were a few reports of its use in wide-necked terminal artery geometry (i.e. T-shaped with branch arteries at near right angles) such as the basilar artery and ICA bifurcations [284].

More recently, several devices with similar indications have been reported in preclinical [285] or early clinical trials. These include PulseRider (Pulsar Vascular) with devices for T- and Y-aneurysm geometries [286] and pCONus (Phenox GmbH, Bochum, Germany] [302]. Both devices have entered clinical trials, but reports are too small or still recruiting for further meaningful discussion.

8.6.2.6 Flow Diverters

The potential for covered stents to close aneurysms in the extracranial circulation led to the development of a flexible stent with low porosity and the expectation that if porosity was low enough, blood flow would be reduced sufficiently to cause spontaneous endosaccular thrombosis. Porosity is defined as the proportion of open area to total area of the stent. The optimum porosity sufficient to induce thrombosis has been found to be 70% [287]. Several reports have shown the effectiveness of low-porosity stents manufactured from woven nitinol wire. They are generally termed flow diverter stents (FDS) and specifically designed for this purpose. Several manufacturers are now marketing this type of device. To achieve the same effect of slowing blood flow within the sac, two overlapping conventional stents can be used [288]. FDS are used to treat complex wide-neck saccular or fusiform aneurysms or those that have recurred after coil embolisation [289, 290].

(a) *Technique*: The technique for FDS placement is similar to SAC. The principle differences are whether to use adjuvant endosaccular coils and behaviour differences due to their woven construction. The latter makes it more important to use devices of the correct width and length. Furthermore, because of the greater amount of deployed metal, effective dual antiplatelet prophylaxis is required. Endosaccular coils are considered a sensible precaution to reduce the chance of aneurysm recurrence and delayed aneurysm bleeding. Early woven stents had less radial force than current designs, and generally this is less than stents manufactured by laser cutting. It can impede their opening and make deployment difficult. A solution is to perform balloon inflation within the stent to force it to conform to the artery wall. FDS are subject to shortening as they expanded and the stent's length needs to be chosen carefully since they need cover the aneurysm neck plus at least a 0.5 cm margin at each side of the neck. In some instances (particularly for fusiform aneurysms), it may be necessary to place a series of FDS to reconstruct a long diseased arterial section [291].

(b) *Complications:* Complications include thromboembolism, procedural rupture and branch artery occlusion as well as two complications particularly associated with FDS use. These are delayed spontaneous aneurysm bleeding and parenchymal haemorrhage in the first weeks after treatment. The frequency of ipsilateral stroke following FDS deployment was 5.6% in a multicentre trial [292]. Delayed haemorrhage occurring some weeks or months after deployment has been studied in retrospective study [293] and reported to affect 1% of treatments. The incidence of parenchymal haemorrhage was 1.9% in the same study, and both complications remain unexplained, though use of dual antiplatelet drug treatment is likely to be a contributing factor.

(c) *Results*: To date, they have been used in aneurysms unsuitable for endosaccular packing usually with very wide necks. Initial reports of their efficacy were encouraging [294, 295]. Complete aneurysm occlusion was achieved in >60% of large and giant aneurysms. A meta-analysis report in 2013 reported early procedural morbidity as 7.9% and mortality 2.8% and late morbidity as 2.6% and mortality 1.3% [296]. After a mean of 9 months follow-up, occlusion rate was 76.2% (95% CI 72.1–80.2). Prospective and retrospective manufacturer-sponsored trials have been relatively small, and no RCT data is available to fully understand the role of FDS. However, these devices are likely to have a role in treatments of complex and very wide-necked aneurysms. It is too early to predict how widely the concept can be applied.

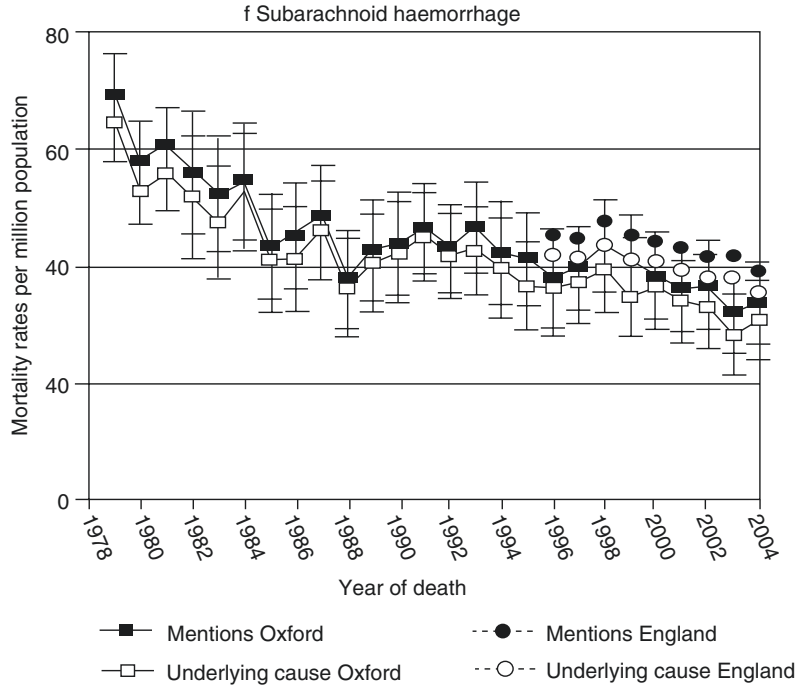

Fig. 8.9 Age-standardised mortality rates in England from subarachnoid haemorrhage from 1996 to 2004 (Courtesy of Professor Michael Goldacre, Professor of Public Health, University of Oxford)

8.6.2.7 Flow Disruptors

An extension of the principle of endosaccular packing with coils is the use of a single embolic device placed within the aneurysm sac. This concept has been used in the development of endosaccular devices, which have become known as flow disruptors. A woven nitinol sphere, which expands from a microcatheter introduced into the aneurysm sac, is currently in clinical trials having completed preclinical evaluations [297]. The device is made of braided nitinol and platinum wire and designed to treat wide-necked aneurysms with T-shaped geometries. The cage structure traps circulating blood and so induces thrombosis within the device. Subsequent fibrous tissue replacing the blood clot is anticipated to cause shrinkage and permanent exclusion of the aneurysm. The device is retrievable with controlled electrolytic detachment.

A multicentre trial of its use in terminal aneurysms has reported a technical success rate of 92.9%, a procedural complication rate of 10.8% and morbidity rate of 1.3% with no mortality [298]. After a mean follow-up of 5.3 months, angiography showed complete occlusion in 56.9%, neck remnants in 35.4% and aneurysm remnants in 7.7% of aneurysms studied. A more recent report of the prospective WEB Clinical Assessment of Intrasaccular Aneurysm Therapy (WEBCAST) trial in which basilar termination, ICA termination, MCA and AComA aneurysms were treated has reported a higher incidence of thromboembolic events (17.6%) but a similar rate of permanent morbidity at 2% with no deaths [299]. Reports of the long-term stability of this new treatment approach are awaited.

A salutary postscript to this tutorial is the graph Fig. 8.9, which shows the standardised mortality rates for SAH haemorrhage in the Oxford region from 1978 to 2004. The credit for the steady improvement shown must go to medicine in general and not to the wonderful coil alone, since we only started using detachable coils in 1992.

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Vascular Malformations of the Brain

9

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Preamble

This tutorial covers the topic of cerebral vascular malformation first in terms of their description and classification, and then their aetiology and natural history. Our understanding is limited by the relative rarity of these lesions and the bias of study from the perspective of a single centre or individual practice. Uncertainty about the nature of the most important type of vascular malformation is reflected in its utilitarian name, brain arteriovenous malformation (BAVM). This tells us little more than that arteries and veins (of the brain) are malformed.

In the first part of this tutorial, the emphasis is on the nature of cerebral vascular malformations. We could spend considerable time discussing attempts to classify vascular malformations of the brain, and we would still be unable to agree on a completely inclusive system. The problem is due to their individual variations and the need for definitions that accommodate extreme atypia. The tutorial will therefore attempt to balance good nosology with pragmatism in order to organise our thinking about clinical managements. But I hope readers will be left with a sense of uncertainty about the aetiology of these lesions and remember that despite their different names they are probably closely related.

A more pressing problem for endovascular therapy is the current controversy over interventions for people with BAVMs that have not bled.

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Its resolution remains a challenge because of the potential confounding effect of phenotypic variability. With this in mind, the data on which we base our advice and management protocols for patients diagnosed with these lesions should be seen as 'work in progress'. As with unruptured intracranial aneurysms, natural history data, however good, is only a best guess of the individual's prognosis.

9.1 Types of Vascular Malformations of the Brain

A discussion of the definitions of arteriovenous malformation (AVM) used by different writers is a good starting point because it highlights the 'usual', and a trap for the novice is not being able to recognise that a particular case is exceptional. Without a clear idea of commonly encountered features, detailed descriptions of all known variations of a disease risk creating misconceptions. Concentrating on the infrequent exceptions can bias perception, analogous to the blind man describing an elephant only after feeling its trunk.

9.1.1 Early Descriptions of Vascular Malformations of the Brain

There were case descriptions in the nineteenth century by Virchow [1] and Steinheil in 1895 [2]. Cushing and Bailey [3] described the pathology of a small series in 1928 and Bergstrand et al. [4] reported the first demonstration of AVM by angiography in 1936. Like aneurysms, the introduction of cerebral angiography led to rapid advances in the diagnosis, understanding and treatment of vascular malformations. Hilding Bergstrand, a Swedish pathologist, described vascular malformations of the brain as angiomas and separated them from hypervascular tumours (e.g. angioblastoma) [4]. He divided them into cavernous and racemose types on the basis that the vessels of the cavernous angioma connected without separating parenchyma. Whereas, racemose angiomas (the term means vessels arranged as a cluster) were separated by parenchyma. He further divided racemose angiomas into (a) telangiectasia, (b) Sturge-Weber disease, (c) angioma racemosum arteriale, (d) angioma racemosum venosum and (e) aneurysma arteriovenosum [5]. We would recognise the last type (called arteriovenous aneurysms by Olivecrona) as arteriovenous malformations.

9.1.2 Definitions of Arteriovenous Malformations

Several authors have proposed definitions of arteriovenous malformation of the central nervous system. These include:

- Doppman 1971: AVMs are tangled anastomoses of blood vessels of varying calibre in which arteriovenous shunting occurs in a central nidus (Latin, *nidus*, nest), which is the area towards which one or multiple feeding arteries converge, and from which enlarged veins drain [6].
- Valavanis 1996: Cerebral AVMs are inborn errors of vascular morphogenesis caused by a defect or malfunction of the embryonal capillary maturation process and resulting in the formation of abnormal arterial, venous or capillary channels with or without shunt [7].
- The Arteriovenous Malformation Study Group 1999: Brain arteriovenous malformations are a complex tangle of abnormal arteries and veins linked by one or more fistulas [8].

These are useful in setting out the component features on which there is a consensus, i.e. arterial and venous feeders, a nidus and arteriovenous (AV) shunting. The last definition though includes fistulas and therefore AV connections without an intervening nidus, i.e. direct arteriovenous fistulas (AVF), described as cavernous by Bergstrand [4]. Thus, we can separate them from the definition of AVMs only if the nidus is absent. The 1996 Valavanis' definition includes lesions without a shunt. So, the situation becomes more difficult and the process takes us further away from a description of a 'usual' lesion.

9.1.3 Classifications of Cerebral Vascular Malformations

Against this background, several classifications of cerebral vascular malformations have been proposed more recently. McCormick in 1966 defined five groups of cerebral vascular malformations: capillary telangiectasia, venous angioma, varix, cavernous angioma and arteriovenous malformation [9]; all subsequent authors have based their classifications on this and a more recent example is that of Chaloupka and Huddle [10], shown in Table 9.1. This separates lesions that grow from those that don't, though it would be better stated as 'don't generally grow' because examples of enlargement of lesions in this group have been described.

This classification includes vascular tumours, as proposed by Mulliken et al. [11] and a mixed lesion category, thus, reflecting a shift towards considering transitional lesions as a part of a continuum of vascular developmental abnormalities.

Having strayed into taxonomy, this part of the tutorial now refocuses on the four main divisions of vascular malformations included in the McCormick classification, though its main subject will be the brain arteriovenous malformation (BAVM) because they are the most common lesion types to be referred to endovascular therapists. Dural fistulas, vein of Galen malformations and non-Galenic arteriovenous fistulas are covered in separate tutorials.

Table 9.1 Classification of Chaloupka and Huddle [10]

Benign proliferating vascular anomalies: Haemangioma
Nonproliferating vascular anomalies:
Capillary malformation [telangiectasias]
Venous malformation
Cavernous malformation [cavernoma]
Arterial malformation [angiodysplasia and aneurysm]
Arteriovenous shunting malformation
Brain AVM
Brain AVF
Dural AVM
Vein of Galen AVF
Mixed malformation

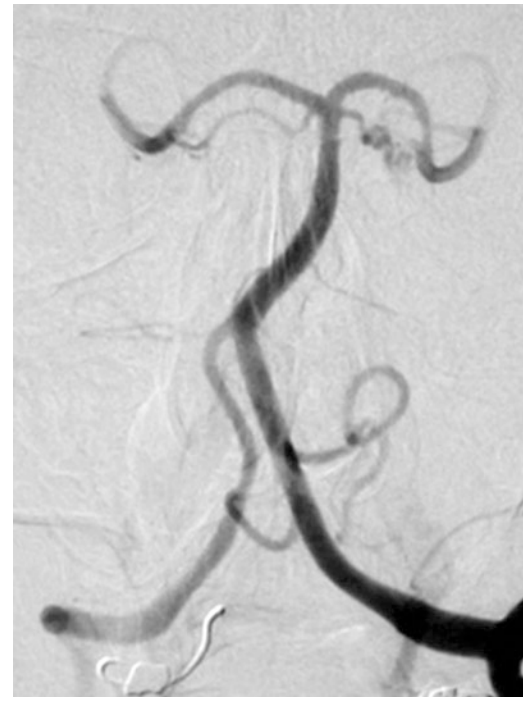

Fig. 9.1 Telangiectasia. Vertebral angiogram showing a collection of small irregular arteries on the *left side* of the brainstem, supplied by the anterior superior cerebellar arteries. Histological confirmation of this lesion was not possible

9.2 Capillary Telangiectasia

These lesions are usually diagnosed post mortem and are typically found on the pial or immediate subpial surface of the brain stem or pons (Fig. 9.1).

9.2.1 Pathology

The macroscopic appearance of cerebral telangiectasia is of a small collection of vessels on the cerebral surface. Microscopically, they are composed of thin-walled capillaries without smooth muscle layers or elastic lamina. The surrounding brain is normal.

9.2.2 Aetiology

This is unknown but multiple lesions occur in hereditary haemorrhagic telangiectasia (HHT) or

Rendu-Osler-Weber syndrome, which is an autosomal dominant disorder characterised by multisystem vascular dysplasias in which those affected develop multiple telangiectasias. Telangiectasia occurs on skin, and in the mucosa of the nose and mouth, lung and gastrointestinal tract. Patients present with recurrent nosebleeds or other episodes of bleeding. The cerebral vascular abnormalities associated with HHT include brain AVMs, cavernous malformations and aneurysms [12]. Cerebral lesions were found on MRI in 23% of HHT patients screened for brain lesions [13].

In patients with multiple BAVMs reported by Willinsky et al. [14], the most frequent cause was HHT. In a series of 638 patients with cerebral AVMs, there were 14 (2%) patients with HHT; of these 50% were multiple, 42% of lesions were less than 1 cm (micro-AVM) and 29% were AVFs with high flow and venous ectasia [15]. Most of the patients were young.

HHT is caused by mutations in elements of the transforming growth factor-β (TGF-β) receptor complex [16]. The genes responsible for the commonest types of HHT (types 1 and 2) have been identified as ENG on chromosome 9q (which encodes for *endoglin*) and causes HHT type 1 and ALK1 (activin receptor-like kinase 1) on chromosome 12q, which causes HHT type 2 [17]. A relationship with cavernous malformations (see below) has also been proposed since telangiectasias may be found within cavernous malformations and be a mechanism for their enlargement.

9.2.3 Epidemiology and Natural History

Telangiectasias are not usually seen on catheter angiograms and therefore rarely diagnosed in vivo, so there is no useful epidemiological data concerning their frequency or natural history. However, Lee et al. [18] reported 18 patients diagnosed by MRI and calculated a prevalence of 0.4%. None of the patients developed haemorrhage during 3 years of follow-up.

9.3 Developmental Venous Anomaly (Venous Angioma)

The developmental venous anomaly (DVA) or venous angioma is recognised as an abnormally prominent collection of medullary veins, which drain to a single trunk (Fig. 9.2). The latter has, in the past, been termed a varix, but this term should be dropped since it is now generally agreed that these lesions are caused by abnormal venous development.

9.3.1 Pathology

On microscopy, they have a thin endothelium, with thin smooth muscle cell and elastic tissue layers within a wall that is mainly composed of collagen but may be thickened by hyalinisation.

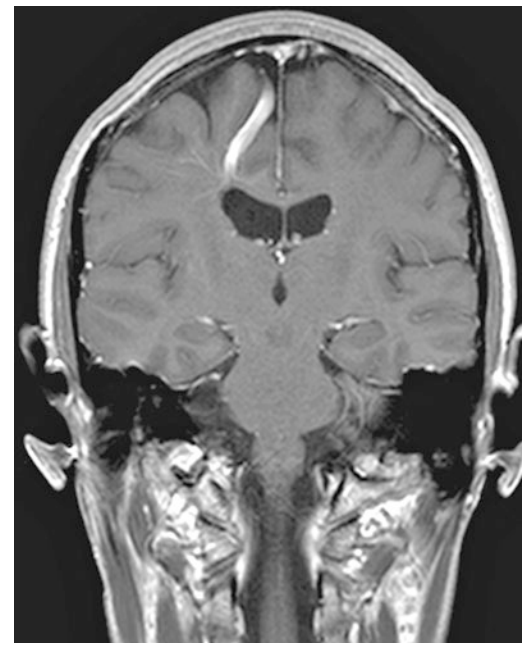

Fig. 9.2 Developmental venous anomaly. MRI (coronal T1W sequence) showing an enlarged vein in the right frontal lobe. Small tributary veins are seen arising in the deep white matter and from the margin of the ventricle

9.3.2 Aetiology

The conclusion that they are caused by a development failure of a normal section of the cerebral venous system is based on their having been identified in neonates and their nonprogressive behaviour. The initiating event probably occurs at about the third week of intrauterine life during formation of medullary veins. A malconnection of deep and superficial veins also occurs in Sturge-Weber syndrome, and DVA may be a variation of the same failure of normal development [19]. Crucially, the DVA drains normal brain and therefore should not be embolised.

9.3.3 Epidemiology and Natural History

They are found in up to 2.5% of autopsies and are the most common vascular abnormality of the brain. They comprised 63% of McCormick's series of 165 malformations found at 4669 autopsies [20]. They are rare causes of spontaneous haemorrhage. Their natural history was studied by Garner et al. [21], who reported a haemorrhage in only 1 of 100 patients followed for 14 years. They calculated a lifetime haemorrhage risk of 0.22%. Other presentations were seizure, headache and transient deficits.

They are increasingly recognised as incidental findings on MRI, alone or in association with cavernous malformations. Since intervention is not indicated (except for the rare situation of an emergency evacuation of haematoma), their importance to the endovascular therapist is that they should be correctly diagnosed so that embolisation can be avoided.

9.4 Cavernous Malformations

These are hamartomatous lesions containing thin-walled vessels with more circumscribed borders than capillary telangiectasias and without intervening normal brain (Fig. 9.3). There are no associated feeding arteries or veins, so they are not detectable on catheter angiography or CT if non-calcified but are easily demonstrated on MRI because they contain haemosiderin.

9.4.1 Pathology

The macroscopic appearance is a capsulated blood-filled tumour resembling a grape. On microscopy, they are composed of channels, which have an endothelial lining and thin fibrous adventitia without elastin, smooth muscle cells or the other elements of mature vessels. They contain old haemorrhage, haemosiderin, calcification or cholesterol crystals. The walls may show hyaline thickening and the adjacent brain gliosis. Endothelial leakage causes microhaemorrhages [22]. They can occur anywhere in the brain but are most frequently found in subcortical white matter, periventricular white matter, the pons and the external capsule.

9.4.2 Aetiology

Sporadic and familial forms are recognised. Multiple lesions probably always occur at some stage in the familial disease, and they are found in at least 30% of patients without a positive family history. The genetic basis of the familial disease has been recently linked to chromosomes 7 and 3. The condition has an increased frequency in Americans of Mexican descent, in whom a defective CCM1 gene has been described. Associations have also been described with capillary telangiectasia, DVAs and previous radiotherapy [23].

9.4.3 Epidemiology

There is no gender difference, and patients may present at any age, but most do so in the second to fourth decades. Reported estimates of prevalence in the general population are 0.5% at autopsy [24] and 0.4% on MRI [25]. They account for 5–16% of central nervous system vascular malformations.

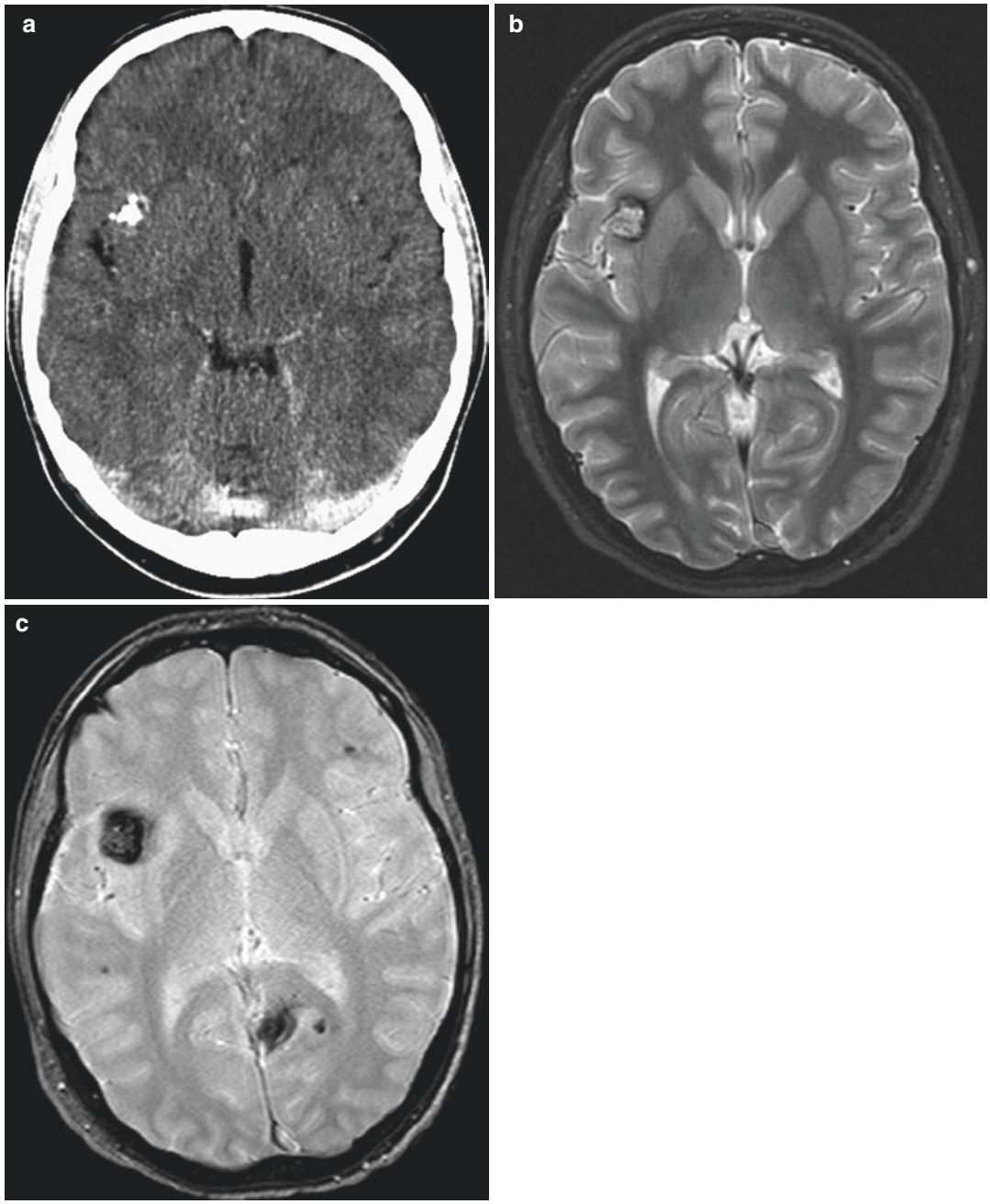

Fig. 9.3 Cavernous malformation. On CT performed after contrast enhancement (**a**) calcification is seen. T2W MRI (**b**) shows the typical appearance of this lesion and a gradient echo sequence (**c**) shows additional lesions because of the magnet susceptibility effect of blood breakdown products

9.4.4 Symptoms and Natural History

Diagnosis is by MRI and the various possible appearances were classified as four types by Zabramski et al. based on signal characteristics [26]. Small lesions can be distinguished from telangiectasia by their lack of enhancement after gadolinium administration. Asymptomatic

cavernous malformations may appear de novo and enlarge or regress on serial MRI studies [27]. Symptoms are presumably initiated by enlargement. These are, in descending order of frequency, seizures, focal neurological deficit, headache and haemorrhage. Symptoms are often progressive, in a stepwise fashion, and presentation is more commonly due to haemorrhage in children and seizures in young adults.

When discussing rates of haemorrhage, symptomatic bleeding has to be distinguished from the more common asymptomatic lesion demonstrable on MRI. Symptomatic haemorrhage at presentation has been reported in 10–26% of patients and annual rates of symptomatic bleeding on follow up calculated as 0.7–1.6% [25, 28]. Bleeding is usually intraparenchymal and only rarely subarachnoid or intraventricular.

9.4.5 Treatment

Since there is no endovascular access, these lesions are not referred to the endovascular therapists for treatment. Management is generally conservative and intervention only for symptomatic lesions. Interventions are surgical resection, which is generally reserved for symptomatic large accessible lesions, or focused radiotherapy. Stereotactic radiotherapy is performed for control of seizures and is generally not considered effective in preventing symptomatic haemorrhage [29].

9.5 Brain Arteriovenous Malformations (BAVM)

The definitions of this lesion had been discussed above but can be summarised as a vascular lesion composed of an abnormal tangle of vessels (nidus) with pathologic shunting of blood flow from the arterial to the venous tree, without a normal intervening capillary bed (Figs. 9.4, 9.5 and 9.6). The nidus of BAVMs occurs in supratentorial brain (85–90%) or the cerebellum (10–15%) and involves superficial (70%) or deep (30%) structures of the brain. They vary in size from micro-AVM (<1 cm) (Fig. 9.9) to large lesions (>6 cm).

9.5.1 Pathology

The macroscopic findings are of a variety of vessels ranging from well-differentiated

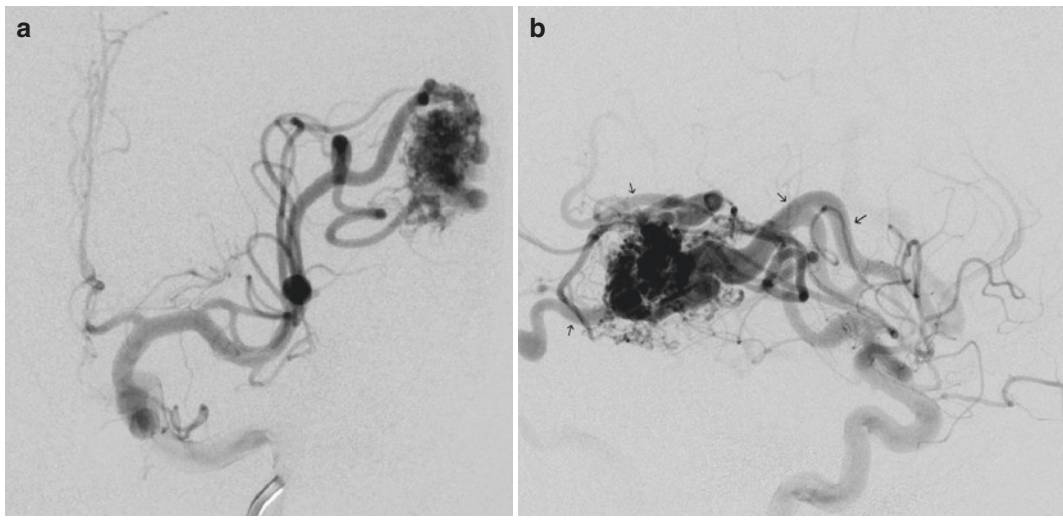

Fig. 9.4 Sulcal brain arteriovenous malformation. The lesion lies in the posterior temporal lobe and is shown on internal carotid angiograms as the nidus starts to fill (**a**) and after shunting to cortical vein (**b**). The *arrows* on (**b**) indicate veins

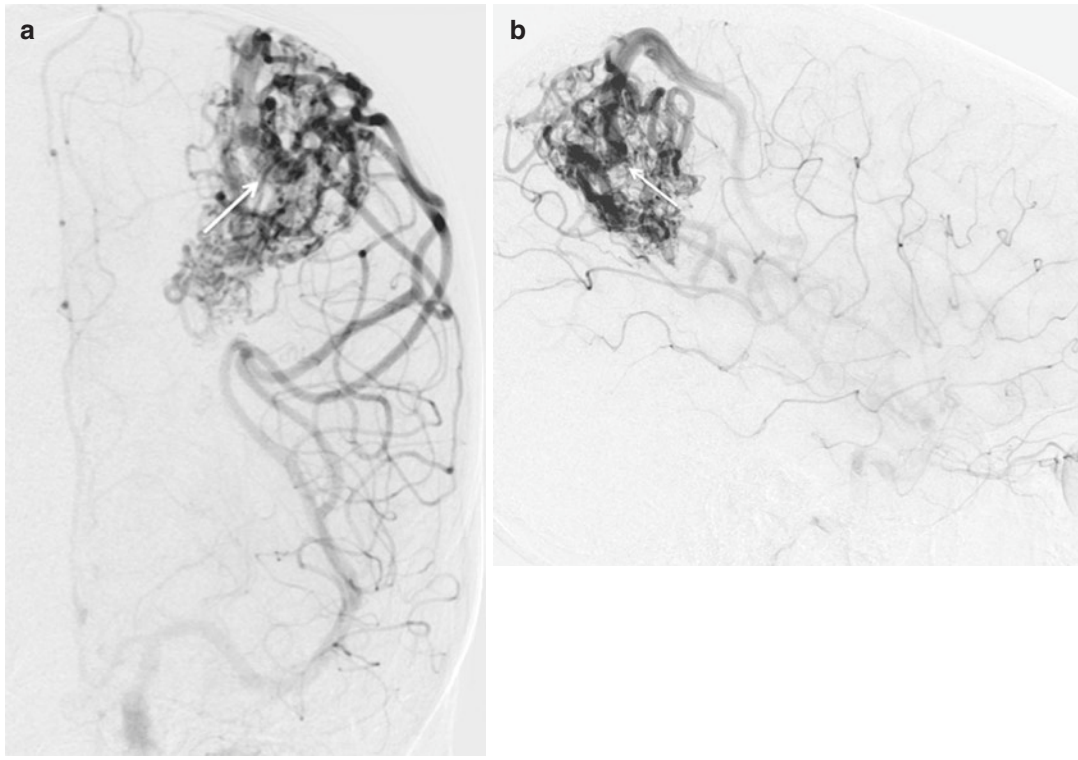

Fig. 9.5 Brain arteriovenous malformation. Internal carotid DSA in the frontal (**a**) and lateral (**b**) projections. This typical wedge shaped nidus (**a**) is seen in arteriovenous malformations which extend into white matter. The origin (*foot*) of the draining vein is marked (*arrows*)

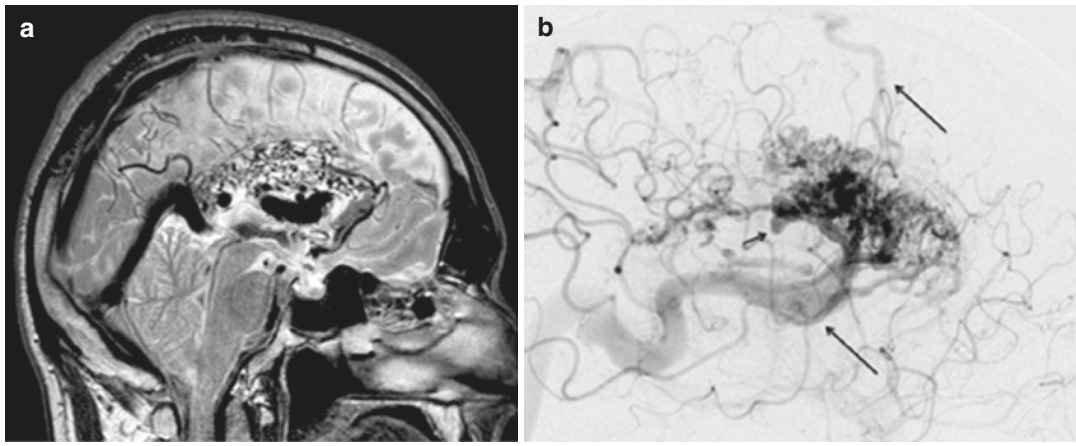

Fig. 9.6 Brain arteriovenous malformation of the corpus callosum. Sagittal T2-weighted MRI (**a**) and lateral DSA (**b**) show the nidus in the corpus callosum which drains to a massively enlarged internal cerebral vein. On (**b**), this vein and a cortical vein on the medial surface of the frontal lobe are marked (*long arrows*). There is also a nidal aneurysm (*short arrow*) shown on the DSA

arteries and veins to highly malformed, hyalinised, poorly differentiated vessels with thick or thin walls. The abnormal vessels are variably dilated with saccular aneurysms or narrowed with segmental or focal areas of stenosis.

Microscopy of the feeding arteries shows irregular endothelium and elastic layers with vacuolisation and necrosis of smooth muscle cells, invasion of the adventitia by foreign cells and small blood vessel as well as changes in the mural matrix. Aneurysms presumably develop in areas where the elastic tissue and smooth muscle is thin or absent. In some areas, the vessel walls are thickened by medial hypertrophy, collections of fibroblasts and thickening of the basal lamina and interstitial tissue. These changes are induced by high blood flow and shear stress.

The nidal vessels are indeterminate as either artery or vein. Draining veins may resemble arteries because of hypertrophy of smooth muscle and media, but they are distinguished by the lack of an organised elastic lamina. They may be massively dilated with ectasia and varices. Any intervening brain is typically gliotic, and gliosis may be seen in the immediately adjacent brain. Calcification may be seen in the vessel walls, and haemosiderin staining in the surrounding tissue indicates prior bleeding.

Locations: There are several systems in use for describing BAVMs by their location within the brain, and the advent of MRI and 3D reconstruction of angiograms has helped to show the relationship of feeding vessels and the nidus to normal brain structures. Valavanis and Yasargil [30] developed a system based on the principal location of nidal vessels. This divides superficial BAVMs into sulcal (nidus located in the subpial space within a sulcus), gyral (nidus completely surrounded by a cortical mantle) and mixed sulcal-gyral lesions. Deep lesions are found in the subarachnoid space (within basal cisterns or fissures), the parenchyma (within deep nuclear structures) and the ventricle (originating in choroid plexus). Individual lesions can involve one or more of these compartments, i.e. mixed. An alternative system proposed by Lasjaunias, Berenstein and Ter Brugge [31] recognises similar deep and superficial locations but emphasises the role of the feeding arteries and draining veins. Thus, lesions confined to cortex are defined as being supplied exclusively by cortical arteries and veins whilst subcortical lesions are supplied by cortical arteries but may drain to both superficial and deep veins. Cortico-ventricular BAVMs are supplied by both perforator and cortical arteries and drain to superficial and deep veins. This classification separately defines cortico-callosal BAVMs as not being supplied by perforated arteries and, like Valavanis and Yasargil, choroid and deep BAVMs with centrally directed (deep) venous drainage.

The angioarchitecture of BAVMs has been extensively studied, principally to identify features that relate to the risk of bleeding. These will be discussed below. One final point on the macroscopic appearance of lesions and their location is the effect of a low pressure, high blood flow shunt on adjacent vessels. Superficial lesions are not infrequently additionally supplied by transpial arteries. These are generally considered to be secondary and recruited as a result of the primary pial-based arteriovenous shunt. They are sometimes found to 'appear' after partial embolisation but whether this is a response to the abnormal haemodynamics of the shunt is uncertain and needs to be confirmed from longitudinal observational data, which currently remains incomplete. Another feature, which is presumed to be secondary and may be stimulated by partial treatment, is angiomatous change in arteries adjacent to the nidus, often termed neovascularisation. These vessels though tortuous and appearing similar to those of the nidus should not be confused with them because they show normal contrast transit times on angiography. Cure of the AV shunt leads to their disappearance, but our understanding of their aetiology and the underlying haemodynamic factors is incomplete [32].

9.5.2 Aetiology

The majority of lesions are thought to be 'congenital' rather than acquired. Implicated acquired causes are trauma (which includes surgery) and ionising radiation, but the links are vague. Congenital causes involve an embryological cause or a genetic cause. Postulated theories can be summarised as involving a congenital predisposition, which is triggered by extrinsic factors. The observations that any theory has to explain

are that AVMs are rarely (if ever) identified in the foetus and that the adult phenotype is unusual in children. AVMs have been reported to appear in previously normal (on imaging) brain and recur after successful surgery or radiotherapy [33]. The vast majority of patients don't give a positive family history.

Yasargil (1987) postulated a proliferative capillaropathy [34], whilst Mullan et al. [35] suggested that an initiating event occurs in foetal life (possibly due to failure of regression of pial-dual veins at the 40–80-mm stage) and that the changes are too small to be detected at birth. An abnormality of normal capillary development has been proposed by Lasjaunias [36], and Mullan, in a second paper [37], postulated they were caused by a form of venous angioma.

If you accept that they are developmental anomalies, it is then likely that the combination of a genetic predisposition and extrinsic factors leads to their formation. First the congenital defect expressing itself as the malformation and then a vascular response to the presence of the malformation. As far as a genetic factor is concerned, we have the observation of the occasional report of patients with a positive family history and the associations of BAVMs with HHT and conditions such as Wyburn-Mason and Sturge-Weber syndromes.

The focus of research has been to identify abnormalities of gene expression in the cells of AVMs and genetic studies of familial case pedigrees. Rhoton et al. [38] found that the preproendothelin-1 gene is locally repressed in HHT lesions. This results in a lack of endothelin-1 peptide, which is a vasoconstrictor with a role in vascular cell growth.

A more recent finding is increased endothelial expression of VEGF-R receptors Flk-1 and Flt-1 in surgically resected BAVM vessels compared to controls [39]. This finding leads to the attractive theory that these agents contribute to the maintenance and slow growth of BAVMs.

To explain their role, we have to remember the embryology of vascular development. Vascular morphogenesis is a two-stage process in which angioblasts differentiate into endothelial cells to form the primary vascular plexus (see Tutorial 1). The second stage is angiogenesis when the primary vascular plexus undergoes remodelling and organisation including recruitment of periendothelial cell support. Two main systems are involved in these processes:

1. Vascular endothelial growth factors (VEGF-R1, VEGF-R2), which mediates endothelial cell proliferation, migration, adhesion and tube formation.
2. Angiopoietins 1 and 2 (a group of cytokines) and their receptors Tie-1 and Tie-2, which play an important role at the later stage of vascular development.

These findings suggest a link between what happens in embryonic life with the growing realisation that BAVMs 'appear' towards the end of childhood and 'grow' in response to haemodynamic drivers. Once a shunt is present, the altered haemodynamics literally drive the required alterations in gene expression. Genetic expression research probably holds the key to this puzzle. The role of epigenetic mechanisms was recently reviewed by Thomas et al. [40], who propose that BAVMs result from aberrant epigenetic modifications in the genome of endothelial cells.

9.5.3 Demography

Brain AVMs affect men and women equally [41]. Earlier studies reported a small male dominance: Crawford et al. [42] 1.2:1 and the Cooperative study [43] 1.1:1, but these reports included all types of cerebral vascular malformations. No racial variation has been reported in the largest series, but anecdotally, brain AVMs are considered more common in China than Japan. The commonest age at diagnosis is consistently reported as between 20 and 40 years. Deruty et al. [44] reported the age distribution at presentation in their series as 33.5% (<30 years), 49% (31–50 years) and 15.5% (>50 years).

9.5.4 Epidemiology

Brain AVMs are relatively rare lesions. Their prevalence in the general population of Scotland (>16 years) has been estimated as 16–18/100,000 based on a retrospective study [45]. The incidence, i.e. proportion of the population newly diagnosed over a 1-year period, can only be calculated with complete ascertainment of cases from a population of known size. It is therefore difficult to obtain. Al-Shahi and Warlow reviewed this subject in 2001 [45], and they calculated an incidence of approximately 1/100,000, which was largely based on data from two large studies. These were a study performed over 10 years in the Dutch Antilles [46] which found incidences of 1.1/100,000 person-years and a longer study performed in Olmstead County, Minnesota [47], which found an incidence of 0.82/100,000 per year. Autopsy studies, which theoretically provide more reliable data on prevalence, have reported a range of 0.04–0.60% (i.e. up to 600/100,000) [48–50] and 3% in autopsies performed after cerebral haemorrhage [49]. This wide discrepancy has stimulated further research.

Two prospective population studies in Scotland and New York have produced interim reports. The Scottish study documented incidences of 0.56/100,000 per year for BAVMs compared with 0.43/100,000 per year for cavernous malformations and an overall detection incidence of 1.2/100,000 per year for all cerebral vascular malformations [51]. The New York study found higher detection rates for BAVMs at 1.34/100,000 a year and an incidence of haemorrhage of 0.51/100,000 per year [52].

The frequency of the diagnosis of BAVMs as the cause of first ever presentation with stroke was found to be 1.4% in the Lausanne Registry [53]. This is similar to a 10-year study of hospital admissions in Northern California which reported the detection rate as 1.4 (95% CI 1.3–16) per 100,000 person-years [54]. BAVMs are more likely to be the underlying cause in younger patients and a prospective population study found that they accounted for about 3% of stroke in young adults [55]. This rate is probably an underestimate since approximately 10% of all stroke is haemorrhagic [56, 155] and about 15% of spontaneous cerebral haemorrhage is due to BAVMs [49, 156].

9.5.5 Natural History

In 1949, Olivacrona [57] wrote ‘in the end, probably most, if not all patients (with arteriovenous malformations) die of haemorrhage or are completely incapacitated’. This statement has influenced medical management for over 50 years but is it correct?

9.5.5.1 Symptoms at Diagnosis

Most patients present after spontaneous intracranial haemorrhage or the onset of seizures. The relative rates for symptoms at diagnosis are 50–60% with haemorrhage and 25–30% with seizures [56, 58, 59]. Of the rest, about 10% present with focal neurological symptoms or signs without haemorrhage and about 3–5% present with migraine or other types of headache referable to the BAVM [60]. Headache may be co-incidental and there remain a proportion of asymptomatic people, estimated at up to 15% of all diagnosed BAVMs [45]. In children (<16 years), bleeding is the most common presentation and accounts for 30–50% of haemorrhagic stroke in this age group. Epilepsy tends to present in younger patients: 44% in the second decade, 30% in the third decade and only 6% in the 30–60-year age group [61]. BAVM is not uncommonly discovered during pregnancy. Crawford [42] reported that 25% of women in the third decade of life were pregnant at diagnosis. AVMs are diagnosed in 20–50% of women presenting with spontaneous intracranial haemorrhage during pregnancy and accounts for 5–12% of maternal deaths. The incidence is highest early in the third trimester, and vaginal delivery is not considered to increase the risk of haemorrhage [62].

Patients presenting with seizures alone are more likely to be young with cortical lesions in the temporal lobe [63]. Seizures amongst BAVM patients may occur in association with haemorrhage, so the presence of other symptoms are important in considering the likelihood of future epilepsy. Crawford [42] reported an overall rate of epilepsy

in 18% of unoperated patients over 20 years and rates of 22% in patients presenting with haemorrhage, 44% for the age range 10–19 years and 37% for temporal lobe lesions. The Scottish Audit of Intracranial Vascular Malformations reported that patients presenting with a first-ever seizure developed epilepsy over the next 5 years in 58% (95% CI 40–76%) and 8% of those presenting without seizure, haemorrhage or neurological deficit experienced at least one seizure [64].

Though focal neurological deficits without haemorrhage are uncommon at presentation, subsequent progressive neurological deficits are common in patients on observation and usually attributable to the effects of repeated haemorrhage. However, there are several possible causes for progression of neurological deficits without haemorrhage, including secondary effects of epilepsy, focal brain compression by dilated vessels, vein thrombosis, steal effects on adjacent brain and chronic venous hypertension. Mass effect is relatively frequently observed on MRI and may be related to the size of the nidus and vessels [65]. A decrease in cerebral blood flow has been demonstrated in the brain surrounding AVMs, but the functional significance is uncertain [66, 67]. Because the potential effects causing deficits are so various, it is difficult to generalise and often difficult to draw firm conclusions in practice.

9.5.5.2 Risk of Haemorrhage

The diagnosis of a brain AVM makes the individual at risk for future adverse events. The important issue for deciding how to advise patients about treatment is the risk of future bleeding since this is the major contributor to acute and long-term morbidity associated with the diagnosis. In what is probably the best clinical paper written on this subject, Crawford et al. [42] showed that without surgical treatment, the risk of death was 29%, risk of haemorrhage 42%, risk of neurological handicap 27% and risk of epilepsy 18% during a mean follow-up period of 10.4 years for symptomatic AVM.

Observational studies of untreated AVMs have estimated an annual rate of haemorrhage of 2–4% per annum; Crawford 2.5% [42], Brown 2.2% [47] and Ondra 4% [60]. Kim et al. reported a meta-analysis of untreated patients and calculated an overall annual rate of haemorrhage of 2.3% (95% CI 2.0–2.7) [68]. In Crawford's cohort, patients presenting with haemorrhage were found to have an increased risk of subsequent haemorrhage compared to patients presenting without haemorrhage (36 vs. 17% over 10 years). In the Kim pooled data, the haemorrhage annual rates were 1.3% (95% CI 1.0–1.7) for unruptured and 4.8% (95% CI 3.9–5.9) for ruptured BAVM patients at presentation [68]. Graf et al. [69] reported that this increased risk was mainly during the first year after bleeding. A range of factors that different reports have recognised as either being associated or not with haemorrhage are listed in Table 9.2.

Table 9.2 Reports of factors associated with haemorrhagic episodes

	Significant association with haemorrhage	Contradictory data
Age		
Increasing	Crawford et al. [42]	Graf et al. [69]
		Mast et al. [56]
		Stapf et al. [70]
		Halim et al. [71]
Sex		
Male	Mast et al. [56]	
Size		
Small	Khaw et al. [72]	Mast et al. [56]
	Graf et al. [69]	Stefani et al. [73]
	Crawford et al. [42]	
	Stapf et al. [70]	
	Kader et al. [74]	
	Langer et al. [75]	
Large	Stefani et al. [73]	
Presenting symptom		
Previous haemorrhage	Halim et al. [71]	Stefani et al. [73]
	Kondziolka et al. [76]	
	Mast et al. [56]	
	Pollock et al. [77]	
Headache	Kondziolka et al. [76]	Mast et al. [56]
Hypertension	Langer et al. [75]	

The most consistent factor is the occurrence of prior haemorrhage.

Brown et al. [78] followed patients with unruptured BAVMs and used Kaplan Meier curves to calculate the actuarial risk of haemorrhage as follows:

1.3% per year at 1 year
1.7% per year at 5 years
1.5% per year at 10 years
2.2% per year at 15 years

These data suggest that the risk of bleeding is steady overtime. On this assumption, Kondziolka et al. [76] constructed a probability of bleeding equation as follows:

$$\text{Risk of bleeding} = 1 - (\text{risk of } \textit{no} \text{ bleed})^{x} : (\text{X} = \text{expected years of life}).$$

$$\text{Based } \textit{on} \text{ an annual risk of bleeding of 3\%, i.e. 0.03}$$

$$\text{Chance of remaining bleed free } \textit{for} \text{ 1 year} = 1 - 0.03 = 0.97.$$

$$\text{Chance of remaining bleed free } \textit{for} \text{ 2 years} = 0.97^{2} = 0.94.$$

$$\text{Chance of remaining bleed free } \textit{for} \text{ x years} = 0.97^{x}.$$

$$\text{Therefore the probability of bleeding} = 1 - 0.97^{x}.$$

This exercise has been refined by Brown who proposed a formula in which the lifetime risk (%) = 105 − patient's age in years. From these equations, risk/benefit tables can be constructed to assist patients and physicians in calculating individual risk rates [79].

9.5.5.3 Risk of Death in Patients with BAVM

The long-term crude annual case fatality rate has been estimated at 1–1.5% by Al-Shahi and Warlow [45]. The observed combined morbidity and mortality in observational studies is between 3% and 4% per annum. In Brown et al.'s patients [47], the mortality rate was 3.5% per annum (29% over 8.2 years in the patients who haemorrhaged). The overall combined incidence of major morbidity and mortality was 2.7% in Ondra's patients [60] followed for a mean period of 23.7 years. This risk was higher in patients who had haemorrhaged (85% versus 34%), and this trend was also seen in Brown's series [47] with a 23% risk of significant morbidity in survivors of haemorrhage compared with 7% in those with no haemorrhage. Fatality rates of 5–10% per episode of bleeding [45, 69] are not as high as after aneurysm subarachnoid haemorrhage, but up to a third of survivors are left with a permanent disability after each event. Bleeding is therefore the major factor in the poor long-term prognosis of this diagnosis.

The mean age of death in Ondra's patients was 51 years (compared with 73 years in the general Finnish population) [60]. Thus, BAVMs reduce the life expectancy of patients, and the issue that has to be resolved in recommending treatment is how the natural history compares with the risk of iatrogenic morbidity following intervention. The risks of both rebleeding and death are at least a factor of 2 higher in the patients who haemorrhage and at 3% annually, sets the level of risk that justifies recommending direct intervention to cure BAVMs.

9.5.6 Angioarchitecture

Identifying the vessels supplying a BAVM is obviously crucial to management. Traditionally, this has depended on catheter angiography (DSA) and this continues to provide both anatomical and flow data. We now have the option of contrast-enhanced planar scanning for angiography and multimodality imaging (e.g. MRA/CTA/Flat Detector CT) and reconstructions of 3D and 4D data with image fusion techniques. These can reliably separate arteries and veins from nidal vessels to provide a complete anatomical display of the angioarchitecture. Additionally, MRI techniques, such as phase contrast sequences and arterial spin labelling,

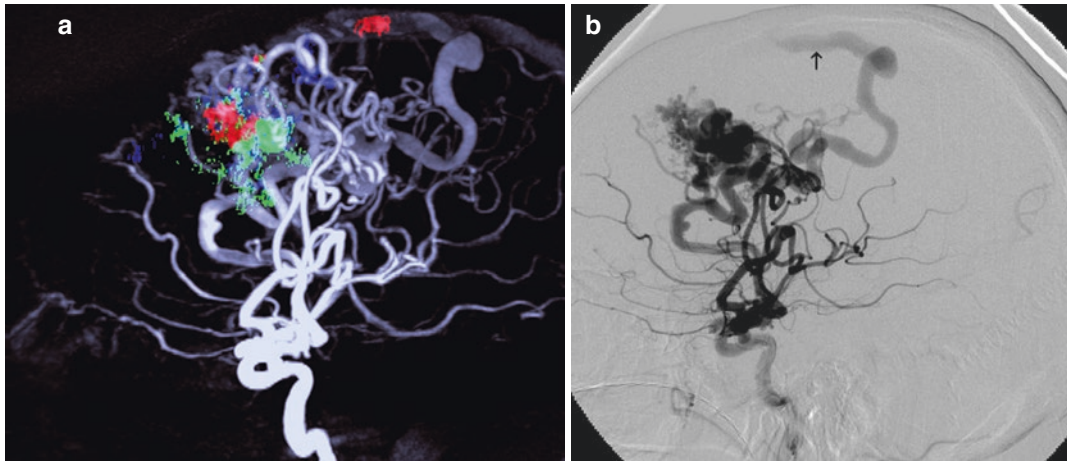

Fig. 9.7 Brain arteriovenous malformation with reconstructed flow data following partial embolisation. A reconstructed lateral view from a phase-contrast MRI has been coloured to show areas of decreased blood flow velocity (*green*) and intravascular NBCA in *red* (**a**). The 2D DSA (**b**) is shown for comparison. Note that some NBCA has migrated to the distal portion of the large draining vein and is shown in *red* on (**a**) and at the *arrow* on (**b**)

can interrogate blood flow patterns and pathways within the nidus (Fig. 9.7). Several authors have emphasised the additional value of superselective angiography (i.e. injection of individual arterial pedicles) to the definition of a lesion's angioarchitecture but this is now unnecessary, except as part of an embolisation procedure.

9.5.6.1 Identification of Prognostic Features

Various authors have described features of the angioarchitecture that were associated with haemorrhage. These are shown in Table 9.3. The list seems to grow with each report, as does the degree of controversy over particular features.

Four features are particularly important:

1. Arterial pedicle aneurysms: These are probably only relevant if they arise from hypertrophy arteries directly supplying the nidus. Aneurysms found remote from arterial pedicles should be considered coincidental and be managed in the same way as unruptured aneurysms in patients without a BAVM. The decision to treat a pedicle 'flow' aneurysm depends firstly on whether it is considered the cause of a presenting (subarachnoid) haemorrhage and secondly whether it affects access to the nidus for endovascular treatments [93]. A general principle is that if the nidus is successfully obliterated, then pedicle aneurysms will probably regress and/or be at reduced risk of future rupture [90].
2. Intranidal aneurysms: The reported frequency of aneurysmal dilatations, saccular aneurysm and pseudoaneurysms within the nidus varies from 10% to 40% and largely depends on how assiduously they are sought and in the past, whether superselective angiography was performed. What is clear is that identification of intranidal aneurysms from 2D DSA is imprecise [94] and superselective angiography has been advocated because it improves their detection rates [89]. CT angiography (CTA) with 3D reconstuction is an alternative. After acute bleeding, a demonstrated intranidal pseudoaneurysm represents a target for early embolisation since it may enlarge and rebleed in the short term (Fig. 9.8).
3. Nidal size: Micro-AVMs (<1 cm) and small BAVMs (<2 cm) are generally considered at higher risk of rebleeding than large lesions, but this assumption may be observational since small lesions are unlikely to cause symptoms other than haemorrhage. They are also more likely to have a single arterial sup-

Table 9.3 Angioarchitecture factors associated with haemorrhagic episodes

	Significant association with haemorrhage	Contradictory data
Location of nidus		
Deep	Crawford et al. [42]	
	Stefani et al. [73]	
Ventricular/periventricular	Nataf et al. [80]	
	Miyasaka et al. [81]	
Basal ganglia	Brown et al. [82]	
Posterior fossa	Khaw et al. [72]	
	Stapf et al. [70]	
	Brown et al. [82]	
Venous drainage		
Single vein	Nataf et al. [80]	
	Miyasaka et al. [81]	
Fewer veins	Todaka et al. [83]	
	Stefani et al. [73]	
Deep	Kader et al. [74]	Halim et al. [71]
Only deep	Khaw et al. [72]	
	Duong et al. [84]	
	Mast et al. [56]	
	Brown et al. [82]	
	Marks et al. [85]	
	Nataf et al. [80]	
	Pollock et al. [77]	
	Miyasaka et al. [81]	
	Stapf et al. [70]	
	Stefani et al. [73]	
	Langer [75]	
Ectasia	Stefani et al. [73]	Nataf et al. [80]
Stenosis	Mansmann et al. [86]	Marks et al. [85]
	Nataf et al. [80]	
Arterial feeder		
High pressure	Todaka et al. [83]	Henkes et al. [87]
	Leblanc et al. [88]	
	Duong et al. [84]	
	Stapf et al. [70]	
	Kader et al. [74]	
Perforators	Brown et al. [82]	
Aneurysms		
Intranidal	Graf et al. [69]	
	Brown et al. [82]	
Flow related[a]	Khaw et al. [72]	Doung et al. [84]
	Turjman et al. [89]	Meisel et al. [90]
	Lasjaunias et al. [91]	Stefani et al. [73]
	Thompson et al. [92]	Mansmann et al. [86]
	Stapf et al. [70]	
	Cagnazzo et al. [93]	
Multiple	Mansmann et al. [86]	Thompson et al. [92]
Diffuse AVM morphology	Pollock et al. [77]	

[a]Flow-related (aneurysms with intranidal location or along feeding arteries)

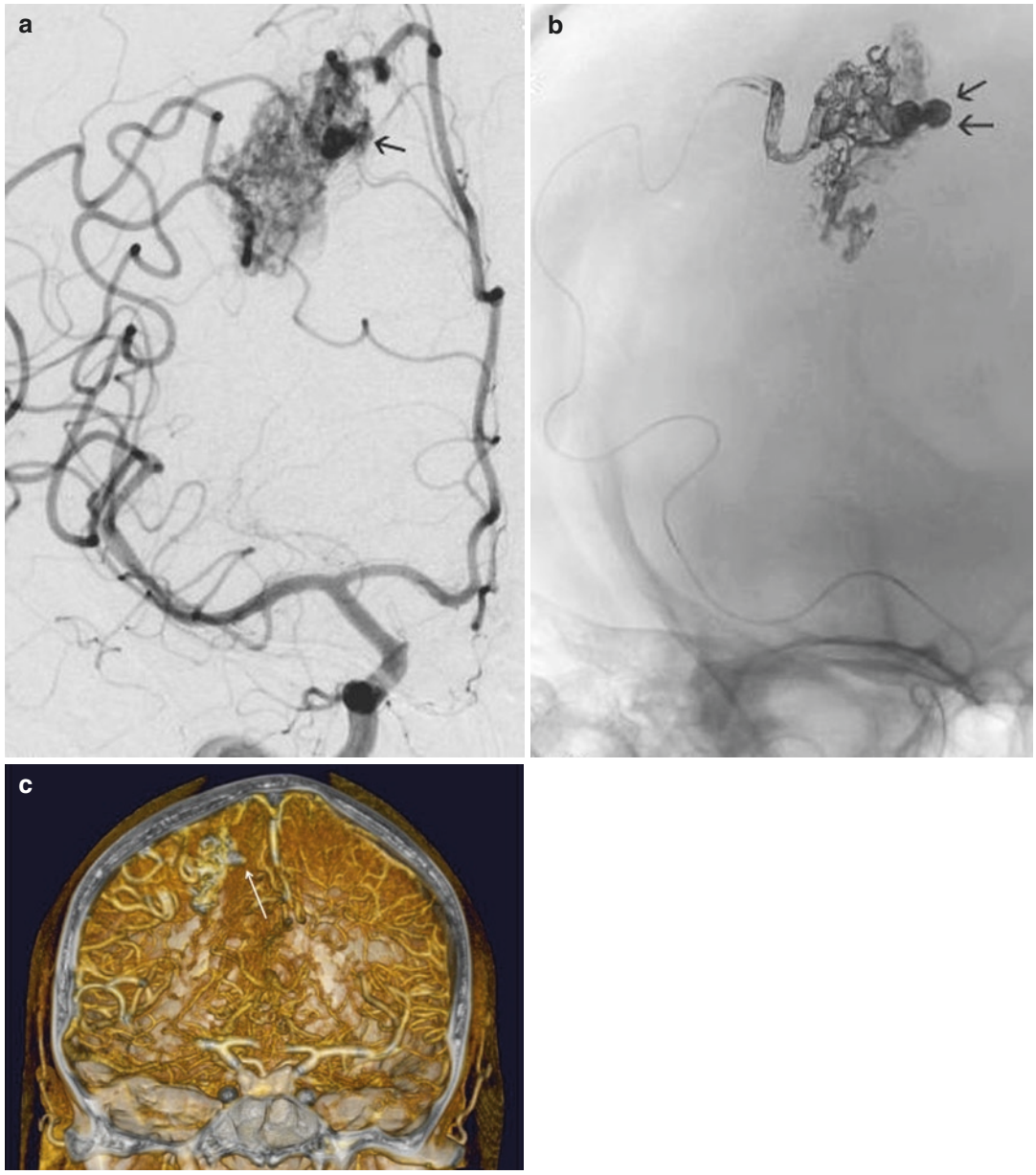

Fig. 9.8 Arteriovenous malformation with intranidal aneurysm. The images show an internal carotid DSA (**a**) and an unsubtracted image showing the aneurysm caste with Onyx (*arrows*) (**b**). CT angiography (**c**) demonstrated bleeding from this aneurysm (*single arrow*)

ply (Fig. 9.9). Occult intracerebral bleeding is sometimes attributed to a ruptured micro-AVM, which has spontaneously obliterated.

4. Location: The influence of location on prognosis is complex. Deep and periventricular locations imply deep venous drainage and the involvement of perforator artery feeders. So a number of poor prognostic features may contribute to their reported higher rate of rebleeding. Posterior fossa lesions may or may not have higher risks of bleeding but the morbidity caused by haemorrhage is greater than for supratentorial lesions, so intervention is generally recommended for unruptured lesions on

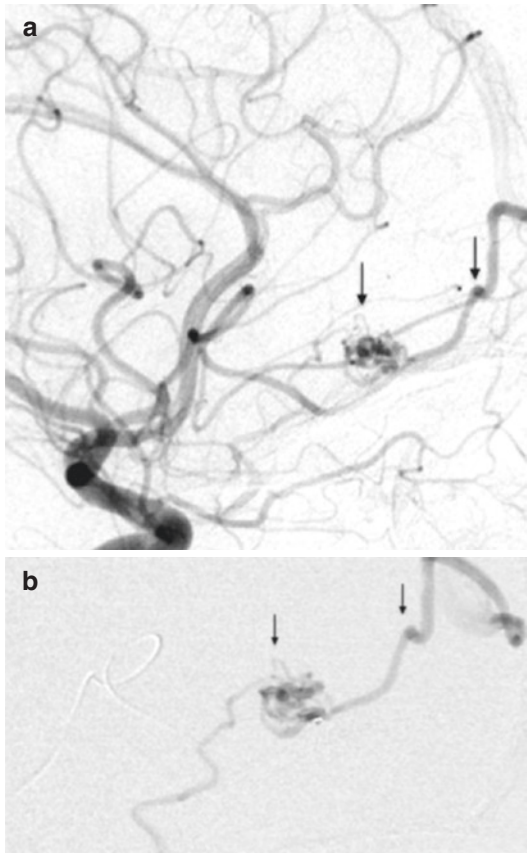

Fig. 9.9 Microarteriovenous malformation. A small brain arteriovenous malformation is seen on the lateral internal carotid DSA (**a**) in the cortex of the inferior frontal lobe. The superselective angiogram (**b**) shows two draining veins which are marked with *arrows* on (**a**) and fill because of shunting through the nidus

the basis of location alone. Location can also sometimes be related to the symptoms a BAVM causes, e.g. seizures are common with temporal lobe-located lesions and visual disturbance with BAVMs in the occipital lobe. The presence of a recruited transpial blood supply involving scalp arteries, in some cases, may be the cause of cranial pain.

9.5.6.2 Influence of Angioarchitecture on Selection of Treatment Method

Planar scanning (without the need for catheter angiograms) often provides sufficient information to identify the anatomical features used to select patients for particular treatment methods, i.e. stereotactic radiotherapy, surgical resection or embolisation (Figs. 9.6 and 9.8).

Table 9.4 Spetzler and Martin scores for grading BAVM [97]

Size of Nidus	BAVM score
Small (<3 cm)	1
Moderate (3–6 cm)	2
Large (>6 cm)	3
Location	
Eloquent	1
Non-eloquent	0
Venous drainage	
Superficial only	0
Deep	1

The size of the nidus is related to the effectiveness of radiotherapy and results are best for lesions less than 10–12 cc in volume. Size, position and venous drainage are recognised as features correlating with outcomes after surgical resection. Several grading systems, e.g. Luessenhop and Rosa [95] and Pellettieri [96], based on anatomical features have been described, but the Spetzler and Martin grading system [97] is most commonly employed. This categorises BAVMs according to their size, location and venous drainage (Table 9.4). The sum of the scores is used to define five Grades. Good surgical results can be expected for Grades 1–2 lesions, intermediate results for Grade 3 lesions and poor results for Grades 4–5 lesions. Its merit lies in its simplicity but it fails to recognise patient variables such as age, gender and symptoms, which obviously are factors in treatment selection. Supplements to this basis plan for grading BAVMs have been proposed by Spears et al. [98] and Lawton et al. [99].

These features obviously affect the selection of patients for embolisation but additional angiographic features are important in deciding whether endovascular treatment is feasible. The number of arterial pedicles, their size, the presence of 'en passant' arteries and the eloquence of adjacent areas are all factors to be considered. An angiographic assessment should also assess for collateralisation from transpial arteries which may increase the risk of vessel tearing during catheter withdrawal. Angiomatous changes in adjacent arteries (identified as separate from the

nidus by their normal contrast washout rates) and evidence of venous hypertension which is a poor prognostic feature (and would favour intervention) should all be assessed.

Functional testing for 'at risk areas' of eloquent brain by superselective injection of barbiturate is generally not employed because of its logistical difficulties and mixed reports of its efficacy [100]. Noninvasive functional testing using fMRI is now a useful alternative for identifying eloquent adjacent structures, e.g. language area, and advising patients about the risk of intervention [101].

9.5.7 Treatments to Eradicate BAVMs

The principal aim of treatment is to eliminate the lifelong risk of haemorrhage. The assumption underlying any form of intervention is that complete eradication of the BAVM means that the patient is no longer at risk of future haemorrhage. Incomplete treatment risks recurrence and future bleeding. The effects of anatomical cure on other symptoms are less certain. The historical milestones in the development of direct interventions to eradicate BAVMs are listed in Table 9.5. These show how embolisation and stereotactic radiosurgery (STR) have been introduced to extend the therapeutic options [102]. The availability of different intervention methods means the decision to intervene and what method to use, requires opinions from a range of specialists, i.e. neurologists, neurosurgeons, radiotherapists and endovascular therapists. The patient and their preferences remain pivotal in this process.

Table 9.5 Milestones in the development of endovascular treatments for BAVM

1500 BC – Egyptians recognised AVMs
1757 Hunter – describes extracranial AVM
1863 Virchow – first pathological description of an intracranial AVM
1895 Steinham – first clinical diagnosis
1908 Krause – unsuccessful feeder ligation
1927 Moniz – introduction cerebral angiography
1928 Cushing and Bailey – describe a series of eight surgical cases
1957 Olivacrona, Fadheim and Tonnis – perform surgery without prohibitive morbidity
1960 Luessenhop – injected coated particles via a carotid arteriotomy
1970 Kricheff – transcatheter technique for injection of embolic particles
1972 Steiner, Leksell, Greitz – introduce sterotaxic radiosurgery
1976 Kerber – calibrated leak silastic balloon for flow control
1990 'Magic' flow-guided catheters introduced
1990 Taki – uses ethyl vinyl alcohol liquid embolic

Is the case proven for intervention in individuals who have suffered a haemorrhage? There have been no randomised trials but it is generally accepted that if treatment can be undertaken with a reasonable expectation of complete cure, it is then justified. When treatment is unlikely to completely cure a lesion or to do so carries a substantial risk of morbidity, then partial targeted treatment to isolate an identified cause of bleeding is intuitively sensible. The question becomes more difficult when proposing treatments for lesions which have not bled.

The 'A Randomised trial of Unruptured Brain Arteriovenous malformations' (ARUBA) multicenter study was conducted to answer this question [103]. The rationale for the trial was an analysis of the Columbia University database (n = 622) with 340 (55%) of patients presenting without haemorrhage. It found an increased risk of haemorrhage during follow-up of treated patients [104]. ARUBA recruited 223 participants between 2007 and 2013 [103]. They were randomised to medical management (observation) or intervention to eradicate the BAVM by the most appropriate methods decided at the recruiting centre. The primary end point was set as new stroke or death. The trial was stopped when the intervention arm results were deemed unacceptably worse. The trial reported stroke or death in 11 (10.1%) patients randomised to medical management and 35 (30.7%) randomised to intervention over a mean of 33.3 months of follow-up. The hazard ration for the medical arm was 0.27 (0.14–0.54) and so lower than intervention. The result has been a virtual moratorium on interventions in UK patients with unruptured BAVM. Though any potential benefit of BAVM eradication will not show in life tables until the natural history morbidity of the untreated BAVM has time to reveal itself. As things stand, follow-

up of the cohort continues and further reports may modify or reverse the trial result.

9.5.7.1 Medical Management

Observation of asymptomatic lesions, given the low risk of haemorrhage in the short term, is generally accepted in patients with no angiographic features associated with a higher risk of bleeding. There are currently no universal guidelines on which to base these decisions (hence the rationale for randomisation in ARUBA) nor agreed protocols for imaging surveillance.

Medical management for the control of symptoms:

1. Headache: Symptomatic treatment for headaches associated with the diagnosis can be difficult. Failure to respond to usual analgesics is not uncommon and headache may be diagnosed as migraine or take the form of spasmodic cranial pain. Migraine-like headache associated with visual disturbance may indicate involvement of the occipital cortex and treatment with antimigraine drugs including beta-blockers, minor antidepressants and the antiepileptic carbamazepine can be considered. Management is best undertaken by a neurologist or pain specialist.
2. Epilepsy: Management should be undertaken under the guidance of a specialist neurologist, but persistent poor control despite drug therapy is an indication to consider intervention. Seizures may be abolished by anatomical cure and their frequency is reduced in the majority of patients [105, 106].

9.5.7.2 Surgical Resection

The goal of microsurgical resection is complete removal of the nidus in a one stage operation. This objective may require preoperative embolisation to reduce the size of larger lesions and facilitate surgery.

Patient Selection for Surgical Resection

When AVMs are diagnosed, the selection of patients for surgical resection is based on an assessment of surgical risk and likelihood of success. This depends on the available surgical expertise, Spetzler-Martin grading criteria [97], patient-specific factors and an analysis of the angioarchitecture. In all but the emergency situation, this process involves multidiscipline consultations.

Surgical selection criteria:

1. Maximum nidus size (best estimated by MRI and DSA).
2. Venous drainage: The Spetzler-Martin grading system [97] defines deep veins as those not accessible at craniotomy. Thus, superficial drainage is defined as cortical only. Anatomically deep veins, such as interhemispheric veins, can be difficult to be distinguished and pose practical difficulties during resections.
3. Eloquent areas: These are the sensorimotor cortex, Broca's area and occipital cortex, deep nuclei of the brainstem and cerebellum, thalamus, hypothalamus, internal capsule and cerebral and cerebellar pedicles. In this definition, cortical structures are assumed to maintain their normal functional representations, but this may not be the case in AVM patients, and functional testing (by fMRI) may help to refine the analysis of operative risk.
4. Patient factors: These include age, gender, medical comorbidity, the patient's occupation and the possible consequences of any iatrogenic disability on their lifestyle.
5. Angiographic features: In addition to an assessment of features identified to increase the risk of bleeding, an analysis of the angioarchitecture may suggest the cause of symptoms such as epilepsy (i.e. an enlarged cortical vein) or headache (i.e. enlarged dural arteries).

Modes of Presentation and Surgical Selection

The mode of presentation influences the decision to intervene, thus:

1. Acute haemorrhage: Emergency evacuation of haematoma and BAVM resection may be life-saving. In the emergency situation, the extent of resection may have to be restricted to that required to control intraoperative bleeding. The time available for preoperative investigations and consideration of embolisation

may be limited and dictates management decisions. Postoperative angiography is mandatory to show the extent of the resection and embolisation or radiotherapy may be appropriate to manage any residual.
2. Symptomatic patients with previous haemorrhage: Generally, intervention is recommended, and its form will be dictated by the above surgical selection criteria.
3. Asymptomatic and symptomatic patients without previous haemorrhage: Resection is performed when the surgical risk is judged lower than the natural history and therefore generally only for patients with Spetzler-Martin Grades 1–2 lesions. In this situation, radiosurgery alone may be indicated. For patients with Grade 3+ lesions, preoperative embolisation may be appropriate.

Surgical Results

For low Spetzler-Martin grade lesions (Grades 1 and 2), the reported complete resection rates are excellent at 90–100% [107–110]. For high Spetzler-Martin grade lesions (Grades 4 and 5), complete cure is only possible in a small minority (5%) and should only be attempted in patients with history of recurrent haemorrhage or existing neurological deficits. Most patients with large lesions are not treated surgically and if they are, it is combined with radiotherapy and/or embolisation [111]. Partial surgical resection is generally performed (20% of Spetzler's series) only if symptoms are progressive [112]. Surgical resection is reasonably effective at curing epilepsy with 40–80% cure rates in patients with a history of seizures [113, 114] (Table 9.6).

Table 9.6 Surgery outcomes

	n	Complete obliteration rate (%)
Davidson et al. [115]	529	96.9
Pikus et al. [108]	72	100[a]
Vinuela et al. [116]	101	96[b]
Hartmann et al. [117]	119	96[b]

[a]Grades 1–3 of Spetzler and Martin scale
[b]Combined endovascular embolisation and surgery

Surgical Complications

Reported rates of complications after microsurgical resection of small, i.e. <3 cm AVMs (Spetzler-Martin Grades 1–2) are low, 0–5% morbidity and 0–4% mortality [107, 108, 118]. Operative complication rates rise dramatically for surgery of larger lesions. Outcomes after surgical resections of Spetzler-Martin Grades 4 and 5 lesions have been reported as morbidity rates of 12–22% and mortality rates of 11–38% [109, 113, 119]. A meta-analysis by Castel and Kantor [120] estimated overall surgical morbidity rates of 8.6% and mortality rates of 3.5%.

Complications after surgery are due to:

1. Cerebral oedema and swelling (up to 3%) due to normal perfusion pressure breakthrough and hyperaemia induced by an acute alteration in regional haemodynamics.
2. Early rehaemorrhage (2%).
3. Vasospasm of arteries exposed during surgery (1%).
4. Thrombosis of arterial or venous 'stumps' associated with large vessel ligation.

9.5.7.3 Stereotactic Radiotherapy

Stereotactic radiotherapy (STR) is performed using a focused high dose of ionising radiation (12–25 Gy) delivered (usually in a single dose) to the nidus in order to induce vessel wall thickening and vessel occlusion. The Gamma knife system (Elekta AB, Sweden) focuses multiple beams of gamma radiation using a multiport helmet that surrounds the patient's head and protects all but the selected tissue volume from a cobalt-60 radiation source. Targets are typically limited to a maximum diameter of 3 cm or a target volume of 10 cm^3, and treated with a marginal dose of 13–30 Gy to a 50% isodose. Adapted conventional radiotherapy units can also be used.

Radiation-induced damage is primarily to the vessel endothelium and smooth muscle cells. It induces an inflammatory reaction which, when healed, causes vessel narrowing and nidal obliteration. The process takes at least 24 months.

Patient Selection Stereotactic Radiotherapy

The most important criterion for the efficacy of STR is the nidus size. The method is most effective for small compact lesions with nidal dimensions of no more than 3 cm because the doses required to treat larger lesions are more likely to damage adjacent brain. In practice, the indications are generally based on a multidisciplinary assessment with patients referred because surgery is contra-indicated due to lesion size and location (i.e. Spetzler-Martin Grade 3+), unruptured status and angioarchitecture features which make embolisation difficult or of high risk. The delay in therapeutic effect is a factor against treatment after recent haemorrhage since patients remain at risk of rebleeding for at least 1–2 years after irradiation. Combination with embolisation may be used to reduce the nidus size and allow treatment of lesions greater than 3 cm^3 [121]. A recently proposed alternative is to use staged radiotherapy, i.e. volume-staged stereotactic radiotherapy, to reduce the nidus prior to surgical resection [122].

Results of Stereotactic Radiotherapy

Complete obliteration rates of 75–95% are reported for small AVMs (<3 cm maximum nidus dimension) (Table 9.7) [93, 113, 114] and for all lesions, the cure rate is lower 50–90% [130]. In general, treatment is less effective the larger the lesion because their treatment requires larger doses of radiations which are more likely to cause complications. The rate of complete obliteration increases over time. In a report of a large cohort (n = 105) of patients retreated after incomplete cure following initial treatment, complete obliteration rates were 35%, 68%, 77%, and 80% at 3, 4, 5 and 10 years, respectively [131]. Pre-treatment by embolisation, associated aneurysms, and previous haemorrhage reduce the chance of cure [129]. However, recently there has been interest in the use of fractionated treatments and improvements in dose delivery techniques allowing treatment of larger lesions. Single-dose treatment can be repeated after 3 years if the lesions fail to occlude.

Table 9.7 Radiotherapy outcomes

	n	Complete obliteration rate
Lunsford et al. [123]	351	86%
Liscak et al. [124]	330	92%
Shin et al. [125]	400	88.1%[a]
Bollet et al. [126]	188	54%
Pollock et al. [77]	144	73%[b]
Flickinger et al. [127]	351	75%
Schlienger et al. [128]	169	64%
Touboul et al. [157]	100	51%
Ding et al.[c] [129]	891	63% at 5 years: 78% at 10 years

[a]Obliteration percentage is best-case scenario
[b]Obliteration without deficit, n = 96; obliteration with minor deficit, n = 9
[c]Large lesions (Spetzler-Martin Grade 3)

Complications

Complications are proportional to the amount of radiation and the volume treated. Local brain swelling due to inflammatory change and blood brain barrier effects can occur in the first 3 months and cause symptoms in eloquent locations. They are treated with oral steroids. Radiation necrosis is more difficult to manage and may require treatment with a combination of pentoxifylline and vitamin E. In severe cases, barbiturates, hypothermia, or hyperbaric oxygen therapy have been used [130].

It is assumed that the latency between treatment and observed obliteration of nidal vessels means that patients are not protected against spontaneous haemorrhage. Bleeding during this period certainly occurs but not at an increased rate relative to natural history estimates. In fact, there is some evidence for a partial protecting effect during the latent period after treatment and before anatomical cure is complete [132]. But when comparing treatments, most specialists factor the natural history risk rate as part of the complication risk.

In an analysis of pooled data of treated patients, Flinkinger et al. [133] reported permanent neurological deficits in 4.8% and an overall neurological complication rate of 8%. Radiation injury in the adjacent brain was identified in 6.4% of treated patients.

The frequency is directly related to the size of the radiation dose and treated volume.

A small residual risk of spontaneous bleeding (0.3% per annum) after demonstrated nidal occlusion has been reported [134]. This risk is greater in patients undergoing repeat treatment, with a 4.05% risk in post-treatment years 0–2 and 1.79% in years 2–10 [131]. Thus, specialist radiotherapy is an effective low-risk treatment for small BAVMs. The lack of immediate protection from bleeding and risk (albeit low) of delayed complications are disadvantages, but for surgically inaccessible small lesions, it is generally the treatment of choice.

9.5.7.4 Embolisation

Embolisation is used alone or as an adjuvant treatment combined with surgery or radiotherapy. The techniques will be covered in a separate tutorial and the emphasis here is to understand its indications and why it is chosen. The goals of treatment are different if it is attempted for complete cure, to facilitate surgery or radiotherapy or used as palliative treatment.

Role of Embolisation

Its role in the multimodal management of brain AVMs depends, to some extent, on where you work. In many countries, embolisation is performed as the initial intervention for BAVMs for a variety of 'unscientific' reasons such as lack of alternative expertise, unavailable resources and because of patient preference, whereas in others, its role is primarily as a presurgical or preradiotherapy adjunct treatment.

The list of milestones in Table 9.5 highlights some of the technical advances that have allowed endovascular navigation and location techniques to develop. This field is not static, and in the last 10 years, the introduction of detachable tip microcatheters and re-formulation of liquid embolic agents has altered the way embolisation is performed and its efficacy. The cyanoacrylate agent, N-butyl-2-cyanoacrylate (NBCA), was approved by the FDA after a randomised controlled trial showing its equivalence to the injection of polyvinyl alcohol particles [135]. Ethylene vinyl alcohol copolymer was introduced in 1990 but used almost exclusively in Japan [136] until it was reformulated and marketed as Onyx (ev3 Endovascular Inc. Irvine, CA USA).

As with other interventions, publication of the interim results of ARUBA has reduced the number of patients with unruptured BAVMs undergoing endovascular treatments. To redefine its role, a series of related prospective randomised studies have been recently proposed [137]. This initiative reflects the evolving clinical role and the new technologies associated with embolisation for BAVM patients.

Embolisation Results

These have to be separated by the aims and indications for the treatments. These are sometimes not clear from series reports, which limit the definition of success to %nidal volume reduction. Criteria for assessing embolisation are:

(i) Complete obliteration: Published results (largely small single-centre series) show a relatively low cure rate for AVMs managed by embolisation alone in the 1980s and 1990s (Table 9.8). These may reflect the fact that the most easily cured are those that can also be resected or treated by radiotherapy.

(ii) Partial treatment: Objective assessments of the effect of partial embolisation are difficult. One method is to count success as preparing an inoperable/untreatable lesion for

Table 9.8 Embolisation outcomes

	n	Complete obliteration rate (%)
Frizzel et al. [138]	1246	5[a]
Reig et al. [139]	122	15[b]
Panagiotopoulos et al. [140]	82	19.5[c]
Katsaridis et al. [141]	101	27.7[c]
Mounayer et al. [142]	94	28[c]
Weber et al. [143]	93	20.4[c]
Van Rooij et al. [144]	44	15.9[c]
Pérez-Higueras et al. [145]	45	22.2[c]
Saatci et al. [146]	350	51[c]
Pierot et al.[d] [147]	117	23.5

[a]Review of all embolisation types 1960–95
[b]NBCA and Onyx
[c]With Onyx
[d]Multicentre study with Onyx

adjuvant treatment. If pre-surgery, the conversion is one factor. Another is the more subjective value of whether embolisation facilitated the resection. This can be evaluated by a reduction in anticipated blood loss during surgery. For pre-radiotherapy, the conversion relates to volume reduction. So success is measured by reductions in size, which is logical if treatment is performed to reduce the size of BAVMs to below a 10 cm^3 volume threshold. However, embolisation pre-radiotherapy needs to be carefully considered because of the negative effect of prior embolisation on cure rates after radiotherapy [148].

(iii) Relief of symptoms: Embolisation has been reported as successful in reducing neurological symptoms attributed to the 'steal' effect on adjacent brain blood flow by Sugita et al. [149].

Complications

Procedural complications are those associated with catheterisation of small cerebral vessels, e.g. perforation or rupture of flow aneurysms, or due to the inadvertent occlusion of normal arteries. Use of adhesive embolic agents risks causing catheter retention or tearing of vessels on catheter removal. Pulmonary embolism due to emboli reaching the lungs is also reported. The most devastating complication is provoked bleeding of the AVM, which may occur acutely or be delayed. Acute post-embolisation haemorrhage is often difficult to explain in individual cases but is most often caused by the spread of embolic agent to draining veins. Delayed bleeding may occur in association with the occlusive hyperaemia syndrome [150] or normal perfusion pressure breakthrough. Progressive thrombosis of draining veins may occur after embolisation and contribute to the occlusive hyperaemia syndrome but the aetiology of both conditions remains the subject of speculation. Pressure monitoring studies have been inconclusive but suggest that embolisation does not cause sustained increases in pressure in the occluded pedicle [151]. The conclusion of several studies is that staged embolisation and limiting the extent of embolisation on each occasion is safer and less likely to cause haemorrhage.

Reported complication rates vary from permanent morbidity in 2–10% and mortality in 1–4% of patients. The incidence of complications was calculated as 4.8% in a review by Piccard et al. [152] for all types of embolisations, but if intranidal injections were made, it was lower at 1% per procedure and 3% per patient. Morbidity and mortality rates are difficult to assess because there have been no reports of studies with large numbers of patients and techniques have evolved rapidly over the last 20 years. Lasjaunias and Berenstein [153] in a combined series reported morbidity rates of 7% (1.4% severe and 5.6% minor) and mortality 1.6%. A systematic review of surgical results found that the permanent morbidity associated with pre-surgical embolisation varied from 4% to 8.9% [104].

In the more recent BRAVO study, treatment-related mortality was 4.3% and morbidity 5.1% [147]. The major cause was treatment-related bleeding which occurred in 8.5% of patients. In a single-centre study using Onyx, the mortality was 1.4% and permanent morbidity 7.1% [146]. Complications included adverse findings on imaging which totalled 137 of 350 (39.1%) of patients. These were asymptomatic in 95 (69%) of those affected and reported as oedema, acute ischaemic lesions and haemorrhage. Treatment-related bleeding within 48 h of embolisation was the cause of mortality in the series. The higher complication rate, compared to earlier reports, in the BRAVO study suggests that the use of Onyx may be a factor but a single-centre study comparing complications after treatments with NBCA or Onyx found the rates to be the same, though this group also reported relatively high treatment-related complication rates with morbidity of 9.6% for permanent and 1.8% transient deficits and 1 death in 446 treatment sessions [154]. The difficulty in comparing reports is the variations in therapeutic objective for the procedures. These are now generally tailored to the individual patient and based on national guidelines and local skill sets after multidisciplinary team discussions.

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Cranial Dural Arteriovenous Fistulas

10

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Preamble

The subject of this tutorial presents one of the most interesting technical challenges to the endovascular therapist. Interpretation of different symptoms, which may affect patients, requires good clinical acumen for diagnosis and high levels of anatomical skill for analysis of angiograms. Recent changes in endovascular treatment strategies have improved cure rates and increased the number of lesions that can be successfully embolised. These developments and challenges place the endovascular therapist at the centre of the management paradigm and, in that position, the responsibilities required for specialist patient care.

10.1 Definition

Dural arteriovenous fistulas involve the meninges and by definition are supplied by dural arteries. They comprise abnormal connections between dural arteries and venous sinuses and/or cortical veins.

10.1.1 History

A dural arteriovenous fistula (DAVF) was first reported by Sachs in 1931 [1]. They were initially thought to develop from pre-existing dural arteriovenous microshunts by Kerber and Newton [2]

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or to develop in response to abnormal venous pressures by Brainin and Samec [3]. In the 1970s, it was realised that venous drainage influenced their behaviour, notably by Aminoff and Kendall [4] who differentiated fistulas draining to the cavernous sinus from those draining to the transverse/sigmoid sinuses and Castaigne et al. [5] and Djindjian et al. [6] who proposed classifications based on venous drainage patterns. The former divided lesions into three groups depending on whether venous drainage was to sinus or cortical veins, anticipating the seminal classification of Djindjian and Merland [7] published in 1973.

10.1.2 Aetiology

The current consensus is that they are acquired lesions, usually developing in response to thrombosis of a sinus or a lesion that causes abnormally high venous pressure. The arguments for a congenital aetiology are weak and based on the additional finding of aneurysms, brain arteriovenous malformations or other arteriovenous fistulas in some patients.

The evidence for their being acquired is more compelling. DAVFs have been reported in patients with:

- Histories of previous local trauma (including surgery, e.g. injection of the Gasserian ganglion)
- Hypercoagulability states, such as pregnancy, use of oral contraceptives, middle ear infection and protein S deficiency [8]
- A documented previously normal sinus [3, 9, 10]

A history of previous local trauma or hypercoagulability state was present in 66% of patients in a meta-analysis [11]. Trauma may rupture arteries adjacent to veins to create a fistula acutely or result in thrombosis of a sinus. It is assumed that sinus thrombosis may cause venous hypertension and local cerebral hypoperfusion which stimulates production of endothelial growth factors [e.g. vascular endothelial growth factor (VEGF) and hypoxia-inducible factor-1alpha]. The resulting angiogenesis leads to the development of arteriovenous shunts. An alternative, but not contradictory hypothesis, is that a change in arteriovenous pressure gradients opens arteriovenous microshunts between dural vessels. This latter process being triggered by raised arterial pressure, head injury, partition and sinus compression by tumour or surgical occlusion of a sinus, though these are also factors that might precipitate sinus thrombosis.

However, the relationship with sinus thrombosis is not clear, since sinus thrombosis does not always cause a DAVF and thrombosis may occur within them. Thus, lesions may evolve with changing degrees of venous thrombosis causing changes in venous drainage patterns, fluctuations in symptoms and signs and even spontaneous closure of fistulas [12]. Progressive restriction of venous outflow may cause retrograde cortical venous drainage and venous hypertension [13].

10.1.3 Epidemiology and Demographics

Age: Lesions have been reported in children but most present in adults [14]. In a literature review of 248 treated cases, Lucas et al. [11] found a mean age at presentation of 50.3 years (range 1–87 years).

Sex: There is a modest male predominance, which is most evident for higher-grade lesions (55% male in Lucas et al.'s review).

Incidence: It is difficult to establish an incidence for this diagnosis from the literature. Most authors quote an estimate of Newton and Conquist (made in 1969) that they represent 10–15% of all intracranial vascular malformations [14]. The incidence (detection rate) in the Scottish Intracranial Vascular Malformation Study (SIVMS) was 0.16/100,000 (95% CI 0.08–0.27) adults per annum and therefore somewhat lower at 7% of all intracranial vascular malformations in this cohort [15].

10.1.4 Pathology

The dura is thickened with intense vascular proliferation within and around the sinus wall. A spongy mass of fibrous tissue is found inside the sinus, and primary and secondary arteriovenous

shunts are seen on the venous side of the network. Stenosis or occlusion of sinuses is frequent but not always present.

10.2 Clinical Consequences

A DAVF is usually diagnosed after patients develop bruit or present with spontaneous intracranial haemorrhage. The nature of symptoms varies depending on the site of the fistula. Location is also a factor in the likelihood of a fistula bleeding but the risk depends more on the angioarchitecture of the lesion. Its importance is encapsulated by classifications used for DAVFs. These will be considered first so to understand how they relate to the symptoms and signs caused by DAVFs and lead to their diagnosis.

10.2.1 Classifications

Much has been written about the classification of DAVFs. This is not surprising since they compose a group of lesions with heterogeneous symptoms, signs and natural histories. One approach is to separate progressive from non-progressive lesions based on their symptoms and signs (which in turn is related to the location of the DAVF). Another is based on an analysis of the angioarchitecture (i.e. venous drainage pattern) and whether drainage involves cortical venous reflux (CVR). Both have been shown to correlate with prognosis and natural history (Figs. 10.1, 10.2, 10.3, 10.4 and 10.5).

The three important classifications based on angioarchitecture are presented in Tables 10.1, 10.2 and 10.3. The first generally accepted classification was by Djinjian and Merland [7]. It was enlarged by Cognard et al. [16] and, about the same time, a simplified system was proposed by Borden et al. [17]. Today, these last two systems are used almost equally frequently. The Borden system captures the important distinction between lesions with progressive or benign natural histories but lacks the detail of the French authors.

These classifications emphasise the importance of increased pressure in cortical veins to the development of symptoms or spontaneous haemorrhage. Lesions with CVR are higher grades with angiographic evidence of retrograde drainage into leptomeningeal (i.e. veins of the arachnoid and pia mater) and cortical veins. They are more likely to cause symptoms. Type I

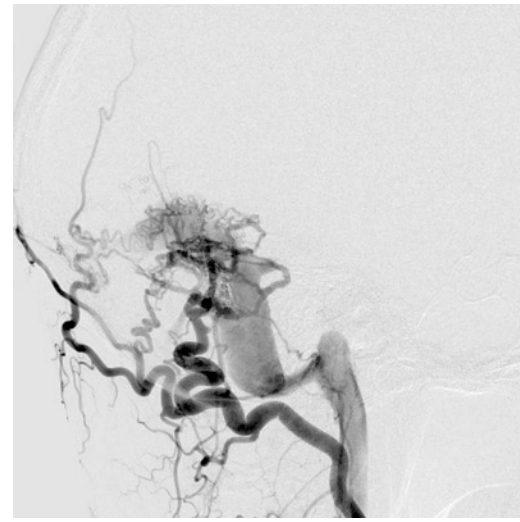

Fig. 10.1 Dural arteriovenous fistula of the distal transverse sinus with its principal supply from branches of the occipital artery. Type I fistula; the sigmoid sinus is dilated because the increased blood flow but no retrograde flow is evident in the transverse sinus or to cortical veins

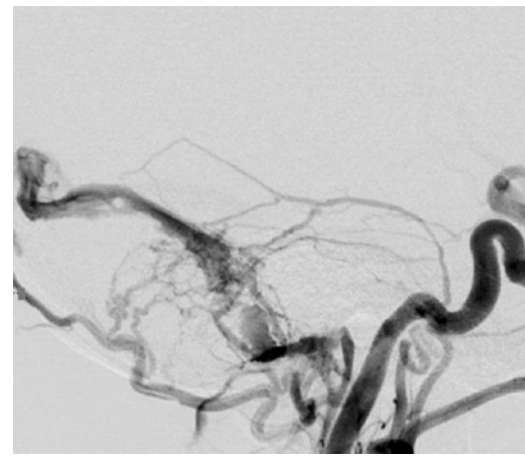

Fig. 10.2 Dural arteriovenous fistula of the transverse sinus with arterial feeders from occipital and middle meningeal arteries. There is antegrade and retrograde flow in the sinus. This is therefore a type IIa fistula. Note the stenosis in the sigmoid sinus. This is thought to develop in response to abnormally high blood flow

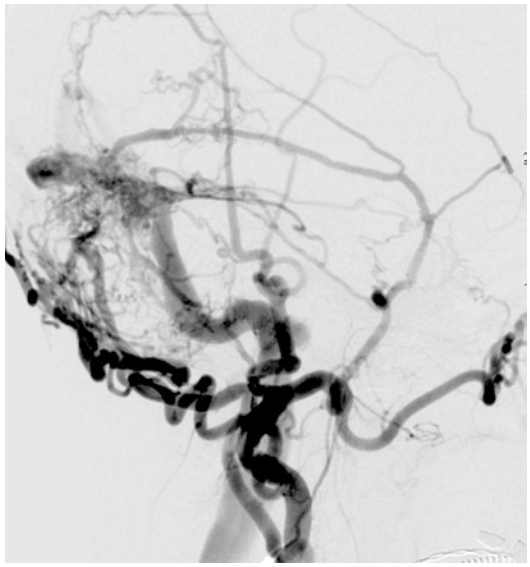

Fig. 10.3 Dural arteriovenous fistula of the transverse sinus. The principal contributing feeding arteries are the posterior branch of the middle meningeal, occipital and posterior auricular arteries. Angiography shows that drainage to the transverse and sigmoid sinuses occurs in antegrade and retrograde directions with reflux to cortical veins. This is therefore a Type II a + b DAVF

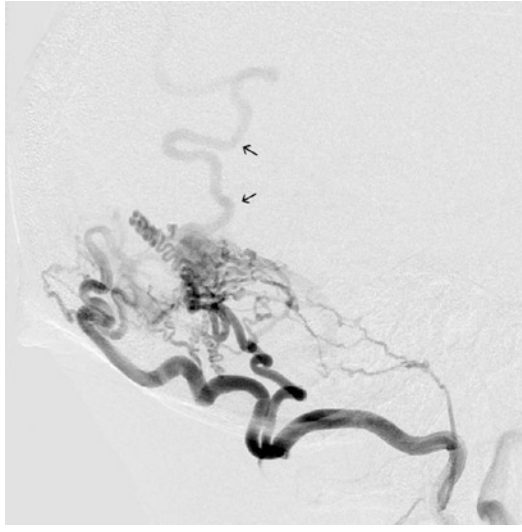

Fig. 10.4 A type III DAVF of the transverse sinus with arterial feeders from the occipital and posterior auricular arteries. There is direct filling of a prominent cortical vein (*arrow*) and no drainage of an isolated section of the sinus to the sigmoid sinus or proximal lateral sinus

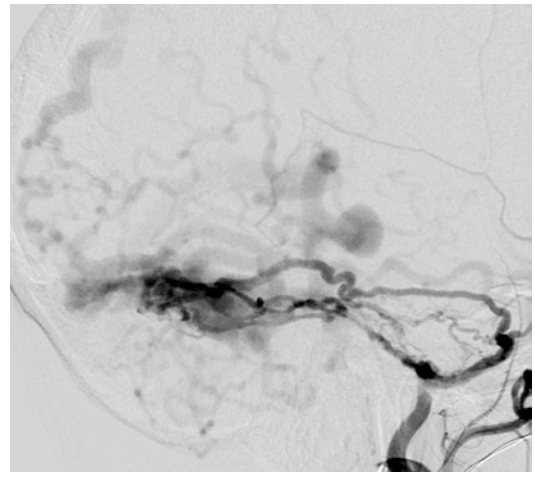

Fig. 10.5 A dural arteriovenous fistula of the transverse sinus with arterial feeders from the middle meningeal and posterior auricular arteries. An isolated section of the sinus fills and drains to enlarged cortical veins. This is a type IV DAVF

Table 10.1 Djinjian and Merland's classification of dural arteriovenous malformations

Djinjian and Merland [7]	
Type I	Drainage into a sinus (or a meningeal vein)
Type II	Sinus drainage with reflux into a vein discharging into the sinus
Type III	Drainage solely into cortical veins
Type IV	With supra- or infratentorial venous lake

Table 10.2 Modified Djinjian and Merland's classification by Cognard et al.

Cognard et al. [16]	
Type I	Antegrade drainage into a sinus or meningeal vein
Type IIa	As type I but with retrograde flow
Type IIb	Reflux into cortical veins
Type IIa + b	Reflux into both sinus and cortical veins
Type III	Direct cortical venous drainage without venous ectasia
Type IV	Direct cortical venous drainage with venous ectasia
Type V	Spinal venous drainage

Table 10.3 Borden et al.'s classification of dural arteriovenous malformations

Modifications of Borden [17]	
Type I	Drainage directly into dural venous sinuses or meningeal veins
Type II	Drainage into dural sinuses or meningeal veins with retrograde drainage into subarachnoid veins
Type III	Drainage into subarachnoid veins without dural sinus or meningeal venous drainage

lesions, in which drainage is confined to an adjacent sinus without backflow or reflux, are unlikely to bleed or cause symptoms other than bruit or headache (Fig. 10.1). Type IIa lesions are similarly unlikely to cause serious symptoms but DAVF of the cavernous sinus is an exception because if drainage is directed anteriorly to orbital veins it may overwhelm their drainage capacity and cause sight-threatening symptoms due to venous hypertension, i.e. proptosis, ophthalmoplegia and raised intraocular pressure. An additional classification for fistulas involving the cavernous sinus was proposed by Barrow et al. in 1985 [19], but this is confusing because it mixes carotid–cavernous fistulas with DAVFs of the cavernous sinus. I suggest it is best avoided.

Baltsavias et al. [20] have recently proposed a classification based on a more detailed analysis of venous drainage patterns. They use three angiographic criteria to define eight subgroups of DAVFs with leptomeningeal venous drainage. These are: (a) direct or non-direct drainage depending involvement of leptomeningeal veins alone or in addition to the sinus, respectively; (b) exclusive or non-exclusive drainage depending on this being only by leptomeningeal veins or involving sinus, dural or emissary veins, respectively; and (c) cortical veins showing features of venous hypertension or not. The classification emphasises the role of bridging veins (between sinus and cortical veins) in the angioarchitecture of type III lesions [21]. Time will tell how useful it is in practice.

10.2.2 Clinical Presentation

Location and arterialisation of cortical veins are the primary features determining the symptoms and signs caused by DAVFs. Both influence the behaviour and natural history of lesions. The approximate proportions of DAVF at intracranial locations and frequency of most common presenting symptom are presented together in Table 10.4.

Table 10.4 Frequency of DAVFs at different locations and their usual presenting symptom

Location	%	Commonest symptom at presentation	%
Transverse	55	Intracranial murmur/bruit	70
Cavernous	15	Ocular symptoms	50
Tentorial	10	Haemorrhage	20
Superior sagittal	9	Headache, seizure, raised intracranial pressure	15
Anterior cranial fossa	6	Progressive neurological deficit, haemorrhage	Rare
Others	5	Dementia, myelopathy, etc.	Rare

Symptoms and signs due to DAVFs include:

- Pulsatile tinnitus. This is the most common symptom and its onset is often quite sudden with patients able to recall the exact time it started. It is variable in intensity, synchronous with the heartbeat and usually audible on auscultation. It is common because of the frequency of DAVFs involving the transverse and sigmoid sinuses and obviously related to their proximity to the inner ear. There may be retro-auricular pain. Diminishing or abolishing the noise by manual pressure (over the mastoid area for transverse sinus DAVFs) is a pathognomonic feature. Patients may find it unbearable.
- Intracranial hypertension. This causes headache, papilloedema, up gaze palsy, and may (rarely) progress to cognitive impairment, drowsiness and coma. It is assumed to be due to reduced CSF absorption to the superior sagittal sinus due to increased intra-sinus pressure. In response, intracranial pressure rises to maintain a gradient for CSF drainage. It is not common, occurs in lesions with CRV and the increased venous pressure probably reflects a lack of available alternative venous drainage pathways in the affected individuals.
- Ocular symptoms. Patients with DAVFs of the cavernous region may develop chemosis,

exophthalmos and diplopia due to arterialisation of orbital veins. Vision is at risk if the intraocular pressure rises, and this should be monitored. Orbital pain and bruit may be present. Diplopia is most frequently due to VIth and/or IIIrd nerve palsies and IVth nerve palsy is rare and never an isolated finding. Reduced visual acuity and raised intraocular pressure are present in 30–40% of patients [22].

- Dementia and Parkinsonism. Dementia is secondary to CVR but may occur without features of raised intracranial pressure. Focal neurological deficits, such as aphasia, paraesthesia and ataxia without cerebral haemorrhage have been reported as well as symptoms of Parkinson's disease [23].
- Seizure, venous infarction and haemorrhage. These are also consequences of CVR. Seizures are usually associated with haemorrhage and this event is discussed below. Focal neurological deficits may also be the result of haemorrhage.
- Myelopathy. It is well described that intracranial DAVF may cause symptoms of cervical myelopathy. Patients present with symptoms of progressive limb weakness, bulbar and autonomic dysfunction. These include episodes of postural hypotension, spontaneous bradycardia and systemic hypertension. The diagnosis is by MRI showing hyperintense T2-weighted changes in the cranial spinal cord.

10.2.3 Risk of Haemorrhage

Spontaneous haemorrhage causes parenchymal haematoma and/or subarachnoid haemorrhage and it may be secondary to venous infarction. The risk is 2% per year for all types of DAVFs but consistently reported to be higher in the presence of CVR and therefore in type 11b – V lesions [24]. In a meta-analysis, Kobayashi et al. calculated an odds ratio of presentation with haemorrhage of 23.2 (95%CI 13.8–39.0) in patients with CVR [25]. The risk of future haemorrhage is also increased for patients after haemorrhage [26]. A follow-up study of patients with CVR reported annual haemorrhage rates of 3.7% for all and 1.5% and 7.4% for patients without or after haemorrhage, respectively [27]. This increased haemorrhage risk also applies to patients with symptoms of venous hypertension secondary to CVR. Strom et al. [28] reported the incidence of haemorrhage on follow-up was 5.9% in patients with no or minimal symptoms and 18.2% in those with symptoms of CVR. The highest risk of rebleeding is in the acute period after haemorrhage; a 35% rate of rebleeding within 2 weeks of presentation with haemorrhage has been reported [29].

10.2.4 Risks of Clinical Progressive

It is well recognised that symptoms due to DVAFs may alter over time [24]. This is assumed to be due to evolution to a higher or lower grade lesion. Spontaneous resolution is well recognised to occur sometimes. This has been attributed to thrombosis of the sinus but cases with spontaneous resolution and patent sinuses have been observed [30].

The severity of symptoms at presentation is a factor in progression and Zipfel et al. suggested that it should be a criterion for the classification of DAVFs [31]. It is difficult to separate the effect of haemorrhage from other causes of symptoms in some reports. However, it is clear that location is important in determining symptoms and the risk of progression. Awad et al. [32] reviewed 377 case reports in the literature and calculated a ratio of those with an aggressive neurological course (defined as heamorrhage or progressive focal neurological deficit other than ophthalmoplegia) to those with benign serious symptoms (100 cases) according to location. They concluded that no location was immune from progression but this was least often seen in DAVFs involving the transverse-sigmoid sinuses and cavernous sinus and most often seen at the tentorial incisura and anterior fossa locations (see Table 10.5). Angiographic features associated with progression were CVR, venous aneurysm or varices, and Galenic drainage. Unlike other fistulas, the rate of shunting did not correlate with progression [32].

Table 10.5 Relative frequency of 'aggressive to benign' features at presentation according to location [32]

Location	Frequency $n = (\%)$	Progression $n =$	Ratio Aggressive: benign
Anterior fossa	22 (5.8)	15	2.1:1
Convexity/sagittal sinus	28 (7.4)	14	1:1
Sylvian/middle fossa	14 (3.7)	10	2.5:1
Cavernous	45 (12)	6	1:6.5
Tentorial	32 (8.4)	31	31:1
Transverse/sigmoid	236 (63)	24	1:8.8

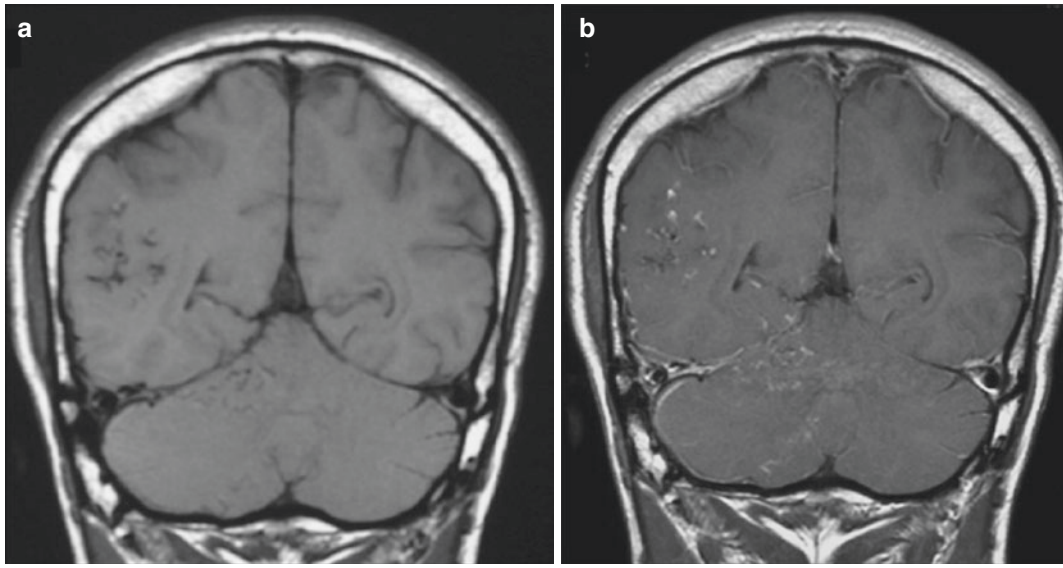

Fig. 10.6 Coronal T1-weighted MRI before (**a**) and after (**b**) gadolinium administration. Enlarged cerebral veins are evident in the right hemisphere due to a Type III DAVF of the right transverse sinus

10.2.5 Imaging

The diagnostic pathway depends on the patient's clinical presentation and the likely location of the DAVF.

- CT may be normal or show cerebral oedema and intracranial haemorrhage. Enlarged vessels (e.g. an enlarged superior ophthalmic vein) will be best shown after contrast enhancement.
- Positron emission tomography (PET) or single-photon emission computed tomography (SPECT) scans may show increases in regional cerebral blood volume and decreased cerebral blood flow in areas affected by CVR and raised venous pressure.
- MRI may show secondary features of raised intracranial pressure, cerebral oedema and intracranial haemorrhage. After contrast administration it is more likely than CT to demonstrate enlarged cortical veins or venous lakes in DAVFs with CVR (Fig. 10.6).
- MRA/MRV is best performed using a 3D phase contrast technique with low velocity encoding, in order to identify the fistula, feeding arteries and flow reversal in draining veins. It may be negative if blood flow is slow, and its relatively poor resolution is not able to delineate the detailed angioarchitecture.

Venograms should identify occlusion or stenosis of major dural sinuses.

- CTA and time-resolved CTA (4D) has better resolution than MRA, but unless it replaces DSA, the additional radiation dose is probably not justified [33].
- DSA remains the 'gold standard' modality and the only entirely reliable way of excluding the diagnosis of DAVF. In patients being investigated for myelopathy with MRI signal changes in the spinal cord, cranial angiography is needed to identify a type V DAVF.

10.3 Management

10.3.1 Indications for Treatment

Though treatment should be considered for all lesions, spontaneous closure has been reported in about 10% of DAVFs. In a follow up study of DAVFs of the cavernous region, spontaneous complete regression of symptoms occurred in 19 of 26 patients followed but fistula closure was only confirmed by angiography in 4 patients [34]. Thus for type I lesions, intervention is only indicated if symptoms are distressing for the patient. Although evolution between types (due to opening or closing of the primary drainage) has been reported, it is unusual, and if it occurs, it is usually accompanied by an alteration in symptoms. Therefore, if symptoms are stable and tolerated by the patient, there is no indication for intervention but they should be monitored. For most type II lesions, intervention is usually recommended, and for type III and IV lesions, urgent surgical or endovascular treatment is indicated.

10.3.2 Aims of Treatment

These are either cure or palliation of symptoms. For cure, the treatment's aim is to completely close the fistula and the abnormal venous outlet. Palliative treatments can be difficult to engineer without risking alterations of the venous drainage pattern and so are usually performed transarterially. In Table 10.6, vascular supply and usual treatment approaches are summarised for DAVFs at different locations. The treatment approaches recommended are based on the observed differences in natural history for DAVFs.

10.3.3 Treatment

The decision on how and whether to treat is based on clinical presentation, location, anticipated natural history and venous drainage.

The treatment options are:

Conservative management with observation or percutaneous arterial compression
Surgery
Radiotherapy
Embolisation
  Transarterial embolisation
  Transvenous embolisation

10.3.3.1 Conservative Management

Observation without intervention is suitable for a type I fistula if symptoms are tolerated, since spontaneous regression of DAVFs can occur [35]. The decision to pursue this management should be re-evaluated if symptoms change.

Arterial compression may be useful in asymptomatic or minimally symptomatic type I and IIa DAVFs. It involves the patient compressing the cervical carotid or occipital artery using their contralateral hand. The procedure should start with short periods of compression, repeated several times a day, and the frequency and duration of compression increased over 3–4 weeks [36]. Compression is performed sitting or lying and has been shown to be effective in inducing thrombosis of the DAVF in 20–30% of patients. It is contraindicated in patients with atherosclerosis.

10.3.3.2 Surgery

Surgery is now generally reserved for lesions that have failed embolisation or as an adjuvant technique to access an isolated sinus. Obliteration of the draining vein is required for cure and ligation of feeders is inappropriate therapy [11]. Skeletisation of the dura around a DAVF for excision of the

Table 10.6 DAVFs at different locations. Relationship of location to presentation and management, based on [11]

Anterior cranial fossa:
Feeders – Anterior and posterior ethmoidal arteries or anterior falcine artery
Drainage – Frontal cortical, basal veins, sphenoparietal sinus
S&S – Up to 90% chance of haemorrhage
Treatment – Usually surgical
Cavernous sinus:
Feeders – Branches of ILT and MHT, recurrent meningeal artery, capsular artery, MMA, accessory meningeal artery, artery of foramen rotundum, contralateral supply
Drainage – Ophthalmic veins, inferior/superior petrosal sinuses, sphenoparietal sinus and frontal cortical veins
S&S – Headache, bruit, ocular symptoms (chemosis, proptosis, visual disturbance, raised intraocular pressure, ophthalmoplegia)
Treatment – Conservative (spontaneous closure recognised) compression therapy or endovascular (transvenous or transarterial). The venous approach is usually the treatment of choice
Sigmoid/transverse sinuses:
Feeders – Jugular artery, transmastoid branch of OA, MMA, meningeal branches of VA and marginal tentorial artery
Drainage – Sigmoid sinus, transverse sinus, IJV
S&S – Headache, pulsatile tinnitus and bruit. Neurological deficits: focal deficits, memory changes, visual disturbance
Treatment – Compression therapy, endovascular (transarterial or transvenous). Transarterial with sinus preservation is optimum. Surgery is now rarely performed
Superior sagittal sinus:
Feeders – MMA, STA, OA. Also anterior and posterior falcine arts
Drainage – Superior sagittal sinus
S&S – Headache, haemorrhage, bruit uncommon
Treatment – Endovascular (transvenous or transarterial), combined endovascular and surgery, surgery alone
Tentorial incisura:
Feeders – Marginal tentorial artery, meningeal branches MMA, ICA and VA
Drainage – Tentorial veins, BVR, lateral mesencephalic vein
S&S – High incidence of haemorrhage
Treatment – Endovascular (transarterial is now the treatment of first choice), combined surgical/endovascular
Basal tentorial:
Feeders – Basal tentorial artery, lateral clival artery, meningeal branches MMA, ICA and VA
Drainage – Superior petrosal sinus, petrosal vein
S&S – Headache, haemorrhage
Treatment – Endovascular (transarterial is the treatment of first choice), combined surgical/endovascular
Torcular:
Feeders – Meningeal branches of OA (bilateral), VA
Drainage – Medial occipital, infratemporal and cerebellar veins
S&S – Bruit uncommon. Headache and haemorrhage
Treatment – Endovascular (transarterial if possible or transvenous)
Foramen magnum:
Feeders – Hypoglossal artery, anterior meningeal artery, transmastoid branch of OA, medial clival artery
Drainage – Subarachnoid, vertebral veins
S&S – Bruit, myelopathy, haemorrhage
Treatment – Endovascular (transarterial or transvenous). The venous approach is usually the treatment of choice

ICA internal carotid artery, *ILT* inferolateral trunk, *MHT* meningohypophyseal trunk, *MMA* middle meningeal artery, *OA* occipital artery, *VA* vertebral artery, *STA* superficial temporal artery, *IJV* internal jugular vein, *BVR* basal vein of Rosenthal

nidus, sinus and venous drainage is now rarely performed and targeted surgery is assisted by operative angiography and navigation techniques [37]. A cure rate of 92% for high-risk lesions was achieved but at the cost of a 13% rate for morbidity and mortality [38]. It is still considered the treatment of choice for anterior cranial fossa lesion though combined treatments are also useful [39].

10.3.3.3 Stereotactic Radiotherapy

Reports of treatment with stereotactic radiosurgery claim complete occlusion rates of 44–87% without serious complications [40]. Its major disadvantage is the delay in response and so it is generally used for low-risk lesions or otherwise untreatable lesions. In a series of 40 patients, Yang et al. reported cure rates of 83% after 2 years [41]. It is less effective in lesions with larger shunts. In a meta-analysis, Chen et al., calculated cure rates for lesion with cortical drainage of 56% compared to 75% for those without [40]. It is thus commonly used for DAVF of the cavernous sinus region. Its use in combination with transarterial embolisation has been reported as effective after incomplete treatments [42].

10.3.3.4 Embolisation

The technical objective of endovascular treatment is occlusion of the fistula by occluding the proximal portion of the draining vein. The key to success is identifying this point in the angioarchitecture and the best route for catheter access. Thus, prior to any endovascular treatment, comprehensive catheter angiography must be performed. This should include six-vessel cranial angiography (DSA) with careful assessment for arterial variants and extracranial to intracranial (EC–IC) anastomoses. Contralateral anastomoses and collaterals are commonly found.

The choice of transvenous or transarterial approach depends on location, venous drainage pattern and the available endovascular access. Since the introduction of ethylene vinyl alcohol co-polymer liquid embolic agents, transarterial treatment has become the preferred route for DAVFs at all location except cavernous sinus and foramen magnum regions, because of the greater risk of complications. Embolisation, via the ascending pharyngeal artery, risks causing cranial nerve damage. Lesions with multiple arterial pedicles draining to a redundant sinus have traditionally been treated transvenously but it is usually worth attempting transarterial occlusion first. Occasionally no endovascular route to a sinus is available and percutaneous access is needed via a surgically created window [43]. Type III and IV DAVFs do not have a simple connection to the sinus, and treatment of these types of lesions is usually transarterial but may require a combination of methods:

(a) *Transarterial embolisation is performed with particles or liquid agents.*

Transarterial embolisation with particles

There is a high incidence of recurrence after arterial embolisation with particles and so it is rarely performed except prior to surgery or for palliation of symptoms. In palliative treatments for type I and IIa DAVFs, the aim is to reduce the flow through the fistula, in order to reduce symptoms, such as bruit.

Technique: Embolisation is performed using particles in the 150–250 μm range. It is usually unnecessary (and unwise) to embolise meningeal feeders arising directly from ICA or VA. A free-flow injection, which avoids wedging the microcatheter tip, is best. Particles are injected until stasis is achieved in the distal pedicle.

Complications: If particles >150 μm are used, cranial nerve palsies are very rare. Other complications are generic, i.e. those associated with selective catheterisation and cranial angiography:

Transarterial embolisation with liquid embolic agents (Figs. 10.7 and 10.8)

Transarterial use of *n*-butyl-2-cyanoacrylate (NBCA) or ethylene vinyl alcohol co-polymers, e.g. Onyx (ev3 Endovascular Inc., Irvine, CA, USA), Suid (Emboflu, Switzerland) and PHIL (Microvention, Terumo, Japan) has become the method of first choice and enabled the treatment of previously incurable DAVFs [44]. Liquids, such as Onyx, can be injected from both transarterial and transvenous routes and extensive filling of small fistulas

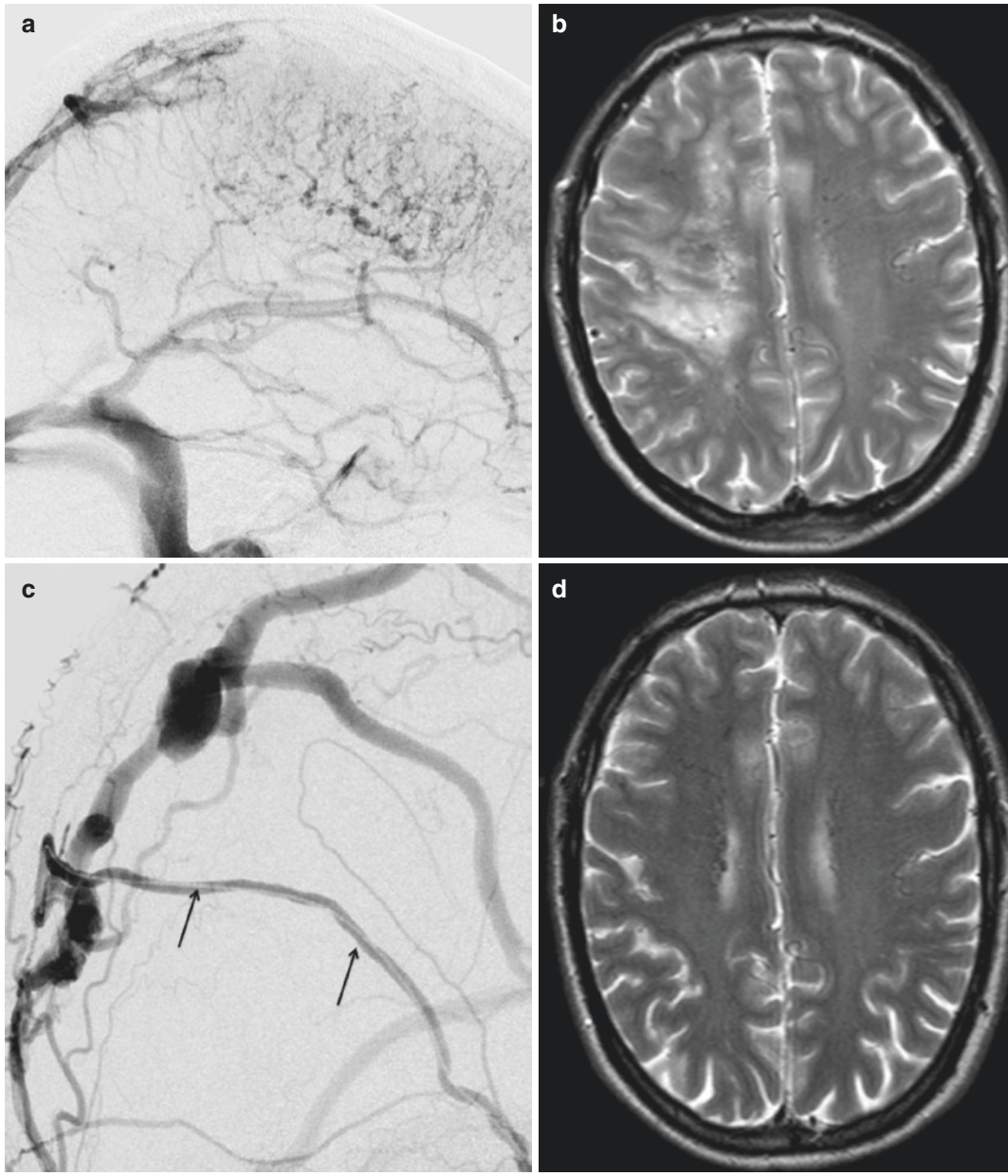

Fig. 10.7 DAVF with engorged ependymal veins on DSA (**a**) and hyperintense signal return on T2-weigthed MRI (**b**). Transarterial embolisation of this Type IV fistula was performed via the posterior middle meningeal artery with Onyx (**c**) (*arrows* show the microcatheter). Symptoms and MRI signal change (**d**) resolved after closure of the fistula

achieved from these antegrade and retrograde approaches. In some instances, using NBCA may be more appropriate, but generally the transarterial injection of Onyx is preferred. It is easier to control than NBCA and retrograde reflux in the access pedicle can prevented using a double-lumen balloon (e.g. Sceptre C catheter, Microvention, Terumo). Injections are stopped before Onyx enters functional cortical veins (Fig. 10.8).

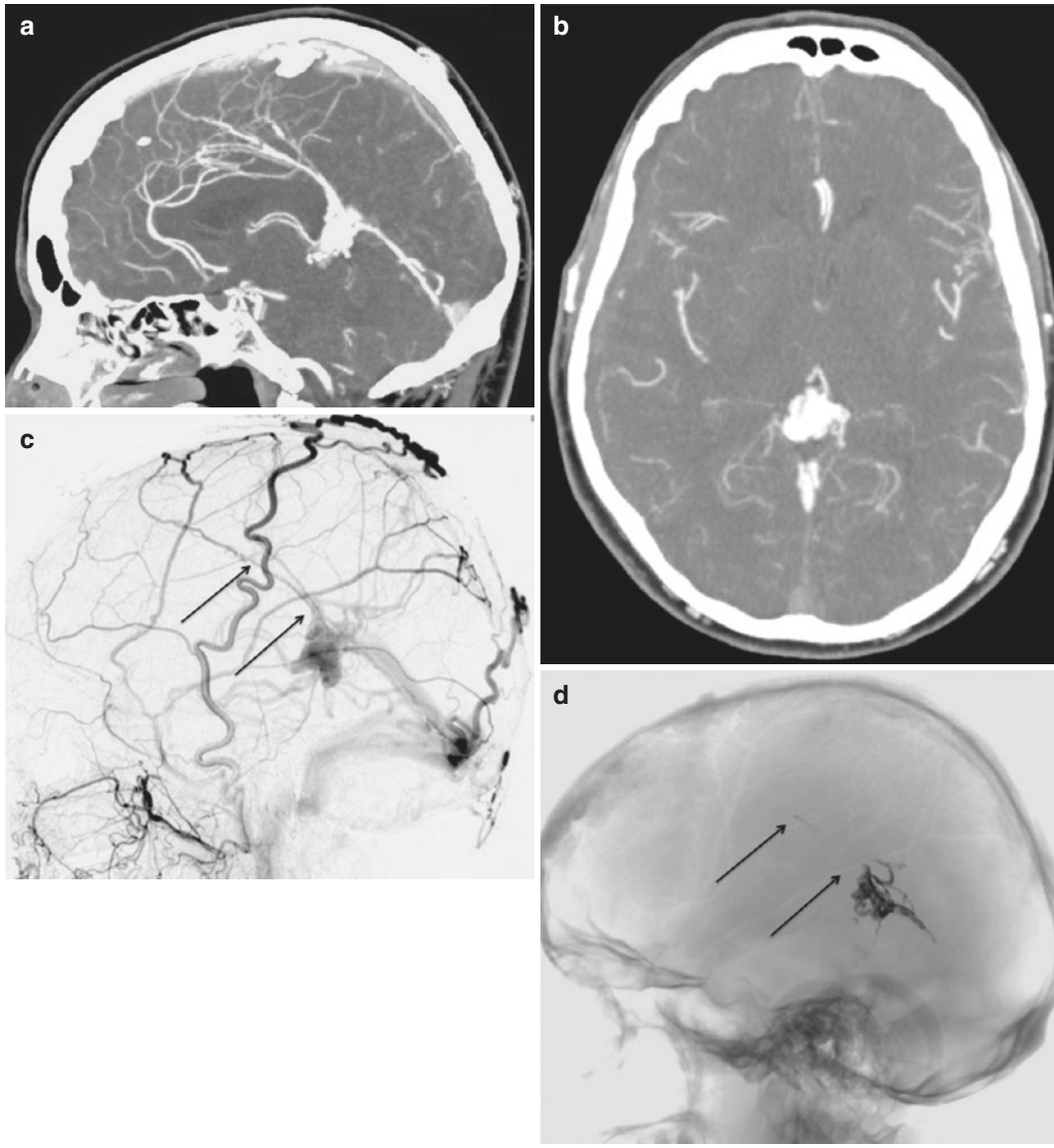

Fig. 10.8 DAVF of the falx. The shunt involves a varix at the vein of Galen, shown on CTA (**a**, **b**). DSA shows the transarterial route for injection of Onyx (*arrows* on **c**). In (**d**) the post-embolisation Onyx caste is shown with and a small amount of Onyx around the detached tip (*arrows*) of the delivery microcatheter

Technique: A standard plug-and-push technique is used with Onyx. High-density preparations help visualisation, especially when injecting vessels around the skull base. A non-detachable balloon placed transvenously, can be used to protect sections of a draining sinus during transarterial injections. Detachable-tip catheters, double-lumen balloons and using two catheters simultaneously, allow multiple small feeding vessels to be excluded in a single procedure. For NBCA, a low-pressure injection under high-resolution fluoroscopy is performed in order to avoid opening EC–IC anastomoses using dilute mixtures with Lipiodol. It is usually impossible to inject as much NBCA as Onyx, and the choice of which to use often depends on the extent of the intended embolisation.

Complications: Adverse effects specific to endovascular treatments include vessel injury and provoked haemorrhage, cerebral infarction (embolic and venous), cranial nerve palsy, redirection of venous drainage and recurrence.

(b) *Transvenous embolisation*

The aim of transvenous embolisation is to occlude the draining system (usually a dural sinus) of the DAVF so that the low-pressure arterial blood supply is secondarily occluded. To prevent complications, it has to be performed without occluding unique normal venous drainage pathways from the brain. It can be performed with fibre coils, controlled detachment bare or coated coils and liquids. The disadvantage of using coils is that it may take time for thrombus to completely occlude a sinus, and they are expensive in time and money [45].

Technique: After careful angiographic assessment of the venous drainage of the brain and the DAVF, sections of dural sinus (classically the transverse sinus) are selected for occlusion. Access to the sinus is via the DAVF's primary drainage route or draining veins or secondary sinuses, e.g. inferior petrosal sinus or superior ophthalmic vein to the cavernous sinus. Coils are placed in the section to be occluded. The technique is to use controlled detachable coils first in order to define the boundaries of the segment to be occluded and then more thrombogenic fibre coils are deployed or liquid embolic agents injected inside the defining boundary coils. This increases the thrombogenicity of the embolus. Temporary inflation of an arterial balloon to prevent reflux of liquid embolics (e.g. in ICA during cavernous sinus embolisation) may be needed. A technique for temporarily obstructing part of a sinus with a balloon and then injecting Onyx so that it refluxes into dural vessels has been described, but transarterial injection of Onyx is generally easier.

Complications: The risks of the transvenous approach are venous infarction of a territory being drained by a normal vein and changing the venous drainage of the DAVF from a benign to a more aggressive pattern. Transient worsening of symptoms occurs in about 10% of patients [46]. The technique is therefore best reserved for embolisation of veins or sinuses, which no longer contribute to drainage of normal parenchyma. The additional use of transarterial particles or liquid embolic to slow venous flow is an option.

Post-operative Care: It is usually sufficient for patients to recuperate with bed rest for 24 h with prescribed oral analgesics. A careful post-procedure-documented neurological assessment should be performed. A short course (48–72 h) of corticosteroids may be useful to reduce tissue swelling, particularly when treating lesions causing orbital oedema. After, treatments involving substantial venous occlusion, anticoagulation should be continued in the post-procedure period. This is best performed using low molecular weight heparin and subcutaneous administration of 5000 IUs daily for up to 2 weeks prescribed to prevent excessive venous thrombosis.

Follow-up Imaging: DSA or MRA should be performed at 3–6 months. A preliminary MR scan is helpful in deciding whether any residual or recurrent symptoms are related to the DAVF and if this may require retreatment. Retreatment, should it be required, can then be planned without the need for an additional DSA examination.

10.4 Treatment Results

There has been no randomised trial comparing different types of treatments, and most reports have consisted of single centre case series. Trials will require substantial multicentre collaboration to collect comparative data for the range of DAVFs encountered. In 1997, Lucas et al. [11] reviewed reports of 258 cases, and found that cure rates for embolisation performed as the sole intervention vary from 40% to 80% and that combined treatment improved success

rates. Since the introduction of Onyx, cure rates for embolisation have improved considerably (see below) and it has become the primary treatment method. Surgery is therefore now reserved for more complex lesions and it is no longer sensible to compare the reported outcomes from single centre studies because of possible selection bias. In a recent review of reports on 2329 patients, Kobayshi et al. [25] found a morbidity rate after all treatments of 2.5%, comprising; 1.2% deaths, 0.5% nonfatal haemorrhage and 0.7% nonfatal infarction. In this cohort, 40% of patients underwent embolisation alone. If embolisation alone was performed, the overall morbidity rate was 2.2% (95%CI, 0.7–4.4). This is in contrast to 13% morbidity reported in a surgical series of high-risk lesions [38]. Surgery is now generally reserved for lesions in the anterior fossa, tentorium and craniocervical junction [47].

There have been several reports of the value of radiotherapy. O'Leary et al. reported cure in 59% of lesions treated with radiotherapy alone in a small series with minimal complications [48], and Friedman et al. [42], in combination with transarterial embolisation. However, it is difficult to compare the efficacy of radiotherapy with endovascular treatments because of the differences in case mix. A recent review of its role argued that it should be part of a multidisciplinary approach to management of DAVFs [49].

10.4.1 Endovascular Treatment Results

Anatomical cure rates are shown in Table 10.7 together with rates for treatment-related morbidity. Reports of cure rates have been consistently better since the introduction of Onyx. Anatomical cure, in one of the largest series in the pre-Onyx era, was only achieved in 30% of lesions but improvement or stabilisation of symptoms was achieved in 84% of patients [50]. A recent single centre study, comparing results of transarterial embolisation before and after the introduction of Onyx, reported cure rates of 33% and 83%, respectively [51]. The remaining questions therefore are whether use of the newer embolic agents is associated with more frequent complications and if it will be as durable in the long term. On the first point, the literature is reassuring and the rate of complications appears to be similar to those of older studies, and more recent reports don't consider complications worse using Onyx. Data on recurrence are sparse but Onyx embolisation is not immune to recurrence. The follow-up report of Rangel-Castilla et al. [52] found that 5 of 58 successfully treated DAVFs recurred during follow-up, though not all were treated with Onyx alone. It is unlikely that recurrence rates after use of ethylene vinyl alcohol co-polymers will be substantially different from treatments with NBCA, but we will have to await long-term follow-up studies to be sure.

A final point is that cavernous sinus region DAVFs and their treatments involve particular consideration. Complications related to their embolisation include transient symptomatic worsening of orbital tissue swelling, vision, cranial nerve palsies and cerebral infarction due to emboli. As discussed above, transvenous embolisation is still the initial treatment approach. In a report of 76 patients treated for cavernous sinus region DAVFs, the most appropriate approach was determined locally as transvenous in 52.6%, transarterial in 36.8% and combined venous and arterial in 10.6% of lesions [46]. Initial shunt closure was achieved in 62.5% after transvenous and 32.1% after transarterial embolisation. Five complications occurred immediately after embolisation (1 embolic cerebral infarction, 1 venous perforation and 3 puncture site haemorrhages) and additionally, 12.5% of patients experienced delayed and transient worsening of symptoms. These involved IIIrd and VIth cranial nerve palsies and were successfully managed conservatively with analgesics and corticosteroids. They are a reminder of the importance of DAVF location in determining patient's symptoms and treatment recommendations.

Table 10.7 Results of embolisation prior to and after the introduction of the liquid embolisation agent – Onyx

Report	*n* =	Location	Cure (%)	Morbidity
Pre-Onyx				
Roy and Raymond [12]	24	Mixed	87	4% permanent
				33% transient
Kim et al. [50]	115	Mixed	30	1% permanent
				7% transient
Jung et al. [46]	76	Cavernous	70	2% permanent
				16% transient
Post-Onyx				
Hu et al.[a] [53]	63	Mixed	79	2% permanent
				4% transient
Rangel-Castilla et al. [51]	63	Mixed	92	9.2% unspecified
De Keukeleire et al. [54]	21	Mixed	85.7	15% permanent
				5% transient
Cognard et al.[a] [55]	25	Non-Cavernous	92.5	8% transient
Macdonald et al.[a] [56]	52	Mixed	Pre-Onyx: 27 Post-Onyx: 65	6% transient

n number of lesions treated, cure is complete occlusion of the DAVF
[a]exclusively transarterial treatments

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Endovascular Management of Carotid Cavernous Fistulas

11

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Preamble

In the past, students would confuse this condition with dural arteriovenous fistulas of the cavernous sinus. Happily that no longer happens because it has become obvious to nearly all that the carotid cavernous fistula is the result of the circumstance of the cavernous sinus, i.e. that a large artery runs within a venous sinus. If the artery ruptures, an arteriovenous fistula is caused. It is that simple. Why the past confusion? I assume it arose because of the similarities in symptoms and abnormal clinical findings of parients with these two types of arteriovenous shunts.

Before continuing, it is worth considering the purpose of the arrangement where an artery passes through a defined space substantially filled with venous blood. You might conclude that it is 'asking for trouble'. The answer probably lies in comparative anatomy. The English expert in this field was the late George Du Boulay who told me that the mammalian cavernous sinus was probably a heat exchange mechanism to protect the brain, hence the panting dog cooling the upper airways and the adjacent cavernous sinuses, but then he mused on the rete mirabile of ungulates. These are found in animals that spend much of their lives grazing with their head near the ground and below the level of the heart. He thought rete help to maintain an even cerebral blood pressure. When he started to consider the situation in the giraffe, I am afraid I lost him. So, I don't know, but please leave this tutorial recognising that the carotid cavernous fistula (CCF) is caused by a breakdown in the wall of the internal carotid artery, which normally separates its blood flow from the sinus.

J.V. Byrne, *Tutorials in Endovascular Neurosurgery and Interventional Neuroradiology*,
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11.1 Definition

A carotid cavernous fistula (CCF) consists of an abnormal connection between the cavernous segment of the internal carotid artery (ICA) and the cavernous sinus. The resulting high-flow shunt raises pressure to arterial levels, increases blood flow and dilates the sinus and its drainage pathways. Secondary venous stenosis may occur due to endothelial (mural) hyperplasia and further increase local venous pressure. Increased blood flow and venous hypertension occurs in veins of the orbit, skull base and rarely cortical veins. The cavernous sinus is the most frequent location of direct intracranial arteriovenous fistulas and they are usually caused by trauma. The fistula is primarily a direct communication between the ICA and sinus but after trauma, abnormal dural arteries of the ICA vessels may be torn in the injury or recruited as part of healing [1]. Spontaneous fistulas (i.e. no history of trauma) are caused by rupture of an aneurysm or other arterial diseases that weakens the wall of the cavernous ICA. The connection is usually a single hole or a small number of individual holes. The point of rupture in the arterial wall is often large (1–10 mm) and spontaneous cure is therefore rare.

The classification of spontaneous arteriovenous fistulas involving the cavernous sinus proposed by Barrow et al. [2], in my opinion, inappropriately includes CCF. It thus confuses them with DAVFs of the cavernous sinus region. The CCF discussed in this tutorial is a direct fistula and not a DAVF since involvement of any dural arteries is rare and due to collateral injury [1].

11.1.1 Aetiology

CCFs are traumatic (80%) or spontaneous (20%). The incidence of CCFs is difficult to quantify from the literature. An often-quoted estimate that they comprised 1/20,000 hospital admissions was made in 1956 [3], and is now irrelevant since the introduction of car seat belts and air bags has led to a dramatic fall in traumatic CCFs in European hospitals.

(a) Trauma

Accidental blunt trauma due to motor vehicle accidents (MVA) with direct deceleration injury to the face and cranium is the commonest history followed by falling from ladders, buildings, horses, etc. Arterial injury may occur due to penetrating injury, gunshot and other missile wounds.

Iatrogenic trauma: Iatrogenic injuries to the ICA can occur during trans-sphenoidal hypophysectomy, paranasal and other types of intracranial surgery. Endovascular treatment involving angioplasty or Fogarty catheters for endarterectomy has in the distant past been blamed for causing arterial injury and fistulas [4].

The passage of the ICA through the skull base creates bends with fixed sections below the cavernous sinus where it runs through its canal in the petrous temporal bone and foramen lacerum, and above at the dural ring where it is tightly adherent to dural. Though held within the arachnoid reflections and dura of the cavernous sinus, this ICA section is less supported and particularly prone to injury following craniofacial deceleration trauma. It is also vulnerable to trauma causing fractures (e.g. facial bones, skull base) or penetration wounds. The mechanism of arterial wall injury is thus either direct traumatic penetration, tearing of the wall or avulsion of branch arteries [5].

If the injured patient is comatose, the diagnosis of CCF may be delayed because objective signs take time to become evident or because they are initially attributed to direct traumatic soft tissue damage. Furthermore, the onset of the fistula may not necessarily occur at the time of trauma, since a traumatic pseudoaneurysm of the ICA may be caused, which later ruptures to cause a delayed fistula.

(b) Spontaneous

The CCF is caused by breakdown in the wall of a diseased ICA. The arterial diseases that may be responsible are:

- Intracavernous aneurysm. The incidence of intracranial aneurysms in the cavernous ICA was only 1.5% in a single centre study and CCF was found in a quarter of symptomatic patients [6], and in a recent review of 316 cases of cavernous ICA aneurysms, 55 patients presented after subarachnoid haemorrhage (SAH) and 6.6% with CCFs [7]. This is probably an underestimate since it is usually difficult to demonstrate the remnants of an aneurysm without prior imaging. The presumed cause is atherosclerosis.
- Ehlers–Danlos syndrome. CCF is the most common intracranial complication of this autosomal

dominant abnormality of collagen metabolism. It is associated with defects in arterial media and bleeding due to increased vessel fragility. As discussed in Tutorial 8, affected people may develop intracranial aneurysms, and CCFs may be due to rupture of an intracavernous aneurysm, but when it occurs, a section of arterial wall is affected in a series of fistulas, consistent with a diseased (and weak) arterial wall [8, 9] (see Fig. 11.4).

- Pseudoxanthoma elasticum. Autosomal recessive and dominant forms cause disruption of elastic fibres in the skin, arteries and eyes. It is a rare cause of G1 bleeding and CCFs [10].
- Fibromuscular dysplasia. An association between fibromuscular dysplasia and CCF was first reported by Zimmerman et al [11] in 1977. They attributed it to rupture of microaneurysms. It is rare because there have only been a few case reports since.

11.1.2 Anatomy of the Cavernous Sinus

The cavernous sinus lies lateral to the pituitary gland and the body of the sphenoid bone. It extends from the superior orbital fissure to the apex of the petrous temporal bone. It is portioned by numerous fibrous strands and traversed by the cavernous portion of the ICA. The lateral wall is thicker than the medial wall (which separates it from the pituitary gland) and is formed by a double layer of dura. The oculomotor (IIIrd), trochlear (IVth) and the ophthalmic division (V^1) of the trigeminal (Vth) cranial nerve run within the layers of the lateral wall. The abducens (VIth) cranial nerve runs within the sinus. Sympathetic fibres on the surface of the ICA in the sinus run with the VIth nerve in the sinus before joining V^1 and passing forward into the orbit to supply ciliary muscles [12].

Anteriorly the sinus receives the superior and inferior ophthalmic veins, cerebral (uncal) veins and the sphenoparietal sinus. It communicates with the opposite cavernous sinus via a series of intercavernous sinuses, anterior and posterior to the pituitary gland. The normal outflow is to the superior and inferior petrosal sinuses, the pterygomaxillary venous plexus via emissary veins, the contralateral cavernous sinus and, depending on head position, to the superior and inferior ophthalmic veins. The VIth cranial nerve lies closest to the ICA within the inferior portion of the sinus [13] (Fig. 11.1a, b).

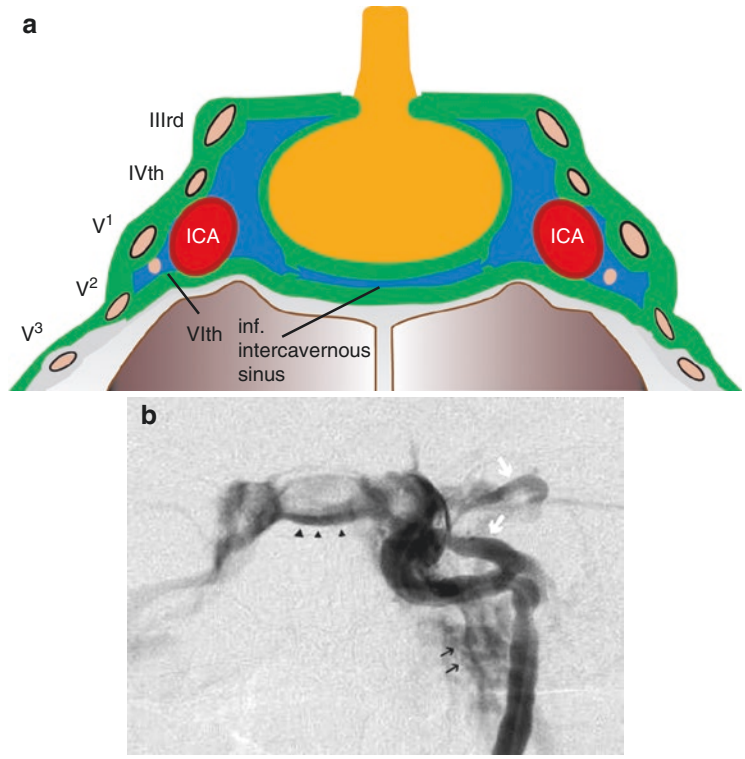

Fig. 11.1 Coronal illustration of the cavernous sinus in the coronal plane showing the cranial nerves and the intercavernous sinus (**a**). (Published with kind permission of © Henry Byrne, 2012. All rights reserved.) (**b**) The same view of a patient with a cavernous carotid fistula of the left side after internal carotid injection. On the left side, contrast is seen in orbital veins (*white arrows*) and the pterygoid plexus (*short arrows*). The intercavernous sinus (*arrowheads*) drains to the right cavernous sinus and then to the right inferior petrosal sinus

11.2 Diagnosis

11.2.1 Clinical Symptoms and Signs

The commonest presentation of a CCF is visual dysfunction and orbital congestion because the fistula is draining to orbital veins. The typical signs on examination are chemosis, exophthalmos, ocular pulsation and orbital bruit. Patients complain of bruit, diplopia, ocular pain or hypalgesia in the V^1 territory. CCF may be difficult to distinguish from direct injury after trauma on ophthalmic and neurologic examinations.

Unilateral fistulas may cause bilateral orbital congestion (about 20% of cases). Localisation to the side of the fistula is usually obvious by asymmetry of proptosis or bruit (unless the SOV is thrombosed). Only 1% of traumatic fistulas are bilateral.

Occasionally, if the superior ophthalmic vein (SOV) is thrombosed or absent, orbital signs may be minimal or evident only in the contralateral eye (because venous flow is directed through intercavernous connections). Less often, sinus drainage occurs posteriorly (via the inferior petrosal sinus), laterally (via the superior petrosal sinus), inferiorly (via emissary veins of the foramen rotundum and foramen ovale to the pterygoid plexus) or superiorly (via the sphenoparietal sinus).

It is unusual for leptomeningeal and cortical veins to be involved by cortical venous reflux (CVR) but since the cavernous sinus connects to the sphenoparietal sinus, uncal veins and the petrosal sinuses, this may occur and venous pressure raised in either the superficial or deep cerebral venous systems.

The relative frequencies of common symptoms at presentation are [14]:

Subjective bruit	80%
Visual blurring	59%
Diplopia	53%
Headache	53%
Pain (ocular or orbital)	35%

(a) Bruit

The most consistent complaint in the conscious patient is bruit, which may be heard on auscultation. The site at which it is loudest gives a clue to the direction of blood flow from the cavernous sinus. Thus if the bruit is loudest over the orbit, flow is anterior and if loudest over the mastoid bone, flow is predominantly posterior. Other causes of bruit on auscultation over the orbit are dural arteriovenous fistula (DAVF), absence or hypoplasia of the sphenoid wing and transmitted sound from turbulent blood flow in carotid stenosis.

(b) Visual disturbance and diplopia

Visual loss caused by damage to the optic nerve at the time of trauma should be distinguished from secondary visual disturbance due to CCF. Permanent post-traumatic monocular

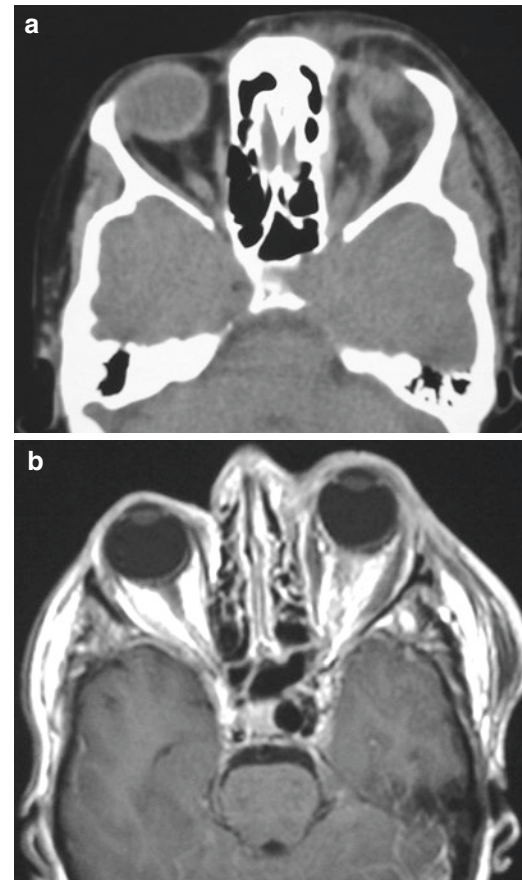

Fig. 11.2 Axial CT (**a**) and MRI (**b**) of a patient with left side proptosis due to enlarged orbital veins and soft tissue swelling. The T2W MRI shows an aneurysm in the left cavernous sinus. The fistula is the result of its rupture

blindness is caused by irreparable damage to the IInd cranial nerve. Otherwise, visual acuity is rarely severely affected by CCF alone. The signs are an afferent papillary defect, mild constriction of the visual fields and rarely central scotoma. The mechanism is probably a combination of compression by the enlarged SOV, and ischaemia due to the reduced arteriovenous gradient. Venous hypertension within the orbital veins causes functional changes that lead to symptoms. Most serious is secondary glaucoma caused by reduced drainage of aqueous humour and a rise in intraocular pressure (IOP) [14].

Orbital venous congestion causes:

- Raised IOP: It is due to elevated pressure in episcleral veins, causing back pressure on drainage through the canals of Schlemm.[1] Venous congestion of iris, ciliary muscle and ciliary body reduces the angle of the anterior chamber so narrowing the inlet to the trabecular network. About 20% of patients develop glaucoma-like visual loss and 2% severe visual failure if the IOP rises to levels that obstruct blood flow in the central artery of the retina [15].
- Venous retinopathy: On fundoscopy, the veins are dilated and only rarely are disc blurring and haemorrhages evident.
- Proptosis: The globe is usually displaced down and laterally by a dilated superior orbital vein (SOV). Palpable pulsation of the globe occurs in 30% and is more evident on ophthalmodynamometry.
- Chemosis: Oedema of the eyelids and dilated conjunctival vessel occurs secondary to orbital venous hypertension and engorgement.
- Ophthalmoplegia: This symptom is common and usually difficult to ascribe to a specific cranial nerve (see below). It may be due to swelling and 'stiffness' of the extraocular muscles secondary to the venous engorgement. Ophthalmoplegia caused by orbital congestion may be distinguished from cranial palsy by the forced duction test, but this is rarely indicated and contraindicated if the conjunctiva is swollen.

(c) Cranial nerve palsies

Damage to the orbital cranial nerves at the time of trauma can be distinguished from secondary palsies by the history and findings on initial examination. Early complete cranial nerve palsy has a poor prognosis and is usually caused by direct trauma. Palsies of the cranial nerves in the cavernous sinus are common secondary effects of CCF. The findings on examination are isolated IIIth or VIth or combined IIIth + IVth + VIth cranial nerve palsies. An isolated IVth palsy is said never to occur [14] and palsies of V^1 and V^2 are seen, but less often. Muscle weakness due to palsy of the trigeminal motor division is never caused by CCF alone [14]. The mechanism of palsies affecting the cavernous cranial nerves is thought to be due to interference with their blood supply in the sinus either by a steal effect or compression of their vasa nervorum by the enlarged sinus.

(d) Epistaxis

This is usually associated with traumatic CCF and is attributed to acute vessel injury which may or may not progress to cause a CCF [16]. The exact mechanism is often difficult to demonstrate though delayed epistaxis can be due to rupture of a traumatic pseudoaneurysm into the sphenoid or ethmoid air sinuses.

(e) Cerebral dysfunction

Cerebral ischaemia or infarction occurs if the CCF reduces perfusion to the hemisphere. Cerebral hypoperfusion may be seen on carotid angiography (DSA) when all the injected contrast flows to the cavernous sinus and none reaches the arteries of the circle of Willis. The ipsilateral hemisphere then depends on collateral blood flow via anterior and posterior communicating arteries. Symptoms of cerebral ischaemia or infarction occur if the collateral support is inadequate. Alternatively, venous reflux to cortical veins, i.e. cortical venous reflux (CVR), affects cerebral function and cause symptoms due to cerebral ischaemia. In

[1] Friedrich Schlemm (1795–1858) was a German anatomist and professor at the University of Berlin.

this situation, CVR is evident on DSA and hyperintense signal changes may be seen on MRI. Reflux to posterior fossa veins causes brain stem symptoms [17] but symptomatic CVR is less frequent than in DAVFs of the cavernous sinus [18].

(f) Spontaneous intracranial haemorrhage

Intracerebral haemorrhage is rare and caused by raised venous pressure within subarachnoid or cortical veins [19]. Retrograde drainage to dural veins and the sphenoparietal sinus are relatively common, but spontaneous intracerebral haemorrhage has only been described in case reports. These have involved different sites, including the brain stem [19].

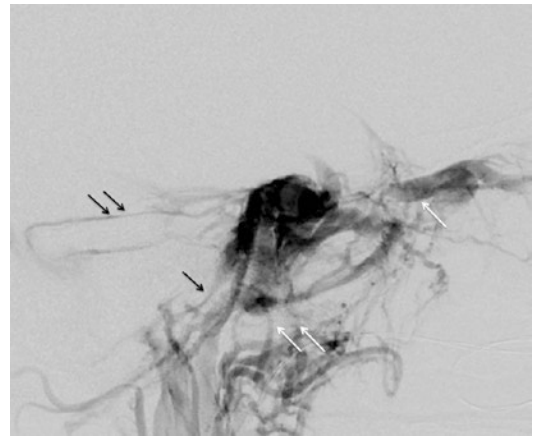

Fig. 11.3 Lateral internal carotid DSA showing a cavernous carotid fistula draining to an enlarged superior ophthalmic vein (*single white arrow*) to pterygoid veins via the inferior ophthalmic vein (*double white arrows*), to the inferior petrosal sinus (*single black arrow*) and to the superior petrosal sinus (*double black arrows*)

11.2.2 Imaging Diagnosis

Orbital ultrasound: This may show a dilated superior orbital vein (SOV) and disc swelling suggesting the diagnosis.

CT and CTA: Cranial CT is useful for demonstrating the extent of injury after trauma. It will demonstrate fractures around the orbit, paranasal sinuses, skull base and intra- or extra-axial haematomas or small cerebral contusions. A dilated SOV is usually well demonstrated after contrast enhancement, and the ipsilateral cavernous sinus may be enlarged (Fig. 11.2). CTA is useful in diagnosis and fistula localisation. One report found it comparable with DSA for diagnosis and superior to MRA in fistula localisation [20].

MRI: It is generally not better than CT for diagnosis and is inferior for pre-operative fistula localisation. However, it will show cerebral signal changes due to CVR and is the best modality for follow-up imaging after treatment. MRA with high-frequency imaging techniques are being developed and may improve localisation of fistulas [21].

DSA: It is required to evaluate the fistula prior to endovascular treatment. Its benefit is the additional temporal resolution needed for pre-operative fistula localisation, which will be discussed below (Fig. 11.3).

11.3 Treatment

The first recorded successful treatment was by an English surgeon B. Travers in 1811, who ligated the CCA [22]. The technique proved to be unreliable and additional embolisation by introducing a muscle embolus into the ICA was performed by Brooks and a combination of surgical ligations and muscle embolisation by Hamby and Gardner in 1931 [23]. Because it was recognised that trapping the ICA was inadequate to close the fistula, two neurosurgeons developed techniques to embolise the sinus at craniotomy. Hosobuchi [24] inserted wires into the sinus and performed electrothrombosis and Mullan [25] embolised the sinus with copper wires or gelfoam. With the introduction of detachable endovascular balloons for artery and aneurysm occlusions in 1974 by Serbinenko [26], the potential of balloons for embolisation of CCF was recognised and developed by Debrun et al. [27], setting the stage for current endovascular managements.

11.3.1 Aims of Treatment

The aim of treatment is to occlude the connection(s) between ICA and cavernous sinus, and this condition was one of the first in which the value of endovascular treatment was demonstrated. To achieve this objective, the high antegrade blood flow into the fistula is exploited to deliver emboli transarterially. An inflatable detachable balloon, mounted on a flexible catheter, can be 'floated' through the fistula, like a fly into the mouth of a feeding trout at the top of a river pool. Once through and in the cavernous sinus, it is inflated to close the arterial breach from the venous side and then detached. This is one of the most rewarding treatments in the whole of our repertoire because the angiographic result is immediate; the patient reports relief of the bruit and signs of orbital congestion reduce within hours. The endovascular technique described by Debrun in 1981 [27] has since been adapted to cope with the technical problems associated with the use of detachable balloons.

11.3.2 Risks and Benefits of Balloon Embolisation

Cure rates of 85–95% have been reported with immediate resolution of bruit, normalisation of intraocular pressure within 48 h and resolution of orbital congestion in 7–10 days [28, 29]. On the other hand, two major risks are associated with balloon embolisation. These are cerebral ischaemic symptoms or infarction caused by obstruction to the ICA and exacerbation of venous hypertension. First, closure of the fistula may cause (by design or inadvertently) ICA occlusion. In most cases, the patient may tolerate this because the fistula has already reduced the effective blood supply to the brain from the ICA, but functional testing prior to embolisation should be considered. There is also a risk to the cerebral blood supply if distal migration of the balloon occurs. The second major concern is exacerbation of orbital congestion because in complete closure the fistula redirects drainage to the orbit or secondary thrombosis in large orbital veins leads to extensive orbital thrombophlebitis. The patient should be warned that swelling may temporarily worsen after 'successful' treatment.

Other risks involve damage to artery or veins during catheterisation, ophthalmoplegia due to cranial nerve damage and delayed recurrence of the fistula. The last occurs mostly in the first few days after treatment due to incomplete closure or premature balloon deflation. Delayed cranial pain is associated with enlargement of silicone balloons as a result of osmotic pressure differences between the fluid (i.e. contrast media) used to inflate them and body fluids. This complication has been managed by percutaneous transforamen ovale [30] or trans-sphenoidal puncture and deflation of the balloon [31].

11.3.3 Pre-procedure Assessment

DSA: A six-vessel angiogram is recommended for a complete understanding of the fistula morphology. This should be with high-frame-rate angiography, because the hole is obscured by rapid contrast filling of the cavernous sinus. Injection into the contralateral ICA or a vertebral artery with compression of the ipsilateral ICA is performed to identify the fistula site by reducing the rate of contrast filling of the sinus and demonstrate retrograde filling of the fistula. It is important to demonstrate the integrity of the circle of Willis and exclude other lesions (e.g. pseudoaneurysm or CCF of the contralateral sinus). External carotid artery injections are needed to exclude a coexisting DAVF and development of collaterals. When trauma has ruptured a branch of the inferolateral trunk, the fistula may be fed by meningeal branches of the ECA. 3-D reconstruction of the angiograms is very useful in identifying the fistula point(s) and is now performed as a routine method of showing the anatomy [32]. The need for a test occlusion of the carotid artery prior to endovascular treatment is controversial since the goal is to occlude the CCF and preserve the ICA, and temporary inflation of a balloon proximal to the fistula will not reliably simulate the effect of carotid occlusion at the level of the

fistula. I think showing the integrity of the circle of Willis is all that can be done to assess the risks of carotid sacrifice, should it be needed.

11.3.4 Endovascular Treatments

Endovascular treatment has replaced surgical trapping and is required for virtually all CCFs since visual loss has been reported in 26% of untreated patients due to glaucoma, retinopathy, optic neuropathy or corneal ulceration [33]. Though, it is often preferable to wait 1 or 2 weeks following trauma or the onset of a spontaneous fistula, because delaying treatment allows the fistula (morphology and flow) to stabilise and collateral cerebral blood flow to develop. However, some fistulas have clinical and angiographic features that require treatment in the acute phase. Venous hypertension, within the draining leptomeningeal and cortical veins, is a risk factor for cerebral haemorrhage and is a common reason for early intervention. Progressive loss of vision or suspected 'steal' of cerebral flow by the fistula are other instances where emergency treatment should be considered, and once IOP is consistently elevated, definitive treatment should be performed within 1 week.

11.3.4.1 Medical Management

Medical treatment should be given to protect the cornea (if proptosis is severe) and simple measures such as sleeping with the head elevated suggested. Treatments to reduce IOP include topical adrenaline or pilocarpine (with care) especially in patients with a family history of glaucoma and, if ineffective, with carbonic anhydrase inhibitors (acetazolamide or methazolamide).

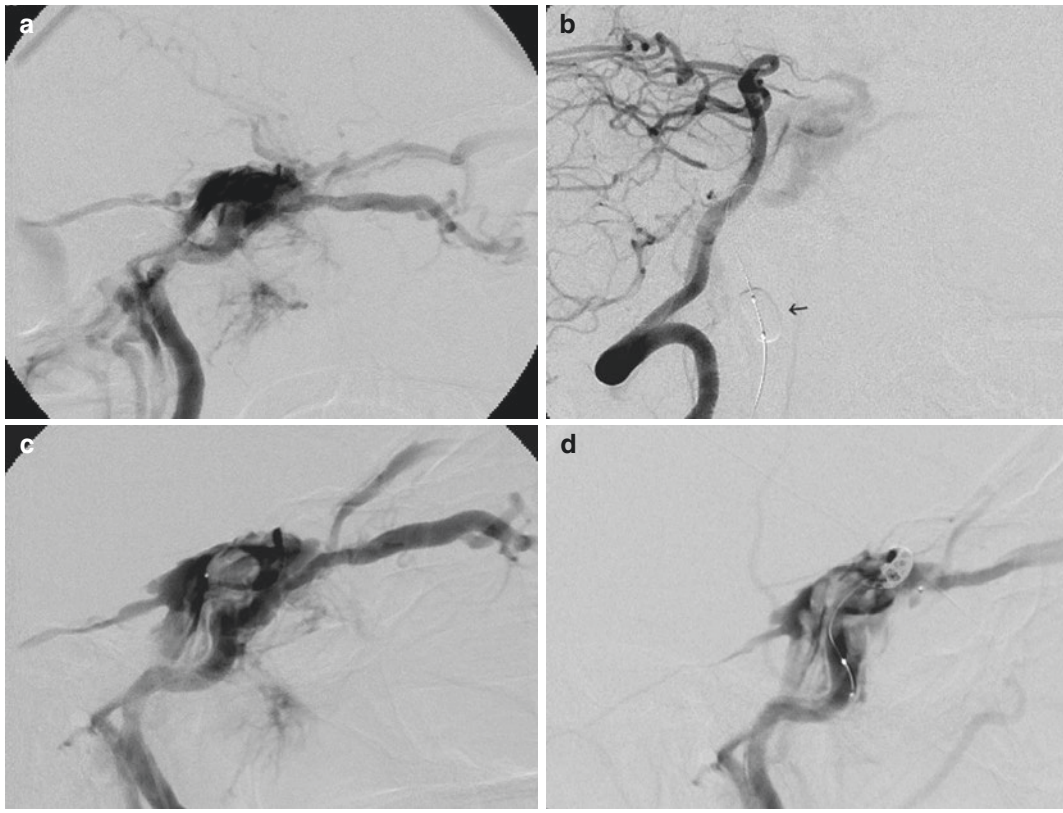

Fig. 11.4 Spontaneous caroticocavernous fistula in a patient with Ehlers–Danlos syndrome. Lateral views of internal carotid (**a**, **c**, **d**) and vertebral artery (**b**) DSA. In (**a**), the internal carotid artery distal to the fistula fills faintly. In (**b**), the internal carotid artery has been temporarily occluded with a balloon (*arrow*) and flow in the distal internal carotid artery is reversed so the posterior communicating artery fills the fistula. An attempt to close the fistula with a balloon (**c**) failed because there were several separate fistula points and so the cavernous internal carotid artery was occluded with coils (**d**)

11.3.4.2 Transarterial Embolisation

The endovascular treatment techniques are divided into transarterial and transvenous approaches (Fig. 11.4). The transarterial route is generally preferred because the venous route is usually more difficult and is associated with higher failure rates. For these reasons, it should be considered second choice [34].

(a) Balloons

This technique has until recently seen little modification since its introduction in the 1970s [27, 28]. Detachable balloons are made of either latex or silicone and are mounted on 2–3 F single catheter or 2 F/4 F coaxial systems. They are introduced via a 6–9 F guiding catheter, depending on the size of the balloon. Partial inflation of the balloon allows it to be flow-guided through the fistula.

However, there were several potential difficulties when using detachable balloons. These are unreliable detachment control, flow-dependent navigation with only limited control in positioning and unpredictable volume variations. The current shortcomings of balloons reflect a lack of research and development over the last 20 years. Thus, they still use a simple one-way valve through which the delivery microcatheter is inserted and a connection that relies on friction between valve and the tip of the delivery catheter. The risk of premature detachment when the balloon is retrieved against the traction force generated by blood flow to the CCF has made many practitioners wary of using them. Other problems are caused by the failure of the fully inflated balloon to control the fistula so that additional balloons may be needed and a risk of causing stenosis in the ICA by compression from a balloon in the cavernous sinus. Delayed changes in the volumes of balloons which are inflated with contrast media cause either reopening of the CCF, if it leaks and deflates, or pain if the balloon swells because the semipermeable wall of silicone balloons allows water to diffuse across an osmotic gradient between the contrast mixture and plasma.

Often a single balloon is adequate to achieve complete occlusion of the fistula. However, where there is a large venous compartment within the cavernous sinus, typically seen in chronic CCFs, more balloons will be needed. The more balloons needed, the less compliant the venous side becomes, and consequently, the greater the risk that the last balloon will protrude into and occlude the ICA. Alternatively, if a balloon will not pass through a small fistula, the operator has the option of using it to occlude the ICA at the site of the arterial hole, if functional testing has predicted that the patient will tolerate the occlusion. Acutely after trauma, it may be best to defer ICA occlusion until any cerebral swelling or subarachnoid haemorrhage has resolved. ICA occlusion is obviously best performed as an elective procedure after test occlusion of the ICA above the fistula combined with clinical testing, but this is seldom practical, and an angiographic assessment of an adequate collateral blood supply to the ipsilateral hemisphere has to be accepted prior to ICA sacrifice to close the fistula. An alternative technique is to use a combination of nondetachable and detachable balloons. The first is inflated distal to the fistula both to protect the distal circulation from migration of a premature detached balloon and help to direct the detachable balloon through the fistula [35]. If ICA occlusion is performed, deployment of tandem balloons to insure against deflation is a standard precaution. The distal balloon is placed across the fistula or if this is not possible, then the balloons are deployed in the ICA at the level of the CCF to ensure the artery is occluded above and below the fistula entrance [35].

(b) Coils

Transarterial packing of the cavernous sinus with coils is performed after a microcatheter has been passed through the fistula [34]. This technique is indicated if the fistula is too small to permit a balloon to pass into the sinus. Packing is best performed with highly thrombogenic coils (e.g. fibre coils or hydrogel-coated coils). The technique involves packing the sinus adjacent to the fistula as densely as possible. Though technically easier than using a balloon, its main drawback is the risk of incomplete closure of the sinus and redirection of the outflow drainage, recurrence of the fistula and cranial nerve palsy (particularly of the intra-sinus VIth nerve).

(c) Stent with or without coils

The use of a stent to ‘reinforce’ coils placed within the sinus is a logical extension of their

adjuvant use in aneurysm treatments. A high-metal-density (low-porosity) 'flow-diverter' stent is often chosen. The stent is deployed in the ICA at the fistula site either alone [36] or in combination with coils introduced either transarterially or transvenously into the sinus [37, 38].

There have been several reports of the successful use of covered stents in the treatment of CCF [39] and in one single centre trial they proved better than balloons [40]. However, the use of antiplatelet drugs to prevent in-stent thrombosis limits their use acutely after trauma and the stiffness of current stents makes deployment difficult. Therefore the combination of conventional or flow-diverter stent with coils is likely to remain an endovascular treatment option

(d) Liquids agents

N-butyl cyanoacrylate (NBCA) was first used to treat recurrent CCF when a balloon had deflated or coils had been inadequate to contain the fistula. In this situation, a small quantity of NBCA may be adequate to close the remnant whilst preserving patency of the ICA [41]. More recently, reports using Onyx (ev3 Endovascular Inc., Irvine, CA, USA), and a nondetachable balloon placed in the ICA to protect its lumen during injections, have been described [42]. The use of combinations of techniques has improved the cure rates of endovascular treatments [43].

11.3.4.3 Transvenous Embolisation

About 5% of CCFs have more than one communication between the ICA and the cavernous sinus [44] which makes transarterial treatment without stents difficult. In this situation and when the transarterial route is considered impossible, the transvenous route is appropriate. Access to the cavernous sinus is via the inferior petrosal sinus, superior ophthalmic vein or even the pterygoid plexus [45]. Access to the cavernous sinus through the inferior petrosal sinus is more straightforward than via the SOV. In my experience direct puncture of the SOV should he avoided in CCF because it risks causing uncontrollable haemorrhage in the orbit.

Once in the cavernous sinus, the catheter tip should ideally be positioned adjacent to the fistula but navigating within the sinus is often difficult. It may then become necessary to pack the whole sinus with coils, and care must be taken to avoid partial closure of the sinus/fistula and redirection of blood flow to cerebral or orbital veins. Redirection of drainage to orbital veins may exacerbate or cause a rise in venous pressure within the orbit and threaten vision. Therefore, embolisation should be planned to exclude orbital or subarachnoid veins first.

Transvenous packing with coils is slow and occlusion of the IPS (or other access route) should be deferred until the operator is confident that the CCF is closed and that orbital and any cerebral veins have been disconnected. As for transarterial embolisation, it is performed with thrombogenic coils (e.g. fibre coils). Care should be taken using fibre coils or hydrogel-coated coils because swelling of the thrombosed sinus may cause cranial nerve palsy or pain. Liquids agents, and in particular Onyx, are an effective alternative to coils in this situation.

11.3.4.4 Postoperative Care

A minimum period of 48 h bed rest is recommended with analgesia, depending on the severity and frequency of headache. Pain is a common complaint due to meningeal or vessel wall stimulation. Temporary worsening of ophthalmoplegia and orbital swelling can usually be managed with medical therapy. The extent of exophthalmos and ophthalmoplegia should be carefully monitored and auscultation performed to monitor bruit (which usually disappears as soon as the fistula is closed). In a series of 32 patients, 5 patients required further treatments after initially successful embolisation [46]. If the fistula reopens, the bruit generally reappears. A simple technique after balloon placement is to perform a cranial radiograph in two projections. This can be used as a baseline against which future comparison can be made to assess for any volume changes.

11.3.4.5 Follow-up

A suggested regime is for a review at 3 months to assess vision and to ensure continued symptomatic improvement. It is doubtful whether delayed follow-up imaging studies are needed for

asymptomatic patients since a CCF that is still occluded 4–5 days after embolisation is unlikely to recur. In some centres, catheter angiograms are performed before the patient leaves hospital, but increasingly, MRI is used at this stage (i.e. a baseline study) and then repeated after 3–6 months to confirm satisfactory resolution of soft tissue swelling and reduction in size of the SOV and cavernous sinus.

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Vein of Galen and Non-Galenic Cerebral Arteriovenous Fistulas

12

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Preamble

The subjects of this tutorial are important as they introduce the student to direct arteriovenous fistulas of the brain. The term 'vein of Galen malformation' (or vein of Galen aneurysmal malformation) has replaced two older terms: aneurysm of the vein of Galen and aneurysmal dilatation of the vein of Galen. This is because the original terms have been misunderstood and frequently used incorrectly in the past. Both terms have specific anatomical definitions and until quite recently were used somewhat indiscriminately for a range of angioarchitectures involving arteriovenous shunts to an enlarged deep venous collecting system.

The history of the definitions we now use and the scholarship that underpins them exemplifies how difficult it is to identify angiographic patterns and formulate therapeutic rules in low volume conditions. We should always remember this when we make a diagnosis, suggest a prognosis and formulate a treatment plan for individual patients. Equally, advances in medicine depend on our willingness to question the assumptions of our predecessors.

This chapter will therefore cover the features that distinguish the vein of Galen malformation from arteriovenous fistulas and malformations draining to the vein of Galen, with which they were confused in the past. It is also a chance to revisit the embryology of the cerebral circulation. Finally, cerebral arteriovenous fistulas that drain

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to other cerebral veins, i.e. non-Galenic, are included because they affect predominantly paediatric patients and because they contrast the vein of Galen malformation with lesions that pose similar challenges in their endovascular treatment.

12.1 Arteriovenous Fistulas and Malformations Involving the Vein of Galen

These are intradural lesions, which mostly occur in infants and children. These are generally high-flow lesions with overlap in their mode of presentation and the neurological disturbances they cause. The incidence is difficult to gauge, but they represent no more than 15% of paediatric patients seen in large neurovascular centres. Because they are rare, it is generally agreed that neonates and infants are best managed in specialist centres, so numerically they are likely to represent a very small component of the practice of most endovascular therapists.

There are three main types:

- Vein of Galen malformation (VOGM). This lesion is defined as an arteriovenous fistula draining to the embryological precursor to the vein of Galen (VOG), i.e. the median prosencephalic vein of Markowski. The vessels involved are situated in the subarachnoid space.
- Cerebral arteriovenous fistula (CAVF). These comprise arteriovenous fistulas supplied by cerebral arteries which initially drain to pial veins lying in the subpial space. Some then drain to an enlarged VOG and some to superficial cortical veins, i.e. non-Galenic CAVF. They are characterised by a single pedicle or a small number of pedicles draining to a single fistula.
- Brain arteriovenous malformations (BAVM). This is a BAVM involving deep parenchymal structures and draining to an enlarged VOG. They may present at any age and will not be considered in any detail in this tutorial.

12.1.1 History of the Definition of the Vein of Galen Malformation

The literature testifies to considerable confusion about the difference between the VOGM and the finding of a dilated (aneurysmal) VOG secondary to an AVM or arteriovenous fistula because of their similar clinical findings. The solution and the angiographic definition of the VOGM was provided by Raybaud, Strother and Hald in 1989 [1] (see below), who were the first to recognise that the dilated midline vessel seen in the VOGM was in fact a persistent median vein of the prosencephalon or vein of Markowski. Before going on, it is worth revisiting the embryology of the cerebral vasculature.

12.1.2 Embryology

As was described in Tutorial 1, prior to the choroidal vascular stage, the neural tube is nourished by amniotic fluid. After closure, the neural tube is initially supplied by surface vessels of the meninx primitiva, but as the cerebral vesicles develop at the rostral end of the neural tube, an increasing demand for blood supply is met by choroidal vessels (choroidal stage).

The choroidal and quadrigeminal arteries are present by the 5th week and supply the developing choroid plexus. The plexus of the primary prosencephalic vesicle develops along the junction of its division into diencephalon and telencephalon secondary vesicles. The expansion of the telencephalic choroid plexus is accompanied by differentiation of a dorsal vein on the ventral surface of the diencephalon to drain the choroid plexus. This was called the ‘vena medianna prosencephali’ by Hochstetter [2]. He identified that it was transient and only evident between the 8th and 11th week (8–50-mm stage), i.e. at the time the pallium was growing. I will refer to it as the median prosencephalic vein (MPV) (see Fig. 12.1).

Because the choroid plexus develops before vessels have penetrated the neural parenchyma, the MPV is the first vein to drain an intracerebral

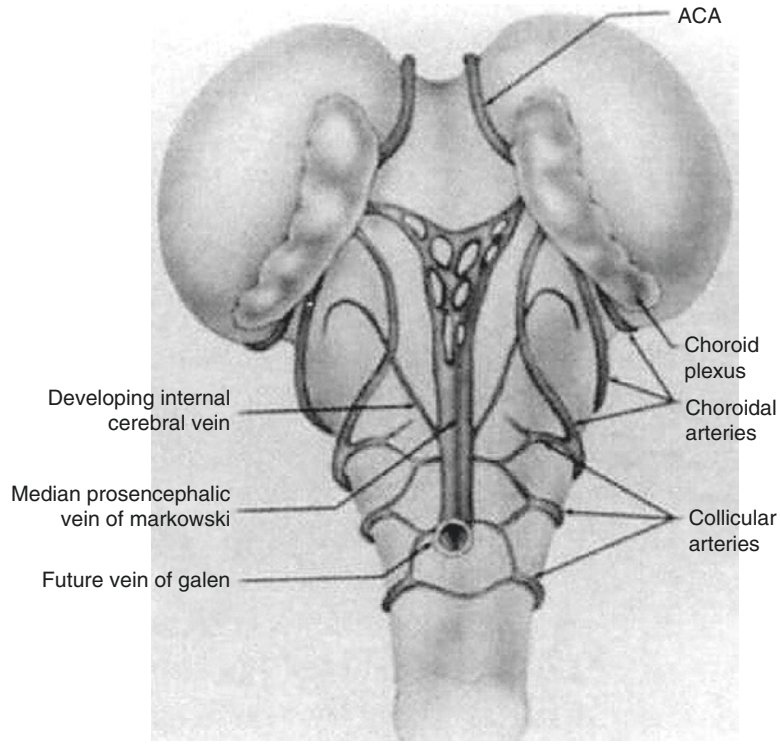

Fig. 12.1 Median prosencephalic vein of Markowski shown in an artist's impression. Its afferent arteries are the choroidal arteries and the anterior cerebral artery (ACA) (Reproduced from Raybaud et al. [1] with permission)

structure. At this stage, the choroid plexus is supplied largely by choroidal branches of the anterior cerebral artery. By the 12th week, the MPV regresses and its distal remnant joins with the paired internal cerebral veins to form the vein of Galen. It is assumed that the efferent veins of the MPV (and rostral VOG) persist with it, as one possible configuration (choroidal type) of VOGM.

The formation of the dural sinuses is complex and results from the fusion of multiple separate venous plexi. A transient falcine sinus connecting the VOG to the superior sagittal sinus has frequently been observed in the foetus and is often present with the VOGM. It is occasionally present in neonates and infants as a normal variant, but the embryology is unclear.

12.1.3 Early Descriptions of the Vein of Galen Malformation

Early descriptions of the VOGM failed to appreciate that the cause lay in a regression failure of this embryology. Enlargement of the 'VOG' was first described by Steinheil in 1895 [3] as a varix aneurysm, and the condition became known as the aneurysm of the vein of Galen.

Litvak et al. in 1960 [4] were the first to recognise the difference between the lesion associated with the MPV and other causes. They described primary and secondary aneurysms of the VOG, distinguishing midline arteriovenous fistulas from AVMs as causes for the dilated VOG. Gold et al. in 1964 [5] provided a clear description of the modes of presentation of what they called the vein of Galen malformation. They recognised three clinical types: (a) neonates presenting with congestive heart failure, (b) infants presenting with hydrocephalus and seizures and (c) older children and adults presenting with headaches and spontaneous intracranial haemorrhage. Amacher and Shilitto [6] added a fourth group: infants and young children presenting with increasing head size and mild congestive heart failure.

In 1988, Yasargil [7] described a classification of the angiographic findings in patients with

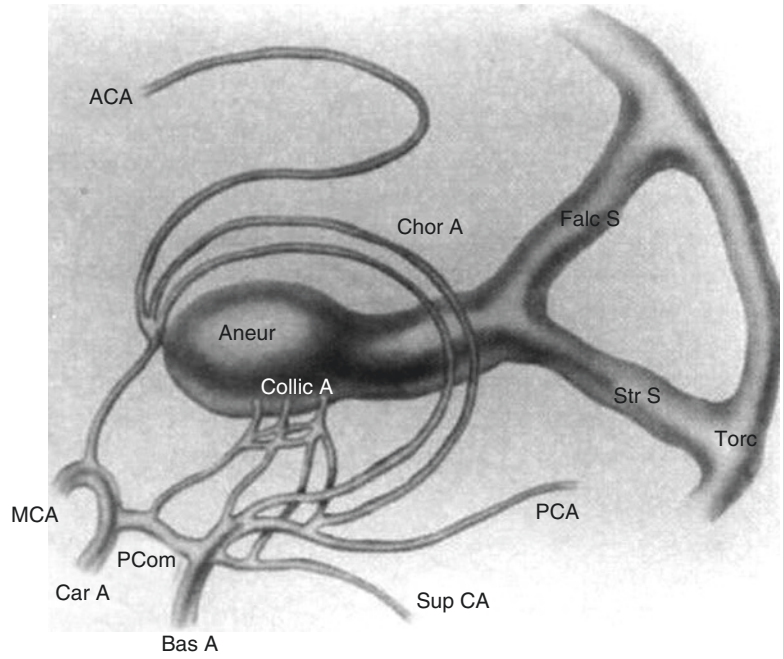

Fig. 12.2 Vein of Galen malformation drawn from two anatomical dissections. Two fistula sites are shown; an anterior fistula receiving choroidal vessels [anterior cerebral artery (*ACA*) and choroidal branches (*Chor A*) of the posterior cerebral artery (*PCA*)] and an inferior fistula receiving vessels from an arterio-arterial collection of collicular arteries (*Collic A*) [branches of superior cerebellar arteries (*Sup C A*), *PCA* and posteromedial choroidal arteries] (Reproduced from Raybaud et al. [1] with permission)

arteriovenous shunts to the VOG. This distinguished four types:

- Type I: pure fistulas with a direct connection from an enlarged artery to the VOG. Any nidus occurred only at the ampula of the VOG. The whole lesion is extra-axial.
- Type II: an AVM of transmesencephalic and transdiencephalic thalamoperforator arteries with branches to normal brain tissue. This lesion is both intra- and extra-axial.
- Type III: mixed type I and type II.
- Type IV: brain AVM with draining veins proximal to and draining into the VOG.

In 1989, Raybaud et al. [1] published their paper advancing a coherent argument that aneurysmal dilation of the VOG was due to persistence of the rostral component of the MPV based on a detailed analysis of 23 cases with only 12 complete sets of angiograms. They argued that an embryonic insult between 6 and 11 weeks caused the condition in neonates and infants. They showed that the fistula arose from subarachnoid choroidal and quadrigeminal (collicular) arteries and that normal deep venous drainage of the brain was diverted away from the dilated VOG (because no normal connection was ever established between the developing internal cerebral veins and the persistent MPV). They identified several abnormalities of the venous drainage from the MPV: principally absence of the straight sinus in 50% of their cases, stenosis and absence of the sigmoid sinus, persistence of the falcine sinus and an anomaly they described as a falcine loop. However, they proposed that the term aneurysmal VOG be retained (Fig. 12.2).

12.1.4 Current Descriptions of the Vein of Galen Malformation

The classification of aneurysmal VOGs was simplified by Berenstein and Lasjaunias [8] who proposed separating malformations draining to the persistent MPV into mural and choroidal types and that the term vein of Galen malformation (VOGM) be used only for arteriovenous shunts to the MPV.

The two VOGM types were defined as:

- Choroidal type: Comprised of multiple fistulas in the cistern of the velum interpositum[1] which communicate with the anterior MPV. They are subarachnoid in position and therefore extra-axial. They drain to the anterior aspect of the MPV and represent a persistent component of the embryonic choroidal vascular pattern. This is the usual pattern in neonates presenting with heart failure.
- Mural type: In which the fistula occurs in the wall of the MPV with a small number of feeding arteries, principally derived from the choroidal and quadrageminal arteries (collicular arteries). This type of fistula pattern is seen in children usually presenting in infancy with macrocephaly and failure to thrive.

The features common to both types are drainage to the MPV, no connection with the normal deep venous drainage of the brain and an arterial supply from the posterior choroidal arteries (Raybaud et al. found it difficult to distinguish posterior medial from posterior lateral choroidal arteries, Fig. 12.2).

12.1.5 Distinguishing Features of Choroidal and Mural Types of Vein of Galen Malformation

Relative distinguishing features are the earlier presentation in the neonatal period (i.e. within 28 days of birth) of the choroidal VOGM. It is always associated with heart failure, a falcine sinus (together with absence of the straight sinus) and usually with patent sigmoid sinuses. Babies presenting with congestive heart failure have abnormalities of CSF absorption and failure to thrive.

[1]The velum interpositum is the space between the roof of the third ventricle inferiorly and the corpus callosum superiorly. It is the anterior part of what was described by Bichat [9] as 'the great transverse cleft of the brain'. The posterior part (with which it is continuous) is the quadrageminal cistern, i.e. the subarachnoid space over the dorsal surface of the midbrain.

The mural VOGM tends to present later in infancy (i.e. 6 months to 3 years) with symptoms and signs of increasing head size, cardiac failure (of lesser severity than neonates with choroidal VOGM), failure to thrive and hydrocephalus. Falcine sinuses may or may not be present and obstructions of the sigmoid sinuses are more commonly seen, in which case drainage of the VOGM is redirected anteriorly via the basal veins, to the cavernous sinuses, orbital veins or transosseous scalp veins. The cavernous sinuses are normally rudimentary at birth and develop over the first 18 months of life. Without them, drainage from the VOGM is redirected to these alternative routes.

The VOGM arterial feeders were summarised by Brunelle [10] as 100% posterior choroidal arteries (medial and lateral), 69% anterior cerebral artery (trigonal branch of the pericallosal artery) and 30% 'transmesencephalic' (midline arteries arising directly from the basilar artery (BA). The relative contributions of common arterial feeders to the two types distinguished by Berenstein and Lasjaunias [8] are summarised in Table 12.1. Less commonly, either type receives contributions from anterior choroidal or lenticulostriate arteries and rarely from the middle cerebral artery.

All other fistulas associated with aneurysmal dilatation of the VOG do not involve a persistent MPV and therefore develop subsequent to the embryonic period and after the development of a normal pattern of deep venous drainage to (and from) the VOG. In this tutorial, they will be considered together with cerebral arteriovenous (non-Galenic) fistulas that arise elsewhere in the brain and also usually present in children and young adults.

Table 12.1 Arterial feeders to VOGM

Choroidal type	Mural type
Posterior choroidal arteries	Posterior choroidal arteries
Pericallosal artery	Collicular (quadrageminal) arteries
Thalamoperforator (subependymal branches) arteries	

12.2 Vein of Galen Malformation

It is now time to leave aside the discussion of terminology and consider the clinical problems posed by the phenotype of the individual patient.

12.2.1 Presentation

The presenting symptoms in a series of 232 patients (predominantly children) were reviewed by Johnston et al. [11] and are summarised in Table 12.2. Only 9% were adults and approximately 50% presented with congestive heart failure. There is a modest male predominance in the incidence of the VOGM (1.7:1).

Symptoms due to the high-flow arteriovenous shunts are:

(a) Congestive heart failure (CHF)

High output cardiac failure secondary to arteriovenous shunting commonly occurs soon after birth (with loss of the low resistance placental circulation). Neonates with choroidal rather than mural types of VOGM are usually affected. The severity of heart failure does not relate to the size of the shunt, arterial supply or venous drainage pattern, or the presence of outflow restrictions. It may be associated with persistent right-to-left cardiac shunting and requires emergency medical treatment. Failure of medical treatment is an indication for emergency endovascular treatment. Associated atrial septal defect or persistent ductus arteriosus is common and may need treatment to reduce strain on the right side of the heart. The prognosis is worse if CHF is present at birth or in neonates under 2 weeks of age. CHF is usually less severe when it first occurs in older children.

Table 12.2 Presenting features of the VOGM

Symptom and signs[a]	*n* =
Congestive heart failure	110 (47%)
Hydrocephalus	44 (19%)
Bruit	57 (25%)
Focal neurological deficit	37 (16%)
Seizures	26 (11%)
Haemorrhage	25 (11%)
Total	232

[a]Symptoms and signs at presentation in a review of reported cases [11]

(b) Failure-to-thrive and developmental delay

Neurological dysfunction is attributed to poor or reduced cerebral perfusion caused by a combination of CHF and hydrocephalus. Signs of neurological dysfunction are difficult to assess in infancy and they manifest cerebral dysfunction as failure to thrive or delayed achievement of developmental milestones. Venous hypertension affecting the hypothalamus and pituitary has been implicated in the process as well as hydrocephalus causing a reduction in cerebral tissue perfusion.

(c) Increasing head size and hydrocephalus

Hydrocephalus occurs with enlargement of all the CSF spaces secondary to raised intracranial venous pressure and poor CSF absorption, i.e. communicating hydrocephalus. Aqueduct compression by the enlarged vein of Galen is a secondary and less important cause (because ventricular shunting of CSF is notoriously unhelpful). A degree of venous outflow obstruction caused by atresia or absence of venous sinuses, i.e. straight sinus and sigmoid sinuses, may contribute to raise venous pressure. If the cavernous sinuses are underdeveloped and this route to the pterygoid plexus is unavailable, orbital and transosseous scalp veins enlarge. If the cavernous sinuses have developed, engorged scalp veins are less evident. Obstructions in the venous sinuses are less frequent in neonates, and enlarged head veins and cephalomegaly are signs more often seen in infants. Spontaneous thrombosis of draining veins can occur at any age and exacerbate venous hypertension and hydrocephalus.

(d) Cerebral calcification and encephalomalacia

Calcification may occur in the walls of draining veins or secondary to haemorrhages. Areas of subcortical calcification occur at the junction ('watershed') between medullary and cortical

venous drainage and are attributed to reduced cerebral perfusion. They are associated with cerebral atrophy (or failure to develop), a process best described by the neutral term encephalomalacia. These changes carry a poor prognosis and may precede the development of symptoms, i.e. they are present at diagnosis. They can be precipitated by a CSF shunt operation.

(e) Seizures

Seizures are generally attributed to the raised venous pressure, encephalomalacia with calcification and atrophic cerebral changes. Direct cortical pressure from enlarged veins is a potential cause in older children.

(f) Haemorrhage

Spontaneous intracranial haemorrhage is relatively rare in association with the VOGM. Intracerebral parenchymal haemorrhage is more frequent in older children and young adults. It is attributed to venous outflow obstruction, spontaneous thrombosis of draining veins or following surgical shunting. It may cause obstructive hydrocephalus.

12.2.2 Pathology of Vein of Galen Malformation

Pathological studies of patients with VOGM have largely involved post-mortem examinations of neonates and young children. These have reported changes of cerebral haemorrhage, periventricular leucomalacia and cortical laminar necrosis [12, 13]. The vein of Galen itself is dilated and its wall is thickened and hypertrophied, i.e. arterialised with myointimal proliferation on microscopy [12].

12.2.3 Incidence/Epidemiology/ Natural History

The VOGM and CAVF are rare lesions. Their incidence is difficult to estimate from the literature; they comprised <1% of patients in the cooperative study but 60–100% of cerebral arteriovenous malformations that cause congestive heart failure. Berenstein and Lasjaunias estimated that fistulas comprised 15% of cerebral vascular malformation, with VOGM 12% and other direct fistulas 3% [8]. The angiographic subtypes in a cohort of 41 VOGM patients treated at the University of California, San Francisco, were mixed 32%, mural 29% and choroidal 26% [14].

The natural history of untreated VOGM was studied in a review and meta-analysis by Yan et al. [15]. They calculated the risk of sudden death prior to surgery or embolisation as 6% (95%CI, 3–9%]. This occurred overwhelmingly in infants (94%) and was attributed to CHF (68%), hydrocephalus (19%), encephalomalacia (9%), cerebral ischaemia (7%), seizures (5%) and haemorrhage (3%) [15]. Thus, VOGM is a high-risk condition and emergency intervention may be life-saving but neonates are less likely to tolerate embolisation (or any intervention) than older children. As a result it is generally accepted that that intervention should be delayed as long as possible. Even so, it remains a sad reality that for some patients the likelihood of achieving a good outcome is low and so criteria have been developed to guide these difficult management decisions. The best example of this approach was developed at the Hospital Bicêtre, Paris [16] where a systematic evaluation score was developed to triage neonates for embolisation. It is presented in Table 12.3. These selection criteria, developed to guide management of paediatric patients with intracranial arteriovenous diseases, emphasises how angiographic findings are not the only things to consider pre-intervention. This holistic approach is adopted in a more recent classification proposed by Mortazavi et al. [17] which attempts to combine both clinical and angioarchitectural features important to prognosis.

Embolisation is contraindicated if the score is less than 8, emergency embolisation is performed if the score is more than 8 but less than 12 and embolisation is delayed if the score is more than12. If encephalomalacia is seen on neuroimaging, the score is considered below 8 and

Table 12.3 Neonatal evaluation score used at the Hospital Bicêtre [16]

Score	Cardiac function	Cerebral function	Hepatic function	Respiratory function	Renal function
5	Normal	Normal	–	Normal	–
4	Non-treated overload	Intraclinical isolated EEG anomalies	–	Polypnea, finishes bottle	–
3	Failure stable under treatment	Non-convulsive intermittent neurological signs	No hepatomegaly, normal function	Polypnea, does not finish bottle	Normal
2	Failure not stable under treatment	Isolated convulsive episode	Hepatomegaly, normal function	Assisted ventilation, normal saturation $FiO_2 < 25\%$	Transitory anuria
1	Ventilation necessary	Seizures, permanent neurological signs	Moderate or transient hepatic insufficiency	Assisted ventilation, normal saturation $FiO_2 < 25\%$	Unstable diuresis under treatment
0	Resistant to treatment	–	Coagulation disorder, elevated enzymes	Assisted ventilation, desaturation	Anuria

embolisation not performed. *EEG* electroencephalogram. Reproduced with permission from Lasjaunias [16].

12.2.4 Imaging Assessments

12.2.4.1 Prenatal

- Ultrasound: Intrauterine diagnosis by ultrasound is well described [18] and will show the dilated MPV as a midline sonolucent or mildly echogenic structure with associated enlarged vessels. Colour flow Doppler ultrasound should confirm the vascular nature of the mass and the high blood flow and may be able to define the arterial supply [19]. Cardiac function can also be assessed and cardiac dysfunction suggested by finding tachycardia (a heart rate greater than 200 bpm), frequent extrasystoles and tricuspid regurgitation.
- MRI (Fig. 12.3): Requires a high standard of imaging, which should better localise the VOGM to the quadrigeminal cistern and similarly show enlarged vessels [18]. It may show additional features after diagnosis of VOGM on ultrasound [20].

12.2.4.2 Postnatal

- Transfontanelle ultrasound: This is usually the first postnatal cerebral imaging performed. It is indicated for any cyanosed neonate born with signs of congestive cardiac failure and should show the dilated MPV and the size of the ventricles. It is particularly useful for rapid assessments and follow-up after endovascular treatments of VOGM.
- CT scanning: On unenhanced CT, the enlarged collecting system is isodense or mildly hyperdense relative to the brain but enhances dramatically after contrast administration. Filling defects within the enlarged vessels of the VOGM suggest they contain thrombus. Unenhanced CT is needed to demonstrate calcification since subcortical calcification and changes of encephalomalacia are contraindications to endovascular or surgery interventions. Similarly, the presence of atrophy and hydrocephalus are important considerations in management planning (see below).
- CTA (Fig. 12.4): This is a quick method of defining the angioarchitecture of the lesion if the patient (particularly neonates) can tolerate the rapid administration of radiographic contrast.

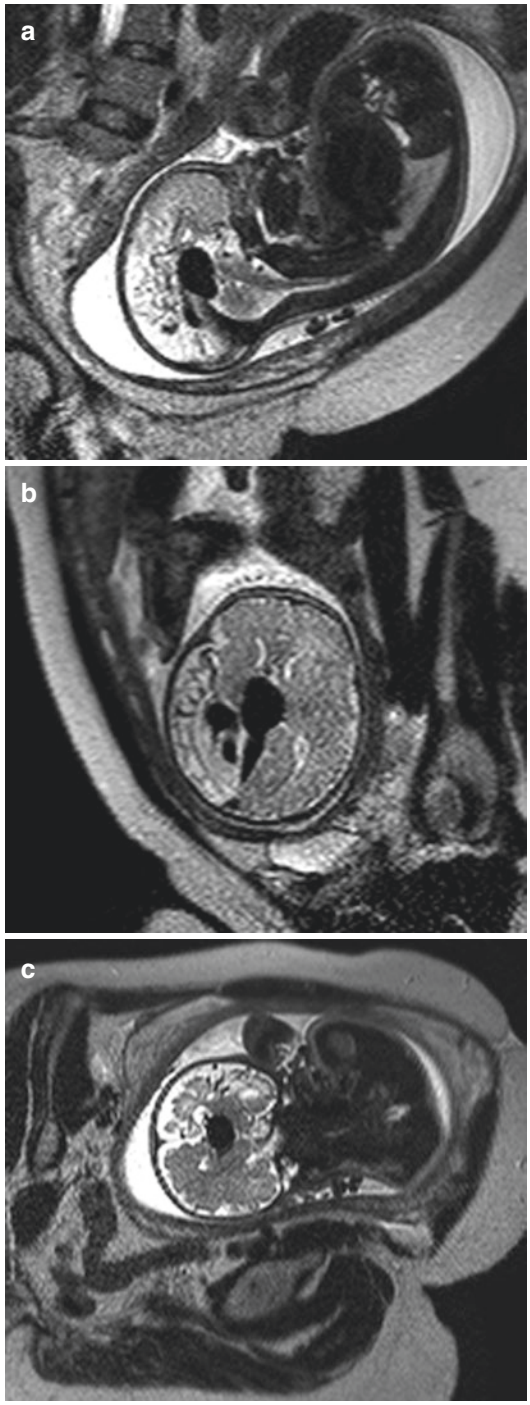

Fig. 12.3 In utero diagnosis of vein of Galen malformation. MRI performed in the third trimester showing a dilated midline vascular structure in sagittal (**a**), axial (**b**) and coronal (**c**) planes (Courtesy of Dr. G. Quaghebeur)

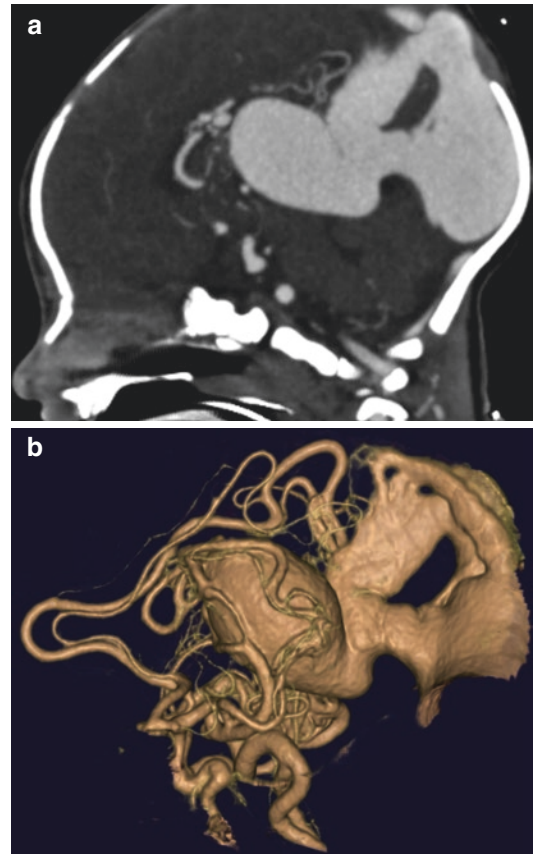

Fig. 12.4 (**a**, **b**) Sagittal reconstructions of CT angiograms showing choroidal type, vein of Galen malformation in a neonate. The falcine draining sinuses are massively enlarged because of narrowing of both sigmoid sinuses

- MRI: This is now the method of choice for demonstrating the VOGM and its effect on the brain. Less applicable for practical reasons in the neonate, it can be performed without contrast and helps to localise the fistula and demonstrate any associated nidus. If thrombosis is present in the MPV or draining veins, it should be well demonstrated on MR.
- Catheter angiography: This remains the definitive imaging technique since it will provide the best discrimination of smaller feeding arteries, any nidus and shows the speed of blood flow through fistulas. It should be reserved for an immediate pretherapy assessment, i.e. com-

bined with endovascular treatment in neonates and small children, because of the limited volumes of contrast that can be used.

12.2.5 Endovascular Treatment of Vein of Galen Malformation

In neonates presenting with congestive heart failure, medical management is the initial priority and only after its failure to control the degree of heart failure should direct treatment of the malformation be considered. Endovascular treatment has now replaced microvascular neurosurgery as the first-line intervention because recent results have shown it to be consistently better [21].

12.2.5.1 Therapeutic Aims

- Neonates: Closure of the shunt and reduction of cerebral blood flow to relieve heart failure. The goal of embolisation is to assist medical management to control heart failure. Since cure may require multiple treatment sessions (particularly for the choroidal type of VOGM), emergency treatment is confined to this objective.
- Neonates and infants: To prevent patients from developing hydrocephalus and encephalomalacia secondary to venous hypertension and possible aqueduct compression. Again this is best achieved by closure of all arteriovenous shunts, but if the clinical and imaging findings allow, it is best deferred until infancy (optimum age 6 months) [22].
- Neonates, infants and children: To reduce the size of draining veins, if they are causing compression symptoms such as hydrocephalus (aqueduct obstruction) or seizures.
- All ages: To reduce the risk of spontaneous haemorrhage or rehaemorrhage.

12.2.5.2 Endovascular Techniques

Both transarterial and transvenous access to the VOGM has been practised, though the latter has now been largely superseded [14].

- Transarterial technique
- This is performed under general anaesthesia, access is transfemoral with a 4 F catheter system for diagnostic angiography. The same catheter is used to guide a microcatheter for superselective embolisation. For older children (>5 years), a 5 F coaxial system can be used. Intraprocedural heparin is given (e.g. 50 IU/kg) and the vertebral artery is selected first. The posterior choroidal arteries are selected and embolisation performed with n-butyl-cyanoacrylate (NBCA) mixed with either lipiodol or tantalum powder. Ethylene vinyl alcohol co-polymer liquid agents, e.g. Onyx (ev3, Endovascular Inc., Irvine, CA, USA), are the alternative. It may be helpful to place coils in very high-flow pedicles to slow the progress of NBCA and usually best to use a high concentration of NBCA to achieve rapid solidification and prevent migration to the lungs or to a major sinus distal to the MPV/VOG [23].
- Transvenous approach
- This technique was originally devised as a percutaneous method for transtorcular access and catheterisation of the straight sinus and MPV/VOG [24]. A transfemoral venous access and catheterisation of the MPV/VOG via the internal jugular vein is now preferred if this route is patent [14, 25]. Either way multiple coils are deposited in the venous side of the fistula and their effect assessed by transarterial angiography. Both transarterial and transvenous techniques have been used simultaneously.

12.2.6 Other Interventions for Vein of Galen Malformations

(a) Stereotactic radiotherapy:

It has been described for treatment of small remnant lesions after embolisation (less than 3 cm) [10]. As after treatments for brain arteriovenous malformations, occlusion of the nidal vessels is delayed and typically takes 24–36 months, during which time the VOGM may cause irreversible damage to the brain. It is therefore only appropriate for older children with stable lesions. Despite this drawback, radiosurgery has proved effective in selected cases [26].

(b) Neurosurgical CSF diversion procedures:

Surgical treatment by shunting is controversial because venous hypertension is the cause of a communicating hydrocephalus for which closure of the fistula is the only effective management. In some cases, when a direct compression of the aqueduct is shown on MRI, a ventriculoperitoneal shunt is placed, but closure of the fistula is still a more logical method since it will shrink the dilated vein as well as reduce venous pressure. Shunting is associated with higher rates of poor cognitive outcomes [27].

12.2.7 Outcomes of Interventions

Immediate outcomes: Complications of endovascular treatment include cerebral haemorrhage, infarction, vessel damage during navigation and worsening of hydrocephalus. In a systematic review of reports of embolisation in 667 patients, mortality was 10% (95%CI, 8–12%) and complication occurred in 37% (95%CI, 29–45%) [28]. The treatments involved 40% neonates and have to be balanced against previous mortality rates of up to 90% in neonates without embolisation (see below).

Late outcomes: The late outcome of treated patients is difficult to assess because the rapidity of technical improvements makes comparing current patients with those treated in the past pointless. Follow-up of neurological outcome should include assessments of cognitive development since rates of mental retardation as high as 62% have been reported in some series.

Surgical results: The review by Johnston et al. [11] of surgically managed patients before endovascular treatment was available is widely regarded as the best data for comparison with current practice. They reviewed 245 patient reports and calculated an overall mortality rate of 56% (after both medical and surgical treatments) with the highest mortality amongst neonates (91%) with and without treatment. The results of direct surgical treatments improved with patient age and the mortality amongst infants was 32%, falling to 26% in children (1–5 years). The surgical rates for mortality were 37% and morbidity 46%, so only 17% survived surgical treatments without disability.

Endovascular treatment results: In comparison, mortality rates after endovascular treatment are 10–15%, and even allowing for case mix variations, this represents a dramatic improvement [28, 29]. A recent review compared outcomes in 200 patients treated before 2000 with 337 patients treated between 2000 and 2010 [29]. Mortality rates were 15% for all endovascular treated patients, and good outcome rates improved over the study period, being 72% in 1983–2000 and 84% in 2000–2010. Over a 10-year period (1984–1994), Lasjaunias et al. [30] reported on the management of 120 consecutive paediatric patients, of whom 90% presented as neonates or infants. Treatment was contraindicated in 17% because of evidence of encephalomalacia and poor prognosis. Embolisation achieved anatomical cures in 53% and improvement in 80% of patients with permanent neurological or cognitive deficits in 8.5% and 9% mortality. Similar results were reported in the meta-analysis by Yan et al. [28], with complete anatomical cure in 57% and good outcomes in 68% (95%CI 61–76%) of patients treated by endovascular embolisation. Endovascular treatment is now the first-line intervention, but it should be recognised that improved outcomes are the result of simultaneous improvements in patient selection, medical treatment of cardiac failure and treatment being concentrated in specialist centres.

12.3 Non-Galenic Cerebral Arteriovenous Fistulas

Cerebral arteriovenous fistulas (CAVFs) are direct communications between arteries and veins and so represent the simplest form of arteriovenous shunt. They occur after cranial trauma and usually involve dural vessels; some of the effects of high-flow shunts are considered in

Tutorial 11. Cerebral, i.e. pial or subpial, arteriovenous shunts are found within the nidus of BAVMs, but occasionally solitary spontaneous shunts occur. These were first recognised, and the surgical management described, by Walter Dandy [31]. They are characterised by a dilated collecting system or varix and supplied by a single or two to three enlarged arteries. The enlarged venous component drains to deep or superficial veins depending on the location of the fistula.

12.3.1 Epidemiology

Non-Galenic CAVFs occur in children and adults but predominately in the former. Lownie et al. [32] reviewed 41 case reports and separated them into neonates (12%), infants less than 2 years old (27%), children less than 16 years (37%) and adults (24%). Some authors feel they should be classed as part of the spectrum of paediatric brain AVMs [16].

12.3.2 Clinical Presentations

In neonates, the presentation is virtually always with acute cardiac failure. Children and adults present with a variety of symptoms including headache, seizures or focal neurological deficits. Increasing head size affects infants, in whom mild chronic cardiac failure is frequently seen, as well as seizures and other features caused by the mass effect of a varix. Spontaneous haemorrhage is rare and affected only 7% of Lownie et al.'s series [32]. It occurred in each of the age groups except neonates.

12.3.3 Imaging

On angiography, the fistula may involve more than one arterial territory. In adults, a single artery usually contributes to a single fistula site, but in children, multiple fistulas may be seen, especially when several arteries are involved (Fig. 12.5).

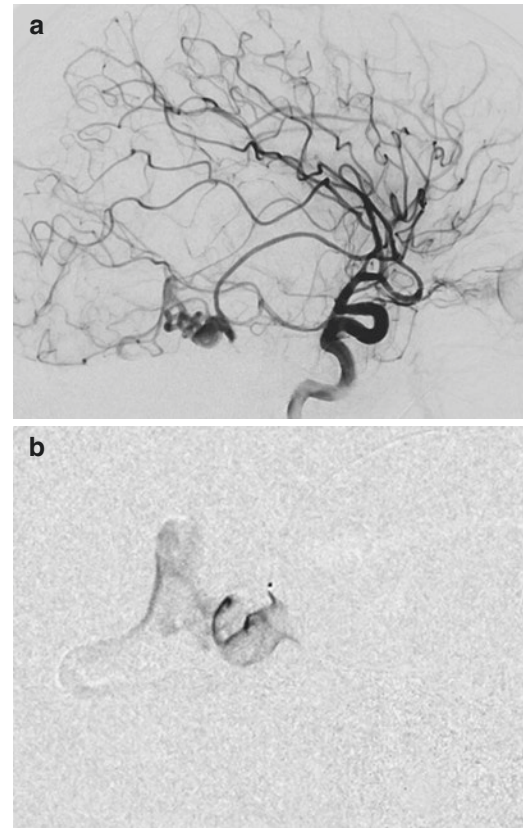

Fig. 12.5 Lateral angiogram (**a**) showing arterial displacements due to a temporal lobe haematoma caused by an AVF supplied by a single middle cerebral branch artery (middle temporal artery). Superselective injection (**b**) of middle temporal artery demonstrating a direct arteriovenous shunt

12.3.4 Treatments

A multidisciplinary team should make the selection of patients for interventions and recommendation on the form of intervention, since in the absence of guidelines, treatment has to be tailored for each patient [33]. The rarity of this type of lesion makes comparisons between open surgical occlusion and endovascular occlusion difficult. For both, the goal is disconnection of the arterial feeder from the draining vein.

Surgery: If the fistula site is accessible at craniotomy, surgical ligation of the fistula is curative. This may be combined with excision of the varix, but this is probably not necessary since once the fistula is closed, the varix will involute.

Endovascular treatment: Transarterial embolisation is performed with coils and/or liquid agents. Use of detachable balloons was performed in the past, but the availability of control detachable coils allows the accurate placement of initial coils, which are used to slow injected liquid embolic agents and give them time to solidify. As with any high-flow shunt, there is a risk of an injected embolus passing through the fistula to the venous circulation and the lungs. Cyanoacrylate (NBCA) is generally preferred for embolisation in this situation because of its fast polymerisation time. Use of recently introduced double-lumen balloons to control flow of liquid embolic agent may, in the future, improve the technique.

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Spinal Vascular Malformations 13

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Preamble

If one reviews the history and the various descriptions that have been used to classify spinal vascular malformation, it is clear that the usual problem of a wide variety of phenotypes has made the endeavour difficult and the literature overly complicated. In order to apply a uniform approach, and hopefully not to cause additional confusion, this tutorial will use anatomical descriptions, as much as possible, and not rely on numerical classifications.

Also, it is worth bearing in mind that the angioarchitectures of spinal vascular malformations are similar to their intracranial cousins. Arteriovenous malformation shunts in the spinal cord are essentially the same as those in the brain, and arteriovenous fistulas of the spinal dura are analogous to cranial DAVFs but with very different consequences for the patient. Thus, applying our knowledge of spinal vascular anatomy, we can anticipate the behaviour of lesions at different sites.

13.1 History

First reports of spinal vascular lesions were autopsy reports made in 1885 by Hebold [1] and in 1888 by Gaupp [2]. In 1915, Cobb

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described various clinical features and an association with skin lesions [3]. Michon described spinal subarachnoid haemorrhage due to an AVM and the first successful surgical excision was performed by Perthes in 1921 [4]. However, these early reports are dwarfed by a detailed description of 122 cases (96 from the literature and 16 of his own cases) made by Wyburn-Mason in 1943 [5]. He distinguished two major types: arteriovenous angiomas (32%) and venous angiomas (68%). Later, he divided them into five groups:

1. Angioma racemosum
2. Arteriovenous anomalies
3. Arterial anomalies
4. Syphilitic anomalies
5. Telangiectasias

The first diagnosis by vertebral angiography was reported by Hook and Lidvall in 1958. Embolisation of spinal lesions was first performed by Doppman et al. [6] and Newton and Adams [7]. Kendall and Logue in 1977 [8] and Merland et al. in 1980 [9] recognised the lesion, previously described as retromedullary angioma, to be a fistula. With the wider availability of spinal angiography, a series of descriptions and classifications of spinal cord vascular malformations were proposed, notably by Yasargil et al. [10], Rosenblum et al. [11], and Bao and Ling [12] and Spetzler et al. [13] (see below).

13.2 Spinal Vascular Malformations

Spinal vascular malformations (SVM) are rare lesions, constituting 5–10% of all vascular malformations of the central nervous system. In this tutorial, only vascular lesion will be discussed and not neoplastic lesions which some authors group together. The commonest specific type is the spinal dural arteriovenous fistula (SDAVF), accounting for 50–85% of SVM, and then spinal cord arteriovenous malformations (SCAVM) accounting for 20–30%, followed by perimedullary AVF which is rare and then epidural AVF (intradural and extradural) which are even rarer [14].

13.2.1 Symptoms and Modes of Presentation

The modes of presentation of patients with spinal vascular malformations reported in the early literature are contradictory, with Aminoff and Logue [15] describing presentation as gradual with progressive myelopathy, whereas Djindjian et al. [16] reported a rapid onset myelopathy with paralysis. These reports exemplify the two common modes of presentation, i.e. following spinal cord haemorrhage or due to slowly progressive symptoms of cord dysfunction. The explanation lies in different haemorrhage rates for different types of lesions. Haemorrhage occurs in intramedullary AVMs; it is infrequent in perimedullary AVFs and is virtually unknown in patients with SDAVF.

The modes of presentation can be summarised as follows:

(a) Spontaneous haemorrhage: Patients present with acute onset myelopathy (i.e. paresis or plegia, sensory loss and incontinence). Haemorrhage may be subarachnoid or intramedullary or both. It is most commonly caused by SCAVMs or spinal aneurysms and least often caused by small AVFs.
(b) Venous hypertension: This mechanism is commonly the result of an SDAVF. The AV shunt raises blood pressure to arterial levels in radicular and perimedullary veins which causes stasis of spinal cord venous drainage. It is worth remembering that the intraspinal venous system has no valves and is subject to gravity so the caudal cord is most affected. The resulting reduction in the normal artery to venous pressure gradient results in reduced spinal cord profusion and oedema.
(c) Arterial steal: Symptoms due to focal spinal cord ischaemia are relatively uncommon. They occur in high-flow lesions, particularly involving the anterior spinal artery [17]. It causes a variety of symptoms and abnormal findings on neurological examination. MRI shows hyperintense signal of T2-weighted sequences and DSA prolonged contrast transit times through the spine, which may be >12 s.
(d) Mass effect: Neural compression symptoms and signs may be due to dilated veins or large aneurysms.

The natural history is unknown. In a mixed group of 60 patients followed for a mean of 8 years without surgical treatment, haemorrhages occurred in 10%, rapid progression of motor weakness (within 6 months) in 19% and slower progression in the other 71%. In this last group, motor disturbances had progressed to severe disability after 3 years' follow-up in half the patients, and the other half had shown very slow progression or no progression at all. During follow-up, nine patients died from complications of chronic paraplegia and one after spinal subarachnoid haemorrhage [15]. Symptoms specific to the types of spinal vascular malformations are described below.

13.2.2 Classifications

The literature appears very confusing to the student because authors seem to need a reclassification, whenever they report their experience of treating patients with spinal vascular lesions. For this tutorial, I think it is helpful to avoid numerical types (at least initially) and consider classifications on anatomical grounds.

To start, spinal vascular lesions can be separated into three groups:

- Vascular malformations, which can be separated into arteriovenous fistulas (AVFs) and arteriovenous malformations (AVMs)
- Neoplastic vascular lesions, which can be primary or secondary and benign or malignant
- Aneurysms

All classifications of spinal vascular malformations separate arteriovenous malformations (AVMs) from arteriovenous fistulas AVFs and generally include other vascular lesions of the spinal cord, specifically cavernous malformations, aneurysms of the spinal arteries (these may or may not be associated with SCAVM) and metameric lesions.

Between AVMs and AVFs, we should distinguish three basic patterns based on the location and presence or absence of a nidus. Locations are either intradural or extradural or both. Lesions within the spinal cord are usually associated with a nidus and therefore described as intramedullary SCAVMs. Lesions on the surface of the cord are described as perimedullary AVMs or AVFs depending on the presence of a nidus and lesions in the spinal dura as SDAVF with or without a nidus.

With this simple pattern in mind, the following description is based on Spetzler et al. [13] which was a modification of a classification first proposed in 1992 by Anson and Spetzler [18]. It separates vascular tumours and aneurysms from vascular malformations and puts cavernous malformation with the former group. In a modified classification, a separate group for spinal cord AVMs at the conus was recently proposed by Kim and Spetzler [19].

Thus, a summary classification is as follows:

- Dural AVF, i.e. SDAVF (Type I, AVF on nerve root sheath, intradural or extradural)
- Intramedullary AVM, i.e. SCAVM (Type II, spinal cord or glomus AVM with nidus)
- Intradural perimedullary AVF (Type IV, direct AVF without nidus)
- Intradural and extradural AVM (Type III, complex, metameric or juvenile AVM, Cobb's syndrome)

To this list can be added:

- Cavernous malformation
- Spinal aneurysms
- Spinal vascular tumours
- AVMs at the conus/filum terminale

I now appear to be guilty of creating a reclassification, but the above is based on several authors and is intended to encapsulate their terms and aid the student in reading these original papers [10, 11, 13, 16, 18, 20, 21]. The whole topic is well described in a detailed historical review by Black [22].

13.3 Spinal Dural Arteriovenous Fistula (SDAVF)

This is the commonest spinal vascular malformation, constituting 80% of all patients diagnosed. The AVF is located in the dura,

usually within the intervertebral foramen. They occur in the lower thoracic and upper lumbar spines and consist of a small collection of dural arteries draining to a single intradural vein. They are supplied by a branch of the radicular artery (a meningoradicular branch) and may receive contributions from the adjacent vertebral levels. The venous drainage is to a radiculomedullary vein with retrograde flow to the spinal perimedullary veins.

13.3.1 Aetiology and Pathophysiology

They were first identified by Kendall and Logue in 1977; these authors did not suggest a cause [8]. They are assumed to be acquired lesions, but the cause is unknown. Symptoms are due to the venous hypertension caused by increased pressure in perimedullary veins.

13.3.2 Presentation and Natural History

Most patients are over the age of 50 years and present with progressive weakness of the lower limbs. There is a strong male predominance (9:1) [11]. Neurological abnormalities are motor weakness with modest sensory disturbance and incontinence. Patients also complain of back or root pain. Symptoms of pain and weakness are typically exacerbated by exercise. Symptoms are slowly progressive with a notably insidious onset, which often delays diagnosis [23]. Occasionally, patients report an abrupt onset, which is attributed to venous thrombosis rather than haemorrhage. Haemorrhage is not a feature of the presentation or natural history [11].The myelopathy may progress to complete paraplegia [24, 25]. Upper limb weakness is unusual because they are usually found in the thoracolumbar spine. The insidious onset of symptoms may delay the diagnosis and neurological deficits may be surprisingly profound at presentation (Table 13.1).

Table 13.1 Relative frequency of SDAVF symptoms

Motor weakness	90%+
Sensory loss	80–90%
Bladder dysfunction	80%
Bowel dysfunction	60%
Impotence	5–40%
Back pain and root pain	30–50%

13.3.3 Imaging

The imaging diagnosis is made on MRI, and contrast myelography is now generally obsolete. On MRI, the spinal cord is slightly expanded and returns increased signal on T2W sequences due to oedema (Fig. 13.1). Dilated veins are usually evident in the subarachnoid space. Increased T2 signal usually extends to the conus but its extent has no prognostic value [26]. Enhancement occurs after gadolinium administration in the oedematous cord and enlarged perimedullary veins.

MR angiography with contrast-enhanced studies may show an enlarged pedicular artery(ies) and predict the level of the fistula prior to catheter angiography. Localisation of the fistula level requires 3D reconstruction of MRA and fast acquisition sequences such as fast imaging employing steady-state acquisition (FIESTA) and constructive interference steady state (CISS) [26]. Recently, the use of time-resolved imaging of contrast kinetics (TRICKS) has improved the detection rate and accuracy of MRA and DSA for diagnosis, and localisation can then be performed as a pre-embolisation procedure [27]. CTA will also show enlarged blood vessels and is a substitute.

DSA: Spinal angiography with selective injections of the intercostal and lumbar arteries is best performed under general anaesthesia for optimum imaging. The shunt is usually at the level of the intervertebral foramen and supplied by a single artery, though additional contributions from adjacent levels should be sought. Filling of the perimedullary venous plexus is slow, and delayed exposures should be obtained. The artery of Adamkiewicz should be identified and at least three levels above and below the localised SDAVF studied by selective injections (Fig. 13.1).

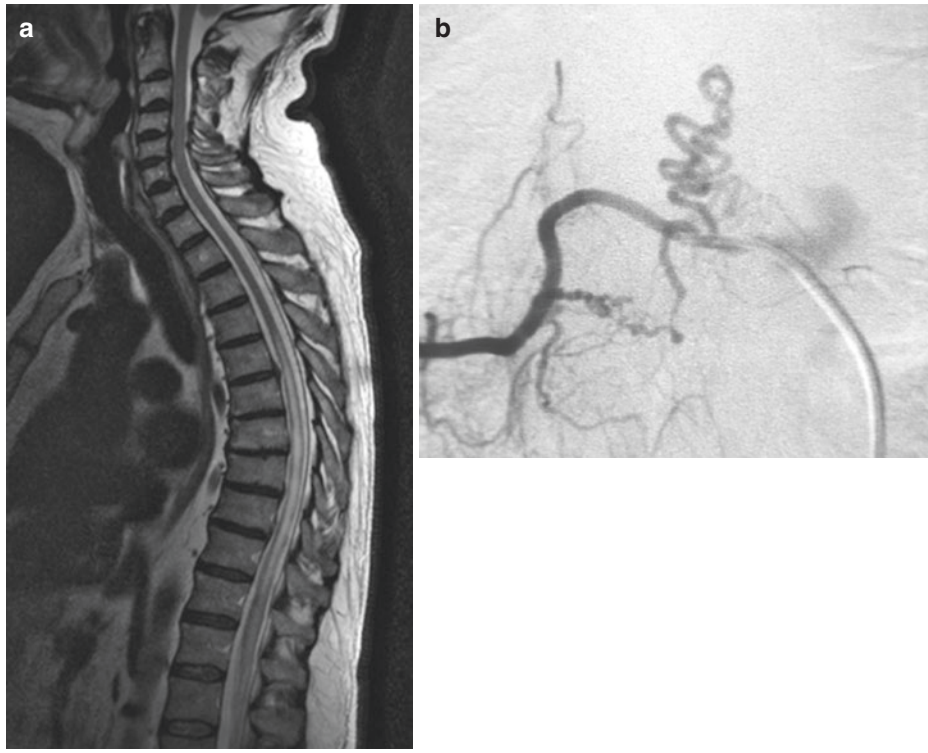

Fig. 13.1 Spinal dural arteriovenous fistula. MRI (T2 weighted) shows hyperintense signal in the dorsal cord (**a**) due to an SDAVF at D8 on the right. Injection of the right D8 intercostal artery (**b**) fills a small dural nidus and a tortuous perimedullary draining vein

The major difficulty is the occasional patient with positive MRI findings in whom no fistula can be identified on selective angiography. In this case, additional injections of the cervical and sacral spinal arteries must be performed since SDAVFs can occur at any level of the spine [28, 29] and if MRI shows signal change in the cervical cord, cranial angiography must be included to exclude a cranial DAVF. Lesions may also arise caudal to the conus and represent a heterogeneous group of SVM sometimes associated with spinal dysraphism [30].

13.3.4 Endovascular Treatment

The choice of surgical treatment or embolisation is often finely balanced since both have strengths and weaknesses. The difficulty for open surgery is localisation of the correct level and the risk of ligating intradural veins remote from the primary drainage of the SDAVF. Embolisation requires skill for optimum imaging and catheterisation in relatively small vessels. A 4 F or 5 F guide is positioned in the intercostal artery, and a microcatheter is used to select the radicular branch artery feeding the SDAVF. Embolisation is performed with dilute N-butyl-2-cyanoacrylate (NBCA) (1:4 or 1:5 mixtures with lipiodol) or Onyx (ev3 Endovascular Inc., Irvine, CA, USA). Penetration of NBCA to the start of the draining vein is necessary to obtain a lasting cure. In the past treatments were performed with particles but this has been generally abandoned because of the high recurrence rate.

It is a common practice to perform embolisation first and reserve surgical ligation of the SDAVF for patients in whom this fails or is incomplete. If the arteria magna, i.e. artery of Adamkiewicz, arises from the same intercostal artery as the fistula, then surgery is considered safer because the artery can be better protected.

13.3.5 Treatment Results and Complications

Treatment outcomes depend on the length of history and the degree of disability of patient at diagnosis. Aminoff and Logue [31] developed a scoring system, which quantifies the level of gait disturbance and continency of patients with SCMs in order to monitor their level of disability and treatment outcomes. The Aminoff–Logue scale (ALS) of disability distinguishes six levels of gait disturbance (0–5, with 5 = complete paraplegia) and four levels of disturbance of micturition (0–3, with 3 = complete incontinence). It is a useful objective measure.

Anatomical cures can be achieved with surgery or embolisation, but reversal of pre-existing disabilities is less certain. Symon et al. [32] reported gait improvements in 80% of moderately and 65% of severely disabled patients treated surgically. However, on long-term follow-up (1.5–24 years), all of their patients showed delayed deterioration [33].

The results of embolisation alone are mixed with anatomical cure possible in about 30%. In a series of 44 patients, attempted embolisation achieved cures in only 25% without complications [24]. No delayed deterioration was reported in this series, but others have reported recurrence after embolisation, especially when performed with particles [34], or when the liquid embolic agent does not penetrate to the vein. Using NBCA, delayed recurrence rates are comparable to surgery [35]. Use of Onyx in this situation is controversial because it is less likely to penetrate to the draining vein than NBCA [36]. In a meta-analysis of surgical versus embolisation outcomes, Steinhall et al. [37] reported successful occlusion rates of 95% and 46%, respectively, with similar low complication rates. Therefore, there does appear to have been a steady improvement in the results of embolisation with the wider use of liquid embolic agents.

In 2001, The American Society of Interventional and Therapeutic Neuroradiology published standards of practice covering embolisation of SVM [38]. This document defined indicators for complication rates, above which a practice review was recommended. For SDAVF embolisation these were 7% complications (0% mortality and 2% for major and 5% for minor deficits).

13.4 Intradural Perimedullary Fistula

These fistulas were first described by Djindjian et al. in 1977 as intradural extramedullary spinal arteriovenous malformations supplied by the anterior spinal artery [16] and comprise a shunt without nidus. The definition has been expanded to include lesions, on either the ventral or dorsal spinal cord surfaces and supplied by the anterior and/or posterolateral spinal arteries or even a radiculomedullary artery [39]. They are usually found in the thoracolumbar region or at the conus or in the upper cervical spine. Rarely are they found in the lower cervical or upper thoracic spines [9].

Merland distinguished three types (Types 1–3) depending on the size, level of blood flow and venous drainage [40], which Spetzler et al. [13] subsequently called Types A, B and C. The Merland system defined Type 1 as a single arterial feeder to the vein with slow flow, Type 2 as a medium-sized fistula with dilated feeding arteries and slow flow and Type 3 as a large AVF with high-flow and highly dilated draining veins. The Spetzler system is very similar with Type A, supplied from the anterior spinal artery only, and Types B and C from both anterior and posterolateral spinal arteries. The Type 3/C is the commonest, and Type 1/A, which is usually located at the conus, the least frequent. In all types, drainage is to perimedullary veins and these may extend a considerable distance cranial to the fistula level.

13.4.1 Aetiology and Pathophysiology

The aetiology is unknown though they have been described after spinal surgery and in association with dysraphism [40]. They usually present in young adult life with no gender difference described. The symptoms they cause are various and due to haemorrhage, venous hypertension, mass effect of enlarged vessels and steal

phenomena. They comprised 38% of a large single centre series of treated SCMs [12].

13.4.2 Presentation and Natural History

Symptoms at presentation are of a slowly progressive myelopathy or following haemorrhage. Spinal subarachnoid haemorrhage is one mode of presentation and occurs in about 30% of patients. It is frequently recurrent, if the fistula is untreated. Symptoms may progress rapidly after presentation, and the neurological findings are asymmetric sensory or motor disturbances (i.e. paraparesis) accompanied by sphincter disorders (a feature if the conus is involved) [41, 42]. Natural history data is sparse, but symptoms and neurological progression lead to paraplegia over 5–10 years and may be hastened by repeat haemorrhages [16].

13.4.3 Imaging

As for SDAVF imaging diagnosis now relies on MRI. The findings on T2-weighted sequences are similar with hyperintense signal return from within a swollen cord. If haemorrhage has occurred, then T2* changes will be evident though these may be difficult to detect if the bleeding has been subarachnoid rather than intraparenchymal and imaging is delayed. The signal characteristics of haemorrhage change over time, but the hypointense signal due to haemosiderin may last for months or years. It can be masked by the effects of high blood flow in vessels of the malformation. Enlarged vessels with flow voids due to high blood flow may extend considerable cranial or caudal distances from the fistula site making localisation more difficult than for SCAVF. MRA with enhancement and fast sequences or CTA will help to show the extent of enlarged vessels, but DSA is usually required to fully image and localise the fistula. Some centres prefer CTA to MRA in SVM with enlarged vessels and when high-flow shunting is present.

Spinal catheter angiography with selective injections of the involved spinal arteries is the definitive imaging for diagnosis and pre-treatment fistula localisation. The addition of 3D-rotational angiography helps to distinguish perimedullary from intramedullary lesions [36] (Fig. 13.2).

13.4.4 Endovascular Treatment

The progressive natural history justifies intervention, and the choice of surgery or embolisation depends on the type and location of lesions. The objective is to identify the fistula site and occlude the AV connection by ligation or embolisation. Combined approaches may be appropriate with embolisation performed to facilitate surgery. Using the Merland descriptors of different types, the relative indications for the two approaches are as follows:

- Type I: Embolisation is not indicated if the fistula is surgically accessible since surgery is the safer and more reliable treatment. Catheterisation in the anterior spinal artery can be difficult and is always hazardous. Fistulas situated on the ventral cord surface are candidates for embolisation, which has been performed with particles (as a presurgical manoeuvre) [43] or NBCA [40].
- Type II: If the fistula is situated on the dorsal surface of the cord, surgical ligation and embolisation are of equal value and efficacy. Ventral lesions are difficult to approach surgically but difficult to completely exclude by embolisation, if there are multiple feeders [42, 44].
- Type III: The high-flow and dilated vessels in this type make surgery difficult, and embolisation with coils or liquids is usually performed as curative or presurgery procedures. [12, 45]. The use of functional testing by selective injections of amytal and lignocaine prior to embolisation has been described. This may be performed under sedation for assessment by neurological examination or general anaesthesia when assessment is performed with electrophysiology tests, i.e. SEPs and MEPs [46].

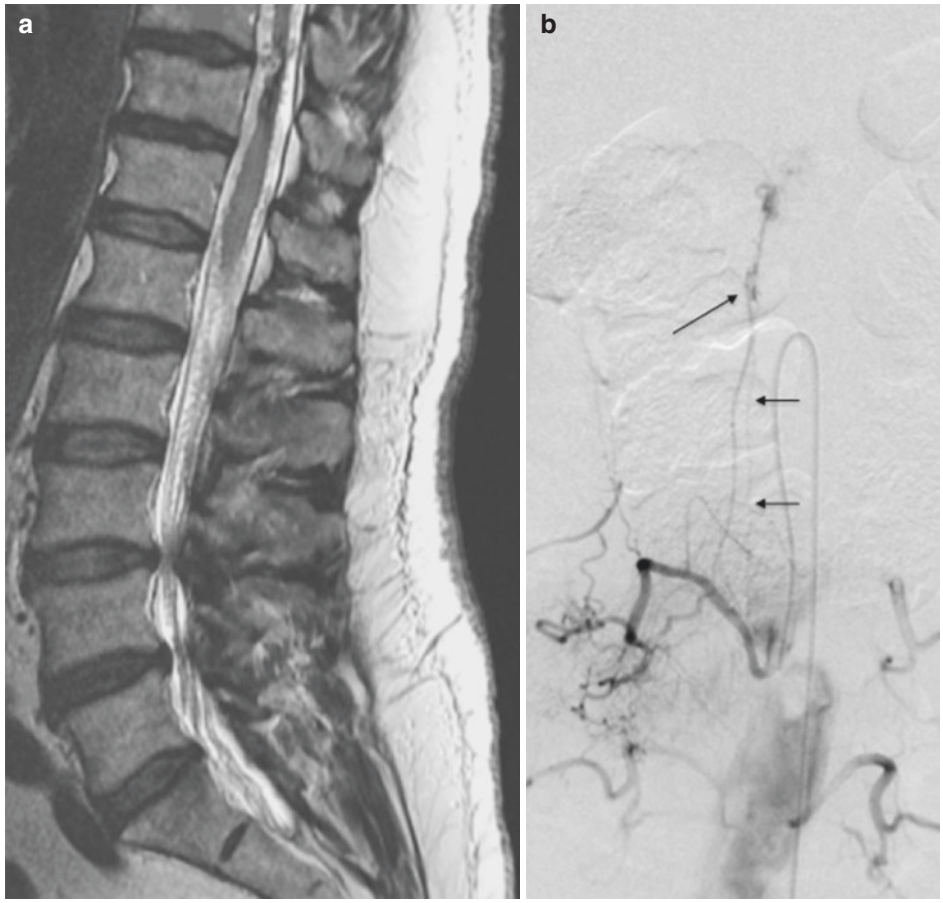

Fig. 13.2 Perimedullary fistula. MRI shows haemosiderin staining at the site of previous haemorrhage at the D10/11 level (**a**) with enlarged perimedullary and intradural veins. DSA by injection of L1 lumbar (**b**) artery shows a spinal radicullopial artery feeding the fistula (*large single arrow*) and perimedullary veins as well as the right posterolateral spinal artery (*small arrows*)

13.4.5 Treatment Results and Complications

The reported results of treatment for these lesions have been generally good, but the numbers of patients treated are small, and the variety of lesions and angioarchitecture makes comparisons difficult. In practice, management is decided on the basis of multidisciplinary discussion [47]. In a recent review of patients treated at the University of California over 25 years, Antonietti et al. [43] reported that 30 of 32 patients evaluated were treated (4 by embolisation, 11 by surgery and 15 by a combination). Improvements in ALS were observed after treatment in 62% of Type 3 lesions but in only 26% of Type 1 and 27% of Type 2 lesions. Merland et al. [48] reported failure of

embolisation in 10% and clinical improvements after embolisation in 70% and worsening in 10% of patients. Results are similar in other reports [12, 45, 49]. A 10% threshold for the incidence of worsening after embolisation was a standard of acceptable practice set by the American Society of Interventional and Therapeutic Neuroradiology [38]. Appropriate multidisciplinary patient selection is an important factor in achieving good results.

13.5 Intramedullary Spinal Cord Arteriovenous Malformation (SCAVM)

These lesions are similar to AVMs found in the brain. The ratio of SCAVM to brain AVMs is 1:6. They usually extend over one or more vertebral segments and are supplied by anterior and posterolateral radiculomedullary arteries with high-flow/low-resistance shunts. They have a nidus but the architecture frequently includes direct AV fistulas and aneurysms. Venous drainage occurs via perimedullary veins. They comprise the second largest group of spinal vascular malformations (35–50% of SVM) and are regarded as congenital in aetiology [12, 41].

13.5.1 Aetiology and Pathophysiology

Two varieties of angioarchitecture are recognised, with different clinical features.

- The glomus AVM consists of a compact nidus of abnormal vessels within the spinal cord. Patients are typically adults in the second–fourth decade of life [11]. They occur throughout the spinal cord with one-third in the cervical and two-thirds in the dorsolumbar regions. They are high-pressure and high-flow lesions, usually supplied by the anterior spinal artery with associated flow aneurysms in 40%. The majority (60%) present acutely (usually with spinal subarachnoid haemorrhage) and the rest with chronic myelopathic symptoms.
- The juvenile AVM consists of a looser tangle of vessels occupying almost the entire canal with extramedullary or paraspinal extension of enlarged vessels. They usually present in adolescents or young adult life. The lesion is high flow with multiple feeders and is usually found in the cervical spine. It is rarer than the glomus type.

They are generally regarded as congenital in aetiology and associated with other conditions such as Klippel–Trenaunay–Weber syndrome [50] and hereditary haemorrhagic telangiectasia [30]. Flow aneurysms are found in 20–40% of lesions [51, 52].

13.5.2 Presentation and Natural History

The first symptoms and signs occur in young adulthood or even earlier. Berenstein and Lasjaunias found that in more than 50% of their patients, initial symptoms were present before the age of 16 years [53]. An apoplexic presentation with sudden onset excruciating pain due to haemorrhage occurs in 10–20% of patients, and in half it is present at the time of diagnosis. Several authors have emphasised the risk of repeated haemorrhage, especially in children [53–55]. Untreated, the majority of patients experience progressive deterioration in function with a stepwise increase in disability due to repeated minor haemorrhage [11]. The annual risk of haemorrhage before treatment was calculated in a meta-analysis as 4%

(95% CI, 3–6%) and 10% (95% CI, 7–16%) if there had been a prior haemorrhage [56].

Neurological symptoms may be due to haemorrhage (either subarachnoid or within the spinal cord), arterial steal or neural pressure caused by dilated vessels. Myelopathic symptoms include motor weakness, sensory disturbances (typically loss of pain and temperature sensation) and sphincter disturbances. There may be a definable sensory level on examination, indicating the level of the lesion and which will determine the extent of motor weakness. Radicular pain is associated with lesions at the conus [13].

13.5.3 Imaging

As described above, MRI is the best scanning technique for the diagnosis of SCAVM and to show remote changes in the cord. MRI has replaced conventional myelography, and CT myelography is an acceptable substitute for patients in whom it is contraindicated. Susceptibility signal changes due to haemosiderin staining in the surrounding cord indicate previous haemorrhage, and cord swelling with increased signal on T2-weighted sequences indicates cord oedema.

Angiography as for perimedullary fistulas is improved by 3D reconstruction techniques of CTA, MRA or DSA images. Spinal catheter angiography is required to plan interventions with selective and super selective injections prior to embolisation. It is often needed to distinguish between perimedullary and intramedullary lesions and generally is best performed under general anaesthesia [53, 57] (Fig. 13.3).

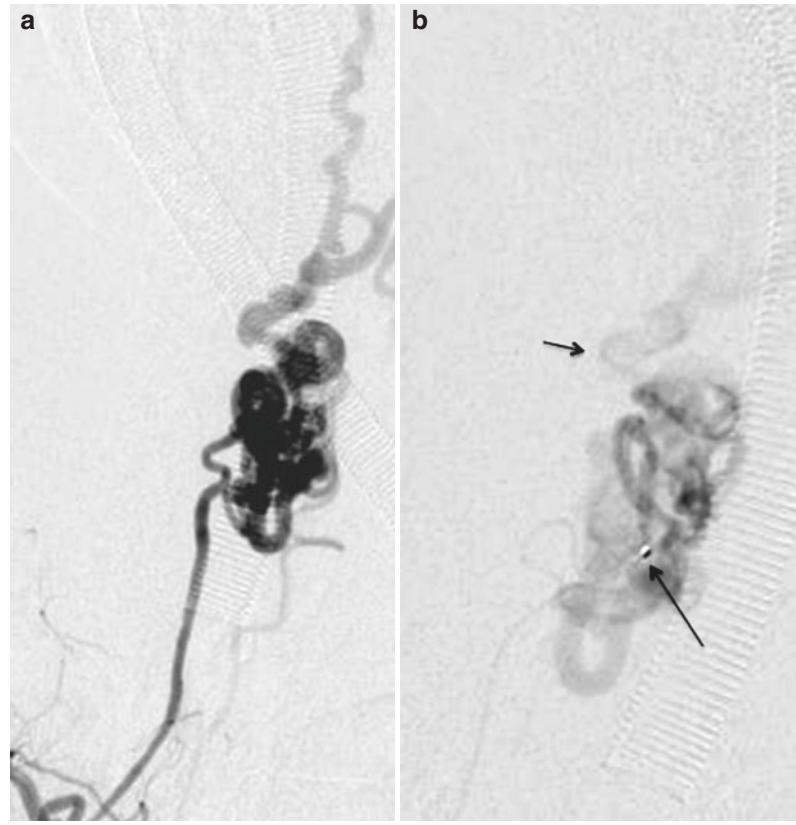

Fig. 13.3 Intramedullary spinal cord arteriovenous malformation. Selective spinal DSA shows a compact intramedullary nidus (**a**) and filling of a high-flow shunt to a large perimedullary vein after selective catheterisation (**b**). On (**b**), the *long arrow marks* the microcatheter tip and the *short arrow* the draining vein

13.5.4 Endovascular and Other Treatments

Endovascular treatment should be considered for all symptomatic patients. Its objectives should be clearly defined after DSA as (1) attempting cure, (2) preparative for adjuvant treatments (i.e. surgery or radiotherapy) or (3) for palliation of symptoms. Palliative therapy is indicated when total obliteration is not possible and symptoms are progressive or imaging has identified angioarchitecture features of high risk for haemorrhage (i.e. aneurysms or previous haemorrhage). Evidence for the value of partial treatment in providing protection against repeat haemorrhage is anecdotal.

13.5.4.1 Endovascular Treatment

Reports of techniques and outcomes of endovascular treatments have relied on case series. Some authors have advocated embolisation with particles on the basis that they are safer than liquid embolics [55] and others NBCA because vessel occlusions are more likely to be permanent [49, 53]. Coils and balloons have been used to reduce flow in large shunts, and Onyx, though more difficult to control, is preferred by some practitioners [58].

Merland et al. [48] reported good results after particle embolisation, which stabilised the clinical symptoms and prevented recurrent haemorrhage in all patients. Revascularisation was relatively common and patients were frequently retreated. During an extended follow-up period (1–15 years; mean 6 years), clinical improvement was maintained in 63%, but 20% deteriorated and complete durable elimination was not achieved in any of the patients. Berenstein and Lasjaunias [53] treated 38 of 47 patients with NBCA (or its predecessor IBCA) and achieved complete elimination of the lesion in 53%. Their overall complication rate was 11% for permanent and 11% for transitory deteriorations. After a complete angiographic cure, no further haemorrhages occurred, but two patients treated by partial embolisation had further haemorrhages (follow-up 1–14 years; mean 7.5 years). In a small series of treatment with Onyx, Corkill et al. [58] reported complete occlusion in 38% and minimal remnants in a further 31% of lesions and functional improvement in 14 of 16 patients treated. Transient neurological deteriorations occurred after 43% of embolisation treatments. Gross and Du [56] reviewed 16 studies in which embolisation was the only intervention (with particles, NBCA or Onyx) and calculated a complete occlusion rate of 33% (95% CI, 24–43%). The long-term outcomes were; 66% (95% CI: 56–75%) of patients improved, 21% (95% CI: 14–30%) were the same and 13% (95% CI: 7–21%) were worse [56].

It is likely that treatment is best performed as early as possible because the chances of recovery after therapy have been linked to the duration of prior symptoms and the severity of any abnormal neurological findings at diagnosis [59]. The acceptable thresholds for outcomes of endovascular therapy set by the American Society of Interventional and Therapeutic Neuroradiology standards of practice were 10% failure, 50% improvement. Limits for complication rates above which a practice review was recommended were 10% for transient, 10% for permanent deficits and 0% for death [38]. Patient selection is again an important factor in achieving good results and probably a factor in the variations evident in reports of outcomes.

13.5.4.2 Surgical Treatment

Microsurgical therapy is technically difficult because of the intramedullary location of the nidus. Generally, a compact nidus is easier to resect, and procedure complication rates are highest for operations on the juvenile type of AVM. In a single centre report, Connolly et al. [60] reported achieving angiographic cure in 94% (40% improved, 53% stabilised and 7% were worse) in a series of 15 patients with glomus SCAVMs. Chronic pain was a significant symptom in a third of their patients before and after surgery. In the meta-analysis of Gross and Du, treatments of 244 patients were reviewed. Complete resection was achieved in 78% (95% CI, 72–83%), and long-term 57% patients (95% CI: 51–63%) improved, 31% (95% CI: 26–38%)

were the same and 12% (95% CI: 8–16%) were worse [56].

13.5.4.3 Combined Therapies and Radiotherapy

There have been a few reports describing combined embolisation and surgery, and the benefits for patient management are difficult to assess [42, 61].There have been very few reports of treatment with radiotherapy. Hida et al. reported a small series of inoperable SCAVMs treated with fractionated radiotherapy and followed for a mean of 49 months. None of the lesions completely resolved though half were smaller. During follow-up there were no haemorrhages or adverse effects of the treatment [62]. The use of stereotactic radiosurgery in a cohort of 15 patients was reported by Sinclair et al. [63]. Anatomical cure was achieved in 1 patient and significant reduction in size in 6 of 7 patients followed beyond 3 years. There was no bleeding in treated patients during follow-up.

For what should now be obvious reasons, patients with SVM should be managed in specialist centres and multidisciplinary management of patients is clearly appropriate to this patient group. The intervention options are listed in Table 13.2.

13.6 Spinal Aneurysms

There have been a few reports on isolated spinal arterial aneurysms. The literature is complicated by the imprecise use of the term. Biondi et al. [51, 52] reported aneurysms in 20% of patients with SCAVMs, all of whom had haemorrhaged. They considered the association highly significant. After successful treatment of the intramedullary SCAVMs in 4 patients, the aneurysms disappeared, but they later reappeared with recurrence of the SCAVM [52]. Isolated aneurysms are very rare and fewer than 17 cases had been reported in the literature before a review in 1993 [64]. The majority of aneurysms were fusiform and were associated with comorbidities such as arteritis, syphilis and fibromuscular dysplasia.

13.7 Metameric Syndromes

The involvement of vascular malformations of the spinal cord, with vascular malformations in dura, vertebral bodies and the skin of the same segmental dermatome, is what the term metameric lesion describes. In its pure form, it is known as Cobb's syndrome, which was first described in 1915 and is rare [65]. The combination of cutaneous vascular lesions and SVMs is far more frequent and does not necessarily involve the same dermatomas as the spinal lesion [11]. In larger case series and particularly with more extensive intramedullary SCAVMs, they are found in 10% of patients [53]. The principles of treatment of the SVM are based on the angioarchitectural features as described above. Cobb's syndrome was diagnosed in 10 of 72 children with SVMs reported by Du et al. [66]. They were treated by either embolisation or surgery.

Spinal cord AVMs are also associated with vertebral body haemangiomas and vascular dysplasias involving nonneural tissues remote from the spine, such as Rendu–Osler–Weber and Klippel–Trenaunay–Weber syndromes, AVMs at

Table 13.2 Summary of treatment options for spinal vascular malformations

SVM type	Intervention	Goal of intervention
Intramedullary SCAVM	Surgery	Curative resection if possible
	Embolisation	Curative or palliative
	Stereotactic radiosurgery	Palliative
Perimedullary AVF Type I	Surgery (or embolisation)	Curative resection
Perimedullary AVF Type II	Embolisation (or surgery if incomplete)	Curative or palliative
Perimedullary AVF Type III	Embolisation (surgery if incomplete)	Curative or palliative
SDAVF	Surgery or Embolisation	Anatomical cure

other sites, neurofibromatosis, Parkes Weber syndrome and von Willebrand disease [11, 50].

13.8 Cavernous Malformations

There are no differences in the pathology and therapeutic challenge of cavernous malformations in the brain and spinal cord. They comprise dilated endothelium-lined sinusoidal spaces, and patients usually present with abrupt onset or progressive myelopathy. The diagnosis is by MRI, though haemorrhage and enhancement may be evident on CT. In the spine, they are more common in women, and usually present in young adult life. Symptoms at presentation vary from rapid progressive disability or stepwise deteriorations. About half of patients present following haemorrhage [67]. They represent approximately 10% of spinal vascular lesions and are found anywhere in the cord with no regional predilection [68, 69]. There may be additional cerebral cavernous malformations in about 40% of patients [70]. The natural history is poorly described but recurrent bleeding occurs [71]. The frequency of symptomatic bleeding was calculated as 1.6% per patient year by Cohen-Gadol et al. [70]. They are accessible for endovascular treatment, and surgical resection is generally reserved for symptomatic lesions [72–74].

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Head and Neck Vascular Lesions 14

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Preamble

This chapter presents an interesting but uncommon group of lesions, some of which any practising endovascular therapist is bound to encounter. They occur mostly in children and young adults, and patients are referred from various specialist services, e.g. paediatricians, otolaryngologists, dermatologists and plastic surgeons. Decisions about their management are best taken after a multidisciplinary review, but unlike treatments of brain AVMs, this may involve a variety of specialists, some of whom will have little experience with a particular pathology. Because of these several referral pathways and the relative low incidence of individual lesion type, the endovascular therapist is likely to concentrate the available experience in a particular geographical region and become a key contributor to the multidisciplinary review process.

It often presents a challenge to fit a particular lesion to the accepted taxonomy, and I frequently find myself resorting to the description of a 'mixed pattern'. This is because of overlap between particular features and the not uncommon reality of lesions comprising multiple vascular components. So I would advise the student to regard the following definitions as an attempt to describe a spectrum of conditions. In addition to haemangiomas and vascular malformations, other head and neck pathologies will be discussed. This is to avoid the need for a separate tutorial for the small number of such lesions ame-

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nable to embolisation, which are not been covered in other chapters.

14.1 Birthmarks and Vascular Lesions of the Head and Neck

This grouping of vascular lesions of the head and neck together is justified on the basis that they generally are diagnosed in childhood and often associated with a cutaneous lesion or 'birthmarks'. The majority of lesions are unsuitable for endovascular treatment or it is unnecessary. The challenge for the endovascular therapist is to determine when to intervene and what form any intervention should take.

14.1.1 Classification of Vascular Tumours of the Head and Neck in Children

The best available classification of this complex group is the biological description of lesions of infants and children published by Mulliken and Glowacki in 1982 [1]. This exemplifies the best in clinicopathological classifications and can be applied to vascular lesions of the head and neck in all patients. It is based on cellular features and correlated with clinical findings and natural history. It separates two main biologically different lesion types: haemangiomas and vascular malformations (Table 14.1). This tutorial will refer extensively to the subtypes it defines. Mulliken and Glowacki's classification [1] has stood the test of time and was adopted by the International Society for the Study of Vascular Anomalies in 1996. It is widely used as the basis for describing a group of conditions, often characterised by a 'birthmark'. A minor modification was proposed in 1988 [2] which additionally divided vascular malformations into low- and high-flow lesions (Table 14.2).

Table 14.1 Mulliken and Glowacki classification of childhood haemangiomas and vascular malformations [1]

Vascular tumours	Vascular malformations
Haemangiomas[a]	Malformations
Proliferative phase	Capillary
Involuting phase	Capillary venous
	Venous
	Lymphatic
	Arterial (AVM or AVF)
	Angiodysplasia

[a]Vascular tumours (such as haemangiopericytoma and Kaposi's sarcoma) can be included in the haemangioma category

Table 14.2 Modified clinical classification of Jackson et al. [3]

I	Haemangioma
II	Vascular malformations
IIa	Low-flow lesions (venous malformations)
IIb	High-flow lesion (arteriovenous malformation)
III	Lymphatic malformation (lymphovenous malformation)

14.1.2 Assessment Prior to Treatment of Haemangioma and Vascular Malformation

The history and examination are the lynchpin of diagnosis in these conditions. The family history is rarely positive for vascular malformations [4], but establishing whether the lesion was present at birth is crucial. The characteristic appearances of different lesion types are described below, but in general terms, the examination should include an assessment of skin lesions for blanching on pressure and the firmness and compressibility of mass lesions. Skin temperature, pulsation, trills and auscultation for bruit may confirm a hypervascular lesion. Photography is useful for documenting changes over time, and investigations should include a coagulation profile. The distinction between haemangioma and vascular malformation lesions is usually possible without imaging, but it may be difficult, and imaging is important for demonstrating the extend of a lesion, its relationship to adjacent structures and for planning any surgical or endovascular intervention [5, 6].

MRI and CT scanning will demonstrate the presence of a soft tissue mass that may or may not enhance. Phleboliths may be present and bony involvement is best assessed on CT. Ultrasound is helpful to show the presence of increased blood flow and distinguish high- and low-flow vascular malformations. Catheter angiography is generally reserved for pretreatment assessment after a decision to intervene has been taken. The angiography features to be analysed include location, nidal architecture, speed of blood flow, collateral circulations, arterial ectasias and mass effect.

Both haemangioma and vascular malformations group lesions can result in impaired vision, airway restriction and oral malfunction because of mass effect. Complications include haemorrhage (usually as a result of ischaemic ulceration), cardiac failure and consumptive coagulopathy (Kasabach–Merritt syndrome), infection and glaucoma in orbital vascular malformations. Since involution can be expected in the majority of haemangiomas, treatment is supportive unless a developing complication precipitates intervention. Children often cope well with the signs of a vascular malformation and often only seek treatment for cosmetic reasons, as adolescents. The therapist needs to appreciate the psychological impact of what may appear a disfiguring lesion and how its impact on a young patient may differ from its impact on their parents.

14.2 Haemangioma

Haemangioma are mostly diagnosed in the first year of life and usually referred to as infantile haemangioma. They typically appear soon after birth and enlarge rapidly. They are commoner in girls and reach 80% of maximal size by about 6 months of age. Growth is almost always complete by 9 months of age, and they then involute during early childhood [7]. In contrast, vascular malformations of childhood are present at birth in 90% of cases with an equal gender distribution, grow with the child and don't involute [8].

14.2.1 Infantile and Childhood Haemangiomas

These are the most common tumours of the head and neck region in infancy and childhood. They are benign tumours and affect up to 5% of all infants. They occur anywhere on the body with a third on the trunk (particularly genital areas), a third on limbs and 40–50% in the head and neck, usually involving the face, eyelid, lip, oral cavity or subglottic regions [9].

14.2.2 Pathology and Aetiology

In its early stage, the infantile haemangioma is characterised by the presence proliferating endothelial cells lining vascular spaces and a large number of mast cells. The endothelial cells contain histochemical markers that are the same as those of placental blood vessels, namely, GLUT1+, LeY+, FcyRII+, Merosin+ [10]. This discovery leads to the theory that the cells have originated (possibly embolised) from the placenta, but other hypotheses concerning their aetiology include a somatic mutation in a gene controlling endothelial cell proliferation and their origin from specific endothelial progenitor cell [9]. Also implicated is hypoxia due to placental insufficiency stimulating angiogenesis. Elevated expression of an inhibitor to new blood vessel formation has been reported during the involution phase [11].

14.2.3 Presentation and Natural History

Typically, they appear in infancy, though a minority may be recognised at birth, the majority are evident by the age of 3 months. Risk factors are prematurity, female sex (female/male ratio 3:1) and Caucasian ethnicity. They grow rapidly, usually in the first 6 months, and then undergo fatty replacement and involution. Involution usually begins after the age of 1 year and is completed by adolescence. Complete involution

occurs in 80–95% of cases. They were multiple in 23% of patients in a large population-based study [12].

Initially, there is an erythematous macular cutaneous patch, with a blanched spot or localised telangiectasia surrounded by a pale halo. An old descriptive term was strawberry naevus or strawberry haemangioma. Deeper lesions may cause a bluish hue to the overlying skin, or the skin may be normal. As they grow, the appearance is that of a nonspecific soft tissue mass. Intraosseous invasion is rare, unlike vascular malformations. Complications are caused by about 10% of lesions. The most common is bleeding (6%), then ulceration (5%) and then dysfunctions due to lesion affecting feeding, vision or the airway (4%) [12].

14.2.4 Imaging

Imaging has a limited role in diagnosis. MRI is the commonly performed imaging investigation because it shows the deeper relationship of cutaneous lesions and any displacement of vital structures.

Ultrasound: Shows a combination of solid parenchyma and dilated vessels. Colour flow Doppler cannot distinguish haemangioma from arteriovenous malformations because both show high blood flow due to shunts but this reduces with involution.

MRI: MRI shows a lobulated lesion with heterogeneous signal on T1-weighted sequences and hyperintense signal on T2-weighted sequences with flow voids. Foci of increased T1 signal intensity, which are less hyperintense on T2-weighted sequences, are due to fatty replacement as the tumour involutes. Satellite lesions may be seen in the periphery of deep lesions.

DSA: DSA demonstrates displacement of adjacent vessels with an organised pattern of arterial supply from local arteries and drainage into enlarged superficial veins. There is an intense capillary blush, filling of the vascular spaces in the capillary phase, and areas of arteriovenous shunting (Fig.14.1).

14.2.5 Management and Treatment

In general, management of haemangiomas is conservative, and medical treatment instigated only if the lesion's growth becomes symptomatic. If treatment becomes necessary, systemic or intra-lesion corticosteroids are used. Systemic prednisone in doses of 2 mg/kg/day for 4–6 weeks is sometimes given to stimulate involution. It is then reduced with a tapered reduction over 3–4 months. It is effective in about 50–80% of patients. Percutaneous injections of corticosteroids in small daily amounts have been shown to hasten tumour regression. Other options include interferon alpha and vincristine. Interferon alpha-1, administered daily by subcutaneous injection for 6–12 months, has shown a good response in most steroid-sensitive lesions [13]; however, the treatment is associated with potential serious side effect and is slow and costly. Like vincristine, it is reserved for larger tumours resistant to other therapies.

Recently, propranolol has been reported to inhibit the growth and induce regression [14] and is undergoing trials with initial results suggesting that it will replace corticosteroids as first-line treatment. In a systemic review, the response rate was 98% to a mean oral dose of 2.1 mg/kg/day over a mean of 6.4 months [9]. An alternative treatment for more complex lesions is bleomycin (reported to cure 50% of haemangiomas [15]) and laser treatment (results are inconsistent) [16].

The major indications for interventions that include surgery and/or embolisation are cardiac failure, coagulation disorders, orbital deformity, oral mass effects and mandible growth impairment, steroid resistance and patient intolerance to the mass (Fig. 14.2).

14.2.6 Specific Treatment Indications for Haemangioma at Different Sites

Subglottic haemangioma: Tumours at this location cause dyspnoea in early infancy (i.e. first 6 months). The presentation is with stridor (85%), and this may cause cyanosis (15%). Subglottic

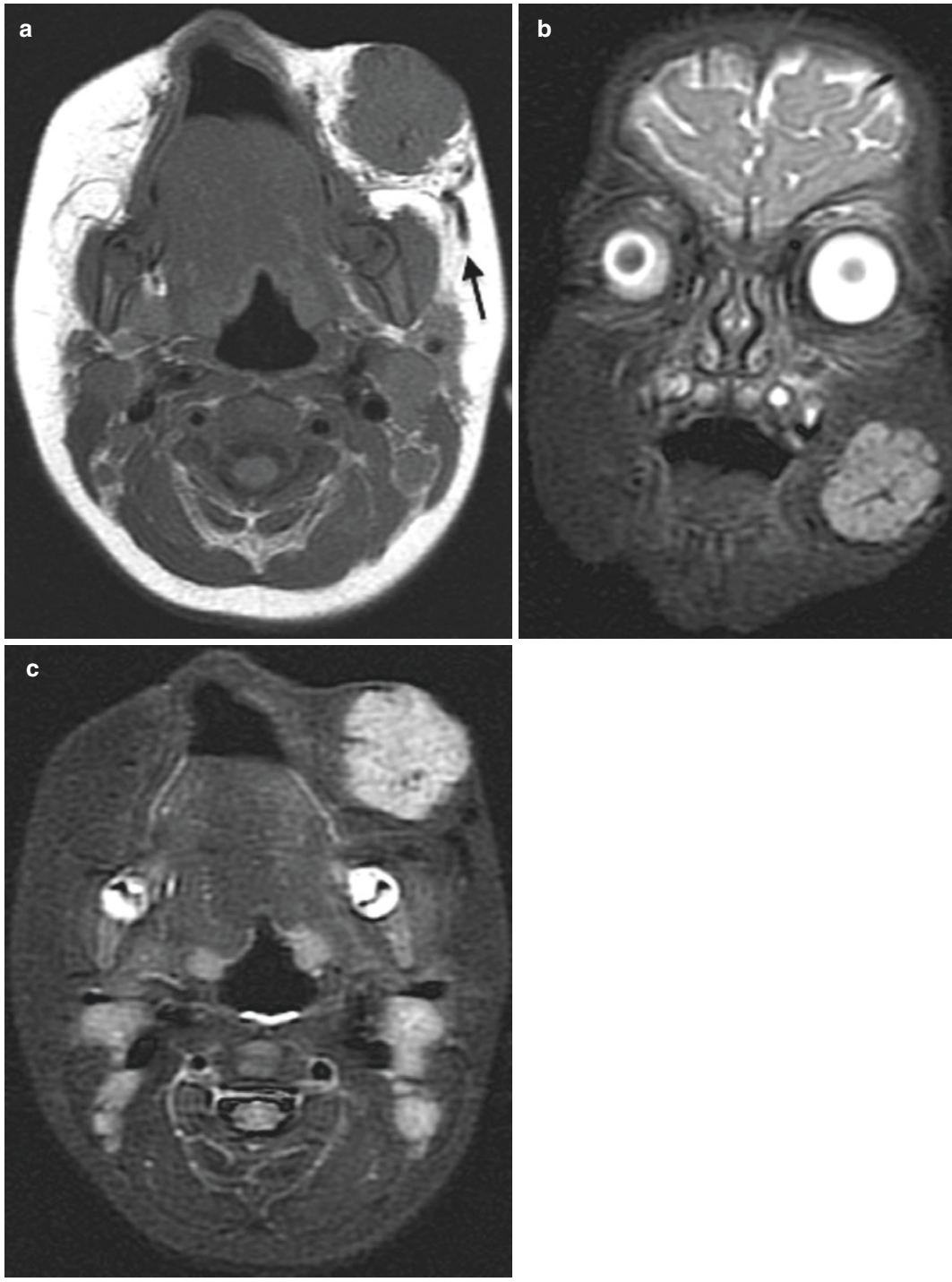

Fig. 14.1 MRI showing an infantile haemangioma of the left cheek of a child aged 6 months. Axial T1-weighted (**a**), coronal (**b**) and axial (**c**) short-time inversion recovery (STIR) sequences show a well-defined mass involving the skin and subcutaneous fat of the cheek; an enlarged branch of the facial artery is evident (*arrow*). No endovascular treatment was proposed because involution is likely

tumours are supplied by the inferior thyroid artery and transarterial embolisation should be performed if medical treatment with steroids fails to control the symptoms. Since most tumours will involute spontaneously, the objective is to 'buy time'.

Eyelid haemangioma: Complete occlusion of the eye by swollen eyelids may result in visual loss in neonates (amblyopia). If eye occlusion persists, vision may be permanently affected after only a week in very young children. Embolisation offers a rapid response and should be feasible, particularly with upper lateral eyelid locations of tumour. Steroid or propranolol treatments may not act fast enough to reopen the eye. Rebound growth is possible after embolisation so careful follow-up is required.

Oral haemangioma: Tumours involving the mouth may present with bleeding and rarely involvement of the jaw. Lesions in the cheek may be well tolerated. Embolisation is indicated to induce involution and avoid disturbance to growth and eruption of teeth. Haemangiomas of the tongue in adults are a cavernous subtype and usually poorly vascularised. They cause pain and mass symptoms. Particle embolisation or sclerotherapy may be used to reduce their size and relieve pain.

Salivary gland haemangioma: This occurs most commonly in the parotid gland. Its mass may cause facial asymmetry but usually not VIIth cranial nerve damage. Since tumours can be expected to involute, embolisation is usually not required.

Bone haemangioma: This is a rare tumour site. It occurs most often in the calvarium (usually temporal bone). There is a female dominance (2:1), and radiological and clinical features are nonspecific. Spontaneous haemorrhage is rare, but if the tumour involves the jaw, dental extraction may provoke serious bleeding. Most are of the capillary type and highly vascular.

14.2.7 Associated Syndromes

PHACE Syndrome: The term is an acronym coined for the association of posterior fossa brain malformations, haemangiomas, coarctation of the aorta and other cardiac defects, and eye abnormalities [17]. Though the association of extra and intra-cranial vascular malformations with cutaneous haemangioma had been described previously [18]. The diagnosis should be considered in children with birthmarks, and though rare, it is probably underdiagnosed [19].

Kasabach–Merritt Syndrome: This syndrome comprises a consumptive coagulopathy in association with haemangiomas. It occurs typically in children and varies in severity from mild to severe forms. The latter may be fatal in the absence of effective treatment. The coagulopathy is characterised by thrombocytopoenia, fibrinogenopoenia and accelerated fibrinolytic activity. It is similar to disseminated intravascular coagulopathy but differs in that the consumptive process is localised to the tumour. Treatment involves the use of high-dose steroid therapy, aminocaproic acid and cryoprecipitate. Embolisation is rarely performed, and consideration should be given to the need for platelet and cryoprecipitate cover before angiograms.

14.2.8 Adult Haemangiomas

Haemangiomas that present in adulthood do not involute. They grow by cellular proliferation, and thrombosis may be seen within the vascular lumen. They are typically avascular, but there may be some parenchymal blush and vascular opacification in the late venous phase on catheter angiography. The pathological descriptions are complex with various terms used, such as cavernous haemangioma, in the International Classification of Disease – ICD – O 9120–9179 for vascular tumours. Because of their hypovascularity, transarterial embolisation is ineffective, but percutaneous intra-lesion injections of bleomycin can be effective [20].

14.3 Vascular Malformation

These lesions are assumed to be due to an error of vascular morphogenesis formed by any combination of abnormal capillary, arterial, venous or

lymphatic channels. They are congenital and usually present at birth, so cutaneous lesions are often described as 'birth marks'. They exert mass effect causing facial deformity and functional disturbances, particularly to dentition. There may be overlying skin discolouration. On histological examination, the vessels have normal endothelial cells without cellular proliferation and no increase in the number of mast cells.

Despite their congenital nature, they may not manifest until later in life. Their appearance may be in response to an external stimulus, such as trauma, infection, tooth eruption, stress, excessive exposure to sunlight, hormones in pregnancy and puberty, and venous or arterial hyperpressure. Bony involvement is seen in 35%.

Normally, they do not grow except in line with normal tissues (nor involute). However, rarer subgroups of mixed vascular malformation shares features of both high- and low-flow malformations but may be highly invasive and grow to enormous sizes. They are generally resistant to therapy, and all forms of vascular malformation may be precursors to an invasive mixed vascular type of malformation.

14.3.1 Clinical Distinguishing Features

The findings on examination of vascular malformations are those of a mass in the soft tissues with skin or mucosal discolouration evident in superficial malformations. The mass may be compressible, well defined or diffuse and have evidence of increase blood flow (i.e. palpable pulsation and/or audible bruit), depending on type. In general, imaging (planar scanning) is helpful for initial diagnosis of type (Fig. 14.2).

MRI/CT: Venous malformations appear homogeneous in density and signal with occasional

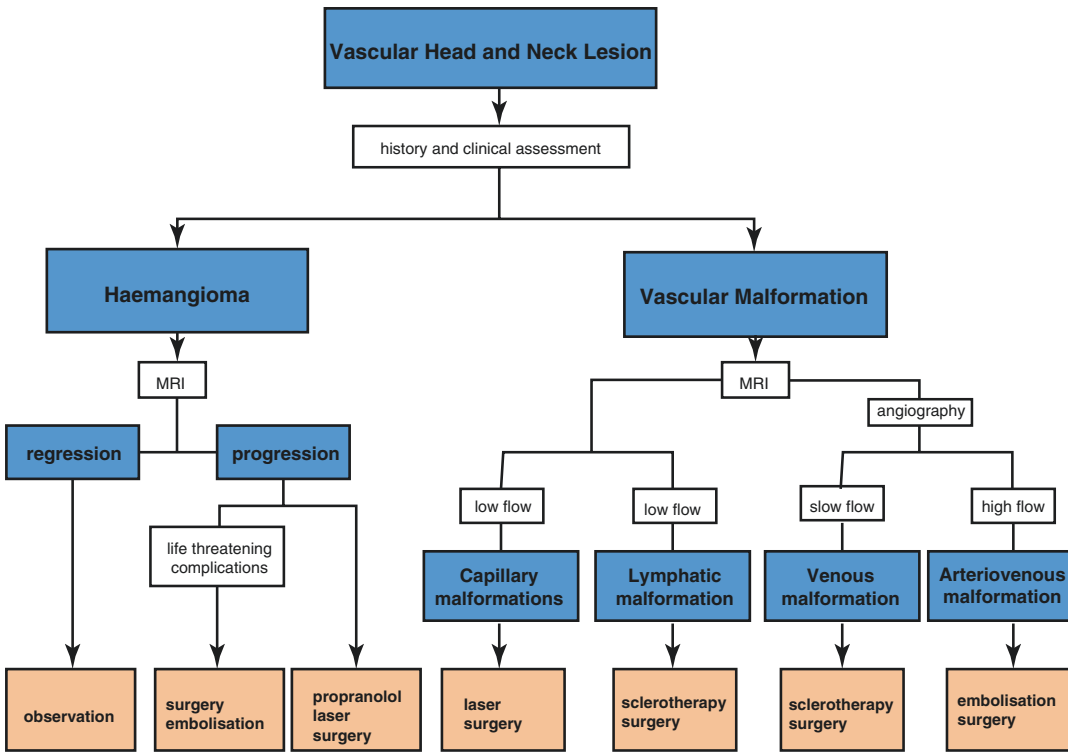

Fig. 14.2 Imaging and management pathways for vascular malformations of the head and neck. MRI = magnetic resonance imaging used to localise lesions and monitor during follow-up. Angiography means both venography and arteriography

linear flow voids consistent with dilated veins. Satellite lesions may be seen; venous lakes are seen as hyperintense areas on T2-weighted sequences. CT may show calcification due to phleboliths.

Lymphatic malformations: These are usually multicystic with heterogeneous signal. They insinuate between facial planes and may show evidence of haemorrhage.

Low flow: These lesions (which may be capillary, venous or lymphatic) show intermediate T1 signal with heterogeneous T2 signal and prominent enhancement after gadolinium.

High flow: These lesions (which are predominantly arterial) are characterised by serpiginous signal voids on both T1-weighted and T2-weighted sequences consistent with high-flow vessels. They are usually associated with minimal distortion of adjacent tissues.

Combined vascular malformations: These are solid, deeply infiltrated masses, which return intermediate T1 signal and high T2 signal. They may have aggressive features, and bony involvement is common.

DSA: The angiographic features vary with lesion type. There is opacification of abnormal vessels in the arterial type and usually no defined parenchymal staining (i.e. tumour blush), except in small vessel (capillary) malformations. Arteriovenous shunting is a variable feature. Venous malformations appear avascular on arteriography or demonstrate minor degrees of tissue staining.

14.3.2 Capillary Malformation

This lesion is also known as ‘port-wine stain’ or naevus flammeus. It is an intradermal capillary or venule malformation. Port-wine stains are common and seen in 0.3% of the population. They are present at birth and usually remain stable in extent, growing with the child. Initially flat and pinkish in colour, the skin may thicken and the colour deepen to purple in adulthood. They are cold to touch and can occur anywhere on the body, though the face and neck are the most common sites.

They are usually an isolated lesion though may be associated Sturge–Weber syndrome (see below). The same somatic genetic abnormality is present in nonsyndromic capillary malformations as in Sturge–Weber syndrome, specifically a c.548G â†’ A mutation in GNAQ on chromosome 9q21 [21]. It is postulated that a somatic mutation in vascular endothelial cells occurs latter in development than in Sturge–Weber syndrome to produce the capillary malformation.

Imaging: This is unnecessary for diagnosis. Angiography, if performed, shows a significant capillary blush and early venous drainage without obvious AV shunts.

Treatment: Embolisation is not recommended because of the risk of causing skin necrosis. Laser treatment is usually the only treatment and surgical removal is rarely undertaken [14].

14.3.3 Lymphatic Malformation

Pure lymphatic malformations have no arterial supply and no venous connections. There are two main pathological architectures: microcystic and macrocystic (i.e. cystic hygroma). These may be combined in mixed-type lesions, sometimes called haemolymphangiomas. They are congenital lesion and present immediately after birth in up to 65% and by the age of 2 years in 80–90% of patients. There are no gender or race associations.

They are well-defined masses of soft consistency, which may contain hard areas. Their size is not positional dependent. They commonly undergo periodic phases of swelling as a result of local infections or inflammation.

Imaging: MRI is useful for defining their extent, particularly the deep margins. Cystic areas return hyperintense signal on T2-weighted sequences and hypointense signal on T1-weighted sequences. There may be fluid debris levels in large cysts and changes due to prior haemorrhage. In microcystic lesions, a more homogeneous pattern of T2 hyperintensity is evident. Flow voids and phleboliths are absent, and enhancement in the margins of cysts is modest (Fig. 14.3).

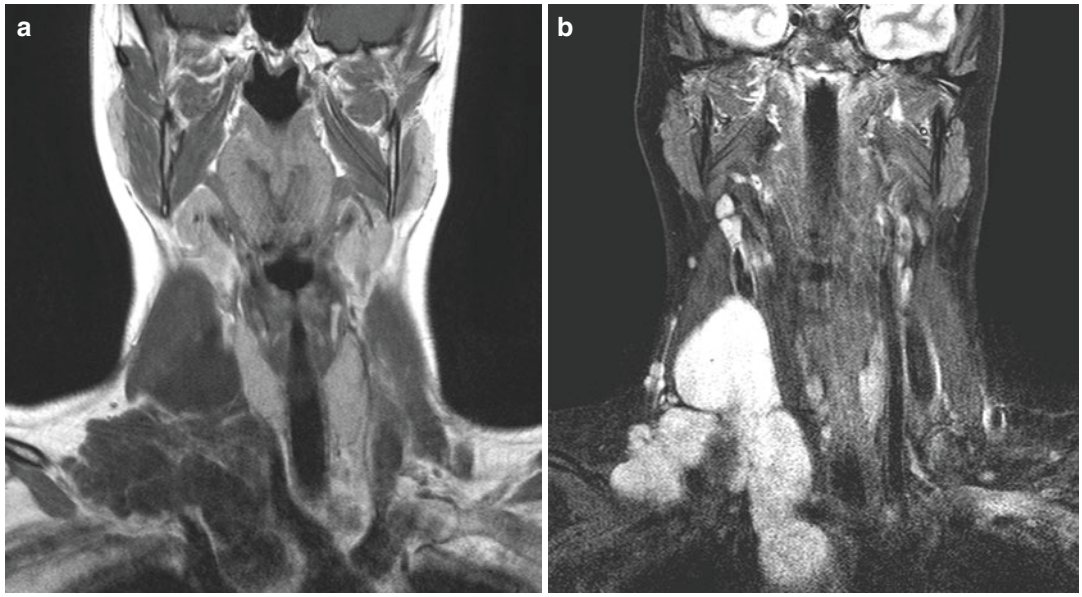

Fig. 14.3 MRI showing a macrocystic lymphatic malformation in the right anterior triangle of the neck. Coronal T1-weighted (**a**) and T2-weighted fat-suppressed (short-time inversion recovery) (b) sequences. These showed the extent of the malformation and how it extends into the upper mediastinum

Treatment: The indications for treatment are functional disability, cosmetic concerns or intracystic bleeding. The microcystic type is treated with antibiotics, corticosteroids or laser therapy, and for the macrocystic type, percutaneous sclerotherapy can be performed using alcohol, sotradecol 1% (sodium tetradecyl sulphate), OK432 or bleomycin [22]. Initial fears over the use of bleomycin for intra-lesion injections have proved unfounded, and in a recent meta-analysis, it was effective in reducing the size of lymphatic malformations in 84% of patients [23]. Occasionally, transarterial treatment may be helpful in mixed lesions, i.e. haemolymphangiomas in which embolisation with particles can shrink the capillary component of the tumour and stabilise the clinical course.

14.3.4 Venous Vascular Malformation

Classically, these lesions develop on the venous side of the arterial tree and have no direct connection with arteries. They therefore do not opacify on catheter angiography. They are more frequent in women (2:1).

Typically, they present as a deep soft tissue mass in late childhood or early adult life. If superficial, they cause a bluish discolouration of the skin or mucous membranes. They are nonpulsatile masses with no bruit. They enlarge in response to an increase in venous pressure (by a Valsalva manoeuvre or placing the head in a dependent position) and can be manually compressed (emptied). This feature is characteristic, and often the young patient has learnt how to enlarge and deflate the mass as a ‘party trick’. They may undergo spontaneous thrombosis and swell with increased pain for a few weeks and occur in association with Klippel–Trénaunay syndrome.

Imaging: MRI/CT: They appear as moderately well-defined masses which contain fluid (i.e. blood). CT will demonstrate phleboliths, which are present in 30% of lesions and ultrasound shows a hypoechogenic mass, which may contain septa. It is useful for controlling percutaneous needle puncture. Catheter angiography is only useful in excluding any arterial supply

but may show slow filling in the late capillary phase. Direct puncture angiography (venography) is the best way to show the extent of the pouch and its drainage. Typically, this outlines a blood-filled lobulated cavity (Fig. 14.4). Determining the drainage pattern is important prior to sclerotherapy. Four patterns were described by Puig et al. [24].

Treatment: Sclerotherapy by direct puncture with absolute alcohol, sodium tetradecyl or other sclerosants is generally considered the best method. Injections may be monitored using ultrasound. It is important for any sclerosant to remain in the lesion and not enter draining veins too quickly. Compression of veins and use of an additional puncture needle as a vent tube help to control injections. Complications caused by extraversation of sclerosants include necrosis of the overlying skin, cranial nerve palsy and the rare idiosyncratic toxic effect of absolute ethanol injections [25]. The use of embolic agents such as Ethibloc (a mixture of zein corn protein, sodium diatrizoate, ouellette oil, oleum papaveris, water and propylene glycol), NBCA and Onyx (ev3) has been described [26].

14.3.5 Arteriovenous Malformation (AVM)

These are a heterogeneous group of high-flow lesions, which will be discussed according to their locations. They are haemodynamically active and may evolve from a latent to an active phase. Progression has been attributed to pregnancy, puberty and trauma.

Their angioarchitectures are highly variable including direct arteriovenous fistulas, arteriovenous malformation with microfistulae and arteriovenous fistulas draining to dilated veins or varices. Treatment is indicated if they cause functional impairment or significant symptoms, particularly bleeding, and management planning (and delivery) requires a multidisciplinary team. Embolisation is generally transarterial with liquid agents (i.e. Onyx or NBCA) or particles (Figs. 14.5, 14.6 and 14.7) [27].

Lesions at specific sites:

Dental arcade AVMs: These are usually of the arterial type with high flow and may bleed spontaneously causing severe blood loss and

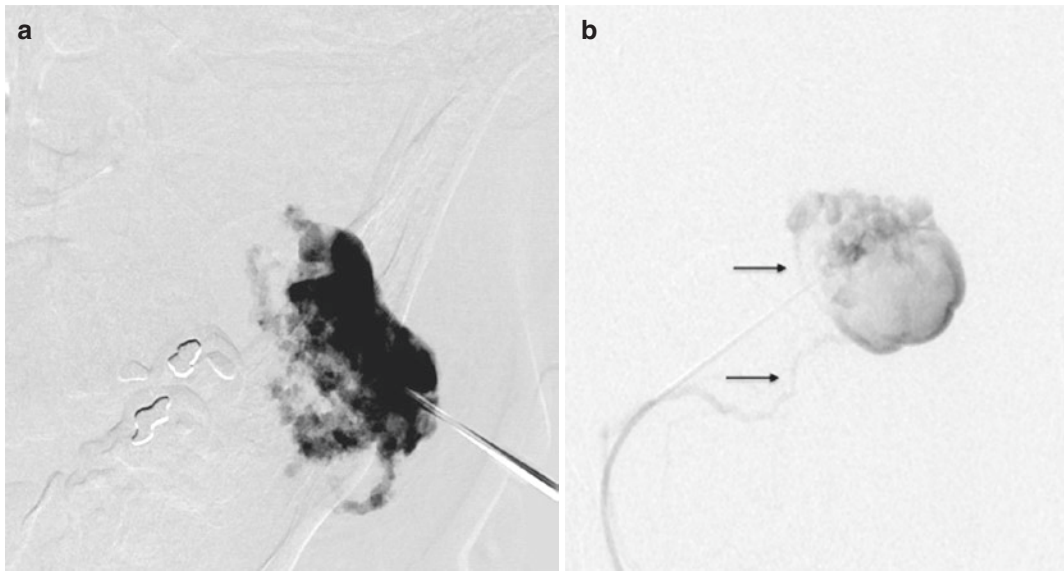

Fig. 14.4 Venous vascular malformations of the cheek. Percutaneous injection of contrast media outlines two lesions. In (**a**) the vascular space is lobulated without apparent draining veins (Puig type1). In (**b**) the lesion drains to a normal size vein (*arrows*) (Puig type 2). Typically, bright-red blood is aspirated after percutaneous puncture performed using Doppler ultrasound imaging

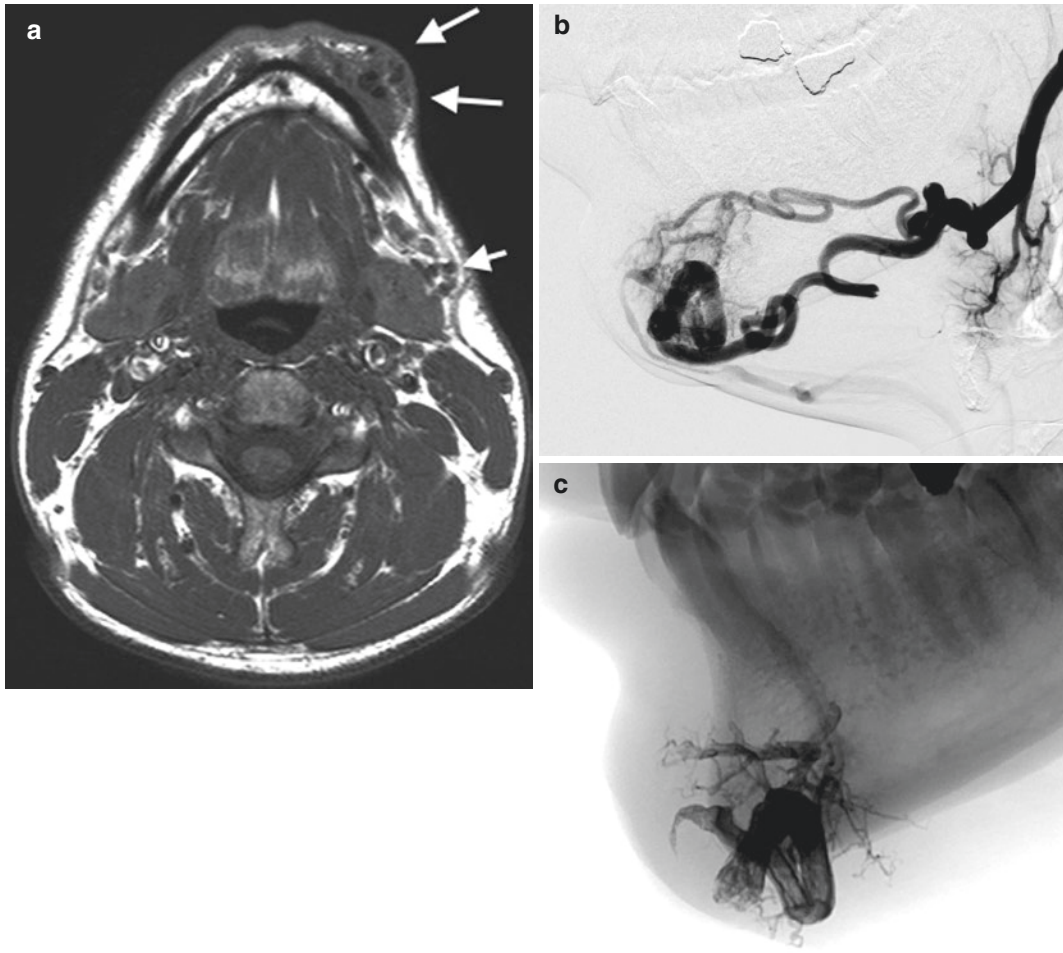

Fig. 14.5 High-flow vascular arteriovenous malformation of the chin. T1-weighted MRI (**a**) shows enlarged vessels within a subcutaneous mass (*arrows*) and an enlarged facial artery (*single arrow*). Digital subtraction angiogram (**b**) performed after injection of the hypertrophied facial artery. The malformation was treated by transarterial injection of Onyx (**c**)

require emergency treatment. Typically, they present with pain, bruit, superficial ulceration or infection. Embolisation with particles is used to control symptoms or as a pre-operative procedure prior to resection. Radical surgery should, ideally, not be performed until adulthood, and growth has finished.

Salivary gland AVMs: These are rare and correspond to the arterial-type malformation. Embolisation, if required, is usually performed with particles.

Face and scalp AVMs: These lesions can be confused with dural AVMs because their arterial supply may arise from dural arteries, e.g. branches of the middle meningeal or occipital arteries. The discriminating feature is the venous drainage; thus, cutaneous lesions will drain to subcutaneous veins, while dural lesions will drain to the intracranial dural sinuses. The mastoid region is especially difficult because branches of the ascending pharyngeal artery supply dural and scalp lesions in this location. Therefore, transosseous connections to intracranial vessels should be looked for.

Ear AVMs: These are usually high-flow malformations. The ear may be overgrown, and there may be a history of local trauma. Embolisation

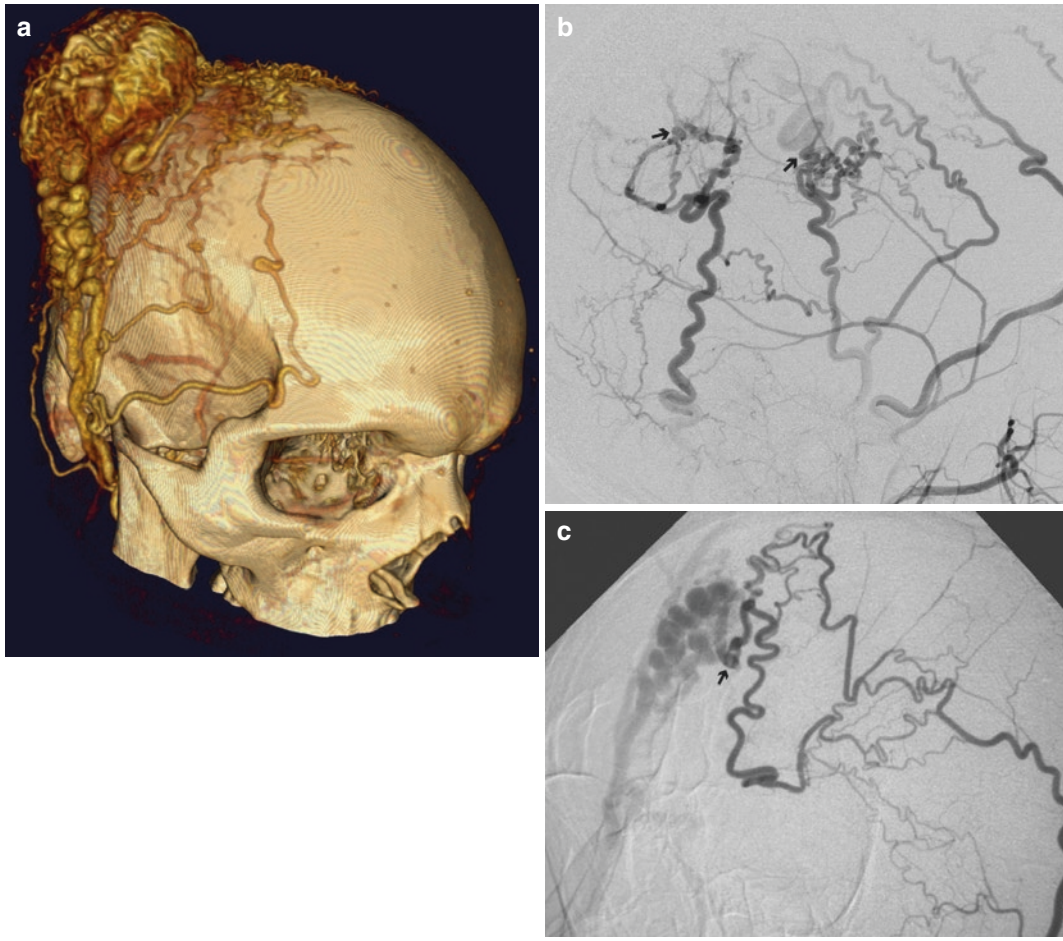

Fig. 14.6 Arteriovenous malformation of the scalp demonstrated on reconstructed CT angiogram (**a**) and digital subtraction angiogram (**b**). The malformation has produced a substantial subcutaneous mass, which is supplied by hypertrophied scalp arteries with areas of direct arteriovenous shunting. The latter can be seen on the angiogram (*arrows*) performed during the arterial phase of a selective injection to the *right* superficial temporal artery. In another patient (**c**) an arteriovenous fistula is shown on the forehead (*single arrow*) (Note how the arterial feeders form multiple pedicles)

can be curative or used to aid surgical resection. There is a risk of skin necrosis after embolisation, and precise intranidal injection of liquid embolic agents is the treatment of choice.

Eyelid AVMs: Embolisation is potentially dangerous because of the proximity of the arterial supply to the eye. Treatment should be reserved for symptomatic lesions. Any intracranial extension needs to be excluded on pretreatment imaging.

Muscle AVMs: These are usually arterial- or capillary-type lesions but can also be venous or capillary/venous. They typically present in young adults and mainly involve the muscles of mastication, particularly the masseter. They cause pain and periodic swelling during eating. Treatment is by embolisation, which may be only palliative.

14.3.6 Associated Syndromes

The lesions described above can occur as part of a generalised abnormality of blood vessels. In particular with:

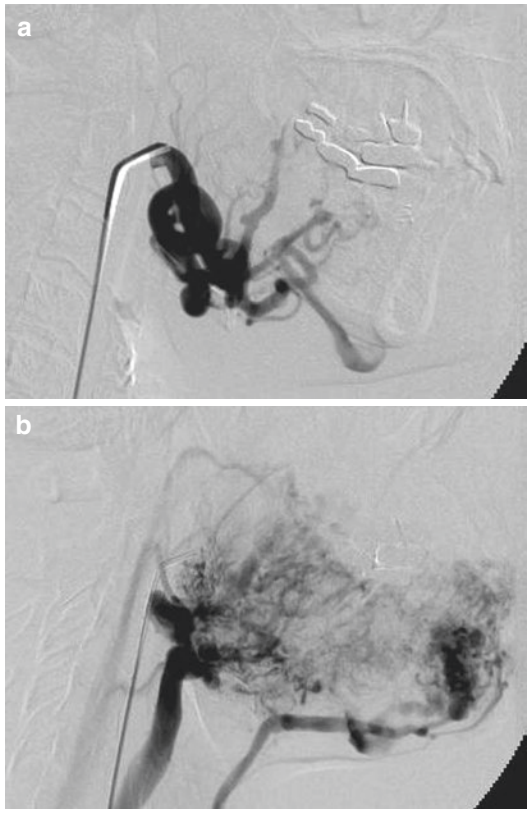

Fig. 14.7 Arteriovenous malformation of the cheek. Lateral views of a digital subtraction angiogram performed by injection of the facial artery. In the arterial phase (**a**), the hypertrophied arteries are seen, and in the venous phase (**b**), contrast is seen filling large irregular vessels within the malformation as well as a series of draining veins. This lesion was treated by presurgical embolisation and resection

Sturge–Weber syndrome (*Encephalotrigeminal angiomatosis*): Only 2–6% of port-wine stains are associated with Sturge–Weber syndrome, but this rises to 26% if they occur in the cutaneous distribution of the trigeminal nerve. In Sturge–Weber syndrome, lesions involve the trigeminal cutaneous territory and are evident by the age of 2 years. Other features are epilepsy, glaucoma, astigmatism, choroidal vascular abnormalities, hemispheric venous malformation with cortical atrophy and cortical calcification. The cutaneous lesions are histologically similar to the capillary malformations described above, with which they share a genetic aetiology.

Telangiectasias and Rendu–Osler–Weber Disease: This is a rare autosomal dominant hereditary condition that most often comes to the attention of the endovascular therapist because of epistaxis. Cutaneous telangiectasias can be treated by laser or electrocoagulation therapy. Embolisation for epistaxis will be discussed in Tutorial 16 and in this condition it is essentially palliative. It is performed with particles.

14.4 Other Vascular Lesions

14.4.1 Sinus Pericranii

This condition consists of a series of abnormal large connection between cerebral veins or sinuses and varicosed scalp veins. The latter produces a compressible scalp swelling, which enlarges under the influence of gravity and during excursion. The mass has a 'boggy' feel which is exaggerated by underlying skull defects through which enlarged scalp veins connect with a dura sinus (usually the superior sagittal sinus). There is no trill or skin discolouration. The condition was described in the nineteenth century and given its current name by Stromeyer in 1850 [28].

The aetiology is unknown. It has been attributed to trauma, congenital and spontaneous causes. In a substantial review of the literature, Akram et al. collected reports of 115 cases reported since 1850 and summarised the possible cause as congenital (arising from an angioma coexisting with another vascular anomaly), secondary to local trauma, or developing spontaneously as a collateral venous channel [29]. There is no gender bias.

Imaging: CT will show the defect or usually multiple defects in the calvarium, and MRI normal cerebral development. CTA may localise the vascular channels to bone defects and DSA will-exclude abnormal arteriovenous connection and aneurysms. A direct puncture venography will show the connections to intracranial veins (Fig. 14.8).

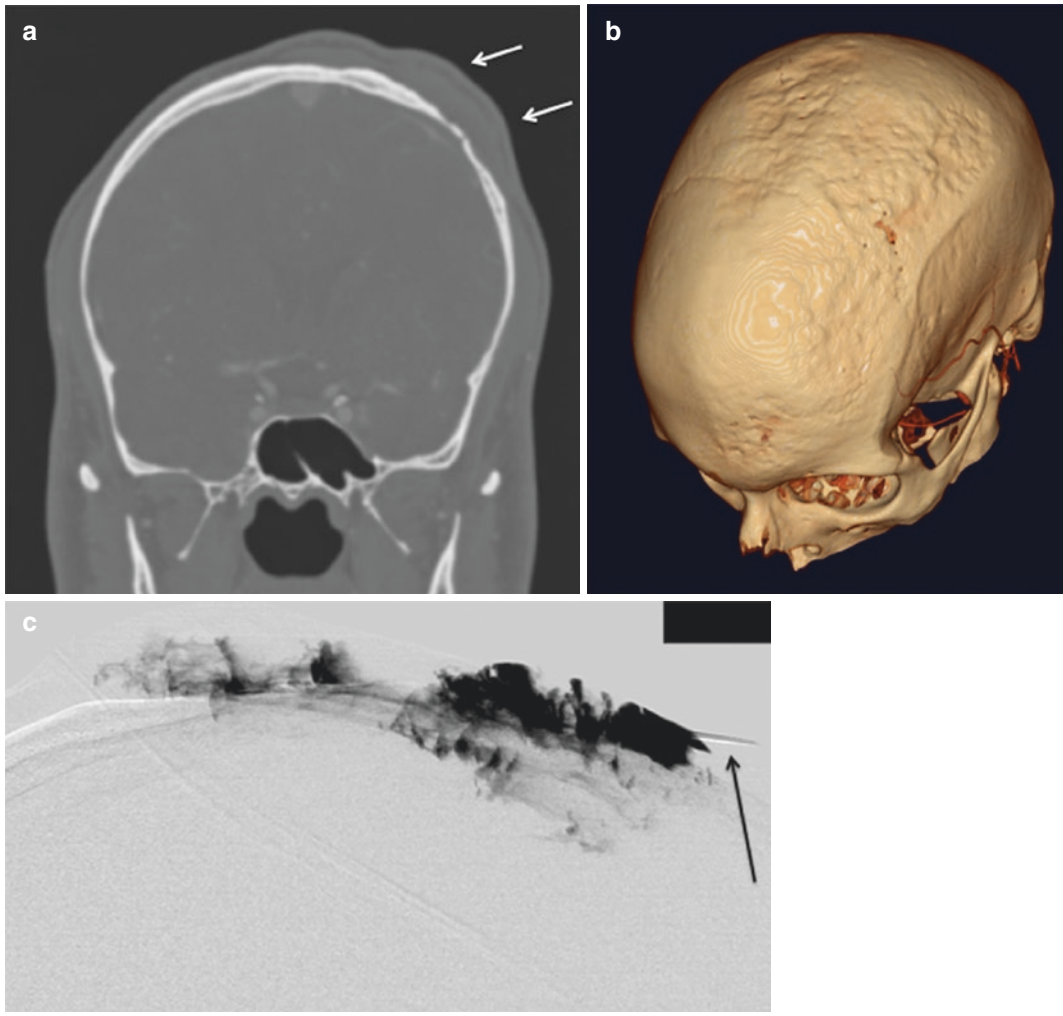

Fig. 14.8 Sinus Pericranii. Coronal enhanced CT (**a**) shows thinning of the *left* side of the skull under areas of soft tissue swelling (*white arrows*). A reconstructed CT image **(b)** shows scalloping and defects in the skull. In **(c)** a needle (*arrow*) has been inserted into large scalp veins and contrast fills intra- and extra-cranial veins which connect via enlarged emissary channels

Treatment: The natural history is uncertain and treatment on cosmetic grounds needs to be considered carefully. A concern is the risk of uncontrollable bleeding or air embolism in the event of scalp trauma. Embolisation of the large scalp veins should only be performed if angiograph demonstrates alternative routes for cerebral venous drainage. It may be difficult to control injected liquid embolic agents for embolisation, which may be performed to enable surgical resection.

14.4.2 Thyroid Gland Tumours

Malignant thyroid tumours are highly vascular. They are, however, rarely referred for pre-resection embolisation. They recruit their arterial supply from the superior and inferior thyroid arteries, and preoperative embolisation is performed with particles, after the patient's thyroid function has been assessed. Embolisation can be performed for palliation and prior to surgical resection. Effective embolisation causes gland

infarction and rises in serum levels of thyroglobulin (Tg). Surgery should therefore be performed soon (i.e. within 24–36 h) after embolisation with particles [30].

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Preamble

Tumour embolisation was first reported in 1974 by Hekster et al. [1] who used Gelfoam to embolise a large convexity meningioma. Embolisation has since been widely used for pre-resection devascularisation of cranial tumours, though with varying degrees of popularity. Quantifying its value as an adjuvant procedure requires assessing both subjective and objective criteria. The former largely depends on the opinion of particular surgeons, so its use in a particular hospital varies with their opinion of the value it adds to surgery. Objective criteria depend on showing benefits such as decreases in operative blood loss (measured from swab counts, volumes of blood transfusions and falls in plasma haemoglobin levels), reductions in the length of operations and cure rates [2, 3].

In this tutorial, a general protocol for preoperative tumour embolisation will be presented and

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then its application in specific pathologies. Tumour embolisation has relevance in all branches of oncology, but only pathologies, the reader is likely to treat, will be covered in detail. This tutorial outlines a generic template that can be adapted when describing embolisation of particular conditions with the intention of encouraging students to describe (and think about) procedures and their patient's management in a standard way. It is hoped that they will develop a personal routine to ensure that all appropriate precautions are taken so that procedures are performed as safely as possible. Like many seemingly easy procedures, tumour embolisation is not difficult to perform but difficult to perform well.

Table 15.1 Summary of steps involved in tumour embolisation procedures

Generic protocol for endovascular procedures
1. Indications for endovascular treatment
2. Aims of treatment (preoperative, adjuvant, pallative)
3. Risks and benefits of treatment
4. Preprocedure assessment
(a) Imaging assessments
(b) Preprocedural review and discussion
(c) Patient examination
(d) Anaesthetic assessment
(e) Preprocedure drug treatments
(f) Informed consent
5. Procedure technique
(a) Angiographic evaluation
(b) Choice of therapeutic agent or device
(c) Technique for endovascular delivery
(d) Postoperative care
6. Follow-up

15.1 Protocol for Embolisation of Tumours

Endovascular treatment of neoplasms can involve the selective delivery of chemotherapy or embolic agents. Only the latter, i.e. embolisation, will be considered here, though several of the principles and techniques involved in the delivery of chemotherapeutic agents are similar. The process of embolisation can be divided into those steps common to the treatment of any tumour type and those specific to a particular type or location. The general principles of embolisation will be described in this section and are summarised in Table 15.1.

15.1.1 Indications for Embolisation

- The selection of patients to be offered tumour embolisation should be the result of a multidisciplinary team discussion. Embolisation is performed for hypervascular tumours. The histological types of the cranium and skull base include meningioma, haemangiopericytoma, paraganglioma and juvenile nasopharyngeal angiofibroma. Cerebral and spinal haemangioblastoma and a range of other spinal tumours may also be considered for embolisation. These include haemangioma, aneurysmal bone cyst and giant cell tumours. Less commonly treated lesions are schwannoma, esthesioneuroblastoma and metastases. Chordoma, chondrosarcoma and other primary bone tumours are rarely suitable for embolisation.

The situations when embolisation is offered are:

- Preoperative embolisation performed prior to surgery to resect or debulk tumour.
- To facilitate other adjuvant therapies, i.e. embolisation performed to stabilise or shrink inoperable tumours for possible adjuvant radiotherapy or chemotherapy treatments.
- For relief of symptoms, i.e. palliative treatment of patients with surgically inoperable tumours. Common situations are when patients have medical comorbidity, which precludes radical surgery, or when the risk of damage to vital structures is unacceptable.
- For treatment of recurrent lesions, when surgery is not possible or appropriate.

15.1.2 Aims of Embolisation

The aims of embolisation should be defined for each patient. If it is to be performed primarily to facilitate complete surgical resection, the procedure plan may include the following aims:

- To devascularise tumour by obstruction of small vessels within tumour tissue.
- To occlude sources of surgically inaccessible blood supply.
- To occlude non-tumour vessels which might need ligation during planned surgery. Endovascular ligation is safer because functional testing and assessments of collateral blood supply can be performed by test occlusions, e.g. the sigmoid sinus, to gain access to the petrous temporal bone.

15.1.3 Risks and Benefits

The risks and benefits of the intended embolisation have to be presented to the patient as part of the process of obtaining their informed consent. In the pre-surgical resection situation, the intention of embolisation is to facilitate another procedure. Since it has its own potential of causing complications, these are in addition to those of the planned surgery, so the combined procedural risk must be considered. This should be less than that of surgery without embolisation or if greater, provide some additional benefit for the patient (e.g. reduce the rate of tumour recurrence after surgery). In practice, this means estimating the risks and benefits of surgery and embolisation together.

For transarterial embolisation, some complications are common (generic) to all procedures and some specific to tumour type and location. The generic potential adverse events include inadvertent spread of embolic agents to sensitive normal tissues. These may cause new neurological deficits due to cerebral infarction or cranial nerve damage. The nature of any resulting disability depends on the specific tumour's location, for example, blindness can be caused by particles refluxing to the retina during embolisation in the anterior cranium via the middle meningeal artery. Other complications, though generic, are more likely to cause problems because of the tumour type, e.g. highly hypervascular lesions are liable to swell after effective embolisation, and this may exacerbate compression symptoms. Add to this are the chance of postembolisation bleeding (about 2%) and the risks of general anaesthesia (if employed), use of radiographic contrast media and cranial catheter angiography and there is a substantial list of things that could go wrong.

Finally, to accurately quantify the risk of a planned procedure, individual operators should know their own rates for success and complications. Thus, deciding whether to recommend pre-surgical embolisation to a patient requires a detailed estimation of two sets of risks. So the process, of balancing risk against the added value of embolisation in the preoperative situation, is completely dependent on multidisciplinary discussion.

15.1.4 Preprocedure Assessment

The following steps should be part of the preparation for any embolisation procedure:

(a) Planar imaging assessments (CT or MRI): These will establish the target tumour's location (from which its blood supply can be inferred) and extent (including evidence of invasion of important vascular structures, e.g. the internal carotid artery or dural venous sinuses). CT is important to show bone invasion or destruction. Tumour enhancement is generally proportional to blood supply, but this assessment depends on obtaining images soon after the administration of contrast media. Delayed imaging may show pronounced enhancement in relatively avascular tumours.
(b) Preprocedural review and discussion with the operating surgeon: The 'rules of engagement' are that preoperative embolisation should assist and therefore reduce the overall risk of tumour resection. Reviewing imaging and defining a combined treatment plan is the best way of achieving this.
(c) Patient examination: There is no substitute for a documented pre-embolisation examination of abnormal physical finding.
(d) Anaesthetic assessment: Procedures are generally best performed under general anaesthesia. Preliminary temporary artery occlusion and testing neurological function must be performed under local anaesthesia (with an anaesthetist monitoring the patient)

and then general anaesthesia administered for embolisation.

(e) Preprocedure drug treatments: Pretreatment with corticosteroids is advocated for large tumours and those causing symptoms of neural compression. Tumours may cause systemic effects that require medical treatment prior to embolisation, e.g. beta-blockers for patients with paragangliomas.

(f) Informed consent: This is the opportunity to explain the treatment plan and to answer patient's questions about the procedure.

15.1.5 Procedure Technique

The stated aim of this book is not to be a manual of endovascular treatment procedures, and so, generally, it avoids technical descriptions. This tutorial is an exception, and the steps involved in an embolisation procedure will be described in detail, as follows:

(a) Angiographic evaluation: This is intended to confirm the blood supply of the tumour, to assess its internal vascular pattern and to exclude coincidental vascular disease. The assessment will concentrate on identifying connections and anastomoses between the arteries supplying the tumour and adjacent normal vessels. The intention is to anticipate dangerous extracranial to intracranial pathways and potential routes of spread of embolic materials. The assessment should also include any likely blood supply to cranial nerves.

In situations when potentially dangerous anastomoses are identified, consideration should be given to temporary or permanent vessel occlusion to protect territories into which embolic agents may inadvertently spread. The order in which multiple pedicles are embolised may also be an important consideration. For example, embolisation with particles in the distal internal maxillary artery (IMA) should be performed before intended occlusion of the internal carotid artery (ICA) since this will reduce the chance of particles spreading to the orbit.

(b) Choice of embolic agents (see also Tutorial 18): The goal of tumour embolisation is obliteration of the vascular bed. If occlusion of feeding arteries occurs proximal to the tumour bed (i.e. at small artery/arteriole level), revascularisation can occur relatively quickly via newly recruited collaterals. This principle dictates the choice of embolic agent. Tumour embolisation is usually a presurgery procedure, so recanalisation is less of a problem and embolisation is usually performed with particles.

(i) Particles can be absorbable or non-absorbable. Examples of absorbable agents are microfibrillary collagen or fragments of autologous blood clot. They are used for temporary vessel occlusion. Non-absorbable particles unfortunately seldom produce permanent vessel occlusions. Examples are polyvinyl alcohol (PVA) particles, trisacryl gelatin microspheres and silicon spheres. Their size determines the likely effect of injections. The smaller the vessels occluded (i.e. more distal in a vascular network), the more effective the embolisation. This means that smaller particles are more likely to devitalise tumour causing tissue necrosis, but they are also more likely to penetrate any potential anastomosis. Thus, the choice of particle size is a compromise because:

Very small particles, i.e. 50 μm, should penetrate to vessels of 40–60 μm diameter. But using smaller particles increases the risk of their passing through low-flow arteriovenous shunts, which are commonly found in tumour circulations.

Larger particles, i.e. >140 μm, increase the risk of ischaemia in normal tissue because they occlude larger proximal arteries which may additionally supply adjacent tissues.

Very large particles, i.e. >400 μm, are more likely to clump together and lodge in pedicles proximal to the tumour bed. This risks encouraging recruitment of a collateral blood supply. The lumen of

arterioles forming the vasa nervorum of cranial nerves is <150 μm, and using larger particles is assumed to reduce the risk of cranial nerve damage, but at the expense of poorer penetration of the tumour vascular bed.

(ii) Liquids are either occlusive or sclerosive to blood vessels. Examples are liquids that solidify after injection, e.g. n-butyl cyanoacrylate (NBCA) and ethylene vinyl alcohol copolymers (Onyx, ev3), PHIL (MicroVention) SQUID (Emboflu) or sclerosants, e.g. absolute alcohol, sodium tetradecyl sulphate. The latter are only used in situations where flow arrest can be guaranteed and tumour necrosis tolerated. NBCA or Onyx is more penetrating than particles and likely to be more effective and permanent in their effect. They may be injected by direct puncture of tumour vessels or via endovascular catheters.

(iii) Balloons or coils are used for temporary or permanent large vessel occlusions.

(c) Technique for endovascular delivery of embolic agents: The safest route of embolisation should be selected and, after identifying a suitable vascular pedicle for embolisation, the microcatheter tip placed as far distally as possible. Vasospasm should be avoided by careful catheter/guidewire manipulation or pretreatment with vasodilators (spasm prevents particle penetration of the vascular bed and increases the risk of reflux). If the catheter is positioned close to a dangerous anastomosis, balloon protection or preliminary occlusion of the anastomosis should be considered. Once the catheter is in position, test injections of contrast should be used to assess blood flow.

There are two options at this stage:

(i) The first method is to inject the particles or liquids into blood flowing to the tumour under fluoroscopic control. Particles are thoroughly mixed with contrast media and repeatedly agitated to prevent them clumping together. Using NBCA, a dilute (e.g. 20%) mixture with ethiodised oil (Lipiodol) is used for opacification and tantalum powder is premixed with Onyx. After pre-filling of the microcatheter with the appropriate solution, e.g. glucose, dimethyl sulphoxide (see Tutorial 18), liquid agents are slowly injected. The injected speed is judged to coincide with the ambient blood flow. Embolisation should stop when flow in the pedicle is significantly reduced but before it stops completely (to avoid reflux).

(ii) The second technique is to inject with flow arrest. The microcatheter can be wedged in the pedicle or a balloon inflated to occlude the feeding artery during the injection. This method prevents reflux but has disadvantages. It is more likely to cause vasospasm, the increased injection pressures may open distal collaterals or previously unidentified connections and the loss of antegrade blood flow decreases the depth of penetration of particles into the tumour vascular bed. Using Onyx, another option is to allow a plug of material to build up around the microcatheter tip so as to impede reflux during sustained injections to fill the tumour bed (plug and push technique). Detachable tip microcatheter and double lumen balloons have been developed to use in this technique.

15.1.6 Postembolisation Care

The timing of surgery after preoperative embolisation will dictate the course of the patient's postembolisation care. The interval for embolisation to be effective is >24 h, but some teams prefer to operate immediately after embolisation because of the possibility of tumour bleeding. Others prefer to operate wait 8–10 days when swelling has subsided and surgery easier but by then recanalisation may have started. A compromise recommendation is that resections are made 1–8 days after embolisation [4]. With these

factors in mind, the following steps may apply to the care of every patient:

- Reversal of anticoagulation: Generally, tumour embolisation procedures are performed without systemic anticoagulation and with only standard doses of heparin in catheter flushing solutions. Anticoagulation is required if temporary balloon occlusion and functional testing are performed and should be reversed at the end of the procedure, because of the risk of secondary haemorrhage of an infarcted tumour.
- Corticosteroids: These are prescribed to reduce tumour swelling and any vasogenic oedema in the adjacent brain. If the latter is evident on CT or MRI, patients should be prescribed steroids prior to embolisation. Prophylaxis with antiepileptic drugs is generally not necessary if there is no history of seizures.
- Analgesia: Consideration should be given to the likely amount of postprocedure pain and analgesics prescribed appropriately. An oral nonsteroidal analgesic is usually sufficient. Antiemetic drugs may also be helpful.
- Bed rest: Patients should be kept in bed with postoperative monitoring of vital signs for 48 h and longer if large artery occlusion is performed. Follow-up imaging usually shows shrinkage of tumours over a 2–6-week period, but symptoms may be exacerbated in the first 24–48 h after embolisation due to tumour swelling and dramatically so if intratumoural bleeding occurs.
- Follow-up: A protocol for review after leaving hospital may include review interviews and follow-up imaging. Outpatient review is important in some circumstances to diagnose late adverse sequelae; it also gives the patient a chance to ask questions and to plan for the future. It is important to ensure they are safe to drive and an opportunity for endovascular therapists will get direct feedback on the efficacy of their treatments (Table 15.1).

15.2 Meningioma

These tumours, which are thought to originate from arachnoid cap cells found in the arachnoids granulations, were first described in 1614 by Felix Plater[1] [5]. They are usually intracranial but also occur in the spine and orbit. They have occasionally been found elsewhere in the body.

15.2.1 Epidemiology

They constitute 13–18% of all primary intracranial tumours and 20–35% of intraspinal tumours. They occur at any age but typically affect adults between the ages of 20 and 60 years with a peak incidence at 45 years. In adults, intracranial meningiomas are more frequent in women (2:1). They are usually solitary but may be multiple. Multiple lesions (i.e. meningiomatous) occur in neurofibromatosis type II (abnormality of chromosome 22). They are late sequelae of radiotherapy.

15.2.2 Pathology

Meningiomas are well-circumscribed globular extra-axial tumours, which are well demarcated from the brain. They may compress adjacent structures but do not infiltrate neural tissue (with the exception of the sarcomatous type), though they may invade dual sinuses and erode bone and bone marrow and may extend through the outer table of skull base into extracranial tissues. Meningiomas that spread along the dura are described as ‘en plaque’. They commonly provoke vasogenic oedema in the surrounding brain, which may cause additional symptomatic mass effect.

The most frequent intracranial sites are parasagittal convexity, falx, sphenoid ridge, cerebellopontine angle, clivus and foramen

[1] Felix Plater (or Platter) (1536–1614) was a Swiss physician and professor in Basel who classified psychiatric diseases, described the basis of Dupuytren’s contracture and made the first description of meningioma.

magnum. The tuberculun sellae and olfactory groove are recognised sites at which tumours cause characteristic syndromes. Rarely, they occur without apparent attachment to dura, in the depths of major fissures or within the ventricles.

15.2.3 Histological Grading

There are three WHO grades of meningioma: Grade 1, benign; Grade 2, atypical; and Grade 3, anaplastic. These are independent of the traditional histological classifications: meningothelial, angioblastic (or haemangiopericytoma), fibroblastic, transitional sarcomatous and psammomatous types. The angioblastic type exhibits the most malignant behaviour. Its incidence is higher in men (4:1), and it occurs in younger patients (mean age 35 years). It represents about 2% of all meningiomas and may have a transpial blood supply from cortical arteries exhibiting a distinctive pattern of small corkscrew tumour vessels. The angioblastic type and the transitional type are more vascular than other types. Psammomatous meningiomas are typically hypovascular and densely calcified.

15.2.4 Clinical Presentation

Neurological symptoms are related to involvement of local structures, e.g. anosmia caused by an olfactory groove tumour. Raised intracranial pressure causes non-localising symptoms and signs, such as headache, visual disturbances, dementia and focal seizures.

15.2.5 Indications for Endovascular Treatment

These vary from centre to centre, but generally preoperative embolisation is performed for large, highly vascular tumours supplied by branches of the external carotid artery (especially those involving the skull base when surgical access to the supplying arteries is difficult) [6].

15.2.6 Aims of Treatment

- To facilitate surgery, improve outcomes and decrease morbidity.
- To reduce recurrence rates by embolisation of tumour spread at dual attachments.
- Palliative treatment for inoperable recurrent tumour.
- Curative embolisation is occasionally performed as sole therapy to stabilise and reduce tumour size.

15.2.7 Risks and Benefits

Benefits: The best available treatment is total surgical excision. The value of preoperative embolisation of meningiomas of the convexity is controversial since dural arteries are usually accessible at craniotomy [7].

But when there is bilateral supply, prior embolisation may reduce the extent of the surgical exposure required, and pretreatment by embolisation may reduce the size of large lesions to assist surgical manipulation. It has been shown to reduce requirements for blood transfusion and the length of operations [2, 8].

Complications: The hazards of embolisation are ischaemia or infarction of adjacent tissues and inadvertent spread of embolic particles, e.g. to the retina (causing visual loss) or shunting to the lungs (causing haemoptysis and lung damage). These complications can be divided into:

Minor adverse events: These principally involve tumour swelling causing local pain. Additionally, injections of particles in extra-cranial arteries can cause skin or mucosal necrosis, alopecia, delayed wound healing or pain due to muscle ischaemia. Trismus due to muscle ischaemia is caused by spread of particles to the muscles of mastication during after embolisation in internal maxillary artery branches. It is common and affects 20–30% of patients. Symptoms due to tissue swelling and oedema can be reduced by the routine postoperative prescription of corticosteroids.

Major adverse events: These involve visual loss and cranial nerve injury, especially VII and

XII cranial nerve palsies. Reported incidences vary from 1.6% to 9% [9]. Complications occur most frequently when small particles (e.g. 50 μm) are used for embolisation in the meningohypophyseal trunk, middle meningeal artery, accessory meningeal artery and the ascending pharyngeal artery [9]. The majority of deficits caused by embolisation particles recover after 3–6 months. Haemorrhage secondary to tumour infarction following embolisation has been reported after 3–5% of procedures [10, 11]. It occurred after 5% of procedures in a series of 198 patients and 2 patients died after emergency surgery [11]. Patients should be carefully monitored in the first few days after procedures [12].

15.2.8 Preprocedure Assessment

Imaging: On CT, meningioma may be hyperdense (55%) or calcified (15%). Enhancement occurs after IV contrast injection in the majority and usually reflects a hypervascular lesion. Bone erosion or expansion is best demonstrated on CT, but MRI is better for diagnosing the extent of soft tissue components in skull base lesions. Generally, the histological variants cannot be distinguished radiologically, but calcification is more common in the fibroblastic and transitional subtypes, and dense calcification indicates a psammomatous type. Marked hypervascularity on imaging usually indicates haemangiopericytoma, i.e. angioblastic subtype.

Angiography is usually only performed prior to embolisation. The angioarchitecture is characterised by supply from dural arteries and varies from a radiating pattern of parallel arteries to dilated irregular tortuous arteries. An early 'blush' with contrast staining within the tumour is characteristic, and the 'blush' persists into the late venous phase. Pooling of contrast within the larger vessels is seen, and early filling of veins (i.e. shunting) is suggestive of a more aggressive tumour [13]. The patency of adjacent major dural sinuses should be assessed in the venous phase (Fig. 15.1).

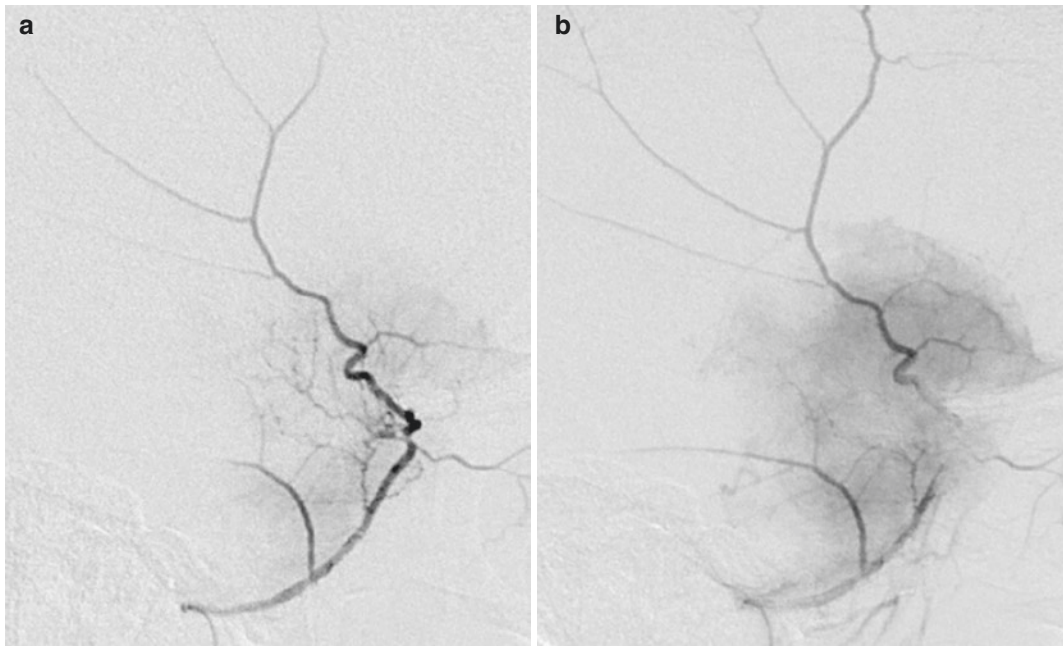

Fig. 15.1 Meningioma of the sphenoid bone. Selective angiography of the middle meningeal artery shows intratumour arteries of decreasing size (a) and late venous contrast retention (b). The angioarchitecture of meningiomas ranges from very regular parallel arteries to an irregular tortuous pattern. This example shows both types of arteries

Clinical assessment: A standard preprocedure examination and assessment is mandated.

Preprocedure drugs: Symptomatic patients should be treated with corticosteroids for several days prior to embolisation to reduce the extent of swelling in the adjacent brain caused by vasogenic oedema. Treatment of asymptomatic patients should also be considered if oedema is extensive on imaging. Antiepileptic drugs should be prescribed if there is a history of seizures.

15.2.9 Embolisation Technique

(a) Appropriate control angiography followed by superselective catheterisation of target meningeal arteries is performed to look for dangerous anastomosis and assess the extent of tumour supply: The angiographic protocol is based on the tumour's location and its likely source of arterial blood supply. These are presented in Table 15.2. Special attention should be given during particle embolisation in the middle meningeal artery (MMA) to prevent particles refluxing into the superficial temporal artery (STA), into the sphenopalatine artery or into potential sites of external carotid artery (ECA) to ICA and ECA to ophthalmic artery (OphA) anastomoses. The arteries that supply cranial nerves are described in Table 7.1 (Tutorial 7). If embolisation is to be performed in these arteries or where there are dangerous anastomoses, larger particles (>150 μm) should be used.

(b) Choice of embolic agent: Polyvinyl alcohol (PVA) or acrylic particles are most often used. Dilute concentrations of NBCA and Onyx may be appropriate if a suitable catheter tip position can be achieved.

(c) Technique for delivery: Free-flow particle embolisation is usually performed under x-ray fluoroscopy control until a persistent blush is seen in the tumour. The proximal MMA may be excluded with a Gelfoam plug to reduce bleeding at the foramen spinosum during surgery. When embolisation is performed in cutaneous branches of the scalp, e.g. STA, care should be taken not to force emboli into small arteries (by using a wedged catheter) as they may occlude normal scalp vessels and impair postoperative healing. Injections of liquid embolic agents are technically more difficult and the objective is to confine the material to intra-tumoural arteries.

Table 15.2 Dural arterial[a] supply to meningiomas at different locations

Location		Principal supply	Secondary supply
Parasagittal, convexity and falx		MMA	Artery of falx (anterior ethmoidal artery)
Parasella and middle cranial fossa		MMA	Accessory meningeal artery
		ILT	Recurrent meningeal artery (OphA)
Frontobasal (sphenoid wing, planum sphenoidale, olfactory groove)		Posterior ethmoidal artery	Anterior ethmoidal artery
		ILT (anteromedial branch)	Artery of foramen rotundum (IMA)
		MMA	Recurrent meningeal artery
Tentorium	Anterior 1/3	Marginal and basal tentorium arteries, petrosquamous artery of MMA	ILT (posterior branch)
	Posterior 2/3	OA (transmastoid branch)	Artery of falx cerebelli
		MMA	Posterior meningeal artery (VA)
Posterior fossa	Cerebellopontine angle	Jugular artery	Lateral clival artery
		OA (transmastoid branch)	Hypoglossal artery
			Subarcuate artery (AICA)
	Clivus/foramen magnum	Medial and lateral clival arteries	Hypoglossal artery
		Anterior meningeal artery (VA)	PICA (postmeningeal branch)
		Posterior meningeal artery (VA)	

[a]NB. Recruited supply from transosseous (scalp arteries) and transpial (cerebral arteries) has not been included (see text for explanation of abbreviations)

(d) Bed rest and neurological observations for 24–48 h with adequate access to analgesic medication: A careful assessment of the patient's vision should be made after embolisation in IMA branches.
(e) Timing of surgery: No formal studies have been carried out to determine the best time for surgical excision following meningioma embolisation. It appears advisable to wait 12–24 h as further thrombosis and reduction in mass effect may occur, but a delay beyond 7–10 days risks allowing time for collateral blood supply to develop.

15.3 Juvenile Nasopharyngeal Angiofibroma

Juvenile nasopharyngeal angiofibroma (JNA) is a benign but locally invasive tumour of the nasopharynx. They are rare lesions, representing only 0.5% of head and neck tumours, which almost always originate in the sphenopalatine fossa.

15.3.1 Demography, Epidemiology and Aetiology

JNAs occur predominantly in young males and present during puberty, though about 20% of tumours are diagnosed in patients over the age of 20 years. Case reports have described the tumour in women, but this is so extremely rare that genetic testing has been advised. There is no racial predominance, but higher incidences have been reported in Egypt, India, Kenya and Southeast Asia [9, 14].

Tumour growth is influenced by sex hormones. Reductions in tumour size have been observed after exogenous oestrogen therapy and increases in size during testosterone treatment. No abnormal levels of hormones are usually detectable in patients, and the tumour's sensitivity to hormone levels is thought to be related to their development. There are histological similarities in the appearance of cells forming the vascular spaces of JNAs and genital erectile tissue and nasal mucosa cells. The cells of the nasal mucosa are assumed to develop into muscularised vascular channels secondary to testosterone stimulation and oestrogen hypersensitivity.

There is a genetic link between JNA and familial adenomatous polyposis, in which mutations of the adenomatous polyposis coli (APC) gene occur. This gene on chromosome 5q regulates the β-catenin regulated Wnt signalling pathway which influences cell-to-cell adhesion. Mutations of the APC gene have also been found in patients with JNA [15] and other tumours of mesenchymal origin such as desmoid tumours [16].

15.3.2 Pathology and Natural History

The origin and behaviour of this tumour is stereotypic. The macroscopic appearance is a nonencapsulated tumour mass in the region of the sphenopalatine foramen in the supralateral part of the nasal cavity. The site of origin may vary slightly, with the tumour arising near the vomer, from the pharyngeal roof or from the pterygoid plates. The tumour base is attached to one of these osseous structures. It does not invade bone but may displace and erode it. JNA is locally invasive and the tumour grows in continuity; multifocal lesions have never been reported. The nasal cavity is invariably involved, and as it grows, the tumour involves the contralateral nose. It typically extends laterally through the sphenopalatine foramen. It may involve sphenoid and ethmoid sinuses, infratemporal fossa, orbit (through the inferior orbital fissure), oropharynx and parapharyngeal space. Intracranial extension usually occurs through the floor of the middle cranial fossa with erosion of the greater wing of the sphenoid and less often the cribriform plate. The natural history of JNA is to grow. The tumour recruits additional blood supply as it extends, which is probably related to production of an angiogenetic factor [17].

Its microscopic appearance is a fibrovascular stoma comprised of myofibroblasts, which form the fibrous component and vascular cavities. An endothelial layer lines the vascular spaces, which have no muscle layer but normal arteries with a muscle layer are also present.

15.3.3 Clinical Presentation

Patients present with a history of recurrent epistaxis and symptoms due to obstruction of the paranasal sinuses and Eustachian tube. These include nasal congestion, purulent sinusitis, rhinorrhoea and otorrhoea. Patients complain of ipsilateral tinnitus, decreased hearing and a nasal voice. Superior extension of the tumour may cause anosmia. Recurrent epistaxis is a universal symptom and may lead to anaemia. On examination, facial or temporal swelling may be evident with proptosis. A mass may be seen extending into the oropharynx, and ophthalmoplegia may develop as the tumour enlarges and invades the orbit or cavernous sinus.

15.3.4 Indications for Endovascular Treatment

The rate of tumour growth is usually rapid, and treatment should not be delayed since it may reach a point when cure (by surgical resection) is no longer possible. Malignant transformation is rare but has been reported after radiation treatment. The results of radiotherapy alone or combined with surgery are similar to those of embolisation combined with surgery. However, there is a 5% risk of inducing malignant transformation (to a sarcoma) after the former. Thus, embolisation is usually performed to assist complete surgical resection.

It may also be performed to reduce the size of recurrent tumour prior to repeat surgery or as the definitive treatment, though usually only as palliation in inoperable lesions [18].

15.3.5 Aims of Embolisation

The objective is to devascularise the tumour and induce shrinkage in order to improve surgical access and facilitate complete curative resection. Surgical removal, which if complete, is curative but intraoperative bleeding and excessive tumour size or spread may make this difficult. Embolisation aims to assist complete resection [19].

15.3.6 Preprocedure Assessment

The diagnosis is usually based on otorhinolaryngological examination, but planar scanning is essential for surgical planning.

Imaging: MRI with contrast enhancement should define the extent of the tumour and differentiate tumour extension into paranasal sinuses from sinusitis due to retained secretions. Diffuse or patchy enhancement with expansion of the sinus suggests tumour invasion and dural enhancement indicates intracranial extension [20]. CT is usually unnecessary but will help to show bone destruction.

Angiography: This requires DSA because the arterial supply arises from branches of the ECA and, if the tumour is large, the ICA. Feeding arteries are only moderately enlarged, and there is typically an intense inhomogeneous blush in the capillary phase that persists late into the venous phase on catheter angiograms. Venous filling occurs relatively late, though sites of arteriovenous shunting are often present [21, 22] (Fig. 15.2). Some authors emphasise a potential difficulty in identifying intradural spread on lateral views because small branches arising from the ICA can be confused with recruited transpial cerebral arteries. The latter are the hallmark of extension into the subarachnoid space and are best identified on a frontal view.

There are several surgical systems for classifying the extent of tumour spread which all have the same objective, i.e. to distinguish tumours with intracranial extension and its extent. The Fisch staging system is listed in Table 15.3. It defines areas of tumour involvement in a four-step system (types 1–4) with subtypes (3a, 3b and 4a, 4b) [23]. Endoscopic resection is performed for Fisch types 1 and 2 and some type 3 tumours, whereas open surgery is required to resect more extensive types [24].

15.3.7 Embolisation Technique

Embolisation for JNA was first performed in the 1970s [18]. Most tumours are supplied exclusively via branches of the ECA, which simplifies

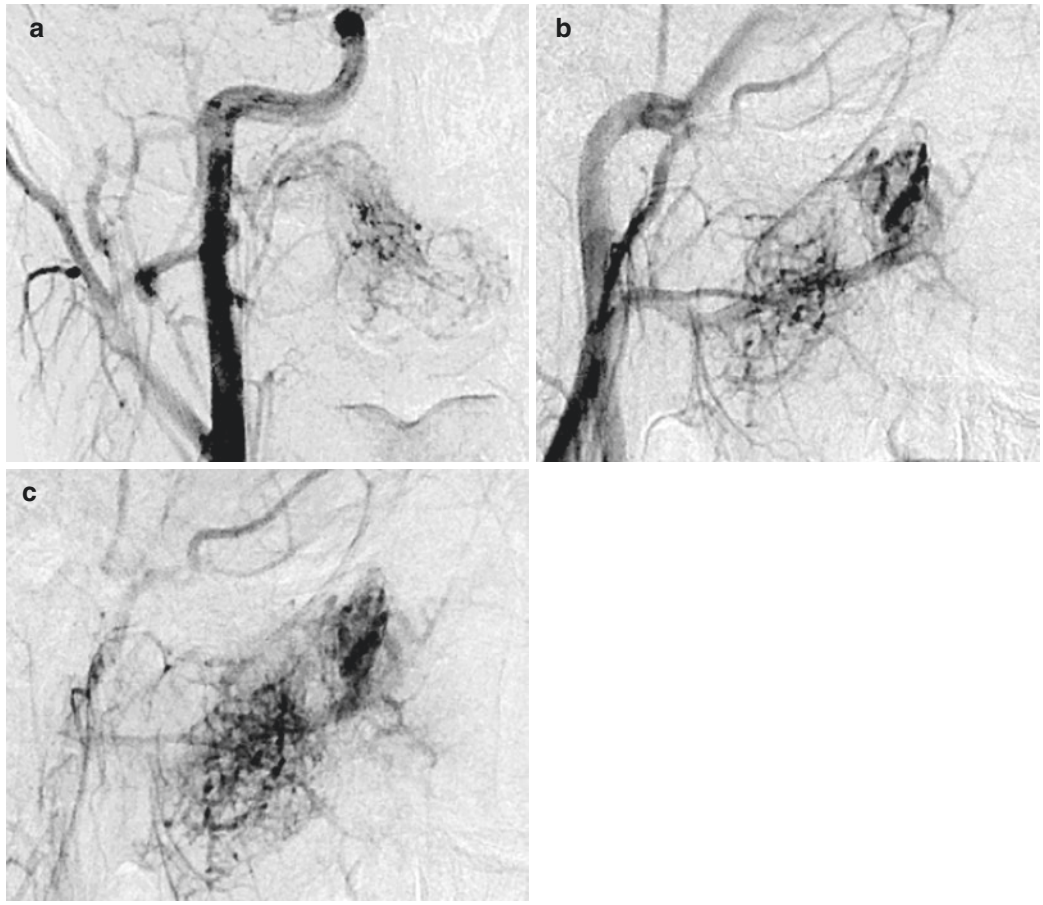

Fig. 15.2 Juvenile angiofibroma in a young man. This external carotid angiogram shows a hypervascular tumour with irregular, relatively small, tumour arteries in the early arterial phase on frontal (**a**) and lateral (**b**) projections. In the venous phase, contrast outlines dilated vessels within the tumour (**c**) *(lateral view)*

Table 15.3 Classification of Fisch for extent of juvenile nasopharyngeal angiofibroma [23]

Class	region	Arterial supply
I	Nasopharynx (NP)	Sphenopalatine artery (IMA)
II	NP + pterygopalatine fossa or the maxillary, ethmoid or sphenoid sinus	Accessory meningeal (IMA)
		Superior pharyngeal (APA)
		Anterior and posterior ethmoid arteries (OphA)
IIIa	NP + pterygopalatine fossa or infratemporal fossa or orbit	Inferior orbital artery (OphA)
		Inferolateral trunk (ICA)
IIIb	A/A + intracranial extradural extension	Recurrent meningeal (OphA)
		Artery of foramen rotundum (ILT/ICA)
IVa	A/A + cavernous sinus	Branches of ICA (ILT and MHT)
IVb	A/A + intradural and/or pituitary fossa	Branches of ICA (ILT and MHT)
		Branches of cerebral arteries

A/A as above, *IMA* internal maxillary artery, *APA* ascending pharyngeal artery, *OphA* ophthalmic artery, *ICA* internal carotid artery, *ILT* inferolateral trunk, *MHT* meningohypophyseal artery

embolisation and potentially makes it safer. If the tumour has entered the cranium and recruited an additional blood supply from dural branches of the ICA or transpial branches of cerebral arteries, embolisation is more complicated and hazardous. It therefore limits the potential of endovascular treatment to achieve complete devascularisation.

(a) Angiographic protocol: Preliminary angiography is performed to demonstrate any ICA supply and the extent of any tumour extension into the ethmoid and sphenoid sinuses or the middle cranial fossa. Injections should be performed in the ipsilateral ICA and in the contralateral ICA with cross compression, together with selective catheterisation of ECA branches. The last involves successive catheterisation of branches supplying the tumour. These can be predicted from the pre-embolisation imaging. If transarterial embolisation is to be performed in several branches, it is preferable to start with the most distal first, followed by possible sources of collateral circulation. A representative protocol for selective angiography and embolisation with particles is:
   1. Ipsilateral distal IMA, sphenopalatine and pterygovaginal arteries.
   2. Accessory meningeal artery.
   3. Superior pharyngeal artery.
   4. Ascending palatine artery.
   5. Sequential catheterisation and embolisation of feeding arteries from the contralateral side are then performed and carried out in the same order.

(b) Embolisation techniques: The majority of JNAs can be satisfactorily treated by transarterial embolisation with particles using pulsed free-flow injections. Particles sized at 150–350 μm are chosen, but smaller particles may be used if no dangerous EC–IC connections are identified before or during the procedure. Transarterial liquid embolic agents or sclerosants are rarely used and reserved for inoperable or large recurrent tumours. Liquid agents can be injected after direct puncture into tumour vessels under fluoroscopic guidance [25].

(c) Postoperative care: Oral analgesic drugs and 24–48 h bed rest are prescribed. In many practices, surgical resection is performed immediately after embolisation.

15.4 Paragangliomas

These are benign neuroendocrine tumours that arise from chromaffin cells in paraganglia or chromaffin-negative glomus cells derived from neural crest. In the past they have been given several names, including chemodectoma, glomus tumour, nonchromaffin paraganglioma and neurocristopathic tumour. They occur anywhere along the embryonic pathway of ganglia migration in the body and skull base and neck tumours are relatively rare. They represent only 3% of all paragangliomas [26]. In the head and neck, they are found in the temporal bone 50% (tympanic or jugular), in the neck 45% (carotid body or vagus) and 5% elsewhere. In the tympanic cavity, they arise from the cochlear promontory.

15.4.1 Demography, Epidemiology and Aetiology

Paragangliomas may occur in multiple locations, and two patterns can be distinguished. The first occurs more frequently in women (2.5:1), and tumours are found in temporal, vagal, nasal and nasopharyngeal locations. The other group has no gender bias, and tumours are found in the carotid body, larynx and orbit. The mean age at presentation is 50–60 years. In younger patients, tumours grow quicker and are more likely to be secretory.

The majority of tumours are sporadic but about 25% of patients give a positive family history. Multiple tumours occur in 30% of patients with a positive family history and in 10% of patients without. The hereditary basis is mutations of the genes encoding for the enzyme

succinate dehydrogenase subunits D and C (i.e. SDHD and SDHC) causing paraganglioma syndromes 1 and 3, respectively They may occur in association with multiple endocrine neoplasia (MEN) syndrome types 2A and 2B, von Hippel–Lindau syndrome and neurofibromatosis type 1 [27]. Tympanic and jugular paragangliomas are the least likely to be multiple.

Approximately 3% of tumours are secretory and cause clinically significant raised levels of catecholamines. The incidence of secretory tumours rises to 40% in patients <25 years of age. Raised levels of catecholamines (i.e. adrenaline and noradrenaline) cause symptoms resembling those of phaeochromocytoma. Malignant transformation is rare and is estimated to involve about 10% for vagal, laryngeal and carotid body paragangliomas and only 3% for temporal tumours.

15.4.2 Pathology

The macroscopic appearance is of an encapsulated polyploid highly vascular mass with a deep red colour. The microscopic appearance is of tumour cells in balls separated by a fibrovascular stroma surrounded by sustentacular cells. The tumour growth pattern is characterised by compartments supplied by a single artery. Arterial feeders are not enlarged proximally but enlarge (by 3–5 times their proximal diameter) within the tumour in a centripetal pattern. Arteriovenous communications at the level of the capillary bed are common.

The ascending pharyngeal artery (APA) supplies the autonomic nervous system in the neck and links the sites of paraganglioma development. Thus, its branches supply tympanic, jugular, vagal, carotid body and laryngeal tumours.

15.4.3 Natural History

Spontaneous regression has not been reported, and malignant transformation may occur. Tumour growth and local invasion may cause fatal complications. Temporal tumours (glomus typanicum and glomus jugulare) spread into the adjacent mastoid bone, jugular foramen, hypoglossal canal and inner and middle ear, and may invade the carotid canal and cerebellopontine angle. Neck tumours (glomus caroticum and glomus vagale) grow locally and displace adjacent structures. Carotid tumours develop between the origins of the internal and external carotid arteries and separate the proximal sections of both arteries as they grow. Vagal tumours arise within the carotid sheath, between the carotid bifurcation and the jugular foramen, and grow in the upper neck or pharynx. They displace both internal and external carotid arteries anteriorly. Malignant transformation is unusual and most common in vagal paraganglioma. Metastases are found in cervical nodes and rarely elsewhere. According to Harrison's series (temporal locations), the mean age of presentation was 45 years, with only 10% of patients being alive and well after 20 years [28].

15.4.4 Clinical Presentation

Temporal tumours: Patients with either tympanic or jugular tumour origins complain of tinnitus (80%) and hearing loss (70%). If the tinnitus stops, the tumour has probably destroyed the cochlea. Tympanic tumours may cause sudden VII cranial nerve palsy. Symptoms due to jugular tumours are sore throat, hypoglossal neuralgia, intermittent tinnitus and retroauricular pain. They are less pronounced when they first develop and may be disregarded by patients over a long period. Large tumours cause palsies of the IX, X and XI cranial nerves. On aural examination, a reddish bulge mass may be seen behind an intact tympanic membrane. This finding does not discriminate the two locations.

Neck tumours: Carotid tumours present with an enlarging neck mass which is non-tender pulsatile and confined to the anterior triangle of the neck. Bruit on auscultation is common in carotid body tumours which characteristically are mobile on lateral movement but fixed on vertical movement. Vagal tumours also present with neck or

pharyngeal pain, mass and cranial nerve palsies (30%). Superior laryngeal nerve involvement by vagal tumours may cause hoarseness and local invasion of the sympathetic chain Horner's syndrome. Occasionally, tumours can extend medially into the parapharyngeal space (10%), the oral cavity and/or larynx.

Catecholamine production causes headaches, palpitations and a sense of anxiety. Hypertensive crisis can be precipitated by surgical manipulation of the tumour or embolisation and has been provoked by injections of contrast for angiography [29]. These complications are caused by high levels of circulating catecholamines.

15.4.5 Indications for Endovascular Treatment

The indications are:

- Embolisation before surgical resection.
- Embolisation of large inoperable lesions to provide symptomatic relief.

15.4.6 Aims of Embolisation

Embolisation is performed to devascularise tumours prior to surgery. Its aim is to reduce surgical morbidity. For inoperable lesions, the aim is to reduce tumour size and growth as sole treatment. It can be combined with radiotherapy (there are reports of the efficacy of radiotherapy with cure rates of up to 90%) [30–32].

15.4.7 Risks and Benefits of Treatment

The effectiveness of preoperative embolisation to reduce intraoperative blood loss and operation times has been shown in several reports [33–35]. The specific complications to consider are cranial nerve damage (e.g. facial nerve palsy) and systemic effects caused by unrecognised catecholamine overproduction [36].

15.4.8 Preprocedure Assessment

The pre-embolisation assessment should include:

(a) Patient examination. This will include a neurological examination and review of specialist opinions. History of excessive anxiety and signs of hypertension/tachycardia suggesting tumour secretory activity warrant a specialist endocrine review. If the patient has symptoms, a 24-h urine collection to assess levels of catecholamines, e.g. VMA (vanillylmandelic acid) should be performed [37].

(b) Imaging. MRI is best to show the location and spread of tumours at all locations. It will demonstrate the distribution of large masses, their relationship to the carotid canal and involvement of soft tissues. On MRI, tumours are hypointense on T1-weighted sequences and iso- or hyperintense on T2-weighted sequences. High blood flow in small tumour vessels produces a 'pepper-and-salt' pattern due to flow voids. High-resolution CT will show bone erosion and destruction particularly of the temporal bone. Jugular tumours expand the foramen and cause an irregular 'moth-eaten' pattern of erosion of the jugular foramen and adjacent labyrinth. On both MR and CT, tumours show marked enhancement. Imaging cervical tumours can be performed with Doppler ultrasound. It will show displacement of ICA and ECA (the ECA is displaced anteriorly) and the severity of any narrowing.

(c) Preprocedural review and discussion. A review of the imaging with surgeon and oncologist is needed to decide on the role of embolisation in the treatment plan and how it may affect additional therapies. Fisch and Mattox [38] classified temporal tumours according to the areas of temporal bone involved (Table 15.4). Evidence of involvement of the ICA, i.e. classes C3, C4 and D, is an indication for preoperative test occlusion and possible pre-resection endovascular occlusion of the ICA. For carotid tumours, the difficulty of surgical resection

Table 15.4 Classification of Fisch and Mattox for extent of temporal paraganglioma [38]

Class	region
A	Tumour in the tympanic cavity only
B	As A plus extension into mastoid bone with intact jugular bulb
C1	Tumour with minimal erosion of the vertical portion of the carotid canal
C2	Tumour with extensive erosion of the vertical portion of the carotid canal
C3	As C2 with erosion of the horizontal portion of the carotid canal
C4	Tumour reaching the foramen lacerum and cavernous sinus
D	Tumour with intracranial extension

is related to the degree of contact with the ICA and may be reported using a three-point scale – the Shamblin classification [39], which can be graded using MRI [40].

(d) Anaesthetic assessment. Involvement of lower cranial nerves is an indication for general anaesthesia. In any case, embolisation is best performed under general anaesthesia because of the difficulty of obtaining high-quality angiograms at the skull base.

(e) Preprocedure drug treatments. Evidence of excessive catecholamine secretion requires pre-embolisation treatment with alpha- and beta-blocking drugs.

(f) Informed consent. If preoperative embolisation is proposed, informed consent is ideally obtained in a joint surgical/endovascular outpatient clinic interview conducted with the patient accompanied by a friend or relation. A rushed interview, with a porter lurking by the patient's bed immediately prior to embolisation, should not be accepted as providing the patient time to make an informed decision.

15.4.9 Embolisation Technique

(a) Angiographic evaluation. The compartmental angioarchitecture classically described for this lesion, in theory, means that the artery supplying a monocompartmental tumour identifies its origin and extent. Thus, a paraganglioma confined to the jugular foramen would be supplied exclusively by branches of the neuromeningeal trunk. However, the majority of tumours are comprised of multiple compartments (85%), and their extent on CT/MRI is a guide to the required angiogram.

Typical angiographic features are moderate enlargement of feeding arteries, an early intense irregular tumour blush and rapidly filling veins. The angioarchitecture is unusual because proximal arteries are smaller than more distal (intratumour) arteries. The calibre of feeding arteries has been estimated at about 90 μm and calibre of vessels in the tumour at 300–600 μm. This has obvious implications for the selection of embolisation particles (Fig. 15.3).

The angiographic protocol is to inject both vertebral arteries (VA), ICAs and ECAs, with selective injections to the ipsilateral ascending pharyngeal artery (APA), posterior auricular artery and occipital artery (OA). The branches of the APA that supply temporal paraganglioma are the hypoglossal, jugular and inferior tympanic arteries. Bilateral APA injections are advised by some authors.

The arterial supply to four regions of spread of temporal paragangliomas is well described by Valavanis [41] as:

1. Infro-medial compartment	HYPOTYMPANUM and JUGULAR FOSSA
	Inferior tympanic artery
	Jugular artery
2. Postero-lateral compartment	POSTERIOR TYMPANIC CAVITY and MASTOID
	Stylomastoid artery
	Mastoid branches of the occipital artery
3. Anterior compartment	PERICAROTID and PROTYMPANUM
	Anterior tympanic artery
	Caroticotympanic artery
4. Superior compartment	EPITYMPANUM and SUPRALABRYINTHINE SPACE
	Superior tympanic artery

Supply by dural arteries implies intracranial extension and not necessarily intradural tumour spread. In addition to the above schema, several

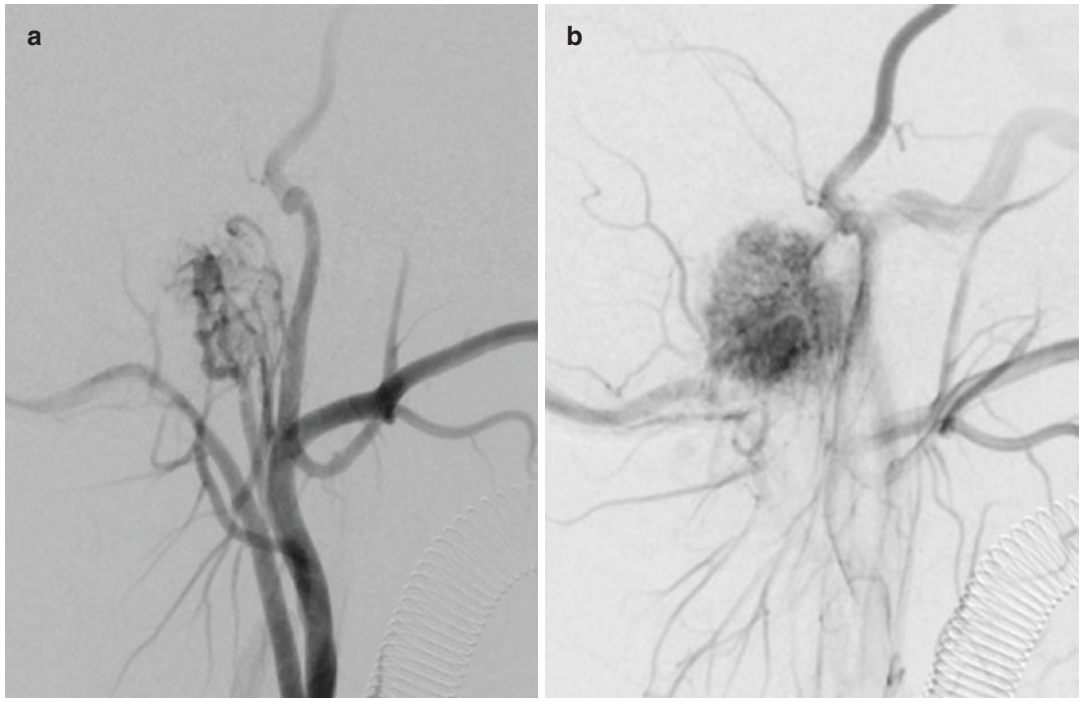

Fig. 15.3 Paraganglioma in the jugular foramen on lateral DSA. The tumour is hypervascular and supplied by the jugular artery (**a).** Opacification of small tumour vessels produces an intense blush during the late arterial phase of the angiogram (**b**)

dural arteries, adjacent to the APA territory, may supply these tumours. These are; the petrosal branch of MMA, accessory meningeal artery, lateral clival branch of the meningohypophyseal trunk (MHT) and/or the branch to the foramen lacerum from the inferolateral trunk (ILT), the anterior meningeal artery and dural branches of the OA. Intradural spread is conformed if a transpial supply is seen arising from the posterior inferior cerebellar artery (PICA) or anterior inferior cerebellar artery (AICA), and selective injections of the VA branches may be required. A careful inspection of the late phase of the dominant VA injection is advised to assess the late venous flow pattern to decide if the jugular vein is occluded with a potential effect on tumour venous drainage [33].

For carotid body tumours, the principal arterial blood supply is from muscular spinal branches of APA, and tumours may recruit from branches of the lingual artery, superior laryngeal artery, ascending cervical artery or deep cervical artery. The principle blood supply to vagal tumours is also from APA via muscular branches and branches of the neuromeningeal trunk (if the tumour involves the skull base) as well as muscular branches of the OA.

(b) Choice of embolic material and delivery techniques. Transarterial embolisation is usually performed with particles (140–250 μm). Smaller particles should not be used because of possible cranial nerve damage. Embolisation can be performed transarterially, or liquid agents (NBCA or Onyx (ev3)) may be used for treatment of inoperable tumours where a higher risk of morbidity due to collateral tissue damage is acceptable. They may be delivered transarterially or by direct injection. It is axiomatic that transarterial embolisation with liquids in the APA causes complications, even in the very best hands. Percutaneous puncture of tumour vascular spaces into tumour vessels with multiple percutaneous injections of Onyx or NBCA is now the preferred route (Fig. 15.4).

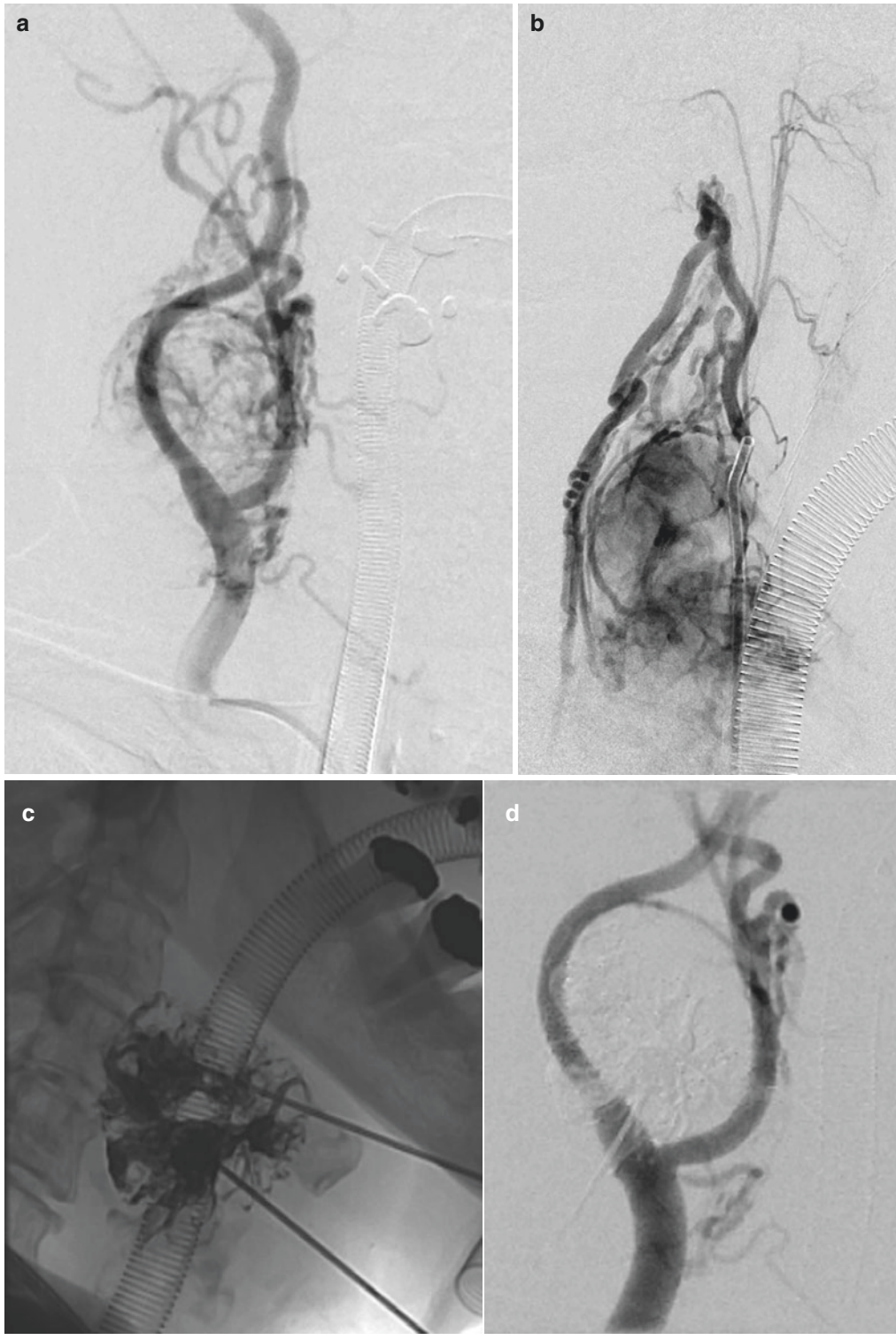

Fig. 15.4 Carotid body paraganglioma separating the proximal internal and external carotid arteries on DSA before (**a**) and (**b**) and after embolisation (**d**). Embolisation was performed by percutaneous injection of Onyx (**c**)

Transarterial embolisation of transpial pedicles (from AICA or PICA) for tumours with intradural spread is usually performed with particles but should be reserved for cases of malignant histology or when excessive hypervascularity prevents surgical excision. In such cases, injection may be performed with a balloon inflated in the distal VA to prevent particle reflux.

(c) Postoperative care. Bed rest analgesia and 24 h of neurological observations are the minimum for postoperative care. There are no guidelines on the appropriate interval before surgery, but it is preferable to recover the patient from general anaesthesia so that any neurological change can be assessed before proceeding to operative tumour resection. Nonsteroidal anti-inflammatory drugs, such as diclofenac sodium, are useful to reduce swelling and for postprocedure analgesia.

15.4.10 Follow-Up

Patients are best managed by a multidisciplinary oncology team. Follow-up protocols should be agreed locally and imaging planned according to the overall management plan.

15.5 Other Cranial Tumours

The principles described in this tutorial have been illustrated with detailed descriptions of their application in the three tumour types commonly referred for endovascular treatment. They are not the only pathologies in which the techniques described can be useful, and embolisation may be considered in the management of the following diagnoses: cranial schwannoma, carcinoid, aesthesioneuroblastoma, neuroblastoma, hypervascular metastatic carcinomas and sarcomas. Chordoma, chondrosarcoma and other primary bone tumours are rarely suitable for embolisation.

In general, it is only relevant in the treatment of hypervascular extra-cerebral tumours. Tumours with predominantly or exclusively intracerebral blood supply, such as haemangioblastoma and haemangiopericytoma, should be considered for embolisation when the risks are considered acceptable on a case-by-case basis (Fig. 15.5). The role of the endovascular therapist

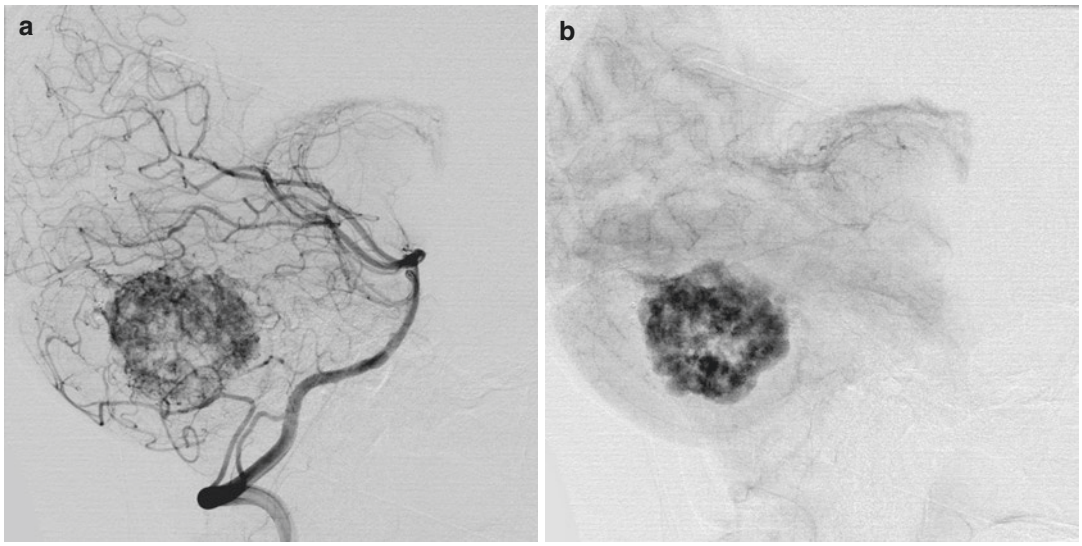

Fig. 15.5 Haemangioblastoma of the cerebellum. This tumour is highly vascular and is supplied by cortical cerebellar arteries, lateral view (**a**). It retains contrast with an intense blush during the early venous phase of the angiogram (**b**). Embolisation was performed with particles prior to surgical resection. Selective catheterisation of a branch of the superior cerebellar artery is shown (frontal view) with injection filling upper components of the tumour (**c**)

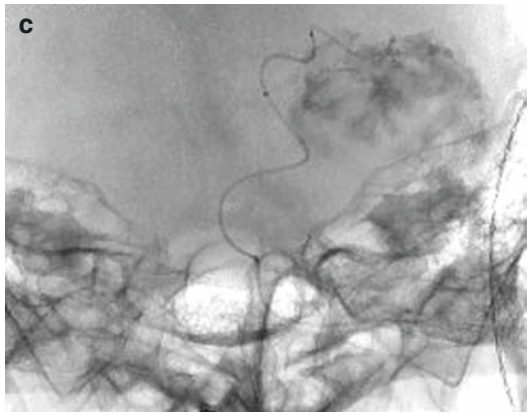

Fig. 15.5 (continued)

has considerable potential for the delivery of chemotherapy, gene therapy (with use of blood brain barrier modulation) and anti-vascular growth factor agents [42] in the future.

15.6 Spinal Tumours

Embolisation is generally not curative for spinal tumours but may reduce their mass and improve patient's symptoms. Treatments involve embolisation or sclerotherapy delivered transarterially or after percutaneous puncture of tumour vessels. It is a useful preoperative procedure because haemostasis can be difficult at surgery with vascular structures often inaccessible at the early stages of a resection operation. Surgery is performed for patients with lesions causing neurological deficits. As with the other procedures described in this tutorial, management decisions should be made in multidisciplinary discussions, and if surgery is the most appropriate primary treatment, preoperative embolisation should always be considered.

The histological diagnoses of spinal tumours that potentially may benefit from embolisation are:

(a) Benign tumours:

Vertebral haemangiomas
Aneurysmal bone cyst
Giant cell tumour
Haemangioblastoma
Meningioma
Schwannoma
Paraganglioma

(b) Malignant tumours:

Plasmacytoma
Ewing's sarcoma
Chondrosarcoma
Osteosarcoma

(c) Metastases:

Renal cell tumours
Melanoma
Multiple myeloma

15.6.1 Vertebral Haemangioma

These are common vascular tumours of the spine. They are multiple in 25% of patients and usually occur in the vertebral body, i.e. anterior elements. The incident increases with age and the locations are thoracic (60%), lumbar (30%), cervical (5%) and sacral (5%). They are slightly more common in women. Histologically, they are more like vascular malformations than true neoplasms. They are often seen as incidental findings, especially with the increased use of MR in the investigation of spinal disorders. The incidence is 10–12% in autopsy series, but only about 2% give rise to symptoms [43].

15.6.1.1 Pathology

On histological examination, they consist of thin-walled blood vessel sinuses lined by endothelium. There are longitudinally orientated bony trabecular between the vascular spaces, and the whole tumour is surrounded by fatty marrow.

15.6.1.2 Clinical Presentation

The majority of lesions are asymptomatic and require no treatment. A minority cause local pain and tenderness or neurological symptoms due to nerve root or cord compression, usually secondary to pathological fracture, vertebral collapse or compression of nerve roots because

the tumour extends beyond the vertebral body [44]. Djindjian stratified this spectrum into three groups [45]:

- Group A, extra-vertebral extension with signs and symptoms of spinal cord compression. This group comprises 20% of symptomatic patients and is found most often in young patients with lesions between D3 and D9. There is intense heterogeneous enhancement on CT /MRI which extends into the epidural space.
- Group B, no extra-vertebral extension with mild symptoms of back pain and occasionally radicular pain. These lesions are more often in the lumbar spine, and CT/MRI shows them localised to the vertebral body with preservation of the cortical margin. There is little enhancement, and angiography shows normal feeding arteries with delayed staining. Progression to neurological symptoms is rare (5%).
- Group C, asymptomatic lesions with no extra-vertebral extension and normal angiography.

15.6.1.3 Imaging

CT shows a 'polka-dot' appearance, due to bony septa. On MRI the fat content gives the characteristic MR appearance of high signal on both T1- and T2-weighted, conventional and fast-spin echo sequences [46]. This together with the mottled appearance of the vertebral body due to a combination of vascular flow voids and the low signal of the bony trabeculae gives a virtually pathognomonic picture. The intensity of signal on T1-weighted sequences may vary, depending on the degree of vascularity and fatty stroma in the tumour.

On DSA angiography shows a hypervascular circulation in a minority of lesions. Djidjian identified angiographic patterns, which correlate with the three clinical groups [45].

- Group A, the vertebral body has a dense stain with dilated vessels but no shunting or hypertrophy of intercostal arteries. This type is associated with extra-vertebral extension of tumour.
- Group B, the spinal angiogram shows pooling of contrast within large vessels and no extra-vertebral extension.
- Group C, the catheter angiogram is normal and the patient asymptomatic.

15.6.1.4 Treatment

Asymptomatic patients are managed conservatively and active treatment is reserved for those with painful lesions. Medical therapy should be tried first and interventions are performed only after it fails to control symptoms or if neurological signs develop. They include surgical resection, endovascular embolisation, direct puncture alcohol ablation and vertebroplasty. Endovascular embolisation was first used in 1972 [47] and is now performed either as a curative procedure or adjuvant to operative resection or radiotherapy. Endovascular embolisation is only relevant in lesion evident on angiography. Transarterial embolisation has been reported with NBCA [48] or particles [49]. In practice, percutaneous treatments are more commonly used either by sclerotherapy with ethanol [50] or by vertebroplasty [51]. Vertebroplasty is usually recommended for patients with unremitting symptoms and surgery for those with signs of spinal cord compression. Pre-surgical embolisation with particles may be performed.

15.6.1.5 Results of Treatment

The results of transarterial embolisation for symptomatic relief vary. Jayakumar et al. [49] reported good symptomatic relief following embolisation in a series of 12 patients, but others have reported treatment as ineffective or only providing temporary symptomatic relief [43, 52]. Sclerotherapy is effective at shrinking tumours and inducing symptomatic improvements. Tumour shrinkage occurs within days, but delayed vertebral collapse may occur [50, 53]. This complication can be managed by vertebroplasty which is increasingly employed for this indication as well as prior to surgery [51, 54]. Radiotherapy alone can produce cure and recovery of paraplegia in about 60–80% of patients [55, 56], though the use of radiotherapy for a benign neoplasm is controversial.

15.6.2 Aneurysmal Bone Cysts

These are rare highly vascular benign bone tumours. They comprise about 2% of all primary bone tumours and about 20% of those in the spine. Found mostly in the posterior elements of the cervical and thoracic vertebra [57], they may involve adjacent vertebra. There is no gender difference, and they affect young people (mean age 16 years) and are rarely found in patients older than 30 years [58].

15.6.2.1 Pathology

They are thin-walled, multi-lobulated, expansive and osteolytic lesions. They are possibly congenital and thought to be triggered to grow following trauma. About 30–50% are associated with other osseous lesions such as fibrous dysplasia and chondrosarcoma (which can occur at the same site).

15.6.2.2 Clinical Presentation

Pain is the commonest presenting symptom followed by neurological symptoms due to cord or root compression. Tumours can expand rapidly, and patients develop progressive signs of neural compression.

15.6.2.3 Diagnosis on Imaging

Radiographs show a lytic expansive lesion, often with a thin intact cortical rim. CT demonstrates the cortical rim more effectively and is better at determining if this is intact and whether there is an associated soft tissue component. On MRI, the appearance is of a lobulated lesion with septa, which may have blood/fluid levels within the lobules and signal characteristics of blood degradation products [59].

On DSA, the angiographic appearances vary, and there may be irregular dilated feeding arteries and a tumour blush or even a rich vascular network of tumour vessels. The decision to perform preoperative embolisation is based on the angiogram appearance.

15.6.2.4 Treatment

Standard treatment is surgical curettage with or without secondary bone grafting or internal fixation; preoperative transarterial embolisation with particles is helpful (depending on the degree of vascularity).

Transarterial or percutaneous embolisation without surgery have been reported to be effective. De Cristofaro et al. [60] reported healing with complete relief of symptoms after transarterial embolisation and suggested that it should be the treatment of choice in the spine and sacrum.

Percutaneous injections of zein corn protein [61] and calcitonin [62] have also been reported, and Bush and Drane [63] injected radioactive ^{32}P chromic phosphate colloid in order to ablate the cyst endothelium and showed that this caused progressive ossification of the lesion.

15.6.3 Other Benign Spinal Tumours

Other vertebral tumour types that may be treated by embolisation will be covered in less detail because they are uncommon referrals. These are:

15.6.3.1 Giant Cell Tumour

This lesion comprises 5% of primary bone tumours, and about 5% occur in the spine (most commonly in the sacrum). They involve the posterior elements of the vertebral body. The age of patients at presentation is 20–50 years with a peak incidence at 30 years. They are predominantly men.

Pathology: The tumour comprises sinusoidal vessels within a hypervascular stroma. Histology shows macrophages and multilayered giant cells. Malignant transformation occurs in 10% of tumours.

Imaging: CT shows a lytic destructive lesion in the sacrum or posterior portion of a vertebra. MRI shows mixed signal from a multicompartment cystic mass that often contains blood degradation products. The findings on DSA are a vascular tumour with intense staining and a network of feeding arteries. There may be arteriovenous shunts.

Treatment is surgical resection with preoperative particulate embolisation. Radiation is not recommended because of a risk of inducing malignant transformation.

15.6.3.2 Intradural Tumours

Embolisation for intradural spinal tumours is rarely performed but is described for meningioma, schwannoma and haemangiopericytoma. The selection of patients is based on finding a hypervascular tumour on imaging and a surgical opinion that preoperative embolisation will assist resection. DSA can be performed before, or combined with, transarterial embolisation since imaging is best obtained (particularly in the thoracic spine) with patients under general anaesthesia, though some practitioners prefer to have patients accessible for periprocedural testing of neurological function. The principles of transarterial embolisation are similar to those of embolisation in the cranium. Embolisation should not be performed if radiculomedullary arteries to the spinal cord are demonstrated in proximity to arteries supplying the tumour [63].

15.6.3.3 Intramedullary Tumours

Intramedullary tumours represent only 5% of spinal tumours. The usual histological types are astrocytoma, ependymoma and haemangioblastoma. Only the last is suitable for embolisation since it is a more vascular pathology.

Haemangioblastoma: These are vascular tumours which are either solitary or multiple (i.e. part of von Hippel–Lindau disease). Imaging shows large cystic areas and small solid components which enhances on CT and MRI. There may be associated hydromyelia [64]. The histology is the same as cranial lesions, and preoperative transarterial embolisation with particles can be helpful [65]. Endovascular treatment has been reported for tumours in both the upper and lower spinal cord [66]. In the caudal cord, it may involve catheterisation of the anterior spinal artery [67].

15.6.4 Malignant Spinal Tumours

Metastatic tumours are the most common extradural malignant neoplasm, and approximately 10% of cancer patients will present with spinal metastases arising from primary tumours of the breast, lung, prostate, kidney, thyroid or haemopoietic system. These patients present with pain and neurological deficits, and imaging will show the site(s) of neural compression and vertebral involvement. Most patients with metastatic tumours of the spine are now treated by radiotherapy and/or chemotherapy, some with additional surgical decompression and only rarely are patients referred for pre-resection transarterial particulate embolisation. There is a role for vertebroplasty in the management of these lesions, and percutaneous biopsy is often undertaken in neuroradiology departments.

Embolisation should be considered in the management plan for primary malignant bone tumours such as plasmacytoma, Ewing's sarcoma, chondrosarcoma and osteosarcoma that are hypervascular. It can be performed either prior to surgical resection or for palliation of symptoms and may be useful for inoperable recurrent tumours.

15.6.4.1 Embolisation Techniques

Preliminary angiography usually cannot distinguish between different types of tumour which typically show varying degrees of vascularity [68]. When catheterisation of arterial tumour pedicles can be performed, embolisation is performed with particles (PVA or acrylic spheres), alcohol (ethanol 95%) or liquid embolics (NBCA or Onyx (ev3)). The decision on which embolic agent to use depends on the indications for the treatment (e.g. particles or NBCA for preoperative treatment and ethanol for palliation of symptoms). Alternatively, percutaneous embolisation can be performed for vascular metastatic lesions originating from primary cancers such as renal cell or thyroid carcinoma [69].

After embolisation, patients should be maintained on corticosteroids for at least 3–4 days and confined to bed for 24 h to avoid compression fractures. Surgery, if planned, is usually performed within 24–72 h.

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Embolisation for Epistaxis

16

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Preamble

This tutorial is an example of the use of embolisation in a particular (and relatively easily defined) medical condition. Particle embolisation for epistaxis was first performed in 1972 by Sokoloff et al. and has remained part of the repertoire of interventional neuroradiology procedures ever since [1]. Some of the principles involved can be extended to almost all endovascular treatments. The tutorial is relatively short and is held at a time during the Oxford University MSc Course after students have had to read and learn a great deal of anatomy. It is thus a chance to take things a little slower and to apply some of the theoretical knowledge the course provides.

16.1 Epistaxis

Epistaxis is common. At least 60% of us will have episodes of nose bleeding at some time [2]. These occur with peak incidences in children (<10 years) and older adults (>50 years). Only 6% of episodes require medical treatment, and these are usually in the older age group. Bleeding can arise from veins, arteries or arterialised veins (e.g. associated with a vascular malformation or an arteriovenous shunt). Most episodes are idiopathic, though epistaxis in adults is frequently associated with systemic hypertension and other medical comorbidities.

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Two clinical scenarios can be differentiated for idiopathic epistaxis. These are commonly termed anterior or posterior nasal bleeding, and the latter is more likely to arise from arteries.

16.1.1 Anterior Epistaxis

The anterior portion of the nasal cavity contains an area where small anastomotic mucosal arteries are concentrated. This is the usual site of anterior epistaxis which accounts for 90–95% of epistaxis. It is on the inferior-anterior surfaces of the septum and known as Kiesselbach's plexus or Little's area[1] [3]. Bleeding in adults commonly occurs from the vessels of these areas or in children from the retrocolumellar vein. Since these areas are relatively accessible, treatment is by local compression, nasal packing and cautery. It is usually effective at stopping episodes of epistaxis.

16.1.2 Posterior Epistaxis

Bleeding in the posterior nasal cavity is far less frequent (5–10% of epistaxis) than anterior epistaxis [4]. It usually originates from the lateral nasal cavity, posterior to the middle turbinate, below the posterior end of the interior turbinate (an area called Woodruff's plexus) or the roof of the nasal cavity [5]. The last area is the least accessible to anterior endoscopy and is the most frequent site for intractable epistaxis since effective packing in this region is difficult. Packing is also difficult if bleeding occurs from the upper pharynx.

16.2 Causes of Epistaxis

(a) Idiopathic

This is the commonest form of epistaxis, affecting 70–90% of all patients. No underlying structural cause is found, but factors considered to trigger spontaneous epistaxis include allergies, infections, cold weather and high atmospheric humidity. It affects men and women equally. In adults, it is associated with systemic hypertension, atherosclerosis, hypercholesterolaemia, smoking, liver disease and excess alcohol intake.

(b) Trauma

Acute bleeding following trauma is caused by direct vessel injury and is usually associated with facial fractures. Delayed bleeding may occur from pseudoaneurysms and false aneurysms in the nose or paranasal sinuses. Haemorrhage from posttraumatic aneurysms of the cavernous carotid artery (which may also cause a fistula) should be considered in the differential of delayed posttraumatic epistaxis. Surgical trauma, e.g. biopsy of a neoplasm, may precipitate epistaxis and bleeding may occur after radiotherapy [6].

(c) Tumours

Nasal and paranasal sinus tumours may present with epistaxis. Primary tumours include carcinoma (squamous, adenocarcinoma, adenoid cystic carcinoma), olfactory neuroblastoma, lymphoma, papillary angioma, angiomatous polyps and juvenile nasopharyngeal angiofibroma [7]. It has been reported in patients with the Wyburn–Mason (Bonnet Dechaume Blanc) syndrome. In this condition, retinal, nasal and intracranial angiomas or AVMs occur in a disease of abnormal metameric development. Secondary tumours occurring in the nose and paranasal tissues include metastases of renal cell carcinoma and malignant melanoma. A small point, when dealing with aggressive secondary tumours, is the possibility of embolisation inducing collateral blood supply. Thus, if the ethmoid arteries are enlarged, it has been suggested that they should be ligated before embolisation is performed in the internal maxillary artery (IMA) in case they become the route of additional collateral blood supply to the tumour from the ophthalmic artery.

[1] Wilhelm Kiesselbach (1839–1902), a German otolaryngologist, is commonly attributed with describing this plexus, but James L. Little, a New York surgeon, first described the area as a source of epistaxis in 1879.

(d) Hereditary haemorrhagic telangiectasia (Rendu–Osler–Weber syndrome)

Epistaxis is the most common presentation of this autosomal dominant disease that causes telangiectasia and AVMs in the nose, skin, gastrointestinal tract, lungs, liver and brain. Epistaxis affects 95% of patients. It is frequently recurrent with serial episodes which may be severe in a minority of episodes [8].

(e) Coagulopathies, blood dyscrasias and anticoagulation medication

Abnormal clotting should always be considered as a possible cause. It may be due to congenital conditions such as haemophilia, Von Willebrand disease and systemic disease such as cirrhosis or iatrogenic in patients on anticoagulant or antiplatelet drugs.

16.2.1 Vascular Anatomy

The blood supply to the nasal cavity is derived from branches of the internal maxillary artery (IMA), facial artery (FA), internal carotid artery (ICA) and the ascending pharyngeal artery (APA) (Fig. 16.1).

(a) Internal maxillary artery

The majority of the blood supply to the nasal mucosa comes from two terminal branches of the IMA: the sphenopalatine artery (SPA) and the greater palatine artery (GPA).

The larger SPA supplies the mucosa of the superior and middle turbinates and septum. It divides soon after passing through the sphenopalatine foramen into lateral short branches, which supply the lateral wall and turbinates and a medial long branch which supplies the nasal septum.

The greater palatine artery (GPA) or descending palatine artery arises from the distal IMA just before this artery enters the sphenopalatine foramen and becomes the SPA. It runs inferiorly to the hard palate in the greater palatine canal. A smaller companion branch of the IMA, the lesser palatine artery, parallels its course in a separate bony canal. They give branches to supply the palate and mucosa of the inferior part of the lateral nasal margin. The GPA is the more anterior branch of the descending palatine arteries, and a terminal branch runs forwards on the hard palate and enters the nose through the incisive foramen where, on the anteroinferior part of the nasal septum, it anastomoses with the septal branch of the SPA (i.e. at Kiesselbach's plexus). It also gives small posterior branches, which supply the superior pharynx and anastomose with terminal branches of the SPA on the posterior inferior septum and inferior turbinate.

(b) Facial artery

Terminal branches of the facial artery (FA) supply the nostril and external nose. The alar artery (or lateral nasal artery) supplies the lateral nostril, and the superior labial artery gives small branches to supply the medial wall of the nasal vestibule and anterior septum. These branches are rarely seen on normal angiograms.

(c) Internal carotid artery branches

The anterior and posterior ethmoidal arteries are branches of the ophthalmic artery (OphA) and pass through the cribriform plate to anastomose with branches of the SPA and supply the roof of the nasal cavity. These vessels are rarely seen on normal angiograms and seeing prominent ethmoidal arteries usually means embolisation in the distal IMA will fail to control the epistaxis. Small branches of the ICA may also contribute to the nasal blood supply. These are the capsular branch arteries (capsular arteries of McConnell), artery of foramen rotundum (from the ILT) and the mandibular artery (from the mandibulo-Vidian trunk).[2]

[2]If present the mandibular artery gives a branch which anastomoses with the Vidian artery and supplies the sphenoid sinus. Its inferior branch anastomoses with the inferior Eustachian branch of the accessory meningeal artery and the Eustachian branch of the APA and pterygovaginal arteries, i.e. at the anastomosis around the Eustachian meatus (see Tutorial 7).

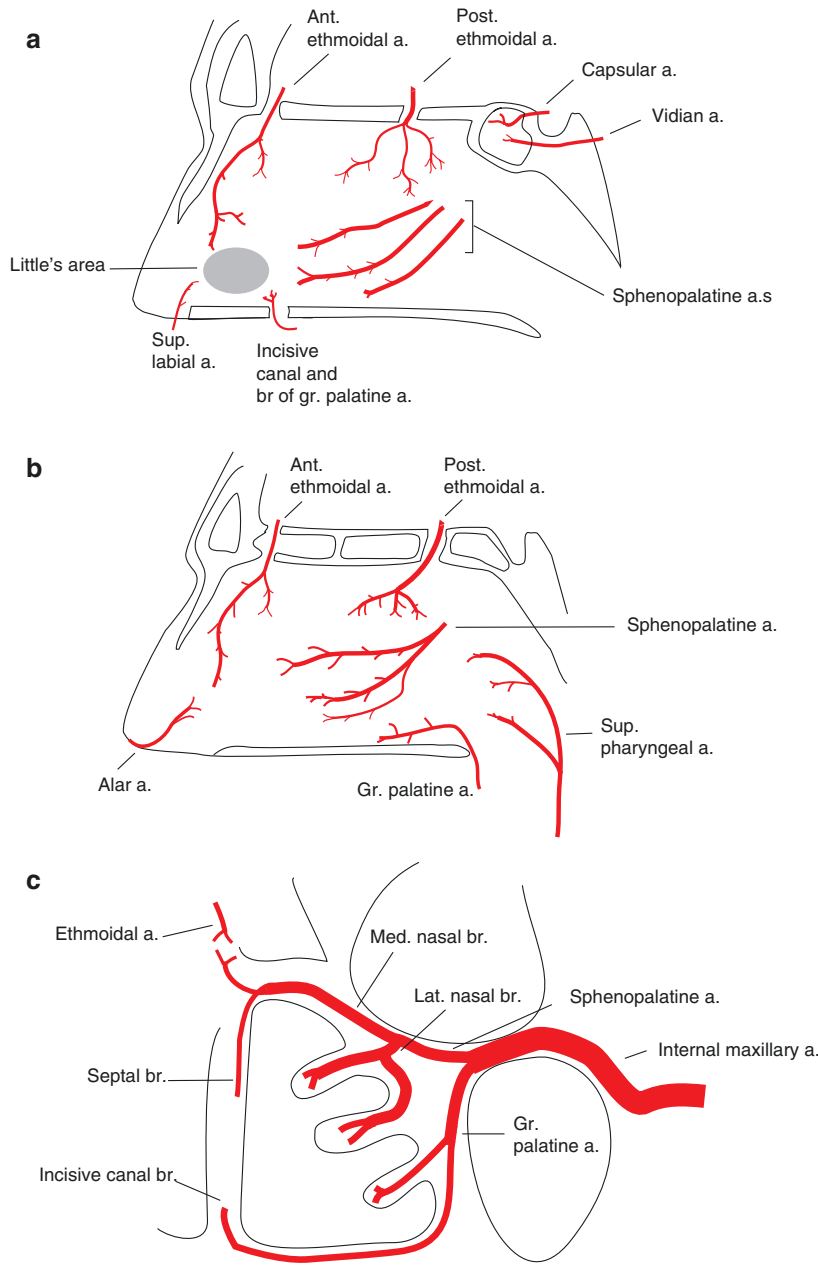

Fig. 16.1 Arterial supply to the nose: (**a**) nasal septum (lateral view), (**b**) lateral wall of the nose (lateral view), (**c**) left nasal cavity (frontal view) (Published with kind permission of © Henry Byrne, 2017. All rights reserved)

(d) Ascending pharyngeal artery
The superior and middle pharyngeal arteries supply the medial and paramedial nasopharynx. They therefore border the territory of SPA and GPA branches.

The main supply to the posterior nose is from the SPA and this is the first target for endovascular treatment. Next, choose the FA and rarely the APA. The anterior and posterior ethmoidal arteries are best occluded by surgical ligation.

16.2.2 Indications for Embolisation

- Embolisation is indicated for intractable epistaxis.
- Failure of preliminary treatment by nasal packing or cautery. These techniques are generally successful in anterior epistaxis but have a relatively high failure rate in posterior epistaxis (about 25–50%) [9]. This is not surprising because it is difficult to tamponade the posterior nasal cavity from an anterior approach. More aggressive posterior packing with inflatable balloons is more likely to tamponade bleeding from the posterior nose but risks causing necrosis of the septum or alar cartilage. Endoscopic cautery is generally more successful, and in only a minority of patients (5–10%), bleeding becomes intractable.
- Excessive blood loss with falling haemoglobin level.
- Prior to surgical ligations. Embolisation is obviously best performed before surgical ligation of the SPA or IMA. Communication and collaboration with the surgical team should be ongoing so that patients are referred for embolisation at the appropriate stage.

16.2.3 Pretreatment Assessment

In practice, most patients have been bleeding for several hours (or days) by the time they are referred. Often, packing initially appears to work and natural optimism delays referral for embolisation. An important initial assessment is whether treatment needs to be performed under general anaesthesia.

1. A detailed history is taken about the epistaxis episode. The details required are: source of bleeding, how long the patient has been bleeding and if they have had previous episodes and if so how they were treated. A general history of the patient's health should include enquiry about any bleeding tendency, previous trauma or nasal disease. Imaging is not usually required (unless the history and examination suggests an underlying lesion causing the epistaxis) since catheter angiography will be performed as part of the endovascular procedure.
2. Laboratory tests should include recent routine biochemistry and blood counts. In particular, current plasma haemoglobin and platelet levels should be available and the clotting time estimated. Abnormalities causing hypocoagulation such as low platelet counts or vitamin K levels should be corrected prior to embolisation.
3. Endoscopic examination of the nasal cavity will almost certainly have been performed, and obtaining an accurate report of any finding is important. Observations made of the site of bleeding will assist embolisation, i.e. if it is lateralised, nasal or predominantly posterior nasal.
4. An assessment of the patient's ability to lie flat should be made. It is usually easier to perform embolisation with nasal backpacks in place, but patients may find this makes lying flat impossible. Occasionally, it may be possible to temporarily remove the packing, but in this situation, it is generally better to perform the procedure under general anaesthesia.
5. Informed consent is obtained. For this you will need to know the chances of the procedures being successful and the incidence rate and type of potential complications, so read on.

16.3 Endovascular Technique

16.3.1 Preliminary Angiography

A preliminary angiographic assessment should be performed. If packs have been removed, it may show active bleeding, but often this is not seen, and the site of bleeding is inferred from the history and findings of endoscopic examination. There are two schools of thought on how much preliminary angiography should be performed. One is that bilateral carotid studies should be performed before selective catheterisation and the

other is that one should identify and embolise the source of bleeding as quickly as possible because the patient may be unable to tolerate a long procedure. The former means that coincidental contralateral pathology or collateral nasal blood supply has been excluded prior to starting embolisation and is, I think, preferable.

Therefore, a detailed angiogram of the cranial vasculature should be performed and include examination of:

- ICA, to exclude an underlying pathology or an anomalous blood supply to the nose. This can usually be done with a common carotid injection using biplane DSA.
- ECA, by selective injection to assess for any contribution to the nose from branches other than those of the distal IMA, i.e. the transverse artery of the face, the ascending palatine artery and other FA branches and branches of the APA. Selective injection of the FA may be needed, and this is best imaged with a lateral projection.
- The IMA is then examined, and its distal section is best imaged using a frontal (Water's) projection. The operator looks for anastomoses with the OphA, anterior deep temporal artery or the artery of the foramen rotundum. Bleeding points are generally difficult to identify.

16.3.2 Internal Maxillary Artery Embolisation

Embolisation is performed after selective catheterisation of the distal IMA. A microcatheter (preferably of the largest usable size, e.g. 0.018–0.27 inch ID) is advanced via a 5 F or 6 F guide catheter placed in the ECA until its tip is in the pterygovaginal portion of the IMA. Selective angiography is performed and may or may not show active bleeding, i.e. contrast extravasation. It should show that the SPA and GPA are filling (it is generally unnecessary to select the long SPA branch). If not, the tip is repositioned or steps taken to counter vasospasm. Catheter-induced vasospasm can be a problem, and some practitioners advocate its treatment with sublingual glyceryl trinitrate rather than intra-arterial injection of vasodilators because of concern that the latter may open anastomotic connections to ICA branches.

Embolisation particles (PVA or acrylic microspheres) are initially selected in the 150–250 μm range, and larger particles in the 300–600 μm range are injected after an initial reduction in mucosal opacification. A slow free flow injection of particles is made under fluoroscopic control.

16.3.3 Embolisation in Additional Pedicles

If there is no clear history of unilateral bleeding, then both distal IMA should be treated in the same way. The question of additional embolisation in the FA is difficult. Selective FA injection on the side of putative haemorrhage may be helpful to see if there is a significant blood supply to the nasal septum, but treatment probably adds to the risk of complications and certainly to the length of procedures. For these reasons, many prefer to treat the FA only if a first treatment session fails to control bleeding. Additional embolisation of the FA increased the success rate from 87% to 97% in one case series [10]. The procedure is the same as treating the IMA. The microcatheter tip should be navigated distally, in order to avoid spill of particles to proximal branches supplying the submandibular gland and to masseter muscular branches (since this is a cause of postprocedure pain).

16.3.4 Following Embolisation

Final control angiography is performed to confirm normal ICA filling. It may identify persistent nasal supply from the anterior and posterior ethmoidal arteries, which, if present, makes recurrent or persistent bleeding more likely. It is an indication to consider surgical ligation of these arteries. The nasal packs can be removed immediately or after 2–6 h. Postprocedure analgesia is rarely required. Haemoglobin levels

should continue to be monitored until the patient is stable.

16.4 Alternative Embolisation Techniques

The standard technique described above will need to be adapted in the following circumstances:

- Atypical bleeding: When a tumour or traumatic fistula is identified as the source of bleeding. The endovascular treatment technique will then be tailored appropriately.
- Using large particles: Large particles, in the 300–800 μm range, are advocated as a way of reducing the risks of the mucosal ulceration and inadvertent spread to ICA branches. There is little supportive evidence for this approach, and large particles are more likely to clump and obstruct in the microcatheter.
- Use of Gelfoam plugs and coils: These are used for occlusion of the proximal IMA and FA. Successful treatment has been reported using large 'plug' embolisation. In a report of 37 patients, this treatment was successful in stopping acute bleeding in all but two cases [11]. However, proximal occlusion, which risks generating collateral blood supply, is generally considered to be less effective than distal embolisation.
- Use of liquid agents: It is unnecessary to use liquid agents for spontaneous bleeding since they are more likely to spread to adjacent vessels and affect cranial nerve blood supply.
- Embolisation for Rendu–Osler–Weber syndrome: In these patients, embolisation is unlikely to be curative because the disease is too extensive. In the acute situation, treatment with particles is performed to stop an episode of severe epistaxis. It can be also useful on an elective basis (i.e. during intervals between active bleeding) to reduce the frequency of episodes. It should be more extensive than the protocol described above and include arteries supplying the nasopharyngeal mucosa, i.e. superior pharyngeal, middle pharyngeal and accessory meningeal arteries. Surgical arterial ligations should be avoided in this condition since recurrent bleeding in the long term is very likely and treatments such as oestrogen therapy, laser ablation and cautery used instead [12]. Bleomycin injections have also been reported [13].

16.5 Complications of Embolisation

These are generally reported as minor or major. Minor complications are common and incidences of 25–59% have been reported [9]. Patients commonly experience muscle ache, pain and even trismus, as well as transient facial numbness, swelling and minor mucosal ulceration after IMA embolisation with particles [14]. Muscle pain may make eating difficult for a few days. It is generally under reported and occurs, to some degree, after as many as 50% of procedures [1]. More serious adverse events include transient facial nerve palsy [15] and skin necrosis [16].

In the early literature, major complications were reported in 3–7% of treatments, but they are now reported with incidences in the 0.1–3% range. The most frequently reported severe complication includes stroke [15, 17, 18], monocular blindness [14], substantial necrosis of the mucosa or skin and permanent partial facial nerve palsy [15].

16.6 Results of Endovascular Treatment

The reported rates for successfully stopping epistaxis in recent series reports are presented in Table 16.1. Though stopping bleeding can be achieved in 90–100% of procedures, it may restart over the next 3 days in about 12% of patients [15]. Thus, a distinction should be made between technical success, i.e. stopping bleeding, and achieving stable relief, i.e. long-term relief. Long-term success is difficult to compare between reports because of differences of case-

Table 16.1 Rates of successfully stopping epistaxis in short (immediately post-EVT) and long term (no retreatment required)

Report	Patients	Immediate (%)	Long term (%)
Siniluoto et al. [19]	$n = 31$	71	90
Elden et al. [16]	$n = 97$	88	82
Tseng et al. [17]	$n = 107$	93	88
Oguni et al. [11]	$n = 37$	95	95
Duncan et al. [18]	$n = 51$	86	97
Christensen et al. [20]	$n = 70$	86	NA
Sadri et al. [21]	$n = 14$	86	97
Fukutsuji et al. [22]	$n = 20$	77	95

mix, follow-up periods and definitions of success. In the reported series, no recurrence of bleeding occurred during follow-up in 80–90% of patients (Table 16.1).

A detailed review comparing embolisation and surgical treatments of epistasis for efficacy, complications and costs was reported by Strong et al. in 1995 [23]. They concluded that surgical ligation was more likely to cause minor complications and embolisation major complications, though the latter were rare. They suggested that the choice of which should be tried first is made on a case-by-case basis, but management protocols still appears to vary from centre to centre. A guideline produced by the report of the Royal Belgian Society of Otorhinolaryngology in 2005 recommends embolisation for posterior epistaxis '…treated with embolization, either as a primary modality in poor surgical candidates or as a second-line treatment in those for whom surgery has failed' [24]. Finally, it is worth remembering that the overwhelming majority of patients with epistaxis are treated successfully by simple nasal packing [25].

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Re-establishing Blood Flow After Intravascular Thrombosis

17

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Preamble

As the reader may guess from the title of this tutorial, its focus is the management of ischaemic stroke from the endovascular therapist's perspective. Our skills can be reduced to blocking up or unblocking blood vessels. The Oxford English dictionary contains the word deoppilation, which is derived from French and means the removal of obstructions. This noble purpose is the primary role we play in the stroke team.

Unblocking thrombosed arteries and veins can be done by thrombolysis which means breaking down the intravascular blood clot by pharmacological means, i.e. stimulating plasmin, to breakdown fibrin and cause clot lysis or by mechanical thrombectomy. Since the first edition of the book, the controversy over the best approach to treat acute ischaemic stroke patients has been resolved, and early thrombectomy has been shown to be effective. The practical implications for the practicing endovascular therapist are profound.

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Is it a revolution, which will replace all? Well no.

Is it a major challenge for service delivery? Definitely yes!

And much more in terms of how our juvenile medical subspecialty will develop as it matures into adulthood. To my mind, its greatest danger lies in our reverting to technicians who, with no ongoing clinical responsibilities, lose touch with their patients. And so lose the rewards of looking after sick people.

17.1 Intravascular Thrombosis

Intravascular thrombosis occurs as a normal response to vessel injury or the presence of foreign material and as an abnormal response to local disease or a general dysfunction of blood clotting. In order to discuss how endovascular therapy can be deployed to re-establish blood flow, we need to understand the haematological mechanisms that we can mobilise to achieve this goal.

17.1.1 Basis of Intravascular Thrombosis

Thrombus formation occurs as the end result of a series of events and reactions. Damage to the endothelium initiates the coagulation cascade, aggregation of activated platelet and the generation of thrombin. Thrombin causes fibrinogen cleavage and the formation of fibrin to stabilise clot. Thrombin-mediated fibrin formation occurs in direct relation to platelet activation.

Platelets promote the activation of the early stages of the intrinsic coagulation pathway by a process that involves a factor XI receptor and high-molecular-weight kininogen, as well as factors V and VIII, which interact with platelet membrane phospholipids to facilitate the activation of factor X to Xa and the conversion of prothrombin to thrombin (see Tutorial 6).

Conversely, fibrinolysis is the process of dissolving clots through activation of the fibrinolytic system. Fibrin degradation is catalysed by plasmin, the product of plasminogen activation. Thrombus dissolution is, in large part, mediated by fibrinolysis inside the thrombus. In consolidating thrombus, plasminogen binds to fibrin and to platelets, allowing local release of plasmin within the thrombus. In addition, the circulating plasminogen activators, tissue plasminogen activator (tPA) and single-chain urokinase plasminogen activator (scuPA), catalyse plasmin formation and the degradation of fibrin to small fibrin degradation products (FDPs) and thereby clot lysis [1].

17.1.2 Therapeutic Thrombolysis

Early attempts to treat stroke patients using thrombolytic drugs were made in the 1970s by Fletcher et al. [2], but urokinase given 24 h after the onset of symptoms caused additional morbidity due to secondary haemorrhage, and its use in stroke stopped. Interest restarted 10 years later, when the benefit of thrombolytics was reported for patients with acute coronary thrombosis. They were initially only then used in stoke patients with vertebrobasilar thrombosis [3].

What was apparent by this stage was that most strokes were caused by arterial thrombosis. Solis et al. [4] reported that angiography, if performed within 12 h of the onset of symptoms, showed occluded arteries (appropriate to any neurological deficit) in 80–90% of patients. The percentage of identifiable thrombotic occlusions decreased markedly, if angiography was performed later, because spontaneous thrombolysis occurs. Thus, leaving aside the issue of neuron vulnerability, therapeutic thrombolysis needs to be performed early.

The aim of therapeutic thrombolysis is to stimulate fibrinolysis by plasmin, through infusion of analogues of tissue plasminogen activator (tPA). The ideal thrombolytic drug would activate only fibrin-bound plasminogen (plasminogen has a high affinity for fibrin) and not circulating plasminogen. This specificity is important because otherwise they risk causing consumption of plasma fibrinogen and generalised hypocoagulability because once activated, the clotting process continues to produce fibrinogen to make more clot and so becomes exhausted. These drugs are discussed in Tutorial 6.

17.1.3 Indications for Thrombolysis and Thrombectomy

Thrombolysis with drugs alone can potentially be used to treat any intravascular thrombosis. However, it may be unnecessary (because of spontaneous thrombolysis), dangerous (causing secondary haemorrhage of infarcted brain tissue) or cause general complications (by interfering with overall clotting). Thus, its indications in the nervous system are limited to: acute ischaemic stroke, central retinal artery occlusion, symptomatic dural sinus thrombosis and in other parts of the body to acute myocardial infarction, selective cases of pulmonary embolism, large artery thrombosis and Budd–Chiari syndrome with hepatic vein thrombosis. Restricting the use of these drugs to serious medical conditions acknowledges their dangers and leaves vascular surgeons, cardiologists and endovascular therapists to perform recanalisation procedures by thrombectomy (e.g. stent retriever, suction clot extraction), mechanical clot disruption or other techniques (e.g. angioplasty, stenting). Procedures that aim to re-establish blood flow to tissues supplied by occluded vessels without or with reduced doses of thrombolytic drugs.

17.2 Evidence for Thrombolysis and Thrombectomy After Acute Stroke

Stroke is the third commonest cause of death in the USA with 500,000 new strokes per year, and the incidence in the UK is 150–200/100,000 pa. Approximately 75% occur in the distribution of the carotid artery, and mortality rates for carotid distribution strokes are 17% at 30 days and 40% at 5 years. The potential benefit of effective treatment to prevent this morbidity is well recognised and described in many recent reviews [5, 6]. The main therapeutic interventions are listed in Table 17.1. The aim of this tutorial is to describe the rationale to recanalise those thrombosed arteries which are within the remit of interventional neuroradiology.

Table 17.1 Main therapeutic interventions in use for treatment of acute/subacute stroke

Medical
Intravenous thrombolysis
Antiplatelet agents
Anticoagulation
Neuroprotective agents
Haemodilution
Intravenous dextran
Steroids
Induced hypothermia
Control of hyperglycaemia
Endovascular
Intra-arterial thrombolysis
Mechanical clot disruption
Angioplasty
Stenting
Clot extraction
Surgical
Carotid endarterectomy
EC–IC bypass (not in general use)

17.2.1 Trails of Intravenous Thrombolysis for Acute Stroke

Early randomised controlled trials (RCT) used streptokinase, but more recent trials of intravenous thrombolysis (IV-TLS) have used either urokinase or tPA analogues (i.e. recombinant tissue plasminogen activator or rtPA). They showed that treatment is effective if instigated in the first few hours after the stroke.

The major RCTs are ECASS I and II (European Cooperative Acute Stroke Study) [7, 8] and the NINDS trial [9]. In ECASS, tPA was given intravenously within 6 h of the onset of symptoms. It showed a statistically nonsignificant trend towards a benefit from treatment. The NINDS trial was a double-blind, placebo-controlled trial of tPA in doses of 0.9 mg/kg IV within the first 3 h of the onset of symptoms (10% given as an initial bolus and the remainder over 60 min). The result was a statistically significant benefit in long-term outcomes in the drug-treated group, who were 30% more likely to have minimal or no disability at 3 months than non-treated controls. Though the rates of neurological improvement at 24 h were the same and the haemorrhage rate at

36 h was slightly higher for treated patients (6.4 vs. 0.6%), the overall mortality rate (at 3 months) was still lower in the treated group (17 vs. 21%). The results of this study supported the use of tPA in patients who can be evaluated and treated within 3 h of the onset of symptoms. This conclusion was emphasised by the findings of another, similar double-blind trial (ATLANTIS), which failed to show a favourable result from treatment with tPA in the same intravenous doses and an increased frequency of symptomatic haemorrhage when given between 3 and 6 h following symptom onset [10].

The NINDS trial result was not supported by a meta-analysis of data from previous trials [1]. The difference was attributed to the very strict inclusion criteria in the NINDS trial (i.e. treatment within <3 h of symptom onset, mild deficit, blood pressure limits and no previous stroke) [11]. As a result, the uptake of IV-tPA in clinical practice has been slow because only a minority of stroke patients are eligible on these criteria [12]. Solutions are to extend the time-to-treat (TTT) limit and improve patient selection [13]. The more recent ECASS III showed that for IV-tPA TTT could be extended to 4.5–6 h [8]. Imaging has been a key element in selecting patients for thrombolysis, and it has become the focus for a great deal of research to develop better triage criteria. Its contribution is discussed below.

An important lesson in the evolution of the treatment guidelines for acute stroke is not to rely on data from small trials. An example is a trial to assess the efficacy and safety of abciximab. An initial trial showed some benefits with a lower risk of secondary haemorrhage in stroke patients [14], but a subsequent larger trial was stopped after 808 participants because of higher secondary haemorrhage rates in the treated patients [15].

17.2.2 Trails of Intra-arterial Thrombolysis for Acute Stroke

The rationale of intra-arterial thrombolysis (IA-TLS) is to target the drug to the site of thrombosis. Its goal is the same as intravenous treatment, i.e. to limit the area of infarcted parenchyma and to enhance the survival of any functionally disabled cerebral tissue in the surrounding ischaemic penumbra. It is obviously only suitable for patients with proven intra-arterial thrombosis and in practice to those with thrombus in the internal carotid and middle cerebral arteries or vertebral and basilar arteries. The advantages over IV-TLS are higher recanalisation rates, only patients with demonstrated arterial occlusion are treated and a reduction in the amount of administered drug. It can also be combined with mechanical clot disruption.

There have been two RCTs of IA-TLS which have confirmed most of these advantages. They were PROACT I [16] and PROACT II [17] and performed comparing IA-TLS with pro-urokinase to IA placebo infusion in PROACT 1. In both studies, the TTT interval between symptom onset and starting AI-TLS was limited to 6 h, and patients in both arms were given heparin. IA-TLS was performed via a microcatheter placed in the proximal middle cerebral artery as close to thrombus as possible and pro-urokinase infused over 2 h to a maximum dose of 9 mg. Mechanical clot disruption was not allowed. Despite an increased rate of early symptomatic haemorrhagic transformation in the treated group (10.2 vs. 2%), the ultimate mortality rates were similar and functional outcomes (mRS $\leq$ 2) were better (40 vs. 25%) which represented a 15% absolute difference. This benefit over intravenous thrombolysis has been confirmed in observational studies [18].

The disadvantages of IA-TLS are the substantial numbers of potential patients that need to be assessed for possible treatment, and the optimum time to treatment remains <3–6 h of symptom onset. This presents a substantial logistic challenge since arterial imaging and selection (together with transfer to a specialist centre) have to be completed within this period. Other considerations are the risks associated with cerebral catheterisation and, if heparin is given during procedures, the potential risk of increased morbidity in the event of a haemorrhagic complication.

17.2.3 Trials of Combined Intravenous and Intra-arterial Thrombolysis for Acute Stroke

For the above reasons, combination treatment or 'bridging' therapy in which IV-tPA is given during investigations and triage for possible IA-TLS, is widely practiced [19]. It has been shown that a substantial proportion of patients still have arterial occlusions after the IV-tPA (about 70%) and that recanalisation rates are better when the two treatments were combined [20]. However, despite improving recanalisation rates, trails of combined therapy generally failed to show a significant clinical benefit at 3 months [21, 22]. The main drawback to combined therapy was high haemorrhage rates; in both the RECANALISE [21] and IMS II [23] studies, symptomatic intracranial haemorrhage occurred in about 10% of patients, whereas IV trials that exclude patients with substantial arterial occlusion reported symptomatic haemorrhage rates of 2–8%, e.g. ECASS III [23] and the Safe Implementation of Thrombolysis in Stroke study [24]. The role of combination therapy became blurred with the commercial introduction of clot extraction devices and their permitted use in trials designed to test the efficacy of IA-TLS. Though consistent in identifying early recanalisation as a benefit most were ambivalent over any long-term outcome advantage. The process culminated with the stopping of the largest of such trials, IMS III (Interventional Management of Stroke) study in 2013 on the grounds of futility after 656 participants randomised to endovascular treatment with IV-tPA (0.9 mg alteplase per kilogramme) or IV-tPA alone achieved mRS $\leq$ 2 function at 90 days in 41% and 39% of patients, respectively [25]. Poor outcomes in the IA-TLS treated group was related to the length of time to recanalisation (mean 325 min) which was achieved in 76% [26].

17.2.4 Trails of Mechanical Thrombectomy for Acute Stroke

The role of thrombectomy was dramatically increased in 2015 following the publication of positive reports of five RCTs comparing IV-tPA with endovascular clot extraction (i.e. mechanical thrombectomy) against IV-tPA alone. These resolved any lingering controversy over its value and repudiated the conclusions drawn from IMS III. The first RCT to report was the MR CLEAN trial [27] conducted in Holland, which randomised 500 acute stroke patients to intra-arterial thrombolysis and/or stent-retriever thrombectomy with IV-tPA versus IV-tPA and standard medical care. This protocol was repeated in the other trials (see Table 17.2) with minor modifications in patient selection criteria and TTT thresholds for instigating IV-tPA and thrombectomy. In

Table 17.2 Summary of RCT reports comparing IV-tPA with and without thrombectomy for acute stroke

Trial	n=	Selection criteria	TBT method	Time to treat (TTT)		mRS recovery (%)[a]	
				TBT	SMT	TBT	SMT
MR CLEAN [27]	500	LAO	STR IA-tPA	<6 h	<4.5 h	32	19.1
EXTEND-IA [28]	70	LAO Viable penumbra	STR	<6 h	<4.5 h	71	40
ESCAPE [29]	315	LAO ASPECTS 6–10	STR suction	<12 h	<4.5 h	53	29.3
SWIFT-PRIME [30]	196	LAO	STR only	<6 h	<4.5 h	61	39
REVASCAT [31]	206	LAO ASPECTS < 7[b]	STR stenting	<8 h	<4.5 h	43	28.2

TBT thrombectomy but clot extraction, *SMT* standard medical treatment with IV-tPA, *LAO* large artery occlusion, *STR* stent retriever

[a]mRS recovery = mRS $\leq$ 2 or NHISS improvement of eight points

[b]ASPECTS threshold increased to eight in second part of the trial. See text for other abbreviations

MR CLEAN, intra-arterial therapy had to be started within 6 h of symptom onset. The number of participants recovering to be functionally independent (defined as mRS ≤ 2) measured outcome. The result was that 32% of thrombectomy and 19.1% of standard care patients achieved function independence. Rates of adverse events were similar in the two groups. The online publication of data from MR CLEAN leads to data monitoring committees stopping other recruiting trials with similar protocols; these included EXTEND-IA, ESCAPE and REVASCAT.

There have since been several data review publications (i.e. meta-analysis), which confirm the efficacy of mechanical thrombectomy. Rodrigues et al. [32] calculated a risk ratio of 1.56 (95% CI 1.38–1.75) for a good functional outcome after adjuvant mechanical thrombectomy and 0.86 (95% CI 0.69–1.06) for mortality. Badhiwala et al. [33] used pooled data from eight RCTs (2423 patients) comparing IV-tPA with and without mechanical thrombectomy and documented a higher revascularisation rate at 24 h, 75.8% versus 34.1% for adjuvant thrombectomy; similar haemorrhage rates, 5.7% versus 5.1%; and higher good functional outcome rates at 90 days, 44.6% versus 31.8%. A common feature of these trials was the use of stent-retrieval devices for thrombectomy.

17.3 Endovascular Treatments of Acute Stroke

The potential advantages of avoiding the use of thrombolytic agents stimulated the design and testing of various endovascular thrombectomy devices. The impetus being the need for rapid recanalisation of occluded arteries by extracting rather than dissolving thrombus, particularly large clot. These devices are designed for intracranial navigation, and the principal target is thrombus in the middle cerebral artery.

17.3.1 Selection of Patients for Endovascular Intervention

The initial neurological status of the acute stroke patient is important and related to their likelihood of recovery. In trials, it is generally compared between patients, using the US National Institute of Health Stroke Scale (NIHSS) [34]. Scores greater than 15 indicate a very poor prognosis with a high probability of death or severe disability and below 6 that recovery is likely [35]. However, patients with low scores may have established cerebral infarction and need to be distinguished from those experiencing transient ischaemic attacks (TIA). This is a dilemma for researchers designing clinical trials since a proportion of patients presenting with the clinical signs of acute stroke will recover spontaneously (presumably because of natural thrombolysis), and therefore for them, intervention is unnecessary. In practice, this seems less of a problem, possibly because of imaging.

Imaging is critical in the selection of patients and is usually performed with CT because it is generally available in hospital receiving areas and is easier to perform than MRI in the acute setting when patients may be neurologically impaired and details of past medical history are incomplete.

CT: This will normally show no parenchymal abnormality in patients with ischaemic stroke. Extensive areas of hypodensity are relative contraindications to thrombolysis. Low-density change exceeding one-third of the middle cerebral artery territory is a contraindication to intravenous thrombolysis. The ECASS trialists set this threshold, but a more sophisticated assessment has been proposed as the Alberta Stroke Program Early CT Score (ASPECTS) [36]. This schema divides the middle cerebral artery territory (as displayed on axial CT scans at specified levels) into 10 segments, and the reader subtracts a point for each area that is hypointense relative to normal brain. Scores less than 7 are associated with poor outcomes [37]. CT will show primary haemorrhage and any secondary haemorrhagic changes in areas of infarction (thereby contraindicating thrombolysis). Hyperintense vessels may be seen and suggest the presence of intravascular thrombosis.

CTA: This is an effective method of imaging arteries and can be combined with CT perfusion imaging to identify areas of reduced cerebral perfusion and intra-arterial thrombosis. It offers the potential of quickly identifying patients who may benefit from IA-TLS or clot removal.

MRI: MR scanning poses some logistical problems for examining the acute stroke patients and is generally less available than CT. Concerns about its inability to identify intracerebral haemorrhage have been exaggerated, and additional susceptibility-weighted scans are sufficiently accurate to exclude primary haemorrhage and anything but the most insignificant secondary bleeding. However, increasing the number of sequences leads to longer scan times and delays in starting therapy. Its main advantage is the capability of diffusion-weighted imaging (DWI). This technique is highly sensitive to early cerebral ischaemia and will show changes within minutes of cerebral infarction [38]. MR perfusion will show areas of absent or reduced perfusion and is used in combination with DWI to assess the viability of brain affected by arterial occlusions. Areas of abnormality demonstrated by DWI which are shown to be still perfused on MR-perfusion scans are described as penumbra regions which are potentially recoverable if blood flow can be re-established before infarction. This is a potentially useful objective parameter for selecting patients for thrombolysis, but cerebral ischaemia is a rapidly evolving pathology and imaging is by necessity only a 'snapshot' of the process. The practical application of the technique has proved difficult in trials [39], and a recent meta-analysis was unable to show a benefit that warranted delaying thrombolysis for the additional data it provided [40].

DSA: It is used only to guide interventions and assess outcomes, i.e. extent of recanalisation. The latter is quantified using the Thrombosis in myocardial infarction (TIMI) trial perfusion grades adopted from cardiology (see Table 17.3).

Imaging guidelines were recently published by the American Heart Association, and all the imaging options for imaging the acute stroke patient were critically reviewed [42]. There remains much that is uncertain in the field of functional imaging but for triage of patients for thrombolysis or thrombectomy demonstrating large artery occlusion is all that really matters, and this can be done by CTA or MRA.

Table 17.3 Thrombosis in myocardial infarction grade

TIMI 0	No antegrade blood flow
TIMI 1	Faint blood flow with incomplete distal filling
TIMI 2	Delayed or sluggish antegrade blood flow with complete filling of the distal territory
TIMI 3	Normal blood flow

The scale was devised to assess success of myocardial reperfusion after IV thrombolysis [41]

17.3.2 Angioplasty and Stent for Thrombectomy in Acute Stroke

The benefit of rapidly re-establishing flow in a thrombosed artery has been recognised by many endovascular therapists since acute intravascular thrombosis is one of the many hazards that may complicate endovascular navigation. Clot retrieval is one solution, but balloon angioplasty to compress clot against the vessel wall can re-establish blood flow and assist endogenous or therapeutic thrombolysis. Successful angioplasty has been reported in case studies, alone [43, 44] and combined with stents [45].

Small clinical studies of the use of stents in acute stroke have been reported [46, 47]. The SARIS study [46] treated patients up to 8 h after onset of symptomatic stroke and achieved TIMI 2 or 3 grades of recanalisation (see Table 17.3) in all cases with a symptomatic haemorrhage rate of 5%. The value of additional stenting was apparent in the Brekenfeld et al. study [47] with recanalisation rates reaching 90% without complicating secondary haemorrhage or vessel perforation, attributed to avoidance of repetitive mechanical disruption [47] This initiative was backed by animal studies showing the potential of angioplasty with stenting [48].

17.3.3 Stent-Retrieval Devices in Acute Stroke

A range of devices, specifically designed for endovascular thrombectomy devices have been tested, marketed and, in some cases, withdrawn from use. The clot-capture devices include Merci Clot retriever (Concentric Medical), Catch Thromboembolectomy System (Balt Extrusion),

Phenox Clot Retriever (Phenox GmbH) which are deployed through microcatheter either within or distal to clot and then withdrawn (with clot attached) into a larger proximally positioned catheter. The proximal catheter may include an inflatable balloon to allow antegrade blood flow in the proximal artery to be suspended during the retrieval manoeuvre. Alternatives are devices that disrupt the clot and actively aspirate debris into a retriever catheter, e.g. Penumbra System (Penumbra Inc.), or combined disruption using a jet of fluid, e.g. Angiojet (Possis Medical Inc.), or ultrasound, e.g. EKOS MicroLysuS Infusion Catheter (EKOS Group) with aspiration. These devices have evolved over the last few years with design changes improving recanalisation rates from about 40–80% [49].

A recent development has been the use of stent-like devices for clot retrieval. Anecdotal reports that a closed-cell design fully retrievable stent called Solitaire (ev3) (designed as an adjunct device in coil embolisation of aneurysms) was an effective clot retriever stimulated the manufacturing and marketing of a new range of stent-retrieval devices, e.g. Solitaire FR revascularisation device (ev3/Covidien) and Trevo (Stryker) [50]. Stent retrievers have since been shown to be more effective than the Merci device in a RCT [30].

The technique involves passing a microcatheter (over a standard guidewire) through the thrombus and then delivering the retrievable stent device across the occluded segment. Unsheathing, i.e. retrieving the microcatheter, deploys the stent retriever, and then a period of 3–5 min should be allowed for the clot to become entrapped within the frame of the device. The device (and contained thrombus) is then retrieved during the arrest of blood flow in the proximal artery. Blood flow is stopped by inflation of a nondetachable balloon, and at the same time, the operator aspirates through the large guide catheter (7–8 F) during retrieval of clot. The procedure can be repeated and performed without thrombolytic drugs or substantial systemic anticoagulation. Since 2015 and publication of positive RCTs, mechanical clot retrieval has become the endovascular procedure of first choice and substantially changed the current paradigms for the transfer, imaging and use of IV and IA thrombolytic drugs in acute stroke patients. Combining mechanical thrombectomy with IA-tPA infusions is generally no longer practiced, but IV-tPA (bridging therapy) continues to be used. Stent retrievers have clearly improved recanalisation rates, but in practice, clot extraction often requires several attempts (Fig. 17.1).

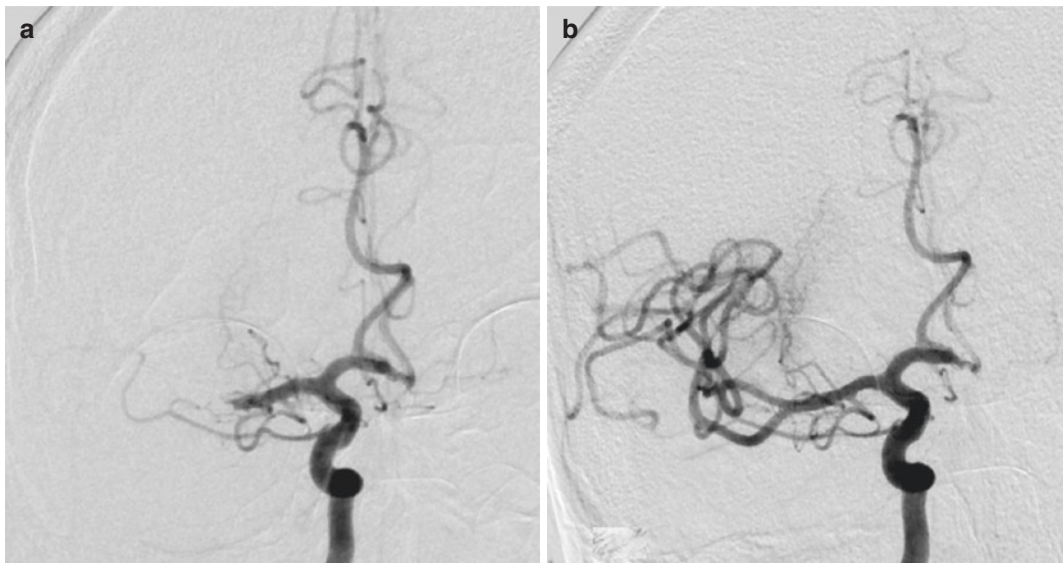

Fig. 17.1 Frontal DSA before (**a**) and after (**b**) removal of acute thrombus from the *right middle* cerebral artery using a stent retriever (Courtesy of Dr. R Corkill)

17.3.4 Complication of Endovascular Interventions for Arterial Thrombosis

Possible complications are those associated with the use of thrombolytic drugs, endovascular navigation and mechanical thrombectomy devices. The single most important complication caused by thrombolysis and thrombectomy is secondary haemorrhage. After cerebral infarction, spontaneous intracerebral haemorrhage may occur due to revascularisation of infarcted brain and thrombolysis adds to this risk. In addition, the use of thrombolytic and anticoagulant drugs may cause systemic bleeding, e.g. gastrointestinal bleeding or bleeding from vascular access sites and hypersensitivity allergic reactions, e.g. swelling of the tongue and lips. The last is usually mild and self-limiting but if severe may require treatment with corticosteroids.

There is no specific antagonist or 'antidote' for thrombolytic agents in current clinical use. If bleeding occurs, the basic principles for reversal of the thrombolytic effects are:

- Stop administration of the thrombolytic agent
- Stop administration of additional anticoagulants (e.g. heparin) and their reversal with protamine sulphate or vitamin K
- Administration of cryoprecipitate or fresh frozen plasma
- Administration of antifibrinolytic drugs to inhibit plasmin activity, e.g. tranexamic acid

Other complications associated with thrombectomy and thrombolysis include:

- Distal thromboembolism
- Vessel perforation and subarachnoid haemorrhage
- Arterial dissection and false aneurysm formation
- Reocclusion of the treated artery
- Reperfusion syndromes
- Allergic reactions and antibody formation (particularly with streptokinase because it is a foreign protein)

17.3.5 Contraindication to Thrombolysis

In order to prevent iatrogenic bleeding associated with thrombolysis, the following are absolute or relative contraindications to its use:

- Active bleeding
- Pre-existing bleeding disorder
- Another recent cerebral infarction
- Other potential bleeding sites, e.g. known peptic ulceration, malignancies, varices
- Recent surgery, serious trauma (head injury), myocardial infarction
- Uncontrolled hypertension
- Proliferative retinopathy
- Pregnancy (see treatment for dual sinus thrombosis below)

17.4 Endovascular Treatment of Cerebral Venous Sinus Thrombosis

Spontaneous thrombosis of intracranial venous sinuses has a variety of causes and may result in a life-threatening condition that requires emergency endovascular thrombolysis and thrombectomy.

17.4.1 Pathology and Aetiology

Cerebral venous sinus thrombosis (CVST) occurs most often in the superior sagittal sinus (70–80%), transverse and sigmoid sinuses (70%) and least often the cavernous and straight sinuses. In 30–40% of cases multiple sinuses and cerebral veins are thrombosed. Thrombosis may spread to cerebral (cortical and central) veins, and this combined with blockage of venous drainage pathways leads to venous hypertension, cerebral hypoperfusion, cytotoxic oedema and infarction. Sinus blockage also obstructs CSF absorption and cause intracranial hypertension.

The annual incidence of CVST amongst adults is 1.32 per 100,000 person-years (95% CI, 1.06–1.61) and represents 1–2% of all strokes [51]. It

may occur sporadically, but in 75–80% of patients, a precipitating cause or causes can be defined. The commonest causes are pregnancy and the puerperium (12/100,000 deliveries), oral contraceptives, intracranial infections (particularly mastoiditis in children) and coagulopathies. For these reasons, it is commoner in women. Other causes are malignancy; systemic illnesses associated with hypercoagulation, e.g. cirrhosis and diabetes; nephrotic syndromes; haematological and connective tissue diseases; vasculitides; trauma due to head injury and neurosurgery; and drugs, e.g. steroids, cyclosporin and tamoxifen.

17.4.2 Presentation and Natural History

The onset of symptoms is insidious, and typically symptoms are slowly progressive over days or 2–3 weeks. Patient's complaints are non-specific with headache (90%), nausea and vomiting (30%) and visual disturbances. They may present after onset of seizures (30%), focal neurological deficits (20%) or impaired levels of consciousness including coma (15%). Papilloedema is evident on examination in 30–40% and visual loss in 10–15%. Atypically, patients may present with sudden onset headache [52]. The symptoms and presenting features are similar to those of idiopathic intracranial hypertension and this is often the initial working diagnosis.

The prognosis is variable with only a mild illness in some patients and rapid progression to coma and death in others. A general deterioration in mental state is common, and the patient's level of consciousness may fluctuate. Mortality rates of 30–50% were reported in older angiographic series, but in more recent reports, it is about 10% [53]. There is often a delay in diagnosis, and because the onset is insidious, it is often difficult to date the onset of thrombosis.

17.4.3 Imaging

Abnormal findings on imaging are often subtle in the early stages and often missed [54].

- CT: There may be evidence of diffuse cerebral oedema, and the involved sinus appears hyperdense and thickened. A classic feature is the so-called delta sign which is due to nonenhancing clot, framed by enhancement in the thickened enhancing walls of the superior sagittal sinus. Cortical venous infarction causes cerebral swelling and low density in the involved region and hyperdensity if secondary haemorrhage occurs. Haemorrhage may be within the parenchyma and/or subarachnoid space. CT may be normal in the early stages but is useful to exclude other causes.
- CTV: The accuracy of spiral CT scanning with 3D image reconstruction is similar to MRV, i.e. 95% sensitivity and 90% specificity. The timing of scanning after contrast administration is critical, and if done well, the resulting images are excellent. It can be used to monitor progress.
- MRI: Typically, T1-weighted and T2-weighted sequences in three planes with Gadolinium-enhanced and susceptibility-weighted (SWI) sequences are performed. SWI is the sequence most sensitive to slow venous flow and stasis. Oedema and cerebral swelling are better appreciated on MRI and thrombosis, because the absence of normal flow void in dual sinuses, may be evident. Gradient echo sequences may show haemorrhagic changes in the cortex and are more sensitive than CT to subacute haemorrhage.
- MRV: Flow-sensitive time-of-flight (TOF) or phase contrast 3D sequences are typically performed. A low-flow-encoded phase contrast sequence will confirm venous or large dural sinus thrombosis [55]. The accuracy of MRV for demonstrating sinus occlusion is generally the same or better than CTV [56].
- DSA: Catheter angiography remains the final arbiter in the diagnosis but is usually not necessary for diagnosis and is therefore performed only as part of an endovascular treatment.
- Raised d-dimer levels (>500 Î¼g/l) will confirm substantial intravenous thrombosis and may be useful in certain situations, e.g. when imaging is unavailable or nondiagnostic [57].

17.4.4 Endovascular Treatment

Medical treatment with steroids and anticoagulation as well as specific treatment of any predisposing condition is the first line of management [58]. Heparin is given by infusion or as subcutaneous LMWH twice daily. There has not been a randomised trial of more aggressive interventions, and recommendations are based on comparative studies. These accept that a minority of patients will deteriorate and that thrombolytic therapy or thrombectomy is then the best option available [59]. Anticoagulation should be prescribed even when cortical venous thrombosis is complicated by secondary haemorrhage. The International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT) identified several poor prognostic factors, which may help to select patients for more aggressive, i.e. endovascular, therapy. These included male gender, thrombosis of the deep cerebral venous system, intracranial haemorrhage, confusion/coma and background malignancy.

The next level of treatment (usually after failure of 12–24 h of medical treatment) is endovascular thrombolysis. Surgical thrombectomy should be considered only if endovascular treatment fails and the patient continues to deteriorate.

17.4.4.1 Thrombolysis and Thrombectomy

Direct thrombolysis of the large dural sinuses has been described by several authors. It is performed by intra-sinus injections of heparin or thrombolytic drugs (e.g. urokinase or rtPA) [60, 61]. The technique used is operator dependent, i.e. there is no defined best way of performing thrombolysis in this situation. Access is obviously transvenous and my preference is from the femoral vein (rather than jugular vein puncture) because it makes additional thrombectomy (if required) easier. Navigation is through the clot to achieve a microcatheter tip position as far proximal in the sinus as possible, e.g. the anterior part of the superior sagittal sinus. Thrombolysis is performed by infusion of tPA (at about 1.5 mg/h) over 24–36 h or longer. The infusion rate should be reduced, rather than stopped if excessive oozing occurs at the puncture site, and should be monitored by repeat DSA (usually the next day) to decide on continuing or instigating thrombectomy [62]. Two or more microcatheters can be placed and infusion doses of tPA adjusted appropriately.

Mechanical disruption or retrieval of the clot can be performed as an adjuvant to obtain access prior to infusion thrombolysis or alternative to thrombolysis (usually after failure to dissolve chronic thrombus). It is described using balloons, snares and guidewires. Rheolytic thrombectomy with extraction devices has also been used to disperse extensive thrombus [63, 64], and more recently stent retrievers used [65]. Stent deployment to maintain the patency of a reopened sinus may be required [66], and intra-arterial administration of thrombolytics by pulsed hand injections can be used to lyse clot in cortical veins [64].

17.4.5 Outcomes

The overall mortality reported in a large patient registry after CVST was 8%, with 4.3% acute deaths and 3.4% within 30 days of symptom onset [67]. This registry has defined the current prognosis for patients after current management, but didn't collect data specific to endovascular interventions or any complications of endovascular treatments, so reports of complications are too few to make any meaningful description [53]. In the ISCVT study, 79% of patients made a complete recovery [54]. Long-term sequelae have been studied, and because of the high incidence of an underlying abnormality of coagulation, recurrent thrombosis (2%) or thromboembolism (13%) has been reported [68, 69], and chronic headache is common amongst survivors [70].

17.5 Thrombolysis for Central Retinal Artery Thrombosis

Spontaneous thrombosis of the central retinal artery is an uncommon but not rare event. The incidence of its diagnosis is 1.90 per 100,000 per

year (95% CI, 1.33–2.47) [71]. The importance of retinal artery blood flow to maintain vision means patients are immediately aware of its occlusion, and so seek medical attention early, unlike after occlusion of many other small cerebral arteries.

17.5.1 Pathology and Aetiology

Central retinal artery occlusion (CRAO) is due to thromboembolism or in situ thrombosis. Emboli may arise from atheroma in the internal carotid artery, aorta or the heart. They generally consist of either cholesterol or fibrin, though they may be a combination of different materials including vegetations from heart valves. The causes of non-embolic thrombosis are less clear; the commonest associated factor is systemic hypertension, but arterial dissection, atheroma and subintimal haemorrhage have been reported [72].

Patients present with sudden onset painless blindness and persistent loss of monocular vision. The peak incidence occurs in the seventh decade of life, and only 4% of patients present under the age of 40 years [73]. It is more common in men, but the gender difference is modest. Fundoscopy shows oedema of the central retina, a cherry-red macula and impaired blood flow in the retinal arteries and veins.

17.5.2 Indications for Thrombolysis

The clinical signs and symptoms are graded as follows:

- Stage I (incomplete CRAO occlusion): Visual acuity is diminished, but the visual field is preserved. The prognosis is good, and conservative treatment is advised but with intense observation because visual loss may progress.
- Stage II (subtotal CRAO occlusion): Completely blind or with only a small island of visual field preserved and near complete occlusion of the CRA.
- Stage III (complete CRAO occlusion with choroidal hypoperfusion or infarction): Blind with CRA occlusion and additional patchy choroidal hypoperfusion or infarction.

Conservative treatments are ocular paracentesis and topical intra-ocular pressure-lowering agents. Additional treatments include a range of measures including, mannitol, steroid, heparin and hyperbaric oxygen. The use of antiplatelet drugs is generally recommended as for other types of thromboembolism; thus, aspirin (high or low doses), clopidogrel or dipyridamole are prescribed alone or in combinations. Thrombolysis is indicated for stages II and III and only for incomplete artery occlusion if vision deteriorates [72]. Contraindications include endocarditis, recent myocardial infarction or stroke, intracardiac aneurysm, atrial fibrillation, haemorrhagic diathesis, cirrhosis of the liver, gastric or duodenal ulcer, untreatable hypertension, recent major surgery and pre-existing anticoagulant therapy.

17.5.3 Technique for Central Retinal Artery Thrombolysis

The procedure is performed by infusion or by pulsed injections of thrombolytic through a microcatheter positioned with its tip in the proximal third of the ophthalmic artery [74]. Patients are anticoagulated with heparin (3–5000 IU bolus), and care should be taken to avoid spasm in the ophthalmic artery, since it will cause reflux of the injected thrombolytic into the internal carotid artery. Described doses of thrombolytics include aliquot injections of tPA (3 mg infused over 5 min and repeated to a maximum of 20 mg) or infusions over 2 h of urokinase 10,000 IU/ml (to a maximum dose of 1.2 million IU) or rtPA 1 mg/ml (to a maximum dose of 50 mg). At this stage, there should be evidence of reopening of the artery, and if not, further treatment is unlikely to be successful. Rarely, injections are made in the internal maxillary artery if catheterisation of the ophthalmic artery is not possible because of internal carotid occlusion [75].

17.5.4 Results

Case studies reported successful recanalisation and restoration of vision if treatment was

instigated early, and best if treatment starts within 6 h of symptom onset [74, 75]. A meta-analysis of the literature by Noble et al. [76] found improvement in vision on average in 93% of patients, but Beatty and Au Eong [77] found complete recovery (6/6 vision) in only 14%, good recovery (6/12 vision) in 27% and poor recovery (3/60 vision) in 60% of treated eyes. The issue was settled by a RCT, EAGLE (the European Assessment Group for Lysis in the Eye) study [78] which compared conservative treatment versus IA-TLS with tPA (alteplase). The study was stopped because of a high complication rate in the IA-TLS group. Analysis of 84 treatments showed significant improvements in vision after thrombolysis in 57%, and 60% after conservative treatment, but the respective adverse event rates were 37.1 and 4.3%.

The incidences of complications calculated in meta-analysis reports are 4–6%, and symptoms were usually transient [76, 77]. In the EAGLE study, serious cerebral neurological complications occurred in both groups; these comprised one ischaemic stroke in the conservatively managed arm and two intracerebral haemorrhages in the thrombolysis arm. Minor events occurred in 1 conservative and 12 thrombolysis patients. In the latter, these varied from headache, eyelid oedema, corneal erosion, intraocular pressure increase and extraorbital bleeding. All patients recovered from the neurological deficits, but given the lack of efficacy, the trial was stopped and the trialist recommended conservative management (haemodilution, ocular massage, application of topical beta blocker and intravenous acetazolamide) pending the development of safer thrombolytics [78].

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Preamble

This tutorial continues the change in emphasis started in the last tutorial from considering the conditions we treat to the techniques of interventional neuroradiology and endovascular neurosurgery. I considered an alternative title for this book 'the art of fly fishing and interventional neuroradiology' because the performance of both activities has many similarities (and encompass two personal passions). The most obvious is the patience that both interventionalists and fishermen and fisherwomen need. The frustration when fish refuse to be tempted by a perfectly delivered fly is similar to those we've all experienced when our catheter or device refuses to obey their instructions, so clearly printed on the packaging. They both provide the same sense of satisfaction—when things go well. Our strategy worked and the prize is won. In the first case, we blame our equipment, and in the second, we congratulate ourselves on our skill.

A keen fisherman has a close working relationship with the fishing tackle supplier. The same is true in our work. We depend on the performance of our 'tackle', i.e. devices and equipment. We need to select the most appropriate tools and our patient's safety depends on their proper application. Understanding how embolic devices are manufactured, tested and their intended uses, is a fundamental component of our work. Ours is a technologically fast-moving

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discipline, and inevitably, the following details will be superseded quite quickly. This tutorial aims to give students an understanding of the principles behind the design and use of generic embolic agents and not instructions on how to use particular items.

18.1 General Principles of Embolic Agents

The word 'embolus' comes from the Greek 'embolos' meaning a wedge or plug. 'Embolos' was derived from 'en' (in) + 'ballein' (to throw), so an embolus is something thrown in. A 1913 medical definition of an embolus was: 'A plug of some substance lodged in a blood vessel, being brought to thither by the blood current. It consists most frequently of a clot of fibrin, a detached shred of a morbid growth, a globule of fat or a microscopic organism'. To this definition, we must now add a foreign material introduced either as a therapeutic agent or inadvertently.

The ideal embolic agent according to Picard et al. [1] is a sterile solidifying agent with an adjustable setting point that is (a) malleable when solid, (b) stable in vivo, (c) nontoxic and (d) radiopaque. These authors were obviously thinking primarily of liquid agents. Standard et al. [2] suggested that it should be (a) nontoxic, (b) nonbiodegradable and (c) easily deliverable. I applaud both attempts to specify the ideal agent, but in some circumstances, a biodegradable or a locally toxic agent may be useful. What is clear from the exercise of trying to formulate a universal specification is that no single agent is suitable in all circumstances.

18.1.1 How Does One Choose the Right Embolic Agent?

The answer to this question depends on the circumstances in which a blood vessel is to be occluded and primarily on the therapeutic intention (i.e. permanent or temporary embolisation). An equally important, but secondary consideration, is the target anatomy and how the embolic agent is to be delivered. The following criteria need to be considered in each situation:

- Specific purpose of the embolisation
- Anatomy and size of vessels to be embolised
- Suitability of the delivery system for the embolic agent
- Access route
- Occlusion point in relation to other vessels (normal and pathological)

18.2 Classification of Embolic Agents

This is an arbitrary process but a useful exercise in the context of a training course. Embolic agents can be classified as:

(a) Absorbable or nonabsorbable
(b) Liquid or solid
(c) Implant devices

They can then be subdivided as coils, balloons, particles, stent polymers, cytotoxics, etc.

18.2.1 Absorbable Materials

The most available and simplest to obtain material for embolisation is an autologous blood clot. The duration of occlusion is highly variable, and spontaneous lysis can be observed after only 15 min. A clot can be made more durable by mixing it with aminocaproic acid or oxidised cellulose. It can be useful for proximal embolisation in order to protect an arterial territory from the inadvertent spread of particles, provided there is a collateral blood flow. However, the fate of elements of the clot after spontaneous lysis is a concern, and it may be difficult to inject through small catheters. It is always an option for stopping life-threatening bleeding in an emergency [3].

Endovascular therapists have historically adapted materials used in other medical (surgical) specialties for embolisation. Two absorbable materials have been commonly adapted: gelatin and collagen.

(a) Gelatin sponge and powder: Gelfoam sponge (Pfizer) was first used by Speakman in 1964 [4] to occlude a caroticocavernous fistula. It is prepared from purified porcine skin gelatin and used as a haemostatic agent in surgery. It is supplied as sheets, which can be cut into appropriately sized pieces and injected through catheters for proximal embolisation of larger arteries. They have been used for preoperative tumour embolisation, to stop haemorrhage and to protect a vascular pedicle during embolisation with particles. Gelfoam powder (Pfizer) is also available (40–60 μm) and used as an emulsion with iodinated contrast for tumour embolisation [5]. Recanalisation occurs in 7–21 days, and because the particles are so small, care should be taken to avoid perivascular necrosis and cranial nerve palsies.

(b) Microfibrillar collagen: The commonest use of collagen sponge in endovascular tharapy is in vascular closure devices, e.g. Angio-Seal (St Jude Medical, St Paul, Minn). For surgical haemostasis, purified bovine collagen is prepared as a microcrystalline polymer in powder form. There is therefore a small risk of hypersensitivity reactions [6]. It can be dissolved in radiographic contrast media and used for embolisation. The particles are 75–150 μm, and their effect is to induce platelet agglutination, thrombosis and a granulomatous arteritis, which clears in 3 months. A less potent alternative form of collagen powder is 'Angiostat' (Regional Therapeutic Inc., Pacific Palisades, CA) which is produced by exposure of the collagen to glutaraldehyde. This agent comes as 75 μm particles and is less likely to cause an arteritis. It is used in endovascular oncology to retain locally delivered chemotherapy agents (chemoembolisation), and in this role, it is reported to be more effective than Gelfoam [7]. New absorbable haemostatic agents are now being used, particularly for endoscopic surgery, which potentially could be adapted for endovascular delivery [8].

18.2.2 Nonabsorbable Agents

It is important to realise that nonabsorbable does not mean the same as permanent when materials are used in vivo. Blood vessels occluded with nonabsorbable embolic agents can still recanalise, and the effect of initial vessel occlusion be lost. The mechanisms of recanalisation vary from the development of bypass collaterals to the embolus simply being absorbed into the vessel wall and the lumen reopening. Thus, the long-term effectiveness of embolic agents should always be considered in deciding which to use.

18.2.3 Particles

Particles have been used since the start of endovascular treatment for the control of haemorrhage, to devascularise hypervascular lesions and to close arteriovenous shunts. Endovascular embolisation with particles is widely practised to treat uterine fibroids and recently to deliver chemotherapeutic agents to the liver. Their use in interventional neuroradiology is predominantly for tumour embolisation and the closure of low-flow shunts. The agents that have or are currently used include:

(a) Silicone spheres: These were the first agents used for endovascular embolisation but have been superseded and now are only of historical interest [9].

(b) Suture material: Silk sutures (6–0) can be cut into short lengths and injected through a 2F microcatheter. It causes an intense inflammatory reaction within the vessel and was used in the USA when cyanoacrylate glue (NBCA) was not available.

(c) Polyvinyl alcohol foam (PVA): This is the 'work horse' material, which has undergone several improvements in recent years. It is formed by the reaction of polyvinyl alcohol foam with formaldehyde and manufactured as a sponge (Ivalon). Particles were originally made by shredding and grading this material. They are available in a range of sizes from 50–1000 μm. These particles had

a high friction coefficient making them difficult to inject and a tendency to clump together [10]. This has been reduced by improved manufacturing processes (e.g. Contour, Boston Scientific) but not entirely abolished. Therefore, a set-up with two syringes on a three-way tap is used to agitate the suspension during free-flow injections. A low concentration of smaller PVA particles mixed with contrast media injected initially will allow distal penetration to small vessels. The concentration can subsequently be increased to achieve larger vessel occlusion. A high concentration will result in faster devascularisation but less penetration [11].

Histological changes in vessels embolised with PVA occur in two phases—an acute inflammatory reaction in the arterial wall and a chronic giant-cell foreign-body reaction. Recanalisation occurs around the nonabsorbable particles. PVA is therefore considered a nonpermanent agent and best used for preoperative devascularisation.

Various so-called cocktails, i.e. mixtures of PVA and other embolic agents, have been suggested to improve the effectiveness of each agent in the combination. These have included PVA with collagen powder, silk and ethanol. Combinations can be used either as separate injections, e.g. silk to slow flow in a shunt and then PVA (which would otherwise have passed through the shunt) or mixed together [12].

(d) Gelatin-coated microspheres: These are made from an acrylic polymer embedded with porcine gelatin and manufactures as spheres (Embosphere, Merit Medical). They are beads of cross-linked acrylic impregnated with gelatin (trisacryl gelatin microspheres) and may be coated (e.g. with gold) for radiopacity. The spheres have a biconcave contour to simulate the 'swim properties' of red blood cells and a hydrophilic surface, which prevents aggregation in the catheter [13]. The occlusion is said to be more predictable and permanent than PVA, but the evidence for this is modest. They can be manufactured to contain a drug, e.g. doxorubicin HCl, for the treatment of liver tumours (e.g. DC Bead, Biocompatibles, UK), a strategy that is current being trialled [14].

(e) Coated particles: An interesting development is particles that are designed to swell after injection. They were made from copolymer material, such as PVA-sodium acrylate (e.g. QuadraSphere microspheres, Merit Medical). Delivered in a desiccated form, they swell by about 40% of their volume after hydration, so they fill vessels better than PVA and resist recanalisation but this has not been proven [15].

18.3 Coils

Coils are nonabsorbable and currently made of biologically inert metals; generally noble metals are used because they are non-magnetic and MRI is not contraindicated after their implantation. They are relatively non-thrombogenic, which is an advantage because they generally do not provoke substantial thrombosis when navigating through blood vessels but a disadvantage because they are less potent at inducing embolisation in high-flow situations. They come in two designs, either with controlled detachment or nonrecovery (uncontrolled) detachment.

18.3.1 Uncontrolled Release Coils

The first coils used in interventional radiology were Gianturco coils (Cook Medical). They were originally lengths of guidewire (stainless steel, beware in MR) whose inner core had been removed and cotton or Dacron thread added to make them more thrombogenic. They are delivered through a microcatheter using an unattached pushing wire and simply extruded from the catheter tip into the vessel or space to be embolised. There is no possibility of their retrieval once delivery has commenced.

Platinum pushable microcoils are relative short coils designed for embolisation in pedicles and situations where very accurate placement is

not required. They are pushed (or flushed by a forceful injection of saline) through the delivery microcatheter (1.5–3 F). They are used in venous spaces, e.g. dural sinuses, or placed within controlled detachment coils for large vessel occlusions. Cotton or Dacron thread is added to make them more thrombogenic, and they are manufactured to take complex shapes when unrestrained, e.g. pretzel and flower shapes. They are MR compatible (except that Dacron may cause artefact on the image) but are less thrombogenic than stainless steel coils, and large numbers are sometimes required.

Berenstein liquid coils (Boston Scientific) are a hybrid design of non-retrievable coil meant for use in AVMs [16]. They are constructed of highly flexible platinum wire and relatively short lengths so they can be flushed through a microcatheter. They were introduced when NBCA was not available in some countries and designed for endovascular treatment of AVMs. Liquid agents have largely replaced their role, but they are still used by some operators to close shunts and reduce blood flow prior to injections of a liquid embolic.

18.3.2 Controlled Detachment Coils

Detachment can be mechanical or non-mechanical. The latter is less likely to disturb the delivered coil and preferable for treating aneurysms; a situation where accurate placement with minimal mechanical disturbance is important. The Guglielmi detachable coils (GDC) were the first non-mechanical retrieval coils which, once positioned correctly, could be detached from a delivery control wire [17]. GDCs are detached from a control wire by electrolysis electrolytic detachment which depends on the platinum of the coil not being affected by electrolysis. Detachment from the control wire occurs at an uninsulated steel connecting bridge [18]. During this process, the coil is given a weak positive charge which will increase its thrombogenicity (by electrothrombosis), but the effect is negligible in practice. Generally, it is detrimental and masked during endovascular coil embolisation of aneurysms by anticoagulation. A variety of technologies have been used to control coil detachment. These detachment methods include hydrostatic pressure, thermal detachment, variations of electrothrombosis and a pull-wire system.

Controlled detachment coils are generally made of coiled platinum wire, with a secondary memory given to the coil so that it forms a predictable shape when delivered from the microcatheter. The shapes are determined by the secondary memory, and these are designed to improve the conformity of the coil to the endovascular space in which they are deployed (e.g. aneurysm sac) and increase the stability and packing density. This principle has been taken a step further with the development of coils with an attached woven mesh (Medina embolic device, Medtronic) [19]. In the past, a mechanically detached coil made of tungsten was available, but this was found to be soluble in the body and the metal dissolved with traces deposited in the liver [20]. No specific toxic complications were ever reported.

18.3.3 Large Artery Occlusion Devices (Plugs)

Endovascular ligation requires placing a permanent embolus in the vessel to be occluded. As described above, this can be done with balloons or coils. Coils are used in cerebral arteries because of their more reliable detachment control, but to occlude a large artery, a series need to be placed, spread over a section of the vessel. Single self-expanding obstructing devices are now available, e.g. Amplatzer Vascular Plug (St Jude's Medical), MVP plug (Medtronic) and Interlock IDC (Boston Scientific) which can be deployed in 2–16 mm diameter vessels over a short vessel section. They are widely used in peripheral vessels [21].

18.3.4 Coated Coils

In order to reduce the recurrence rate after endosaccular coil embolisation of aneurysms, a

variety of coil coatings have been tried to improve the stability of the coil–thrombus complex. [22]. The coatings used in experimental coils include various proteins, e.g. collagen, tissue growth factors and radioactive particles such as phosphorus^{32}, ion-implanted platinum coils as well as cellular elements such as fibroblasts. Two materials are used in clinical practice. These are:

(a) Hydrogel polymer surrounding a platinum metallic core (e.g. Hydrocoil, MicroVention, Inc.); this design has been shown to reduce recurrence of treated aneurysm in a RCT [23].
(b) Polyglycolic–polylactic acid (PGLA) coatings to enhance the initial inflammatory response after thrombosis and increase speed of scar tissue formation. This is applied either as an external coating to platinum coils (e.g. Matrix coils, Stryker Corp.) or as a core thread running within them (e.g. Cerecyte coils, Codman Neurovascular), but this confers no major advantage [24].

18.4 Balloons

Balloons are one of the oldest embolisation devices used in Interventional Neuroradiology. They are either detachable or fixed to a control catheter through which they are inflated by injecting liquids. Detachable balloons are used for large vessel occlusions and nondetachable balloons for various situations when temporary occlusions of a vessel are required or to deploy a balloon-mounted device.

18.4.1 Detachable Balloons

Detachable balloons are made of latex or silicone. They were developed originally by Serbinenko and made of latex with self-sealing valves [25]. Latex is impermeable but biodegrades after implantation so they only remained inflated for 2–4 weeks. In order to stabilise their volume, balloons were filled with HEMA (2-hydroxyethylmethacrylate), a water soluble solidifying liquid. It hardened over approximately 30 min, and the balloon effectively stayed inflated permanently even after the latex shell has degraded. The alternative silicon balloon is semipermeable. It has a higher expansion coefficient and is softer and less rigid, and stays inflated longer than latex balloons, but must be filled with an iso-osmolar solution to prevent its volume changing due to an osmotic gradient with blood. Balloons are available with self-sealing valves and they detached by simple traction. A tractionless system has been described [26]. Their use had declined because of concerns over the reliability of detachment; a reliable electrolytic control system would solve the problem.

18.4.2 Nondetachable Balloons

This type of balloon is generally constructed of silicone and latterly of a formulation that make them resistant to DMSO. They are incorporated in the ends of microcatheters with or without a separate channel for inflation of the balloon (i.e. coaxial catheters). Coaxial catheters have two channels (double lumen), one through which contrast is injected to inflate the balloon and the other, which is usually a larger central channel, is used for flushing the vessel distal to the occluding balloon or aspiration. Double-lumen designs are used for several purposes; including functional testing prior to vessel sacrifice, to create flow arrest during thrombectomy, for angioplasty, deploying stents, balloon-assisted coiling and preventing reflux of liquid embolic agents [27].

Balloons used for distal intracranial catheterisation and particularly for balloon-assisted coil embolisation have a single lumen through which a guidewire can be passed. The guidewire acts as an obstruction to the single channel distal to the balloon so that when it is in positioned, injections into the channel causes the balloon to inflate, e.g. HyperGlide and HyperForm balloons (ev3). This makes their construction simpler and so they can be smaller and more flexible, but the balloon deflates when the obstructing guidewire is removed. Another design, which

was used in the past, was a 'calibrated leak' balloon. This was used to obstruct flow while injecting NBCA. A small hole was made in a balloon fixed to the tip of a single-lumen microcatheter. When a solution was injected rapidly, the balloon inflated because the solution could not escape through the hole fast enough. By altering the size of the hole and viscosity of the solution, the balloon's inflation could be modulated. This proved very difficult in practice, and they fell out of use because of complications due to vessel rupture [28].

18.5 Liquid Embolic Agents

The injection of liquids for endovascular embolisation is a logical development from catheterisation of small branch arteries. In the context of neurological diseases, the supplying arteries are often very small, and their catheterisation can only be achieved with small and highly flexible catheters. In this situation, injectable liquids are the only feasible embolic agent. The problem then is to ensure that their effect is limited to the lesion and does not spread to normal tissues or extend 'downstream' to the venous collecting system or lungs. Therefore, liquids which change their viscosity after injection are required and that means quick-setting agents. The alternative approach is to obstruct blood flow during injections so that the agent is retained in the target lesion long enough to induce thrombosis.

In practice, liquid embolics can be divided into agents that solidify and block target vessels or sclerosants that induce vessel damage and thrombosis.

18.5.1 Quick-Setting Liquids

(a) Silicone fluid mixtures: These were used in the past and reputedly formed an excellent cast of arteriovenous malformation vessels so recanalisation was not a problem. However, there was a very high rate of lung embolisation after their use, and they are now seldom used [29].

(b) Cyanoacrylate adhesives: Isobutyl-2-cyanoacrylate (IBCA), the original glue use for endovascular embolisation, was withdrawn from the market in 1986 on the basis of an unpublished report of a possible carcinogenic effect when injected in the peritoneum of rats [30]. It was replaced by N-butyl-2-cyanoacrylate (NBCA) which has similar properties (except carcinogenicity in rats). Its polymerisation is initiated by free radicals or anions in blood, contrast medium, saline and endothelium. It is mixed with an opacifying agent (for visualisation on fluoroscopy), which may act to retard polymerisation. Mixtures reported include tantalum or tungsten powder, pantopaque, metrizamide and lipiodol. Acetic acid has been added to make an acidic solution which also delays polymerisation [31]. Non-ionic solutions are flushed through the catheter prior to injection to ensure that NBCA does not polymerise in the catheter (I use 20% dextrose). Injections of NBCA are made either as a continuous column or as a bolus followed by a bolus of glucose (i.e. 'sandwich technique'). Polymerisation times can be modified to range from about 5.0 s to several minutes using mixtures with different proportions of lipiodol [32]. Higher concentrations of NBCA are used in high-flow shunts (quick polymerisation) and low concentrations (slow polymerisation) when flow arrest can be achieved (i.e. blocking the pedicle artery with the microcatheter tip) or in slow-flow lesions. The concern when using an adhesive agent is that the catheter cannot be removed at the end of the injection [33]. NBCA is not directly cytotoxic so is extensively used as a tissue adhesive. On histological examination, it produces a foreign-body giant-cell reaction within 5–7 days and subsequent fibrosis. There may be patchy transmural necrosis within portions of vessels of AVMs. This is replaced by fibrosis in the vessel wall [34]. Though the density of lipiodol disappears over months, embolisation is generally considered permanent.

2-Hexyl cyanoacrylate is another cyanoacrylate formulation of cyanoacrylate, called neuracryl, which is currently under evalua-

tion [35]. It is supplied as two vials: one containing liquid 2-hexyl cyanoacrylate monomer and, the second, a mixture of 2-hexyl cyanoacrylate polymer, finely powdered gold and a biologically metabolised esterified fatty acid. It is injected as a mixture and reported to be less adhesive but more viscous then NBCA and to harden more predictably in arterial structures before penetrating to the vein [36].

(c) Solvent-based polymers: These are plastic materials dissolved in a solvent to allow their injection. They harden as the solvent disperses over time. Two plastics have been used: cellulose acetate polymer and ethylene vinyl alcohol copolymer. When dissolved in the solvent dimethyl sulfoxide (DMSO), they form a viscous fluid, which can be injected through a microcatheter. After injection, the DMSO disperses from the surface to initially form a skin around the material. This behaviour makes it much easier to manage than less-viscous liquids, and it can be injected over much longer periods (10–40 min). In theory, the catheter tip will not be glued in the vessel (because they are not adhesives) but in practice, the tip becomes embedded and can be difficult to remove so detachable tip microcatheters or double-lumen balloon catheters (to prevent reflux) are used.

Ethylene vinyl alcohol copolymer dissolved in DMSO and metrizamide (EVAL) was the first formulation of this type of polymer, comprising 6–8% ethylene vinyl alcohol copolymer, dissolved in DMSO and mixed with tantalum powder [37]. It is now marketed as Onyx (ev3) and SQUID (Emboflu) which are made radiopaque by adding tungsten powder and PHIL (MicroVention) which is made radiopaque be bonding with iodine. Onyx was proposed for the treatment of aneurysms but is now principally used to treat AVMs, AVFs and tumours [38]. The alternative plastic cellulose acetate is created by reacting cellulose with acetic acid to produce filaments which are used to make synthetic fabric for clothing and upholstery. It has been used in experimental studies [39].

18.5.2 Sclerosants

Sclerotherapy is extensively used to treat varicose veins, and the same agents can be used in endovascular neurosurgery and neuroradiology to treat vascular malformations. The objective is to damage cells and cause vessel thrombosis and obliteration. The principle agents used act by osmotic damage (e.g. hypertonic saline), disrupting cell membranes (protein denaturing) or chemical irritation (caustic destruction of endothelium). All sclerosants need to be contained within the vascular compartment and cause various levels of complications if extravasation occurs. They are usually introduced by percutaneous injection under visual or ultrasound guidance, and no one agent is the optimum sclerosant for treatment of head and neck vascular malformations [40].

(a) Ethanol: This acts as both a hypertonic solution and a chemical irritant. Ethyl alcohol is available in high concentrations (96%) and causes embolisation secondary to vessel wall ischaemia and anoxia. It can be injected via endovascular catheter or direct puncture. Ideally, it should be injected neat, but for fluoroscopic opacification, it is mixed with a radiographic contrast medium. Slow injections with blood flow arrest produce the longest endothelium contact time and the greater cytotoxic damage. It can cause intense vascular spasm and doses of >1 ml/kg cause intoxication. The end point in arterial use is difficult to ascertain because of the associated spasm. It is painful on injection, and treatments require general anaesthesia and intense cardiovascular monitoring because cardiac (arrest) and pulmonary (oedema) complications can occur. A preparation as a gel (ScleroGel) has been tested in order to increase the time it is in contact with the target vessels.

(b) Sodium tetradecyl sulphate: This agent is a detergent and is widely used in peripheral intervention radiology and vascular surgery. It acts to denature the cell membrane and in practice works like ethanol to cause throm-

bosis but causes less pain. It is FDA approved for sclerotherapy and can be mixed with contrast media but is usually mixed with air to form foam, which can be imaged by ultrasound. Extravasation may cause tissue necrosis, and hyperpigmentation is a problem if used close to the skin. Anaphylaxis has been reported.

Polidocanol (Asclera, Ethoxysclerol): It is also a detergent and acts in a similar way to sodium tetradecyl. It is painless and less likely to cause tissue necrosis if extravasation occurs. I have no direct experience or seen written reports of its use in the head and neck.

(c) Ethibloc: It is a proprietary preparation of ethanol solution 60% with a protein corn mixture (zein). It requires preinjection of glucose and precipitates like NBCA. The active occlusion element is the zein, which precipitates in blood and forms a cast. Large volumes are required (up to 20 ml) [41]. It is painful on injection so these are made very slowly. It is said to have high recanalisation rates and frequently penetrates beyond the fistula or nidus, so it is recommended for embolisation in capillaries and used for kidney embolisation.

(d) Hypertonic solutions: Hypertonic saline (23.4%) and 50% dextrose can be used for sclerotherapy, but injection is painful and solutions difficult to opacify without dilution, therefore reducing their effect. Their use is 'off label' and I have no direct experience of their use.

18.5.3 Chemotherapeutic and Other Agents

The most commonly used agent of this group in our field is bleomycin, but our ability to selectively catheterise arterial pedicles opens up the potential for endovascular treatments in addition to embolisation. These include use in oncology for local delivery of chemotherapy agents, nanoparticles and vectors for gene therapy [42]. The drugs that are currently in use include:

(a) Oestrogen: Conjugated oestrogen dissolved in 25% ethanol is used as a liquid embolic material. Infusion of oestrogen–ethanol mixtures causes local spherocytosis of red blood cells and severe rapid degeneration of the endothelial cells, followed by injury to underlying muscle cells and fibroblasts. It induces immediate occlusion of small vessels (<20 μm) and then progressive obliteration of the larger ones (>200–300 μm) within a few days. The combination has a similar effect to absolute ethanol but no direct damage to perivascular tissue.

(b) Bleomycin: This drug is classified as a cytotoxic antibiotic and used in oncology as a chemotherapy agent. Its use as a sclerosant was first described for the treatment of lymphatic vascular malformations of the head and neck [43]. It has since been used effectively for low-flow vascular malformations [44]. It is generally injected directly into lesions and is relatively painless [45]. However, it can have serious side effects, such as pulmonary pneumonitis, and cause hyperpigmentation so patients need to be warned and pretreatment lung function testing is a wise precaution, though pulmonary damage has not been reported after its use as a sclerosant [45].

(c) Picibanil (OK 432): This agent has been used primarily to treat lymphatic malformation. It acts by stimulating the immune system to cause tumour shrinkage. It is manufactured from *Streptococcus pyogenes* pretreated with penicillin G and heat and injected under ultrasound guidance [46].

18.6 Intracranial Stents, Flow Diverters and Flow Disruptors

Endovascular stents were introduced in the 1960s by Dotter [47]. Their use in coronary artery stenosis has revolutionised cardiology. Their place in carotid and vertebral artery stenosis will be discussed in Tutorial 19 and remains complimentary to medical and surgical treatment. Against

this background, the recent development of stents and hybrid devices sufficiently flexible for intracranial deployment has expanded their uses. Flow diverters, neck bridge and flow disruptor devices are challenging endosaccular coil embolisation in the treatment of aneurysms.

18.6.1 Stents

Endovascular stents are mounted on a delivery wire or balloon. The former are self-expanding when released from the restraint of the delivery catheter. Balloon-mounted stents are positioned and then expanded by inflation of the balloon. This type is generally too rigid for intracranial navigation.

Stents used in intracranial vessels are therefore generally self-expanding and may be fully or partially retrievable. A fully retrievable device is detached from its control wire (usually by electrolysis of a short junction) after deployment, whereas other self-expanding stents can be resheathed if only partially deployed. Apart from being available in different lengths, most stents have a relatively narrow range of expanded diameters. The effective diameter of a self-expanding stent depends on the configuration of the metal struts (i.e. its design parameters and the type of metal used) and the size of the vessel into which it is deployed. Usually, stents are designed to expand to an optimum diameter; optimum in terms of the radial force the stent imparts to the vessel wall.

An important design feature of how the struts connect is whether an open-cell or closed-cell structure is used. The former makes the stent more flexible but with lower radial force. The radial force of the stent is an important factor in their use to treat arterial stenosis or dissection. It is also important for anchoring the stent within the vessel. Other factors that ensure the stent is stable after deployment are sizing and design features, such as flared ends. The use of fully retrievable stents to extract clot lead adjuvant devices to ensure endosaccular to the development of a range of clot retriever devices with similar design features. Intracranial conventional stents are used to treat stenosis, as adjuvant to aneurysm embolisation and as salvage devices after dissection or endovascular thrombosis.

18.6.2 Flow Diverters

The first use of braided alloy wire was the Magic Wallstent (Schneider) in 1996. The technology has been adapted in a range of stents generally known as flow diverters (FDs). Stents with this construction are capable of inducing thrombosis of intracranial aneurysms by redirecting blood flow away from the neck and slowing endosaccular blood flow sufficient to cause thrombosis. A covered stent, which completely isolates the vessel lumen from the wall, has a porosity of 0%, which would be ideal for covering the neck of an aneurysm, but risks occluding side branches of the parent artery. It would also be too stiff for intracranial navigation. Systematic haemodynamic flow studies of FDs have established 70% porosity (defined as the proportion of open area to total area of the stent) as the optimum for inducing thrombosis [48]. This reduction in porosity is achieved by increasing the metal content of the stent and reducing the pore size. FDs are now in clinical use, e.g. Pipeline (ev3, Covidien) and Silk (Balt International) for the treatment of intracranial aneurysms with and without endosaccular packing with coils [49]. An alternative is the use of double or overlapping conventional stents to reduce the effective combined porosity [50].

18.6.3 Neck Bridge Devices

These devices are designed to be placed in the parent artery and obstruct the neck of aneurysms. They differ from FDs because of the focal nature of the obstruction and their principle use is as adjuvant devices to ensure endosaccular coils are retained. They are generally known as neck bridge devices to distinguish them from stents, which cover a more substantial portion of the

Table 18.1 Range of materials used in interventional neuroradiology

Type	Material	Size of embolised vessels	Conditions
Liquids	Cyanoacrylate	>80 μ	AVM/AVF
	Ethylene vinyl alcohol	>80 μ	AVM/AVF
	Ethanol	<100 μ	Malformations/tumours
	Oestrogen	<100 μ	Malformations/tumours
	Sodium tetradecyl sulphate	<100 μ	Malformations
	Bleomycin	<100 μ	Malformations/tumours
Particles	Polyvinyl alcohol	>100 μ	Tumours
	Gelfoam	>800 μ	Tumours
	Silk sutures	3–10 mm	AVM
	Trisacryl spheres	50–500 μ	Tumours
Balloons	Latex, silicone	>4 mm	Large vessel occlusion
Coils	Platinum	>1 mm	Aneurysms, AVFs
Plugs	Nitinol alloy	2–16 mm	Large vessel occlusion
Stents	Steel, nitinol	2–5 mm	Stenosis, aneurysms
Flow diverters	Nitinol alloys	3–6 mm	Aneurysms
Flow disruptors	Nitinol alloys	3–18 mm	Aneurysms

parent vessel lumen [51]. They are positioned in the parent artery at the aneurysm neck. Several designs are currently under clinical trial for use in wide necked aneurysms, e.g. PulseRider (Pulsar Vascular) and pCONus (Phenox) (see Tutorial 8).

18.6.4 Flow Disruptors

The concept of flow disruptors is to obstruct blood flow into aneurysms by placing a device within the sac. This was the original objective of Serbinenko [25] when he first placed detachable balloons in aneurysms. Balloons proved unreliable because of difficulties in making them conform to the sac lumen and their rigidity. The next attempt to apply this principle used a Dacron woven bag which could be electrically detached from a microcatheter after being filled with coils [52]. This created a compressible obstruction to blood flow, but the Dacron proved too fragile a material to contain metal coils. The introduction of braided sheets woven from nitinol alloy wire has solved this problem, and devices with this construction, e.g. WEB (Sequent Medical/MicroVention), are now undergoing clinical trials [53] (Table 18.1).

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Angioplasty and Stenting for Cranial Vessel Stenosis

19

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Preamble

In this tutorial, the uses of angioplasty and endovascular stents in the treatment of arterial stenosis are discussed together. The endovascular techniques involved are similar, but the indications and the conditions treated vary. Endovascular treatments of atheroma of cerebral arteries will be separated into its use for extra- and intracranial arterial disease, and the application of angioplasty and stenting in two other medical conditions is discussed. Unlike topics of previous tutorials, the role of endovascular techniques in the treatment of cerebral atherosclerosis has reduced over recent years, and initial enthusiasm for its application waned as a result of clinical trial evidence. The number of patients referred for endovascular treatment often reflects local skills, and even if you work in low volume centres, remember we are in a field with evolving technologies and one never knows what is around the corner.

19.1 Carotid Artery Stenosis and Stroke Prevention

Despite several large trials, the value of endovascular treatments by angioplasty and stents to relieve symptoms of cerebral ischaemia and prevent stroke has not been proven to be better than surgical carotid endarterectomy (CEA). There are arguably no indications for angioplasty without

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stenting for atherosclerotic carotid stenosis and endovascular treatment is now only performed in selected patients by stenting. The background to this situation is outlined in this section.

19.1.1 Pathology and Natural History

Ischaemic stroke is most commonly caused by large artery atherosclerosis, cardiac thromboembolism or small vessel cerebrovascular disease. Large artery atherosclerosis occurs in the carotid and, to a lesser extent, vertebral arteries. It is a disease of the intima leading to arterial narrowing. Focal disease is thought to arise after an initiating endothelium injury followed by smooth muscle proliferation, lipid accumulation and an inflammatory cell reaction. The result is formation of a plaque of tissue comprising a fibrous cap over a core of lipid and necrotic tissue. Plaques may fissure, ulcerate or rupture exposing thrombogenic material to circulating platelets. Platelet activation and adhesion causes further narrowing and/or distal embolisation. Approximately 15% of ischaemic strokes are caused by carotid atherosclerotic stenosis [1].

Risk factors for stroke are older age, male gender and previous stroke, together with hypertension, smoking, diabetes, excessive alcohol consumption and hyperlipidaemia. The risk for the individual with carotid atherosclerosis suffering ischemic stroke depends on several factors but principally on the severity of disease as defined by whether they have symptoms and the degree of arterial narrowing. Approximately 15% of stroke patients have had a prior transient ischaemic attack (TIA), and this event is frequently a warning of impending stroke. The risk of stroke in the first month is 5%, and over the next 12 months, stroke occurs in 12% of patients.

19.1.1.1 Asymptomatic Carotid Artery Stenosis

Observation of patients with asymptomatic carotid stenosis shows that 2% will develop transient ischaemic attacks (TIA) or suffer stroke annually, and this rate rises to 5% if there is evidence of severe stenosis [2]. The stroke rate in asymptomatic patients with severe stenosis (i.e. 70–99% narrowing of the carotid lumen) in the European Carotid Surgery Trial (ECST) was 1.2% per year [3] and 4.2% per year in the North American Symptomatic Carotid Endarterectomy Trial (NASCET) [4]. The ECST rate was similar to an 11% 5-year risk of stroke amongst participants in the Asymptomatic Carotid Surgery Trial (ACST) with severe stenosis randomised to medical treatment [5].

19.1.1.2 Symptomatic Carotid Artery Stenosis

The risk of future stroke is higher in symptomatic patients and at least 10% pa [6]. Both the NASCET [4] and ECST [3] found higher risks of stroke in symptomatic patients with more severe stenosis (though not in the subgroup with very severe narrowing, i.e. only a trickle of contrast on angiography). Annual stroke rates in these trials for patients with moderate stenosis (50–69% narrowing) were 6–7%, and with severe stenosis (70–99%) 7–13% [3, 4].

The annual stroke rate was related to the type of symptom in a meta-analysis by Wilterdink et al. [7], whose data are summarised in Table 19.1. This study showed that the calculated annual stroke rate (and therefore the risk) was related to the severity of symptoms and presumably the severity of atherosclerosis.

Table 19.1 Estimates of annual stroke rates according to symptoms of atherosclerotic cerebrovascular disease

Symptoms	Risk of stroke per year
Asymptomatic carotid stenosis	1.3% (95%CI 1.0–1.6)
TIA	3.7% (95%CI 3.1–4.3)
Transient monocular blindness	2.2% (95%CI 1.3–3.0)
Minor stroke	6.1% (95%CI 5.7–6.6)
Major stroke	9.0% (95%CI 8.0–9.9)

Data from Wilterdink and Easton [7]

19.1.2 Medical Treatment

Antiplatelet drugs are effective in the prevention of stroke and anti-hyperlipidaemia agents for the treatment of atherosclerosis. These are prescribed together with advice about life-style risks such as smoking and treatment of co-existing diabetes and hypertension. In patients with evidence of carotid artery stenosis, triple therapy is started at diagnosis. This consists of antiplatelet, statin and antihypertensive agents. The antiplatelet drugs most commonly used are aspirin, clopidogrel and dipyridamole. The UK's National Institute for Health and Care Excellence advice on their use to prevent occlusive vascular events is that clopidogrel should be used alone and dipyridamole with aspirin or alone (https://www.nice.org.uk/guidance/ta210/chapter/1-guidance). Statins are recommended for treatment of hypercholesterolaemias and patients at high risk of stroke. Warfarin is generally not used to prevent stroke in patients at risk of stroke due to carotid disease alone but is used to prevent cardiac causes of stroke.

19.1.3 Endovascular Treatment

Percutaneous transluminal angioplasty (PTA) was first described by Charles Dotter and Melvin Judkins in 1964 to treat atherosclerotic narrowing of lower limb arteries [8]. They performed antegrade catheterisation of the femoral artery, passed a guidewire through the stenosis which was then dilated using catheters of increasing size, i.e. bougies. Surprisingly, the technique was not immediately adopted, and it was not until 1977, following the introduction of balloon angioplasty by Andreas Grüntzig, that angioplasty 'took off', first in coronary and then peripheral arteries [9]. Early carotid procedures were reported about the same time by two pioneers of endovascular treatments, by now familiar to readers, Sean Mullan [10] and Charles Kerber [11] in 1980. There was initial understandable caution in use of the technique in cerebral arteries. In 1982, over-the-wire coaxial balloons were introduced, and in 1984, Zubkov et al. [12] described the use of angioplasty to treat post-subarachnoid haemorrhage vasospasm. All cerebral arteries as far distal as second branches above the circle of Willis can now be reached with a balloon.

Angioplasty for atherosclerotic stenosis causes a controlled injury to the vessel. It splits atheromatous plaque and denudes the endothelium. Microscopy shows desquamation of the superficial plaque elements and dehiscence of the media and intima. Macroscopically, the plaque and intima are separated from the media, and the media and adventitia are torn. Over the first few days after treatment, there is deposition of platelets in the area of the traumatised vessel, and then a new layer of endothelial cells form. The physiological healing response, which follows, should result in a smooth neointima. Postmortem examinations have shown that the intima is covered by thrombus for up to a month after treatment. This is followed by a period of smooth muscle proliferation and after approximately 2 years, complete replacement by fibrous tissue. However, excessive cellular proliferation (hyperplasia) can lead to restenosis. For this reason and other reasons (see below), treatment of carotid artery stenosis by stenting has substantially replaced PTA for the prevention of stroke.

19.1.4 Surgical Treatment

Surgery is performed to excise atheromatous plaque by endarterectomy. Two large RCTs were needed to show that carotid endarterectomy (CEA) was effective at preventing future stroke in symptomatic patients with carotid artery stenosis due to atherosclerosis. The NASCET and ECST compared (CEA) to best medical treatment and showed improved outcomes (i.e. reduced the risk of stroke and symptoms) in patients with severe stenosis, i.e. >70% luminal narrowing [3, 4]. The NASCET (with similar results in ESCT) showed that the lifetime cumulative stroke risk was 26% in medically treated and 9% in surgically treated patients—an absolute risk reduction of 17 ± 3.5%.

Small surgical trials in asymptomatic patients, e.g. the CASANOVA Study Group [13], did not show benefit from CEA, but the larger Asymptomatic Carotid Atherosclerosis Study (ACAS) did [14]. This trial recruited 1662 patients with stenosis greater than 60%. The annual event rate amongst patients treated medically was 2.2%, and CEA reduced this to 1%. The patients were, however, selected on the basis of a reasonable life expectancy and no contraindication to surgery. In a review, Rothwell et al. calculated that it is necessary to operate on 50 patients to prevent one stroke with a perioperative complication rate of only 2% [15]. In these circumstances, it has been a slow and difficult task for endovascular treatment to show its worth and define its role.

The American Heart Association issued guidelines that recommend CEA for symptomatic patients with a history of prior stroke or TIA and carotid stenosis ≥70%. These specified levels of acceptable surgical risk for different indications according to the surgeon's audited morbidity and mortality figures. For indications carrying the highest risk for stroke, morbidity rates <6% and for lower stroke risk patients rates <3% were acceptable [16]. The perioperative, stroke, and death rates in NASCET and ECST were 5.8% and 7.5%, respectively. The subsequent introduction of pre-operative triple (medical) therapy has improved surgical results.

19.2 Endovascular Treatments for Extracranial Carotid Stenosis

The primary role of surgery for treatment of extra-cranial carotid and vertebral stenosis has been challenged by endovascular treatment first by angioplasty (PTA) and then stenting because of its potential benefits in avoiding surgical trauma. Unfortunately, neither can be described a minimally invasive.

19.2.1 Carotid Artery Angioplasty

This treatment has only been partially tested against CEA in one randomised trial, the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS) [17]. It randomised 253 patients to CEA and 251 to PTA. The majority of patients were symptomatic, but some asymptomatic patients were randomised. Initially, only balloon angioplasty was performed, but operators were allowed to use stents, and additional stenting was performed in 26% of the PTA group. The rates of major adverse events within 30 days after CEA and PTA were 5.9% vs. 6.4% for disabling stroke or death and 9.9% vs. 10.0% for any stroke respectively [17]. Restenosis rates were 4% vs. 14% at 1 year and 10.5% vs. 30.7% at 5 years after CEA and PTA, respectively. However, there was no difference in the rate of late ipsilateral stroke up to 3 years after randomisation, and patients in the endovascular arm who were treated with a stent had a significantly lower risk of developing restenosis compared with those treated with balloon angioplasty alone (n = 145; HR 0.43, 0.19–0.97; p = 0.04) [18].

By the time CAVATAS reported, stents had become established for the endovascular treatment of cranial artery (carotid and vertebral) stenosis, and PTA relegated to preliminary arterial dilation prior to stent deployment. Most interventionists prefer CAS because the higher restenosis rate and the risk of dissection caused by PTA. Some degree of dissection is inevitable after the trauma of angioplasty. Placing a stent is a salvage action if the dissection is substantial and threatens blood flow. A stent, in theory, limits the amount of atheromatous debris dislodged by angioplasty and reduces the risk of restenosis.

19.2.2 Carotid Artery Stenting (CAS)

There have been several important recent trials of CAS and CEA – The Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE), Stent-Supported Percutaneous Angioplasty of the Carotid Artery versus Endarterectomy (SPACE), Endarterectomy versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3 S), Carotid Revascularization Endarterectomy versus Stenting

Trial (CREST) and International Carotid Stenting Study (ICSS). The results were:

1. SAPPHIRE: This trial randomised high-risk surgical patients with symptomatic stenosis >50% and asymptomatic stenosis >80%. It showed a modest benefit for CAS performed with a distal protection device and a significantly lower rate of major adverse cardiac events at 30 days [19].
2. SPACE: The early ipsilateral ischaemic stroke or death rates (i.e. <30 days) were 6.84% with CAS and 6.34% with CEA. The trial thus failed to prove CAS was better than CEA [20].
3. EVA-3 S: This trial was stopped prematurely after the inclusion of 527 patients, for reasons of safety and futility. The 30-day stroke or death rate was 3.9% after CEA and 9.6% after CAS. The morbidity rates at 6 months were 6.1% and 11.7%, respectively [21].
4. CREST: The overall stroke or death rates after a median follow-up period of 2.5 years were not different. The 4-year rate of stroke or death was 6.4% for CAS and 4.7% for CEA. The rates for symptomatic patients were 8.0% and 6.4% and for asymptomatic patients 4.5% and 2.7% for CAS and CEA, respectively [22].
5. ICSS: This study of symptomatic patients reported periprocedural morbidity rates of 8.5% for CAS and 5.2% for CEA [23].

The conclusion of all this effort was summarised by Brott et al. [22] that carotid stenting is as effective as carotid endarterectomy for prevention of ipsilateral stroke in the medium term, but the safety of carotid stenting needs to be improved before it can replace CEA. A Cochrane meta-analysis by Ederle et al. [24] looked at published data comparing PTA and stenting to CEA up to March 2007 and reviewed 12 trials (3227 patients). The primary outcome measure of any stroke or death within 30 days was not significantly different but favoured CEA (odds ratio (OR) 1.39, $p = 0.02$). The comparators that favoured PTA/stenting over CEA were cranial neuropathy (OR 0.07, $p < 0.01$) and 30-day neurological complication or death (OR 0.62, $p = 0.004$, NS). There was no difference in the 30-day stroke, myocardial infarction or death rates (OR 1.11, $p = 0.57$ with significant heterogeneity) or stroke during long-term follow-up (OR 1.00). Comparison between PTA/stenting performed with or without protection devices showed no significant difference in 30-day stroke or death. The author concluded that data did not support a change in clinical practice away from CEA as the treatment of choice but added that it was difficult to interpret the current data because of different trial methodologies and because five trials were stopped early leaving the possibility of an overestimate of the risks of endovascular treatment.

Since 2007, despite further trials including ACT 1 [25] which randomised asymptomatic patients, the situation remains unchanged. A recent meta-analysis, which included data from studies with long-term follow up, came to the same conclusion, i.e. that CAS is no better than CEA [26]. However, improved protection devices, hybrid operations involving operative stent placement and use of membrane covered stents may reduce perioperative stroke rates and change the future risk balance between CEA and CAS.

19.2.2.1 Stenting Procedure

Patients for stenting are usually taking antiplatelets but should be pretreated with dual antiplatelets (aspirin and clopidogrel) for 5–7 days prior to stenting and anticoagulated during procedures. Stenting is usually performed with the patient sedated, and protection devices (to capture emboli created during the procedure) are increasingly deployed. Atropine and vasopressors may be required to treat provoked bradycardia and hypotension and should be readily available. Arch aortography is performed to define the anatomical situation of the access artery prior to selective catheterisation and DSA to show the extent of disease, in particular whether tandem lesions are present. Dilatation angioplasty may be required to facilitate stent positioning (pre-dilation). Stents are selected on the basis of diameter (usually 1–2 mm greater than the calibre of the largest section of the artery to be covered) and length (to cover the entire lesion). Post-dilation balloon inflation may be

required to ensure good apposition of the stent to the arterial wall.

19.2.2.2 Complications of Stenting

The complications specific to stenting procedures include: access vessel damage, vasospasm, carotid dissection and perforation, stroke and systemic complications due to co-incidental cardiovascular disease (e.g. myocardial infarction). The relatively large access catheter and stiff guidewires needed in these procedures make dissections and perforations more likely. The consequences of bleeding will be exacerbated by the need for anticoagulation and antiplatelet drugs as prophylaxis against embolic stroke. The incidence of procedure-related stroke ranged from 3.6% to 9.1% in the five trails listed in Sect. 19.2.2 [19–23] and 7.2% in CAVITAS [17]. The incidence of minor stroke was calculated as 6.1% in a recent meta-analysis of reports [26].

19.2.3 Vertebral Artery Stenting (VAS)

The risk of stroke due to vertebral artery stenosis is difficult to separate from disease in the intracranial artery and basilar artery stenosis. Posterior cerebral circulation disease is generally considered to be worse than the anterior circulation. The Warfarin–Aspirin Symptomatic Intracranial Disease (WASID) study showed an annual stroke rate of 7.4–10.7% in the territory of vertebral or basilar arteries with stenosis [27]. Surgery for vertebral artery stenosis is rarely performed because it is so difficult, and endovascular treatment is currently considered the more appropriate intervention.

Proximal vertebral artery stenosis is easily accessible for PTA or VAS. The same applies for the uncommon proximal stenosis of the subclavian artery. There have been several reports of patients treated with PTA for vertebral artery stenosis [28]. However, the frequency of restenosis in the vertebral artery limits the value of angioplasty alone, so stenting is the technique of choice. Stenting for symptomatic high-grade stenosis of the vertebral artery origin has a high success rate and low rates of neurological complications [29].

Eberhardt et al. reported and reviewed the literature on VAS both in the proximal (extracranial) and distal circulations in 2006 [30]. The morbidity rates they found for proximal vertebral artery stenting were 5.5% neurologic complication, 0.3% mortality and 0.7% delayed stroke. For distal vertebral or basilar artery stenting, the rates were 17.3% neurologic complication, 3.2% mortality and 2% delayed stroke.

The role of endovascular treatments (stenting) in the distal vertebral artery was assessed in the Vertebral Artery Stenting Trial (VAST) RCT, which randomised patients with symptomatic vertebral stenosis and >50% artery narrowing to VAS or best medical treatment and measured rates of stroke, vascular death or nonfatal myocardial infarction within 30 days of starting treatment and on follow-up [31]. It stopped after recruiting 115 participants and showed that VAS was no better than medical treatment. Over a mean of 3-year follow-up, 7 (12%) stented patients and 4 (7%) of the nonstented patients suffered strokes [32].

19.3 Endovascular Treatment of Intracranial Artery Stenosis

The use of PTA to treat stenosis of intracranial arteries was first reported over 30 years ago [33]. Intracranial artery stenosis is relatively uncommon in Western populations but accounts for about 8–10% of ischaemic strokes. Treatment by surgical extracranial to intracranial surgical bypass was first performed by Yasargil in 1967 [34] and popular in the 1970s but stopped after a landmark RCT showed that it was no better than medical treatment [35]. In this trial, patients with internal carotid or middle cerebral artery stenosis were randomised to EC-IC bypass or medical treatment, and though surgical patency rates were good, there were a 4.5% perioperative stroke rate and no improvement in the subsequent stroke or death rates. In the absence of a surgical option for intracranial disease, endovascular treatments by PTA or stenting have developed.

19.3.1 Natural History of Intracranial Stenosis

Before looking at the natural history of intracranial artery stenosis (ICAS), it is worth remembering the difficulty we have in distinguishing between embolic and haemodynamic causes of stroke. Simply increasing the arterial lumen size may not be the solution in the prevention of embolic stroke. Data from the prospective arm of the WASID study has shown stroke rates of 8–10% in patients with ICAS of >50% arterial narrowing on medical therapy [27] and that 73% occurred in the symptomatic arterial territory [36]. WASID was another important trial. It compared two medical treatments and showed that aspirin was preferable to more aggressive treatment with warfarin [37]. It has provided the 'yardstick' against which new interventions can be evaluated. Another factor that emerged from the WASID data is that stroke occurs early after a patient becomes symptomatic. Mazighi et al. reported an event rate of 38.2% (13.7% stroke, 24.5% TIA) over 2 years in a prospective study of the natural history of ICAS [38]. This rate increased to 60.7% if the stenosis was haemodynamically significant.

19.3.2 Classification and Techniques of Endovascular Treatments for Intracranial Artery Stenosis

The current role of endovascular treatments for anterior and posterior intra-cranial cerebral artery disease has been well reviewed by several authors, many of whom advocate the need for agreed classifications and data from randomised trials [39]. Because ICAS is more common in oriental populations, much of the literature on clinical practice of PTA and stenting comes from China and the Far East [40].

Techniques for PTA in intracranial arteries generally involve using an undersized balloon (e.g. 0.2 mm smaller than the vessel to be treated) and inflating the balloon very slowly to decrease the risk of intimal damage, acute platelet/thrombus deposition and acute artery closure. Routine antiplatelet drugs are given by most therapists [41].

Definitions used for the severity of lesion treated have not been universally adopted though simply measuring the vessel lumen size rather than trying to express it as a percentage of an estimated per-diseased diameter has been proposed and would be a very pragmatic solution [42]. The length of narrowing was shown by Mori et al. to correlate with anatomical outcomes and is often referred to as the Mori Classification [43, 44]. Lesions are categorised by their length, plaque eccentricity and degree of occlusiveness.

Type A lesions are <5 mm long, concentric or moderately eccentric and none occlusive.

Type B lesions are 5–10 mm long, tubular in configuration and eccentric or moderately angulated.

Type C lesions are >10 mm long, with a tortuous configuration and >90° angulation.

Type A lesions have better endovascular treatment outcomes than type B and C lesions.

19.3.3 Results of Endovascular Treatments for Intracranial Stenosis

There have been no prospective trials of PTA for intracranial stenosis, and only data from observation studies are currently published. The results of these retrospective reports vary widely with 30-day stroke rates of 4–40% [45] and restenosis rates of 24–50% [46, 47]. A review of multicentre data found a delayed stroke rate of 4.4% after 1 year [48].

The situation is slightly better for stenting with prospective data from the 'stenting of symptomatic atherosclerotic lesions in the vertebral or intracranial arteries' study (SSYLVIA) [49] and registries [50]. In SSYLVIA, the 30-day stroke rate was 7.2%, delayed stroke rate 10.9% and the documented restenosis rate 35%. In the Wingspan studies, the 30-day stroke rate was 6% and restenosis rate 30% [50, 51]. A randomised trial of PTA and stenting versus medical management – The

Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) Trial – was stopped [52]. A total of 451 participants were enrolled, and the rates for stroke or death at 30 days were 14.7% for PTA and stenting and 5.8% for medical management. This result has effectively curtailed stenting for ICAS, at least with the current technology.

The appearance of new, and modification of current, devices, e.g. drug-eluting stents, makes this a fast-changing situation and one that is likely to increasingly involve the endovascular therapist of the future. This is exemplified by an unexpected effect of the publication of WASID, which was to increase referrals of ICAS patients for endovascular treatment in one centre [53].

19.4 Angioplasty for Vasospasm

Though the commonest indication for PTA in intervention radiology is atherosclerotic stenosis, balloon angioplasty can be used for the dilation of vessel stenosis in other conditions. Vasospasm after subarachnoid haemorrhage is one such condition, but PTA has been described in patients with stenosis following craniofacial irradiation [54], neurofibromatosis [55] and fibromuscular dysplasia [56]. Balloon angioplasty to dilate vasospastic arteries after subarachnoid haemorrhage (SAH) was first performed by Zubkov et al. [12]. It has proved to be more effective than intra-arterial injections of vasodilator drugs (chemical angioplasty) but at the cost of an increased risk of complications.

19.4.1 Vasospasm After Subarachnoid Haemorrhage

This complication of aneurysmal subarachnoid haemorrhage (SAH) is a delayed reaction of subarachnoid arteries to blood applied to their adventitia (abluminal surface). There is currently no unifying hypothesis to explain its cause and no effective preventative treatment. The aetiology is probably multifactorial involving the release of spasmogens from red blood cells and an inflammatory response in the arterial wall. What is clear is that the incidence is proportional to the amount of SAH, i.e. 'blood load' and the proximity of subarachnoid collections of haemorrhage to arteries of the circle of Willis. As was discussed in Tutorial 8, angiographic evidence of vessel narrowing is most frequently seen 8–12 days after SAH. It affects up to 60% of patients, but only about 20% will develop symptomatic vasospasm. It is this minority who are candidates for angioplasty. Angioplasty is generally used after the failure of less invasive treatments. These include calcium channel blockers (e.g. nimodipine), treatments to maintaining an above average mean systemic arterial pressure and optimum hydration.

19.4.2 Timing of Angioplasty for Vasospasm

Choosing the right time to intervene is difficult. There is a natural tendency to persist with medical treatment for patients who develop delayed ischaemic symptoms after SAH rather than intervening early, but to be beneficial, angioplasty must be performed before ischaemia has progressed to cerebral infarction [57]. There is also a technical advantage to early treatment because the inflammatory process reduces the plasticity of vasospastic arteries. This process occurs over the first 10–14 days after SAH and means greater balloon pressures are needed for late angioplasty, increasing the risk of vessel rupture [58]. There have been studies to determine the optimum length of time for medical therapy before angioplasty. These have suggested trial periods vary from 2 to 24 h [59] with better clinical results with early treatment.

19.4.3 Indications for Endovascular Treatment of Vasospasm

These include the following:

- Persistent symptoms of cerebral ischaemia attributable to vasospasm despite maximum medical therapy

- No CT evidence of infarction
- Elevated velocities on transcranial Doppler ultrasonography (TCD) and/or angiographic evidence of vessel narrowing in a location that correlates with clinical symptoms

19.4.4 Imaging for Vasospasm

CT scan is the minimum imaging required before intervention. It is required to exclude other causes for the patient's symptoms (e.g. hydrocephalus or rebleeding) and to exclude major established areas of irrecoverable infarction.

Functional studies are useful to show evidence of cerebral ischaemia in the appropriate area. Currently, the simplest method is serial TCD estimates of middle cerebral and anterior cerebral artery velocities. Perfusion CT or MRI estimates of cerebral blood flow (CBF), cerebral blood volume and mean transit time may help to correlate areas of vasospasm identified on CTA or MRA and show the potential benefit of angioplasty [60]. C-arm flat detector CT, which can be combined with DSA, is a useful technique for correlating (and monitoring) cerebral perfusion data with sites of angiographic vasospasm [61].

19.4.5 Endovascular Treatment Techniques for Vasospasm

Angioplasty for the treatment of SAH vasospasm can be performed by selective intra-arterial injection of vasodilator drugs, i.e. chemical angioplasty or by balloon angioplasty with mechanical dilation of the arteries in spasm.

19.4.5.1 Chemical Angioplasty for Vasospasm

Several vasodilator agents have been proposed and used for intra-arterial injection. The aim of the treatment is to subject the spastic arteries to a higher concentration of the drug than could be achieved if administered systemically. Delivery can be made via a 4-F or smaller catheter in the relevant carotid or vertebral artery or using a coaxial system via microcatheter with injections as close as possible to areas of narrowing. A slow infusion is made and the response monitored by angiography. The drugs used include:

(a) Papaverine: This is a benzylisoquinoline opium alkaloid with nonspecific smooth muscle relaxation activity. Its half-life is 45–60 min but in practice its effect may last as long as 24 h. A typical dose is 300 mg mixed with 100 ml of normal saline (i.e. 3 mg/ml) infused into the target area over a period of 1 h or longer. Its advantages are that it is simple to use and also affects small distal arteries. Its disadvantage is that the effect is temporary and inconsistent [62]. Specific complications are risks to the eye, especially if prolonged injected is performed into the ophthalmic artery. It may elevate intracranial pressure, lower systemic blood pressure, increase heart rate and cause seizures [63]. Infusion in the posterior cerebral circulation has been reported to depress brain stem function [64]. Awake patients complain of nausea and pain during injections.
(b) Nimodipine: This calcium channel-blocking drug is used routinely to prevent vasospasm (IV or orally) and has now substantially replaced papaverine for angioplasty by intra-arterial injection. The usual dose in 0.1 mg/min infused over 30 min to a maximum dose of 3 mg per vessel [65] or by slow infusion of 4 mg per hour over 2 h [66].
(c) Milrinone: This is a phosphodiesterase inhibitor and acts as a vasodilator and cardiac inotrope; it has been described in one enthusiastic report to be an effective vasodilator in SAH vasospasm [67].

19.4.5.2 Balloon Angioplasty for Vasospasm

Ideally, this procedure should be performed under local anaesthesia to allow continuous neurological monitoring, but in practice, this is extremely difficult because patients are usually restless and find it difficult to cooperate. Intravascular manipulations may be painful and so general anaesthesia is required. In either event, very careful procedural monitoring is mandatory.

A standard transfemoral technique is used with systemic anticoagulation (5000 IU bolus of heparin) and a 6 F guiding catheter in the vertebral or internal carotid artery. The narrowed arterial segment is localised by control angiography, and a noncompliant nondetachable balloon, sized no larger than the assumed normal diameter of the target vessel, is introduced. Compliant balloons are used by some operators but either type should not be inflated by more than the original vessel's diameter [68]. Inflation pressures should be kept low and inflation times as short as possible. Inflations by hand injections for only 3–5 s are made, and following each deflation, control angiography performed to decide if further inflation is required or if the balloon should be resited. Using a single-lumen balloon, is safer than a double-lumen system, because the guidewire of the latter increases the risk of vessel perforation.

19.4.5.3 Results of Angioplasty for Vasospasm

It is difficult to compare the efficacy of the two approaches because, in most practices, one or other is used depending on the location(s) of stenosis. If a focal area of vasospasm is present in the internal carotid or proximal middle cerebral arteries, balloon angioplasty is relatively easy and much quicker. If distal vessels are affected by vasospasm or access is difficult, chemical angioplasty is generally preferred.

A small comparative study between papaverine and angioplasty [69] showed the latter is superior (on CBF studies at 24 h after treatment) in a small group of patients. After chemical angioplasty, improvements in vessel diameters are seen in about 70% of patients, and some patients show clinical improvement despite angiographic evidence of residual vasospasm [65]. Balloon angioplasty is effective at opening vasospastic arteries with angiographic improvement in about 90% of cases. Clinical improvement is less certain but is reported in 65–70% of patients treated [70]. The effect of balloon angioplasty is more durable than intra-arterial infusions of vasodilators because fewer patients require retreatment [71]. Recently use of a stent-retriever has been described as an alternative [72]. Following successful balloon angioplasty continued monitoring with Doppler ultrasound and angiography has shown that recurrence is uncommon (unlike chemical angioplasty). But monitoring should be continued, particularly if patients are electively sedated for mechanical ventilation.

19.4.5.4 Complications of Angioplasty for Vasospasm

The specific complications in addition to transient events described about include vessel rupture, secondary cerebral haemorrhage due to reperfusion and distal thromboemboli. The incidence of vessel perforation during balloon angioplasty is 2–5%. It is higher if small vessels are treated [73], and currently it is advised that only vessels with diameters between 1.5 and 3.5 mm are treated. Smaller arteries should only be treated by chemical angioplasty.

19.5 Angioplasty and Stenting for Venous Disease

The use of stents after thrombectomy procedures was discussed in Tutorial 17, including their use in cerebral venous sinus thrombosis. A possible late sequel to this event is chronic sinus narrowing and symptoms of idiopathic intracranial hypertension (IIH or benign intracranial hypertension). Angioplasty and stenting have been described in patients with angiographic evidence of sinus stenosis and symptoms of IIH [74].

The mechanism of IIH is unknown, but it has been attributed to sinus stenosis due to a variety of causes including sarcoidosis [75], hypercoagulopathy [76] and prior sinus thrombosis [77]. However, relief of symptoms following stenting has not been consistent and a demonstrable pressure gradient is generally regarded as a prerequisite before stenting [74, 77]. Despite some encouraging reports of stenting in this condition, its use remains controversial.

Finally, a far more controversial use of angioplasty and stents is to improve drainage in venous pathways in the treatment of multiple sclerosis. A condition termed chronic cerebrospinal venous

insufficiency was reported to be a cause of multiple sclerosis in 2009 [78]. As a result, angioplasty and stenting procedures in various veins of the head and neck have been reported [79, 80]. There is no consensus that the condition exists or that endovascular treatment is or isn't effective. There is a government-funded trial (Canadian Interventional CCSVI Trial) ongoing, and such studies will hopefully resolve the controversy. I don't intend to offer readers my opinion because I have yet to read a plausible explanation of the pathophysiology behind any cures and have no personal experience on which to draw.

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Complications

20

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Preamble

Out of a clear blue sky, when least expected, they come. You set sentries against them and do not send invitations, but still they come. We all have to accept that complications are an inevitable component of what we do. This fact does not exonerate us from the duty to maintain all possible preventative precautions and to instigate a process of objective analysis of any adverse event. For all concerned, patients and medical staff, understanding the mechanism of a medical accident is important. Discussion and peer review of the circumstances surrounding a complication is needed to correct any system failures, plan any appropriate changes in practice and alert others of the danger.

For the novice, complications are disturbing, and it is the role of seniors to protect them as much as possible by ensuring that they work within their capabilities and with appropriate supervision and guidance. In my department, we review all procedures at a weekly meeting of practitioners, trainees, nurses and radiographers. This ensures that everyone in the department knows if something has gone wrong, we are all alerted to any equipment or system failure as quickly as possible. Decisions are taken concerning immediate remedies and how far the lessons learnt need to be escalated, i.e. to the rest of the hospital, to specialist network groups or to the wider medical community through statutory

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agencies and/or publications. It gives the junior members a chance to hear the views of colleagues not directly involved in a particular complication and has proved enormously beneficial. In the event of a complication resulting in serious morbidity to a patient, it is my practice to meet with all the involved staff, as soon as the situation permits, to talk about what happened. This is to ensure that young people do not leave the hospital with a sense of culpability for what was an accident or the result of several contributing factors whose combined effect could not be anticipated.

In the last few years, an objective reality has emerged about this subject with doctors now expected to audit their practice in terms of the efficacy and safety of the treatments they perform. This is a relatively simple process, particularly when it becomes routine, and benchmark data are now published against which a practitioner can compare their personal audit figures. Appraisal and revalidation processes give us a chance to ensure that we are working to the highest possible standards of safety; we need that knowledge to face the consequences of complications.

20.1 Generic and Specific Complications

Complications can be divided into generic groups, which are common to endovascular treatments in general and those that are specific to treatments of a particular condition. In addition, some complications are caused, or more likely to occur in a particular patient because of medications they are taking or a pre-existing condition, e.g. dissection in Ehlers–Danlos syndrome. Some complications are specific to the technology used. For example, embolisation with particles may cause alopecia, retinal blindness or cranial nerve damage, angioplasty vessel dissection, sclerotherapy systemic toxic and adhesive liquid embolic agents stuck catheters.

When formulating a list of possible complications, it is helpful to separate complications due to endovascular navigation and those associated with treatments for specific conditions, as set out in Table 20.1. The purpose of the table is to provide a framework for thinking through the things that can go wrong prior to a procedure so that a checklist of precautions can be generated, and the operator and assistants start each operation prepared. This process is second nature to most interventionalists but tends to concentrate on complications associated with the specific techniques they plan to use to treat a particular patient. Generic complications associated with angiography and endovascular navigation are often forgotten.

Table 20.1 Examples of generic and specific complications

Generic	Specific conditions
Complications due to vascular access	*Aneurysms*
Haematoma/Bleeding	Thromboembolic events
Nerve damage	Rupture
Pseudoaneurysm	Implant misplacement or migration
Acute artery thrombosis	Vasospasm
AV fistula	Hydrocephalus
Infection	Aneurysm regrowth
Manipulation of catheters and guidewires	*AVM and AVFs*
Dissection	Collateral embolisation
Embolism	Procedural bleeding
Perforation	Delayed haemorrhage
	Haemoptysis
Complications due to drugs	*Angioplasty and stenting*
Nephropathy	Ischaemic events
Allergic reactions	Dissection
Anaphylaxis	Early thrombosis
Thrombocytopenia	In-stent stenosis
Complications due to ionising radiation	*Tumour embolisation*
Erythema	Swelling
Alopecia	Skin necrosis
Teratogenicity effects	Nerve damage
	Secondary haemorrhage

Enquiry about patient-specific factors and the likely effects of known comorbidities, e.g. allergies, anticoagulants, etc., is part of the standard pretreatment work-up. Its purpose is primarily to ensure that the appropriate treatment is given, but a major component of this process is the prevention of iatrogenic disease. One final point is that we do not usually include intracranial infections on our checklist because they are so rare (except at puncture sites). The low incidence of serious infection in interventional neuroradiology occurs despite the fact that we often deploy intracerebral foreign bodies in sterile but not class 1 or 2 theatre conditions [1]. However, rarity is not a reason for complacency when planning and using facilities, and infection control is a duty of all medical professionals.

20.1.1 Severity of Complications

Complication can also be separated according to their effect on the patient and whether their consequences are transient or permanent. The Society of Interventional Radiology clinical practice guidelines recognise two classes and six categories of outcomes after a complication [2]. These are:

1. Minor Complications:
   (a) No therapy, no consequence
   (b) Nominal therapy, no consequence; includes overnight admission for observation only
2. Major Complications:
   (c) Require therapy, minor hospitalisation (<48 h)
   (d) Require major therapy, increased level of care, prolonged hospitalisation (>48 h)
   (e) Permanent adverse sequelae
   (f) Death

This is useful shorthand for service audits and highlights that the clinical effect of a complication is an unpredictable spectrum of severity and thus difficult to present in pretreatment discussions with patients.

20.2 Complications Caused by Catheter Angiography

20.2.1 Complications at the Puncture Site

The femoral artery is the more common site of endovascular access, and the following section concentrates on complications at this location, but similar adverse events can be expected when other arteries are punctured. Venipuncture is less likely to cause more than minimal local bleeding, but needle puncture and injections can cause local trauma including nerve damage.

20.2.1.1 Groin Haematoma

This is the commonest of all complications associated with catheter angiography by femoral artery puncture. A minor haematoma with bruising and moderately severe discomfort occurs after about 5% of studies and probably some degree of periarterial haematoma in 100%. A major haematoma can be defined as one requiring transfusion, surgical evacuation or delay in discharge from hospital. These are rare after diagnostic angiograms, i.e. 0.5% but occur after about 3% of interventional procedures [3].

Causes and prevention: Anticoagulation, large catheters or sheaths (>6 F) and increasing patient weight are risk factors. Larger catheters are associated with small haematomas and high patient weight with large haematomas, the latter presumably because detection and compression are more difficult [4].

Femoral artery puncture should be performed below the inguinal ligament. After higher punctures, it is more difficult to control the bleeding point and retroperitoneal bleeding is more likely. If the puncture is too low, it is more likely to be complicated by an arteriovenous fistula (this is because of the relative position of the femoral artery and vein). Adequate time for compression prevents these complications.

The use of closure devices is associated with an increase in complications at the puncture site. Despite this, they are widely used because of their convenience, especially after procedures

using anticoagulation [5]. The incidence of minor complication is 2–8% and major complications 1–5% for the range of device in current use [6].

Clinical signs: Symptoms due to haematoma vary from mild groin discomfort to considerable pain, swelling and skin necrosis. Haemorrhage may be severe enough to reduce plasma haemoglobin levels, and if retroperitoneal extension is suspected, a CT scan should be performed.

Treatment: Manual compression concentrated as accurately as possible at the puncture site is best instigated early. Once overt bleeding has stopped, the margins of the haematoma should be marked and monitored every 15 min for 2 h and then hourly to detect any continued deep bleeding. If the haematoma is very large, surgical exploration of the groin should be considered and may be required to evacuate the haematoma. Limiting the degree of swelling is important to reduce the risk of secondary infection and prevent skin necrosis and ulceration.

20.2.1.2 Retroperitoneal Haematoma

This is a rare but potentially fatal complication (incidence of 0.15%) that carries a significant morbidity. The risk factors are the same as groin haematoma, i.e. anticoagulation or antiplatelet drugs and a high double wall femoral artery puncture.

There are two patterns of haematoma spread, either along iliopsoas (which may cause a compression neuropathy) or true retroperitoneal spread (which can lead to haemodynamic instability and compression of the ipsilateral kidney).

Clinical findings: Patients complain of lower abdominal or thigh pain. The groin and lower abdomen are tender, and there may be quadriceps weakness and numbness over the thigh. Tachycardia, systemic hypertension and other signs of active bleeding may progress to cardiac instability.

Treatment: Emergency CT is indicated as soon as this complication is suspected and a high-intensity observation regime instigated. Any anticoagulation or antiplatelet prophylactics treatments should be stopped and appropriate antidotes to reverse their effects given. Blood haematocrit, haemoglobin, bleeding time and platelet function should be assessed. Consider giving haemostatic drugs such as tranexamic acid and fresh platelet or whole blood transfusions. Surgical decompression and arterial repair are indicated if the patient develops neurological signs or becomes haemodynamically unstable.

20.2.1.3 Pseudoaneurysms and Arteriovenous Fistulas

The incidence of these complications after femoral artery puncture is 1% and 0.3% respectively. The cause is a failure of compression to close the puncture site so that a circulation is established within a haematoma or to the femoral vein. Pseudoaneurysms usually develop early (24–48 h) and the rare arteriovenous fistulas later (1–2 weeks) [7].

Clinical findings: Failure of a haematoma to resolve, a pulsatile mass and persistent local swelling are present. A thrill or bruit suggests the diagnosis, which should be confirmed by ultrasonography. A characteristic sound due to the circulation within the sac of a pseudoaneurysm is described as ‘yin/yang’.

Treatments:

(a) Pseudoaneurysms: Intervention is usually required because once established, the sac is unlikely to thrombose spontaneously. They are effectively treated by ultrasound-guided compression or thrombin injections [8]. Ultrasound-guided compression is the first-line treatment. It is performed using the ultrasound probe to compress the aneurysm neck, but it may take 20–120 min of firm compression and is not as reliable as percutaneous injection of thrombin (500–1000 units), which is made into the sac (under ultrasound imaging control) [9].
(b) Arteriovenous fistulas: Usually require surgical repair but a covered stent is an endovascular treatment option.

20.2.1.4 Femoral Artery Thrombosis

This is a serious but fortunately rare complication leading to acute arterial ischaemia in the lower limb. It is usually caused by pre-existing atherosclerosis of the femoral artery, use of

occlusion devices, dissection or hypercoagulability states.

Clinical signs: Symptoms may be minimal, but the limb may be cold and pulseless. Early diagnosis is important, and a regime of observations that includes assessing the distal arterial pulses should be part of routine postangiography patient care.

Treatment: Emergency thrombolytic therapy and/or mechanical thrombectomy, angioplasty and, if these measures fail to restore the circulation, surgical bypass should be considered.

20.2.1.5 Infections of the Percutaneous Puncture Site

Puncture site infections are rare and associated with comorbidities such as diabetes, obesity and impaired immunity. Other risk factors are early repeat arterial punctures and the use of closure devices, which involve residual implants.

Treatment: Antibiotics initially and, if an abscess develops, surgical drainage or debridement may be required.

20.2.1.6 Entrapped Closure Devices

This complication occurs when a closure device fails to operate properly and becomes entrapped. Management usually requires surgical exploration, arteriotomy and retrieval.

20.2.1.7 Complications at Other Access Sites

A haematoma in the neck following carotid or jugular puncture is a potentially life-threatening complication because it can obstruct the upper airway. Special care should be taken to ensure adequate haemostasis when common carotid artery punctures are performed, especially for procedures involving anticoagulation. This complication may require emergency intubation or tracheostomy.

20.2.2 Complications Caused by Catheters and Guidewires

20.2.2.1 Dissection

This is caused by intramural contrast injections or by guidewire or catheter tip penetration of the vessel intima. It is more likely in patients with pre-existing arterial diseases, e.g. atherosclerosis, Ehlers–Danlos syndrome (particularly type IV) and Marfan syndrome. Though minor arterial wall damage is probably common, dissection causing arterial occlusion is rare (about 0.1–0.4% of angiograms) and symptoms as a result, even rarer [10]. It should be suspected when contrast fails to clear from the site of a test injection.

Prevention: Since the operator causes this adverse event, it is less likely if catheter and wire manipulations are performed carefully and gently. The operator must ensure good backflow into catheters before injecting contrast media and observe a small test injection after catheters are positioned and prior to fast injections for angiograms.

Treatment: Once dissection is detected, its management is to retrieve the catheter or wire, assess the extent of any flow reduction and, if this is compromised or there is evidence of an extending flap, place a stent [11].

20.2.2.2 Thromboembolism

This is the most common cause of a new neurological deficit after catheter angiography. It occurs during about 1.0–2.6% of cerebral angiograms and results in permanent neurological deficits in 0.1–0.5% of patients [12]. The risk is greater in patients over 60 years, those with a history of cerebral vascular disease (the frequency in angiograms for TIAs or previous stroke is about 4.5%) or sickle cell disease and during long and complex procedures [13]. Emboli include blood clots, atheromatous plaque, cholesterol, air or foreign materials.

Prevention: A meticulous technique will prevent this complication. The commonest preventable cause is blood clot forming in catheters and delivery devices (the brain is surprisingly tolerant to injected air). Flush saline solutions should therefore contain heparin (500–2500 units per litre), and closed systems are used to draw up and inject all liquids. In high-risk procedures, pretreatment with antiplatelet agents and higher levels of periprocedural anticoagulation should be considered and blood tests performed to confirm

effective anticoagulation (i.e. activated clotting time (ACT) estimation) and antiplatelet activity.

Treatment: When thromboembolism is identified (e.g. new occlusion of a cerebral artery), the first step is to establish the extent of collateral support by angiography and, if not contraindicated, give a thrombolytic or antiplatelet agent. The initial priority is to establish the effect of any identified embolus on cerebral perfusion; this may require additional imaging (see below, complications during aneurysm treatments). The next steps will depend on the response to these measures.

20.2.2.3 Vessel Perforation or Rupture

Can be caused by guidewires and catheters, but this is extremely rare during diagnostic angiography and is usually associated with interventions such as angioplasty, balloon-assisted coiling and distal catheterisation during treatments of arteriovenous malformations. It will be discussed in the circumstances of specific treatments.

20.2.3 Reactions to Radiographic Contrast Medium and Periprocedural Drugs

20.2.3.1 Allergic Reactions

In the past, radiographic contrast was a frequent cause of allergic reactions during angiography. They occur less often after intraarterial than intravenous injection, and the incidence has been substantially reduced by the introduction of nonionic contrast media. Mild reactions (tachycardia, hypertension, nausea or vomiting) occur in 3/100 and severe reactions (skin rash, oedema, bronchospasm, hypotension) in 1/2500 intravenous injections and are fatal in about 1/170,000 patients.

Reactions to other procedural drugs are now more common, and adverse reactions have been reported to almost all the drugs we commonly use. These include lignocaine, heparin, aspirin, atropine, papaverine, nimodipine, abciximab, protamine sulphate and chymopapain. An important reaction to diagnose is thrombocytopenia that may occur after heparin administration. A transient fall in the platelet count 1–4 days after initiation of treatment in common but a more serious autoimmune-mediated response occurs in 3–5% of patients exposed to heparin and was discussed in Tutorial 5. Heparin-induced thrombocytopenia (HIT) is caused by antibodies against the heparin platelet factor-4 complex and occurs between days 5 and 10 after starting heparin [14].

Prevention: Pretreatment of patients with allergic histories may be given using prednisolone (e.g. 40–50 mg given 12 and 2 h before the procedure).

Treatment: Minor reaction should be treated with antihistamine drugs and IV fluids, and more severe reactions with adrenalin, oxygen, high-dose corticosteroids and ventilation support.

20.2.3.2 Toxic Effects

Toxic effects are dose related, but an individual's response to a drug varies. Two agents will be considered for their potential toxicity during catheter angiography.

(a) Local anaesthetic agents: Lignocaine, like other amide local anaesthetic agents (prilocaine, mepivacaine and bupivacaine), can cause dose-related side effects as well as hypersensitivity or idiosyncratic reactions. These involve the central nervous system (excitation, confusion, blurred or double vision, convulsions and respiratory depression) and the cardiovascular system (bradycardia, hypotension and cardiac arrest).

The safe upper limit for local anaesthesia with lignocaine is estimated at 3 mg/kg when used without adrenaline [15]. This means that a 2% solution contains 20 mg/ml, and the safe dose for a 70-kg adult is 10.5 ml. Allergic reactions are rare.

(b) Contrast media: Acute tubular necrosis leading to renal failure can be induced by the injection of radiographic contrast media in patients with pre-existing renal impairment, especially if they are dehydrated or have diabetic nephropathy or multiple myeloma. Life-threatening lactic acidosis can occur in diabetic patients on metformin. This reaction is an interaction between the contrast agent and metformin and is prevented by stopping

Table 20.2 Indicators and thresholds for complications in diagnostic arteriography

	Reported rates (%)	Major adverse event threshold (%)
Puncture site complications		
Haematoma (requiring transfusion, surgery or delayed discharge from hospital)	0.5–1.7	>3
Occlusion	0.14–0.76	>1
Pseudoaneurysm/arteriovenous fistula	0.04–0.1	>0.2
Catheter-induced complications (other than puncture site)		
Distal emboli	0.0–0.10	>0.5
Arterial dissection	0.43	>1
Subintimal injection of contrast	0.0–0.44	>1
Systemic complications		
Major contrast reactions	0.0–3.13	>5
Contrast-agent-induced nephropathy	0.6–0.23	>5

Adapted from Dariushnia et al. [19]
Note: All values supported by the weight of literature evidence and panel consensus

metformin for 48 h after contrast media injections. Renal function tests should be normal before restarting the drug.

Other adverse events related to contrast media used in cerebral angiograms are cortical blindness [16] and transient global amnesia [17].

20.2.4 Radiation-Induced Skin Damage

Erythema and alopecia in areas exposed to X-rays during fluoroscopy is a dose-dependent response. The ionising radiation delivered during an individual procedure is easily calculated, and doses to the skin should normally not exceed 2 Gy. Mooney et al. measured absorbed skin doses in patients undergoing embolisation of brain AVMs; these were up to 4 Gy [18]. The threshold level of radiation exposure to cause transient erythema is 2 Gy, transient epilation 3 Gy, permanent epilation 7 Gy and skin necrosis 18 Gy.

Prevention and treatment: A 2Gy threshold should be established and procedures stopped when this is reached to prevent this complication. If procedures require an excessive fluoroscopy time, patients should be warned of possible transient hair loss and advised to seek help if they develop erythema.

20.2.5 Benchmark Levels for Complications Related to Angiography

The Society of Interventional Radiology has developed the concept of peer benchmarks for acceptable incidences of particular complications. Its Standards of Practice committee has produced guidelines for diagnostic angiography which set threshold levels for the incidence of particular complications, which if exceeded should prompt operators to review their practice, consider external investigation and additional training [19]. A consensus panel has agreed on these thresholds, and they are both relevant across specialties and helpful when considering generic complications. The thresholds for complications during diagnostic angiography are reproduced in Table 20.2.

20.3 Complications Specific to Endovascular Treatments for Specific Conditions

20.3.1 Aneurysms

In this section, treatments are considered as being performed in the standard or usual way. However, coil embolisation procedures are now frequently performed with adjuvant devices, e.g. balloon

assist, neck-bridge devices and stents, and the use of these technologies adds to the risk of complications because they make procedures more complex.

20.3.1.1 Periprocedural Thromboembolism or Inadvertent Parent Artery Occlusion

The frequency of these related complications are about 2–5% and 1–3%, respectively. The factors that may contribute are the coagulation status of the patient, mechanical compression of adjacent vessels by coils or their herniation into the lumen of parent arteries. Balloon-assisted coiling is not considered to add to the risk of intraarterial thrombosis, but deployment of stents is and requires specific prophylaxis (see below).

Prevention: Use of heparinised saline flush solutions and procedural systemic anticoagulation (levels of anticoagulation should be monitored because of individual variability in the response to heparin and doses adjusted to maintain the activated clotting time 2–3 times baseline values).

Treatment: Responses to iatrogenic intraarterial thrombus or branch occlusion should be incremental starting with simple measures, such as induced systemic hypertension and local flushing injections. If these fail, then thrombolysis is performed using platelet antagonists (i.e. aspirin or glycoprotein IIb/IIIa receptor inhibitors) or fibrinolytic agents (i.e. tPA) but during treatments of recently ruptured aneurysms, fibrinolytics should not be used. One protocol is an initial bolus of 10 mg abciximab (given intraarterially or intravenously) and reassessed with angiography after 10 min. Smaller doses (2 mg increments) may be given via the microcatheter. If there is no response, the treatment is repeated up to a maximum of 20 mg. A post-procedure infusion may be prescribed, see delayed thromboembolism below. Intravenous aspirin is an alternative, given when thrombus is identified. Failure to reopen the vessel may require thrombectomy or placement of a stent.

20.3.1.2 Rupture of the Aneurysm or Vessel Perforation

The frequency of this event is 2% during treatments of recently ruptured aneurysms and 0.2–0.5% during treatments of unruptured aneurysms. It is caused arterial or aneurysm wall penetration by coils or guidewire or microcatheter. Arterial rupture is caused during balloon-assisted treatments by overinflation of the balloon or perforation of a distal artery by the stabilising guidewire tip. Bleeding is usually detected by the operator, but a sudden change in heart rate and blood pressure will alert the anaesthetist to onset of pain or an increase in intracranial pressure. If a ventricular drain is in situ, fresh haemorrhage appears in the drain.

Prevention: Use of soft-tip guidewires, accurate catheter tip control, correct coil sizing and softness choices, precautions against balloon overinflation and careful fluoroscopic monitoring of guidewire tip positions.

Treatment: Immediate reversal of anticoagulation by administration of protamine sulphate, cardiovascular support and investigation of the likely cause. If a balloon is in situ, it should be inflated. In-room CT will confirm the diagnosis (if available). Contrast administration (i.e. for angiography) should be kept to a minimum during bleeding since it causes vasospasm and is an irritant to the meninges, when extravasation into the subarachnoid space occurs.

If the aneurysm wall has been penetrated, it may be best to place more coils via a second catheter to occlude any residual aneurysm sac rather than risk further damaging the wall by immediately retrieving the extruded coil or microcatheter. Once active bleeding has ceased, the procedure should be completed as quickly as possible to ensure the aneurysm is secured and then CT performed to assess the extent of haemorrhage and possible acute hydrocephalus. Decisions on subsequent management will be guided by the imaging, intracranial pressure and cardiovascular parameters.

20.3.1.3 Coil, Stent or Neck-Bridge Device Misplacement or Migration

The frequency of this complication is 3%. It may be due to displacement of a detached coils by

blood flow or during placement of coils or stents. Part of a coil may accidentally extend into the parent artery and not be recognised prior to detachment. The length of misplaced coil can be just a short length of its distal portion or the majority of the coil if accidental detachment occurs when removing a malposition coil.

Prevention: The position of a single endosaccular coil is stabilised by additional coils, so it is unwise to treat, even very small aneurysms, with a solitary coil. Use of a double-catheter technique is useful when there is concern about the stability of a deployed coil. In this situation, delivering a second coil through a new catheter means the first is stabilised before either is detached. Balloon-assisted coiling or placement of a stent when treating wide-necked aneurysms prevents coils herniating into the parent artery. Reinserting the guidewire or coil control wire after detachment of the last coil, to insure that the coil tail has been delivered from the catheter tip, is a simple precaution against migration during microcatheter removal.

Treatment: Retrieval of a migrated coil can be performed with one of several retrieval devices (each department seems to have its own preferences). Retrieval of short lengths of extruding coil is usually unnecessary since they are unlikely to cause thromboembolism. In this situation, post-procedure prescription of low-dose aspirin (for 3 months) is a sensible precaution.

20.3.1.4 Delayed Thromboembolism

Arterial thrombosis may occur within the first few hours after endosaccular coil embolisation; its frequency is 3–5%. Additionally, a minority (about 5–7%) of patients experience one or more delayed TIAs for up to 6 weeks after procedures. Both these events are assumed to be the result of a large surface of coils exposed to blood flow at the aneurysm neck and are therefore more frequent after treatment of wide-necked aneurysms. The same response to endovascular metal implants occurs after stent procedures and is discussed below.

Clinical signs: The onset of a new neurological deficit or deteriorating level of consciousness in the postoperative period may be due to thromboembolism, unrecognised procedural haemorrhage or aneurysm rebleeding, vasospasm or hydrocephalus. Emergency CT should be performed, and angiography, if vasospasm is suspected.

Prevention: There is no current consensus concerning the use of post-procedure anticoagulation for treatments involving coil embolisation alone. A simple regime is to prescribe intravenous heparin for 24 h after endosaccular coil embolisation of wide-neck aneurysms or when there has been evidence of intraarterial thrombosis during procedures. Antiplatelet treatment as prophylaxis against delayed TIAs is similarly appropriate after treatment of wide-neck aneurysms. Patients should be prescribed aspirin (75 mg/day) for 6 weeks.

Treatment: Once CT has excluded new haemorrhage or hydrocephalus as the cause for deterioration, arterial thrombosis diagnosed soon after coil embolisation should be treated by thrombolysis using intravenous aspirin or platelet glycoprotein IIb/IIIa receptor inhibitors. My protocol is an initial bolus of 10 mg abciximab (given intravenously), and the patient reassessed for signs of improvement after 15–20 min; if these are absent or incomplete, the treatment is repeated up to a maximum dose of 20 mg as boluses and then an infusion of 0.125 μg/kg instigated for 24 h. Heparin is stopped because of the risk of spontaneous bleeding. This regime should be used with care in patients after subarachnoid haemorrhage since the antiplatelet effect would need to be reversed if emergency surgery was required. Delayed TIAs should be treated with low-dose aspirin (e.g. 75 mg daily).

20.3.1.5 Other Delayed Complications

Aneurysm recurrence due to coil compaction, rebleeding from a treated aneurysm, hydrocephalus and reactions to coated coils are adverse events that may occur after endosaccular coil embolisation. Aneurysm recurrence and consequent rebleeding is generally considered a failure of the primary treatment, but the reported reaction to coated coils is a poorly understood complication, which exemplifies the difficulty of predicting the biological response to a foreign body implant.

A minority of patients treated for unruptured aneurysms have been reported to show asymptomatic enhancement around the aneurysm and hydrocephalus on follow-up MRI [20]. This response has been reported after treatments with bare metal and coated coils but more frequently after use of coated coils. It is assumed to be part of an inflammatory reaction to the coating [21]. Some coated coils are designed to expand after deployment, and this mechanism may exacerbate symptoms due to compression of adjacent structures [22].

20.3.2 Arteriovenous Malformations and Arteriovenous Fistulas

Techniques for the endovascular treatment of arteriovenous malformation of the brain and spine have evolved gradually over the last 30 years, but the major risk remains that of causing haemorrhage.

20.3.2.1 Periprocedural Bleeding

The incidence of procedural intracerebral haemorrhage is about 2–5% using NBCA [23] and about 5–7% using ethylene vinyl alcohol polymers (i.e. Onyx (ev3)) [24]. Bleeding is caused by vessel perforations or damage during removal of microcatheters, rupture of flow aneurysms or from nidal vessels with obstructed drainage. The last is thought to be due to intranidal rerouting of blood flow and pressure, as may occur when an intranidal fistula or draining veins are occluded. Excessively high-injection pressures may result in vessel rupture. Delayed bleeding in the 1–4 h postprocedure period is probably due to delayed thrombosis of draining veins causing spontaneous rerouting of blood flow and intravascular pressure changes [25].

Prevention: A complete demonstration of the angioarchitecture using 3D angiography should be obtained so that flow aneurysms, intranidal arteriovenous shunts and major venous drainage pathways are identified in advance. Other precautions include use of detachable microcatheters, reversal of any anticoagulation at the end of procedures and staging embolisation procedures.

Treatment: Effective management depends on early recognition of this complication. Procedural bleeding may occur without extravasation of contrast being evident, and any change in the disposition of vessels during roadmap angiography should alert the operator to a developing haematoma. If recognised, bleeding from distal arteries is usually best managed by immediate embolisation with NBCA to seal the bleeding site. On recovery, patients should be carefully assessed for any new neurological deficit and CT performed if the patient's neurological status deteriorates. Management is either emergency surgical evacuation or expectant intense observation.

20.3.2.2 Ischaemic Complications

Ischaemic complications are either due to thromboembolism during catheterisation or inadvertent occlusion of normal arteries by embolic agents [26]. They are associated with neurological deficit or deterioration more often during treatment of spinal cord AVMs with approximately 11% of patients made worse, including 4% with serious deteriorations in neurological function.

Prevention: The use of anticoagulants during embolisation for AVMs is controversial because of the risk of induced haemorrhage and the perception that navigation towards a substantial arteriovenous shunt is less likely to cause neurological symptoms because any thromboemboli generated are likely to be directed through the shunt. Other precautions include confining embolisation to intranidal vessels or pedicles distal to any normal side branches and avoidance of embolisation in 'en-passant' feeding arteries.

Treatment: Supportive measures to maintain cerebral perfusion and encourage collateral blood supply. Thrombolysis is rarely indicated.

20.3.2.3 Microcatheter Failures

There is a range of complications associated with very distal cerebral catheterisation using flexible microcatheters. Two specific examples are worth considering: a burst catheter and a 'glued' catheter.

A burst catheter is generally caused by solidification of a liquid embolic agent in the catheter and continued injection against this blockage

causing an excessive rise in pressure so that the wall of the catheter gives way. In some instances, this failure can be caused by damage to the catheter either in its manufacture or during preparation for use. Alternatively, catheter contamination with an ionic material may cause early polymerisation of NBCA. Operators must be sensitive to any change in the anticipated flow pattern of an injected embolic agent on fluoroscopy and resist any temptation to increase injection pressures when absence of forward flow is detected.

A glued catheter is associated with distal catheterisation in tortuous vessels. It was thought to be confined to the use of adhesives such as NBCA [27] but can occur with non-adhesive agents such as Onyx. The adhesive properties of NBCA depend on the strength of the mixture used. That is, mixtures with lipiodol of 1:1 will precipitate and harden within seconds of injection, and the operator should not allow any degree of reflux to occur around the catheter tip, whereas using a 1:5 mixture allows injections to be prolonged for 3–4 min with little risk of adhesion within the vessel. The ease with which a catheter can be retrieved after injections with Onyx depends on the extent of reflux around the catheter tip. Retrieval is usually possible despite reflux extending up to 2 cm proximal to the catheter tip using steady and prolonged retraction pressures.

Prevention: Detachable-tip microcatheters are now available which allow the operator to reflux liquid agents for a prescribed distance around the detaching tip and then retrieve the catheter.

Management: Operators should identify when a catheter cannot be retrieved, and in this situation, the proximal portion is cut at the puncture site and the patient is prescribed antiplatelet for 3 months starting 24 h after the procedure.

20.3.3 Angioplasty and Stenting

20.3.3.1 Ischaemic Events

The incidence of ischaemic events in patients treated for atherosclerosis is about 5–7% because they are more likely to have complications caused by the migration of plaque or debris created during angioplasty. This problem has prompted the development and use of distal protection devices, which are available with a variety designs intented to prevent dislodged thromboemboli reaching the brain. It is generally agreed that stroke after large artery angioplasty is less likely if a stent is used to contain wall debris, and it is one reason why self-expanding stents are usually used with angioplasty performed for pre- or post-stent dilation.

Prevention: Generic measures described in Sect. 20.2.2.2 above, anticoagulation, correct balloon sizing, pretreatment with antiplatelets prior to stent placement (e.g. aspirin 325 mg/day + clopidogrel 75 mg/day for 3–5 days), avoiding overinflation of balloons, use of distal protection devices [28].

Treatment: Thrombolysis with fibrinolytic agents.

20.3.3.2 Dissection

The incidence of this complication is substantial during balloon angioplasty, since it is part of the process. How often it leads to symptoms and requires an additional intervention is difficult to calculate from reports. It may cause acute or delayed artery occlusion, pseudoaneurysm formation and haemodynamic or embolic stroke.

Prevention: Many operators prefer to perform a minimal degree of predilation of the stenosis and then place a stent.

Treatment: Observation and antiplatelets if no flow obstruction occurs and stenting if blood flow is reduced. For iatrogenic dissection, many operators prefer to place a stent in either event [29].

20.3.3.3 Early Thrombosis

This complication is defined as occurring in the first 24 h after angioplasty and/or stenting.

Prevention: Good patient selection and pre-procedure treatment with antiplatelet agents (at least 3 days). Prophylactic anticoagulation should be maintained for 3 days post-procedure and antiplatelet treatment for at least 3 months.

Treatment: Thrombolysis.

20.3.3.4 Cerebral Haemorrhage

Vessel rupture can occur during treatment of intracranial artery stenosis due to balloon over

inflation, wall perforation by guidewires or catheters and stent misplacement. Bleeding may be difficult to control because of prophylatic treatment with antiplatelet and anticoagulants drugs.

Post-procedure haemorrhage caused by the cerebral hyperperfusion syndrome is due to a sudden increase in blood flow within an arterial territory with impaired autoregulation [30]. It is associated with treatment of high-grade carotid or vertebrobasilar artery stenosis, severe uncontrolled hypertension, severe contralateral carotid stenosis and poor collateral cerebral blood flow. It is also more frequent in patients who have suffered recent stroke. The signs are headache, vomiting, alterations in mental state, seizure or new focal neurological deficit.

Prevention: Careful sizing of balloons and stents with optimum imaging. The cerebral hyperperfusion syndrome is prevented by control of systemic blood pressure with systolic pressure maintained <140 mmHg.

Treatment: Procedural bleeding is managed by reversal of anticoagulation, infusion of fresh frozen plasma and the measures as described above in Sect. 20.3.1.2. Cerebral hyperperfusion syndrome is managed by control of blood pressure, antiepileptic drugs for prophylaxis against seizures and corticosteroids.

20.3.3.5 Reflex Bradycardia and Hypotension

This is caused by carotid sinus stimulation during inflation of an angioplasty balloon in the region of the carotid bifurcation. The signs are acute bradycardia or asystole. Persistent hypotension may last several hours after carotid sinus stimulation.

Prevention: Pretreatment with atropine (0.5 mg intravenously, 5 min prior to angioplasty). Minimising the number of balloon inflations.

Treatment: Acute bradycardia is usually self-limited and resolves in a few minutes. Having the patient cough may help to reduce the carotid stimulation effect. Systemic hypotension is managed with IV fluids, postural measures and, if severe, vasoconstrictor drugs. Persistent cardiac arrhythmias may require defibrillation or external cardiac pacing.

20.3.3.6 Late In-Stent Stenosis

This is well recognised in coronary artery stenting and is due to the development of neointimal hyperplasia. It is seen after treatment with stents or angioplasty and more frequently after treatments for intracranial than extracranial atherosclerosis. Frequency rates range from 10% to 50% [31]. It typically occurs 3–9 months following stenting and may be asymptomatic and shown on follow-up angiographic or after recurrence of symptoms or stroke.

Prevention: In coronary arteries, drug-eluting stents have shown some benefit, but this has yet to be proven for the treatment of cerebral vessels.

Treatment: Angioplasty if symptomatic.

20.3.4 Embolisation for Tumours

Particles are the most common embolic agents used for the embolisation of tumours. The following is therefore focused on complications resulting from their use.

20.3.4.1 Spread of Embolic Agents to Normal Arterial Territories

This complication may cause neurological deficit, and any resulting disability depends on the vessels occluded. The incidence of stroke or ophthalmic complications caused by embolisations of cranial tumours is about 0.25–1%. It can be caused by spread of liquid agents or particles to the intracranial circulation through physiological anastomoses, variant anastomoses and the development of abnormal external to intracranial communications as a result of the tumour. Cranial nerve palsies are associated with the use of very small particles (<150 μm).

Clinical signs: Hemiplegia, hemianopsia, paraparesis, paraplegia, nerve palsies, etc. Visual loss due to particles entering the central artery of the retina may be mild to severe, and particles may be visible in retinal vessels on fundoscopy. Particles may also cause skin or mucosal ulceration trismus

and delayed but permanent alopecia. Sclerosants often cause local pain and swelling.

Prevention: Avoiding transarterial embolisation in territories where dangerous anastomoses are likely (e.g. the ascending pharyngeal artery), use of plug emboli (e.g. coils or Gelfoam) to alter blood flow patterns in advance of particle injections, superselective pre-embolisation angiography to identify anastomoses and the choroidal blush so as to predict the destination of injected agents and finally, and most importantly, an adequate knowledge of vascular anatomy.

Treatment: In many instances, deficits caused by particulate embolisation will recover, given time and supportive measures. Deficits after injections with liquid agents are more likely to be permanent.

20.3.4.2 Tissue Necrosis and Tumour Swelling

Tissue damage is an inevitable component of tumour embolisation, and tumour swelling or secondary haemorrhage may exacerbate symptoms or neurological signs due to mass effect. Collateral damage to adjacent normal tissues may cause exacerbation of symptoms or a range of new adverse effects.

Clinical signs: Embolisation may cause local pain and tissue oedema. Rapid swelling of intracranial tumours due to haemorrhage may cause focal neurological deficits, raised intracranial pressure, subarachnoid haemorrhage and reduced levels of consciousness.

Prevention: Limiting the scope of embolisation to the immediate vicinity of the target tumour is the best way of preventing collateral damage. Post-procedure CT is useful to exclude secondary haemorrhage, and close monitoring of patients after embolisation of intracranial masses is mandatory. Patients with symptoms of neurological compression should be given corticosteroids prior to embolisation, and any procedural anticoagulation should be reversed at the end of procedures.

Treatment: Analgesia, nonsteroidal anti-inflammatory agents such as voltarol, corticosteroids (e.g. dexamethasone 4 mg qds for 48 h) and emergency decompression surgery. Skin or mucosal ulceration may heal spontaneously or require skin grafting.

20.3.5 Functional Testing and Large Artery Occlusion

In this final section, a technique rather than condition is considered because it can cause complications, and this risk should be added to the estimate of risk for any treatment it anticipates.

20.3.5.1 Vessel Damage Caused by Temporary Balloon Occlusion

Transient ischaemic complications (not transient abnormal neurological signs caused by an inadequate collateral blood supply, i.e. failed test) occur in 4% of procedures and permanent deficits in 0.5% [32]. These events are generally caused by balloon inflation dislodging atheromatous plaque or causing dissection. Use of coaxial balloons has been reported to increase the chance of vessel trauma because the balloons are less compliant and the catheter system stiffer [33]. Interpretation of test occlusions is notoriously difficult in the posterior circulation where deficits after large artery occlusions are more common.

Prevention and treatment: Use of compliant balloons and adequately monitored of levels of anticoagulation. The ACT should be 3–4 times baseline before balloon inflation. The benefit of a coaxial system with perfusion of the artery distal to the occluding balloon is unproven [34].

Treatment: Supportive measures and thrombolysis or thrombectomy if the putative thrombus is accessible. Stenting of focal arterial dissections may be required.

20.3.5.2 Delayed Ischaemic Deficits

After large artery occlusions with detachable balloons, coils or plug endovascular devices, symptoms due to cerebral ischaemia or infarction can occur for up to 2–3 weeks post procedure. The cause is inadequacy of collateral blood flow.

Prevention: A satisfactory 30-min occlusion test with neurological testing and assessment of collateral blood flow on simultaneous contralateral

angiography is considered adequate to ensure sufficient collateral blood. Additional evaluations of cerebral perfusion can be performed during test occlusions by Xenon CT, SPECT and transcranial Doppler ultrasound examinations and supplimentary provocative-induced hypotension to identify patients at risk of stroke. However, none of these tests have been shown to be absolutely reliable in predicting and preventing symptoms of delayed ischaemia. Antiplatelets (e.g. low-dose aspirin) are frequently prescribed for 6 weeks after large artery occlusions, but there have been no randomised trials to support this prophylactic measure. My protocol after large artery occlusion is 24 h bed rest and then gradual in-hospital mobilisations. Patients are then advised to restrict their physical activity for 4–6 weeks.

Treatment: Bed rest, anticoagulation (if there is no evidence of established cerebral infarction on CT) and antiplatelet drugs. If severe, consider continuous blood pressure monitoring and induced hypertension with general measures to maintain optimum cerebral perfusion. Transient symptoms generally become less frequent and eventually disappear.

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Preamble

This tutorial discusses issues we often take for granted. Studying the background to obtaining informed consent, we stray outside the technical and into ethical territory, which for most doctors is a foreign land. We are trained to evaluate the scientific evidence for or against a treatment, learn how procedures should be performed, and then practise and develop our personal skills. As a result of this preparation, we pride ourselves that operations and procedures are as safe as possible. How do we react when confronted by a patient who, after a lengthy explanation, refuses treatment? Can we really understand another human being's concept of their own body, what they consider to be safe and what conforms or doesn't conform to their personal beliefs and cultural values? The informed consent process makes us confront these realities, and sometimes our own preconceptions and prejudices.

The 'elephant in the room', when discussing informed consent, is the possibility that we may be facing a medicolegal negligence claim, if things go wrong. Developing a rational and disinterested attitude in presenting balanced information about a proposed procedure is one of the hardest and most important skills needed to practise our subspecialty. We have to develop the skill of providing technical information with an appreciation of the individual patient's capacity to understand that information. The information has to be discussed in a manner that the

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concerned individuals can understand and, whilst obeying the principle of honest disclosure, tempered so as not to unnecessarily worry or alarm our patient.

To cope with this challenge, we need to understand the legal and ethical principles on which informed consent is based. There will inevitably be local statutes and laws that apply to medical practice in a particular legal jurisdiction, but globalisation has seen the development of an international consensus regarding human rights on which local regulations are generally based. This tutorial concentrates on the development and application of English law to illustrate these principles. The student obviously needs to be familiar with their national law and its practice in their state or country.

21.1 The Legal Principles of Consent to a Medical Procedure

Consent can be defined as an agreement to do something or to allow something to happen to us, made with knowledge of all relevant facts, such as the risks involved and any available alternatives. The UK National Health Service describes consent as 'Consent to treatment is the principle that a person must give permission before they receive any type of medical treatment, test or examination. This must be done on the basis of an explanation by a clinician' [1].

The patient has the autonomy to give or withhold consent to the chosen treatment but must be competent to do so. This should be given only after explanation and discussion of the treatment and without fraudulent misrepresentation or undue influence of drugs, alcohol or sedatives. Thus, adults must be of sound mind at the time of making the decision.

The basis of the patient's autonomy is their human right to determine what happens to them. This was stated as 'a human being of adult years and sound mind has the right to determine what shall be done with his body and a physician who performs a procedure without a patient's consent commits an assault for which he is liable for damages' by Justice Cardozo[1] in 1914 in what is known as the Schloendorff decision [2]. This sets out the legal principle but leaves the dilemma of how to consent children and mental ill or unconscious patients, for example.

In England, the legal definitions of consent have been established by case law because of the absence of a written constitution. They separate real consent from informed consent. What this means is that to perform a procedure on someone without their consent can be construed as an assault. Under common law, this would make the doctor liable to the criminal charge of battery.

A lesser offence is trespass, which is defined legally as a tort, and implies negligence or a breach of a doctor's duty-of-care, which in this case amounts to their giving insufficient information before a procedure. If this second duty is broken, the patient may claim that had they known what the doctor failed to tell them, they wouldn't have given consent.

The principle was tested in the case of *Chatterton versus Gerson* (1981) in which the judge ruled that consent is real if given after a patient has been informed in broad terms of the nature of the intended procedure [3].

21.1.1 Duty of Care

There are two elements to the doctor's duty-of-care:

(a) To protect the individual from an unreasonable risk of harm
(b) To provide sufficient information to the patient for them to make up their mind

The obtaining consent therefore requires providing sufficient information and to withhold information may be negligent but not necessarily illegal because in discussing the risk of a procedure, the doctor is permitted some discretion, provided this is consistent with a full disclosure of the facts necessary for an informed decision.

[1] Benjamin Nathan Cardozo (1870–1938). New York appeal court and later US Supreme Court judge.

This distinction relies on use of what has become known as the Bolam test. In the case of *Bolam versus Friern Hospital Management Committee* (1957), it was established that a doctor is not guilty of negligence if he has acted in accordance with a practice accepted as proper by a responsible body of medical men skilled in that particular art [4]. It is applied to ensure that the proposed course of action is appropriate and that the appropriate level of risk has been disclosed.

However, this principle has been superseded in a recent judgement by the UK Supreme Court, which established the principle of a patient-related standard. In *Montgomery v Lanarkshire Health Board* (2015), a diabetic woman whose child suffered shoulder dystocia during vaginal delivery argued that if she had been aware of this risk, she would have opted for caesarean delivery. The doctor, supported by a body of medical opinion, argued that the risk of this complication was small and not disclosed because a caesarean section was not in her best interest. The court found in favour of the patient and effectively overturned the Bolam test by ruling that the standard of information about the risks, benefits and alternative treatments should no longer be determined by what a responsible body of physicians but by what a reasonable patient deems important [5]. The patient-related standard appears to place an additional burden on the doctor in deciding what to disclose in order to ensure that the patient has sufficient information to make an informed decision but it also clarifies what is now generally considered good practice [6].

Thus, it is negligent not to ensure that the patient is aware of any material risks and of any reasonable alternative or variant treatments. This represents a breach of the doctor's duty of care. To establish medical negligence, there is also the need to show a causal link between a breach in duty of care and harm incurred. In practice we rely on a team approach to deciding on the appropriate treatment to offer to patients. This largely satisfies the Bolam test but we now need to ensure to apply the patient-related standard. A final point is that if there is medical controversy, i.e. two conflicting bodies of opinion, then a court may have to decide on which is in the patient's best interest.

21.1.2 Level of Risk

This is another legal issue to consider before we discuss what is now defined as 'informed' consent, and that is the amount of information on risk that needs to be given to the patient. English law has evolved with the Sidaway ruling, *Sidaway versus governors of Bethlem Royal Hospital* (1985) [7]. This case involved a situation in which a patient suffered a rare but serious complication of a procedure and argued that this risk should have been disclosed by the surgeon. The surgeon's position was upheld on the basis that the risk was less than 1% and what he disclosed, in obtaining consent, was what other neurosurgeons like him would have done. The judgement set a level of risk but relied on the Bolam test, which now is unlikely to be successful, as the process of obtaining consent in the UK has evolved to include the patient-related standard.

The Supreme Court judges in their ruling on the Montgomery case stated 'The doctor's advisory role cannot be regarded as solely an exercise of medical skill without leaving out of account the patient's entitlement to decide on the risks to her health which she is willing to run (a decision which may be influenced by non-medical considerations). Responsibility for determining the nature and extent of a person's rights rests with the courts, not with the medical professions' [5]. They thus ruled that patients must be told of material risks, and the level of risk is determined by what a reasonable person in the patient's position was likely to consider as significant and left the question of the patient's rights to the courts.

21.1.3 Competency

The Cardozo ruling established that it is a person's right to give (or withhold) consent without coercion but did not include children and incapable adults. The ability to understand the implications of giving consent thus depends on competency.

An adult (defined as >18 years in English law but >16 years for the purpose of medical consent) is assumed to be capable. The law for children (<16 years) is that consent should be obtained from their mother (or father, if the parents are married). It is, however, complicated by the Gillick ruling (Gillick vs. West Norfolk and Wisbech Area Health Authority 1986) [8], which established that a person under 16 years could consent to treatment without parental permission, if they were of sufficient maturity and understanding (i.e. competent). The case involved a mother who wished to be informed if her under 16 years old daughters were to be prescribed contraceptive agents by their general practitioner.

The situation for patients with a mental illness is partially covered, in England and Wales, by the Mental Health Act (1983) and its amendment in 2007 [9]. This law permits the treatment of mental disorders without consent. However, informed consent is still required from psychiatric patients undergoing treatment for other medical treatments, and the principles of informed consent apply. The issue of competence when a patient is unconscious or neurologically impaired will be discussed further below.

21.2 Informed Consent

The doctrine of informed consent is thus a logical consequence of the right of autonomy, which is now encoded in the European Convention of Human Rights. The Convention was adopted into British law in 2000, becoming part of the Human Rights Act 1998 [10] (see Table 21.1).

Table 21.1 Relevant articles of the European Convention of Human Rights (ECHR)

Articles of the ECHR	
Article 2	Right to life
Article 3	Prohibition of torture (inhuman or degrading treatment)
Article 5	Right to liberty and security
Article 8	Right to respect for private and family life
Article 9	Right to respect thought, conscience and religion

21.2.1 Guidance on Obtaining Patients Consent to Medical Procedures

The General Medical Council of the UK in 1998 published a guidance booklet for doctors entitled *Seeking patients' consent: the ethical considerations* and in 2008 updated it with *Consent: patients and doctors making decisions together* [11]. The Royal College of Radiologists published Standards for patient consent particular to radiology in 2005 and a second edition in 2012 [12] which relates to the responsibilities of doctors involved in imaging and interventional radiology and the Royal College of Surgeons published broader guidance in 2008, which was updated in 2014 [13]. In their introductions, these documents stress that any successful relationship between doctor and patient depends on trust. To establish this trust, doctors are reminded that they must respect the patient's right to decide whether or not to undergo any medical intervention and must be given sufficient information to exercise that right and therefore to make informed decisions about their care.

Effective communication is seen as the key to enabling patients to make informed decisions, and the doctor should take appropriate steps to find out what the patient wants and ought to know about their condition and its treatment. Open dialogue with patients leads to clarity of objectives, understanding and strengthens the quality of the doctor/patient relationship. It provides an agreement framework within which the doctor can respond to the individual needs of the patient and for them to be able to make properly informed decisions.

The current guidance is that written consent should be obtained if:

- The investigation or treatment is complex or involves significant risks.
- There may be significant consequences for the patient's employment or social or personal life.
- Providing clinical care is not the primary purpose of the investigation or treatment.

- The treatment is part of a research programme or is an innovation.
- The treatment is designed specifically for the patient.

21.2.2 The Informed Consent Process Under Ordinary Circumstances

Informed consent is thus a contract between two parties based on an understanding of what both want the treatment to achieve and both accept the involved risks. Obtaining consent for medical treatments thus involves more than telling a patient what treatment is proposed and them signing a form. The process depends on the following:

1. Sufficient information: The doctor proposing the treatment provides sufficient information, in a way that can be understood, so the patient can exercise their right to make an informed decision about their care. This should include the diagnosis, its prognosis, what the treatment involves, its purpose, alternative options (including no treatment), the risks and their potential consequences. Possible complications with severe consequences should be discussed, however rare and those with moderate or minor consequences, if common. Potential consequences that might affect the specific patient's occupation or livelihood should be discussed.
2. Capacity: The doctor needs to provide information in a manner that the patient can understand. So it should be tailored to their level of understanding, which may involve the use of translators and translations of written material. The patient's beliefs and cultural should be taken into consideration and their concerns explored. They must be given an opportunity to ask questions.
3. Specificity of consent: Consent is obtained for a specific examination or procedure, and the doctor must not exceed the scope of the authority given by the patient, except in an emergency (Marshall versus Curry 1933) [14].
4. Surrogates: No one can make decisions or give consent on behalf of a competent adult. In English law, only the patient can give consent. Surrogates, such as relatives, should be involved in the consent process, and the patients may ask you, or nominate a relative or third party, to make decisions for them. They may even ask that details are withheld from them, but in either instance, you should ensure that the patient is aware of basic information about the treatment for which they are giving the consent and document the process.
5. Primary physician: The doctor providing the treatment or undertaking the investigation is responsible for obtaining consent. They are in the best position to explain how it is to be carried out and the risks involved. If this responsibility is delegated, they have to ensure that the delegate is suitably trained and has sufficient knowledge to provide information and obtain informed consent in accordance with current regulations and guidelines.
6. Oral consent: Consent can be explicit, e.g. when a patient offers their arm for a blood test. The law does not prescribe that a written form has to be used. So patients may give oral consent, provided the attendant documents the process and records the names of suitable witnesses, the consent is valid. It is therefore the doctor's responsibility to document the patient's agreement to the procedure and the discussion that led to it. This can be done on a 'consent form' or in the patient's notes.
7. Consent forms: In England and Wales, the Department of Health issued a series of documents after the Bristol enquiry in 2001 [15] (this was an inquiry into the conduct of paediatric cardiac surgery at a hospital with unusually high mortality rates). There are now at least ten documents on the Department of Health's website relating to different aspects of medical consent. The principal numbered forms are:

   Consent form 1: used for the patient who is able to consent for himself or herself.

Consent form 2: used for those with parental responsibility, consenting on behalf of a child or young person.

Consent form 3: used for both patients able to consent for themselves and for those with parental responsibility consenting on behalf of a child/young person, where the procedure does not involve any impairment of consciousness.

Consent form 4: used for the patients who lack capacity to consent to a particular treatment; this is the 'inability to consent' form and is discussed below.

The Department of Health stipulates that the text included in these forms should not be amended or removed. The forms should be standardised across the NHS, and individual organisations may add details relevant to their style of practice, as long as it does not make it too cumbersome to read and does not decrease the font size of the document so as to make it difficult to read.

8. Withdrawal of consent: It is important to realise that a patient, having signed a consent form, may withdraw from treatment at any stage and that the patient is made aware of this prerogative.
9. Timing of obtaining consent: It is advised for an elective procedure, that consent is obtained in two stages. A preliminary discussion and documented consent is obtained as an outpatient and then a second consent obtained immediately prior (within 24 h) to the intended procedure. The principle is that the patient should be given time to consider their decision.
10. General anaesthesia: If the intended procedure involves general anaesthesia, it is the responsibility of the anaesthetist to consent the patient for that part of the procedure.
11. Special consents: Separate consent is needed from individuals taking part in research and for procedures that will be videoed. For patients undergoing fertility treatments, written consent is required by law.

21.2.3 Situations in Which Obtaining Informed Consent Is Impossible or When Patients Are Judged Incompetent

A legal framework for situations regarding patients who lack the capacity to give consent was created in the UK by the Mental Capacity Act [16]. It brought into English law the provisions agreed by the government at the Convention on the International Protection of Adults and signed in The Hague on 13 January 2000. This, for the first time, set out rules about advance decisions to refuse medical treatment and research involving people who lack capacity. The following is a summary of things to consider.

1. In emergencies, when informed consent cannot be obtained, the medical treatment should be limited to what is immediately necessary to save lives or to avoid significant deterioration in the patient's health. The 'inability to consent' procedure requires documentation of the reasons for proceeding with a treatment without consent. In most instances, this involves the patient being unconscious or temporally incapable and the treatment cannot wait until the patient is well enough to provide consent. Relatives should be consulted to ensure that the proposed treatment is not contrary to the patient's prior known wishes, e.g. if they have made a 'living will' or if the treatment, and what it involves, would contravene their known faith principles. Though relatives can't provide consent for adults in the UK, the doctor should make efforts to ensure that they are aware of the reasons for the proposed treatment and its risks and benefits.
2. If a patient's choice appears irrational or does not accord with your view of what is in their best interest, it does not mean they lack the competence needed to give informed consent.
3. Treatment of mentally incapacitated patients may be performed without consent but within the safeguards laid down by the Mental

Capacity Act 2005 [16]. This does not extend to treatments not directed at a mental disorder, and compulsory treatment in this situation can only be performed after a court's approval.

4. The legal situation with children has been discussed above. In general, you should assess a child's capacity to understand the nature, purpose and possible consequences of the proposed investigation or treatment, and it is assumed that anybody over the age of 16 years has the capacity to decide. Under this age, the situation can only be assessed on a case-by-case basis, and when a competent child refuses treatment, a person with parental responsibility or the court may authorise investigations or treatments (which they consider is in the child's best interest). This is not the situation in Scotland where a competent child has the right to refuse.
5. In deciding what may be reasonably considered as the patient's best interest, the doctors should take into account any evidence of the patient's previously expressed preferences, such as an advanced directive. They should consider what is known about the patient's background and the proposed treatment in the context of the patient's cultural, religious or employment background. This may be helped by considering the views of any third party who has knowledge of the patient.
6. In situations where the patient's capacity to consent is in doubt, or when differences of opinion about his or her best interest cannot be resolved, more experienced advice should be sought. This may involve the hospital medical director or a legal opinion. Ultimately, as expressed in the Supreme Court ruling on the Montgomery case, it is for the courts to decide on a patient's rights [5].

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