Pediatric Vascular Neurosurgery

Technical Nuances in Contemporary Pediatric Neurosurgery (Part 2)

Abhishek Agrawal
Gavin Britz
Editors

Springer

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Foreword

Pediatric Vascular Neurosurgery is a valuable contribution to the medical literature. This two-volume overview on pediatric vascular neurosurgery, edited by Drs. Agrawal and Britz, provides timely, superb, and wide-ranging information. The authors, selected by the editor, are well-recognized experts who provide insightful and comprehensive information. Each chapter contains multiple pertinent illustrations that greatly enrich the text.

Volume I is titled *Pediatric Vascular Neurosurgery: Principles and Practice of Neurovascular Disorders (Part 1)*. The initial chapters of this volume provide an overview on the fundamental background of pediatric neurovascular disorders, whereas subsequent chapters review in detail specific vascular entities.

Volume II focuses on the technical nuances in contemporary vascular neurosurgery. Like Volume I, the initial chapters deal with basic information such as the embryology of the cerebral circulation and in uterine vascular disorders. The remaining chapters then comprehensively cover the treatment options of individual vascular entities and uniquely focus on technical advances and approaches.

I congratulate the editors and the contributing authors for this definitive and comprehensive book. I am confident that medical students and residents will find these volumes a valuable source of information and that pediatric neurologists, pediatric neurosurgeons, and vascular neurosurgeons will want to add *Pediatric Vascular Neurosurgery* to their library.

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Foreword

"A vicious bag of bleeding worms" was how a vein of Galen aneurysm was described to me during my training. The fact that the paediatric neurosurgeon now rarely has to lose sleep over the thought that they would have to tackle such a beast is a measure of how far the practice of paediatric vascular neurosurgery has come in the last 25 years. A glance at the table of contents of these volumes shows how the subject has developed and matured in that time. It has become commonplace to explain how much a medical discipline has changed over the years and neurosurgical practice as a whole has changed dramatically since I began my training in the late 1980s. There can be little doubt that the discipline of paediatric vascular neurosurgery is one branch of our practice which has been transformed beyond recognition. Advances in imaging technology, stereotactic radiosurgery, endovascular treatment and progress in operative neurosurgical techniques are some of the ways in which the subject has developed. It is therefore timely that Drs. Britz and Agrawal have brought together experts in the field to produce these volumes which will serve as the definitive reference for the subject for many years to come.

The foreword to such a textbook is generally written by an emeritus professor or other worthy who has made a major contribution to the subject at hand. I can lay claim to neither of these accolades, and so I am flattered to be asked to make this contribution. Children with vascular pathology, although not presenting a large numerical burden on most neurosurgical practice, can and do represent a significant emotional drain both to their families and their treating physicians. By its very nature, vascular pathology often presents in a dramatic fashion with potentially devastating consequences for young patients and their families. The need to have a sure grounding in the diagnosis and management of these varied conditions is paramount. An understanding of the pathophysiology, the natural history and treatment options is essential if an appropriate management plan is to be formulated and put into practice. Profound knowledge and great technical skill, however, are

insufficient alone in the management of these conditions. There can be few other fields of neurosurgical practice, let alone medicine as a whole, where the relationship between the patient, their family and the neurosurgeon is so important. In such a technically demanding specialty, it is essential not to lose sight of the human side and that the wellbeing of the child remains at the centre of everything we do.

A close relationship between the neurosurgical units of Seattle, Washington, and the Atkinson Morley Hospital, UK, developed from the late 1980s onwards, and it was as part of this programme that I first met Dr. Britz. This trans-Atlantic collaboration produced a prolific exchange of ideas and continues to this day with Dr. Britz's unit in Houston. It is perhaps no coincidence that the field of paediatric vascular neurosurgery is one in which the sharing of methods and technology is conspicuous and which has led to the advances seen in recent years and described in this book. The importance of the involvement of all related disciplines in the management of such complex cases cannot be overstated. The paediatric neurosurgeon therefore plays a pivotal role in bringing all this together, and he or she must ensure that the related disclipines works as a team. "Multidisciplinary team working" has become something of a mantra over the last decade and is perhaps used too freely without much thought as to what it should really mean, but there are few better examples than in the field of paediatric vascular neurosurgery where this applies. The importance of the role of the paediatric vascular neurosurgeon is in bringing an overarching view of all the disciplines involved to the management of these conditions. A clear grasp of the range and scope of the subject is therefore essential. This book completes that view.

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Preface

There are numerous hospitals with dedicated neurosurgery services catering to thousands of children. However, only a handful of dedicated pediatric vascular textbooks are available as comprehensive guides for review. This book is part of a two volume series which provides an overview on the fundamental background of pediatric neurovascular disorders.

Pediatric Vascular Neurosurgery: Principles and Practice of Neurovascular Disorders (Part 1) updates the readers on basic pediatric vascular anatomy and most commonly encountered neurovascular diseases including – but not limited to – vein of Galen aneurysmal malformations (VGAMs), developmental venous anomalies (DVAs), pediatric stroke, and Moya-Moya diseases. Topics such as intra-arterial delivery of chemotherapeutic agents and stereotactic radiosurgery in pediatric neurovascular diseases have also been discussed at length by experts in the field.

Volume II focuses on the technical nuances in contemporary vascular neurosurgery. It delves into different kinds of complex conditions like craniofacial arteriovenous metameric syndrome (CAMS), spinal arteriovenous metameric syndrome (SAMS), non-Gaelic fistulas, and in utero fetal imaging using non-invasive modalities like ultrasound and MRI.

This two-volume set also aims to replace "excessive information" obtained on the Internet about a neurosurgical disease, which may be too overwhelming, improperly written, not updated, or may be misinterpreted, misunderstood, or irrelevant. The series is specially compiled and illustrated for medical students, residents, fellows, or faculty in pediatric-related specialties, including but not limited to neurosurgery, neurology, pediatrics, intensivist, radiology, or anesthesia involved in pediatric care, to get a quick glimpse of pediatric neurosurgical conditions encountered on a day-to-day basis.

Part I: *Pediatric Vascular Neurosurgery: Principles and Practice of Neurovascular Disorders.*

Part II: *Technical Nuances in Contemporary Pediatric Neurosurgery.*

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Acknowledgments

The key to success of any project depends upon the inputs and guidance received from people associated with the project. Fortunately for us, there was encouragement, guidance, and support from all quarters of life.

Great are those who teach and inspire. They deserve gratitude which can be expressed at a time like this. Our inestimable gratitude goes to the authors who spend their precious time contributing and making this compilation a huge success.

We are also thankful to Ms. Peggy Kelly for her immaculate organization and management. In addition, we would like to express our gratitude to Ms. Advika, Mr. Avik, Ms. Morton, Ms. Darbutaite, Mr. Johnson, Mr. Chozhan, Ms. Nilambari, Ms. Chandwani, and the entire team from Springer- Nature publishers for their collegiality.

Behind all this are the unconditional support, motivation, and encouragement from our family, parents, and children who have always been a source of strength and inspiration.

We extend our special appreciation to all the healthcare workers for making sacrifices to commit to the fight against COVID-19 pandemic, during these unprecedented times. Their work is truly inspiring and meaningful, every day their compassion is appreciated, and their dedication is admired.

'May you be proud of the person you are, the work you do, and the difference you make in the lives of others.'!

Abhishek Agrawal, M.D.

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The Embryological Development of the Cerebrovascular System

Kaitlin Reilly and Jose Gutierrez

1 Introduction

The cerebral vascular architecture develops in concert with the developing fetal brain as part of a delicate dance to pair the demands of the emerging brain parenchyma with adequate blood supply, resulting in the network of vessels that supply the adult brain. Understanding the embryological development of the cerebrovascular system is key to understanding both its unique arterial geometry, which has implications in stroke risk, and the development of variants. This chapter will describe the pattern of events that give rise to the cerebral arteries.

2 Development of the Cerebrovascular System

Modern understanding of the development of the cerebral arterial and venous systems stems from the work of Dorcas Hager Padget, a Johns Hopkins trained medical illustrator who went on to conduct her own research on human embryos [1]. She published her seminal paper on cerebral arteron the development of the "cranial arteries in the human" in 1944 [2, 3] and followed it up with a description of the development of the venous system in 1956 [4]. Further work using ultrasound and MRI technologies in the 1990s and 2000 s in combination with a greater molecular appreciation for the development of vasculature have helped complete the picture [5–9].

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3 Vascular Morphogenesis: Matching Supply and Demand

The development of the vasculature occurs by two primary mechanisms: **vasculogenesis** and **angiogenesis**. During the initial period of vasculogenesis pluripotent hemangioblasts differentiate into angioblasts and congregate to form primitive vascular plexi. Then, vessels begin to form by sprouting through angiogenesis, which is the primary mechanism of vascularization in the brain [7, 10]. The brain tissue develops in the absence of brain vessels, initially, creating a period of relative, transient hypoxia, which is the ultimate driver of angiogenesis. The presence of hypoxia leads to the selective expression of hypoxia-inducible factor-1 (HIF-1), a transcription factor, which then leads to the expression of all of the major angiogenic growth factors, including **vascular endothelial growth factor** (VEGF), the major driver of angiogenic growth, as well as stromal derived factor 1 (SDF1), angiopoietin 2 (ANGPT2), placental growth factor (PGF), platelet-derived growth factor B (PDGFB), and stem cell factor (SCF) [11]. VEGF stimulates both the formation of initial neural capillaries and the coalescence of these capillaries into larger vessels [12]. Thus, VEGF is the major regulator maintaining the critical link between the requirements of the developing brain parenchyma (as indicated by hypoxia) and the developing vasculature, a relationship that is maintained into the postnatal period [13]. In truth, it provides the basis for **neurovascular coupling**, the relationship between the brain's metabolic demands and cerebral blood flow, which is key to the brain's function throughout adulthood.

The initial neural plate of the yolk sac and embryo receive nutrients via diffusion. It is only during the fourth week, when the neural tube closes, that vasculogenesis takes place, forming the initial vascular plexus amid a dense connective tissue network known as the meninx primitiva. The meninx primitiva then invaginates into the neural tube, creating the primitive choroid plexus and vascular plexus which become the choroidal arteries [5]. The tube then thickens and becomes relatively hypoxic, stimulating the generation of VEGF and the first neural capillaries via angiogenesis [12]. This stage highlights the importance of HIF-1 and VEGF signaling in vascular development: an embryo incapable of making HIF-1 will complete vasculogenesis normally but will not initiate angiogenesis [11]. Hypoxia-induced growth factors continue to play a key role in the post-natal period, when energy-consuming processes of neurogenesis, synaptogenesis and maturation of astrocytes again create a relatively hypoxic state, leading to VEGF-mediated angiogenesis and vascular remodeling [13].

4 The Origins of the Major Arteries

4.1 The Aortic Arches

E.D. Congdon first described a series of six paired **aortic arches** which appear beginning in the fourth week of development in succession corresponding to the six pharyngeal arches that form the structures of the head and neck [14]. As a result,

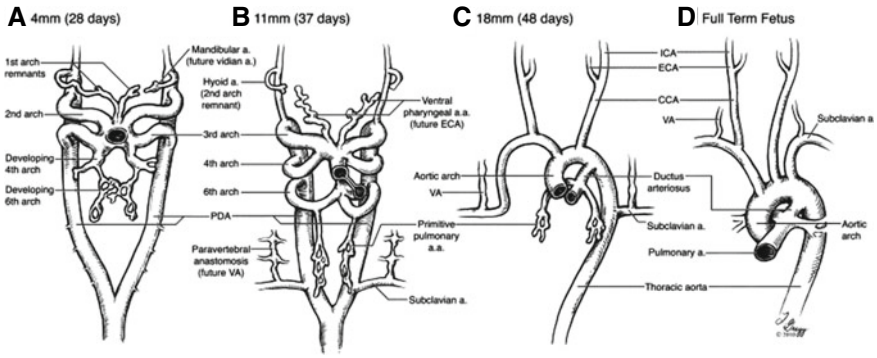

Fig. 1 The aortic arches form (4 mm stage), (**A**), (**B**) the first and second arches regress (11 mm), the PDA segment between the third and 4th arches regress to release the ICAs (**C**, 18 mm) and the orientation of the vessels at full term (**D**) [5]

they are also known as pharyngeal arch arteries. The progression of emergence, coalescence and regression of the aortic arches is seen in Fig. 1.

The first arch appears at the 1.3 mm stage from the paired dorsal aortae, regresses by the development of the fourth aortic arch (the left half of the pairing forming the true adult aortic arch while the right becomes the right subclavian artery) and becomes the mandibular artery [15]. Similarly, the second aortic arch becomes the hyoid artery, of which the adult stapedial artery is one branch, and the ventral pharyngeal artery, which forms the external carotid artery [5]. The third aortic arch, however, which begins forming when the embryo is 4 mm, coalesces with the dorsal segments of the paired dorsal aortae (PDA) to form the primitive internal carotid arteries (ICA) [5, 16]. The segment of the paired dorsal aortae between the third and fourth arches regresses, forming the carotid duct which narrows to a thin fibrous cord by the 14 mm stage, releasing the ICAs [5]. The fifth aortic arch is present only briefly and gives rise to adult structures [14] only rarely [17]. The sixth aortic arch forms at the 5–7 mm stage and become the pulmonary arteries [14].

5 The Anterior Circulation

The development of the internal carotid arteries via the coalescence and regression of the third aortic arches and the PDA both initiates and occurs concomitantly with the development of the anterior circulation [15]. A ventral portion of the second aortic arch, the ventral pharyngeal artery, then fuses proximally to the ICA to become the common carotid artery (CCA) [5]. The ICA then branches into an anterior division and a posterior division, the anterior supplying the optic and olfactory regions through primitive arteries, which are among the first areas of the

brain to develop [3]. The anterior division will give rise to the anterior cerebral artery (ACA), the middle cerebral artery (MCA) and the anterior choroidal artery (AChA), while the posterior division becomes the posterior cerebral artery (PCA), the posterior communicating artery (PCOMM) and the posterior choroidal artery (PChA) [3]. The AChA and PChA develop first, at the 7–9 mm stage, forming an anastomosis in the choroidal fissure [3]. At the 7–12 mm stage, small buds appear on the primitive ICA that are the first distinguishing features of the primitive MCA and ACA [18]. Initially plexiform, at the 16–18 mm stage, the MCA fuses and extends into the hemispheres [19]. At 18 mm, the ACA begins to grow medially, approaching its contralateral twin and by 21–24 mm stage a channel will fuse between them, forming the anterior communicating artery (ACOMM) and completing the circle of Willis [19].

6 The Posterior Circulation

At the time the primitive ICAs are forming, at the 4–5 mm stage, the primitive vasculature that will become the posterior circulation is developing as well, through development of the longitudinal neural arteries (LNA). These vessels are supplied by three transient arteries which branch from the ICA and then regress: the trigeminal artery (TA), otic artery (also known as the acoustic artery) and the hypoglossal artery, which together form the **carotid-vertebrobasilar anastomosis** [20]. The proatlantal intersegmental artery (ProA), the last primitive artery to form, arises from the ICA [5]. As the ProA emerges, the TA loses caliber. By the 5 mm stage, the LNAs expand and begin to merge, forming the basilar artery at the 5–7 mm stage [5]. At this stage, branches from the primitive PCAs form and connect to the developing basilar. Similarly, as more of the supply to the basilar is provided by the PCA and the developing PCOMM, the role of the transient arteries (TA, OA and HA) diminishes and they regress, rarely present in the adult as part of a persistent carotid-vertebrobasilar anastomosis.

This occurs concomitantly with the development of six cervical intersegmental arteries arising from the subclavian arteries [21]. At the 7–12 mm stage, the primitive vertebral arteries (VA) begin to form from an anastomosis of these intersegmental arteries and the ProA, beginning with the ProA, part of which forms the horizontal segment of V3, and continuing to the sixth intersegmental artery, which forms the V1 segment off the subclavian arteries [16, 20]. Prior to this connection forming at the 11–12 mm stage, the posterior circulation is dependent on blood supply from the carotid.

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Pediatric Neurovascular Conditions

Jennifer L. Quon and Gerald Grant

Understanding pediatric neurovascular pathology and the how it differs specifically from the adult disease can inform management and importantly, prognosis. Management, in turn, should rely on data derived from pediatric patients specifically, rather than extrapolated from the adult literature. Unlike in adults, there aren't well-established guidelines for management. Often associated with other genetic conditions and anomalies, understanding the underlying genetics and pathophysiology of pediatric vascular conditions will significantly advance our treatment strategies [25].

1 Pediatric Stroke

The incidence of stroke has been reported in 2–3 children per 100,000 per year, with intracerebral hemorrhage accounting for a large proportion of these cases [89]. Both vascular lesions and moyamoya disease are important and potential debilitating causes of pediatric stroke, ischemic and hemorrhagic, respectively [120].

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1.1 Diagnosis

Computed tomography (CT) is the first imaging modality that should be used when a stroke is suspected, especially in an emergency setting [133]. CT has the capability to show hemorrhage, even from an underlying vascular malformation [133]. CT perfusion can also be used now with lower contrast dosing and radiation than in the past [19]. MRI perfusion and diffusion is more sensitive for diagnosing ischemic stroke, but is more difficult to obtain in children as it may require sedation [133]. In neonates, due to the lack of mature myelination and high water content, MRI sequences need to be adjusted for higher relaxation times and smaller brain structures. An increase in T2 signal and a decrease in T1 signal will lead to a "missing cortex" appearance, in which cortex and unmyelinated white matter are difficult to distinguish [19]. Ultrasound is also commonly used to detect neonatal stroke [19]. In children, DWI sequences can show ischemic areas quickly and reliably while ADC mapping can confirm areas of infarction [19]. ADC maps will normalize within a week as the ischemic area begins to contrast enhance. This contrast enhancement normalizes within several weeks [19]. MRI perfusion techniques such as arterial spin labeling (ASL) can provide additional information in the setting of acute and chronic ischemic stroke, certain ischemic conditions such as Moyamoya disease, as well as vascular malformations [21, 24, 27, 47, 96, 125, 128, 133]. Much like in adults, angiography can also detect pathology such as vascular malformations and aneurysms with great sensitivity, but is also more invasive [133].

1.2 Etiology

There are a number of causes of pediatric stroke which can be broadly categorized into arterial, venous, and hemorrhagic strokes [19] (Table 1.). In this chapter, we will focus on intracranial vascular lesions as well as the etiologies that are most likely to warrant neurosurgical intervention.

2 Pediatric Vascular Lesions

Pediatric vascular lesions often occur in the setting of other rare conditions such as genetic syndromes (such as PHACES—posterior fossa anomalies, hemangiomas of the cervical facial region, arterial cerebrovascular anomalies, cardiac anomalies, eye anomalies and sternal anomalies) and other vasculopathies [25, 76]. In this chapter we will discuss the most common pediatric vascular lesions: Arteriovenous malformations (AVMs), cavernous malformations, Moyamoya disease, and aneurysms. Other pediatric-specific vascular lesions include infantile hemangioma, vein of Galen malformation, and dural sinus malformation [25] (Table 2).

Table 1 Causes of pediatric stroke [19]

(a) Arterial Stroke	
Cardiac	Congenital heart disease, cardiomyopathy Infectious endocarditis, cardiac arrhythmia Valvular disease (congenital or acquired) Persistent foramen ovale
Hematologic disorders	Sickle cell disease, Thalassemia Iron deficiency anaemia Inherited prothrombotic risk factors Lupus anticoagulant/antiphospholipid antibodies Lymphoproliferative disorders (CNS leukaemia, asparaginase therapy)
Vasculopathy	Transient cerebral arteriopathy/postvaricella angiopathy Moyamoya syndrome (primary or secondary) Fibromuscular dysplasia, Vasculitis, post-infectious vasculopathy Exsarythematousus/rheumatic diseases Isolated angiitis of the central nervous system Down syndrome Post-irradiation Dissection (e.g., trauma) Sickle cell disease
Pulmonary	Arterio-venous shunts (e.g., Morbus Osler)
Malignancy	Lyphoma Leukaemia Brain tumors
Drugs	Cocaine, oral contraceptives, l-asparaginase and steroids
Neurocutaneous diseases	Neurofibromatosis, Sturge–Weber
Migraine	
Hypertension	
Infection	Meningitis, varicella
Hypoxia/ischemia	Obstructive sleep apnea/chronic hypoxemia, hypotension
Genetic	Neurofibromatosis type 1 Tuberous sclerosis PHACE syndrome Fabry disease Homocystinuria
(b) Venous stroke	
Sinus thrombosis	Hypoxic ischemic encephalopathy Birth trauma Dehydration Otitis Meningitis Infection Congenial heart disease Trauma Hypercoagulable/haematological Post-irradiation

(continued)

Table 1 (continued)

(c) Hemorrhagic stroke	
Neonatal (preterm)	Germinal matrix hemorrhage IVH PVH *Epidural, subdural, SAH
Neonatal (term)	IPH: plexus hemorrhage, venous thrombosis*Vascular malformations *Tumors
Childhood	AVM Cavernous malformation Malignancy Thrombocytopenia Hemophilia, coagulopathy Iatrogenic (ECMO, anticoagulation) ITP Sickle cell disease *Aneurysm Hypertension

*Rare

This table gives an overview of common causes, reasons and associations that can be observed in children with arterial (1a), venous (1b) and haemorrhagic (1c) stroke

Abbreviations: AVM: arterio-venous malformation, ECMO: extracorporeal membrane oxygenation, IPH: intraparenchymal haemorrhage; ITP: idiopathic thrombocytopenic purpura, IVH: intraventricular haemorrhage, PVH: periventricular haemorrhage, SAH: subarachnoidal haemorrhage

2.1 AVMs

AVMs are direct connections between arteries and veins without intermediate capillary beds [127].

2.1.1 Incidence

Despite their early development, children comprise only 3–19% of AVM patients [72, 91]. AVMs have an incidence of 1 in 100,000 in children, but are responsible for 14–57% of pediatric cerebral hemorrhages [22, 103]. Dural AVMs are even more rare in children, with only 59 reported cases [12]. It is estimated that 12–18% will present with symptoms, and therefore be detected, during childhood [22]. Children have a mean nidus size of 3.4 cm, and Spetzler-Martin grade 2 [72]. Different age groups appear to have different hemorrhage patterns [93]. AVMs can be located anywhere in the brain, though in the children they have been found most commonly in the parietal lobe, followed by the cerebellum, frontal lobe, occipital lobe, thalamus, and other regions [72]. Children have a higher incidence of posterior fossa and basal ganglia malformations than adults [72]. The majority of children have a compact type AVM, with few having diffuse AVMs [72].

Table 2 Imaging for pediatric vascular malformations [19]

Malformation	Imaging	Imaging findings
Vein of Galen malformation	US, MRI, MRA, conventional angiography for intervention	Hydrocephalus, dilated vein of Galen, feeding vessels, thrombosis, myelination impairment
AVMs	MRI, MRA intra + extra-cranial; fMRI preop., acute haemorrhage: CT, CTA Conventional angiography for intervention	AV-nidus, haemorrhage, calcification, dilated venous drainage pathways, hypertrophic arterial feeder, hydrocephalus Most common course of atraumatic ICH age < 15 years
Cavernous malformations	MRI (ev. with contrast) 80% supratentorial mostly (sub)cortical 20% infratentorial (pons common)	Different signal intensities, nearby venous malformation on CE-images
Venous malformations	MRI (ev. with contrast), most common in frontal lobe	Dilated medullary/subcortical vein, drain into single dilated venous structure (caput medusa) separated by normal brain parenchyma, no AV-shunt
Capillary telangectasia	MRI	Dilated capillaries usually in the pons, rarely cause haemorrhage
Dural AVM	Screening MRI, MRA, in small infant US; CT in acute haemorrhage, catheter angiography for treatment	Meningeal/occipital arterial supply to torcular, transverse or superior sagital sinus venous varices, calcifications
MoyaMoya Disease	MRI, MRA, CTA, catheter angiography	Occlusion of large vessels, collateralization, IVY sign on FLAIR, T1, T1 CE, + dot sign in BG, fresh ischemia in DWI
Aneurysm	MRI, MRA, CTA, catheter angiography (intervention)	Saccular: Peripheral—ICA 50% Circle of Willis—25% ACA Mycotic: MCA peripherally, more fusiform

Abbreviations: ACA: anterior cerebral artery; BG: basal ganglia; CE: contrast enhanced, CTA: computed tomography angiography; DWI: diffusion-weighted imaging, FLAIR: fluid attenuated inversion recovery; fMRI: functional magnetic resonance imaging; ICA: internal carotid artery; ICH: intracerebral haemorrhage; MCA: middle cerebral artery; MRA: magnetic resonance angiography, MRI: magnetic resonance imaging; SAH: subarachnoidal haemorrhage; US: ultrasound

2.1.2 Etiology

AVMs are congenital vascular malformations that begin to develop during the third week into the 8th week of gestation when capillary and venous vessels are forming [98]. Feeding vessels occur as a result of exogenous expression of basic fibroblast growth factor and vascular endothelial growth factor (VEGF) that is further stimulated by local ischemia and inflammation [72, 94]. Macrophages contribute to this inflammatory state by secreting cytokines such as TNF-α, IL-6, and VEGF that promote pathological angiogenesis and remodeling [94]. Inflammation and angiogenesis are present on surgically resected AVMs, suggesting that they are dynamic lesions that continue to evolve [94]. Microhemorrhages further stimulate

macrophage infiltration, which in and of itself can affect vascular integrity and risk of hemorrhage [94].

Pediatric AVMs are more likely to have multiple foci of arterio-venous shunting, though this may be a manifestation of vascular immaturity, rather than a uniquely pediatric phenomenon [25]. AVMs have been described in the setting of *Ras1* mutations [49]. Patients with hereditary hemorrhagic telangiectasia (HHT) have autosomal dominant mutations in growth factor-β signaling genes (*ENG, ALK1, ACVRL1 or SMAD4*) and often present with intracranial AVMs, in addition to other vascular abnormalities [45, 68, 109]. Children with HHT1 mutations more often present with cerebral AVMs than those with HHT2 mutations [45]. Pediatric AVMs have also been reported as de novo lesions forming during childhood [131]. Some evidence suggests that de novo AVMs may occur as a result of intractable epilepsy, with seizures triggering the release of VEGF [129].

Pediatric dural AVMs are thought to occur as abnormalities in venous sinus development with expansion and remodeling of the posterior sinuses beyond the normal time period [12]. Arteriovenous malformations have also been noted to occur after trauma, though less commonly than in the adult population [10, 100, 130].

2.1.3 Diagnosis

(a) *Clinical symptoms*: Pediatric AVMs most commonly present with intracerebral hemorrhage (50 to greater than 80%), followed by seizures, or headaches [72]. In fact, ruptured AVMs are the leading cause of intracerebral hemorrhage in children (30–50%) [32, 89]. Children present with hemorrhage (80–85%) more often than adults (50–65%) [72]. In adults AVMs are more likely to be discovered in incidentally whereas in children they are only occasionally discovered incidentally in the setting of other screening or neurologic symptoms [25, 72]. Seizures are the most common presenting symptom in unruptured AVMs, with large AVM size as a risk factor [91]. Hemorrhage may also lead to seizures [91].

In children, AVMs with a small nidus, a periventricular nidus location, and diffuse morphology are at greater risk of rupture [39, 95]. Single draining veins and deep venous drainage are also predictive of hemorrhage [67]. Approximately a third of children with AVMs also have associated aneurysms [11]. Aneurysms within the arterial portion of AVMs may be associated with a higher risk of rupture [11].

Pediatric spinal AVMs are even more rare than intracranial ones, and are typically associated with other hereditary syndromes [63]. They are more commonly located in the thoracic spinal cord, and can present with either congestive or compressive myelopathy, back pain, or as pulsating masses [63].

Dural AVMs consist of three different subtypes, each with a unique set of presenting symptoms:

(1) Infantile dural arteriovenous shunts [12]—High flow, low pressure anomalies often with direct involvement of the meningeal and occipital vessels. They consist of patent sinuses and no venous lakes. They usually present in early childhood with macrocrania, hydrocephalus, seizures, and progressive neurologic deficits.
(2) Adult-type dural arteriovenous shunts [12]—Typically located in the cavernous sinus, adult-type dAVMs present with symptoms of venous hypertension, proptosis, and chemosis. Venous hypertension, if present in the cortex, may also manifest cause intracerebral hemorrhage.
(3) Dural sinus malformations such as Vein of Galen malformations—these will be discussed in a later section.

(b) *Imaging*: Vessel imaging with DSA is the gold standard for diagnosing and visualizing AVMs. This is often obtained after initial imaging with CT or MRI, depending on the initial presentation. Surveillance imaging with MRA or CTA can serve as an adjunct to angiography. Ultrasmall superparamagnetic iron oxide (USPIO) nanoparticles such as ferumoxytol are quickly emerging as valuable contrast agents for visualizing vascular malformations on MRI [46]. One study found that ferumoxytol was superior to gadolinium for visualizing AVMs whereas another demonstrated uptake of ferumoxytol within the vacular wall of the AVM nidus [46] (Fig. 1).

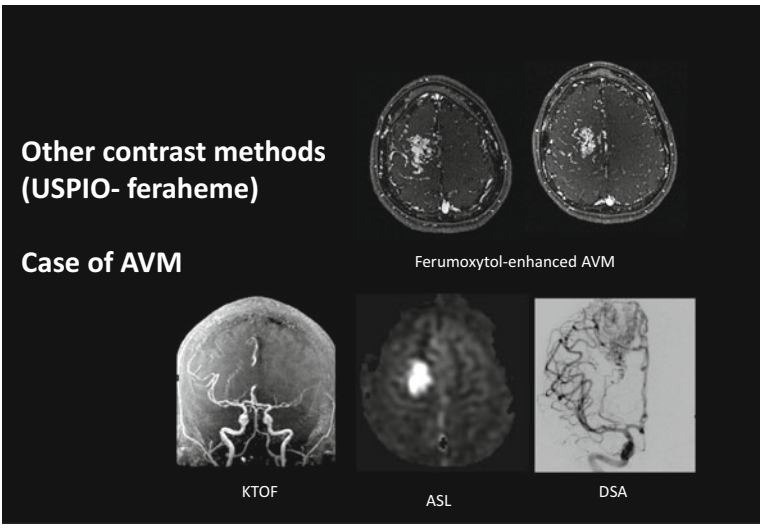

Fig. 1 Ferumoxytol enhanced MRI (**a**), KTOF (**b**), ASL (**c**) and DSA (**d**) demonstrating a pediatric arteriovenous malformation

2.1.4 Treatment

For pediatric patients, the main goal of treatment is complete elimination of the AVM since children are thought to have a higher annual bleeding risk (1–3% vs. 2–4% in adults) [54, 72]. While children have a lower risk of initial hemorrhage in untreated AVMs, they have a higher cumulative lifetime risk [35]. The treatment modalities for pediatric AVMs are similar to that in adults, and include surgical resection, radiation therapy, embolization, or a combination of these treatments [76]. Multimodality therapy may improve obliteration rates and decrease hemorrhage rates substantially [32]. Lower grade AVMs have a faster obliteration time (1.8 compared to 6.4 years) and require fewer procedures (2.2 compared to 6.1) for obliteration than higher grade ones [32].

Microsurgical resection can offer complete obliteration (87–94%) and is therefore the preferred mode of treatment, especially for low grade, accessible lesions [32, 44, 72]. Perioperative angiography can allow for higher rates of post-operative obliteration [51, 77]. The rate of complications is typically low, but can include neurologic deficit, stroke, or infection [51]. A laminectomy with microsurgical resection either with or without embolization is also the treatment for spinal AVMs with good outcomes [63].

Alternatively stereotactic radiosurgery (SRS) can be used as primary treatment but is usually reserved for cases that would carry a high operative morbidity such as AVMs with located in deep or eloquent regions, or as adjuvant therapy [32, 35, 65, 72]. SRS can offer a cure rate of 81% with a 5% risk of complications [32]. In a dose response analysis, 16 Gy was the dose needed to obliterate 70% of an AVM and efficacy improved with margin doses of at least 18–22 Gy to the nidus [35, 54, 121]. Reduced doses are used for larger AVMs or those in eloquent regions [65]. It is difficult to predict the precise time for complete obliteration but it can take up to 3 years [32]. The use of SRS for unruptured pediatric AVMs allows for obliteration rates at 3, 5, and 10 years of 29%, 54%, and 72%, respectively [35]. Across all AVMs, even those previously ruptured or treated, obliteration rates with SRS are slightly higher at 45%, 64%, 67%, and 72% at 3, 4, 5, and 10 years, respectively [65]. If patients do not have complete obliteration at interval follow-up, there may be benefit to repeating radiation treatment [65]. Long-term follow-up of pediatric patients who received SRS demonstrated that smaller nidus size, fewer draining veins and higher doses of radiation led to a higher obliteration rate [35, 54, 65]. Patients with a lower Virginia Radiosurgery AVM score which takes into account AVM volume, location, and history of hemorrhage correlated with greater chances of obliteration [22, 35]. Similar to other forms of radiosurgery, large doses, single fraction therapy, and modified AVM scores are associated with higher rates of obliteration [127]. It is unclear whether prior embolization affects the efficacy of radiosurgery but it can help reduce the AVM size, theoretically increasing the cure rate [32, 35, 65]. Potential complications of SRS include post-treatment hemorrhage, edema, hematomas, radiation necrosis, radiation induced white matter changes and radiation induced neoplasms [35, 54, 65, 121, 127]. Patients are at particular risk for hemorrhage during the latency interval prior to obliteration

[32, 65]. Lower doses of radiation lower the risk of post-procedure neurologic deficit, but increase the risk of post-radiation hemorrhage [114]. Larger target volumes also lead to a greater risk of hemorrhage [65]. Proton-beam SRS, which minimizes radiation delivery to normal tissue beyond the lesion, has reported obliteration rates from 35–94%.

Pre-operative embolization can be an important adjunct to AVM treatment with the goals of reducing bleeding risk as well as, in some cases, treating cardiac failure and venous hypertension [8, 72]. AVMs are embolized either with n-BCA or Onyx [8]. Whether transarterial or transvenous, endovascular embolization is the primary treatment for dural AVMs, though embolization can often lead to the recruitment of secondary arterial feeders [12]. One group described transvenous onyx embolization to treat pediatric AVMs with unfavorable arterial anatomy [99]. Some of the patients had tranvenous embolization alone whereas the other had a combined transarterial-transvenous approach. The average follow-up was just under 2 years, and all patients were noted to have angiographic cure [99]. Endovascular treatment can also be used exclusively for spinal AVMs [63] (Fig. 2).

Following treatment, angiography (1 year post-treatment for resection, 2 years for stereotactic radiosurgery, and 5 years for diffuse AVMs) is recommended to assess for cure, followed by repeat MRI/MRA every 5 years to check for recurrence [72, 76]. In a retrospective study Morgenstern et al. report that conventional angiography was more sensitive than MRI/MRA since the latter failed to detect any recurrences [105]. They suggest DSA at regularly scheduled intervals to assess for recurrence while minimizing associated risks [105]. CTA can also be used as an adjunct to angiography for post-treatment follow-up. Diffuse-type AVMs, named for their appearance on angiogram, are more difficult to treat and are therefore more likely to recur [72]. Patients with residual nidus can typically undergo additional treatment of their AVM, depending on the lesion's location [72] (Fig. 3).

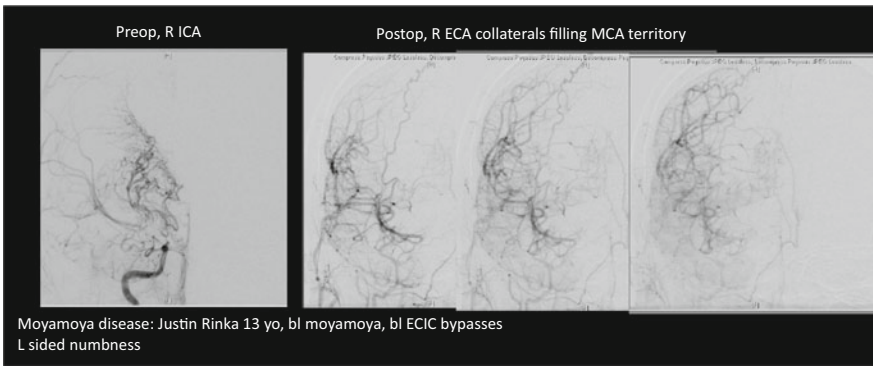

Fig. 2 Pre-operative (**a**) and 6-month post-operative (**b**) DSA showing collateralization of the R MCA territory after EC-IC bypass

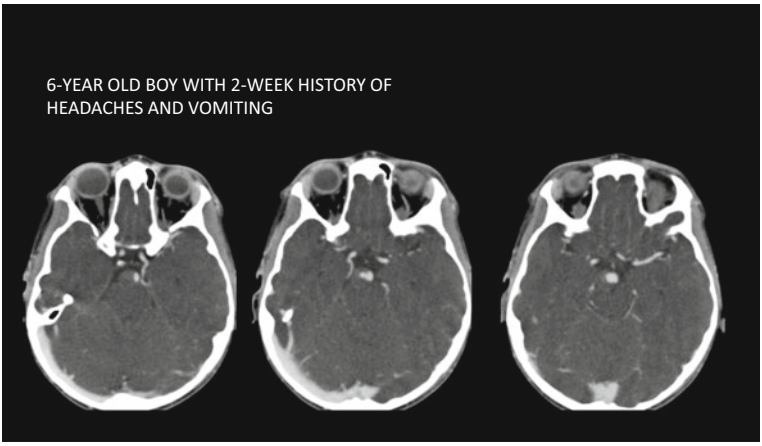

Fig. 3 Axial CTA demonstaing basilar tip aneurysm

2.1.5 Prognosis

Children have a higher morbidity and mortality related to AVM rupture and have a higher cumulative lifetime risk of rupture than adults [35, 39, 72]. Especially in lesions that have already ruptured, treatment is preferred over observation [103]. Pediatric AVMs with a single draining vein or deep drainage are more likely to rupture, or rerupture [20, 35]. Those that present with hemorrhage or risk factors for hemorrhage also have a worse prognosis [39, 67]. Patients with a higher Glasgow coma score (GCS) on admission were found to have a better functional outcome at discharge and conversely those with a lower baseline modified Rankin score have a worse clinical outcome [67]. One study found that patients with a worse clinical outcome had a higher age at presentation [93]. Higher AVM grade is also associated with a worse clinical outcome [32]. Partial treatment may worsen the natural history of AVMs [20, 32]. Pediatric AVMs with associated aneurysms are at greater risk for rerupture [20]. Pediatric dural AVMs, in particular, are more aggressive than their adult counterparts with a mortality rate of 25% [12]. Some have argued that children with HHT mutations, who are at higher risk for AVM development and have a slightly higher presence of cerebral AVMs ($\sim$16% in one screening study compared to 11% in the general population), should undergo routine screening [45].

Children comprise the majority of reported AVM recurrences (69%), perhaps related to the immaturity and plasticity of pediatric vasculature [72]. One study reported recurrence an average recurrence at 33.6 months after surgery [105]. Recurrences have been reported as late as 16 years from treatment and can also present with hemorrhage, seizures or neurologic symptoms [72, 98]. AVM compactness is predictive of recurrence with less compact AVMs having a higher risk of recurrence after surgery [40]. Particularly in young patients, deep venous drainage is associated with a higher rate of recurrence [104]. Multiple theories have

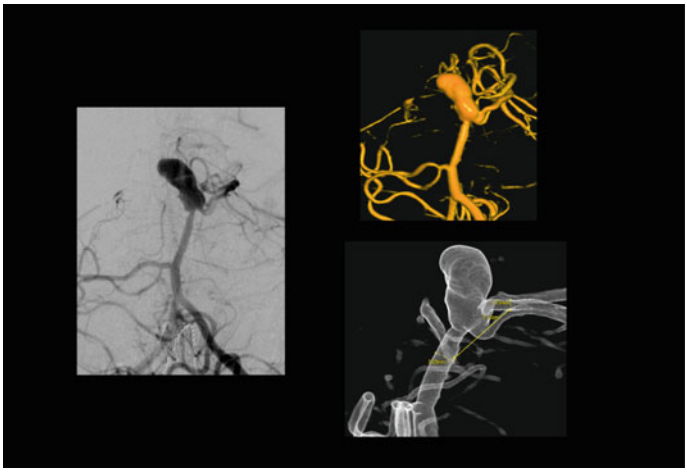

Fig. 4 DSA (**a**) and 3D DSA (**b**) demonstrating a basilar tip aneurysm

been proposed to explain why angiographically "cured" AVMs recur including the "hidden nidus" or "reserve nidus" theory in which angiographically negative areas that are contiguous with the AVM are responsible for regrowth [72]. Alternatively, other authors suggest that immature vasculature makes AVM formation an active process that is maintained throughout childhood and that ceases with AVM maturity [72]. Given the risk of recurrence, even at over a decade after angiographic cure, long-term follow-up with vessel imaging is recommended [98]. At Stanford, serials MRI's are obtained at 6 months, 1 year, 3 years and every 2 years after surgical intervention until the age of 18. After endovascular therapy or radiosurgery, interval MRI's are also obtained to demonstrate whether complete obliteration of the nidus has occurred in addition to a post-procedure DSA to confirm obliteration. Serial imaging is obtained at regular intervals during adulthood (Fig. 4).

2.2 Cavernous Malformations

Cerebral cavernous malformations (CCMs) are clusters of vessels without intervening brain tissue [73]. The thin vessel walls lack smooth muscle [73]. These malformations are prone to hemorrhage and hemosiderin is often visible in the surrounding brain [73].

2.2.1 Incidence

Cavernous malformations comprise 2–20% of intracranial vascular malformations in children [59, 73]. In turn, the pediatric population comprises 25% of all patients with cavernous malformations [59, 73]. They tend to present either around 3 years

or between 11 and 17 years of age and occur equally in boys and girls [73]. Familial CCMs are more common in Hispanic populations, and about half of Hispanic patients with CCMs have the familial form [73].

CCMs have a reported size of 0.1 to 9 cm but tend to be larger in children (average size of 6.7 cm compared to 2–3 cm in adults) [73]. This may be due to the more cystic nature of pediatric CCMs [73].

Similar to adults, in children the majority of CCMs are supratentorial (80%), more specifically in the cortex or subcortical white matter [73]. In the children they are found in the brainstem more than in adults, most commonly in the pons (14.7%) [73]. CCMs of the basal ganglia, hypothalamus, and spinal cord are all relatively rare in children [73]. Spinal CCMs comprise only 3–16% of pediatric spinal vascular malformations [73].

2.2.2 Etiology

The majority of cavernous malformations occur sporadically (50–80%) though they can also form as an inherited condition [73]. Familial CCM is characterized by the occurrence of CCMs in at least two family members, the presence of multiple CCMs, or a disease-causing mutation in one of the CCM loci. CCM genes have three different loci, deemed CCMI (7q12.2), CCM2 (7p15-p13), and CCM3 (3q25.2-q27) that encode for the K-Rev interaction trapped 1(Krit 1), MGC4607, and programmed cell death 10 (PGCD) proteins, respectively [73]. These proteins are involved in endothelial cell adhesion [73]. Disease-causing mutations at the CCM loci occur according to the two-hit hypothesis [73]. Familial CCM has an autosomal dominant inheritance pattern with incomplete penetrance and variable expressivity [73].

The appearance of cavernous malformations has also been reported after radiation therapy, though it is unclear whether radiation caused them to appear or rather become symptomatic [73].

While CCMs are not intrinsically epileptogenic, they can induce seizures via their effect on the adjacent brain tissue [73]. Feric ions released during microhemorrhages are highly epileptogenic, and overtime the surrounding brain parenchyma can become an epileptogenic focus [73]. Repetitive seizure activity may even cause secondary epileptogenic foci away from the site of the lesion [73].

2.2.3 Diagnosis

(a) *Clinical symptoms.* Up to 70% of children with cavernous malformations present with seizures [73]. They may also present as intracerebral hemorrhage (~30%), though less commonly than AVMs in this setting [73, 89]. Pediatric patients have a higher rate of bleeding than adults—27.3–78% compared to 8–37%, respectively [73]. Hemorrhage can occur in the brain parenchyma, the ventricles or the subarachnoid space, and symptomatology may be based on lesion location. Patients may have headache, seizures or other neurologic symptoms as a result of hemorrhage [73].

(b) *Imaging*. The presence of hemorrhage may obscure vascular anatomy and can visualization on imaging somewhat difficult [73]. On non-contrast CT, CCMs are well-circumscribed hyperdense lesions with minimal surrounding mass effect. CCMs may demonstrate blood or calcifications, as well as a capsular rim defining the hemorrhagic portion of the CCM [73]. Pediatric CCMs are more likely to have large hypodense cysts than their adult counterparts [73]. MRI is sensitive and specific for CCMs [73]. On T2-weighted MRI, CCMs demonstrate a characteristic "popcorn" like appearance with mixed signal, surrounded by a ring of decreased signal caused by the presence of hemosiderin [73]. GRE and SWI images are extremely sensitive for detected CCMs and may show enlarged areas of hypointensity [73]. Contrast administration will show whether a DVA is present. CCMs are not well demonstrated on DSA.

2.2.4 Treatment

Treatment of pediatric cavernous malformations must consider the lifetime risk of hemorrhage and potential for the development of seizures [73]. Surgical resection, when feasible, can offer a cure and is generally recommended in the pediatric population setting of acute hemorrhage, focal neurologic deficits, or radiographic enlargement [73]. Resection may be delayed up to a month following hemorrhage to allow edema and symptoms to resolve [73]. CCMs present in eloquent cortex are generally observed and the risk of surgical resection must be weighed carefully against that of recurrent hemorrhage [73]. Epilepsy may be difficult to cure following resection of the CCM depending on the chronicity of seizure activity [73]. Patients with seizures may therefore benefit from early resection of the offending CCMs [73]. Surgery is generally effective either alone or with antiepileptic medication and 50–90% of patients are reported to be seizure-free following surgery [59, 73]. The evidence for surgery is less well established for incidentally discovered asymptomatic lesions, or with multiple CCMs [73]. In particular there may be significant morbidity associated with the resection of brainstem cavernous malformations [2, 84]. Brainstem cavernous malformations also have a higher rate of recurrence after surgical resection in children compared to adults [2].

Laser ablation as an adjunct to surgical resection has allowed for safe resection of CCMs in precarious regions such as the brain stem, thalamus, and spinal cord [73]. It can help minimize bleeding and thermal damage but cannot penetrate blood or calcium [73].

Unlike in AVMs, radiosurgery is generally not recommended for CCMs because it can cause edema and exacerbate symptoms, as well as temporarily increase the risk of hemorrhage up to 22.4% per year [73]. Based on the adult literature, it takes 2–4 years following radiosurgery treatment for the hemorrhage risk to decrease, reducing the frequency of hemorrhage by 4.5–17.3% per year [73]. The rate of permanent deficit and mortality reported from brainstem studies is high at 1.7–22.7% and 12%, respectively.

2.2.5 Prognosis

The morbidity associated with CCMs depends on the location of the lesion. CCMs, located in the basal ganglia, cerebellum or brainstem, are more likely to cause symptoms. The annual risk of hemorrhage is approximately 3% per patient-year (0.25–6.4%) across all patients, including those with familial CCMs which have a higher tendency to bleed [73]. Children have a bleeding incidence of 27, 3–78% compared to 8–37% in the adult population [73]. Brainstem cavernous malformations also have a greater tendency to bleed at 5% per patient per year [73]. Worsened functional status can occur in the setting of recurrent hemorrhage, more so for infratentorial compared to supratentorial lesions [73]. Children with CCMs should undergo MRI surveillance to assess for interval growth of their CCMs, as well as the presence of microhemorrhages [73]. Individuals who have relatives with known CCMs should undergo genetic screening so that they can undergo appropriate surveillance [73].

CCMs grow as a result of repetitive microhemorrhages that cause release of angiogenic factors [73]. Partial resection of CCMs can also lead to a recurrence [73].

Patients with longstanding seizures are at an increased risk for intractable epilepsy and lifelong disability [73]. Microhemorrhages can also lead to the development of epilepsy, therefore repetitive hemorrhages on surveillance imaging may warrant surgical removal [73]. A more extensive resection, including the surrounding hemosiderin ring, and a CCM size < 1 cm are associated with a better chance of being seizure-free after surgery [73]. Patients who do not undergo surgical resection should be monitored clinically for seizures [73].

2.3 Moya Moya

Moyamoya is a disease that involves the progressive occlusion of intracranial blood vessels without evidence of intra-arterial plaques [28].

2.3.1 Incidence

Moyamoya disease is typically diagnosed either between the ages of 5 to 10, or after 40 [43, 52]. The disease appears to present equally in boys and girls but the age of presentation may affect this ratio [17, 28]. It is most prevalent among Asians and is conversely the most common pediatric cerebrovascular disease in Asia [17]. Moyamoya disease accounts for approximately 10% of transient ischemic attacks in the pediatric population [3].

This differs from transient cerebral arteriopathy, which may also present with stroke but is a focal inflammatory process that is limited to several months [132].

2.3.2 Etiology

Similar to in adults, the etiology of pediatric moyamoya disease is unclear [113]. Similar to adults, hypoperfusion and ischemia rather than vaso-occlusion appears to be the predominant mechanism [115]. The process of new blood vessel growth may

even precede any overt impairment in blood flow [69]. An anastomosis network of collateral vessels may grow from both the anterior and posterior circulations [15, 16]. However, a number of variants have been identified in association with moya moya including those in the RNF213, ACTA2, BRCC3, GUCY and other genes [26, 31, 60, 61, 83, 92, 120]. In turn, moyamoya has been reported in association with a number of genetic syndromes such as trisomy 21, sickle cell disease, and neurofibromatosis type I [14, 53, 61, 120]. One study found a familial occurrence of 9.4% [17].

Moyamoya syndrome, on the other hand, occurs secondary to another underlying condition such as sickle cell anemia, neurofibromatosis type-1, neurocutaneous syndromes, smooth muscle disorders, Down's syndrome, thyroid disease and following radiation [9, 41, 101, 112].

2.3.3 Diagnosis

(a) *Clinical symptoms*: Unlike in adults, children with Moyamoya disease more often present with ischemic symptoms rather than cerebral hemorrhage [48, 52, 82, 113]. The onset of ischemic events can be triggered by hyperventilation in the setting of fever, dehydration, crying or increased activity [52]. In turn, hyperventilation may cause vasoconstriction, which can worsen cerebral perfusion [52]. Cortical ischemia can also secondarily cause epilepsy [52]. Pediatric patients are more likely to have epilepsy than adult patients [28]. Chronic ischemia can cause intellectual disability unrelated to, but often correlated with a history of strokes [52]. Silent microbleeds are more common in the adult moyamoya population and are a predictor of subsequent hemorrhagic stroke [75]. Hypertrophy of the collateral vessels within the basal ganglia can also lead to chorea as a presenting symptom [4]. Although extremely rare, children with moyamoya may also have concurrent intracranial aneurysms, which in turn, may cause mass effect or rupture [90].

Pediatric moyamoya can present with different radiographic findings that vary by developmental stage [62]. Blood flow to the brain is related to metabolic demand, which decreases with age and a reduction in neuronal mass [82]. Also, other comorbidities in the adult population may also affect cerebral blood flow [82]. In the pediatric moyamoya population, cerebral blood flow is decreased across imaging modalities compared to normal controls [82]. In an acetazolamide or CO2 challenge, cerebrovascular reserve is also significantly lower in children with moyamoya [82].

(b) *Imaging*: Cerebral angiography, due to its invasiveness, is used less liberally in the management of pediatric moyamoya [134]. Less invasive imaging techniques such as PET, single photon emission computed tomography (SPECT), xenon-enhanced CT, dynamic perfusion CT, MR imaging with dynamic susceptibility contrast and with arterial spin labeling have a large role to play in the

pediatric population [74]. At Stanford, patients also receive MRI perfusion imaging with an acetazolamide (ACZ) challenge: Patients with Moyamoya demonstrate an exhaustion of cerebrovascular reserve and therefore decreased cerebral blood flow after ACZ administration [124]. Perfusion magnetic resonance imaging is often favored for post-operative follow-up. More specifically, regional time to peak and regional cerebral blood volume measurements can help determine whether sufficient collateralization has occurred [134].

On EEG, children with moyamoya have characteristic high amplitude slow waves as well as the "rebuild-up" phenomenon, which is the reappearance of these waves a minute after hyperventilation [29]. These findings correlate with abnormal perfusion and post-operatively is thought to predict worse clinical outcomes [29].

2.3.4 Treatment

In pediatric moya moya, there is a high risk for complications after surgery [88]. Given the small diameter of pediatric vessels, the most common surgical treatments in children are forms indirect bypass, in which the STA is sutured to the dura, arachnoid, or pia, or alternatively the temporalis muscle is placed on the surface of the brain [30, 71]. Unlike in adults, some authors advocate for indirect procedures as first line treatment [1]. Indirect methods depends on angiogenesis and the gradual revascularization of vulnerable vascular territories, a process which appears to normalize at 6 months after surgery [71]. In patients for whom initial surgical treatment is ineffective (meaning, there are insufficient collaterals and the patient continues to be symptomatic), repeat or a combination of revascularization procedures may be necessary [111]. One study found that encephaloduroarteriosynangiosis (EDAS), in which the STA is sutured to an incised dural margin, allows for greater clinical improvement in children who first present with seizures rather an ischemic symptoms [30]. The authors suggest that children with ischemic symptoms may require even better perfusion than indirect methods allow in order to see clinical benefit [30]. There is also some evidence that EDAS, by decreasing the hemodynamic stress on collateral vessels, may indirectly allow for the disappearance of associated aneurysms and decrease the risk of recurrent hemorrhage from these aneurysms [90].

Other indirect procedures used in children include multiple burr holes, as well as omental-cranial transposition, a technique which can be performed laparoscopically, and used when children have progressive disease despite previous surgical interventions [108]. Children who have undergone omental-cranial transposition show good collateralization on post-operative angiogram and improved perfusion on MRI [108].

Though often limited to older children, those who are able to have a direct bypass of the STA to MCA may have better growth of collaterals and clinical outcomes compared to children who undergo EDAS [97]. Direct bypass may be technically challenging in small children, but also has the advantage of an immediate increase in blood flow [48]. Using a combination of direct and indirect or

several indirect procedures can also allow for better revascularization as well as clinical outcomes [38, 48, 70].

Following surgery, repeat imaging and angiography (usually at 12 months) are recommended to assess perfusion and revascularization [76].

2.3.5 Prognosis

Of patients with moya moya, patients that are younger at symptom onset are more likely to have worsening of their disease as well as repeated ischemic strokes [17, 41]. Those with younger symptom onset are especially prone to cognitive impairments in memory and processing [57]. Even with seemingly normal intellectual function, children with moyamoya can have varying levels of cognitive impairments with put through rigorous neuropsychological testing [57]. Children, overall, present with a more severe form of the disease that more often progresses from unilateral to bilateral, though this may reflect some level of detection bias [52, 113]. Cerebral autoregulation may be even more impaired in pediatric patients than in adults, making children at greater risk for perioperative ischemic events [80].

Pediatric patients can also have delayed involvement of the posterior circulation, but show improvement of symptoms with indirect revascularization [81]. Children can present with posterior circulation involvement at less advanced stages of internal carotid artery disease than adults [56]. Those children with posterior circulation involvement are more likely to present with a stroke [56]. Involvement of the posterior circulation has been shown to be a risk factor for difficulty attending in school and maintaining regular employment [42].

Even after direct revascularization procedures, children remain at risk for ischemic stroke or hemorrhage with an incidence of approximately 0.41% per year [43].

2.4 Aneurysms

2.4.1 Incidence

The incidence of aneurysms in the pediatric population is extremely low [33, 34]. Children comprise 0.5–4.6% of the patients with aneurysms, with <1% under the 15 years of age [34]. Pediatric aneurysms may have a male predominance [23, 58, 85]. In the youngest pediatric population, saccular aneurysms are more commonly found in girls compared to fusiform or dissecting aneurysms, which were more prevalent among boys [50]. Some studies have shown a higher proportion of posterior circulation aneurysms in children compared to adults [18, 58]. Pediatric aneurysms occur at the ICA terminus more often than their adult counterparts [58, 122]. Aneurysms in adolescents are primarily in the anterior circulation, with a high prevalence of MCA aneurysms [18, 23, 50, 86]. Small aneurysms occur more often in the anterior circulation [18]. Patients <1 yr-old have an average aneurysm size of ~1.8 cm [50]. Giant aneurysms are found in equal to greater proportions in children than in adults, and more often found in the posterior circulation [50, 85, 123]. In children, saccular aneurysms are less common than giant aneurysms [118].

Saccular aneurysms are more common in the anterior circulation whereas dissecting aneurysms occur more often in the posterior circulation [78]. Children overall have a lower rate of multiple aneurysms than adults (8.7%), with an average of 2.17 aneurysms per patient [18].

2.4.2 Etiology

In the pediatric population, aneurysms form as a result of predisposing congenital conditions or environmental factors such as trauma or infection [33]. Aneurysms are more likely to be associated with comorbid conditions compared to adults, who develop aneurysms in conjunction with modifiable risk factors [18]. Aneurysms do not manifest as commonly in the setting of familial syndromes, suggesting that these develop later on in life [18].

Aneurysms have been associated with a number of genes, including TNFRSF1A, PKD1, and COL3A1 [7, 18]. MAPKs are also elevated in aneurysms [7]. Aneurysms have been associated with a number of genetic conditions such as Marfan's syndrome, Ehler-Danlos syndrome, Moyamoya disease, Kawasaki's disease, polycystic kidney disease, fibromuscular hyperplasia, pseudoxanthoma elasticum, sickle cell disease, tuberous sclerosis, multiple scelerosis, and childhood AIDs [5, 7, 37, 66, 85, 90, 106, 110]. Approximately 30% of children with aneurysms also have comorbid conditions [122]. Children with sickle cell are at particular risk for developing multiple intracranial aneurysms, and may do so in a slightly different distribution than the average population [106, 117]. While coarctation of the aorta had previously been associated with an increased risk of intracranial aneurysms, one study found that aneurysms were not present in pediatric patients with coarctation [36]. This suggests that early treatment can help prevent later aneurysm formation [36]. Trauma can cause vessel dissection and infection can weaken vessel wall integrity leading to mycotic aneurysms [50].

The pathophysiology of aneurysm formation in children, similar to adults, is thought to be related to one of two etiologies: (1) hemodynamic and shear stress at particularly vulnerable sites such as vessel bifurcations or (2) a weakening of the vessel wall due to either congenital or environmental factors [18]. The contribution of these factors leading to aneurysm formation may differ slightly between adults and children [18]. Children without associated conditions are found, on histopathologic analysis, to have inflammation within the vessel wall [18]. Further histopathologic and genetic studies will provide further insights into the mechanism of aneurysm formation in children [18].

2.4.3 Diagnosis

(a) *Clinical symptoms*: In children, 30% aneurysms present with symptoms associated with mass effect on surrounding structures [33, 86]. Approximately 62% of unruptured aneurysms are symptomatic [13]. Forty-six to 80% of pediatric patients with aneurysms present with subarachnoid hemorrhage [18, 50, 58, 85]. Much like in adults, ruptured aneurysms and subarachnoid hemorrhage

may cause sudden-onset headache, nausea, vomiting, inconsolable crying, bulging fontanel, Parinaud's sign, or seizures [33]. Children, on average, present with better Hunt-Hess grades than their adult counterparts [58, 85, 86]. Patients presenting with hemorrhage are, on average, younger and have smaller sized aneurysms [23]. Ruptured aneurysms occurred most commonly in the anterior communicating artery [18]. Approximately 15% of children present with non-specific symptoms, such as headache, without associated subarachnoid hemorrhage [18].

(b) *Imaging*: Vessel imaging with CTA or MRA can be used to diagnose aneurysms, though DSA remains the gold standard for visualization [33].

2.4.4 Treatment

Treatment options for pediatric aneurysms include surgical, endovascular, and combined treatment approaches [64, 85]. Pediatric patients have a better therapeutic outcome from aneurysm treatment than their adult counterparts [85]. The different etiologies of aneurysm formation in children makes treatment stratification important [78]. Due to a higher risk of recurrence, dissecting aneurysms with SAH and without associated thrombosis require more aggressive management than those with partial thrombosis [78]. In pediatric patients, aneurysms smaller than 7 mm in the anterior circulation have been documented to rupture [122]. The presence of nonsaccular aneurysms in very young children poses particular treatment challenges [50]. One study found that microsurgical clipping led to higher obliteration rates than endovascular treatment [118]. Initially surgical intervention had a particularly high mortality rate in the pediatric population but has since improved to be comparable with adult rates [33]. One study reported in-hospital mortality rates of 6.09% compared to 1.65% after microsurgical clipping compared to endovascular coiling, respectively [6]. There is no difference in post-procedure stroke or hemorrhage, though surgery has higher rates of infection and pulmonary complications [6]. Hospital stays are generally shorter following endovascular treatment compared to open surgery [13].

The majority of aneurysms treated microsurgically are in the anterior circulation [122]. Surgical treatment includes aneurysm neck clipping and, for large complex aneurysms with parent-artery occlusion, cerebral revascularization procedures [64, 123]. Microsurgical clipping has an obliteration rate of 94% with only one case of aneurysm recurrence [119]. Data on long-term bypass patency and efficacy is also encouraging, with 83% aneurysm obliteration and one case of aneurysm recurrence [64]. Potential complications include ischemic stroke and graft occlusion.

Endovascular treatment is often favored in the majority of pediatric aneurysms, in particular for basilar tip aneurysms [13, 78, 85]. This may also be related to parental bias against surgery [119]. Posterior circulation aneurysms are particularly difficult to treat in children, therefore many favor endovascular treatment [34, 122]. Aneurysms treated endovascularly are, on average, larger than those treated microsurgically [122]. The most common endovascular procedures are coiling and stent-assisted coiling [18]. Flow-diversion alone has also been reported [107, 126].

Endovascular treatment leads an obliteration rate of 82% [119]. The durability of endovascular treatment in the pediatric population is not well established and long-term follow-up of these patients is necessary to better understand these outcomes. Durability is especially important when considering the pediatric population. Recurrence rates have been reported between 20–40% following endovascular treatment, and 14–21% require re-treatment of the index aneurysm [13, 119]. De novo aneurysms may also occur following treatment [119]. In addition, endovascular treatment necessitates greater radiation exposure [122]. Despite differences in physiology and anatomy, children tolerate endovascular procedures with a complication rate lower than that of adults [87].

2.4.5 Prognosis

The majority of patients with ruptured and unruptured aneurysms have a favorable clinical outcome [58]. Most do well after treatment with rates of 88% and 86% for good clinical outcomes following microsurgery and endovascular treatment, respectively [18]. Children need serial vessel imaging and long-term follow-up [118]. They require close follow-up for aneurysm recurrence and de novo aneurysm formation, and may require multimodal therapy throughout their lifetimes [64, 118].

The reported rates of vasospasm are much lower than in adults [18]. Children often develop radiographic vasospasm without clinical signs or symptoms of delayed cerebral ischemia, likely due to robust collateral blood flow [18, 102]. The majority of children who developed vasospasm were male. Ruptured aneurysms in the anterior circulation led to vasospasm more often than ruptured aneurysms elsewhere [18]. Open fontanelle windows facilitate serial monitoring for vasospasm using transcranial Doppler ultrasound, however the criteria used in adults may overestimate vasospasm in children [102]. In the pediatric population, nimodipine does not appear to eliminate vasospasm and is associated with significant hypotension [55]. Treatment for vasospasm still generally includes nimodipine, hypertension, and hypervolemia [18]. The majority of children had a good clinical outcome after vasospasm, with clinical outcome correlating with clinical status on initial presentation [18].

2.5 Other Vascular Lesions

2.5.1 Infantile Hemangioma

Infantile hemangiomas are benign vascular tumors that are characterized by a "strawberry red" skin lesion [25]. The cutaneous portion of hemangiomas is often only a small subset and extension into the neuroaxis, though rare, is contiguous with the skin lesion [25]. They occur predominantly in females [25].

Hemangiomas undergo a proliferative phase within the first few weeks after birth, followed by an involutive phase from a year onwards [25]. Medical therapy, either with steroids or, in one report, propranolol, is effective for shrinking the lesion [25].

2.5.2 Vein for Galen Malformation

In the prenatal period, vein of Galen malformations will manifest as loss of brain tissue or calcifications [25]. Later on, children can present as cognitive delay, venous prominence, hydrocephalus, venous sinus stenosis or intracranial venous hypertension [25]. In adults, hemorrhage or severe headache may be the presenting symptoms, though this is extremely rare [25].

According to Raybaud et al., these malformations arise from an arteriovenous fistula between the embryonic median prosencephalic vein of Markowski, a precursor to the vein of Galen, and feeding choroidal and/or quadrigeminal arteries [116]. Vein of Galen malformations can be classified into mural and choroidal subtypes. In the former, there is a direct arterio-venous connection whereas in the latter multiple small arterial vessels form nidus-like connections with the vein, similar to an AVM [25]. They have been associated with *Ras1* mutations [49].

Prior to endovascular therapy, the prognosis for vein of Galen malformations was overall poor, and open treatment for vein of Galen malformations had a high morbidity (46.3%) and mortality (37.4%) [25]. In a 2006 series of 216 patients, Pierre Lasjaunias reported a morbidity and mortality of 36% and 10.6%, respectively, with endovascular transarterial embolization [79]. His group also established a grading scheme to inform the timing of intervention: those without significant organ system failure can have embolization deferred to 6 months, those with cardiac failure but without significant brain damage should undergo urgent embolization, and finally those with either multiple organ failure or evidence of parenchymal brain loss should not undergo treatment [79]. The cutoff for treatment has since become more inclusive than the original criteria described by Lasjaunias et al. with elective treatment of asymptomatic patients occurring between 3–5 months of age [25]. Even more favorable outcomes following embolization have since been published in more recent series [25]. One challenge has been endovascular access since these patients are so young at the time of treatment [25].

2.5.3 Dural Sinus Malformation

Dural sinus malformations, one subtype of dural AVMs, are the enlargement of one of the dural venous sinuses, usually the torcular or superior sagittal sinus [25]. Sinus enlargement can occur idiopathically, or as a result of either an arteriovenous fistula or sinus thrombosis [25]. Arteriovenous fistulas form from dural feeders such the middle meningeal or occipital arteries. Dural sinus malformations have been reported in relation to *Ras1* mutations [49]. They can have a clinical presentation similar to that of vein of Galen malformations, though hemorrhage is much more common [25].

Given the poor prognosis reported in the literature, parents often elect to terminate these pregnancies [25]. However, the morbidity may be lower than actually reported [25]. Favorable features include only unilateral sinus involvement away from the torcula and superior sagittal sinus as well as the presence of bilateral cavernous sinus drainage and absence of jugular bulb occlusion [12].

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Pediatric Intracranial Aneurysms

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Abbreviations

ACA	Anterior cerebral artery
CTA	Computed tomography angiogram
DSA	Digital subtraction angiogram
ICA	Internal carotid artery
MCA	Middle cerebral artery
MRA	Magnetic resonance angiogram
SAH	Subarachnoid hemorrhage

1 Introduction

Despite their rarity, pediatric intracranial aneurysms have diverse etiologies, making them challenging to diagnose and treat. In most hospital series, children account for only 0.5–4.6% of all aneurysm patients [1–3]. Eppinger reported the first case of pediatric aneurysmal subarachnoid hemorrhage (SAH) in 1871: a 15-year-old boy who collapsed during exercise, in whom postmortem examination revealed a ruptured aneurysm arising from the right anterior cerebral artery (ACA), associated with stenosis of the aorta [4, 5]. Over a century later, it is widely accepted that the

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dictum "children are not miniature adults" could not be truer for pediatric aneurysms.

Large prospective trials have generated recommendations for the treatment of ruptured and unruptured aneurysms in adults [6–8]. The same cannot be said for aneurysms in children, in whom treatment decisions are often guided by relatively smaller case series and pooled case reports [2, 9–13] (See Table 1). The two patient groups differ substantially in predisposing factors, etiologic mechanisms, aneurysm morphology and location, clinical course, and prognosis [14–16]. As such, it is far from ideal to extrapolate natural history, treatment, and outcome data from the adult experience.

2 Epidemiology

Although extremely uncommon during the first year of life [17], intracranial aneurysms affect all pediatric age groups. The incidence is highest among adolescents [5, 16]. In a large autopsy series, no incidental aneurysms were found in children, supporting the view that pediatric aneurysms are acquired lesions [13, 15]. A congenital weakness in the vessel wall may lead to formation of aneurysms in neonates [18, 19].

Most studies have reported a male predilection [11, 16], with an overall M:F ratio of 1.46:1 in the present data set (See Table 1). This is in contrast to the female preponderance commonly observed for intracranial aneurysms in adults [20]. It has been hypothesized that genetic factors influence the early formation of aneurysms in males, while environmental factors lead to a reversal of the sex ratio later in life. Using data from 15 case series, the distribution of patients by age and sex is shown in Fig. 1. It can be seen that the male predominance is most apparent in childhood and is not observed among infants. The sex ratio approaches adult figures in adolescence.

3 Location

In Locksley's cooperative study [21], aneurysms were most commonly seen in the anterior communicating artery (28%) and the internal carotid artery (ICA)–posterior communicating artery junction (25%). These are less frequently involved in children (See Table 2). The predominant site of pediatric aneurysms is the ICA bifurcation, representing 24–51% of cases, followed by the middle cerebral artery (MCA) at 14–21%. Children also have a greater proportion of posterior circulation aneurysms, at approximately 21–25%, which is almost three times the rate in adults [2, 13, 15]. Aneurysms in neonates and infants most often affect the MCA [17, 19]. It is postulated that the vessel is exposed to greater hemodynamic stress, due to its early appearance during embryogenesis and its relatively higher amount of blood flow [17].

Table 1 Clinical characteristics, treatment, and outcomes of 881 pediatric patients with 1044 intracranial aneurysms

Year	First author	Country	# of patients	# of aneurysms	Multiple aneurysms (%)	M:F Ratio	Ruptured (%)	Good Grade[†] (%)	Anterior circulation (%)	Giant (%)	Primary treatment		Good outcome[§] (%)	Mortality (%)
											Micro surgery (%)	Endo vascular (%)		
2001	Proust et al. [11]	France	22	25	14	2.67	95	62	92	12	77	18	64	23
2001	Wojtacha et al. [3]	Poland	17	18	6	3.25	94	75	100	0	100	0	71	12
2005	Agid et al. [32]	Canada	33	37	9	0.94	27	*	70	30	27[‡]	35[‡]	64	15
2005	Huang et al. [1]	USA	19	19	0	2.17	58	73	58	37	68	16	95	5
2005	Lasjaunias et al. [16]	France	59	75	15	1.46	46	*	69	*	13	32	54	8
2006	Aryan et al. [4]	USA	50	54	8	*	70	44	76	22	93[‡]	7[‡]	84	2
2008	Mosiewicz et al. [54]	Poland	16	19	6	0.78	69	100	84	37	69	25	63	0
2008	Sencer et al. [61]	Turkey	14	16	14	0.56	100	100	94	0	100[‡]	0[‡]	93	7
2008	Stiefel et al. [55]	USA	12	13	8	0.5	100	67	69	8	62	38	75	17
2009	Hetts et al. [62]	USA	77	103	16	0.93	32	*	78	11	38	39	*	1
2009	Liang et al. [33]	China	24	25	4	1.4	46	82	64	32	16	60	92	4
2009	Lv et al. [47]	China	25	25	0	4	44	100	40	68	0	96	96	4
2010	Kakarla et al. [45]	USA	48	72	31	1.4	17	*	76	22	100	0	94	2
2010	Requejo et al. [40]	Argentina	17	17	0	3.25	82	71	88	12	24	65	47	18

(continued)

Table 1 (continued)

Year	First author	Country	# of patients	# of aneurysms	Multiple aneurysms (%)	M:F Ratio	Ruptured (%)	Good Grade† (%)	Anterior circulation (%)	Giant (%)	Primary treatment		Good outcome§ (%)	Mortality (%)
											Micro surgery (%)	Endo vascular (%)		
2011	Fulkerson et al. [56]	USA	28	30	4	0.75	68	*	77	7	64	36	79	7
2012	Koroknay-Pál et al. [53]	Finland	114	130	11	1.5	78	79	89	12	62	2	64	12
2012	Mehrotra et al. [28]	India	57	73	19	0.84	88	76	71	19	100	0	77	9
2013	Garg et al. [63]	India	62	74	13	2.65	58	78	82	15	58	31	72	2
2018	Chen et al. [64]	China	64	66	*	2.2	59	92	77	26	52	42	80	8
2018	Thioub et al. [57]	Senegal	10	10	0	0.67	60	*	100	10	70	10	60	20
2018	Yasin et al. [52]	USA	42	57	10	1.47	36	*	72	4	23	44	88	5
2019	Kim et al. [65]	Korea	26	33	15	1.89	62	81	76	6	38	38	77	4
2019	Nam et al. [58]	Korea	23	31	4	2.29	48	73	71	10	17	87	83	4
2019	Slator et al. [59]	UK	22	22	0	2.14	77	*	77	0	18	73	59	18
Overall			881	1044	12	1.46	59	78	77	17	–	–	–	7

Data obtained from case series with at least 10 patients, published from 2001 onwards. Studies included all types of intracranial aneurysms, except for Slator et al. and Wojtacha et al., which excluded traumatic and mycotic aneurysms. When neurovascular centers published more than one case series, only the most recent study or the largest series was included. Denominators used for overall percentages excluded studies where relevant data points could not be extracted

*Information missing, ambiguous, or with discrepancies in the original research articles

†Percentage of ruptured aneurysms; good grade is defined as Hunt and Hess I to III, except for Aryan et al., which included only Hunt and Hess I and II

‡Percentage of all aneurysms; others, percentage of all patients

§Glasgow Outcome Scale score 4–5, modified Rankin Scale score 0–2, or as defined by respective study authors

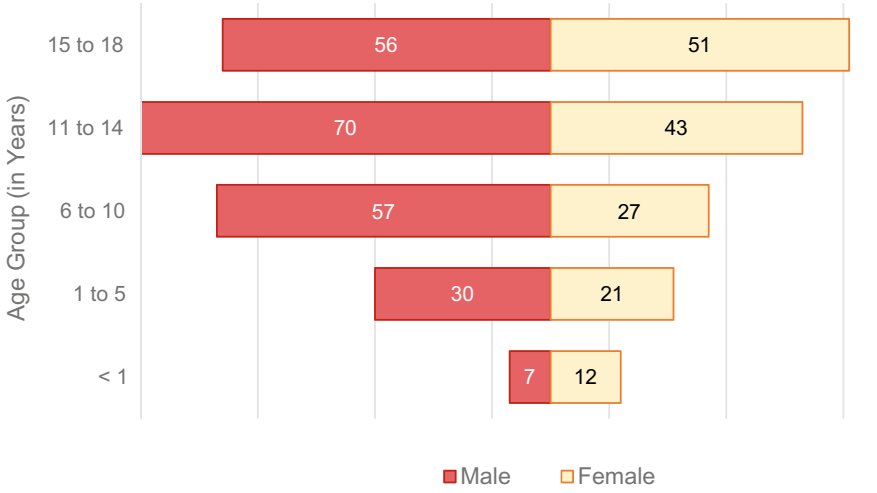

Fig. 1 Distribution of pediatric patients with intracranial aneurysms by age group and sex. Data obtained from references [1, 11, 16, 23, 33, 40, 45, 47, 54–60]

Table 2 Location of 917 pediatric intracranial aneurysms in 23 case series

Location		%	Number	%
Anterior Circulation			705	77
Internal carotid artery	333	36		
Anterior communicating artery	110	12		
Anterior cerebral artery	74	8		
Middle cerebral artery	188	21		
Posterior Circulation			212	23
Vertebrobasilar junction	10	1		
Vertebral artery	30	3		
Basilar artery	73	8		
Posterior cerebral artery	62	7		
Anterior inferior cerebellar artery	10	1		
Posterior inferior cerebellar artery	20	2		
Superior cerebellar artery	7	1		
			917	100

Data obtained from references [1, 3, 4, 11, 16, 28, 32, 33, 40, 45, 47, 52–61, 63, 65]

Multiple aneurysms are seen in about 20–30% of adult patients [22]. Many studies have observed a lower frequency in children [9–11, 23, 24], but multiplicity is now believed to be dependent on etiology, being more frequent in infectious aneurysms [13, 15].

4 Pathogenesis

Cerebral aneurysms form because of hemodynamic stress, endothelial dysfunction, and inflammatory pathways that eventually lead to weakness in the blood vessel wall, predisposing to rupture [25]. Histologic studies in infants had previously documented fragmented or missing internal elastic lamina and deficiency in the muscularis media, not unlike those seen in adults [17, 26].

However, because classic risk factors for aneurysm formation such as old age, hypertension, and smoking are typically not present in children [20], different mechanisms for the development of aneurysms in the pediatric population have been proposed [10]. Authors have described the interplay of "offensive" (e.g., hemodynamic stress, trauma, infection) and "defensive" factors, and it is believed that the latter may play a more important role in pediatric aneurysms [27, 28]. These include faulty self-repair mechanisms in the vessel wall, extracellular matrix disorders, and systemic or genetic vasculopathies.

As many as one-third of pediatric patients will have an underlying disease [13]. These include connective tissue disorders such as Ehlers-Danlos syndrome type IV, Marfan syndrome, Loeys-Dietz Syndrome, and fibromuscular dysplasia. Other associated conditions include polycystic kidney disease, coarctation of the aorta, hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu syndrome), neurofibromatosis type 1, tuberous sclerosis complex, and sickle cell disease [9, 14].

5 Clinical Presentation

The majority of pediatric patients with an intracranial aneurysm will be symptomatic, and most (60–70%) will present with subarachnoid hemorrhage and headache [13, 15]. In a large population-based study, 13% of pediatric patients with hemorrhagic stroke had an underlying aneurysm [29] (See Fig. 2). Among those with a ruptured aneurysm, around two-thirds will have a good clinical grade (i.e., Hunt and Hess I to III [30]). This is higher than what is observed in adults, and has been attributed to the lack of comorbidities in this patient population.

Mass effect from unruptured aneurysms may lead to cranial nerve dysfunction, focal neurologic deficits, brainstem compression, and seizures [31]. Children may also present with alteration in consciousness, ischemic symptoms, and hydrocephalus. Incidental aneurysms may be found on imaging for an unrelated head injury, or on surveillance scans for syndromic patients.

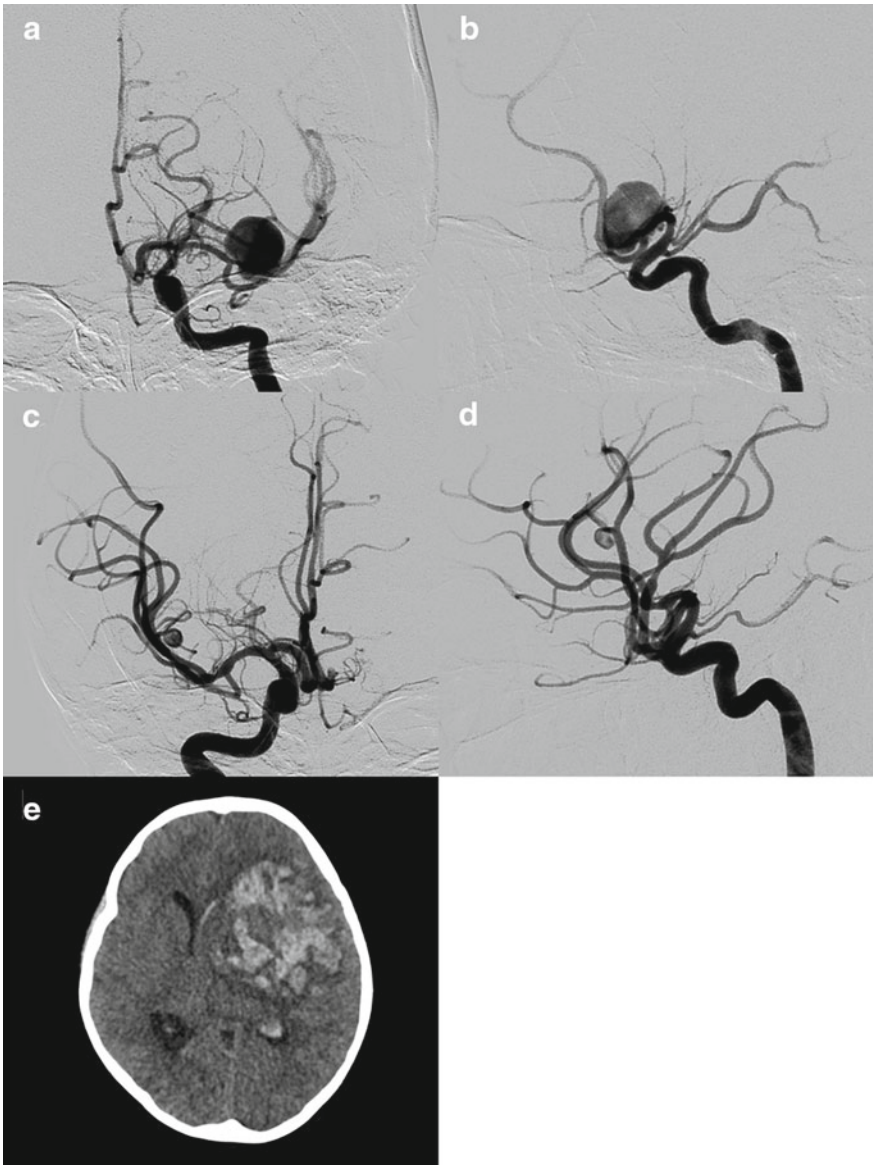

Fig. 2 An 11-year-old girl previously diagnosed with rheumatic heart disease presented with sudden headache and right hemiparesis. Initial CT (not shown) revealed left basal ganglia hemorrhage. Catheter angiography on day 13 post-ictus showed a 13.5 mm saccular aneurysm arising from the M2 segment of the left MCA (**a** and **b**), and a smaller 4.5 mm unruptured aneurysm at the ascending frontal branch of the right MCA (**c** and **d**). Re-bleeding occurred day after the angiogram (**e**), prompting emergency craniotomy, evacuation of hematoma, and clipping of the ruptured aneurysm

6 Classification

A standard system for classifying pediatric aneurysms does not exist. Based on etiology, an aneurysm may be considered traumatic or infectious, both of which are more frequent in children [15, 16]. However, about half of pediatric aneurysms will have no known etiology, and these are therefore classified as either saccular or fusiform based on their morphology. Giant aneurysms, defined as a diameter $\geq$ 25 mm, have a higher incidence in pediatric patients (12–37%), and they are more likely to present with compressive symptoms than rupture [2, 31].

6.1 Saccular Aneurysms

Saccular or berry aneurysms account for approximately 32–70% of cases [15, 16]. They are more common in older children and adolescents, and often arise in vessel bifurcations. The natural course and treatment in adolescents are similar to those in adults [27]. Nevertheless, they still require special care because underlying causes tend to have a bigger role in disease pathogenesis and natural history (See Fig. 3).

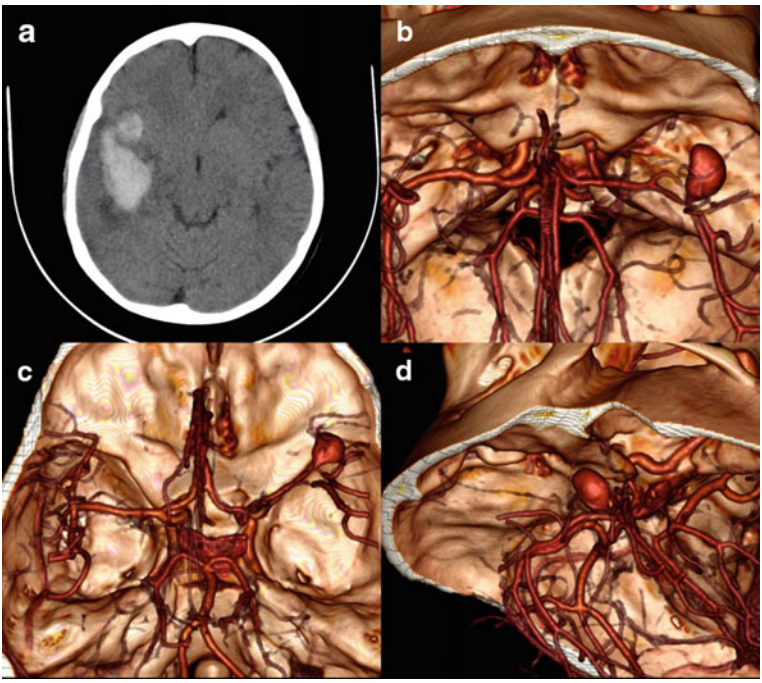

Fig. 3 A 7-year-old boy with severe headache and vomiting, in whom noncontrast head CT several days later (**a**) showed perisylvian intracerebral hemorrhage. 3D-reconstructed CT angiogram (**b**, **c**, **d**) revealed a prebifurcation narrow-necked saccular aneurysm arising from the right MCA. The aneurysm was surgically clipped

6.2 Dissecting Aneurysms

Dissecting aneurysms are about four times more frequent in children [15, 27]. In some series, they are the predominant aneurysm subtype. They tend to develop in the P1 and P2 segments of the posterior cerebral artery [32, 33], and this may account for the higher incidence of posterior circulation aneurysms in children. Other sites include the supraclinoid ICA and MCA [16, 34] (See Fig. 4).

Dissecting aneurysms occur when blood enters the intramural space from the intimal or adventitial layer (i.e., through the vasa vasorum), or even from the medial side, with the end result of "dissecting" the vessel layers away from each other. On luminal studies, they are characterized by alternating areas of stenosis and dilatations, intimal flaps, tapering occlusions, fusiform vessel enlargement, and pseudoaneurysms [15, 16]. Patients may present with ischemia due to progressive parent vessel stenosis, occlusion of perforators, or embolic events. Transmural dissection may lead to SAH, or rarely, to intracerebral hemorrhage without SAH [27]. Pseudoaneurysms may or may not be found on imaging, but their presence makes the natural history more aggressive.

6.3 Infectious Aneurysms

Infectious aneurysms primarily develop from septic emboli among patients with bacterial endocarditis [35]. They can also arise from contiguous spread, such as in cavernous sinus thrombophlebitis, skull base osteomyelitis, sinusitis, and postoperative infection. The ensuing arteritis, which particularly involves the adventitia,

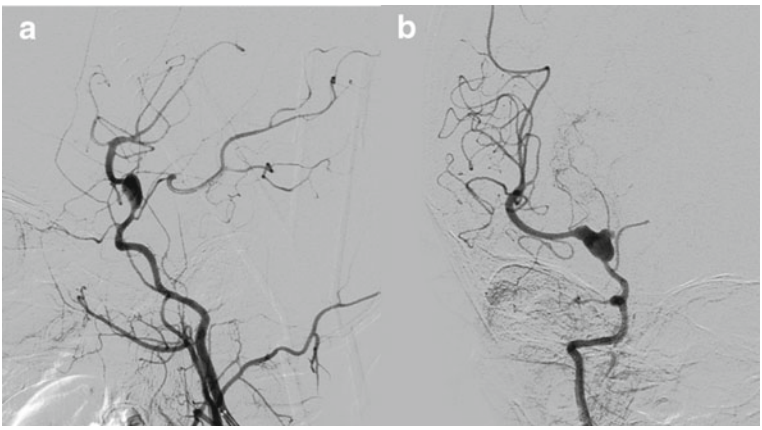

Fig. 4 A dissecting aneurysm involving the right ICA terminus in a 2-year-old child who had decrease in sensorium, left central facial palsy, and left hemiplegia. Lateral (**a**) and oblique (**b**) views

leads to weakening of the arterial wall and pseudoaneurysm formation. Bleeding, in the form of intraparenchymal hematoma, usually occurs within 48 h after the embolic event (See Fig. 5).

Although the term "mycotic" that began with Osler has persisted, the most common causative organisms are *Staphylococcus sp.*, *Streptococcus sp.*, and gram-negative bacteria [13, 36]. Fungal organisms (specifically, *Aspergillus sp.* and *Candida sp.*) are isolated almost exclusively from immunocompromised children [35]. The occurrence of multiple aneurysms among pediatric patients with human immunodeficiency virus is well-described [37].

6.4 Traumatic Aneurysms

Shearing forces from both blunt and penetrating head injuries may result in the formation of traumatic aneurysms, with the former being more common [38, 39]. Rarely, they may be iatrogenic, following a surgical procedure. Vessel wall injury

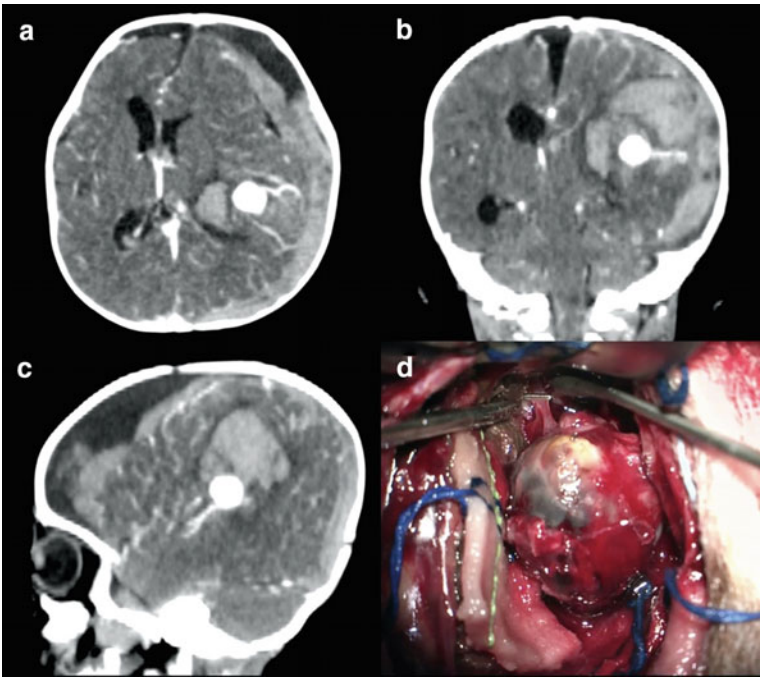

Fig. 5 An infant being treated for infective endocarditis had rapid neurologic deterioration with right-sided weakness and a blown left pupil. Contrast CT (**a**–**c**) showed intracerebral and subdural hemorrhage from a ruptured infectious aneurysm arising from the left MCA. Intraoperative photo (**d**) shows the aneurysm dome that was excised after parent vessel ligation (*Case courtesy of Dr. Jay Villavicencio*)

leads to extravasation of blood into a false lumen, therefore these aneurysms are highly prone to rupture. Typically involved are the distal ACA and the cavernous ICA, which are fixed against dural infoldings [15]. Cortical aneurysms may develop underneath skull fractures. On average, hemorrhage occurs two to four weeks after trauma [27].

6.5 Others

Oncotic aneurysms arise when tumor cells infiltrate the arterial wall, either through hematogenous or contiguous spread [14]. Lenticulostriate aneurysms are seen in patients with moyamoya disease and present with intraventricular or basal ganglia hemorrhage [40, 41]. Flow-related aneurysms associated with arteriovenous malformations are also seen in the pediatric age group.

7 Diagnosis

The workup of children suspected to have an intracranial aneurysm is similar to that in adults, with some special considerations [2, 36]. A noncontrast computed tomography (CT) scan readily demonstrates acute SAH. Magnetic resonance imaging is also useful to detect SAH. If these are normal but the index of suspicion for a ruptured aneurysm is high, a lumbar puncture to document xanthochromia and erythrocytes is warranted. In neonates, transfontanel ultrasound with color flow Doppler as an initial imaging study has been recommended [42].

Upon confirmation of SAH, the aneurysm may be localized using CT angiogram (CTA), magnetic resonance angiogram (MRA), or digital subtraction angiogram (DSA). The choice depends on the patient's age, clinical status, and anesthetic requirement, as well as the availability of resources and capacity to perform therapeutic interventions.

For older children, some centers immediately proceed to a CTA, which has a higher sensitivity for aneurysms and is faster than an MRA. However, the latter may be preferable to avoid radiation and nephrotoxic contrast in younger children [43]. A contrast MRA may identify aneurysms that are not apparent on a time-of-flight angiogram [19]. Vessel wall imaging on MRI has been useful in the evaluation of dissecting aneurysms [44].

DSA remains the gold standard for diagnosing and characterizing pediatric intracranial aneurysms, providing essential information for treatment [2, 36]. Visualization of the vertebrobasilar system is a must, considering the high incidence of posterior circulation aneurysms. Children with an unruptured aneurysm may require long-term surveillance, hence, a high-quality MRA is preferred to limit radiation exposure [43].

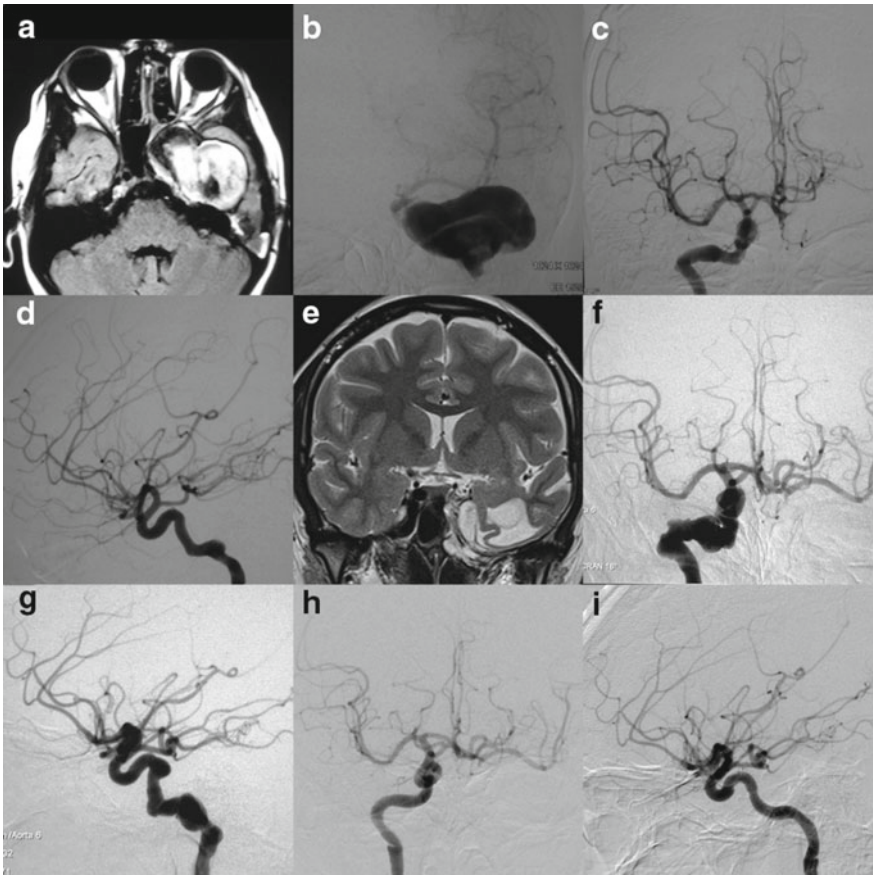

Fig. 6 A 10-year-old girl complained of sudden severe headache associated with left ptosis, lateral rectus palsy, and decrease in visual acuity leading to blindness. Imaging revealed a giant dissecting aneurysm arising from the left petrous ICA, extending to the left temporal fossa (**a**), and causing significant flow delay (**b**). Angiogram of the contralateral side showed collateral flow to the left (**c**) and a diseased right petrous ICA (**d**). She tolerated programmed occlusion of the left cervical carotid artery using a Poppen clamp, and the vessel was subsequently ligated. MRI after one year showed regression of the aneurysm, with malacic changes in the temporal lobe (**e**). However, three years after carotid ligation, DSA showed progression of the right ICA abnormality, with development of new aneurysms, the largest of which is found on the cavernous segment (**f** and **g**). Flow-diversion was performed at this point. One year later, DSA showed reconstitution of the right ICA and disappearance of previously noted aneurysms, stenoses, and dilatations (**h** and **i**). Since then, the patient has remained well

8 Treatment

Because pediatric patients have a longer lifespan, selecting the best management option must consider the durability of treatment and risk of recurrence or de novo aneurysm formation (See Fig. 6). In ruptured aneurysms, the primary goal is to prevent rebleeding. To optimize care, decisions are ideally made by a multidisciplinary team consisting of vascular neurologists, vascular neurosurgeons, interventional neuroradiologists, and intensivists, after a comprehensive discussion of risks and benefits with the patient's family.

8.1 Microsurgery

Surgical options include aneurysm clipping, wrapping, proximal artery occlusion, and trapping [2, 45, 46]. Open surgery may be necessary to relieve mass effect or avert herniation. Direct clipping may not be possible in aneurysms with a friable neck, such as in dissections or Ehlers-Danlos syndrome. Younger patients may tolerate parent vessel occlusion due to their extensive collateral circulation. However, in older children, a bypass maybe required to avoid distal ischemia. Skull fixation, brain retraction, and neuromonitoring—if they will be used—must be carefully planned. Intraoperative rupture should be avoided because of patients' smaller blood volume. The operating room must be kept warm to prevent hypothermia.

8.2 Endovascular Therapy

Endovascular therapy includes coiling, stenting, parent vessel sacrifice, glue embolization, and flow diversion [32, 34, 47–49]. In recent years, advances in interventional techniques and microcatheter technology have paved the way for the increasing role of endovascular therapy in the management of pediatric aneurysms [9]. The smaller caliber of blood vessels may add to the technical difficulty of some endovascular procedures. The interventionist must be mindful of the radiation dose, fluid balance, and amount of contrast given to children.

8.3 Medical and Conservative Therapy

Antibiotics are the cornerstone of treatment for infectious aneurysms, especially when they are unruptured [35]. Dissecting aneurysms may require antiplatelet or anticoagulant therapy. Spontaneous thrombosis of these lesions has been documented [50]. The benefit of any therapy may be marginal for moribund patients, and in these cases, supportive therapy has been advocated. Although many of these

patients will have a poor outcome, it does not completely preclude the possibility of recovery.

For unruptured aneurysms, it remains unclear whether the results of studies in adults can be extrapolated to children [8], especially those younger than 15 years old. In a study of 51 patients with 61 incidental aneurysms, only 13% increased in size by 1–4 mm, and none ruptured during a mean follow-up of 4 years [51].

9 Outcome

In general, children with intracranial aneurysms tend to have a better outcome than adults. As seen in Table 1, mortality rates range from 0–23%. Good outcomes, usually indicated by a Glasgow Outcome Scale score of 4–5 or a modified Rankin Scale score of 0–2, have been observed in as high as 82–96% of patients [13].

Up to half of patients may re-bleed before the aneurysm is secured, and thus, several authors have advocated early treatment (*i.e.*, within 72 h of rupture) [3, 11]. Vasospasm occurs in about 10–30% of patients, but a lower incidence of delayed ischemic neurologic deficits has been consistently documented [1, 2, 13]. This is believed to be due to the presence of a robust collateral circulation and higher cerebral blood flow, especially in young children [9].

A meta-analysis that included 560 patients showed comparable rates of favorable outcomes for open surgery and endovascular therapy, in both ruptured and unruptured aneurysms [52]. Long-term studies in children have documented annual recurrence rates between 0.6–2.6%, and annual rates of de novo formation or growth between 1.3–7.8% [45, 46, 53]. Hence, surveillance imaging is generally recommended between 6 and 12 months after treatment, with life-long follow-up at 3- to 5-year intervals [43, 53].

10 Pearls

- Pediatric intracranial aneurysms represent less than 5% of all aneurysms, but they are potentially devastating and life-threatening
- Aneurysms in children are more likely to be located at the ICA terminus and posterior circulation, less frequently multiple, and more likely to be giant
- The majority of pediatric intracranial aneurysms manifest with headache and subarachnoid hemorrhage
- Non-hemorrhagic presentation (*e.g.*, mass effect, cranial nerve dysfunction, focal deficit, seizures) is more common in children than in adults
- Based on morphology and etiology, aneurysms may be classified as saccular, dissecting, infectious, or traumatic
- Patients with ruptured aneurysms typically present with a good clinical grade, lower incidence of symptomatic vasospasm, and better clinical outcomes

- Comparable rates of good outcomes have been demonstrated for microsurgery and endovascular therapy
- Pediatric aneurysms are best managed through an individualized treatment approach, by a multidisciplinary team that is well-versed with pediatric vascular diseases

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Developmental Venous Anomalies

Brian M. Howard and Daniel L. Barrow

Percival Bailey and Harvey Cushing first described venous angiomas in their monograph, *Tumors Arising From the Blood-Vessels of the Brain; Angiomatous Malformations and Hemangioblastomas*, in which blood vessel abnormalities of the central nervous system were first classified as neoplasms or malformations [1]. In his classic publication, McCormick designated venous angiomas as one of five vascular malformations of the central nervous system [2]. While Bailey and Cushing correctly characterized venous angiomas as non-neoplastic, the contemporary term developmental venous anomaly (DVA) did not come into medical parlance until nearly 60 years later, when Lasjaunias described their histologic, radiographic, developmental and clinical features [3]. The present appellation was given on the basis that DVAs do not proliferate and are not true malformations as they do not demonstrate abnormal filling or drainage on conventional angiography [3]. DVAs are defined by five criteria [3]: (1) they drain normal brain; (2) no other venous pathway drains the region of brain drained by the DVA; (3) they drain into a normal, extraparenchymal venous structure; (4) they opacify in the normal venous phase on conventional angiography; and, (5) their angiographic appearance is that of several, small medullary veins that converge on a larger collecting vein.

1 Epidemiology

DVAs were once believed to be quite rare with relatively few reports that describe DVAs published prior to 1978. However, in that year, Sarwar and McCormick demonstrated that DVAs were the most commonly encountered "malformation" in an autopsy study of over 4,000 brains and that between 2 and 3% of the general

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population may harbor a DVA [4]. Radiology based studies reveal that DVAs account for approximately 60% of intracranial vascular malformations [5]. Other imaging based population studies have been more mixed. The largest such study in North America, which investigated the prevalence of vascular malformations in Olmsted County Minnesota from 1965–1992, revealed that DVAs were the second most common abnormality identified over the entire period behind arteriovenous malformations (AVM) [6]; however, none were detected between 1965 and 1974, whereas only 2 were detected between 1975 and 1984. Yet, in the period of more modern imaging (1985–1992), detection of DVAs overtook AVMs as the most commonly detected abnormality [6]. Contrarily, DVAs were the third most commonly discovered lesion in the more recently published Scottish Intracranial Vascular Malformation Study behind AVMs and cavernous malformations [7]; while a large, three-year study published by a group in China revealed that DVAs were the most common vascular malformation in their population [8]. No comprehensive epidemiological study of cerebrovascular malformations, including DVAs, in the pediatric population has been completed to date.

2 Venous Anatomy

A working knowledge of venous anatomy is of utmost importance to understand the development and clinical manifestations of DVAs [9]. Venous drainage of both the supra- and infratentorial brain is divided into two, parallel systems [9–11]. The superficial system drains the cerebral cortex and subcortical white matter via sub- and intracortical medullary veins, which subsequently flow to pial veins followed by larger cortical veins, and finally into the dural venous sinuses [10, 11]. The deep medullary and dorsal nuclear veins drain into subependymal veins and ultimately the Galenic system. The deep venous system drains the periventricular white matter, the corona radiata, and the deep grey structures [10, 11]. A third network of veins, the transcerebral veins, connects the two systems. Though first to appear embryologically, most transcerebral veins regress throughout development, such that a relative paucity of transcerebral veins are present by the end of gestation [11]. The venous drainage of the cerebellum, with a superficial system for the outer gray matter and underlying white matter and a deep system for the deep nuclei and periventricular white matter follows a similar pattern to that of the supratentorial brain [9].

3 DVA Architecture and Histology

DVAs consist of numerous, radially oriented, medullary veins that converge into a single, dilated venous collector [2, 3, 9–15], the result of which appears as a “caput medusa” on conventional angiography and MRI (Fig. 1) [3, 9, 15]. The medullary veins of a DVA are dilated and thin walled, but otherwise normal. The collecting

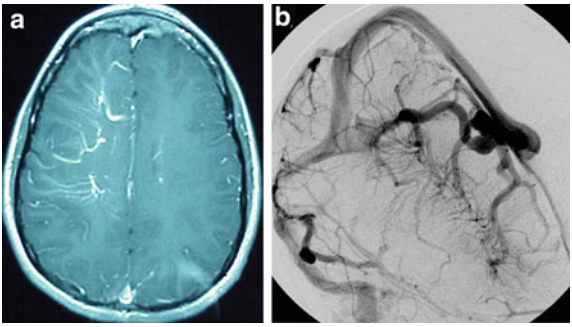

Fig. 1 **a** MRI and **b** cerebral angiogram that demonstrate the classic angio-architecture of a developmental venous anomaly (DVA) in a patient with multiple DVAs. The medullary veins comprise the caput medusa that drains into a single venous collector

vein, however, is not only dilated, but consists of abnormally thickened, fibrous walls, with no elastic laminae and disorganized smooth muscle [2, 9, 16]. In addition, hyalinization of the walls of the collecting vein is also common [2]. The intervening brain parenchyma that interdigitates between the medullary veins of the DVA is histologically normal [3, 16].

4 DVA Physiology and Development

A DVA is a benign variant of normal anatomy [3]. However, a DVA typically drains a larger volume of brain than would be expected of normal single venous structures [11]. Normal pial or subependymal veins are absent in deep and superficial DVAs, respectively, which leads to reversal of normal venous flow. For instance, in deep DVAs, the cortical ribbon and underlying white matter drain to deeper, subependymal veins, which converge in a centripetal fashion into a single collector that, in turn, drains into the deep venous system [10, 11]. Contrarily, in superficial DVAs, the deep white matter and gray nuclei are abnormally drained centrifugally toward a pial, venous collector that ultimately empties into a cortical vein, venous lake, or dural venous sinus [10, 11]. The exact etiology of DVAs remains unclear; however, DVAs are thought to be congenital because the territory of a DVA lacks normal venous anatomy [3, 11]. Lasjaunias and colleagues argue that DVAs develop out of normal, transhemispheric anastomotic pathways that are recruited due to hemodynamic demand [3]. Another theory suggests that DVAs develop around a normal medullary vein to compensate for the loss of adjacent medullary veins, such as in cases of thrombosis [11, 17–19]. Some authors speculate that DVAs represent an arrest in normal, embryological or fetal development [9, 18]; while Raybaud refutes the theory of halted development on the basis that the histological and morphological appearance of DVAs is not a known intermediate stage of venous development [11, 20].

5 Imaging

Since McCormick's autopsy study dispelled the belief that DVAs are rare lesions, the advent of modern imaging has confirmed that DVAs are common and are most frequently discovered incidentally. While the classic caput medusa appearance of DVAs was described on the basis of catheter-based angiography [4, 9], this modality is rarely used to diagnose DVAs in the current era. Irrespective of the imaging modality employed, the venous collector of a DVA is typically visualized coursing from the white matter to a cortical or deep vein or a dural venous sinus [14, 17, 21]. While the collecting vein is easily identified as a linear focus of enhancement on contrast-enhanced computed tomography (CT), the medullary veins of the caput medusa are less consistently seen [14]. Magnetic resonance imaging (MRI) provides higher resolution than CT and may reveal a parenchymal abnormality associated with the DVA (Fig. 2). The venous collector is typically seen as a transhemispheric flow void on T2-weighted MRI sequences in the absence of gadolinium; whereas the entire DVA (the medullary veins and venous collector) is identified on post-gadolinium T1-weighted MRI sequences [14, 17, 21, 22]. Digital subtraction angiography (DSA) remains the gold-standard modality to evaluate the hemodynamic characteristics of DVAs [9]; however, time-resolved, 3D magnetic resonance angiography has recently become a viable, noninvasive alternative to assess flow dynamics, particularly in the venous collector of a DVA [23, 24]. Lastly, recent imaging analysis demonstrates parenchymal abnormalities other than cavernous malformations (CM) within the drainage zone in upwards of two-thirds of DVAs. The most frequently seen abnormalities were regional cerebral atrophy, non-specific white matter signal changes and calcifications [25].

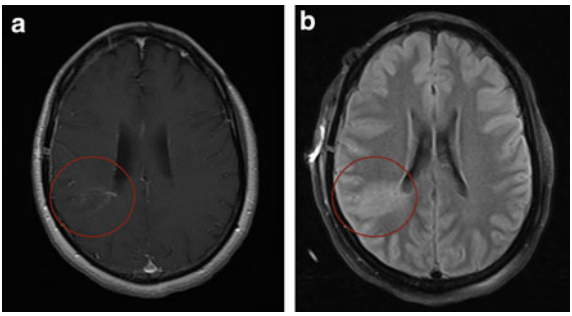

Fig. 2 **a** Post-contrast MRI demonstrating a DVA within the deep, periventricular white matter with the venous collector draining to the Galenic system. **b** T2-FLAIR images reveal signal abnormality in the peri-Rolandic region, which is drained by the medullary component of the DVA and likely represents venous hyperemia in the area. Area of interest demarcated by the red circles

6 Associated Vascular Malformations

DVAs are associated with several other vascular malformations. CMs are associated with DVAs between 6.2 and 13.3% of cases in retrospective series [25, 26], but in 40% of cases in a prospective analysis [27]. Conversely, DVAs are reported to be associated with CMs upwards of 86% of the time [5]; though Spetzler and colleagues assert that with sufficiently diligent radiographic and surgical search the association of DVAs with brainstem CMs may approach 100% [28]. While the pathophysiologic nature of the relationship between CMs and DVAs is not definitely known, two predominant theories pervade the literature. One theory contends that repeated microhemorrhages from the medullary veins of the DVA result in upregulation of proangiogenic molecules, particularly vascular endothelial growth factor, which results in the formation of a CM [9, 10, 28, 29]. Others hypothesize that alteration in hemodynamics within the DVA lead to development of a CM [30]; while still others emphasize that the two posited pathophysiological mechanisms are not mutually exclusive [28]. Recent genetic analysis indicates that no common mutational link exists between DVAs or CMs [31], but such data does not preclude the possibility of the aforementioned theories. Moreover, reports of de novo CM formation in the drainage territory of a known DVA bolsters the theory that, in some fashion, DVA physiology may lead to CM formation [32–35] Fig. 3.

DVAs may drain into a sinus pericranii, which is an aberrant extracranial drainage of the brain via diploic emissary veins [36, 37]. When surgical or endovascular obliteration of sinus pericranii is contemplated, vascular imaging is required to assure a DVA does not drain predominantly via the involved emissary vein as treatment of the sinus pericranii in such circumstances can lead to venous hyperemia and infarction in the cerebral territory drained by the DVA [9, 37].

DVAs are commonly discovered in patients with venous and venolymphatic malformations of the head and neck [9, 38], and neurocutaneous disorders such as Sturge-Weber Syndrome [39] and Blue Rubber Bleb Nevus Syndrome [40].

7 Pathobiology

DVAs are overwhelmingly benign as evidenced by the estimate that nearly 3% of the population possesses a DVA, but case reports of clearly symptomatic DVAs number fewer than 100 [14]. In addition, the reported risk of hemorrhage from a DVA is estimated to be between 0.22 and 0.68% per annum, though a large percentage of such hemorrhages are likely from associated CMs rather than the DVA itself [9, 41, 42]. Pereira et al. recently published a comprehensive series of their own data and an extensive literature review that detailed the pathophysiological mechanisms by which a DVA may become inherently symptomatic [14]. The authors found that symptomatic DVAs could be broadly classified into one of two patho-mechanistic categories, mechanical and hemodynamic. Obstructive hydrocephalus, primarily from compression of the aqueduct of Sylvius, and cranial

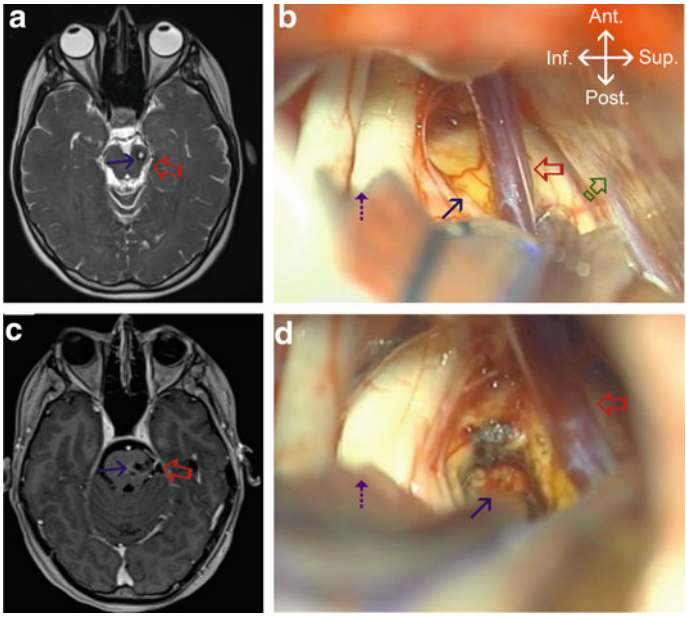

Fig. 3 **a** Preoperative MRI that reveals a cavernous malformation (CM—dark blue arrow) in the left aspect of the pons with an associated DVA (red arrow), the draining vein of which extends into the pontine cistern. **b** Intraoperative image taken prior to extirpation of the CM. The lesion was approached from a retrosigmoid craniotomy and the pons was accessed via the safe entry zone between the fifth cranial nerve (CN V) and the seventh and eighth cranial nerve complex (CN7/8 complex). The tentorium is seen at the right of the panel (green, broken arrow). The venous collector of the DVA is visualized in the pontine cistern (red arrow). An area of hemosiderin staining on the lateral aspect of the pons demarcated the site of the cavernous malformation, which lies just deep to the surface (dark blue arrow). The CN7/8 complex is seen exiting the pons immediately inferior to the CM (purple dashed arrow). **c** Postoperative MRI reveals complete extirpation of the CM (dark blue arrow), but that the DVA has been left uninjured (red arrow). **d** Intraoperative image shows the resection cavity (dark blue arrow) and the venous collector of the DVA (red arrow). The CN7/8 complex is seen at the inferior margin of the photo (purple dashed arrow). Ant.—anterior; Sup.—superior; Post.—posterior; Inf.—inferior

nerve compression resulting in trigeminal neuralgia, hemifacial spasm and tinnitus constituted over 90% of patients in the mechanical complications group [14]. Symptomatic DVAs in the altered hemodynamics group fell into one of two subcategories, DVAs with increased inflow and those with impeded outflow [14]. DVAs with increased arterial inflow can be further substratified into those with microshunting into the DVA at the level of the medullary veins of the caput medusa [14, 43] and AVMs that drain via a DVA, either in the presence of a true AVM nidus or enlarged arterial feeders without a angiographically defined nidus, the so-called "venous-predominant parenchymal AVM" [9, 14, 44–46]. Patients with symptomatic DVAs due to augmented arterial inflow present with headache,

seizures and intraparenchymal as well as intraventricular hemorrhage [14, 44]. Mechanical obstruction of DVA outflow may be compressive, but is most often due to thrombosis of part or all of the venous collector and on occasion, the entire DVA [12, 14]. Patients come to clinical attention due to sequelae of venous hyperemia in the form of headache, neurological deficit, seizure and venous infarction with or without hemorrhage [9, 12, 14, 25, 41].

8 Treatment

Consensus dictates that DVAs do not require treatment, particularly given leviathan majority of DVAs are asymptomatic and drain normal brain. When symptomatic CMs that are associated with a DVA are surgically extirpated, care should be taken not to resect any of the DVA to avoid the well-known and potentially devastating consequences associated with venous hypertension and hemorrhage [15, 28, 34, 44]. For DVAs that present with symptoms related to mechanical compression that fail conservative therapy or observation, treatment is often indicated, but aimed at the effector, not the DVA. In cases of hydrocephalus due to aqueductal compression by a DVA, a ventricular shunt or ventriculocisternostomy should be considered; and in cases of DVA-associated nerve compression, microvascular decompression may be employed [14, 47, 48]. No consensus exists regarding treatment of AVMs that drain via a DVA, either in the presence of a true AVM nidus or in the setting of the aforementioned "venous-predominant parenchymal AVM". However, most authors contend that if resection of the AVM is contemplated, either in the setting of hemorrhage or electively, the DVA collector should be left in situ to limit the possibility of venous infarction [9, 14, 44]. Should resection of the DVA collecting vein be necessary, *en bloc* resection of the territory drained by the DVA should also be removed to avoid venous hyperemia, infarction and possible hemorrhage [9, 49]. When DVAs present due to venous outflow obstruction from thrombosis of the collector, anticoagulation can be used to recanalize the vein [14, 50], including in the setting of related hemorrhage similar to treatment of dural venous sinus thrombosis [50, 51]. However, one should recall that treatment of thrombosed DVAs is limited to a handful of case reports and that each clinical situation must be evaluated individually in the absence of a standard of care. Indeed, cases of conservatively managed, thrombosed DVAs with spontaneous recanalization and a good outcome have been published [52].

9 Pediatric Cases

DVAs affect infants, children and adults consistent with their congenital nature. Table 1 summarizes all reported cases of symptomatic DVAs in the pediatric literature.

Table 1 Summary of all cases of symptomatic DVAs in the pediatric literature

Reference	Age (Yr)	Sex	Mechanism—pathology	Clinical presentation	Treatment	Outcome
Truwit [53]	1	M	Flow imbalance—augmented inflow from AVM	IPH, Seizures	AVM resection	Seizures controlled
Truwit [53]	12	M	Flow imbalance—outflow restriction	Venous infarction, Seizures	Conservative	No follow-up
Lindquist et al. [54]	20	M	Flow imbalance—augmented inflow from AVM	IPH	Radiosurgery	AVM obliterated
Blackmore and Mamourian [55]	16	F	Mechanical—HCP, DVA aqueductal compression	HA, Photophobia	Conservative	No change
Kim et al. [56]	13	M	Flow imbalance—outflow restriction, venous collector thrombosis	Venous infarction	Decompressive craniectomy	Death
Aksoy et al. [45]	11	M	Flow imbalance—augmented inflow from AVM	Seizures	Radiosurgery	AVM obliterated
Bannur [57]	11	M	Mechanical—HCP, DVA aqueductal compression	HA, vomiting, vertigo, papilledema	Ventricular shunt	Symptoms resolved
Yagmurlu et al., 2002 [58]	7	F	Mechanical—HCP, DVA aqueductal compression	Progressive HA	Conservative	Unknown
Dudeck et al. [59]	16	M	Flow imbalance—outflow restriction due to slow flow from concurrent DAVF	Pulsatile tinnitus	Conservative	No change

(continued)

Table 1 (continued)

Reference	Age (Yr)	Sex	Mechanism—pathology	Clinical presentation	Treatment	Outcome
Vieira Santos and Saraiva [49]	9	F	Flow imbalance—outflow restriction, venous collector thrombosis	Venous infarction, right hemiparesis	Anticoagulation	Moderate recovery
Shim et al. [60]	5	M	Mechanical—nerve compression	Progressive hearing loss, CN VIII compression	Conservative	No change
Pereira et al. [14]	1	F	Mechanical—dilated ophthalmic vein (venous collector)	Proptosis, eye pain	Conservative	Unknown
Pereira et al. [14]	20	M	Mechanical—HCP, DVA aqueductal compression	HA	ETV	Unknown
Pereira et al. [14]	1 (month)	M	Flow imbalance—outflow restriction, venous collector stenosis	Venous infarction, IPH, seizure	Conservative	Normal development
Pereira et al. [14]	8 (month)	F	Flow imbalance—outflow restriction, venous collector thrombosis	Venous infarction, IPH, SAH HA, seizure	Conservative	Normal development
Pereira et al. [14]	11 (month)	F	Flow imbalance—outflow restriction, venous collector thrombosis	SAH, HA, seizure	Conservative	Unknown
Pereira et al. [14]	5	F	Flow imbalance—outflow restriction, venous	Venous infarction, seizures, left hemiparesis	Conservative	Recovered

(continued)

Table 1 (continued)

Reference	Age (Yr)	Sex	Mechanism—pathology	Clinical presentation	Treatment	Outcome
			collector thrombosis			
Pereira et al. [14]	9	M	Flow imbalance—augmented inflow from microshunting	IPH, HA, seizure	Embolization of arterial feeders	Recovered
Pereira et al. [14]	14	F	Flow imbalance—augmented inflow from microshunting	IPH, HA, ataxia, HCP	Embolization of arterial feeders	Recovered
Pereira et al. [14]	8	M	Flow imbalance—augmented inflow from microshunting	IPH, ataxia, somnolence	Embolization of arterial feeders	Recovered
Pereira et al. [14]	2 (day)	F	Idiopathic	IPH, seizure	Conservative	Normal development
Sepelyak et al. [61]	17	F	Flow imbalance—outflow restriction, venous collector thrombosis	IPH, HA, nausea, vomiting, right nasolabial flattening	Conservative, oral contraceptives stopped, Aspirin started	Recovered
Guhl et al. [62]	10 (month)	M	Mechanical—HCP, DVA aqueductal compression	HCP diagnosed on neonatal ultrasound	ETV	Normal development
Paulson et al. [63]	3 (day)	F	Mechanical—HCP, DVA aqueductal obstruction	Prenatally diagnosed, HCP, Macrocephaly	Ventricular shunt	Normal development
Inoue et al. [64]	10	M	Mechanical—HCP, DVA aqueductal compression	HA	ETV	Recovered
Scheidegger et al. [65]	17	F	Idiopathic	Seizures	Conservative—antiepileptics	Seizures controlled
Andrea et al. [66]	9	M	Idiopathic	Seizures	Conservative—antiepileptics	Seizures controlled

Modified from Peirera et al. [14]. Cases from the literature from 2008 to present were added only if the patient's symptoms could be attributed to the DVA only and not an associated or unique, but coexistent pathology. Patient's were considered pediatric if 21 years of age or younger

10 Conclusion

DVAs are benign venous anomalies of the central nervous system (CNS) that drain normal parenchyma and are the most common vascular abnormality of the CNS. Typically, DVAs require no treatment. In selected circumstances where DVAs result in symptoms from compression of neurological structures or when associated with other symptomatic vascular lesions and surgery is required, resection of the DVA should not be attempted due to the complications of venous hyperemia, infarction and hemorrhage.

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Pediatric Head Trauma

Mirna Sobana and Danny Halim

1 Introduction

Similar to adults, children are prone to any impact that can be caused by trauma to the head. Any types of cranial fractures or intracranial bleeding that have been reported in the adults, including linear and depressed fractures, epidermal hematoma (EDH), subdural hematoma (SDH), subarachnoid bleeding (SAB) and intracerebral hemorrhage (ICH), have also been reported in children [1]. Consequently, indications for neurosurgical treatments in pediatric patients are identical to the adult patients. Despite homogeneity of conditions and treatments, certain situations and characteristics are unique for pediatric head trauma patients, particularly babies and very young children. For example, vacuum and forceps delivery have been identified as the etiology of head trauma and intracranial bleeding in neonates, including subgaleal hematoma, subdural hematoma, subarachnoid hemorrhage and intracerebral hemorrhage. Despite its rarity, epidural hematoma could also be acquired in neonates [2]. Then, during their early years in life, many cases of abusive head trauma (AHT) in infants and children have been reported. In shaken baby syndrome, babies or toddlers were subjected to a repetitive shaking and/or violent blunt trauma, resulting in traumatic intracranial bleeding, mainly subdural hematoma (Fig. 1) [3, 4]. In these cases, the biomechanical impact of shaking in babies and toddlers is exacerbated by the fragility of the head and brain tissues, and physiological weakness of cervical muscles [4]. Outcomes ranging from complete recovery to irreversible brain damage and death have also been reported [4, 5].

As children grow, their structures matured, thus becoming similar to the adults. Nonetheless, different situations and problems could increase the risk of trauma in children. For example, at overpopulated area in some countries, communal play-

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ground does not exist, hence children might seek other ways to play that are potentially more dangerous (Fig. 2a). Furthermore, in many cases of severe head trauma in children at our center, disobedient to simple rules, such as not wearing helmet, prompted the injury (Fig. 2b) [6].

Like in any other cases, prompt diagnosis and treatment in pediatric trauma patients are keys to acquire optimum outcomes. However, acquisition of a detailed diagnosis is often challenging due to difficulties to obtain a proper anamnesis and physical examinations. As an example, in shaken baby syndrome, bruises or any

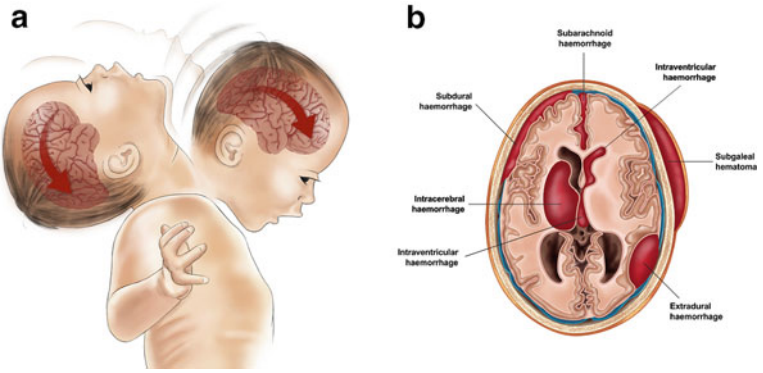

Fig. 1 **a** In addition to the fragilities of head and brain tissue in babies, physiological weakness of their cervical muscles is an important factor that causes risk of shaken baby syndrome when babies are subjected to repetitive shaking movements. **b** As a consequence of head injuries in children, intracranial bleeding could be acquired in almost any head and brain structures, including subgaleal hematoma, extradural (epidermal) haemorrhage, subdural haemorrhage, subarachnoid bleeding, intracerebral haemorrhage and intraventricular haemorrhage

Fig. 2 High prevalence of pediatric trauma is often related to social problems. **a** An over-populated area with no communal playground might lead to higher prevalence of pediatric trauma. **b** Disobedient to simple traffic rules and regulations, such as the maximum number of passengers on a motorcycle and wearing helmet, could lead to accidents that cause head and/or spinal trauma in children

other visible traumatic lesions are not always identifiable [5]. Additionally, physicians are often faced with difficult situations on whether performing CT scan on babies and young children is really necessary, considering its potential exposure to radiation [7–9].

Regardless of any discrepancies between, identification of skull fracture, decreased consciousness, seizure, neurological deficits, and other signs of intracranial hypertension are keys to decide the necessity to perform imaging, such as CT scan or MRI [9–11]. Afterwards, analyses on the presences of bone discontinuity, compression of brain structures, midline shifts and intracranial bleeding would primarily decide whether or not surgery is necessary. To our knowledge, despite differences in the age of infant and very young children would relate to different head circumference and intracranial volume, no surgical age-specific guidelines have been consensually agreed yet. Thus, CT scan and/or MRI findings should never be taken as a sole consideration for surgery.

In majority of cases, Glasgow Coma Scale (GCS) at admission could illustrate the actual severity of the injury itself that are seen in the CT or MRI images. Thus, it is logical to use GCS at admission as one of the prognostic factors in pediatric trauma patients [12]. However, similar to adult trauma patients, GCS at admission in pediatric trauma patients with extradural (epidermal) hematoma has less reliable prognostic values than in patients with other types of intracranial bleeding, owing to the fact that at its early stage, epidermal hematoma might not yet cause any direct injury to the brain parenchyma. In such cases, time interval from the patient's decreased consciousness to surgical intervention is key to acquire optimum outcomes [13, 14].

2 Penetration Injury

As mentioned earlier, in addition to the possible differences of CNS organ structures in children compared to adults, their natural curiosities and in some, rebellious behavior, would make them liable to certain mechanism of injury, such as penetrating trauma. Although intracranial penetration injury only represents a small fraction of head trauma, it is safe to say that in many cases, the severity of penetration injury is worse than any other types of head trauma.

Based on its biomechanics, penetration injury could cause devastating impacts on the brain and spine through 4 mechanisms [15, 16]:

1. **Laceration of soft tissue and bone fragmentation**

   As the penetrating object enters the brain cavity through its surroundings, laceration of the cortex by both the penetrating object and bone fragments will cause an irreversible injury to the brain cortex.

2. **Bleeding**
   One of the main results from brain laceration that could lead to a fatal conclusion is bleeding. Injury to the main brain vessels would cause intracranial bleeding that has the potentials to create mass effect, resulting in brain herniation and death.
3. **Shockwaves**
   As the object penetrates the brain, it creates shockwaves throughout the surrounding tissue, that could potentially cause injuries to small capillaries and the brain tissue itself.
4. **Cavitation**
   Lastly, penetration would create a cavity that might be important as a site of entry for any pathogens.

Likewise, in the case of penetration injury, prompt diagnosis is imperative to plan surgical strategies. Thus, it is very important to obtain information regarding the time and mechanism of injury, along with the details of the penetrating object. In many publications, gunshot has been identified as the etiology in many penetration injury incidences [17–19]. In the case of gunshot wound, surgeons should always consider the existence of projectile fragments in other brain area that could potentially cause brain injury and focal hematoma. Additionally, it is also important to inspect other important parts of the body, such as neck and chest. Injury to major blood vessels in those areas might be more life threatening than the intracranial injury itself [15].

As soon as the patient's condition is stable, imaging on the intracranial penetrating injury is imperative. Non contrast head CT scan is the standard choice of imaging in penetration injury, although when necessary, CT angiography (CTA) might offer a better overview of the potential damages to the brain vasculatures. For obvious reason, MRI should never be performed in cases of penetration injury by metal objects, such as bullet and knife [20, 21] (Fig. 3).

Prophylactic antibiotics and analgesics are the standard treatments in penetration injury. Anticonvulsants, such as Phenytoin and Phenobarbital, are also be important as continuous irritation by penetrating object(s) could induce seizure that is not only harmful for the brain, but could make the penetrating object becomes unstable and migrate. Additionally, procoagulants, such as recombinant factor VIIa (rFVIIa) and prothrombin complex, have been suggested to be used as an adjunctive therapy in patients with penetration injury [15, 22–24].

Surgery in penetration injury have 3 main objectives, including: (1) Extraction of the penetrating object(s), (2) Evacuation of the hematoma, (3) Bleeding control. In order to achieve these main goals, preoperatively, the neurosurgeons have to identify all features showed on the imaging, including the location of the penetrating object(s), the presence of hematoma, and other impacts of the penetration injury on brain structures (i.e. cerebral edema, midline shifts, etc.) [15]. Intraoperatively, the neurosurgeon must first expose the brain area that was identified as the entry and exit sites, before extraction of penetrating object(s) could be performed. In a patient with > 1 lesion in the brain, prioritization must be made to evacuate the hematoma and penetrating object that potentially lead to mortality/morbidity.

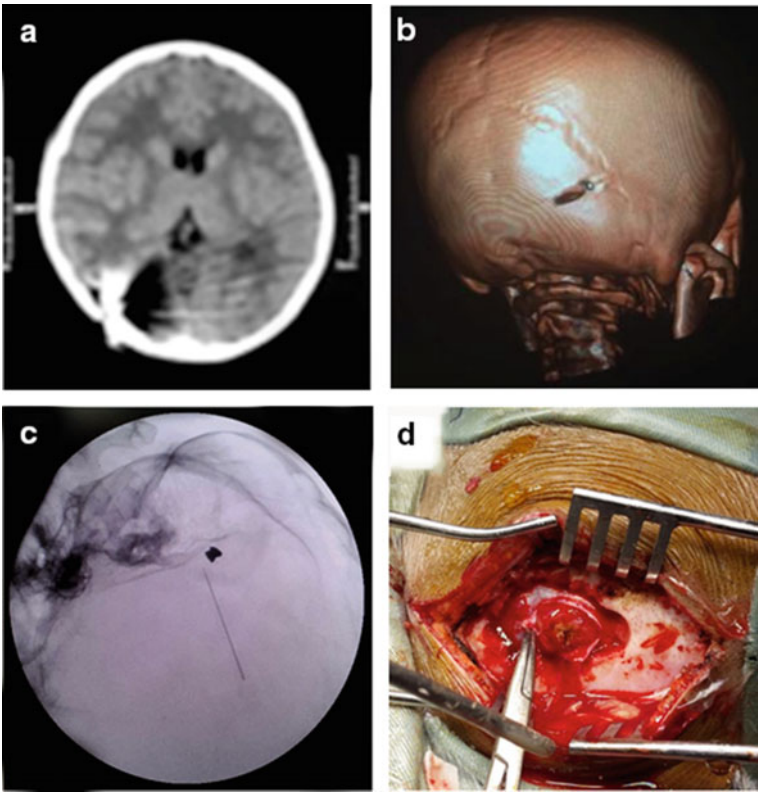

Fig. 3 A 10-year-old girl was accidentally shot by her neighbor using an air riffle. **a** A non-contrast head CT scan identified a hyperdense mass at right occipital lobe, **b** 3D-bone reconstruction confirmed the inlet of bullet just below the right lambdoid suture. **c** Plain radiology using C-Arm identified the exact location of the bullet. **d** After opening the bone and exposing the bullet and its surrounding tissue, bullet extraction and bleeding control should be performed as soon as possible. (*Courtesy of Selfy Oswari, MD*)

3 Case Presentation

In case 1 (Fig. 3), 2 hours prior to admission, a 10-year-old girl was playing at a communal playing ground in an over-populated area, when suddenly, her neighbor accidentally fired an air rifle. She was then rushed into our hospital, and initial physical examination identified the entry site of an air rifle bullet at the occipital bone, suggesting that there might be an ongoing bleeding in her posterior fossa. CT-scan imaging and 3D-Bone reconstruction confirmed the bullet position in right occipital lobe and its entry site, although the detail of its location in the brain could not be confirmed due to the metal reflection. Neither hematoma nor midline shift

were identified on the CT-scan images. Despite her injury, she was fully conscious (GCS 15) when admitted, and retained her GCS score until she was transported into the operating theatre. Preoperative plain radiology obtained by the C-Arm showed that the bullet just missed all the major sinuses and blood vessels. After bone removal and incision of the dura, the entry site of the bullet on the brain could be fully exposed, thus bullet extraction continued with bleeding control could be performed. The patient gained full consciousness immediately after surgery. She was hospitalized for 5 days, then sent home without any complications.

In case 2 (Fig. 4), 5 hours prior to admission, a 14-year-old boy rode a motorcycle at medium speed without using helmet. With no obvious reason, he suddenly slipped and struck a bamboo fence of a house at his left, and had a bamboo stick pierced into his left forehead. He was rushed into a nearby hospital where he was intubated and had the penetrating object stabilized. Then, he was referred to our hospital, underwent non-contrast head CT scan. CT scan images showed that the penetrating object had caused intraventricular hematoma and intracerebral hemorrhage at his right frontal and parietal lobes, along with midline shift > 5 mm to the left. His GCS at admission was 5, and his hemodynamic status was unstable. Nonetheless, since no other significant injuries was identified, and his intracranial bleeding was suspected as the main cause for his instability, he was rushed into the operating theatre to undergo craniectomy evacuation procedure. Despite uneventful surgery, he never gained consciousness afterwards and later succumbed to his injuries after being treated at the intensive ward for 3 days (Fig. 4).

Our experiences in these 2 cases confirmed indicate that time interval, GCS at admission, existence of hematoma and midline shifts were decisive factors on the outcome of patients with penetrating injury.

In patients who survived penetration injury, continuous rehabilitation holds key to gain optimum functional recovery. Furthermore, long term evaluation to identify any late complications from penetration injury, such as intracranial aneurysm, is important to preserve patients' lives and well-being.

4 Traumatic Intracranial Aneursym

Traumatic intracranial aneurysm (TICA) is rare, represents approximately 1% of the total prevalence of intracranial aneurysms (IAs) [25]. However, the prevalence of TIA in pediatric patients constitute approximately 30% of total prevalence of IA in pediatric patients itself [26]. Its risk of mortality and morbidity underlines the necessity of long term follow up in pediatric patients with history of trauma [25]. Based on the physiological anatomy features, children are arguably more liable to the formation of TICA as their cranial bones are relatively softer, with intracranial structures that are more mobile than the adults.

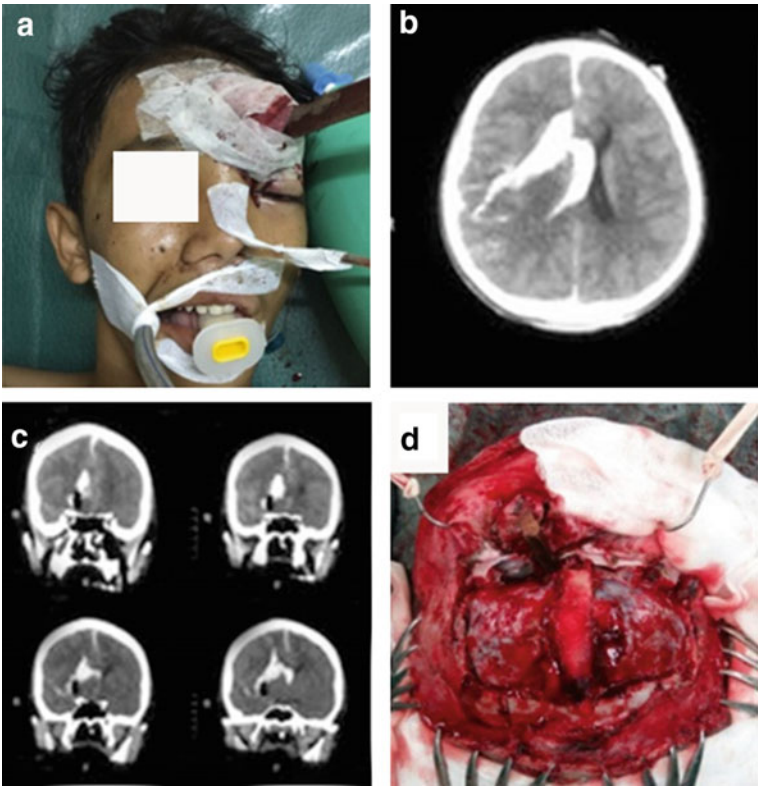

Fig. 4 Another example case of penetration injury was presented when a 14-year-old boy hit a bamboo fence after his motorcycle was accidentally slipped. **a** The bamboo came through his left forehead, **b** and **c** causing massive hemorrhage in his right frontal, temporal, parietal lobes, along with his right lateral ventricle. **d** After exposing the bone and its surrounding tissue, the bamboo stick was extracted and bleeding was controlled. Despite successful surgery, he later died at the intensive care unit. (*Courtesy of Ahmad Faried, MD, PhD*)

In brief, TICA is characterized by the weakness of intracranial blood vessel walls due to past history of trauma. Based on its histopathological findings, IAs can be classified into 3 types, including (1) True aneurysm, (2) Pseudoaneurysm, and (3) Mixed type aneurysm [27]. True aneurysm is characterized by the disruption of intimal layer, with variable involvement of medial layer and its internal elastic lamina, causing dilation of the remaining intact layer and intraluminal dynamic changes. Conversely, pseudoaneurysm is characterized by complete disruption of the arterial walls, commonly associated with a formed hematoma outside the vessel walls, leading to aneurysmal dilation of the vessel itself. Mixed type is defined as a ruptured true aneurysm, causing a formation of hematoma outside the vessel wall, leading to false lumen appearance. The histopathological characteristics of IAs

represent the mechanism of IA formation itself, thus it is logical to say that the histopathological characteristics of TIA fit into pseudoaneurysm [28, 29].

Many publications have elucidated the common causes of injury, such as traffic accidents, fall, sports-related, or even war injury. Regardless of the activities, based on the mechanism of injury itself, etiologies of TICA in pediatric patients can be divided into 3 main categories, including (1) Blunt trauma/closed head injury, (2) Penetration injury, and (3) Iatrogenic injury [30]. In most cases, the etiology of TICA can be immediately identified from anamnesis.

Like in any other types of IA, majority of patients with TICA are presented with subarachnoid hemorrhage. Furthermore, unique signs such as sudden unilateral blindness, neurological deficits, extreme headache and epistaxis might strongly suggest rupture of TICA. The time interval between the injury and onset of symptoms of TICA might ranges from weeks to years, thus it might be challenging to confirm the diagnosis of TICA in cases where symptoms occurred years after the injury.

Confirmation of the presence of intracranial aneurysm can only be made with angiography. At this moment, digital subtraction angiography (DSA) is arguably the ideal angiography technique. However, the use of general anesthesia and elaborate instruments have made this procedure can only be performed at centers with sufficient facilities [31]. Arguably, the easiest angiography technique to date is CTA. It has been known that CTA could be used to identify small aneurysms and arterial dissections. Compared to any other angiography procedures, CTA is relatively faster. Nonetheless, the risks that are acquired in children who are exposed to CTA radiation has to be considered carefully. As an alternative, MRA could be the choice of angiography, particularly in very small children. The drawbacks of MRA are the possible need of sedation to enable MRA imaging that is usually takes longer time than CTA [31, 32].

Once the presence of IA is confirmed, the decision to perform endovascular surgery or clipping is up to the surgeon's preference. Like any other surgical techniques, both endovascular and clipping have pros and cons. It is tempting to say that endovascular surgery might offer a more-minimal-invasive technique. Nonetheless, on the hands of an experienced open vascular surgeon, the risks of bleeding and infection could be minimized.

After surgery, it has been suggested that patients should undergo a routine follow up, involving routine angiography. Consequently, repetitive CTA would cause an increased radiation exposure, Thus, it has been advised to perform MRA, instead of CTA, when possible during follow up imaging. However, in patients who have their aneurysms clipped, MRA is contraindicated. When MRA produces images of poor quality, DSA is recommended.

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Vascular Malformations of the Brain—Overview and Classification

W. Caleb Rutledge, Kurtis I. Auguste, and Michael T. Lawton

1 Introduction

Vascular malformations of the brain are a heterogeneous group of disorders, including arteriovenous malformations (AVMs), arteriovenous fistulas (AVFs), cavernous malformations (CMs), telangiectasias and developmental venous anomalies. AVMs and AVFs shunt blood from the arterial to the venous circulation, while CMs, telangiectasias and developmental venous anomalies are non-shunting. While adults and older children with vascular malformations commonly present with headaches, hemorrhage, seizures or focal neurologic deficits, neonates, infants and young children may present with congestive heart failure (CHF) and multiorgan failure, intracranial hemorrhage, seizures, macrocephaly, hydrocephalus and developmental delay.

2 Arteriovenous Malformation

An AVM is a tangle of abnormal vessels or nidus, which is composed of dilated feeding arteries and arterialized draining veins without intervening capillaries that form a high-flow, low-resistance shunt (Fig. 1). AVMs have long been considered congenital lesions, arising from errors during embryogenesis when arteries and veins are without intervening capillaries, but their pathogenesis is not well understood. Most are solitary and occur sporadically without a clear genetic basis. In

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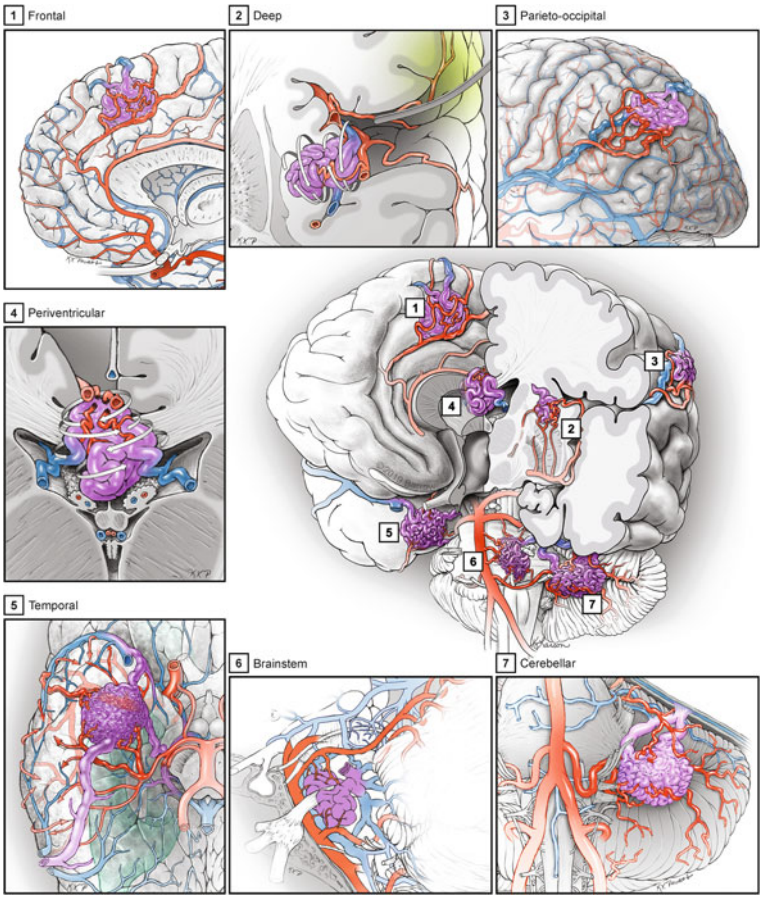

Fig. 1 AVM taxonomy. Although size, shape, and location make AVMs infinitely variable and unique, 32 anatomical categories exist based on their 7 locations: (1) frontal lobe; (2) deep (basal ganglia and thalamus); (3) parieto-occipital lobes; (4) periventricular/ventricular; (5) temporal lobes; (6) brainstem; and (7) cerebellum and the brain surface on which they are based (e.g., lateral, medial, basal, sylvian, and paramedian surfaces in the frontal lobe). Like genus and species that characterize animals, AVM type (location) and subtype (surface) characterize AVMs in a taxonomy that deciphers pathological anatomy and defines surgical strategy. Center image used with permission from Barrow Neurological Institute, Phoenix, Arizona. Parts 1-7 are from Lawton MT: *Seven AVMs: Tenets and Techniques for Resection*, Thieme, 2014 (reprinted with permission)

contrast, multiple AVMs usually signal an underlying genetic syndrome, such as Hereditary Hemorrhagic Telangiectasia (HHT), an autosomal dominant disorder characterized by mucocutaneous telangiectases and AVMs of major organs like lung, liver, and brain. Brain AVMs frequently occur in HHT type 1 from mutation in endoglin, a transforming growth factor- β (*TGF- β*) co-receptor.

The overall incidence of ruptured and unruptured AVMs is about 1 per 100,000 person-years. Peak presentation is in young adulthood during the second and third decade of life, but as many as 25% present during childhood [1]. Patients present

with headaches, hemorrhage, seizures or focal neurologic deficits from mass effect. Children may be more likely to present with hemorrhage, despite absence of high-risk features including venous ectasia and feeding artery aneurysms [2]. The presence of a single draining vein or deep venous drainage, particularly in smaller AVMs, increases the risk of hemorrhage in children [3, 4]. Once ruptured, the risk of another hemorrhage increases significantly [5, 6]. However, children with AVM hemorrhage often have better outcomes and are more likely to make a functional recovery than adult patients [7].

AVMs are classified using the Spetzler-Martin and Lawton-Young grading systems. Both grading systems estimate the risk of surgery. The Spetzler-Martin system includes size, eloquence of surrounding brain and venous drainage patterns [8]. The Lawton-Young system supplements the traditional Spetzler-Martin system by incorporating additional factors important to surgical selection and outcome, including patient age, hemorrhagic presentation and compactness [9, 10]. More recently, Lawton described 7 types of AVMs depending on their location in the brain—frontal, temporal and parietal-occipital lobes, ventricles, deep central core, brainstem and cerebellum (Fig. 1). Within each type of AVM are subtypes defined by the brain surface on which the AVM is based, with each subtype characterized by unique arterial supply, draining veins, eloquent surrounding structures, surgical approach, and management strategy. As examples, temporal lobe AVMs are subtyped into lateral, medial, basal and Sylvian subtypes, and cerebellar AVMs are subtyped into subocciptal, tentorial, vermian, petrosal, and tonsillar subtypes. With this new classification, the broad spectrum of brain AVMs is simplified to 32 different AVM subtypes, which is meant to inform the learning and descriptive processes and guide surgical planning.

Management of unruptured AVMs is controversial as the risk of treatment-associated morbidity and mortality must be weighed against the risk of spontaneous hemorrhage [11]. Conservative management includes anticonvulsants for patients with seizures, but currently there are no medications to prevent hemorrhage. Initial hemorrhage is the strongest predictor of future hemorrhage, but associated aneurysms, deep location, exclusively deep venous drainage and increasing patient age also increase the risk of hemorrhage [6, 12–15].

Modern management of AVMs is multimodal and includes microsurgical resection, endovascular embolization and stereotactic radiosurgery in addition to conservative observation [16–21]. Microsurgery remains the mainstay of treatment, as outcomes in patients with favorable grades are excellent [22–24]. Children may have better outcomes than adults after microsurgical resection of AVMs [25]. Endovascular embolization is most commonly used as preoperative adjunct to microsurgical resection. Stereotactic radiosurgery is an alternative to microsurgical resection, particularly for small AVMs with a single draining vein [26], but patients remain at risk of hemorrhage during the latency period and may experience delayed adverse radiation effects [16, 27]. Volume-staged radiosurgery is an option for high-grade AVMs not amenable to microsurgical resection or conventional single-session stereotactic radiosurgery [28]. Regardless of treatment, the goal is obliteration of the AVM and elimination of the risk of future hemorrhage.

In adults, complete angiographic obliteration is curative and eliminates the risk of future hemorrhage. However, in pediatric patients there is a small risk of AVM recurrence, even after angiographic obliteration [29–32]. Diffuse AVMs may be more likely to recur [30, 33]. Most recurrences are detected within a year of treatment [30, 33]. Thus, follow-up angiography is crucial to detect recurrences in children.

3 Dural Arteriovenous Fistulas

Dural arteriovenous fistulas (dAVFs) are less common than AVMs and a rare cause of intraparenchymal hemorrhage. Like AVMs, there is an abnormal connection between meningeal arteries and dural venous sinuses or cortical veins, but dAVFs lack a true nidus. Feeding arteries are derived from either pia or dura. The most common location is the junction of the transverse and sigmoid sinus, but dAVFs also occur at other locations including the cavernous sinus, tentorium, superior sagittal sinus and anterior cranial fossa.

dAVFs are classified according to pattern of venous drainage in the Borden and Cognard classifications [34, 35]. The key feature is direction of venous drainage. Borden type I dAVFs drain directly into dural venous sinuses or meningeal veins with no cortical venous drainage. Similarly type II lesions drain into dural venous sinuses or meningeal veins, but also have retrograde drainage into cortical subarachnoid veins. Borden type III dAVFs drain directly into cortical subarachnoid veins. Cognard described five types of dAVFs based on the direction of venous drainage, but also type of venous outflow (nonectatic vs ectactic). Cognard type I dAVFs have anterograde flow only. Type II dAVFs reflux into the sinus (IIa), cortical veins (IIb) or both (IIa + b), while type III fistulas have direct cortical venous drainage without venous ectasia and type IV dAVFs have direct cortical venous drainage and ectasia. Finally type V dAVFs have spinal venous drainage.

Most dAVFs have a benign clinical course with some even spontaneously regressing, but others cause symptoms such as an audible bruit or intraparenchymal hemorrhage from rupture, although patients with hemorrhage from rupture of dAVF may have a lower morbidity and mortality than patients with intraparenchymal hemorrhage from other causes [36]. Patients with high-grade lesions with cortical venous drainage are at highest risk of hemorrhage [37]. Symptomatic patients and those with anterior cranial fossa or tentorial dAVFs often have cortical venous drainage and are at higher risk for hemorrhage or progressive neurologic deficits, while transverse-sigmoid and cavernous sinus dAVFs are most often benign [38]. dAVFs may result in high-output heart failure, developmental delay and obstructive hydrocephalus in children. Children with dAVFs may be more likely to have progressive enlarging or recurrent fistulas [39].

Treatment of AVFs is also multimodal and includes microsurgical resection, endovascular embolization with liquid embolic agents such as Onyx, and stereotactic radiosurgery for lesions refractory to surgical or endovascular treatment. The

goal of treatment is occlusion of the fistula or disconnection of the feeding arteries and draining veins. Endovascular embolization is safe, effective and curative for the majority of dAVFs and is usually considered as the first-line treatment, with surgery reserved for those that are not completely obliterated endovascularly [40–44]. Recurrence following angiographic cure in patients treated with Onyx embolization can occur, and long-term follow-up is recommended [45]. Clinical outcomes in children with dAVFs undergoing endovascular or combined endovascular and surgical treatment are excellent [46–49]. Workup for underlying genetic syndromes or hypercoagulability is indicated.

4 Cavernous Malformations

Along with AVMs, CMs are common vascular malformations of the brain, and up to 25% of CMs occur in children (Fig. 2). They are discrete lesions, composed of thin-walled, endothelial-lined caverns filled with blood, but devoid of smooth muscle or intervening brain parenchyma. Like AVMs, they often occur sporadically as solitary lesions, but may be multiple and inherited. Familial cases are inherited in an autosomal dominant manner due to mutations in *CCM1*, *CCM2* and *CCM3* genes. Acquired CMs are far less common, but may develop in children after whole brain radiation therapy.

Microsurgical resection is the treatment of choice for symptomatic patients. Resection of pediatric CMs is safe and effective with low rates of recurrence and excellent seizure control, particularly for supratentorial lobar lesions [50–53]. Resection of brainstem CMs is associated with higher surgical morbidity and mortality; however, new deficits from recurrent hemorrhage arise in children managed conservatively [54–57].

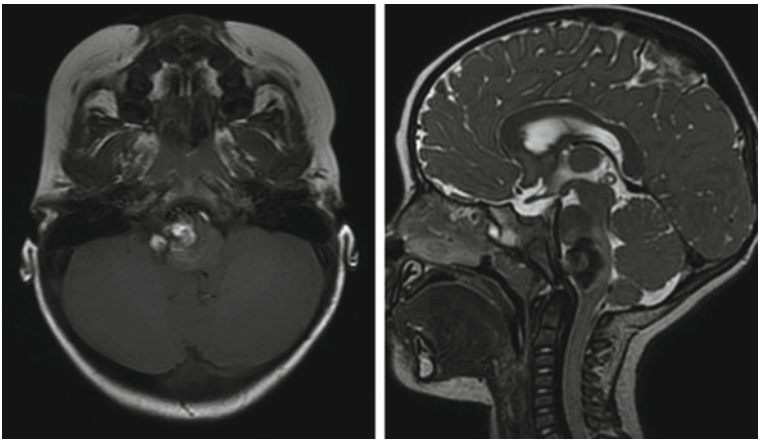

Fig. 2 Axial T1 (left) and Sagittal T2 (right) weighted magnetic resonance images showing 2.5 cm pontomedullary cavernous malformation in a two year-old female who presented with left hemiparesis and cranial neuropathies

5 Vein of Galen Malformation

Veins of Galen malformations are rare congenital vascular malformations occurring in the choroidal fissure. They are characterized by multiple arteriovenous shunts draining into a dilated median prosencephalic vein of Markowski, the embryonic precursor of the vein of Galen. They are most frequently diagnosed in neonates and infants with high-output CHF or seizures, or in young children with macrocephaly, hydrocephalus or developmental delay. Endovascular embolization using n-butyl cyanoacrylate (NBCA) or liquid embolic agents such as Onyx is the primary treatment modality [58, 59]. Treatment is generally delayed until 6 months of age. Many treated children now survive with normal neurologic development.

6 Conclusions

Vascular malformations of the brain are an important cause of stroke and early morbidity and mortality in children and young adults. AVMs and CMs are the most common vascular malformations in children. While adults commonly present with headache or focal neurologic deficits from hemorrhage or mass effect, infants and young children more commonly present with CHF, macrocephaly, hydrocephalus or seizures. Screening for underlying genetic syndromes or hypercoagulability is indicated. While many vascular malformations are benign, some patients may be symptomatic or at high risk of hemorrhage. Treatment is safe, effective and curative in appropriately selected patients.

Pearls.

- Vascular malformations of the brain are an important cause of stroke and early morbidity and mortality in children and adults.
- Their pathogenesis is not well understood and they may be congenital or acquired. Workup for underlying genetic syndromes or hypercoagulability is indicated in infants and children.
- AVMs and AVFs are characterized by abnormal connections between arteries and veins and shunt blood from the arterial to venous circulation.
- Infants with vascular malformations of the brain causing arteriovenous shunting may present with congestive heart failure, macrocephaly, hydrocephalus or seizures.
- AVMs are classified using the Spetzler-Martin or Lawton-Young Supplemental grading scale.
- Microsurgical resection is the treatment of choice for appropriately selected patients with low-grade AVMs and is safe and effective in children.
- dAVFs are classified using the Borden or Cognard classifications according to pattern of venous drainage. dAVFs with cortical venous reflux are at higher risk of hemorrhage.

- Endovascular embolization with Onyx is safe, effective, and may be curative in children with dAVFs, but surgery should be considered when endovascular occlusion is incomplete.
- Cavernous malformations are non-shunting lesions that nonetheless have associated hemorrhagic risk, making microsurgical resection the treatment of choice in symptomatic patients.

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Pediatric Intracranial Dural Arteriovenous Fistulas

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1 Introduction

Intracranial DAVFs is defined by an abnormal connection between dural artery and a dural venous sinus or cortical vein, without an intervening capillary channel or nidus [1, 2]. The majority of DAVFs are located in the torcula, transverse sinus, superior sagittal sinus, and cavernous sinus [2]. In addition to brain AV malformation (BAVMs), pial AV fistulas (PAVFs), and vein of Galen aneurysmal malformations (VGAMs), DAVFs is another intracranial arteriovenous (AV) type that could occur in children [3]. Despite its rarity in children, pediatric DAFVs exhibits a more aggressive clinical course than the adult's DAFVs, thus it could lead to patients' developmental delay and cognitive decline, or even death due to high-output cardiac failure [4, 5]. Although the treatment of pediatric intracranial DAVFs is largely similar to its treatment in adults, it features several principal difference, particularly on the aim to reduce or block the shunt, while also preserving the draining sinus in the affected children [5].

2 Epidemiology

Spontaneous DAVFs are extremely rare in children [2, 4, 6], hence it is difficult to confirm its incidence and prevalence [7]. Nonetheless, DAVFs is suspected to constitutes approximately 5–10% of all intracranial shunts in pediatric population [2, 7, 8]. In 2017, The Japanese Pediatric Arteriovenous Shunts Study (JPAS)

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reported the annual prevalence of DAVFs in patients aged 5 years old or younger were 0.0323 per 100,000 persons [9].

3 Pathogenesis

The pathogenesis of pediatric intracranial DAVFs remained unclear. Nevertheless, there are two hypotheses that have been widely considered as its possible pathogenesis. The first hypothesis stated that DAVFs arise from "dormant" channels between the external carotid circulation and the duramater venous pathways that are opened consequently after venous hypertension. The second hypothesis suggested that the formation of new vascular channels are stimulated by angiogenic factors that are highly elevated at the site of sinus thrombosis, or formed as a result of tissue hypoxia [2]. The important role of both sinus thrombosis and sinus hypertension in the pathogenesis of DAVFs has been elegantly [10]. It has also been theorized that venous thrombosis during fetal life promotes the formation of one or more DAVFs prior to birth [8].

3.1 Risk Factors

Like any other congenital entities, risk factors in development of pediatric intracranial DAVFs are suspected of genetic and/or environmental. Mutations in some disease-causing genes had been reported incases of pediatric DAVFs, including intracranial high-flow AVSs in RAS p21 protein activator 1 (RASA1) mutations and frameshift mutation of the phosphatase and tensin homolog (PTEN) tumor-suppressor gene [11, 12]. Arteriovenous shunts have also been associated with hereditary conditions, such as hereditary hemorrhagic telangiectasia, craniofacial arteriovenous metameric syndrome, and cavernous malformation [2, 4, 5, 13, 14].

Hypercoagulable states, are often identified leukemia patients, are also risk factors for sinus thrombosis thus could potentially induced formation of DAVFs. Trauma whether in accidents or iatrogenic, is another known risk factor for the development of DAVFs [2]. Iatrogenic factor, such as after endovascular treatment or craniotomy, mightprompt hemodynamic changes that leads to the formation of DAVFs [15, 16]. Principally, obstructions of the natural venous outflow cause collateral circulation through crack-like vessels that lead to DAVF formation [17].

4 Classification

Based on its anatomical and clinical aspects, Lasjaunias subdivided pediatric intracranial DVT DAVFs into 3 groups, based on anatomical and clinical aspects: Dural Sinus Malformation (DSM), Infantile-type Dural Arteriovenous Shunts (IDAVS), and Adult-type of Dural Arteriovenous Shunts (ADAVS).

1. **Dural Sinus Malformations (DSMs)**

   DSM with AV shunts are commonly identified in antenatal and perinatal periods [9]. The Majority of DSMs cases are revealed in the first few month thus it has been suspected to be the consequences of failures in the embryological development of the dural sinuses. In theses cases, DSMs are regarded as true congenital lesions, in which the arteriovenous shunts are secondary, and/or accessory to the sinus malformation [3, 6]. Morphologically, it is presented as focally dilated and bulging dural sinus ectasias [3]. Based on the involved sinuses, it is subdivided into 2 types [6]. The first type involves the posterior sinus with or without the torcula, with giant dural lakes and slow-flow mural arteriovenous shunt. Spontaneous thrombosis may further restrict cerebral venous drainage, subsequently lead to intraparenchymal hemorrhagic infarction. The second type of DSM involves the jugular bulb with otherwise normal sinuses, but associated with a high-flow sigmoid sinus AVF [6].
2. **Infantile Dural Arteriovenous Shunts (IDAVS)**
   In a review by Barbosa et al. [7], of 52 cases of intracranial pediatric DAVFs reported from 1985 to 2003, Infantile Dural AV Shunts (IDAVS) was the most frequent subtype. IDAVS are characterized by high flow and low-pressure shunt. Anatomically, the sinuses are large with no lakes and remained patent for a long period. Clinical onset is usually acknowledge in the first few years of life, and the shunts are initially well tolerated. Progressive symptoms due to raised intracranial pressure and venous ischemia would develop at later age and, in the majority of cases, initially respond to partial embolization. However, its long-term prognosis is poor with neurological deterioration is commonly identified in early adulthood [6].
3. **Adult-type Dural Arteriovenous Shunts (ADAVS)**
   Despite what the term implies, adult-type dural arteriovenous shunts (ADAVS) could occur in all age groups. In majority of cases, it occurs in the cavernous venous plexus. Clinically, no event is known to potentially trigger pediatric dural AV shunts [6].

4.1 Venous Drainage Classification

The pattern of DAVF venous drainage could suggest the severity of symptoms and provides the foundation for the classification schemes. The most commonly used classifications are the simplified Borden and the Cognard classifications [18–20] (Fig. 1 and Tables 1 and 2).

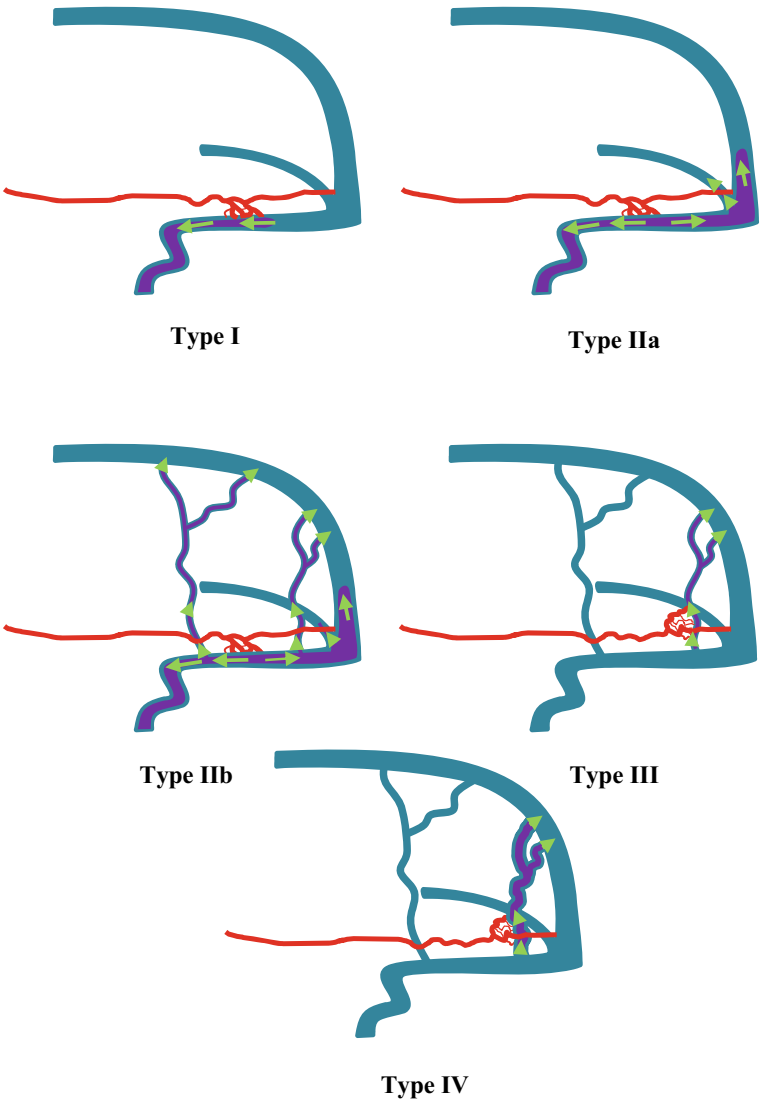

Fig. 1 Cognard classification of dural AVF. Flow directions are indicated by green arrows and venous arterializations areaare marked by purple shade

Table 1 Simplified Borden Classification

Type	Venous drainage
I	Drains directly into the dural venous sinus or meningeal vein
II	Drains into the venous sinuses with retrograde drainage into the subarachnoid veins
III	Drains directly to subarachnoid veins

Table 2 Cognard Classification

Type	Venous drainage
I	Anterograde drainage into venous sinus
IIa	Venous drainage into dural sinus with retrograde flow
IIb	Venous drainage into dural sinus with normal anterograde flow and cortical venous drainage
IIa + B	Venous drainage into dural sinus with retrograde flow and cortical venous drainage
III	Venous drainage into subarachnoid vein (CVD only)
IV	Direct venous drainage into subarachnoid vein with venous ectasia
V	Direct venous drainage into spinal perimedullar vermis

5 Clinical Presentation

Clinically, pediatric patients with DAVFs could be presented with various symptoms in accordance to the age groups. Mostly, neonate patients are presented with congestive heart failure, respiratory failure, and hydrocephalus. Meanwhile, hemorrhage is not a common presentation in infants or neonates with DAFVs. Clinical presentations in later age are including seizures, developmental delays, focal neurological deficits, and hemorrhage [2]. Principally, these clinical presentations depend on hemodynamic disturbances, including high-flowsteal, venous drainage occlusion, and mass effects [21].

As previously mentioned, Pediatric DAVFs might be dormant prior to the occurrence of the progressive symptoms. This might be due to the persistence of high flow within the pial induced shunts and progressive outlet restriction during skull base development with jugular stenosis or even occlusion [5].

6 Evaluation

6.1 Examination

Head circumference measurement, funduscopic examination, and complete neurological examination are mandatory. Auscultation is performed to identify bruits in the head and neck. Since congestive heart failure is often identified in the neonates, detailed cardiopulmonary examination by cardiologist should also be considered. In older children, developmental assessment should be performed to evaluate any signs of developmental delay.

6.2 Imaging and Diagnostic

Several imaging modalities can be employed to identify pediatric DAFVs, such asultrasonography, CT, CTA, MRI, MRA and DSA. On CT, pediatric DAFVS could identify dilatations of the sinuses, a local mass effect, patchy enhancement, decreased density in the parenchyma, and hydrocephalus [14]. Ultrasonography can be useful at prenatal to diagnose DAVFs as early as possible [22, 23]. MR arteriography and MR venography might also be performed to identify the vascular structures of pediatric DAFVs. An early diagnosis based on MR imaging is essential to determine the prognosis and potential treatment options as MR venography can identify thrombosis and stenosis in the draining veins and sinuses.

CT Angiography might be useful to plan surgical treatment by precisely defining the arteriovenous shunt relatives to the surrounding brain and skull structures [24, 25]. However, the gold standard for pediatric DAVFs is Digital Subtraction Angiography (DSA).The current diagnostic capabilities of DSA provides more in-depths on the unique anatomy and hemodynamic compared to other imaging modalities [1, 2, 5, 26].

7 Treatment

Treatment on DAVFs is a complete aims to completely obliterate the lesion, resulting in normal development of the affected child without any neurological deficits [27]. Recent studies suggested pediatric patients with DAFVs to be managed by multimodal treatments, including endovascular embolization, open surgery, and stereotactic radiosurgery (SRS) [1, 4, 9].

7.1 Endovascular Intervention

Endovascular intervention is often considered as the main treatment option in DAFVs treatment [1, 2, 5, 28]. Endovascular therapy should focus on the specific

area of shunting that is suspected to have caused the clinical symptoms in patients. In infants with cardiac decompensation, the area of highest arteriovenous shunting should be embolized first [28].

Various endovascular materials can be employed to treat pediatric DAVFs, including coils, particulate embolic, liquid adhesives, absolute ethanol, detachable balloons, and silk suture [2]. In recent years, Onyx, a liquid embolization agent, has has been suggested to have improved the therapeutic results of DAVFs [5]. However, the selection of materials is patient-specific and surgeon-preference. Some surgeons preferredembolization as the treatment option, and this might be life-saving in the setting of neonatal congestive heart failure [1, 28]. Meanwhile, other surgeons would choose to use coils [2]. In certain cases, endovascular embolization might be performed in several stages, in combination with coils to achieve gradual closure of the shunt and provide time for sinus remodeling [2, 29]. Regardless, optimum outcomes can only be acquired after complete occlusion of the involved venous sinus [28].

7.2 Surgery

Prior to the advancement of endovascular techniques, treatment of intracranial DAFVs was primarily dominated by open surgery to excise the fistula entirely [1, 30]. Nowadays, the current surgical strategy involves disconnecting the venous drainage from the fistula. This is arguably a simpler procedure that carries much lower risks of morbidity compared to the earlier techniques. This procedure involves exposure of the fistula, coagulation of the arterial feeders and arterialized veins that are close to the fistula [30]. Surgery is usually reserved for cases in which endovascular therapy fails or not doable due to the difficult access to the fistula site [2].

7.3 Stereotactic Radiosurgery

Stereotactic radiosurgery has been showed to be a promising adjunct therapy for intracranial DAVFs along with open neurosurgical resection or endovascular treatment in adults [31, 32]. However, the literatures in support of efficacy of radiosurgery in pediatric patients are scarce. Hetts et al. [2] suggested that stereotactic radiosurgery is unable to induce regression of large caliber fistulas, thus should only be performed if endovascular therapy fails or not possible.

8 Case Presentation

A 10-month-old baby boy was presented with decreased consciousness that was preceded with generalized seizure. Head non contrast computed tomography (CT) scan identified a non obstructive hydrocephalus. He underwent VP shunt, then

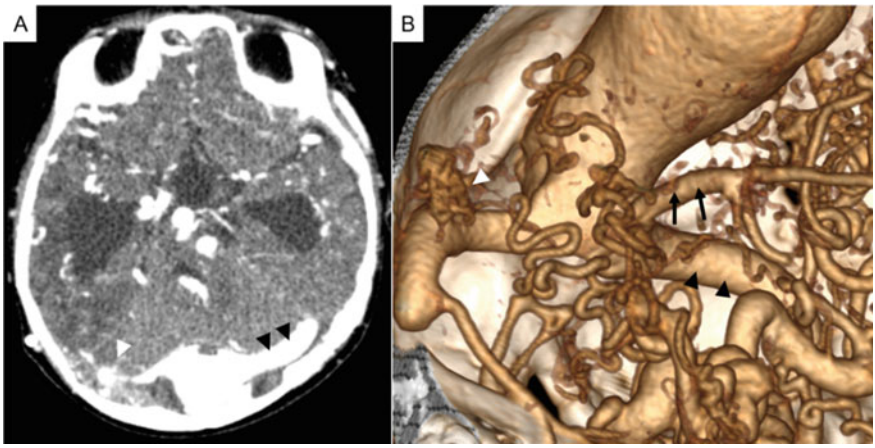

Fig. 2 Arterial phase of head contrast enhanced CT scan and right anterior view of its three dimensional reconstruction showed the connection between the distal branches of posterior cerebral artery with the right transverse sinus (white arrowhead). Further evaluation revealed retrogade filling to the enlarged straight sinus (black arrow), contralateral transverse and sigmoid sinus (black arrowhead). Note the decreased parenchymal density and patchy enhancement on the axial cut CT scan

subsequently underwent contrast enhanced CT scan. The imaging results from the arterial phase showed marked enlargement of superior sagital sinus (SSS) with enlarged and turtous subarachnoid artery. Three dimensional reconstruction of the images identified a Cognard IIa dAVF to the right transverse sinus. Further assessment revealed retrogade filling to the enlarged straight sinus, contralateral transverse and sigmoid sinus, along with a more significantly enlarged posterior third segment of the SSS to the torcula. Nonetheless, the right sigmoid sinus could not beacknowledgedin this study, possibly due to the left sided flow dominance (Fig. 2).

External view showed the injection from superior temporal artery branch to the SSS, with enlarged left mastoid emmisary vein, possibly due to venous arterialization. High dural sinus pressure caused by the fistula might disturb the normal pressure gradient from the subarachnoid space to the sinuses via arachnoid granulation, consequently caused cerebrospinal fluid malabsorption and hydrocephalus. Arterial access is difficult in this patient, thus we decided not to perform any endovascular approach since the risk of bleeding and stroke is high. Other alternative is to access the fistula via transvenous approach. However, after having considered every aspect, we decided to wait and observe the clinical status of this patient. The patient was fully recovered after hospitalized for a month, and currently, he is routinely observed at the outpatient clinic. Since this patient has the tendency to experience seizure, antiepileptic drug was prescribed and his family was given the information about seizure management and the risk of developmental delay (Fig. 3).

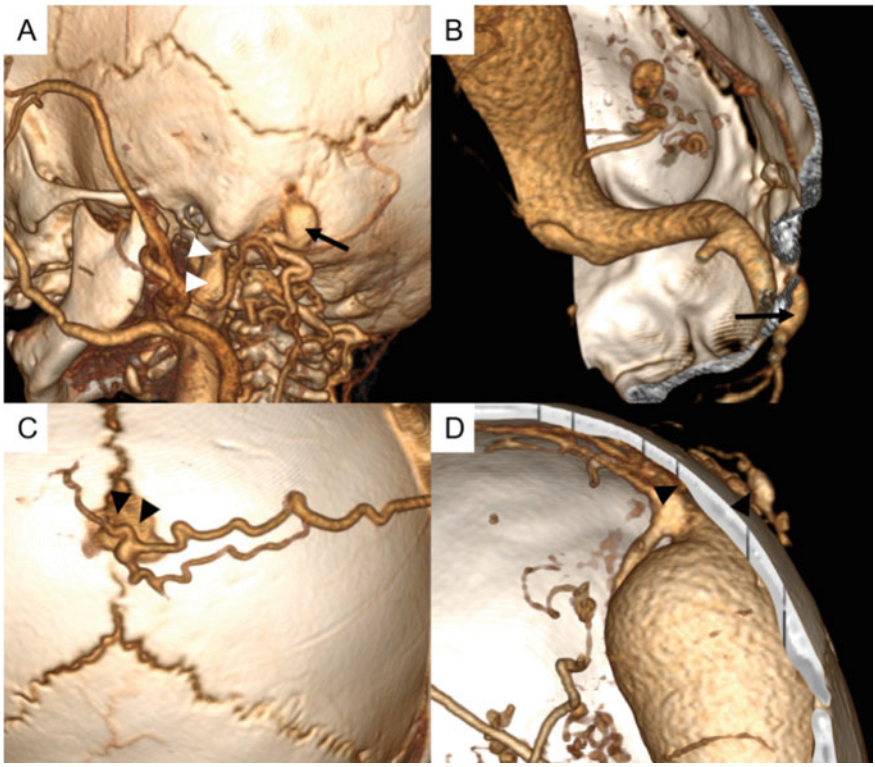

Fig. 3 External view showed the injection from superior temporal artery branch to the SSS (black arrowhead), with an enlarged left mastoid emmisary vein (black arrow). Note the enlarged jugular vein on figure A (white arrowhead). Figure D showed the connection between STA branch with the SSS on the sagittal cut, viewed form the left

9 Outcomes

In 2016, Hetts et al. [2] reported that in comparison to other pediatric AV shunt lesions, DAVFs patients had lower rates of complete AVF occlusion, lower rates of children with no neurological deficit or developmental delay at last clinical follow-up, and higher rates of death at last known follow-up. Kincaid et al. [28] reported the elimination of arteriovenous shunting in 3/7 patients (43%), no neurological deficit or developmental delay are identified in 2/7 patients (29%), while mortality was noted in 2/7 patients (29%) after endovascular treatment.

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Non-galenic Pediatric Fistulas

Lucas Elijovich

1 Introduction

Arteriovenous malformations of the central nervous system may occur sporadically or as part of syndrome. The presentation, natural history, and treatment paradigms are distinct from adult vascular malformations because of their congenital nature in a developing nervous system. In this review, we will focus on non-galenic arteriovenous fistulas (AVF). We will discuss their distinct angio-archictecture and presentations to provide a guide to the diagnosis and proper management.

2 Embryology of the Cerebral Vasculature and Theory of Pediatric AV Fistulas Vasculogenesis

Understanding the development of the neurovascular system was limited until the early twentieth century. The foundation of our understanding is rooted in the work of Drs. Franklin Mall and George Streeter, and equally importantly the medical illustrator Dorcas Padget. She published seminal work on the embryology of the cranial vascular system based on her dissections of human embryos at various developmental stages. The venous and arterial system development were both organized into 8 fluid but distinct stages [1, 2]. This understanding in conjunction with her collaboration as Walter Dandy's operative illustrator formed the framework to propose the mechanism by which CNS fistulas arise.

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She described the subjacent (perpendicular) orientation of primitive pial arteries to the veins and hypothesized that the failure of the longitudinal primitive anastomotic veins to regress would result in AVFs. Her clinical experience illustrating Dandy's neurovascular surgeries allowed her to understand the hemodynamic consequences of these errors and to predict the "downstream effects" with reversals and disturbances of blood-flow in adjacent blood vessels.

Another seminal observation of Padget's was of the immaturity of the cranial venous system at birth. In contrast to the arterial system which reaches maturity in embryonic life at the 40 mm stage with a fully formed Circle of Willis, the venous system does not reach adult configuration, the hallmark of which is the presence of a network of anastomosis between the deep venous system and major dural sinuses until approximately the 3rd month of life. The varied state of development at birth and its pace of maturation has important implications for the clinical manifestations of AVFs.

3 Vascular Biology of Pediatric Arteriovenous Fistulas

Advances in genetic medicine has broadened the understanding of pediatric CNS vascular lesions. Hereditary Hemorrhagic Telengectasia (HHT) and the Capillary Malformation-Arteriovenous Malformation (CM-AVM) Syndrome are autosomal dominant conditions resulting from germline mutations (endologin on ch9q34 (HHT1), *activin receptor-like kinase 1* (HHT2) on ch12q13; and *SMAD4* on ch18q21 (juvenile polyposis, HHT overlap syndrome, and RASA1 for (CM-AVM)). Both conditions demonstrate de novo mutations in up to 30% of cases and have high penetrance >90%. HHT genes are involved in vascular remodeling and angiogenesis via the TGF β pathway. The protein encoded by RASA 1, is an inhibitor of RAS p21, which controls cellular growth, proliferation, survival, and differentiation [3, 4].

CM-AVM patients having multifocal atypical cutaneous lesions distribution throughout the body that are round to oval, pinkish-red. HHT patients present with epistaxis, mucocutaneous telangiectasias, and AVMs. In both conditions, AVMs occur throughout the body. In the brain pial AVM, pAVF, dAVF, and Vein of Galen Malformations have all been reported [5].

AVF fistulas, particularly adAVFs and DSMs are associated with venous thrombosis. There is evidence that the development of dAVF in a sinus that has thrombosed or is under high venous pressure represents the angiogenic response to local endothelial hypoxia. Experimental dAVF animal models demonstrate upregulation of both Vascular Endothelial Growth Factor (VGEF) and fibroblast growth factor (FGF) resulting in splitting and sprouting angiogenesis. These observations are mirrored by reports of de novo adAVF in children who have undergone previous curative embolization of pAVFs [6, 7].

4 Natural History

Most children with AVFs present with symptoms requiring treatment. Therefore, the natural history of asymptomatic and untreated pediatric AVF is not completely understood. Symptomatic high flow AVFs in children have a well described

symptomatology that is distinct from adult AVF due to their congenital nature in a developing brain and neurovasculature. LasJanuais and colleagues described the typical timing and mode of presentation and correlated it to the lesion type [8]. The hallmark of neonatal presentation is high output congestive heart failure. This is seen in patients with extremely high flow fistulas without cerebral venous drainage restrictive pathology.

The presentation in the infantile period is governed by the degree of hydrovenous imbalance. This refers to the interplay of high flow shunting through a lesion with a variably mature and/or pathologic venous system with outflow restriction. This restrictive component is usually the result of thrombosis of a sinus or high flow venopathy which most commonly presents as progressive stenosis of the transverse-sigmoid junction. This in turn will lead to cerebral venous hypertension and subsequent macrocephaly, prominent facial veins, a communicating non-obstructive hydrocephalus, seizures, and developmental delay. It is important to note that these conditions are reversible if the fistula is treated promptly to restore the hydrovenous balance. Hydrocephalus due to hydrovenous imbalance can be made worse by CSF diversion and may lead to subdural or subarachnoid hemorrhage [9].

Presentation during the early childhood period occurs if the early signs of hydrovenous imbalance are not recognized and the natural sequalae of prolonged venous hypertension proceed unchecked. This includes seizures, non-reversible developmental delay, brain calcification, focal or global brain atrophy (also known as melting brain syndrome), and intracerebral hemorrhage.

5 Classification and Angioarchictecture of Pediatric AVFs

Jaeger and Forbes post mortem description of a midline vascular lesion in 4 year old with macrocephaly, seizures, and epistaxis who died after a progressive neurologic decline is typical of a high flow AVF [10]. Without the benefit of MRI and modern neuroangiography the current understanding, classification, and effective treatment were not possible despite the early childhood presentation. The entities that we will discuss include lesions found in the dura: Dural sinus Malformations (DSM) and adult and infantile type-dural arteriovenous fistulas (adAVF & idAVF), and pial arteriovenous fistulas (pAVF).

5.1 Dural Arteriovenous Shunts

Dural Sinus Malformations (DSMs) are a rare congenital condition. The diagnosis is made in utero in up to 26% of case in some series with ultrasound, MRI, and autopsy [11]. These lesions are composed of a massively dilated dural sinus pouch that communicates with the other sinuses and drains cerebral veins. There are often multiple slow flow mural arteriovenous shunts which may be ante-natal or develop

after birth. The two anatomic variants are the midline DSM involving the Torcular and adjacent posterior sinuses and the lateral DSM involving the jugular bulb with otherwise normal sinuses. DSMs all demonstrate some degree of thrombosis of the dilated sinus by 2 years of age. This process in conjunction with fistulalization produces venous hypertension. The most common presenting symptoms include macrocephaly and intracranial hemorrhage. The lateral DSM generally have a better outcome due to the ability to collateralize via the contralateral unaffected sinuses (Fig. 1).

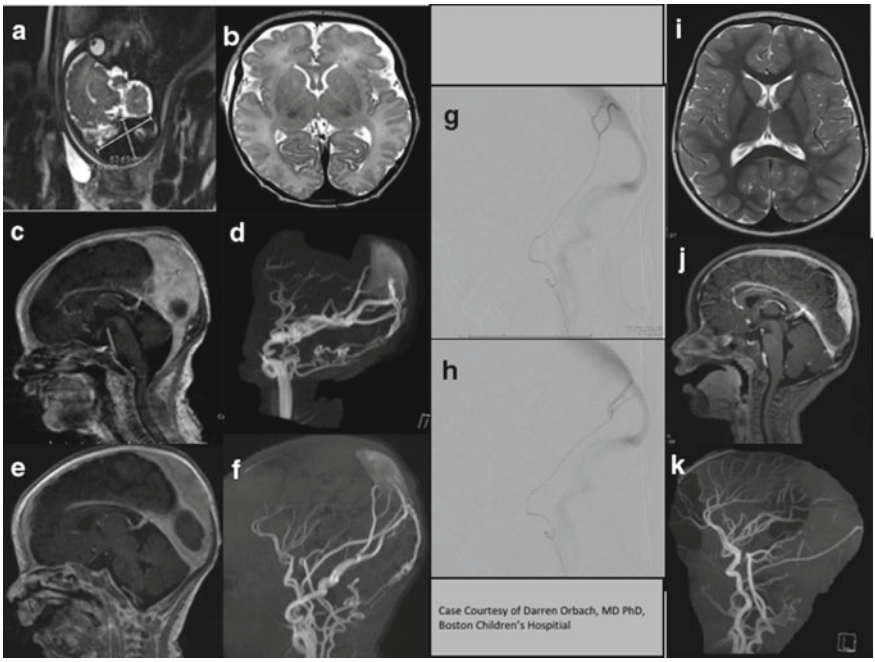

Fig. 1 *Prenatal Diagnosis of Midline Dural Sinus Malformation treated with Onyx Embolization.* Prenatal Saggital T2 MRI demonstrates massively dilated midline flow void consistent with a DSM of the superior saggital sinus. **b**, **c**, **d** Axial T2 MRI, Saggital T1 with Gadolinium and TOF MRA acquired at 1 day of life confirm the presence of DSM of the superior saggital sinus with external hydrocephalus (**b**) due to hydrovenous imbalance. The arterial supply appears is from the middle meningeal and posterior meningeal arteries. **e**, **f** Saggital T1 MRI with Gadolinium and TOF MRA acquired at 3 months of age demonstrates interval partial thrombosis and remodeling of the superior saggital sinus with persistent arteriovenous shunting. **g**, **h** Lateral Digital subtraction angiogram (3 months of age) from two separate middle meningeal artery branches demonstrating the region of shunting—Onyx embolization was performed from these pedicles. **i**, **j**, **k** Post embolization Axial T2 MRI, Saggital T1 MRI with Gadolinium and TOF MRA acquired at 21 months demonstrates resolution of external hydrocephalus (**i**) with further remodeling of the superior sagital sinus (**j**) with no further arteriovenous shunting (**k**)

5.2 Infantile and Adult-Type Dural AVFs

These lesions are similar in angio-architecture to what is seen in adults with shunting into the wall of a dural sinus or cortical vein. The idAVF presents earlier in life, is most commonly located in the major sinuses (which are patent), and occasionally with concomittant pial shunts. In contrast, adAVF often harbor dural sinus thrombosis and the usual localization is in the cavernous and sigmoid sinuses. In neonates and infants congestive heart failure is a common presenting symptom of these lesions. Similar to adults, non-hemorrhagic presentations may occur as a result of hydrovenous imbalance [12] (Fig. 2).

5.3 Pial Arteriovenous Fistulas (pAVF)

Pial AVF are the most common non-galenic AVF encountered in childhood [13]. As with the dAVFs the symptoms and time period of presentation of pAVF are determined by the degree of flow and maturity and associated pathology of the

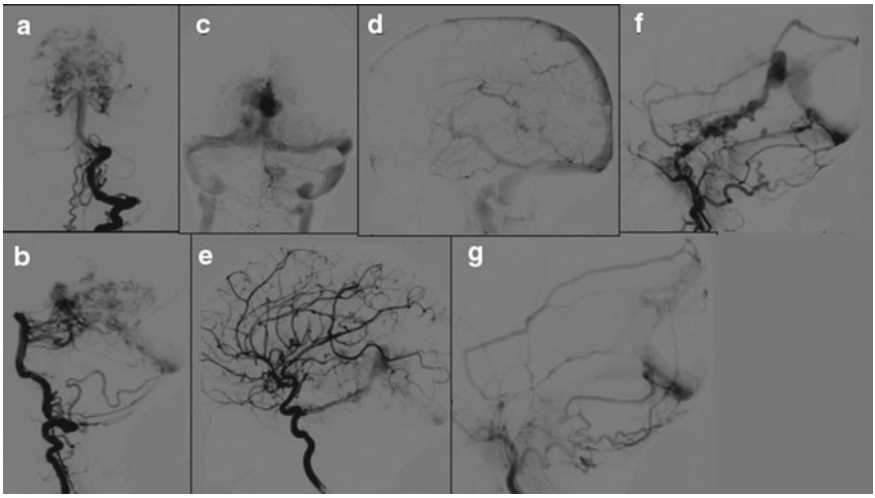

Fig. 2 *Infantile Type Dural Arteriovenous Fistula in a 3 year old boy presenting with Hydrovenous Imbalance with Macrocephaly and Developmental Delay.* **a**, **b** Left vertebral artery PA and Lateral demonstrates shunting from distal dural branches of superior cerebellar, posterior cerebral, and posterior inferior cerebellar arteries into the dura along the straight sinus. There is also contribution to this fistula from the posterior falcine artery. **c**, **d** Left vertebral PA and right internal carotid Lateral venous phase demonstrate no evidence of venous outflow restriction. The hydrovenous imbalance is due to the high volume arteriovenous shunting. **e** Right internal carotid artery lateral demonstrates hypertrophied tentorial marginal artery from the ICA contributing to the fistula along the tentorium. **f**, **g** Right and Left external carotid lateral injections demonstrate multiple dilated external carotid branches including the middle meningeal and transosseous occipital branches which are also contributing to the fistual along the straight sinus and tentorium

venous system. pAVFs are classified by both their morphology (as single hole or multi-hole fistulas) and also by location (supra vs. infratentorial) as both variables influence the presentation. Multi-hole pAVFs with higher flow and supratentorial lesions tend to present earlier in life [14, 15]. In contrast to Vein of Galen Malformations, pAVF are more likely to present with hemorrhage due to direct arterial connection with pial veins [16, 17] (Figs. 3 and 4).

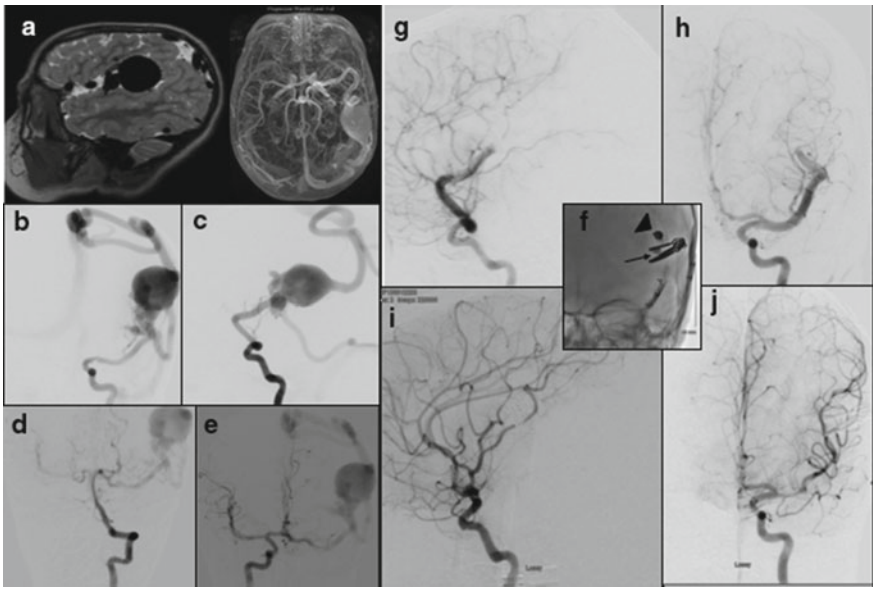

Fig. 3 *Left Middle Cerebral Artery High-Flow Single pAVF treated with Endovascular Embolization and Craniotomy and Clipping.* T2 Saggital MRI and Axial 3D TOF MRA Demonstrates the lesion on the surface of the brain in the posterior sylvian fissure. **b**, **c** Left internal carotid artery AP and Lateral Angiography demonstrates an enlarge middle cerebral artery and no anterior cerebral artery filling consistent with a very high flow lesion which branches into multiple fistulas all entering a giant venous varix. **d**, **e** Left vertebral and right ICA demonstrate high-flow steal via the Circle of Willis away from the right hemisphere and posterior circulation and to the left middle cerebral artery and pAVF. **f** High magnification un-subtracted images demonstrate endovascular coils (arrowhead) and n-BCA liquid embolic agent (arrow) used to reduce the shunting and subsequent surgical clips that were then placed to completely close the lesion. **g**, **h** Immediate post surgical clipping left internal carotid AP and Lateral angiography demonstrates complete obliteration of the fistula with significant hemodynamic change with filling of the bilateral anterior cerebral arteries. This patient experienced post-operative hyperperfusion and seizure despite normal blood pressure. This was controlled by antiepileptics. **i**, **j** Left internal Carotid artery 1 year follow up angiography demonstrates normalization of the caliber of the middle cerebral artery with persistent occlusion of the pAVF

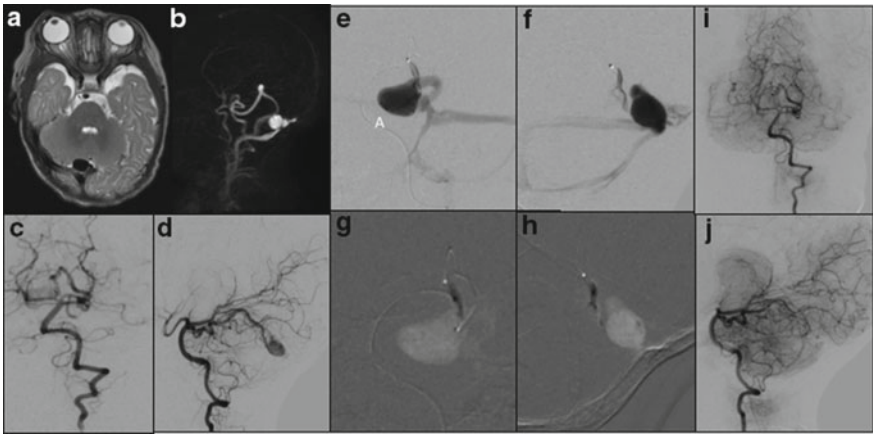

Fig. 4 *Left Superior Cerebellar Artery Pial AVF. Incidentally found pre-nataly on Maternal Ultrasound.* **a** MRI of the Brain T2 axial image at 6 months of age demonstrate a venous varix along the vermis. There is external hydrocephalus consistent with hydrovenous imbalance. **b** TRICKS MRI mid-arterial phase demonstrates a dilated superior cerebellar artery filling the varix with early venous drainage consistent with a vascular malformation. **c**, **d** Left vertebral AP and lateral digital subtraction angiography confirms the presences of a pAVF. **e**, **f** Superselective high magnification digital subtraction angiography from the left superior cerebellar artery demonstrates the pAVF. **g**, **h** Roadmap Fluoroscopic images demonstrate the n-BCA glue cast penetrating the proximal vein. **i**, **j** Left vertebral AP and lateral digital subtraction angiography immediate post-embolization confirms the complete occlusion of the pAVF

6 Endovascular and Microsurgical Treatment

Regardless of the modality, the goal of treatment for pediatric AVFs is normal brain development. Complete angiographic cure is not always necessary or possible due to unfavorable lesion angio-architecture that may carry high risk for significant morbidity or mortality.

Surgical/endovascular intervention should be deferred if the patient is asymptomatic and undertaken ideally around 3–6 months of age. The complications associated with an endovascular procedure: including femoral artery occlusion, intracranial hemorrhage are all significantly higher due to small vessel size and fragility in the neonate and early childhood. In addition, craniotomy and microsurgery for high flow lesions at very young ages is complicated by small circulating blood volume and the potential for significant blood loss with AVFs. There are also concerns regarding the potential neurotoxic effects of anesthetics on the young developing brain [18].

In order to reduce radiation exposure, our protocol is to avoid diagnostic angiography. MRI and MRA imaging with dynamic MRA (Time Resolved Imaging of Kinetics—TRICKS) will allow for diagnosis prior to angiography, an

assessment of flow dynamics, and for preliminary treatment planning [19]. We will then perform endovascular procedures with intent to embolize and/or surgery is planned under the same anesthetic.

Angioarchitercturally, the goal of treatment is the disconnection of the arterial pedicle(s) from the venous connection regardless of the AVF subtype. This requires occlusion of a portion of the receiving vein. Endovascular embolization is the first line treatment for the majority of these patients and often requirs multiple sessions. Factors favoring endovascular treatment including neonatal presentation with high output heart failure, lesion location deep in the brain, or geographically distant multifocal fistulas. Microsurgery should be considered in cases where there are few fistulas and the lesion is readily accessible on the surface of the brain [20]. The most commonly treated subtype with surgery is the pAVF often in conjunction with pre-operative embolization.

Endovascular embolization can be performed either via trans-arterial and/or transvenous routes. The most commonly employed liquid embolic agents include n-butyl cyanoacrylate (n-BCA, Johnson and Johnson) and ethylene co-polymer (Onyx, Medtronic). The individual properties of each agent and techniques of embolization are beyond the scope of this chapter but both can be effective for AVFs. Platinum detachable coils can also be used as a stand-alone treatment for some AVFs.

The post-operative care begins with a focus on managing the expected sequalae of the presenting symptoms including intracranial hemorrhage, seizures, or congestive heart failure. Post-surgical or endovascular reduction or elimination of arteriovenous shunting results in rapid changes in blood flow and may have important physiologic consequences in the brain adjacent or distant from the fistula. This includes hyperperfusion of the brain which can lead to encephalopathy, seizures, or intracranial hemorrhage [21, 22]. Conversely, the venous system is subjected to much lower pressures after treatment. Due to the presence of embolic agent and venous occlusion at the site of the treated fistula there is a risk of progressive venous thrombosis extending beyond the fistulous connections into the normal venous system. This can be controlled with systemic anticoagulation and careful attention to volume status. Understanding, recognizing, and instituting early treatment of these consequences of AVF occlusion are essential to assuring good outcomes.

Finally, it is important to recognize that these children require long term follow up. Incompletely obliterated lesions may have delayed symptoms due to recruitment of additional feeding vessels. Additionally, de novo AV Shunts both adjacent and distant to the original lesion have been observed in patients who had demonstrated angiographic cure [23]. It is our practice to follow these children into early adulthood and repeat vascular imaging.

7 Conclusions

Non-Galenic pediatric AVFs are a unique group of conditions. The biology and pathophysiology, angioarchitecture, and natural history of these lesions are distinct from adult arteriovenous malformations. Treatment is focused on normal brain development rather than complete angiographic cure. Long term follow up is needed given the unclear natural history and angiogenic potential of these conditions.

8 Pearls

1. Pediatric AVFs are congenital lesions which may be part of a clinical syndrome.
2. The genetics of pediatric AVFs are tied to vascular angiogenesis pathways.
3. The angioarchitecture of pediatric AVFs are distinct from adult arteriovenous malformations of the Central Nervous System
4. The pathophysiology and clinical behavior are directly related to the angioarchitecture of the AVF and venous outflow of the brain.
5. Presentation in the Neonatal, infantile, or late childhood period all have distinct symptoms.
6. Hydrovenous imbalance is a distinct phenomenon not encountered in adults with arteriovenous malformations..
7. Treatment is focused on restoration of hydrovenous imbalance and normal brain development—angiographic cure is not always possible or necessary.
8. Treatment in the neonatal period should be avoided in asymptomatic patients.
9. Endovascular treatment is the first line modality for most children but microsurgical or multimodality treatment is also common.
10. Longitudinal long term follow up is necessary due to the possibility of recurrent or de novo vascular lesions.

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Pediatric Cavernous Malformations

Virendra R. Desai and Gavin W. Britz

1 Introduction

Cerebral vascular malformations comprise a spectrum of pathologies ranging from arteriovenous malformations—the most common and the most dire—to cavernous malformations (CMs), which account for 5–18% of all vascular malformations, capillary telangiectasias, and developmental venous anomalies (DVAs) [1–6]. CMs, also known as cavernous hemangiomas or cavernomas, are considered low-flow vascular malformations [7–10]. These lesions are typically well-circumscribed, although occasionally multilobulated, composed of endothelial-lined cavities, and devoid of intervening brain parenchyma, distinguishing these lesions from capillary telangiectasias and arteriovenous malformations [9–12]. Pediatric CMs differ from those of adults in that they have atypical neuroimaging at diagnosis, more rapid rates of growth, larger dimensions, increased vessel wall fragility, and greater release of angiogenic factors given the developing brain—all of which lead to a higher likelihood of hemorrhage at presentation [1, 7, 13, 14].

2 Epidemiology

The exact incidence and prevalence of CMs are unknown as many are asymptomatic, but the prevalence in adults ranges from 0.2–0.53% in autopsy series [15, 16] and 0.3–0.9% in MRI and clinical series [17, 18]. The incidence and prevalence in children are less clear, as reports to date have involved small numbers of patients

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with mixed ages [7, 11, 14]. The prevalence has been estimated at 0.2% in infants and 0.6% in children overall, reflecting the fact that de novo development of CMs occurs [19–21]. Overall, 25% of CMs occur in children, generally presenting in a bimodal distribution between 1–3 and 11–16 years old, with a mean age of 9 [8, 19, 22]. No significant gender differences are reported in children or adults, although some authors report a female predominance at younger ages [8, 11]. 10% of pediatric CMs are familial, and 15–30% have multiple lesions [9, 11, 13].

These lesions occur throughout the neuraxis, distributed according to the volume of the central nervous system component, with about 80% supratentorial, 20% infratentorial and 5% spinal [2, 8, 13]. Of those originating in the supratentorial space, most reside in the frontal lobes in pediatric series, while less appear in basal ganglia in children than in adults [11, 13]. Within the infratentorial space, 57–77% of CMs reside in the brainstem with the remainder mainly in the cerebellum [8, 11, 14].

The etiology of CMs is unclear and although CMs were previously believed to be congenital, de novo formation has been documented [21, 23, 24]. In newly developed CM, an association with radiation therapy has been found, with 3% incidence (95% confidence interval 1–8%) 10 years post-radiation and 14% (95% confidence interval 7–26%) at 15 years in children [23, 25–28]. Moreover, overall incidence correlates with total number of CMs, in that children with more lesions have higher risk of further de novo development – 1.2% per patient per year plus 2.5% per lesion per year [9, 21].

3 Genetics

The genetics of CMs have been partially deciphered: an autosomal dominant pattern of inheritance with incomplete penetrance has been found in some families, with three major loci: CCM1 on chromosome 7q, CCM2 on chromosome 7p, and CCM3 on chromosome 3q [29]. Mutations at the CCM1 locus are the most common familial form of CM, particularly in the Hispanic population, and loci for the CCM1 or KRIT1 protein have been mapped to chromosome 7q11.2-q21 [30]. The CCM3 locus has been mapped to chromosome 3q25.2-q27 and is responsible for 40% of mutations in the familial forms of CM. Mutations of the CCM2 locus on chromosome 7p are responsible for 10–20% of the familial forms of CM [31–34].

4 Natural History

The annual prospective hemorrhage risk in adult patients with CMs has been estimated to be between 0.7 and 4.2% per patient-year [3, 35–46]. In children, the risk is about 0.1–0.9% per lesion per year for incidental CMs [9, 11, 20, 21]. Risk factors for hemorrhage include associated DVA, brainstem location and history of prior hemorrhage [9, 11, 21, 44, 47–50]. After an initial bleed, the recurrent

hemorrhage rate can be as high as 16.7% in the first year, with subsequent bleeds clustering together within 2–3 years after initial hemorrhage and declining thereafter [9, 11, 21, 51]. Relative to adults, pediatric CMs have a higher risk of hemorrhage given increased vessel wall fragility and inappropriate release of angiogenic factors in their developing brains [7]. Other risk factors for hemorrhage suggested by some, but not always confirmed in other studies, include female sex [37, 42, 45], pregnancy [18, 45], and multiplicity [38].

5 Clinical Presentation

In adults, seizures are the most common presenting symptom [52]. The epileptogenic mechanism possibly relates to gliosis, blood breakdown products, associated venous hypertension, if present, and cellular and humoral inflammatory responses [53].

In the pediatric population, 20–62% present with hemorrhage, resulting in headache and/or focal neurologic deficit, 35–51% with seizures, and 5–26% as an incidental finding [1, 9, 11, 13, 54]. Initial hemorrhages are rarely associated with significant disability or death, with one study having a mortality rate of 5.3%, of which no deaths were due to the CM [45]. Size and location are important in symptomatology. Supratentorial CMs more often present with seizures, infratentorial lesions present with stepwise occurrence of focal neurologic deficits secondary to repeated hemorrhages, with occasional neurologic recovery between episodes, and cerebellar lesions present with headache and cerebellar dysfunction [1, 7, 11, 13, 14].

6 Imaging

Computed tomography (CT) is 70–100% sensitive but less than 50% specific in detecting CMs [3, 55, 56]. The typical appearance is a well-circumscribed nodular lesion with calcification. CT may be useful for emergent testing of acute hematomas, mass effect or hydrocephalus, bearing in mind the risks of radiation, especially as related to de novo CM development [57].

Magnetic resonance imaging (MRI) is the most sensitive modality in detecting CMs, especially gradient echo (GE) and susceptibility-weighted imaging sequences [58–61]. CMs appear as well-defined lesions on MRI with a central core of mixed-signal intensity, surrounded by a rim of hypointensity [58–61]. Four types have been classified based on MRI appearance, shown in Table 1 [35].

GE T2-weighted and susceptibility-weighted imaging are the recommended modalities for imaging CMs [62]. Figures 1, 2, 3 and 4 depict CMs in various locations: Fig. 1, brainstem; Fig. 2, supratentorial; Fig. 3, spinal cord; Fig. 4, thalamus.

Table 1 MRI and pathologic findings of types I-IV cavernous malformations

Lesion Type	MRI findings	Pathologic characteristics
Type I	T1—hyperintense core T2—hyper- or hypo-intense core with surrounding hypointense rim	Subacute hemorrhage, surrounded by rim of hemosiderin-stained macrophages and gliosis
Type II	T1—reticulated mixed signal core T2—reticulated mixed signal core with surrounding hypointense rim	Loculated areas of hemorrhage and thrombosis of different ages, surrounded by gliotic, hemosiderin-stained brain; in large lesions, calcification can be seen; classic "popcorn-like" appearance
Type III	T1—iso- or hypo-intense T2—hypointense with a hypointense rim that magnifies lesion size GE—hypointense with greater magnification than T2	Chronic resolved hemorrhage, with hemosiderin stain in and around lesio
Type IV	T1 and T2—poorly seen or not visualized GE—punctate hypointense lesions	Two lesions in this category found to be telangiectasias

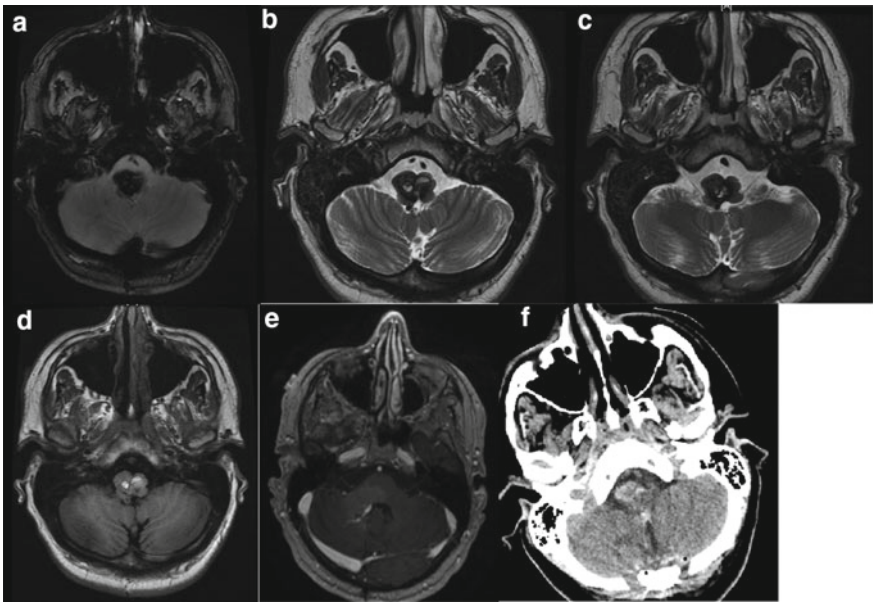

Fig. 1 **a** GRE depicting the brainstem cavernoma with associated hemorrhage; **b** and **c** T2; **d** T1 pre-contrast; **e** T1 post-contrast showing associated DVA; **f** non-contrast CT depicting associated intraventricular hemorrhage

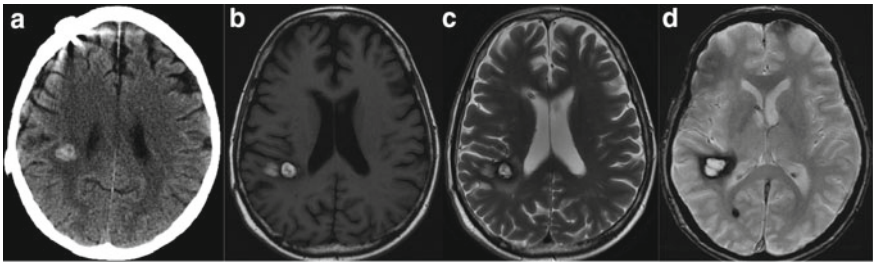

Fig. 2 **a** Non-contrast CT showing right parietal, subcortical CM with frontal shunt; **b** T1 pre-contrast; **c** T2; **d** GRE

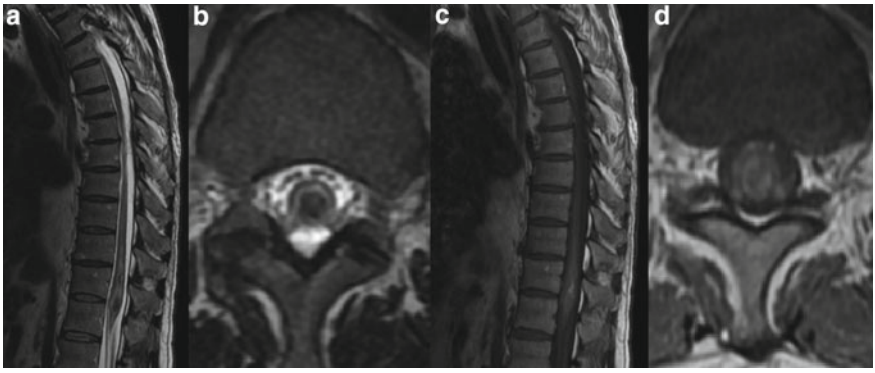

Fig. 3 **a** Sagittal T2 MRI of thoracic spine showing CM in conus medullaris; **b** Axial T2 MRI through CM; **c** Sagittal T1 pre-contrast; **d** Axial T1 post-contrast through CM

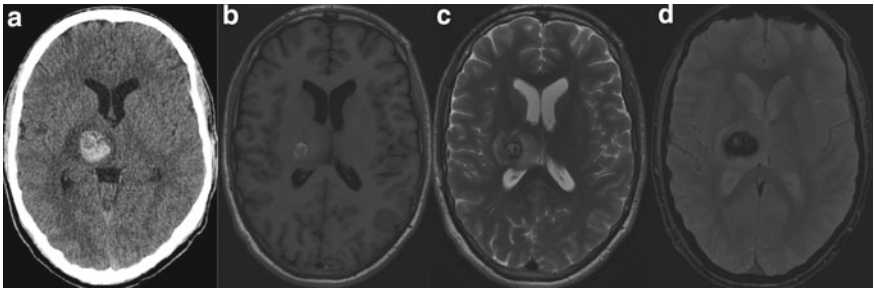

Fig. 4 **a** non-contrast CT showing right thalamic CM; **b** T1 pre-contrast; **c** T2; **d** GRE

Because CMs are angiographically occult vascular malformations, angiography is almost always negative [63]. Occasionally however, formal angiography may assist in ruling out an arteriovenous malformation.

7 Management

Management of CMs depends on several key factors: location, symptomatology, and hemorrhage and/or seizure risk. In general, pediatric cavernomas should be managed like adult ones, with a more aggressive approach given their higher hemorrhage and/or seizure risk and children's longer life spans, inherent synaptic plasticity and neuro-regenerative potential [1, 7, 19, 64]. Observation versus surgical removal must weigh the benefits of avoiding recurrent hemorrhage and/or development of chronic, drug-resistant epilepsy, against the risks of surgical morbidity [11, 19, 64]. Some authors recommend that CMs that have bled and are unresectable should be imaged 3–6 months post-hemorrhage and then annually; incidental CMs can be followed less frequently [9].

7.1 Medical

For asymptomatic, incidental CMs, observation is a reasonable first step. When symptomatic, seizures are common, and anti-epileptic medications should be an initial management option, especially for lesions in inaccessible locations. However, about 30% of CM-associated pediatric epilepsy patients are drug-resistant, necessitating further measures for seizure control [19].

7.2 Surgical

7.2.1 Indications

The decision to operate relies heavily on location. General indications for resecting brainstem CMs include recurrent hemorrhages, lesions >2 cm (cm), severe or progressive neurologic dysfunction, significant mass effect, exophytic lesions, or safely accessible lesions abutting the pia mater (<2 mm [mm] of brain tissue between the cavernoma and pial surface) [7, 65]. In supratentorial CMs presenting with a first-time seizure, some authors argue that early surgery should be considered, as opposed to conservative management, because seizure freedom becomes more difficult as patients progress from a single seizure to chronic epilepsy, and most patients presenting with seizure will relapse within 5 years [19, 64]. Moreover, antiepileptic medications are not without side effects [19, 64].

7.2.2 Surgical Technique

One primary goal of surgery may be to alleviate the seizure burden. Towards this goal, basic resection techniques are simple lesionectomy, with or without excision of the hemosiderin rim, versus extended lesionectomy [10, 12, 19]. In the former, the cavernoma is resected with or without the hemosiderin rim (complete or partial) while the latter involves additional resection of surrounding brain parenchyma [10, 12, 19]. Generally, resection of the hemosiderin rim is recommended when the CM resides in a location other than the brainstem, and when seizure is the presenting symptom, as this rim has significant epileptogenic potential and resection results in high rates of seizure freedom, Engel class I [73–85%) [11, 21, 66–71].

If a DVA is associated, care should be taken not to sacrifice it, as venous infarction may occur [72]. Neuronavigation, intraoperative MRI, electrophysiology/electrocorticography and ultrasonography can help minimize morbidity and aid microsurgical resection [7, 13, 73]. In fact, seizure freedom (Engel classification I) substantially differs with and without electrocorticography (90% versus 77%) at 6 months post-operative [10], though this result is not definite [12]. Timing surgery several weeks post-hemorrhage maximizes surgical feasibility as perilesional edema subsides and the hematoma contents evolve and soften [7, 11, 65].

7.2.3 Outcomes of Surgery

Longterm results after surgery are generally good, with a significant reduction in seizure burden and/or antiepileptic drug use [11, 19, 57, 64, 72, 74, 75]. As noted above, as many as 73–85% of patients achieve seizure freedom, Engel class I [11, 21, 66–71]. Higher rates can be achieved with resection of the hemosiderin rim, early surgery before chronic epilepsy develops, and use of electrocorticography [10–12, 19, 21, 57, 64, 66–72, 75]. Post-operative seizure freedom rates decline the longer epilepsy is present [12, 19, 57, 64].

While a 4–10% rate of neurologic deficit (temporary or permanent) is seen overall, lobar, non-eloquent lesions have low morbidity (0–4%) while brainstem CMs can have about a 50% rate of immediate postoperative deficit with as many as 25% suffering permanent deficit [7, 19, 57, 64, 72, 74–77]. Of those that recover, almost 20% return to baseline with the remainder showing some improvement [7, 77]. Age over 12 years, >2 pre-operative hemorrhages, and modified Rankin Scale (mRS) score > 2 may be risk factors for incomplete recovery [7]. This suggests that CMs displace surrounding structures rather than invade them [75].

7.3 Radiosurgery

In adult patients, radiosurgery for cavernomas is controversial [8, 72, 73, 78–80]. Although it may be safer than microsurgery, in both adults and children its efficacy is questionable [8, 72, 73, 80]. Optimal dosage and technique have not been defined, rendering reported results difficult to interpret [8, 72]. Seizure risk appears to equal that obtained with best medical therapy [8]. While the hemorrhage risk typically declines after a two-year latent period, it is not completely eradicated [8,

73, 78, 79]. In fact, this post-treatment behavior resembles the natural history of untreated CMs, as hemorrhagic events tend to cluster together temporally with intervals of decreased risk [8, 9, 11, 21, 51, 73].

Moreover, radiation morbidity is not negligible, with as many as 50% of cases with transient neurologic morbidity secondary to perilesional edema and 5–10% with permanent, severe deficit, although these numbers are decreasing with the evolution of more advanced technologies and adapted dosing regimens [8, 72, 73, 78]. Interestingly, radiation-induced side effects are higher after treatment of CMs than AVMs, even after controlling for lesion size and location as well as radiation dose [73]. Given its unclear efficacy and significant potential for complication, the current general consensus is against the use of radiosurgery in pediatric CMs [8, 35, 73].

8 Other Management Options

Magnetic-resonance guided focused ultrasound (MRgFUS) is a novel, minimally invasive technique used in multiple lesion types, including CMs [81]. It directs multiple, intersecting ultrasonic waves towards the lesion and causes local thermal rise, acoustic cavitation and immunomodulation [82]. Importantly, the efficacy and longterm results of this modality in CM treatment are yet to be established.

Magnetic-resonance guided laser interstitial thermal therapy (MRgLITT) represents another minimally invasive modality, although this is only beginning to emerge as a treatment option for CMs [83].

9 Pearls/Highlights

- CMs occur in about 0.2% in infants and 0.6% in children.
- Supratentorial lesions typically present with seizure; infratentorial present with hemorrhage causing focal neurologic deficit.
- In children, the hemorrhage risk is 0.1–0.9% per year for incidental CMs. Risk factors for hemorrhage include associated DVA, brainstem location and history of prior hemorrhage.
- Gradient echo and susceptibility-weighted MR imaging are the best modalities to visualize CMs.
- Pediatric CMs are managed more aggressively than those of adults, given their higher hemorrhage risk and the children's longer life spans and greater potential for neuro-regeneration.
- Up to 30% of patients have seizures that are refractory to anti-epileptic medications.
- For CM-associated epilepsy, several factors can significantly reduce seizure burden as well as minimize surgical morbidity: resection of the hemosiderin rim

and utilizing electrocorticography, neuro-navigation, ultrasonography, intra-operative MRI, and electrophysiology.

- Radiation is generally not recommended for pediatric CMs, as its efficacy is questionable and it may incur significant side effects.

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Cerebrofacial Arteriovenous Metameric Syndromes

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1 Background

First identified and named by Bonnet, Dechaume and Blanc in 1937 and subsequently by Wyburn-Mason in 1943, the spectrum of syndromes characterized by the presence of vascular malformations of the midbrain, face and/or orbit in association with cutaneous nevi has come to be known as Cerebrofacial Arteriovenous Metameric Syndromes (CAMS) [1–4]. Since that time, certain presentations of Sturge-Weber syndrome have been categorized as CAMS as well, though this syndrome is typically classified as a distinct entity characterized by a port wine stain and leptomeningeal angiodysplasia [5, 6].

While CAMS have been grouped with neurocutaneous disorders (phakomatoses), this is based on the cutaneous manifestations alone and does not guide the clinician or researcher toward etiology, natural history or management. Furthermore, unlike many of the phakomatoses CAMS have not been shown to have a hereditary basis, though further study in this area is needed [7]. These disorders are rare in and of themselves but studies of CAMS provide opportunities to gain insight

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into cerebrovascular development and shed light on the mechanisms underlying the development of sporadic AVMs [4, 8].

2 Embryology and Developmental Pathology

Vascular development begins with differentiation of endothelial cells from the mesodermal layer of the embryo, while the associated neural structures derive from the ectodermal layer. Chick embryo studies in the 1990s revealed that the origin of cephalic endothelial cells is a committed lineage in the cephalic mesoderm, and that vascular development proceeds in a segmented fashion consistent with the formation of the associated neural elements [9]. Vasculogenesis commences as sprouting of these early endothelial cells to form primitive capillary networks that are subsequently remodeled through angiogenesis [10]. The media of the vascular lining is formed from neural crest cells that are spatially related to endothelial precursors [7]. This segmental development of the embryo provides a framework for evaluating and classifying vascular malformations of the head and neck. Recognition of this association and common patterns in patients with these malformations led Bhattacharya et al. to propose a classification scheme grounded in developmental neurovascular anatomy [1].

Early descriptions of patients with this complex of findings spurred hypotheses about their origins. Dr. Harvey Cushing, for example, postulated that facial nevi developed along the course of the trigeminal nerve [11]. While the exact origins of CAMS remain unclear, embryologic studies and clinical observations suggest that it is a disorder born of neural crest and adjacent cephalic mesodermal development [7, 8]. As a result**,** vascular malformations in CAMS are thought to originate prior to the fourth week of embryonic development, resulting in the formation of lesions along the migration path of mesodermal and neural crest cells that form the vasculature. This theory helps to explain the association of lesions in different CAMS subtypes with their embryonic segmental origin [12]. It should be noted, however, that this timeline remains controversial, as others have suggested that insults as late as week seven of gestation could result in a clinical presentation consistent with CAMS [13, 14]. Further studies are needed to clarify this question.

3 Clinical Presentation and Natural History

Patients with CAMS are usually diagnosed in childhood. However, it is unclear whether they present at an earlier age than those with sporadic AVMs simply because of the increased likelihood of detecting a lesion when multiple are present, or whether the underlying developmental pathology is accelerated or different [8]. There is no difference in incidence of these disorders by sex based on the reported literature [1].

The hallmark of Bonnet-Dechaume-Blanc disease is the presence of retinal, facial, nasal and/or mandibular AVMs. It has now been recognized that these lesions are not seen in all patients with CAMS, but that each patient may demonstrate a range of phenotypic expression [8, 14]. These lesions may be present as a small red spot or angioma for many years in early childhood before growing and presenting clinically as hemorrhage or mass effect leading to facial asymmetry in adolescence. The trigger for their growth is unknown at this time. Dysplastic feeding vessels, often with aneurysms despite relatively low flow, are common and should alert the clinician to a CAMS diagnosis. Notwithstanding their irregularity and dysplastic character, reports of severe hemorrhage are rare and these lesions are considered to be clinically benign, and the most frequent impetus for treatment is cosmetic [8]. Facial lesions may involve any distribution, including cutaneous, orbital, maxillary and mandibular [15].

Patients with CAMS most commonly present with progressive visual loss and/or other neurologic deficit with or without hemorrhage [1, 8]. Visual loss may be the result of any lesion along the optic pathway. Vascular malformations have been reported in the eye, orbit, chiasm, occipital lobes and elsewhere, [1, 3, 6, 12, 16, 17] all potentially causing visual deficits. Orbital AVMs most frequently cause symptoms as a result of a steal phenomenon resulting in retinal ischemia or increased intraocular pressure due to mass effect. Reference [18] optic atrophy has also been reported, either due to compression, ischemia or both. Reference [14] retinal involvement is common [8].

Cerebral AVMs are common manifestations of CAMS, and in the context of this syndrome differ in several key ways from sporadic AVMs. First, the nature of the nidus has been noted to be different, in that instead of a clearly defined nidus there is often a cluster of small fine nidi with intervening normal brain or other neural tissues. Second, high flow shunts, flow related arterial aneurysms and large ectatic draining veins have not been reported in CAMS-associated cerebral AVMs, a point of distinction from sporadic and other hereditary syndromes such as Hereditary Hemorrhagic Telangiectasia (HHT). These lesions are often characterized by progressive enlargement over time, and tend to be multifocal [8].

Cerebral lesions tend to be asymptomatic at presentation, as most patients are identified first by their ocular or facial manifestations [8, 17]. However, cerebral AVMs in patients with CAMS can cause the typical manifestations of seizures, focal neurologic deficits or visual field [1, 6, 17, 19]. These can be related to hemorrhagic sequelae or occasionally infarction [8, 20].

A related but uncommon manifestation of CAMS is a thyroid AVM, though the reported case of this phenomenon was an incidental finding [13]. Mandibular lesions have be recognized by bleeding gums or after episodes of significant bleeding following tooth extraction [21]. This is explained by the presence of intraosseous AVMs with venous lakes in close vicinity to the teeth [8]. Exophthalmos is another rare presenting symptom and can be due to multiple causes. Intraorbital AVMs may cause mass effect and venous congestion, while involvement of the ophthalmic vein can cause venous hypertension in the orbit [21].

4 Radiographic Features

Early descriptions of CAMS in the literature were purely clinical, without the benefit of radiographic evaluation. Modern computed tomography (CT) and angiography have afforded us a better understanding of the anatomy of vascular lesions in CAMS, as well as some associated findings one may observe.

As we have discussed, cerebral AVMs are common in patients with CAMS [8]. These vascular malformations are classically multifocal with extension from the calcarine fissure to the retina with variable locations depending on the type (i.e. I, II or III subtype). Cerebral lesions can appear on imaging as scattered contiguous spots and less commonly multiple isolated foci [1]. Angiographically, cerebral AVMs in the CAMS differ from sporadic AVMs in the character of the nidus. In CAMS, the nidus is a cluster of smoke-like fine nidi with intervening normal brain tissue. Transdural arterial supply is described in some cases, but there are no reports of high flow arteriovenous fistulae or ectatic draining veins [8].

The association between cervicofacial venous malformations and developmental venous anomalies (DVAs) of the cerebral hemispheres is well documented [5, 22]. Cerebral and brainstem cavernous malformations (CCMs) have also been reported in association with a CAMS diagnosis [5]. It is unknown whether the clinical behavior of these lesions in CAMS differs from other familial syndromes or sporadic CCMs.

Facial or mandibular AVMs in CAMS are not angiographically different from sporadic ones. Still, they frequently contain some direct fistulae and some cases may have aneurysms in the proximal arterial feeders despite relatively slow flow [8]. The formation of aneurysms in the absence of significant hemodynamic stress supports the theory of widespread underlying vascular dysplasia in these patients.

5 Diagnosis and Management

Diagnostic investigation of CAMS patients is clinical and radiographic, as there are no known biomarkers of these syndromes. Initial diagnosis is the greatest challenge, as putting together the constellation of findings to reach a diagnosis of CAMS may take time. Patients presenting with a large or enlarging facial angioma should certainly prompt an evaluation. These lesions frequently cause facial asymmetry due to mass effect.

Evaluation should begin with a complete ophthalmologic examination. Importantly, a complete work-up of a patient with CAMS can be guided by the developmental origins each subtype. For example, a patient presenting with an optic nerve AVM and suspicion of CAMS 2 should also be evaluated for maxillary lesions and dysplastic aneurysms of the proximal vessels in the nose and pterygopalatine fossa to avoid potentially life-threatening hemorrhage from an unidentified lesion [8]. This kind of focused and exacting clinical evaluation is necessary in the initial work-up of all CAMS patients, with an eye to the metameric origin of

the sentinel lesion and the potential for other lesions in that segmental distribution. Non-invasive radiographic vascular studies like CT or MR angiography are a useful first step, followed by conventional angiography and more detailed investigation of suspicious lesions that may require treatment. Functional studies can be useful in treatment planning for cerebral AVMs [12].

Management of CAMS patients is highly variable, and largely depends on the presenting symptoms. Cure is not typically the goal, but rather amelioration of the symptoms most significantly affecting the individual patient. The rarity of these patients provides little guidance for treatment decisions, but limited experience suggests that the clinical approach to cerebral AVMs in CAMS patients must be careful and measured. Some have recommended a palliative approach consisting of endovascular treatment of only symptomatic lesions, or fragile parts of symptomatic lesions in order to enhance stability of the lesion without profoundly altering flow dynamics [8, 12]. Reports of symptomatic orbital AVMs treated with embolization and surgical resection demonstrate that management of these lesions carries the risk of visual loss due to embolic ischemia or vascular spasm [18].

Nasal and facial lesions may remain silent for years before progressing to clinical recognition, leaving treatment decisions to depend largely on the perceived angiographic risk of hemorrhage. Functional preservation and reconstruction are also considered when dealing with facial and mandibular lesions in CAMS [8].

Jiarakongmun et al. reported 3 cases with optic, facial and intracranial AVMs that were managed by endovascular embolization of the nidus and proximal arterial aneurysms. Of note, treatment of the nidus was divided into multiple sessions with the goal of controlling progression of the lesion. They suggest targeted embolization of perceived weak points as a means of control and risk management [8].

Treatment of retinal and optic nerve AVMs is typically discouraged. The natural history of these lesions in the limited available literature has been relatively benign. Treatment is thought to carry greater risk than observation [1]. For orbital lesions, however, exophthalmos can be progressive and thus require treatment. Intervention and vascular access are complicated by dysplastic vasculature and the potential for hemorrhage, but preoperative embolization has been used to reduce the risk of surgical resection. Visual complications may occur due to embolism or spasm of the abnormal vasculature [18].

6 Conclusions

Identification of a CAMS diagnosis requires careful consideration and evaluation by the clinician. Understanding developmental neurovascular anatomy is a key component of the CAMS classification and ensures that a thorough diagnostic evaluation is completed. Systematic examination and angiographic studies are

needed to fully characterize these patients and understand risk of future hemorrhagic complications. Understanding the natural history and potential risks associated with intervention in these patients is critical for making treatment decisions and preserving functional.

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Spinal Arteriovenous Metameric Syndrome and Spinal Cord Arteriovenous Malformations

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Abbreviations

AVF	Arteriovenous fistula
AVM	Arteriovenous malformation
SAMS	Spinal arteriovenous metameric syndrome

1 Introduction

Spinal arteriovenous metameric syndrome (SAMS), also known as Cobb syndrome or cutaneomeningospinal angiomatosis, is defined by the presence of at least 2 separate vascular malformations in the same embryonic metamere [1–3]. SAMS was first described in 1890 [4], but because of its rarity, fewer than 80 cases have been reported in the literature [2, 3, 5]. The most common combination of vascular malformations includes a cutaneous malformation and a spinal malformation. In fact, this combination was described in 1915 by Stanley Cobb, a resident of Harvey

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Cushing [1]. In that case, the patient underwent laminectomies, and after Cushing opened the dura, he described a "leash" of blood vessels compressing and overlying the spinal cord. The dura was left open, and the wound was closed.

The most common cutaneous components of SAMS are nevus flammeus (capillary malformations) and angiokeratomas [6, 7]. The most commonly described spinal vascular malformation in this syndrome is the complex spinal extradural–intradural arteriovenous malformation (AVM), at times referred to as a type III spinal AVM [2, 5, 8, 9]. However, case reports have also described the spinal component as an intradural arteriovenous fistula (AVF) [5, 8, 10–13], an extradural AVF [3, 8, 14, 15], or an intradural AVM [5, 8]. Alternatively, the spinal component may be a cavernous malformation [16]. In this chapter, we review the epidemiology, natural history, and treatment options for spinal vascular malformations in SAMS.

2 Epidemiology and Presentation

SAMS is a genetic nonhereditary syndrome [9, 17], and its associated vascular malformations may be located in the cutaneous, muscular, bony, paraspinal, or spinal compartments of the metamere. It is distinct from Parkes Weber syndrome, in which patients have associated limb arteriovenous shunts, and Klippel-Trénaunay syndrome, in which patients have associated limb venolymphatic lesions without arteriovenous shunts [9, 17].

During vasculogenesis, endothelial cells derive from mesoderm cells and the tunica media derives from neural crest cells. Metameric vascular malformations may develop as the result of a genetic defect or somatic mutation in the neural crest cells or adjacent mesoderm before migration [5, 17]. After the original report by Cobb, the important association of cutaneous lesions and spinal AVMs was reinforced in 1969 by Doppman et al. in the *New England Journal of Medicine* [18]. In their review of 28 cases of spinal AVMs, they noted that 6 of these patients (21%) also had a cutaneous lesion. Interestingly, at this time, the cutaneous lesions were occasionally used to facilitate lesion localization and primary feeding artery laterality. In some cases, the Valsalva maneuver was used to facilitate identification of the cutaneous lesion. Twenty-five of the 28 patients in the study by Doppman et al. were male.

Although a cutaneous vascular malformation is often readily apparent, the diagnosis of SAMS is often not rendered until symptoms from a spinal vascular malformation prompt radiographic and angiographic evaluation. Patients with cutaneous lesions and unexplained radicular pain or neurological symptoms must undergo further evaluation. Neonates may present with congestive heart failure [3], whereas older patients may present with acute or progressive neurological deficits. Patients with extradural lesions may present with symptoms caused by mass effect [8, 14, 15].

In one 30-year experience that included 148 patients with spinal cord AVMs, 28 (19%) were associated with SAMS [5]. Of these 28 patients, 24 had AVMs and 4 had AVFs. Compared with other patients in the study without SAMS, these 28 patients were primarily female (71% vs 48%) and presented at a younger age. The most common presentation of the SAMS patients was hemorrhage (n=18 [11 subarachnoid hemorrhage, 7 hematomyelia]); 7 presented with nonhemorrhagic neurological deficits (potentially from venous thrombosis, venous hypertension, or mass effect from venous ectasias or aneurysms), and 3 presented with radicular pain without deficits, likely from mass effect on the nerve root. The SAMS patients had higher rates of hemorrhage on presentation than the patients with nonmetameric disease.

In another series of 119 patients with spinal AVMs, 19 patients (16%) had more than one vascular malformation [9]. Of these 19 patients, 9 had SAMS. Most of the patients with SAMS were male (78%), and 8 of the 9 were younger than age 24 years. Six of the SAMS patients presented with progressive neurological deficits, 2 presented with hemorrhage, and 1 had an incidentally discovered lesion [9].

3 Associated Spinal Vascular Malformations

It is important to underscore that metameric spinal AVMs do not include only extradural–intradural lesions; rather, the term may refer to any spinal vascular malformation in association with another lesion along the same metamere [2, 3, 5, 8, 11, 14–16]. Elkordy et al. recently reviewed 24 case reports published since1990 [8]. They found that half of the patients described in these reports harbored extradural–intradural AVMs, 6 (25%) had extradural AVFs, 3 (13%) had cavernous malformations, 2 (8%) had intramedullary AVMs, and 1 (4%) had a pial AVF.

Extradural–intradural AVMs may be supplied by pial, dural, and paraspinal arteries with expansive nidi spanning the extradural and intradural space (Fig. 1) [2, 19, 20], and symptoms may occur from hemorrhage, mass effect, or venous hypertension [2, 19]. In one systematic review of extradural–intradural spinal AVMs [2] compiling 51 patients, the mean patient age was 15 years, with a slight male sex predilection (1.7:1 male) [5, 21]. Presentation was most commonly secondary to progressive neurologic decline (35%) [2, 16]. Other presentations included acute hemorrhage in 31% of cases and acute deficit without hemorrhage in 22% of cases. The lesion was incidental in 12% of cases. In contrast, patients with intramedullary AVMs present at an older age (mean 29.1 years) without a significant sex predilection [22]. Consistent with findings from studies of patients with cerebral AVMs, half of patients with intramedullary AVMs present with hemorrhage [2, 22, 23]. Although a third of patients with spinal intramedullary AVMs had associated aneurysms [22], nearly half of patients with extradural–intradural AVMs had associated aneurysms; the greatest proportion in comparison to patients harboring other types of spinal vascular malformations [2].

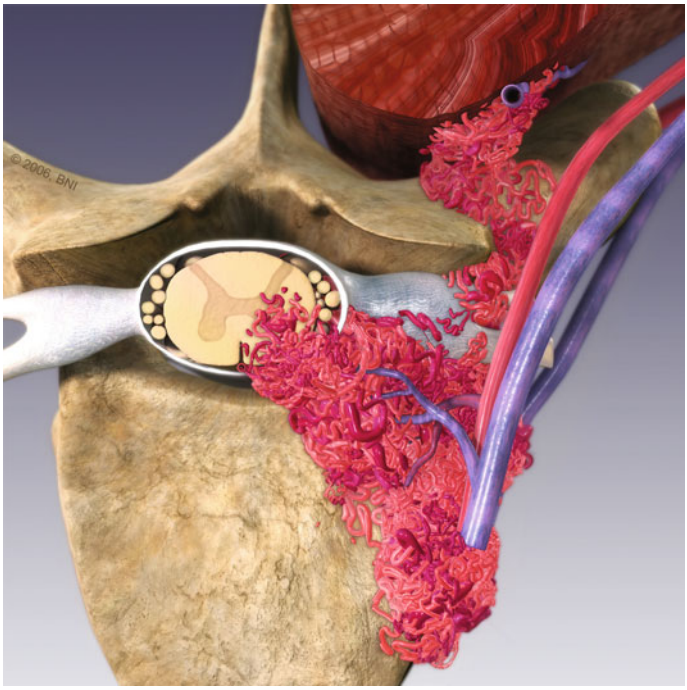

Fig. 1 Extradural–intradural arteriovenous malformation (AVM). These AVMs may be supplied by pial, dural, and paraspinal arteries, with nidi spanning the extradural and intradural space. *From Kim LJ, Spetzler RF. Classification and surgical management of spinal arteriovenous lesions: arteriovenous fistulae and arteriovenous malformations. Neurosurgery 2006;59:S3-195-S3-201, Fig. 4. Used with permission from Barrow Neurological Institute, Phoenix, Arizona*

Extradural AVFs are supplied by radicular branches and become symptomatic as a result of mass effect, hemorrhage, or venous hypertension when intradural venous drainage is present [19, 20, 24] (Fig. 2). The presence of an extradural AVF alone rarely prompts concern for SAMS. In a review of 101 patients with extradural spinal AVFs, the mean patient age was 46 years and there was no sex predilection [24]. Most patients in this study presented with nonhemorrhagic neurological deficits. In this review, the authors reported no associated SAMS. In a separate review of 6 cases of extradural spinal AVFs as a component of SAMS, 5 patients were adults and there was no significant sex predilection [8].

Jessen et al. originally described SAMS in association with spinal cavernous malformations in 1977 [21]. Since then, 6 cases of SAMS have documented a cavernous malformation as the spinal component [16]. The lesion was intramedullary in 3 cases, extradural in 2, and unspecified in 1. There was no sex predilection among the 6 patients, 5 of whom were adults. All lesions were symptomatic.

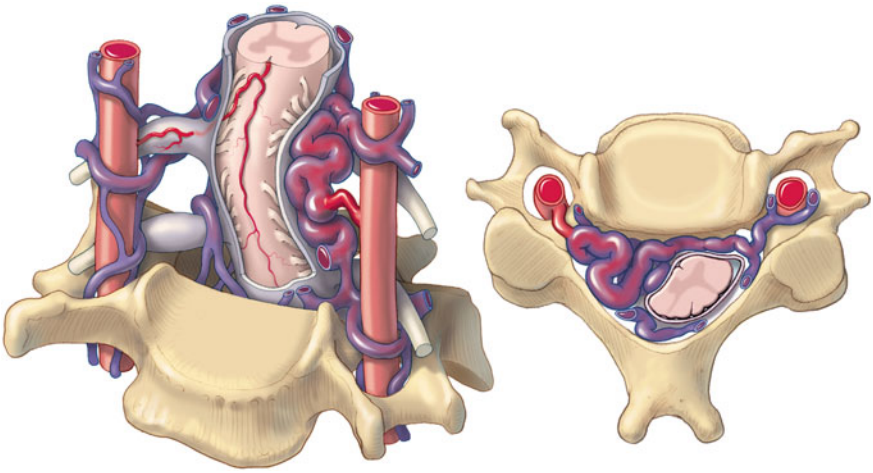

Fig. 2 Extradural arteriovenous fistula (AVF). These AVFs are supplied by radicular branches and may cause symptoms from mass effect or hemorrhage. Venous hypertension may also cause the lesions to become symptomatic if intradural venous drainage is present. *From Spetzler RF, Detwiler PW, Riina HA, Porter RW: Modified classification of spinal cord vascular lesions. J Neurosurg 96 (2 Suppl):145–156, 2002, Fig. 2. Used with permission from Journal of Neurosurgery*

Associated AVMs and AVFs that are exclusively intradural in SAMS have also been described. Because of their rare occurrence in SAMS, their epidemiology and presentation have not been analyzed in this syndrome. In general, the characteristics of patients with spinal pial AVFs are similar to those of patients with spinal intramedullary AVMs, as found in a review of 213 cases with a mean age of 32 years; however, there was a slight male sex predilection [25]. Most patients (93%) had symptomatic lesions. Only a few (5%) of the patients with pial AVFs had SAMS.

4 Natural History

The natural history of spinal vascular malformations in patients with SAMS has not been specifically studied. It is unclear whether the natural history of purely extradural or intradural lesions in SAMS patients differs from that of the collective cohort of patients with these lesions without metameric disease [2, 22, 25]. In one analysis of 28 SAMS patients, 25% developed new aneurysms or their existing aneurysms grew larger over the angiographic follow-up period (mean, 85 months; range, 3–309 months). In contrast, only 3.5% of the non-SAMS patients developed new aneurysms or experienced growth of existing aneurysms [5].

One literature review reported a 2.1% annual hemorrhage risk for extradural–intradural AVMs (17 hemorrhages occurring over 825.7 patient-years) [2]. Multivariate analysis showed that associated aneurysms and younger age were significant risk factors for hemorrhage. It is important to underscore that the true natural history of extradural–intradural AVMs also compounds the risk of hemorrhage with the risk of developing acute or progressive deficits resulting from nonhemorrhagic phenomena (i.e., mass effect or venous hypertension). Although this risk has been poorly quantified, it is generally agreed that the overall natural course of these formidable lesions connotes a poor prognosis [2, 19, 20].

5 Treatment

Extradural AVFs, intramedullary AVMs, pial AVFs, and cavernous malformations diagnosed as a component of SAMS should be treated as sporadic lesions are treated [2, 16, 22, 24–31]. Symptomatic lesions should be excised, as should asymptomatic lesions with high-risk features (e.g., aneurysms, high-flow shunts contributing to venous hypertension, and lesions with considerable mass effect). Extradural–intradural AVMs, the most common spinal vascular malformations found in metameric disease, are far more complex and require individualized approaches. Angiographic cure may not be possible, and treatment should aim to mitigate the progression of neurological symptoms by reducing mass effect, venous hypertension, and the risk of hemorrhage from associated aneurysms. A combination of endovascular and microsurgery is often the treatment of choice, because it allows for decompression of mass effect [19, 28]. Prior to embolization, neurophysiological monitoring in the form of somatosensory- and motor-evoked potentials is crucial [5]. Provocative testing may be performed with superselective injection of amobarbital. Extradural components are embolized via radicular feeders; intradural components, if treatment is feasible, are accessed via the posterior spinal artery, which is safer than approaching via the anterior spinal artery [5].

The concept of palliative embolization of extradural–intradural spinal AVMs was described by Djindjian as early as 1975 [32]. In this original series of 11 cases, Djindjian advocated embolization of the extradural component of the malformation. Multiple subsequent reports of targeted partial treatment, including successful selective treatment of associated aneurysms, have since been published [2, 6, 11, 13, 15, 26, 33].

In one large endovascular series of 28 patients with spinal metameric syndromes, 26 patients underwent treatment in 50 sessions [5]. Neurological deterioration after treatment occurred in 4 patients; in 1 patient it was permanent. Of 9 patients followed postoperatively for less than 5 years, 5 were improved, 3 were the same and 1 was worse. Of 14 patients with more than 5 years' follow-up, 4 were improved, 4 were the same, and 6 were worse.

In one review of 51 patients with extradural–intradural spinal AVMs, 44% of patients were treated with embolization alone, 24% with embolization and microsurgery, 22% did not undergo treatment, and 9% underwent resection alone [2]. Overall worsening after treatment was reported in 17%, a higher rate than that reported for treatment of intramedullary AVMs [2]. Reported angiographic obliteration was achieved in 8 of 25 cases (32%), but this may be an overly optimistic estimate, inflated by amalgamated cases reported only in the context of successful results. No hemorrhages were reported for a follow-up period of 57.9 patient-years, primarily reflecting partially treated lesions and the trend toward protection from hemorrhage compared to the preoperative hemorrhage rate ($p = 0.12$). These findings suggest that the partial treatment of these malformations, especially AVM-associated aneurysms, may lessen the risk of hemorrhage.

6 Pearls

1. SAMS is defined by the presence of at least 2 separate vascular malformations in the same embryonic metamere.
2. The most common cutaneous manifestations are nevus flammeus (capillary malformation) and angiokeratomas.
3. The most common associated spinal vascular malformation is the extradural–intradural AVM.
4. Other associated vascular malformations, although exceedingly rare, include extradural AVFs, intradural AVMs or AVFs, and cavernous malformations. In these cases, the spinal vascular malformation should be approached and treated in the same fashion as sporadic lesions.
5. Patients with cutaneous lesions and unexplained radicular pain or neurological symptoms must undergo further evaluation. Lesions may become symptomatic as a result of venous hypertension, mass effect from venous ectasia, associated aneurysms, or acutely from hemorrhage. Neonates may present with congestive heart failure.
6. Extradural–intradural AVMs have the highest rate of associated aneurysms compared with other spinal vascular malformations.
7. For extradural–intradural AVMs, curative treatment may not be possible; in these patients, treatment should aim to mitigate the progression of neurological deficits by reducing mass effect, venous hypertension, and the risk of hemorrhage from associated aneurysms.
8. For extradural–intradural AVMs, treatment is often primarily endovascular with surgery utilized for the purpose of decompression of mass effect.

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Vascular Malformations of the Spine

Paul M. Foreman, Philip G. R. Schmalz, John P. Deveikis, and Mark R. Harrigan

1 Introduction

Spinal vascular malformations are rare lesions that comprise a variety of unique anomalies of the arterial and venous anatomy of the spine, nerve roots, and spinal cord. These lesions can present with insidious onset of signs and symptoms, subacute neurologic decline, or acute deterioration depending on the type of malformation and mechanism of spinal cord injury.

Virchow is credited with the first reported description of a spinal vascular malformation in a German manuscript entitled *Die Krankhaften Geschwulste* published in 1865, [1, 2]. He described two groups: angioma cavernosum and angioma racemosum, [1, 2]. This was an autopsy report and at the time these were felt, albeit incorrectly, to be neoplastic in origin, [1, 2]. The first operation on a spinal vascular malformation was reported by Berenbruch in 1890 where he describes a case of multiple angiolipomas in association with an "angioma" of the spinal cord [1, 3]. An advancement in the understanding of spinal vascular malformations occurred in 1912 when Charles Elsberg attempted to excise a spinal arteriovenous malformation (AVM) in a thirteen-year-old boy [1, 4]. His three-tier classification scheme of aneurysm, angioma, and dilation of veins provides insight

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into the relative lack of understanding of these complex lesions at the time [4]. The 1960's ushered in a new era in the understanding of spinal vascular lesions led by the emergence of spinal angiography [1, 5].

While several classification schemes of spinal vascular malformations have been described, the following four-tier classification is the most commonly used: Type I, dural arteriovenous fistula (AVF); Type II, intramedullary arteriovenous malformation; Type III, juvenile arteriovenous malformation; and Type IV, intradural perimedullary arteriovenous fistula. Additional vascular lesions that fall outside the four-tier system but are of particular importance in the pediatric patient are cavernous malformations and spinal aneurysms.

This chapter will detail the pathophysiology, clinical features, and treatment of spinal vascular malformations with an emphasis on the pediatric patient population.

2 Dural Arteriovenous Fistulas, Type I

Type I spinal vascular lesions (also known as spinal dural arteriovenous fistulas) consist of an abnormal communication between the radicular artery in the nerve root sleeve and the intradural venous system, causing venous hypertension (Fig. 1). While they are the most common spinal vascular lesions among adults, they are generally thought to be acquired in middle-aged or elderly adults, and they are exceedingly rare in the pediatric population [6]. They will not be discussed in depth in this chapter.

3 Intramedullary Arteriovenous Malformations, Type II

Type II spinal vascular lesions consist of intramedullary arteriovenous malformations, also known as glomus AVMs. The anatomy of Type II lesions are highly variable; the nidus may be compact or diffuse, feeding vessels may be singular or numerous and may arise from the anterior or posterior spinal arteries, and venous drainage can be simple or complex (Fig. 2). Type II lesions represent high-flow, high-pressure lesions with supply derived from the arterial system.

3.1 Epidemiology and Clinical Features

Type II spinal vascular lesions are the second most common type of spinal vascular lesion across all age groups, accounting for just over a third of spinal vascular lesions [8, 9]. Variability in clinical presentation has likely led to under-diagnosis in the general population, and thus the true incidence is unknown. Average age of presentation is in young adulthood, [10] with approximately 20% presenting at 18 years or younger [11]. Spinal cord AVMs are located in the cervical cord in 30%

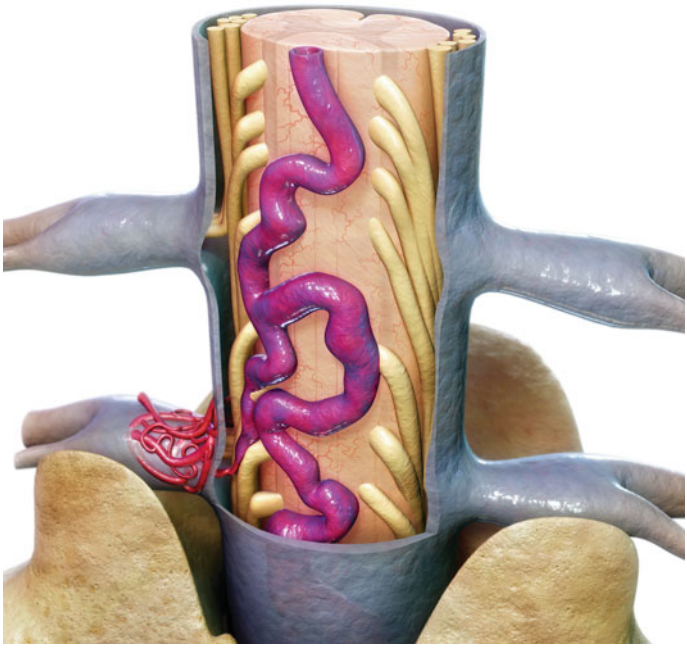

Fig. 1 Type I spinal vascular lesion, also known as a dural arteriovenous fistula. These lesions consist of an abnormal communication between the radicular artery in the nerve root sleeve and the intradural venous system [7] (*Used with permission from the Barrow Neurological Institute, Phoenix, Arizona*)

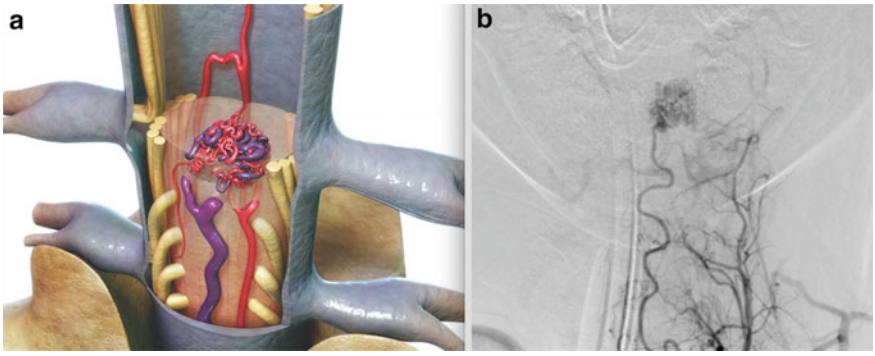

Fig. 2 **a** Type II spinal vascular lesion, also known as an intramedullary arteriovenous malformation. These lesions consist of a nidus fed by vessels that can include branches of the anterior and/or posterior spinal arteries. Anatomy is highly variable [7] (*Used with permission from the Barrow Neurological Institute, Phoenix, Arizona*). **b** Diagnostic spinal angiogram demonstrating a Type II spinal vascular lesion involving the cervical spinal cord

of cases and in the thoracolumbar cord in 70%, which is proportional to the volume of the spinal cord at each segment [12]. Syndromic associations include neurofibromatosis, Rendu-Osler-Weber, Klippel-Trenaunay-Weber, and Parkes-Weber syndromes [13–15].

Clinical presentation can be acute, subacute, or chronic and encompass a wide range of symptoms including but not limited to pain, motor deficits, sensory disturbances, bowel and bladder dysfunction, and headache. Hemorrhage, intraparenchymal or subarachnoid, is the most common presentation [10, 16, 17], and tends to be more common among children than adults [18]. A review of over 70 cases of Type II spinal vascular lesions in the pediatric population found that 53% presented with acute symptoms as compared to 31% presenting with chronic, progressive symptomatology [6]. Re-hemorrhage appears to occur at higher rates for spinal cord AVMs as compared to brain AVMs, occurring in 10% of patients at 1 month and in 40% within the first year after the initial hemorrhage [18]. Associated aneurysms are present in 20–44% (44% includes aneurysms of the venous system) of cases and portend a higher rate of hemorrhage [10]. One retrospective series reported an associated spinal aneurysm in 20% of patients with an intramedullary AVM; all suffered subarachnoid hemorrhage [19]. Venous congestion and vascular steal can also produce symptoms in the absence of hemorrhage, [10] and likely account for the more insidious presentations associated with Type II lesions.

Conus medullaris AVMs represent a distinct subtype of Type II lesions and are characterized by multiple feeding arteries, multiple niduses, and complex venous drainage [20]. They are unique in their propensity to produce symptoms of both radiculopathy and myelopathy [20].

The primary imaging modalities involved in the diagnosis of Type II spinal vascular lesions are MRI and catheter angiography. MRI is highly sensitive for the detection of spinal AVMs [21, 22]. Typical features include a focal dilatation of the cord around the lesion, an area of low signal around the nidus on T1- and T2-weighted imaging that corresponds to hemosiderin deposition, and multiple flow voids (on axial images) and serpentine structures (on sagittal and coronal images) due to feeding and draining vessels. T2 signal change may represent cord edema due to venous congestion [23]. Catheter angiography remains the *gold standard* for the evaluation of spinal cord AVMs. A complete angiogram to characterize all feeding and draining vessels, look for aneurysms, and distinguish the lesion from associated normal vessels is necessary to confirm the diagnosis and plan treatment.

3.2 Management

The natural history of untreated Type II spinal vascular lesions is poorly defined. Progressive evolution of symptoms, by either worsening myelopathy or subsequent hemorrhages, is reported in 31–71% of patients observed over several years [10,

24–26]. Given the risk of hemorrhage and cumulative risk of neurologic deficit, treatment is generally recommended in the pediatric population when feasible.

Because spinal cord AVM anatomy is variable and the risk of potential complications is relatively high, decision making about the management of these patients is highly individualized. Patients with a spinal cord AVM consisting of a compact, surgically accessible nidus may be good candidates for surgery. Embolization may be a useful adjunct to surgery, or, in some cases, may provide symptomatic relief without necessarily obliterating the lesion.

With *appropriate case selection* (i.e., by operating on patients with a relatively compact, surgically accessible nidus), obliteration of the lesion can be achieved in up to 94% of cases with good functional outcome in 86% [16]. As expected, surgical results are better with compact AVMs compared with AVMs with a diffuse nidus [27]. Surgical approach is via a standard laminotomy. Exposure should extend at least one level above and one level below the lesion. A small myelotomy is done in the posterior median sulcus, and the spinal cord is split between the two posterior columns. Alternatively, a posterolateral myelotomy, done in the dorsal root entry zone between two or more nerve roots, can provide access to lateral lesions.

Rates of complete obliteration with endovascular embolization range from 24–53% with permanent complication rates of 10–14% [28]. The first-line agent for embolization of any cord AVM is generally NBCA or Onyx, provided that the microcatheter tip can be placed adjacent to or within the nidus. Particulate embolization should be reserved for cases in which the microcatheter tip is relatively proximal to the lesion (i.e., when the catheter tip cannot be placed within or directly adjacent to the nidus). Because the anterior spinal artery and it's branches are typically <250 μm, particles $\geq$ 300 μm should be used to avoid inadvertent embolization of normal arteries [29, 30].

While early reports of stereotactic radiosurgery for the treatment of Type II lesions have been promising [31], experience with this technique is lacking in the pediatric population.

4 Type III, Juvenile Arteriovenous Malformations

Type III spinal vascular lesions, also known as juvenile arteriovenous malformations or spinal arteriovenous metameric syndromes, are complex AVMs that tend to affect vessels in a metameric pattern often involving the spinal cord, vertebrae, and paraspinal musculature (Fig. 3). Spinal arteriovenous metameric syndrome (SAMS) will be covered in depth in Chap. 10; we include it here for completeness. These lesions are rare and may occur as a part of Cobb Syndrome. Cobb Syndrome represents involvement of the entire metamere including an associated vascular skin nevus overlying the spinal lesion. While these terms (Type III spinal vascular lesion, juvenile AVM, and Cobb Syndrome) are often used synonymously, Cobb Syndrome has been reported in association with less complex spinal vascular

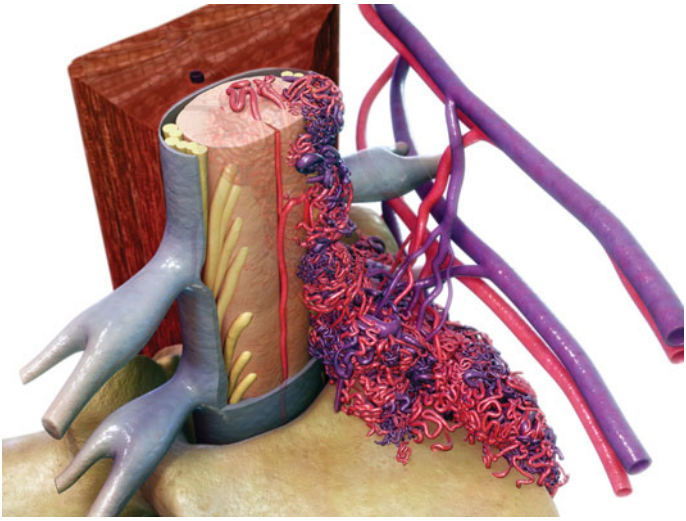

Fig. 3 Type III spinal vascular lesion, also known as a juvenile arteriovenous malformation. These lesions are complex AVMs that tend to affect vessels in a metameric pattern often involving the spinal cord, vertebrae, and paraspinal musculature [7] (*Used with permission from the Barrow Neurological Institute, Phoenix, Arizona*)

lesions such as Type IV intradural perimedullary arteriovenous fistulas [32]. Therefore, type III spinal vascular lesions and Cobb syndrome are not exactly synonymous.

4.1 Epidemiology and Clinical Features

The true incidence of Type III vascular lesions is difficult to estimate due to the rarity, variable presentation, and inconsistent classification of these lesions. Berenbruch is credited with the first description of the syndrome in an 1890 publication entitled *Ein Fall von multiplen Angiolipomen kombiniert mit einem Angiom des Rueckenmarkes (A case of multiple angiolipoma combined with an angioma of the spinal cord)* [3]. However, it was not truly recognized as a clinical entity until 1915 with the work of Stanley Cobb, a resident of Harvey Cushing [33]. An eight-year-old boy presented with acute paraplegia and was noted to have "areas of dark reddish skin" over the 9th and 12th rib [33]. The intraoperative vascular findings were termed "cavernous pial arachnoid angiomas" by Cushing [33]. Cobb reported the case and subsequently was credited with the eponym "Cobb syndrome" [32]. While the complete metatmeric syndrome has been reported in fewer than 40 patients [34], the cutaneous findings can be subtle and easily missed, leading to underestimation of the incidence. Other authors have estimated its

incidence as high as 10% [35] or 20% [36] among patients with spinal vascular lesions. A male predominance has also been noted [37].

Clinical presentation is variable ranging from acute onset plegia to more insidious symptoms of pain and headache. The natural history of these lesions is poorly defined and unpredictable, making accurate prognosis difficult [34]. However, most authors agree that prognosis tends to be poor in patients with these lesions once they develop symptoms [37].

4.2 Management

The most common imaging modalities for the evaluation of Type III lesions are MRI and catheter angiography. MRI provides a sensitive and non-invasive technique for screening, with the benefit of providing high resolution anatomic detail. Catheter angiography is complementary to MRI and provides an understanding of the lesion's complex angioarchitecture. While catheter angiography is regarded by most as the *gold standard* for imaging of Type III lesions, it has been compared to shining a small flashlight on an elephant in a dark room because only a part of the lesion can be seen with injection of contrast into any particular artery.

These lesions are extremely difficult to treat and treatment decisions are individualized on the basis of current neurologic function, angioarchitecture of the lesion, and risks/benefits of the proposed intervention [34]. Although complete lesion resection by staged embolization followed by surgery has been reported [38, 39], fatal complications have been reported with this approach [40]. Expectant management, surgery, endovascular embolization, radiation, and corticosteroid administration have been used in varying combinations [34]. Optimal management depends on a multidisciplinary team with a goal of alleviating the patient's symptoms and, when possible, reducing the risk of future neurologic decline.

5 Type IV, Intradural Perimedullary Arteriovenous Fistula

Type IV spinal vascular lesions consist of a fistula between a spinal cord artery or arteries and the coronal venous plexus, often with an associated varix at the artery to vein transition point (Fig. 4). They are located on the pial surface of the spinal cord and tend to involve the ventral or lateral surface of the cord. Type IV lesions can be further subdivided into A-C based on size and drainage characteristics [20]. Type A fistulas are small shunts in which blood flow is sluggish and venous hypertension is modest. Type B and C have progressively larger shunts with Type C exhibiting a giant fistula and a markedly distended venous system.

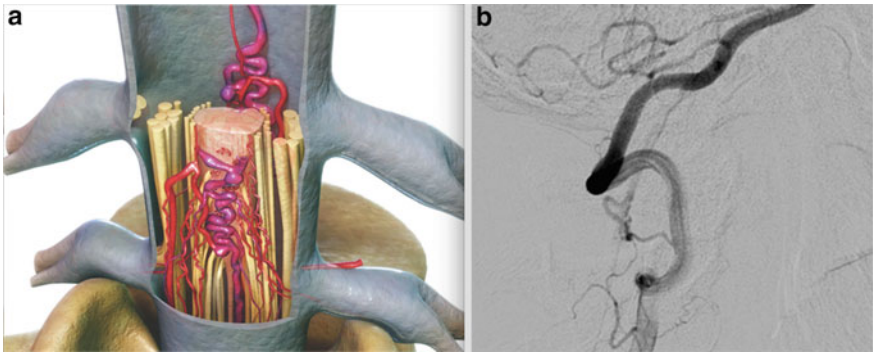

Fig. 4 **a** Type IV spinal vascular lesion, also known as an intradural perimedullary arteriovenous fistula, involving the conus medullaris. These lesions consist of a fistula between a spinal cord artery or arteries and the coronal venous plexus, often with an associated varix at the artery to vein transition point [7] (*Used with permission from the Barrow Neurological Institute, Phoenix, Arizona*). **b** Diagnostic spinal angiogram demonstrating a Type IV spinal vascular lesion involving the cervical spinal cord

5.1 Epidemiology and Clinical Features

Intradural perimedullary arteriovenous fistulas are thought to account for 10–20% of all spinal vascular lesions [9, 10]. Within the pediatric population, Type IV lesions rank only behind Type II lesions in incidence comprising just over 20% of spinal vascular malfomations [6]. Type IV lesions are strongly associated with HHT [37, 41]. The location of these lesions along the spinal axis is bimodal, with most occurring at the thoracolumbar junction, particularly at the conus, and to a lesser extent, the upper cervical region [42].

Average age of presentation is in early adulthood but there are reports of diagnosis in infancy [9, 43, 44]. Pediatric patients with Type IV lesions present with acute versus chronic symptoms in roughly equal proportions [6]. While most patients present with symptoms attributable to venous hypertension or mass effect, subarachnoid hemorrhage may occur.

5.2 Management

Imaging of Type IV lesions most often involves MRI and catheter angiography, and to a lesser extent CT angiography and myelography. Type B and C lesions characteristically demonstrate large flow void on MRI [44]. However, it is important to note that type A lesions may not be apparent on MRI [45], and myelography or angiography should be done if a type IV-A lesion is suspected but not visualized on MRI. Catheter angiography remains the *gold standard* for the evaluation of a Type IV lesion and should be completed to confirm the diagnosis and plan therapy.

The natural history of intradural perimedullary AVFs is thought to be one of progressive neurologic decline and thus most authors recommend prompt diagnosis and treatment. The goal of treatment is disconnection or occlusion at the site of the fistula, which can be accomplished by surgery, embolization, or a combination of both. Treatment decisions must be individualized and are largely determined by the angioarchitecture of the lesion.

6 Cavernous Malformations

Cavernous malformations are well-circumscribed lobulated lesions composed of dilated, thin-walled vascular structures with a gross appearance of a mulberry (Fig. 5). They can occur sporadically or in association with a familial form of the disease. Cavernous malformations are located throughout the central nervous system (CNS), according to the volume of the CNS compartment [46].

6.1 Epidemiology and Clinical Features

Cavernous malformations of the CNS have an estimated incidence of 0.37–0.53% in the pediatric population [47]. Approximately 5% of these are located in the spine,

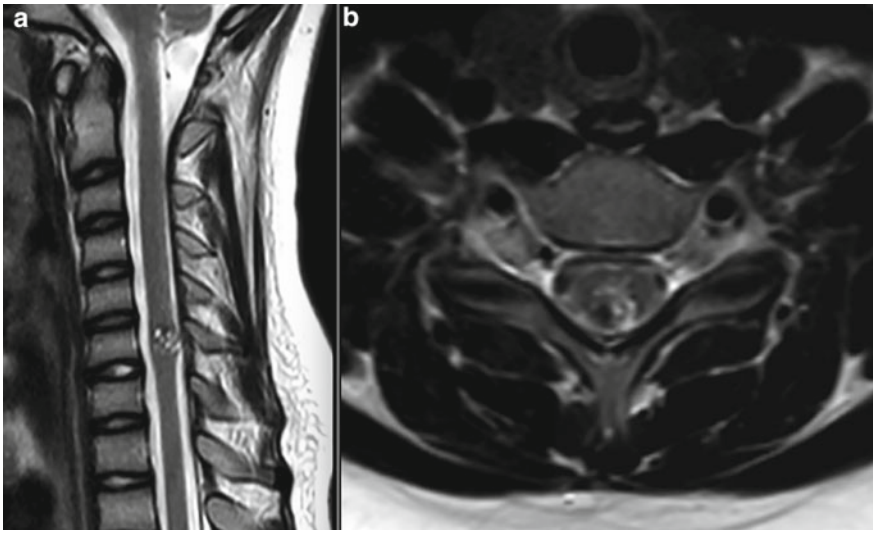

Fig. 5 **a** Sagittal T2 weighted MRI of the cervical spine demonstrating an intramedullary cavernous malformation; note the "popcorn like" appearance. **b** Axial T2 weighted MRI of the cervical spine demonstrating an intramedullary cavernous malformation

making these lesions quite rare among the general population [48]. Within the spine, a cervical or thoracic location is the most commonly reported [48–50].

The majority of pediatric patients present with an acute neurologic decline related to hemorrhage [49, 51]. Typical signs and symptoms include acute onset myelopathy and pain. The natural history of spinal cavernous malformations in the pediatric population is not known. Annual rates of symptomatic re-hemorrhage vary widely [52, 53]. However, given the eloquence of the parenchyma of the spinal cord and the risk of acute and profound neurologic deterioration, surgical resection of accessible lesions is advocated by most authors [54].

6.2 Management

MRI is the radiographic technique of choice for the diagnosis and follow-up of cavernous malformations. Characteristic findings include discrete areas of mixed signal intensity surrounded by a black rim of diminished signal intensity, often referred to as "popcorn like". Catheter angiography is not necessary, as these lesions are classically "angiographically occult".

Complete microsurgical resection remains the proven therapeutic modality for treatment of spinal cavernous malformations. Most intramedullary cavernous malformations are approached dorsally with a midline myelotomy for deep, midline lesions, or entry into the dorsal root entry zone for more laterally located lesions. Surgical results are usually good, with one study reporting improvement of stabilization of symptoms in over 80% of patients [49]. While stereotactic radiosurgery has been used to treat cavernous malformations, its utility is not established and it is generally not recommended for the treatment of the pediatric patient.

6.3 Familial Cavernous Malformations

The familial form is typically manifests as multiple lesions in the setting of a positive family history. Genetic mode of inheritance is autosomal dominant. Three genes have been identified: CCM1 on chromosome 7q, CCM2 on 7p, and CCM3 on 3q [55–58]. No differences in clinical presentation have been identified among the three different mutations. While the incidence of spine lesions associated with the familial form is not known, multiple lesions are found in over half of patients [59–61].

7 Spinal Aneurysms

Aneurysms within the spinal canal are exceedingly rare, with a recent systematic review identifying only 140 spinal aneurysms reported over the last 70 years [62]. Although some spinal aneurysms occur as an isolated lesion, most are thought to

arise in association with an AVM or coarctation of the aorta [19, 62–64]. Isolated spinal aneurysms tend to occur in older patients and are more likely to present with hemorrhage [62]. It is important to note that intracranial subarachnoid hemorrhage, with a negative diagnostic cerebral angiogram, can be encountered in a significant portion of these patients [62]. Thus it is imperative to consider the possibility of a spinal aneurysm during the evaluation of a cerebral angiogram-negative subarachnoid hemorrhage.

7.1 Spinal Aneurysms Associated with AVM

Spinal aneurysms complicate approximately 20% of spinal AVMs and appear to have a strong association with developmental vascular anomalies, such as metameric angiomatosis [19]. Ten percent of all spinal aneurysms occur in children less than 10 year of age; patients with spinal aneurysms associated with an AVMs tend to be younger than those presenting with isolated spinal aneurysms [62]. The presence of a spinal aneurysm in association with an AVM is felt to carry an increased risk of hemorrhage as compared to an isolated AMV [62]. Location of the aneurysm influences its rupture risk with intranidal aneurysms tending to hemorrhage more often than feeding artery aneurysms [62]. While the majority of patients present with signs and symptoms related to hemorrhage, up to 20% can present with complaints not attributable to a hemorrhage [62]. This tends to be more common among young patients [62, 65]. Spinal aneurysms associated with AVMs can be treated with microsurgery or endovascular techniques and treatment decisions should account for the associated AVM. Therapeutic outcome is largely related to the type of associated AVM, with extramedullary AVMs or AVFs faring better than intramedullary AVMs [62]. Resolution or a decrease in size of an aneurysm has been reported following treatment of the associated AVM [66].

7.2 Isolated Spinal Aneurysms

Isolated spinal artery aneurysms are rare lesions typically affecting adults with an average age of presentation of 49 years [62]. They tend to be associated with coartaction of the aorta, connective tissue diseases, autoimmune diseases, and renal transplant [62]. The vast majority of patients presents with signs and symptoms of hemorrhage including headache, back pain, myelopathy, and vomiting [62]. However, particularly large aneurysms may presents with signs and symptoms of myelopathy or radiculopathy due to mass effect [67]. The most common location for an isolated spinal aneurysm is the anterior spinal artery, followed by radicular/radiculopial arteries [62]. Both microsurgery and endovascular techniques have demonstrated efficacy in the treatment of isolated spinal aneurysms; treatment should be tailored based on the angiographic characteristic of the lesion and the clinical situation [62]. Presentation with hemorrhage, cord dysfunction, or associated comorbid conditions predict a poor outcome [62].

8 Conclusions

Spinal vascular lesions are rare entities but pose significant risk to the pediatric patient. The pediatric patient is more likely to have an associated syndromic abnormality (i.e. HHT) and is more likely to presents with an acute neurologic decline. Given that the natural history of these lesions is poorly elucidated, treatment decisions must be individualized. The presumed risk of neurologic decline related to the lesion must be weighed against the risk of therapy. In most circumstances treatment is recommended, as the natural history is believed to be one of neurologic deterioration.

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Vascular Malformations of the Extracranial Head and Neck in Children and Young Adults

Sudhakar Vadivelu, Manish Patel, Adrienne Hammill, and Todd Abruzzo

1 Introduction

Common extra-cranial vascular malformations of the head and neck encountered in the pediatric population include capillary malformations (CM), venous malformations (VM), lymphatic malformations (LM) and arteriovenous malformations (AVM). These subtypes of vascular malformations are differentiated clinically, radiologically and pathologically according to the types of vessels involved. Vascular malformations of the extracranial head and neck are often "combined" lesions, displaying multiple components comprised of different vessel subtypes (i.e. venolymphatic malformations). The basis of this phenomenon likely involves the acquisition of defects during developmental programming in multipotential endothelial progenitor cells.Recent advances in vascular biology have further enabled pathological differentiation of vascular malformations according to specific endothelial molecular phenotypes (lymphatic *vs* venous).

All vascular malformations regardless of their endothelial phenotype origin are characterized by transpatial distribution that extends across fascial boundaries and tissue planes. Vascular malformations are differentiated from vascular tumors such

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as hemangiomas and kaposiform hemangioendotheliomas (KHE) because they are typically congenital errors of vessel morphogenesis, present at birth (ISSVA Classification of Vascular Anomalies ©2014 International Society for the Study of Vascular Anomalies).

In contrast to vascular tumors, vascular malformations in children generally grow in proportion to the child, however the angio-architecture and size of a vascular malformation and individual components of a vascular malformation can be strongly modulated through inflammation, angioectasia, angioproliferative changes, flow-induced mural atrophy,mechanical stresses, and intimal hyperplasia with steno-occlusive change or thrombosis. These processes can be triggered hormonal changes (during puberty or pregnancy or due to estrogen oral contraceptive use), therapeutic manipulation (partial embolization) or complicated by hemorrhage or thrombosis (in the setting of trauma or infection).

1. Diagnostic and therapeutic approaches to vascular malformations of the extra-cranial head and neck encountered in children must consider the type of malformation, the anatomic distribution of the malformation, the symptoms expressed in relation to the malformation, the age of the patient, the anticipated natural history of the lesion and the potential or expected morbidity associated with each of the various treatment options. Specific therapeutic objectives should always be prespecified and expressed clearly to parents prior to initiating treatment. Eradication or more commonly reduction of a vascular malformation should not be considered therapeutic objectives, but rather means of achieving a therapeutic objectives. Therapeutic objectives should be centered around the relief and/or prevention of: Aerodigestive tract impairment.

    a. Swallowing impairment
    b. Speech impairment
    c. Mastication impairment
    d. Chronic aspiration
    e. Progressive or intermittent airway obstruction

2. Oculomotor or optic impairment.
3. Hemorrhage into aerodigestive tract, lacrimal duct system, salivary duct system, sinonasal tract, external auditory canal, or transcutaneous.
4. Pain.
5. Dental malocclusion.
6. Hypomorphic skeletal changes (i.e. orbital hypoplasia, mandibular hypoplasia) or regional tissue overgrowth.
7. Neurologic impairment.
8. Mechanical effects.
9. Circulatory effects 2° to venous congestion or arterial steal phenomena.
10. High output cardiac failure.
11. Psychosocial and emotional impairment.

During the first decade of life, growth and development of the maxillofacial skeleton can be adversely modulated by the mechanical and/or hemodynamic effects of a vascular malformation, and early treatment can prevent or ameliorate these effects.

The care of a child with a vascular malformation of the extracranial head or neck must address several needs that are specific to the pediatric population. This care demands the expertise and skills of a team of pediatric specialists experienced in head and neck surgery, neurosurgery, maxillofacial surgery, dentistry, plastic surgery, hematology/oncology, dermatology, interventional radiology, critical care, anesthesiology, pathology, and genetics.

A wide range of therapeutic modalities are available in modern practice including sclerotherapy, embolization, surgical resection, laser photocoagulation and anti-angiogenic drugs. In children with vascular malformations of the extracranial head and neck, formulating a treatment plan will involve a decision to pursue curative treatment or more commonly a palliative management strategy directed at symptom control and optimization of function. Curative treatment of extracranial head and neck vascular malformations in children is most often not feasible or not indicated. If a curative strategy is likely to exceed the harm and impairment anticipated from natural history, a palliative management strategy is the better choice. Knowledge of normal head and neck development, experience dealing with the consequences of lesion natural history and advanced understanding of treatment related risks are critical for proper decision making.

The successful surgical and interventional management of children with vascular malformations of the extracranial head and neck heavily relies on support from subspecialists in pediatric anesthesiology and critical care. Complex airways requiring advanced intubation techniques or tracheostomy tube placement are not infrequently encountered in this group. In small children with high flow arteriovenous shunts, improper anesthetic management may precipitate congestive cardiac failure and pulmonary edema. Prolonged periods of monitored sedation are often needed to facilitate quiet bed rest after trans-arterial interventions. Some lesions may call for evoked potential monitoring and provocative intra-arterial administration of lidocaine with monitoring of somatosensory evoked potentials and/or motor evoked potentials.

2 Low Flow Vascular Malformations

VMs and LMs are classified as low flow vascular malformations according to the revised ISSVA classification system. VMs are one of the most common types of slow flow vascular malformations. They are comprised of slow-flow ectatic vessels that have abnormal endothelial lining. They are classified into four patterns based on their venous draining patterns (Puig).

Type I: isolated malformation without discernible venous drainage.
Type II: lesion draining into normal veins.

Type III: lesion draining into dysplastic veins.

Type IV: lesion consists primarily of venous ectasia.

VM can be unilocular vs. multilocular (Fig. 1), and typically present as a soft palpable mass with overlying bluish discoloration. These tend to expand when placed in a dependent position. Occasionally, palpable phleobolithis are present. These lesions are often painful, related to localized intravascular clotting and inflammation caused by slow flow and abnormal endothelium. Large, complex, or multifocal lesions may have a disseminated coagulopathy with an elevated baseline D-dimer, low fibrinogen level, and even mild thrombocytopenia.

LMs are another common type of slow flow vascular malformation occurring in the head and neck (Fig. 2). Lesions vary in size and can be classified as macrocystic, microcystic, or mixed based on the size of the cysts. LMs can involve the deep and superficial neck with involvement commonly extending to the airway and tongue. Pure microcystic malformation may appear solid on imaging. Characteristically these malformations stain positive by immunohistochemistry for lymphatic markers such as PROX-1 and D2-40.

Close observation is a common conservative approach to slow-flow vascular malformations, both VMs and LMs, assuming that the patient has patent airway and intact swallowing function. First line treatment of these lesions routinely involves sclerotherapy, by direct puncture of the malformation followed by contrast injection. Assuming no direct communication of the malformation to the underlying

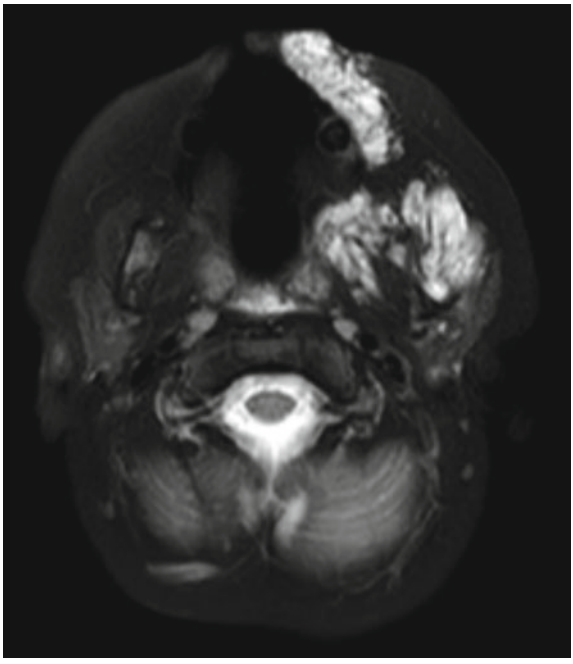

Fig. 1 Venous malformation

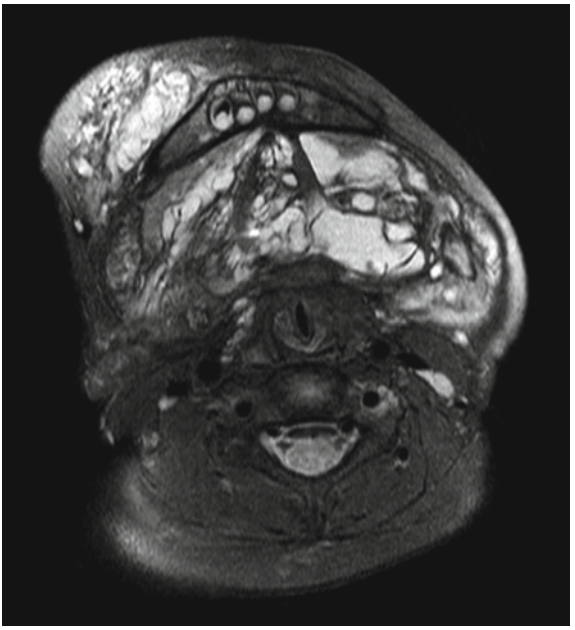

Fig. 2 Lymphatic malformation

deep venous system or skin, a sclerosant is injected. Common sclerosants include sodium tetradecyl sulfate (STS), doxycycline, bleomycin, and ethanol.

Surgical excision is reserved for symptomatic malformations not responsive to sclerotherapy, localized superficial malformations, and extensive microcystic malformations. For most malformations, this is not curative but rather intended as debulking for functional purposes. Depending on degree of and potential for airway involvement, elective tracheostomy may be required prior to intervention. Pre-surgical embolization with liquid embolic agent such as n-Butyl Cyanoacrylate can be used just prior to resection of localized venous malformation to better delineate the extent of the lesion and potentiate more complete resection.

Patients with baseline coagulopathy (elevated D-dimer and especially low fibrinogen) require systemic anticoagulation prior to any intervention to decrease risk of hemolysis, thrombosis and bleeding, and post procedural pain. In cases of severe underlying coagulopathy, fibrinogen infusion may be required during and/or after the procedure. Vigorous hydration post procedure is also required in these patients to minimize these risks.

More recently, medical therapy has begun to play a larger role in the treatment of slow-flow vascular malformations. The mTOR inhibitor sirolimus, and more recently everolimus, have been used in the treatment of complicated vascular malformations in multiple case reports and in a recently completed Phase 2 study. While initially used primarily in lesions with evidence of lymphatic differentiation, mTOR inhibitors have more recently come to be used in predominantly and even purely venous malformations as well. In lymphatic malformations, sirolimus can

decrease size of lesions, but has shown significant improvements in quality of life, including decreased pain, improved function, and decreased frequency of infections within these lesions. In venous malformations, there can be improvement in coagulopathy (decreased D-dimer, improvement or normalization in fibrinogen) with concomitant improvement in pain and function.

Optimal treatment of complicated slow-flow lesions often requires contributions from all modalities, pharmacologic, interventional and surgical, though the timing and order of therapies should be tailored to the individual patient based upon his/her symptoms and functional limitations.

3 Sinus Pericranii

Sinus pericranii (SP) are a subtype of venous malformation consisting of abnormal extracranial—intracranial venous communication; this is usually via an emissary transosseous vein [1, 2]. It is considered a type of low flow vascular malformation. It occurs in close communication with the cranial vault and most frequently involves the superior sagittal sinus (Fig. 3). The most common clinical symptoms include headaches, nausea, dizziness, and vertigo [1–5]. Although the pathophysiology has not been elucidated, it is hypothesized that the formation of SP may be associated with intracranial venous hypertension during early development. Most patients are actually asymptomatic at presentation, but seek care for size changes of this palpable lesion underneath the skin, color change during activities, and its static cosmetic appearance [1, 2]. These lesions are sometimes mistaken for other diagnoses in the differential for palpable skull masses including scalp abscesses, dermoid cysts, growing fractures, epidermoid, eosinophilic granulomas, and meningoencephaloceles [2]. Treatment for misdiagnosed lesions has led to reports of severe complications including hemorrhagic shock, stroke, retrograde cerebral sinovenous thrombosis, and intracranial infection [3]. Though the natural history of these lesions is not well understood, severe symptoms reported include increased intracranial pressure, bradypnea, bradycardia, ataxia, and hearing loss. Complications from observant management alone have included reports of air embolism, hemorrhagic stroke, and cardiac failure [2]. Variations in treatment strategy reported in the literature are largely due to the generalization that treatment is observation or surgical excision; recommendations are often based on limited workup (Fig. 4) because these lesions have historically been considered benign.

Classification systems for SP subtypes include both anatomical and functional. There are three anatomical subtypes: a. cul de sac—diverticulum of dural venous sinus, b. epidural venous collateral—diversion of intracranial drainage to subgaleal veins (intracranial to extracranial), and c. scalp venous collateral—diversion of scalp drainage to dural venous sinus (extracranial to intracranial). The workup algorithm proposed in recent years has suggested importance of a functional classification differentiating type 1 (dominant) from type 2 (accessory) SP [2]. Conventional digital subtraction angiography is the gold standard for diagnosis of SP

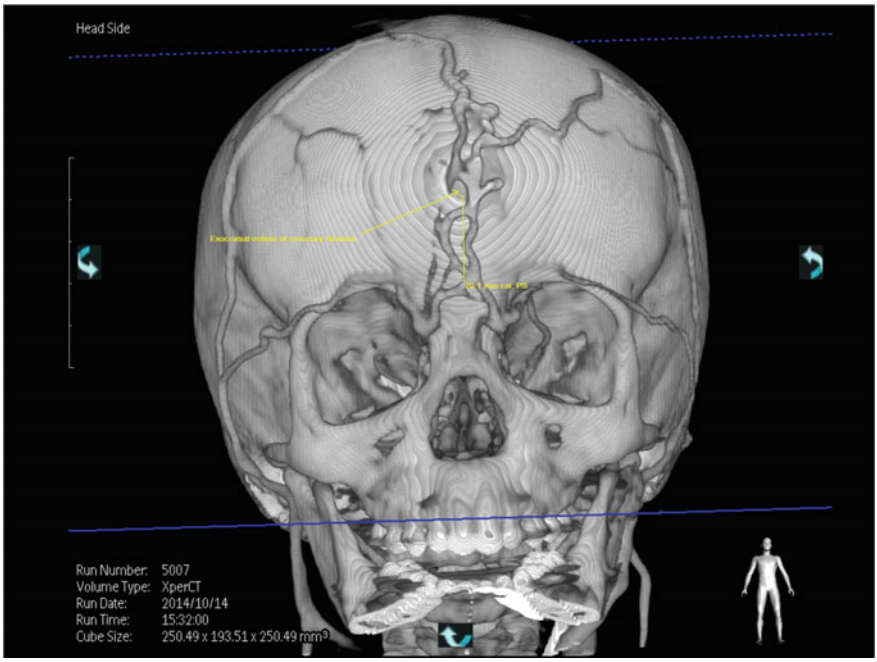

Fig. 3 Cone beam CT imaging of the type 1 sinus pericranii system. Exocranial ostium of of the EC-IC sinus pericranii emissary foramen (arrows)

and the only means for differentiating between type 1 (Fig. 5) and 2 SP [4]. The importance here is that the above mentioned severe procedure related complications are primarily limited to Type 1 SP [5] and as such it is strongly suggested that these not be treated as the brain venous drainage is dependent on this altered venous anatomy. In contrast, type 2 SP where the brain is not dependent on the SP for venous drainage is amenable to definitive treatment. Treatment options include predominantly surgical ligation with transosseous channel occlusion, and more recently trans-venous embolization or direct venous varix puncture embolization. Though uncommon, consideration of intraoperative blood loss during open surgical ligation or sinus occlusion beyond the fistulous connection during embolization techniques should be discussed to aid in determining optimal treatment recommendations for a pediatric patient with sinus pericranii [6].

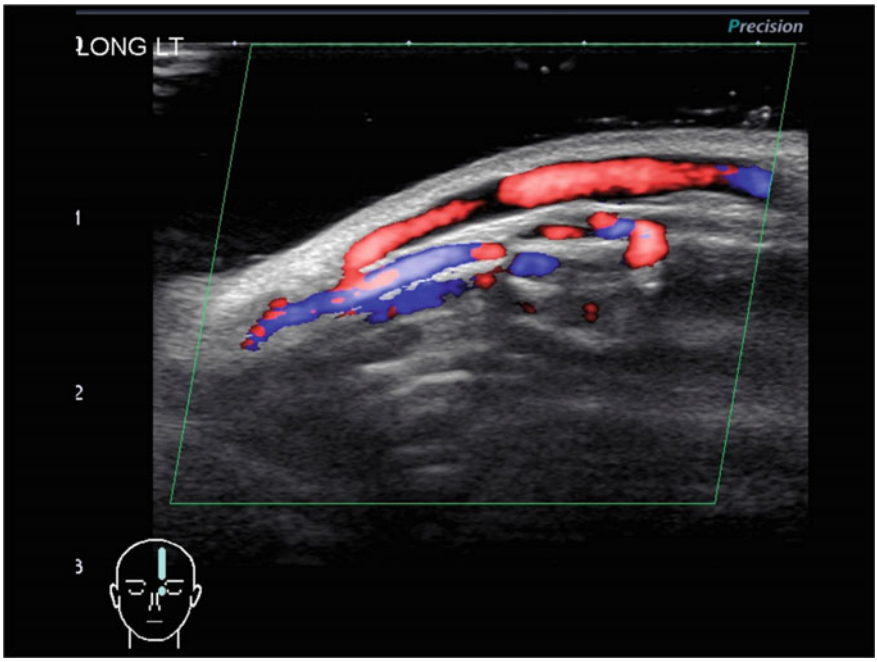

Fig. 4 Extracranial doppler ultrasonography demonstrating prominent frontal (forehead) extracranial vessels with communication within the intradiploic space but without definitive documention of intracranial extension

4 High Flow Vascular Malformations

While arteriovenous malformations (AVMs) and arteriovenous fistulae (AVF) as a group are generally classified as high flow vascular malformations, a wide range of angiographic and clinical phenotypes are encountered, including some phenotypes that are associated with relatively slow flow by angiographic standards. This aspect can make differentiation from hypervascular tumors difficult, particularly because most hypervascular tumors are associated with some degree of arteriovenous shunting. The magnitude of arteriovenous shunting in any lesion is determined by the cross-sectional diameter of the vascular channels forming the arteriovenous shunt zone or arteriovenous interface. AVMs and AVFs are differentiated according to angioarchitecture. While both types of lesions are characterized by developmental failure of the capillary segment of the vascular bed and anomalous vessels that do not express the normal molecular or histological phenotype of arteries or veins, AVMs feature a cluster of angiomatous vessels which form a complex network of arteriovenous shunts comprising the nidus of the AVM. In contrast, AVFs are generally characterized by arterialization of a single "venous structure"

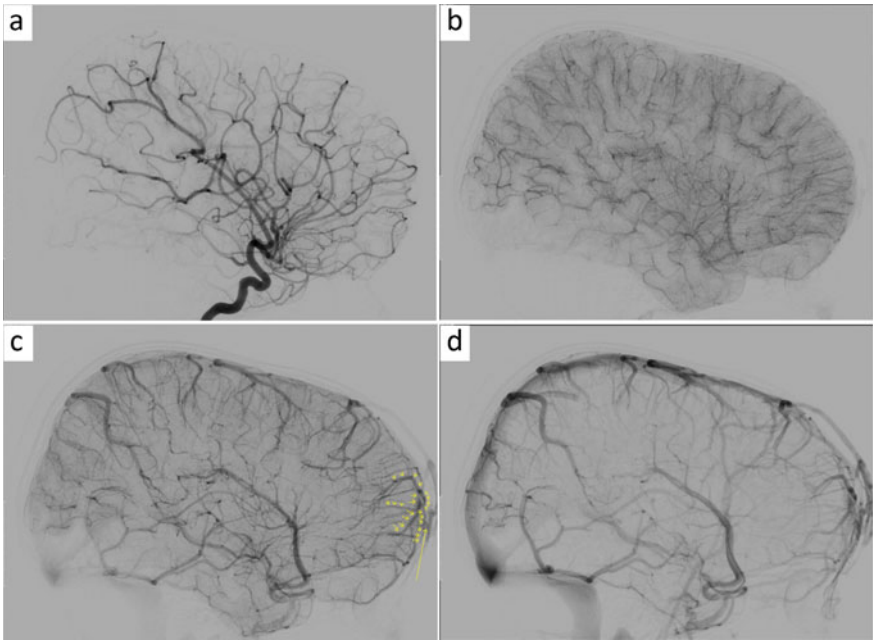

Fig. 5 Diagnostic cerebral angiogram demonstrating type 1 sinus pericranii, lateral projection in the **a** arterial phase, **b** capillary phase, **c** early venous phase demonstrating cortical veins (arrows) of the left anterior frontal lobe (frontopolar and orbitofrontal) are directly collected into a relatively large emissary venous channel that empties into **d** a large network of subgaleal venous channels comprising a dominant (type 1) sinus pericranii system

by one or more arterial feeders through macrofistulous connections. Arteriovenous shunt lesions (AVMs and AVFs) can produce clinical symptoms or interrupt normal development as a result of tissue ischemia (due to perfusion steal or venous congestion/insufficiency), hemorrhage or mechanical effects. The clinical manifestations expressed by an arteriovenous shunt lesion depend on its anatomical distribution, hemodynamic characteristics and evolutional stage. In general, the clinical manifestations of extracranial arteriovenous shunt lesions in the head and neck are the result of locoregional effects, however remote effects may occur when venous hypertension is transmitted across valveless conduits. For example, venous congestive myelopathy can develop when a high flow parachordal arteriovenous fistula (paraspinal type) involves the lateral compartment of the internal vertebral venous plexus and there is reflux into radiculomedullary veins. The Schobinger staging system attempts to correlate the severity of clinical symptoms with the evolutional stage of an AVM (Table). Although patients may progress from one Schobinger stage to the next, progression does not follow a predictable timeline or sequence, nor is progression consistently observed in all patients. Nevertheless, the Schobinger system has become an effective way to summarize the clinical severity of an AVM for interdisciplinary communication. AVM progression may be

Table 1 Schobinger staging system

Stage	Features
Quiescence	Usually asymptomatic. Localized warmth and discoloration are present
Expansion	Lesional enlargement. Pulsations and bruit are present
Destruction	Pain, bleeding and ulceration
Decompensation	High output cardiac failure

promoted by aging, hemodynamic conditioning, thrombo-occlusive changes in the venous outflow tract or by hormonal fluctuations (Table 1).

In pediatric practice, AVMs of the extra-cranial head and neck may be syndromic, or non-syndromic. Syndromic AVMs may be single or multiple, localized or diffuse. Non-syndromic AVMs may be metameric, simple or transitional with absent or incomplete expression of AVM in some metameric derivatives (Fig. 6a–e).

Parachordal arteriovenous fistulae (AVF) differ from other types of AVMs encountered in the extracranial head and neck in that they are typically lack nidal type angioarchitecture. They are so named because they involve the vessels concerned with notochordal vascularization. Parachordal AVF of the extracranial head and neck include a diverse array of lesions that involve arterialization of the internal jugular vein, the maxillary vein, the external jugular vein, or the periarterial vertebral venous plexus by the internal maxillary artery (Fig. 7a–f), ascending pharyngeal artery, occipital artery (Fig. 7g–k), vertebral artery (Fig. 7l–p), ascending cervical artery and/or the deep cervical artery. These lesions are characterized by macrofistulous arteriovenous shunts involving a single vein or venous plexus. They are thought to result from spontaneous rupture of notochordal arteries and have been associated with Ehlers Danlos Syndrome, Marfans, and neurofibromatosis type 1. They present clinically with objective bruit or thrill, pulsatile mass or venous congestive syndrome. Paraspinal parachordal arteriovenous fistulae may develop venous congestive myelopathy when the lateral compartment of the epidural venous plexus is involved and the lesional flow load exceeds the capacity of its venous outflow tract due to acquired thrombo-occlusive changes.

The most common syndromes associated with AVMs of the extra-cranial head and neck are the CM-AVM syndrome caused by RASA-1 mutations, and the PTEN hamartoma tumor syndrome.

RASA-1 is a negative regulator of the Ras signaling pathway. The clinical syndrome caused by RASA-1 mutations resembles HHT in that AVMs occur in a variety of organ systems and cutaneous vascular lesions are associated. In contrast to pulmonary, hepatic and intestinal tract AVMs seen in HHT, the AVMs outside the central nervous system in patients with RASA-1 mutations are predominately head, neck and paraspinal. Extra-cranial head and neck lesions seen in HHT are limited to mucocutaneous telangectasias.

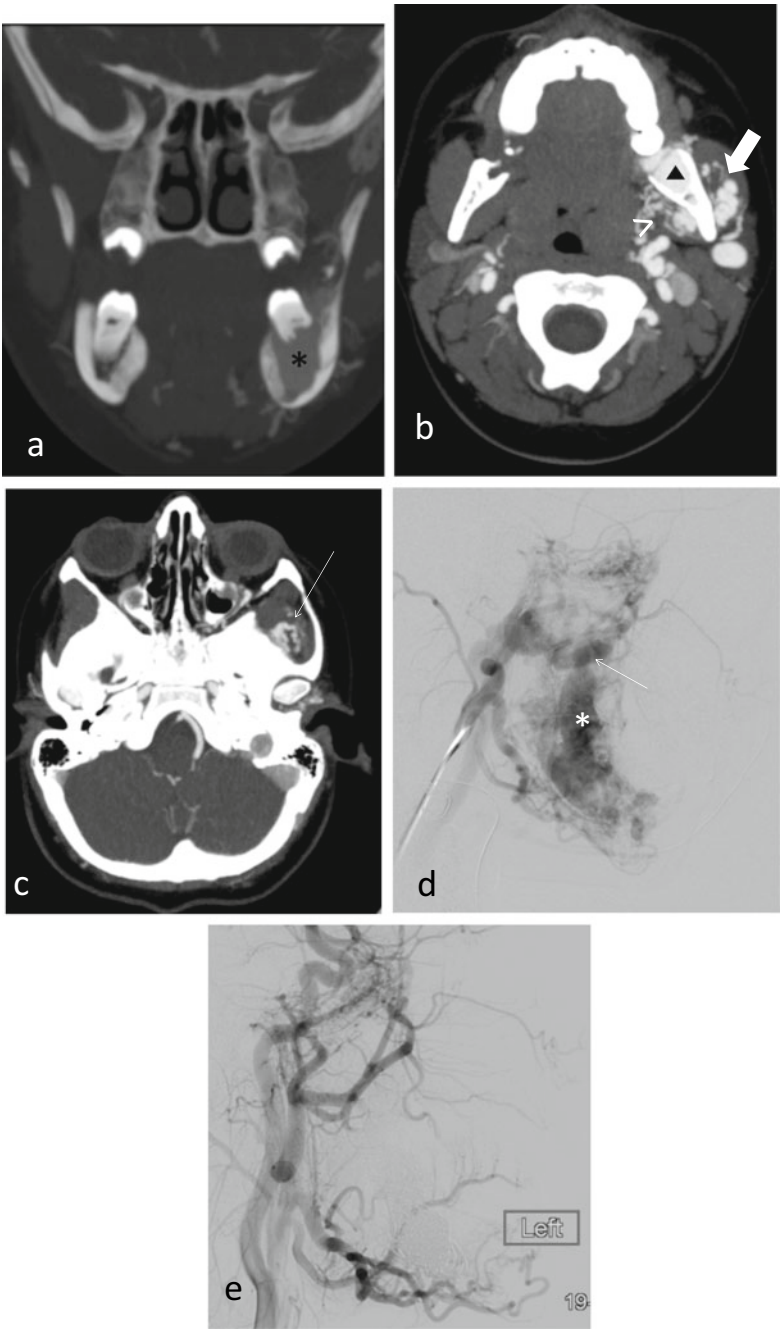

Fig. 6 Mandibular AVM

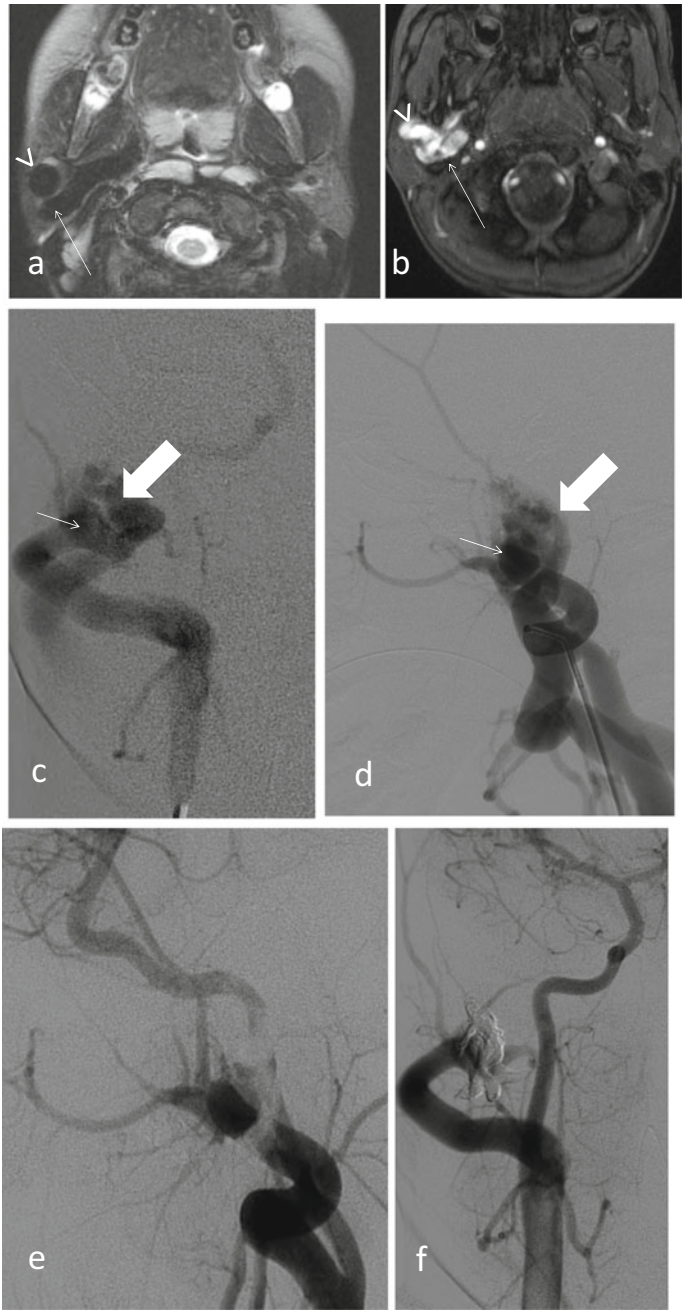

Fig. 7 Parachordal arteriovenous fistulae (AVF)

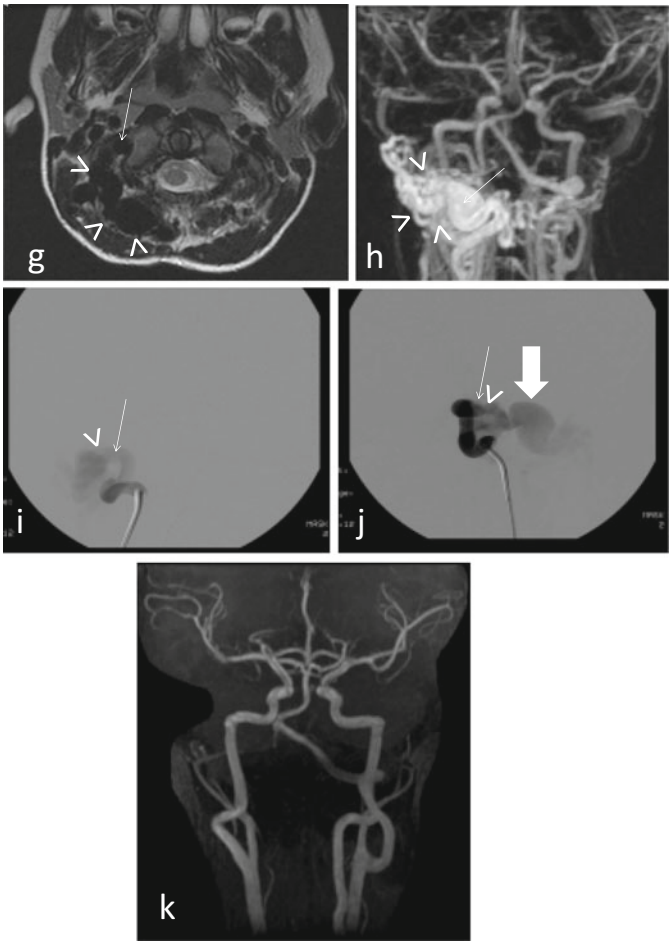

Fig. 7 (continued)

The clinical syndrome caused by PTEN mutations features a variable combination of macrocephaly, endocrine neoplasia and vascular malformations. Approximately half of patients with PTEN mutations have vascular anomalies, some of which are high-flow lesions. These AVMs are topographically diffuse and more than half are multifocal. Intra-muscular location and accompanying lipomatous overgrowth are often associated. They have a characteristic appearance on both imaging studies and histopathological examination, which features an angioproliferative component that blurs the distinction between malformation and tumor.

Metameric AVMs form as a result of programmed defects in vascular development segmentally expressed in all 3 layers (ectoderm, mesoderm, endoderm) of affected embryonic metameres, and thus span multiple anatomic regions and tissue layers originating from the same embryonic segment. Consequently, metameric AVMs of the head and neck may involve some combination of skin, muscle, bone, dura, brain and eye depending on the metameric segment of the embryo that is affected. The cerebrofacial arteriovenous metametric syndromes (CAMS) have been differentiated into 3 distinct groups: midline prosencephalic (olfactory) lesions, lateral prosencephalic (optic) lesions (Wyburn Mason Syndrome) and rhombencephalic (otic) lesions.

Simple AVMs of the extra-cranial head and neck may be expressed in any anatomic region and tissue type however some specific phenotype patterns are recognized more frequently (Fig. 8).

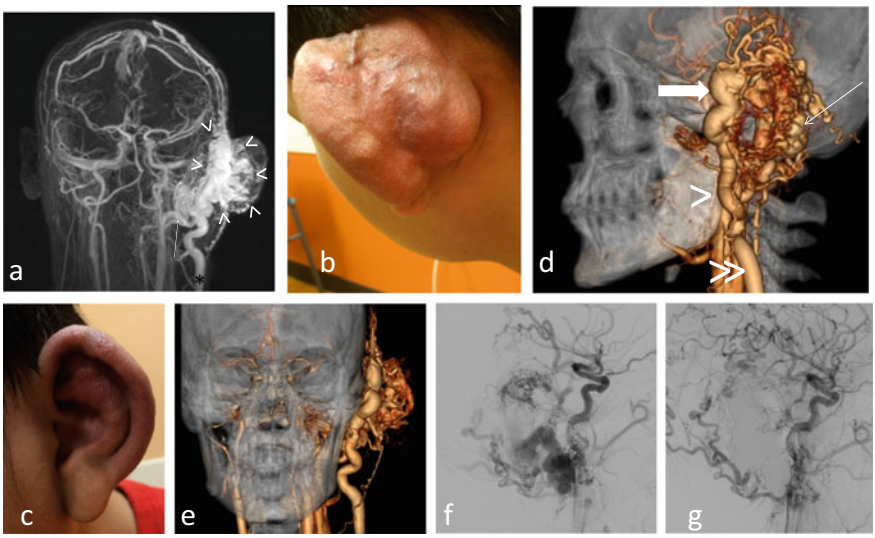

Fig. 8 Auricular AVM

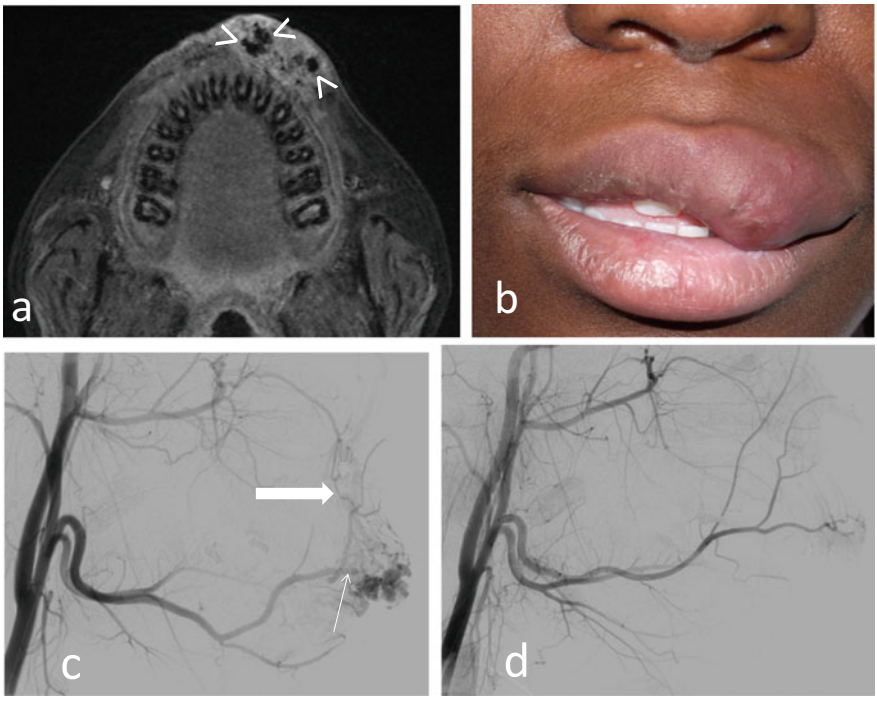

Fig. 9 Maxillofacial AVM

1. Mandibular AVMs (Fig. 6)

    a. These lesions most often present with profuse oral hemorrhage in school age children between the ages of 7 and 12 years as the primary molars are lost. They are sometimes discovered on Panorex films taken in the dentist's office and mistaken for tumors resulting in massive life-threatening hemorrhage at the time of tooth extraction and biopsy.

2. Maxillofacial AVMs (Fig. 9)
3. Tongue and floor of mouth. These lesions interfere with speech, mastication and dental hygiene. Hemorrhagic complications are not uncommon.
4. Auricular (Fig. 8)

    a. These lesions often show accelerated growth during puberty and present with massive ear swelling and intractable pain. Cutaneous ulceration and hemorrhage develop with time.

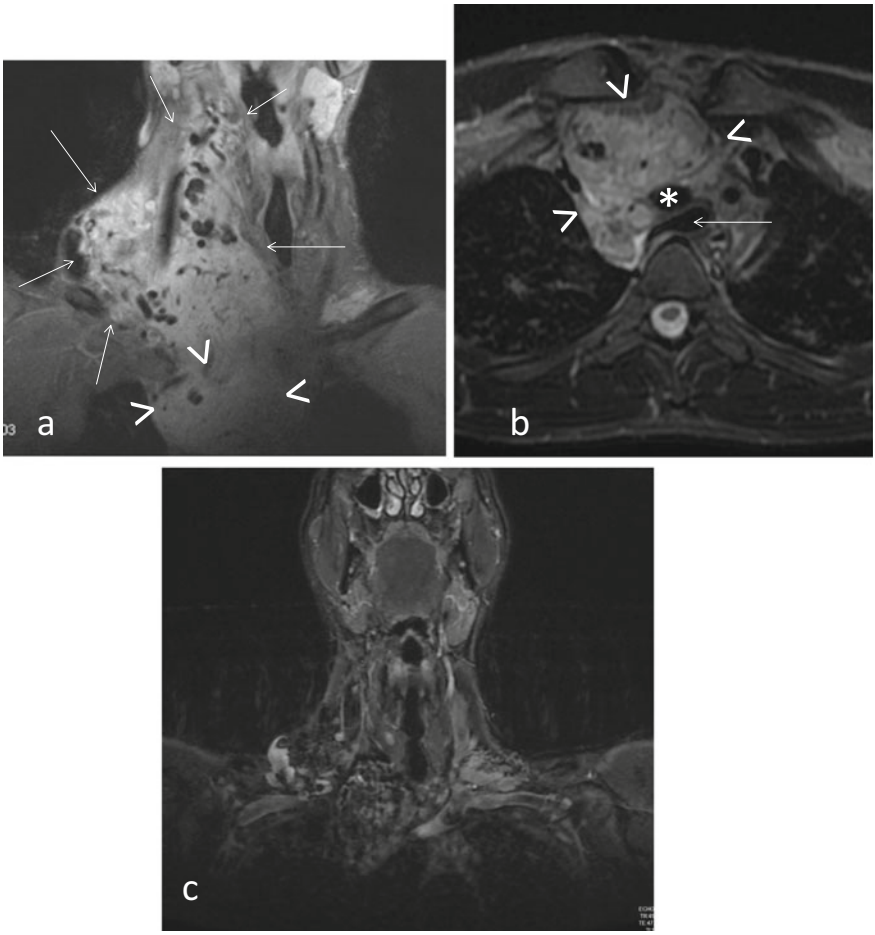

Fig. 10 Neck AVM

5. Neck AVMs (Fig. 10).

   a. Suprahyoid neck.
   b. Infrahyoid neck ± chest wall ± mediastinum.
   c. Diffuse.

Interventional therapies have assumed a central role in the contemporary management of extracranial head and neck AVMs. The primary technical objective of interventional management is permanent obliteration of the arteriovenous junction zone (inclusive of nidus) and adjacent arterialized collecting vein/s. Therapeutic

occlusion of vessels too far upstream will lead to reconstitution of the AVM through existing collateral networks and/or angiogenic proliferation.

Interventional approaches aimed at achieving the stated primary technical objective are constrained by several obstacles in the pediatric population:

1. Errant translesional embolization into venous outflow
    a. May compromise regional venous drainage
    b. May cause pulmonary emboli and right heart failure
2. Reflux into upstream arteries
    a. Entry of embolic agent into circulation of brain, spinal cord or eye can result in severe permanent morbidity
3. Downstream venous thrombosis
4. Access challenges
5. DMSO toxicity
6. Fluid and/or contrast media overload.

Interventional strategies designed to overcome these constraints concern proper selection of embolic agents, the use of flow control techniques, the implementation of adjunctive anti-reflux boundaries, the use of adjunctive anticoagulant therapies, the use of unconventional access strategies, collaboration with surgical and endoscopic specialists and staging of complex interventions.

Particle embolics are advantageous when embolizing nidal type AVMs and a pre-nidal or intra-nidal microcatheter position is not possible due to marked tortuosity or segmental stenoses restricting microcatheter navigation. Particle embolics are less likely to cause premature occlusion of feeding arteries prior to intranidal dispersion by convection compared to liquid agents. Since particle embolics are not capable of producing durable vessel occlusion, they are generally reserved for preoperative embolization prior to surgical resection.

Liquid embolic agents enable durable and near complete volumetric vessel occlusion. Since liquid embolics can be delivered through low profile (1.2–1.5 French) flexible microcatheters, intranidal or prenidal microcatheter positions can be established despite marked vessel tortuosity. Liquid embolic agents include adhesive and cohesive materials. The adhesive cyanoacrylates are the preferred liquid embolic agent for high flow arteriovenous macrofistulae. These agents are well suited to the challenge because they are strongly adhesive and can be made to rapidly polymerize to the vessel wall almost as soon as they exit the microcatheter tip. The cohesive (non-adhesive) ethylene vinyl alcohol (EvOH) type agents are the preferred agent for embolization of large lesions with nidal type architecture requiring slow stepwise penetration. Currently available EvOH preparations contain the organic solvent Dimethyl Sulfoxide (DMSO). DMSO toxicity has been implicated as a cause of hypoxemia, pulmonary edema, acute respiratory distress

syndrome (ARDS), and reversible leukoencephalopathy. Industry guidelines suggest that the lowest toxic dose of DMSO is 600 mg/Kg. Based on those guidelines, commercially available EvOH preparations (Onyx®, Covidien) may result in toxicity if > 1.5 ml of agent is administered to a 5 kg infant or > 2.5 ml of agent is given to a 10 kg child.

Microcoils and vascular occlusion plugs may have a role in the embolization of high flow arteriovenous macrofistulae, either as definitive therapy or as adjunctive therapy in preparation for embolization with liquid embolic agents. These agents are not effective, however, in the management of AVMs with nidal type angioarchitecture.

While conventional access to AVMs of the extracranial head and neck in children centers on transfemoral arterial approaches, retrograde transvenous and direct puncture approaches may provide more flexibility. Direct puncture approaches may be facilitated by ultrasound or cone beam CT guidance. Transnasal approaches to the nasopharynx and central skullbase can be simplified by employing an Amplatz renal dilator as a coaxial guide across the nasal turbinates. Although direct access to intradiploic venous lakes associated with intra-osseous AVMs can often be achieved by pushing a styletted spinal needle through an area of cortical bone thinning, it is advantageous to establish mechanical stability of the access needle by choosing a trajectory through a thick segment of cortical bone. Retrograde transvenous approaches to AVMs of the extracranial head and neck may be initiated from a transfemoral entrypoint or from an entry point above the clavicle. Retrograde transvenous approaches are often the most direct route to the arteriovenous shunt zone of an AVM in the extracranial head and neck. Although the normal arterial circulation is relatively protected during retrograde transvenous embolization, reverse entry of embolic agent through macrofistulae can reach vital arterial territories and precautionary measures should be taken, such as preliminary disconnection of arteriovenous macrofistulae by transarterial embolization.

When performing endovascular treatment of high flow arteriovenous shunt lesions in the extracranial head and neck, the controlled delivery of embolic agents can be thwarted by high shear rates violently flushing everything downstream into the venous outflow tract toward the right heart and lungs. Controlling the inflow of an AVM during embolization with liquid embolic agents can facilitate controlled filling of the venous compartment during transarterial embolization or promote retrograde filling of the arterial feeders during transvenous embolization with liquid agents. A number of flow control techniques can be employed to overcome these challenges. In the extra-cranial head and neck, flow control can be established by direct manual compression (Fig. 7a–f), or temporary balloon occlusion of the arterial inflow or the venous outflow. If the inflow of an AVM in the extracranial head and neck is temporarily occluded too far upstream (i.e. proximal external carotid artery), dangerous pressure gradients favoring retrograde embolization into the external carotid artery may develop. In this scenario, leakage of liquid embolic agents may occur around the balloon.

Adjunctive antireflux boundaries may be indicated to restrict reflux into and occlusion of vital arterial territories when transarterial embolization is performed with liquid embolic agents. Adjunctive antireflux boundaries also enable more extensive anterograde penetration into the nidus of an AVM when transarterial embolization is performed with liquid embolic agents because they enable longer and higher pressure injections. A simple and effective antireflux boundary can be established by depositing an occlusive plug of non-adhesive liquid embolic agent (i.e. ethylene vinyl alcohol) around the working microcatheter tip. Since solidification proceeds centripetally and asymmetrically from proximal to distal, a central channel of unsolidified material will enable the operator to advance embolic agent downstream of the plug through the central channel until the injection pressure exceeds the resistance of the anti-reflux plug (plug and push technique). In practice, the plug and push technique may enable extensive penetration of vast nidal networks in large AVMs. In addition to leveraging pressure gradients and controlling flow, balloon occlusion catheters can be used as antireflux boundaries when embolization is performed with ethylene vinyl alcohol in DMSO. Low profile, flexible, compliant, dual lumen DMSO compatible balloon catheters have expanded the anatomical and hemodynamic range of lesions amenable to balloon assisted embolization with liquid embolic agents. One adjunctive antireflux method that can be used to facilitate transarterial embolization with ethylene vinyl alcohol employs two parallel staggered microcatheter systems (pressure cooker technique). This method employs the upstream microcatheter to deposit an antireflux plug and a parallel microcatheter stationed downstream to deliver the liquid embolic. The advantage of this method is that it establishes a very high resistance antireflux barrier at the upstream catheter station while preserving a wide open channel for antegrade delivery of liquid agent at the downstream catheter station. If a balloon occlusion catheter is substituted at the proximal microcatheter station, the liquid agent used to form the antireflux plug can be more strictly isolated from the downstream microcatheter station. This allows much more effective delivery of liquid embolic agent from the downstream microcatheter station.

Employing balloon occlusion catheters for flow control and as anti-reflux boundaries may require solo over the wire navigation without a guiding catheter in small children since a minimum guide catheter lumen of 5 French is required with current technologies. In children less than 10 kg or less than 2 years of age, it is prudent to use sheaths that are no larger than 4 French. Compared with other methods of reflux control (i.e. plug and push) balloon catheters provide faster and more reliable anti-reflux boundaries and therefore translate into less radiation exposure. Additional benefits afforded by flow control with balloon occlusion catheters include a reduced risk of microcatheter retention, and lower risk of extraction injuries.

While interventional approaches are the mainstay for high-flow lesions, there are medical therapies actively being sought. In general, these medical therapies have not yet been overwhelmingly successful, though there is some preclinical data, and isolated case reports, that MMP inhibitors such as doxycycline and/or angiogenesis inhibitors such as thalidomide and lenalidomide, may have some role in those patients whose AVMs are not amenable to embolization.

In conclusion, pediatric subspecialists from a diverse range of backgrounds support the complex care needs encountered in infants + children with vascular malformations of the extracranial head and neck.

Practitioners should employ lesion oriented, age specific treatment indications and objectives.

Pearls: *Vascular Malformations of the Extracranial Head and Neck in Children.* (Need 8–10).

1. Vascular malformations of the extracranial head and neck in children include low flow vascular anomalies (venous malformations, lymphatic malformations, capillary malformations) and high flow vascular malformations (arteriovenous malformations and arteriovenous fistulae).
2. Vascular malformations of the extracranial head and neck must be differentiated from vascular tumors of the head and neck.
3. Sinus pericranii are a form of extracranial venous malformation associated with abnormal communications between the extracranial venous system and the intracranial venous system. If therapeutic occlusion is considered, it is necessary to exclude a type I lesion.
4. Arteriovenous malformations of the extracranial head and neck associated with capillary malformations are seen in patients with RASA-1 mutations.
5. Arteriovenous malformations of the extracranial head and neck associated with endocrine neoplasia and macrocephaly are seen in patients with PTEN mutations.
6. Parachordal arteriovenous fistula may be associated with Ehlers Danlos Syndrome, Marfans, and neurofibromatosis type 1.
7. Paraspinal type parachordal arteriovenous fistulae may develop venous congestive myelopathy when the lateral compartment of the epidural venous plexus is involved and the lesional flow load exceeds the capacity of its venous outflow tract due to acquired thrombo-occlusive changes.
8. Mandibular AVMs may present with life-threatening oral hemorrhage in school age children between the ages of 7 and 12 years as the primary molars are lost.

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Infantile Hemangiomas of the Central Nervous System

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1 Introduction

Infantile hemangiomas (IH) are typically benign, vascular cutaneous tumors that consist of a collection of immature, or progenitor, vascular cells arising via endothelial hyperplasia. These lesions are the most common tumor of infancy (affecting 4% of children). They typically present within the first few weeks of life in infants weighing less than 2500 g at birth and are more common in females. These tumors can be segregated into three types: localized, segmental, or indeterminate. Localized hemangiomas are confined to one small area, seeming to arise from a particular focus. Segmental hemangiomas often correspond to a developmental segment or simply a more broad anatomic territory, characterized by a

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"plaque-like" geographical or linear pattern. Compared with the other tumor types, they are associated with a wider range of complications from extension or mass effect, often invading deeper tissues and organs. Indeterminate types are not clearly identifiable as either, sharing a mixed constellation of characteristics.

2 Natural History

Due to the variety of vascular lesions with very limited nomenclature, Mulliken and Glowacki pushed for a standardized classification of vascular anomalies throughout the 1980s [1]. In response, the International Society for the Study of Vascular Anomalies developed a classification system in 1996 that divided vascular lesions into two major categories, including tumors and malformations, and developed a distinct nomenclature system [2]. This represented an important shift in the delineation of management strategies for these lesions, including IH, which were now described as tumors, rather than malformations.

Infantile hemangiomas are generally benign tumors. Conventional IH usually present at the time of birth, proliferating rapidly during the first few months of life. Approximately 80% of tumor growth is achieved by the third month of life and often continues until plateauing at month 8. IH are located in the head and neck (60%), trunk (25%), and the extremities (15%). Eighty percent of these lesions are solitary, whereas multiple lesions are found in 20% of patients.

Decision making on the management for extracranial cutaneous IH hinges on the basis of location and potential threat to structures, function, and cosmesis. Although most small lesions spontaneously involute by 5–7 years of age, larger IH may ulcerate (occurring in 15% of patients with cutaneous extracranial IH), hemorrhage, or contribute to high output heart failure in younger children. In essence, IH experience an early proliferative phase, leading eventually to maximal growth and a growth-abortive phase, followed closely by an involutional phase over several years' time, representing a slow process, albeit with great potential for early growth.

Intracranial hemangiomas present an entirely different realm of concern. This is an exceptionally rare entity that has only been reported in a handful of cases as a solitary, intracranial IH or in several series in association or continuity with extraaxial/extracranial hemangiomas [3–14]. They are also encountered in the spine as intradural, extramedullary lesions. However, this is even more uncommon.

The associated signs and symptoms are primarily based on location and extension. Initial signs after birth may be a tense or bulging fontanelle with expanding head circumference, in line with other intracranial lesions that cause hydrocephalus or intracranial pressure elevation. Seizures, lateralizing neurologic deficits, and irritability are the major presenting events or symptoms. Cases of hemorrhage of these lesions are rare in the literature, but the few existing reports have not described this as a clinically significant event [6]. Some of these lesions have shown evidence of calcification, which could indicate remote hemorrhage or recurrent thrombosis within the highly vascular lesion. Beyond the current limited

data, the natural history of intracranial hemangioma is relatively unknown but thought to be similar to extracranial IH in terms of evolution and involution.

3 Imaging

Imaging of IH is relatively distinct. Magnetic resonance (MR) imaging typically portrays a hypo- to iso-intense lesion on T1 with uniform enhancement on contrast-enhanced imaging. T2 sequences are hyper-intense with avid flow voids and multiple lobulations. On CT imaging these lesions are iso- to hyper-dense and, again, multilobulated.

In one of the larger series of CNS IH [13], typical findings were an extra-axial mass along the dural sinuses within the temporal region or the basal cisterns extending from the prepontine, cerebellopontine angle, perimesencephalic, and quadrigeminal cisterns. Intracranial IH tend to also have a predilection for the posterior fossa, including the fourth ventricle. In most patients, these tumors are seen to have continuity with a concomitant extracranial skin lesion, usually through the skull base foramina connecting to a segmental facial lesion.

4 Histology

The pathologic diagnosis of intracranial IH is not common, as most lesions involute and require no further treatment. Basic histologic evaluation of proliferative phase IH shows a solid, infiltrative fibroblastic lesion with small capillaries containing plump endothelium and a thin basement membrane. Recent molecular studies have shown these are typically positive for glucose transporter 1 (GLUT1) and CD31 on immunologic staining [15–19]. In the involution phase, these lesions have a much more flat endothelium, large capillary lumens, and thick basement membranes, testing positive for GLUT1 and CD31.

5 Management

Treatment of intracranial IH, because it is such a rare entity, mostly parallels the treatments known to work for extracranial IH. Although an observational approach is often most appropriate for extracranial lesions with space to expand, the closed compartment of the skull often requires a more diligent and aggressive approach for intracranial lesions. To appropriately monitor IH growth or evolution, we would recommend frequent MR images of the brain every 23 months, along with parallel or even more frequent clinic evaluations depending on the clinical severity.

Beta-adrenergic blockade (beta blockers) is the typical first-line treatment, with an expansive array of literature as a testimony to its success [20–40], specifically with propranolol. Beta-adrenergic activity leads to vasodilation via release of nitrous oxide as well as angiogenesis by stimulating metalloproteinases and vascular endothelial growth factor (VEGF). Thus, propranolol has been a staple of hemangioma treatment, with one large study showing a 60% rate of resolution after 24 weeks of treatment with 3 mg/kg/day propranolol [41]. Side effects include transient blood pressure decrease, agitation, and sleep deprivation.

Corticosteroids have commonly been used, as well [42–44]. Nuclear factor [kappa]-light-chain-enhancer of activated B (NFkB) cells regulates the activity of genes involved in inflammatory responses, cell proliferation, and cell survival, as well as angiogenesis through VEGFR-2 regulation. Steroids are thought to suppress NFkB cells. Prior to 2008, this was the first-line treatment, succeeding in slowing or ceasing growth in nearly 90% of cases. Dosing with corticosteroids is accomplished by placing the patient on 2–3 mg/kg/day of prednisone for at least 1 to 2 months. Adverse effects with steroids include cushingoid appearance, mood lability, gastric irritation, fungal infection, hypertension, steroid myopathy, immunosuppression, Addison's disease, diminished height/weight gain, and weakened bone matrix.

Interferon 2-alpha has also been used for treatment of IH. However, one should be aware of the potential neurotoxic side effects, including spastic diplegia. As such, these effects have been a serious consideration and significant obstacle to its use, which is mostly limited to lesions refractory to other conservative treatments [45, 46].

There is also one reported case of an intracranial hemangioma in which a complete response was achieved with temozolomide and bevacizumab [47]. Bevacizumab works against the VEGF receptor to prevent vascular proliferation. We would be reluctant to recommend this agent with its well-known adverse effect profile in the setting of intracranial disease. This could exponentially increase surgical risk and wound complications should an operative intervention become necessary during follow-up for these patients.

Expansile lesions causing structural compromise, neurologic decline, or hydrocephalus may require urgent surgical treatment. The first step is to determine the immediate threat to the patient and the resectability of the lesion. Once it has been determined that surgical management may be an impending necessity, some important considerations arise.

In light of the patients' typical age group (neonates and infants), blood volume will be a tremendous factor in preoperative preparation. Ample cross-matched blood should be on-hand in case the need for transfusion arises, both from blood loss due to dissection as well as from vascular tumor manipulation and resection. Volume expansion with intravenous fluid infusion will also help mitigate blood loss. Placement of a central line may be vital to having control of the patient's circulation. Finally, a delay in surgery for as long as possible may allow blood volume to increase, decreasing the risk of surgical intervention, with the caveat that the tumor may increase in size in the interim. In this case, conservative measures

with medications to halt or slow growth (discussed above) must be instituted or escalated if already in effect.

One operative case from our experience includes a 15-day-old infant with progressive ventriculomegaly and a dorsal posterior fossa mass with dural attachment. This was all discovered on a repeat ultrasound study where an area of hyperechogenicity in the midline prompted further workup with MR imaging. The MR imaging findings were compatible with a vascular lesion full of flow voids (Fig. 1a–c). The decision was made to resect the lesion as significant mass effect and hydrocephalus were progressing. Prior to surgery, an external ventricular drain was placed. Copious blood products and volume expanders were immediately available. During the surgery, enough blood was lost such that transfusion of blood, plasma, and platelet products was necessary but the procedure was otherwise uneventful; and the mass was completely resected (Fig. 2a, b). Overall, the child is doing remarkably well, regaining developmental milestones during follow up at 8 months of age. This case exemplifies the need for extensive preparation for circulatory management by anesthesia as well as the entire surgical team. It also depicts the clinical situation where conservative management cannot play an immediate role and surgical intervention is imperative to survival.

In another case [6], a large, nonresectable intracranial IH that was followed up conservatively on a monthly basis, increased in size by 307% within 5 months, with a reduction of 16% at the eighth month. By 11 months, the tumor was 57% of its maximum size. The patient underwent ventriculoperitoneal shunt placement for resultant hydrocephalus. The initial treatment was thalidomide (4 mg/kg daily) at 1 month of age with an interval increase of dosing to a maximum of 150 mg daily

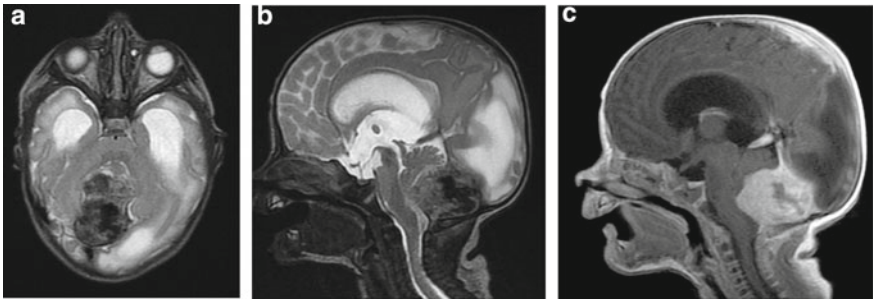

Fig. 1 **a** T2-weighted magnetic resonance (MR) image displaying an iso- to hypo-intense, heterogeneous midline posterior fossa mass with splaying of the cerebellar hemispheres bilaterally, compression of the more ventral structures (including the fourth ventricle), and bilateral temporal horn enlargement indicating evidence of non-communicating hydrocephalus. **b** Sagittal T2-weighted MR image again showing a midline iso- to hypo-intense mass with significant flow-voids causing ventral displacement of the vermis, fourth ventricle compression, some pontine deformation, and evidence of supratentorial hydrocephalus with widening of the ampulla of the cerebral aqueduct. **c** Sagittal T1-weighted post-contrast-enhanced MR image showing diffusely enhancing posterior fossa mass with dural attachment, appearing to arise from the tentorium

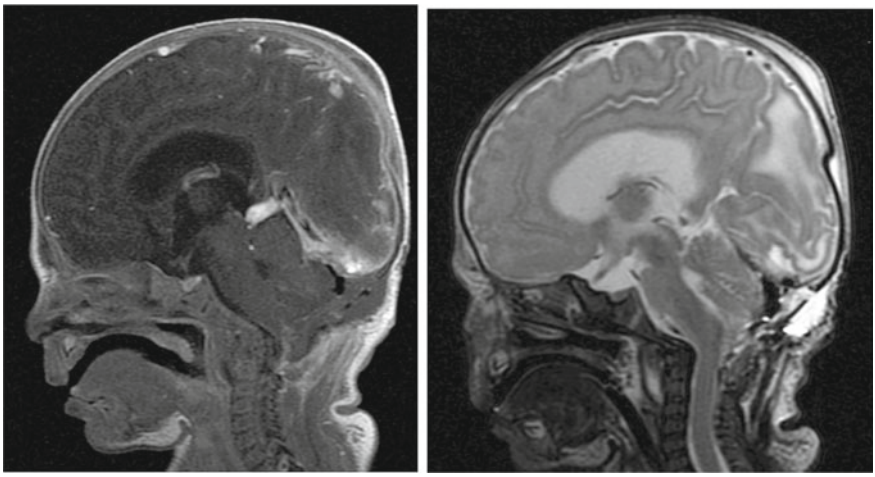

Fig. 2 **a** Sagittal T1 post-contrast injection MR image showing gross total resection of posterior fossa infantile hemangioma. **b** Axial T2-weighted MR image depicting decompression of the posterior fossa structures with expansion of the fourth ventricle and clear resolution of the ampulla widening at the cerebral aqueduct

with surveillance for toxic effects. Thalidomide, an antiangiogen, was chosen in this case due to the recent elucidation of the angiogenic nature behind the pathophysiology of IH [34]. This is an excellent case that depicts the efficacy of combining limited surgical management along with aggressive conservative management.

6 PHACES Syndrome

IH occurs commonly in children with the PHACES (*p*osterior fossa-*h*emangioma-*a*rterial lesions-*c*ardiac abnormalities/aortic coarctation-*e*ye abnormalities-sternal defects and/or supraumbilical raphe) syndrome, which is a neurocutaneous constellation of findings [48]. More than 30% of patients with segmental facial hemangiomas larger than 5 cm have the findings associated with PHACES. In one study, 2.3% of all children with hemangiomas and 20% of those with cervicofacial hemangiomas met the criteria for the PHACE syndrome [48, 49].

Cerebrovascular anomalies were present in a large series of patients with PHACES [50–52]. These included carotid arterial anomalies (hypoplasia, anomalous branches, aberrant origins/courses, stenosis or occlusion, and persistent fetal formations). Structural brain abnormalities include posterior fossa malformations (DandyWalker complex, cerebellar hypoplasias, dysgenesis of the vermis), hypoplasias of the cerebrum, septum pellucidum, and/or the corpus callosum, and arachnoid cysts along with several other malformations [49, 53, 54]. Neurologic

sequelae occur in approximately one-third of patients, including seizures, stroke, and developmental delay. Cardiovascular defects come in many forms, including coarctation, aortic aneurysms of any segment, abnormal arches, congenital aortic stenosis, ventral and atrial septal defects, patent ductus arteriosus, anomalous pulmonary veins, pulmonary stenosis, and tetralogy of Fallot [49, 55, 56]. Ocular findings include vascular anomalies, orbit structural defects, ocular abnormalities, and optic nerve atrophy and hypoplasia. The last group of abnormalities is the ventral developmental defects, including sternal, supra-umbilical raphe, and GI defects (including omphalocele). Management of IH in these syndromic patients remains identical to that for general IH patients [57].

7 Conclusion

Infantile hemangiomas in general may seem a fairly innocuous vascular malformation in comparison to its close relatives, cavernomas and arteriovenous malformations. A rapidly proliferating and growing lesion on the skin or even in deeper tissues will eventually undergo involution without compromising important structures in the majority of cases. This natural history plays out very differently when IH occurs within the closed compartment of the skull. Typical symptoms include neurologic deterioration from mass effect, seizures, and hydrocephalus; and the lesion may present insidiously and asymptomatically with a rapidly enlarging head circumference. Conservative measures remain the same between the extracranial and intracranial groups. However, simple observation must be approached with extreme caution and constant surveillance with intracranial IH. Surgical intervention is only warranted as a necessity or last resort with extensive preparation for complications and bleeding. To summarize, although extracranial IH and intracranial IH share the same histology and evolution, intracranial hemangiomas require more vigilance in treatment strategy.

Clinical Pearls

(1) Infantile hemangiomas are typically a benign process, but intracranial hemangiomas require a much more vigilant approach.
(2) Intracranial hemangiomas occur in a young population where risk of surgery must be weighed against the risk of further decline.
(3) The natural history of intracranial infantile hemangiomas parallels that of extracranial infantile hemangiomas, so conservative management for smaller, less structurally compromising lesions is beneficial.
(4) Conservative treatment includes use of propranolol or corticosteroids most commonly.
(5) Operative intervention requires extensive preparation with preoperative volume expansion and blood products at the ready.

(6) The role of biopsy should be questioned because this vascular tumor has the potential for serious hemorrhage.
(7) Intracranial hemangiomas are commonly associated with PHACES syndrome.
(8) A diagnosis of PHACES syndrome should further increase the vigilance in terms of vascular workup; these patients have an elevated risk of stroke and other neurologic sequelae.

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Para-Gangliomas

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Paragangliomas are highly vascular tumors of neural crest origin, arising along the migratory pathway of the paraganglia during embryogenesis anywhere from the skull base to the floor of the pelvis [1,2]. The historical terms chemodectomas or glomus tumors are no longer used by pathologists [3]. They are now classified by their site of origin in the head, neck, retroperitoneum, or spine. Paragangliomas arise from parasympathetic ganglia in the head and neck (HNPs), and from sympathetic ganglia in the chest, abdomen and pelvis (extra-adrenal paragangliomas [EAPGs]) [4,5]. Pheochromocytomas (PCCs) arise from the adrenal medulla. The vast majority of tumors arising from the parasympathetic ganglia (95%) are non-secretory, while those arising from the sympathetic ganglia usually secrete catecholamines [4]. Up to 85% of paragangliomas occur in the abdomen (of which 20% are EAPGs [6]), and only 3% are HNPs [7]. Most cases occur in patients between the ages of 30 and 60 [8], and there is a female predominance [9]. 10–20% of paragangliomas are diagnosed in children, at a median age of 11 years [10,11]. The majority of reported paragangliomas in children are HNPs [12]. As many as 80% of pediatric patients with paragangliomas are diagnosed with germline mutations [4,13–15].

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1 Head and Neck Paragangliomas

HNPs are rare, comprising 0.03% of all tumors [2]. The most common paraganglioma in the head or neck is the carotid body paraganglioma, followed by the jugular paraganglioma, tympanic paraganglioma, and vagal paraganglioma. Individual case reports have described paragangliomas in the nose and paranasal sinuses [16–18], orbit [2, 19], parotid gland [20], cervical sympathetic chain [21, 22], nasopharyngeal region [19], thyroid or parathyroid gland [23–28], the superior and inferior laryngeal ganglia, and the parasellar region [16]. About 1–3% of HNPs present with elevated catecholamines and tachycardia, tremor and hypertension secondary to this [9]. An investigation for a second paraganglioma should be undertaken in patients with HNPs and increased catecholamine levels, because secretory HNPs are so rare [6]. Dopamine secretion and secondary hypotension are very uncommon in patients with HNP [1]. Jugular or carotid body paragangliomas are the most likely to be secretory [29], and vagal paragangliomas are the most likely to be malignant [16] and multiple [30]. Because these tumors are typically non-secretory, the most common presentation is of mass effect on adjacent structures [31, 32]. These tumors can be multicentric, particularly in familial cases (up to 80%) [2]. Complete surgical excision is the only cure, though resection often results in lower cranial nerve dysfunction and injury to major vessels.

1.1 Presentation

The symptoms of HNPs vary by site of origin and secretory status. The carotid body paraganglia are chemoreceptors that regulate respiration and pH, blood pressure and heart rate through Hering's nerve (a branch of the glossopharyngeal nerve) and are stimulated by hypoxia, hypercapnia, and acidosis [8, 33–35]. The roles of the other head and neck paraganglia are less clear. The carotid body paraganglioma most commonly first comes to attention as a painless, slowly enlarging mobile mass in the lateral neck [8, 35], or later with lower cranial nerve dysfunction, including pain, dysphagia, dysphonia, aspiration, a Horner's syndrome (cervical sympathetic chain), or facial asymmetry [9]. Hoarseness (vagus), pulsatile tinnitus, syncope (carotid sinus or ICA compression), stroke or TIA [35, 36], conductive hearing loss [16], or trouble moving the tongue [5]. Symptoms may indicate more extensive tumors or malignant transformation. The mass is more mobile in a horizontal plane than vertical, termed a positive Fontaine's sign. A carotid bruit or pulsatility of the mass suggests a carotid body paraganglioma. A cranial nerve examination is critical in these patients. Tympanic and jugular paragangliomas, arising from CN IX within the middle ear, most often present as pulsatile tinnitus, sometimes accompanied by conductive hearing loss. Facial paralysis and vertigo may occur. A blue or red pulsatile mass is seen behind the tympanic membrane on physical examination [1, 5]. Those with jugular paragangliomas may also have lower cranial nerve deficits due to compression at the jugular foramen [1]. Vagal paragangliomas arise most

commonly from the inferior nodose ganglion but can occur anywhere along the cervical vagus nerve, so symptoms are much more variable and can include a painless mass posterior to the carotid artery, dysphagia, cranial neuropathy, Horner's syndrome [1], dysphonia, cough, and aspiration due to vocal fold paralysis [5]. A detailed family history, including early unexplained death, must be taken. Symptoms of excess catecholamine secretion (headache, episodic profuse sweating, heart palpitations, anxiety, sustained or paroxysmal hypertension, diarrhea, flushing, sweating) must be elicted. Such symptoms can be triggered by changes in body position, increased intra-abdominal pressure, anesthesia and other medications, exercise, and micturition [5].

1.2 Radiographic and Laboratory Evaluation

The preoperative diagnosis of a HNP is made with a combination of imaging studies and laboratory analysis. Doppler ultrasound has no associated risks (such as radiation or the need for sedation), and is a quick, easy, cheap initial test. B-mode sonography with color Doppler is particularly useful for carotid body and vagal paragangliomas [5]. A carotid body tumor appears as a hypoechoic mass with a clear border that splays the bifurcation, with the external carotid artery (ECA) anteromedial and the internal carotid artery (ICA) posterolateral. Vagal paragangliomas displace both ICA and ECA anteriorly (though if they are large enough, they may splay the bifurcation), and displace the compressed internal jugular vein [37]. Cervical HNPs typically appear hypervascular, though do not always [37]. Large paragangliomas produce bony destruction, best defined by computed tomography (CT) [38]. A CT scan is required for jugular and tympanic HNPs, so that they can be assigned a Fisch classification [39] defining the extent of temporal bone destruction and determining the surgical approach (see Table 1). The bony destruction of a jugular paraganglioma is classically along the lateral border of the canal. Medial destruction suggests a vagal paraganglioma tumor arising from below, and anteromedial destruction should lead one to suspect a cranial nerve IX schwannoma. For an evaluation for a cause of hypertension, a CT abdomen and pelvis, then neck and chest is recommended in adults [40], but magnetic resonance imaging (MRI) is recommended in children to minimize the risks of radiation and particularly, radiation-induced tumors in these frequently syndromic patients [41]. MRI is the most important diagnostic test. Paragangliomas appear hyperintense on T1-weighted imaging, with bright, inhomogenous contrast enhancement on T1-weighted imaging [38]. They have a salt-and-pepper appearance on T2-weighted imaging because of a combination of the many vascular spaces within the tumors and intratumoral hemorrhage [38]. MRI enables carotid body paragangliomas to be stratified into the Shamblin classification (see Fig. 1) for prediction of surgical risk and outcome. MRI allows for the identification of dural infiltration by jugular and tympanic paragangliomas, and excludes other potential diagnoses like endolymphatic sac tumors. MRI is also useful to identify or exclude the presence of additional paragangliomas. MRA

Table 1 Fisch classification (Fisch) [42]

Fisch class	Definition
A	Tumor arising along tympanic plexus on promontory
B	Tumor invading hypotympanum, cortex over jugular bulb intact
C1	Tumor eroding carotid foramen
C2	Tumor destroying carotid canal
C3	Tumor invading carotid canal, foramen lacerum intact
C4	Tumor invading foramen lacerum and cavernous sinus
De	Tumor extending intracranially, extradurally
De_1	Less than 2 cm dural displacement
De_2	More than 2 cm dural displacement
Di	Tumor extending intradurally
Di_1	Less than 2 cm
Di_2	Two to 4 cm
Di_3	More than 4 cm

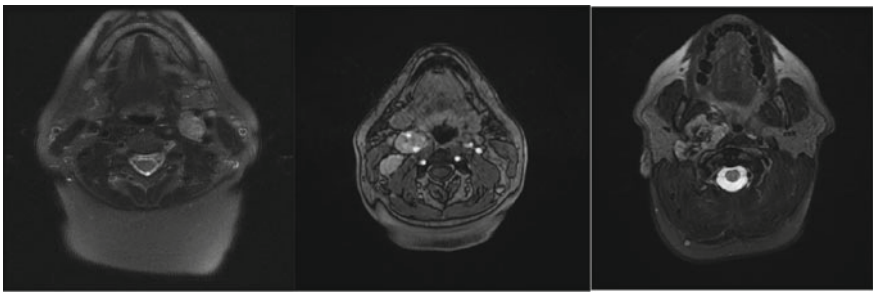

Fig. 1 Shamblin classification. Class I: localized, with splaying of bifurcation and little attachment to vessels. Class II: partially surrounding and invading the ICA and ECA. Class III: intimately surrounding and invading the ICA and ECA

has supplanted angiography in the majority of cases, unless embolization is being considered or carotid sacrifice is planned.

Digital subtraction angiography remains useful for select cases in which embolization is planned, usually medium to large lesions. Performance of a balloon test occlusion should be completed with evidence of carotid invasion for carotid body or vagal paragangliomas, or if an intraoperative carotid sacrifice, reconstruction, or grafting is being considered. [9, 37, 43] Angiography demonstrates a moderate tumor blush, enlargement of the feeding vessels, and rapid venous filling [38]. All four vessels should be catheterized to assess for multiple tumors. For carotid body paragangliomas, there is great variability in the blood supply, which can include the musculospinal branch of the ascending pharyngeal, small branches

at the carotid bifurcation, posterior auricular artery, recurrent lingual artery from the superior pharyngeal artery, ascending and deep cervical arteries, and the occipital artery. Angiography can demonstrate carotid invasion with higher Shamblin grade carotid body paragangliomas. Fisch Class A tympanic paragangliomas are supplied by the inferior tympanic artery. Class B tympanic paragangliomas are supplied by the ascending pharyngeal artery. Class C jugular paragangliomas are supplied by the ascending pharyngeal, maxillary, occipital and posterior auricular arteries. Class D jugular paragangliomas have individual blood supplies that can include the middle meningeal artery, cavernous branches off of the ICA, or caroticotympanic artery. Tumors with intradural extension can be supplied by the anterior inferior cerebellar artery or posterior inferior cerebellar artery, and may extend into the cavernous sinus or invade the ICA, in which case a balloon test occlusion must be performed. Vagal paragangliomas displace the ICA and ECA anteromedially, and compress the internal jugular vein and displace it posteriorly. If a vagal paraganglioma is very large, it may splay the carotid bifurcation. The blood supply of a vagal paraganglioma arises from the ascending pharyngeal artery or muscular branches of the proximal occipital artery, ascending cervical carotid artery, or ipsilateral vertebral artery.

A variety of nuclear medicine studies (fluorine 18-deoxyphenylalanine-positron emission tomography (18F-DOPA-PET) [1], 18F-Fluorodihydroxyphenylalanine-PET [44], fluordeoxyglucose (FDG)-PET [5], 123-I-metaiodobenzylguanidine (MBIG), Indium-111 labeled octreotide) [45] are utilized (often fused with CT to improve their sensitivity and specificity) to assess for metastatic disease.

Laboratory studies can be supportive of a diagnosis, or diagnostic themselves in the case of a secretory paraganglioma. Fractionated plasma free metanephrine and/or 24 h urine metanephrine and norepinephrine must be obtained in patients for whom a secretory HNP is suspected, and in all for whom surgery is being considered [40]. Chromogranin A correlates with tumor size, malignant potential, and a particular subset of genetic cases with mutations in SDHB [40]. Hyperglycemia, an elevated erythrocyte sedimentation rate, polycythemia and leukocytosis may be present [44].

1.3 Treatment

Treatment options include surgery, radiation, stereotactic radiosurgery, embolization, or a combination of these. The best treatment for any case should be determined based on tumor size, classification, location, age, and the presence of preoperative cranial neuropathies. Serial MRIs can be acceptable in select cases because of the slow growth of these tumors (doubling time estimated at 4.2–13.8 years) [46], but is not recommended in children because of their long life expectancy and the increasing difficulty of treatment with increasing tumor size. Biopsy is not recommended for any paraganglioma because of the unreliability of pathologic diagnosis with small samples of these tumors and because of their significant risk of hemorrhage [5]. Surgery is the only curative option for HNPs,

and is the treatment of choice. Cure rates for carotid body paragangliomas are 89–100%, with lower rates for higher Shamblin grade tumors [47, 48]. Surgical cure rates for jugular paragangliomas are about 80–90% [43, 49]. Vagal and tympanic paragangliomas can usually be completely resected. Radiation, whether stereotactic or primary, is used for unresectable, partially resected, or multiple tumors.

For secretory tumors, nonselective alpha-adrenergic blockade with phenoxybenzamine, prazosin, or doxazosin should be begun 2 weeks before preoperative embolization or surgery (if no embolization is planned), then beta-blockade with a nonselective (propranolol) or beta-1-selective (metoprolol) blocker should be instituted. Beta-blockade must not be initiated first because it can worsen hypertension and reflex tachycardia from the unopposed alpha effects, and even precipitate hypertensive crisis [11]. A high-sodium diet is often advocated at the time of alpha-adrenergic blockade initiation, to mitigate the effects of catecholamine-induced volume contraction [50]. A sudden decrease in the blood supply to the tumor can produce an abrupt decrease in catecholamine secretion, and secondary severe hypotension [51, 52]. Additionally, alteration in the blood flow to the tumor with an angiography catheter can produce a catecholamine surge and hypertension. The alpha-blockade should be stopped 1–2 days preoperatively, and the serum sodium may be increased to avoid postoperative hypotension. Urine or plasma metanephrine should be reassessed 1–2 weeks after surgery. If the levels remain elevated or are increased, an unresected second tumor or occult metastases should be suspected [5].

In the surgical approach for carotid body paragangliomas, proximal and distal control of the ECA and ICA must be obtained early [8]. Intraluminal shunts and vascular reconstruction may be necessary, particularly for Shamblin class III tumors. The major surgical morbidity is cranial nerve dysfunction, with rates of 17–50% [8, 9, 53, 54], correlating positively with Shamblin class. In one series, temporary cranial neuropathies occurred in 7% of Shamblin class I tumors, 35% of Shamblin class II tumors, and 58% of Shamblin class III tumors. Permanent cranial nerve injury occurred in 0% of class I tumors, 6% of class II tumors, and 15% of class III tumors [55]. Interestingly, the most common cranial nerve injuries are to the marginal mandibular branch of the facial nerve and the hypoglossal nerve, both likely secondary to retraction [55], though injury to the vagus is also common [35]. A modified Shamblin classification to include neurologic morbidity has been suggested [56]. Surgical mortality for carotid body paragangliomas has been reported to range from 1 to more than 5%, with higher mortality for higher Shamblin grade tumors [35, 57]. Regional lymph node dissection is performed by some surgeons at the time of tumor resection to assess for local metastases.

Jugular paragangliomas of Fisch class C and D (see Table 1) are resected via an infratemporal approach with lower cranial neuromonitoring, though class Di3 tumors are sent for palliative radiation. Regional lymph node dissection is often carried out for these tumors as well. Jugular tumors have a 35% rate of postoperative lower cranial neuropathies (facial palsy, voice, swallowing articulation, shoulder weakness [43, 49]. Ten percent of patients with jugular paragangliomas have malignant tumors in other organ systems. Tympanic paragangliomas have a

very low risk of lymph node metastases, and of cranial nerve damage with surgery [1]. Vagal paragangliomas, arising from the perineurium of the tenth cranial nerve, have the highest incidence of malignancy [16] and bilaterality (92%) [30], and can invade the internal carotid artery. A genetic syndrome must always be considered for these tumors [30]. The vagus nerve usually must be sacrificed to resect a vagal paraganglioma [43].

Embolization can be used as a preoperative adjunct (PVA) to reduce blood loss and simplify surgery, or can be palliative (using cyanoacrylate or coils to permanently reduce the blood supply in elderly or infirm patients) [8, 43]. Preoperative embolization continues, on a superselective, slow basis, until a 60% reduction in tumor blush has been achieved, 24–48 h before surgery [35]. The risks of preoperative embolization for carotid body tumors include a 1.7–17% risk of stroke [36, 58]. 1.1% risk of TIA [36], and up to a 12.8% risk of cranial neuropathy [43]. In one study, preoperative embolization reduced the likelihood of temporary postoperative cranial nerve dysfunction by 50%, and of permanent postoperative cranial nerve dysfunction by 100% in carotid body tumors [36], though another study found no change in the rate of cranial nerve injury [55]. A lower rate of hemorrhage [55], lower risk of transfusion [56], and shorter operative time have been reported [55], though critics argue that the 50% higher cost of treatment [56] and stroke risk [59] are not justified. Consideration of embolization should be given for tumors larger than 4 cm in diameter or at the C2 vertebra or higher [55, 59]. Embolization is mandatory for Shamblin class III carotid body paragangliomas, and can be considered for class I and II. Embolization is the gold standard of treatment for Fisch class C and D jugular paragangliomas, [60–62] and enables surgical resection. Embolization is optional for class B tympanic paragangliomas, and contraindicated for class A tympanic paragangliomas. It is optional for larger vagal paragangliomas.

Primary radiation can achieve long-term tumor control in up to 96% of cases [47]. The recommended dose is 45–56 Gy. Radiation does not affect the chief cells, but the vascular connective tissue [63]. Cranial neuropathies are less common than with surgery, with reported rates for jugular paraganglioma treatment of 2–5% [43, 47, 64]. There is, however, a 9.4% cumulative incidence of chronic otitis media, stenosis of the external auditory canal, temporomandibular joint and more rarely temporal bone osteomyelitis, temporal lobe necrosis, and pituitary insufficiency [47]. The risk of radiation-induced malignancies, particularly in children, must figure heavily in treatment considerations, and is estimated to be as high as 3–5% [46, 65]. Primary radiation is a reasonable consideration only for unresectable or multiple HNPs, or for medically complex or elderly patients. Adjuvant radiation is effective in controlling local recurrence [38].

Stereotactic radiosurgery (SRS) is an excellent adjunct for patients in whom only subtotal resection has been attained, with reported disease control of more than 90% HNPs with 10 year follow-up [63], similar to conventional fractionated radiation treatments. The utility of SRS is limited to tumors measuring less than 3 cm, with doses of 12–15 Gy at the margin [66]. Relief of symptoms secondary to mass effect is unlikely to be achieved with SRS. Doses of 12–18 Gy have been reported to

achieve control of jugulotympanic paragangiomas with lower risk of radiation-induced complications than primary radiation, but there are no large studies with long-term follow-up [46, 47]. Patients with SDHD mutations may harbor the tumors most amenable to SRS, with their multiple tumors and higher risk of recurrence [16].

Chemotherapy is rarely considered for HNPs [2].Paragangliomas are not aggressive tumors, with even malignant tumors reported to survive for many years [67]. Sunitinib (a multiple tyrosine kinase inhibitor) has produced reduced tumor volume and increased progression-free survival for malignant HNPs in several case reports [16]. Angiogenesis inhibitors and drugs to downregulate hypoxia-induced factor activation such as mTOR inhibitors may hold promise for the future.

The management of multifocal HNPs requires a careful stepwise approach. Surgery is recommended for the largest HNP. Resection of the second largest can be considered if no cranial nerve injury results from the first surgery. Remaining tumors should be treated with radiation or palliative embolization [68, 69]. Bilateral vagal paragangliomas should not be resected; the larger one should be resected, and the other radiated.

Patients with HNPs require lifelong monitoring. They should be seen annually for the first five years, and every 3–5 years thereafter. Ultrasound should be performed at each of these appointments for patients with cervical HNP, and MRI/A when ultrasound reveals a change. MRI/A should be performed at every appointment for patients with jugulotympanic HNPs. Recurrences of HNPs have been reported after decades. The overall 5 year survival rate is 89% for benign tumors, and 20–70% for malignant HNPs, dependent on location [70]. Mutation-carrying tumor-free patients should be followed annually to every four years, as described in the section on genetic syndromes [5, 41].

2 Pheochromocytomas and Extra-Adrenal Paragangliomas

2.1 Presentation

Sympathetic paragangliomas (PCCs and EAPGs) arise outside of the adrenal gland anywhere along the sympathetic chain, with 75% arising in the abdomen (most commonly at the junction of the inferior vena cava and the left renal vein, or at the organ of Zuckerkandl) [31]. Individual case reports have described paragangliomas in the skin, GI and GU tracts [19], pre-aortic, aorticopulmonary, and sympathetic trunk ganglia [16]. Contrary to the parasympathetic paragangliomas, most sympathetic paragangliomas are symptomatic from catecholamine secretion as opposed to local mass effect [71]. Symptoms of catecholamine secretion include palpitations, flushing, excessive sweating, diarrhea, anxiety, and headaches. Other than the classic triad of episodic headache, sweating, and tachycardia with accompanying sustained hypertension, children can present with abdominal pain and distension,

back pain, pallor, and dilated cardiomyopathy. [31, 71]. For unknown reasons, the presence of these symptoms varies in patients with PCCs due to congenital diseases such as von Hippel-Lindau (VHL) disease or multiple endocrine neoplasia type 2 (MEN2) syndrome [72].

Spinal paragangliomas are significantly less common than their abdominal and head and neck counterparts, and arise from the filum terminale or cauda equina. While they can present with neuroendocrine symptoms, this is very rare. Instead, they often present with symptoms related to mass effect. Sciatic nerve pain or focal back pain are the most common complaints, though some patients will complain of bowel or bladder dysfunction, weakness, numbness, or parasthesias [73]. Although they are quite vascular, they can typically be completed resected.

2.2 Radiographic and Laboratory Testing

Biochemical testing for the diagnosis of paraganglioma should precede radiological testing if the presenting symptoms are those of excess catecholamine secretion. For PCCs, 24 h urine collection for fractionated metanephrines and epinephrine is the most appropriate study. If obtaining 24 h urine collection in the pediatric patient is not reasonable, plasma fractionated metanephrine testing is a reasonable alternative for diagnosing PCCs [74].

Radiological testing is the next step after positive biochemical PCC testing. In the spine, CT is helpful to evaluate the extent of bony erosion associated with these tumors. Often, an irregular, moth-eaten pattern of bony erosion can be seen. For abdominal and retroperitoneal paragangliomas, CT will identify most symptomatic neoplasms measuring 3 cm or larger in diameter. Post-contrast CT will demonstrate avid enhancement, and further delineate the mass. Caution should be taken with the administration of contrast, as ionic contrast can precipitate catecholamine crisis; therefore, either nonionic contrast should be used or the patient should have confirmative testing of negative biochemical activity prior to ionic contrast administration [75]. Additionally, the risks of administering radiation to a child who may have a genetic syndrome predisposing him or her to malignancy must be weighed. Like HNPs, MRI demonstrates a T1 hypointense and T2 hyperintense lesion with significant contrast enhancement. PCCs will appear hypointense relative to the remainder of the adrenal gland on T1-weighted imaging and markedly hyperintense on T2 (light-bulb sign), with avid post-contrast enhancement. Digital subtraction angiography is useful to identify arterial feeding vessels as well as any early draining veins exiting the tumor. Nuclear medicine plays a role in diagnostic testing when the above cross-sectional imaging is negative in the setting of positive biochemical testing, or to assess for metastatic disease. Imaging with 123-I-metaiodobenzylguanidine (MBIG), Indium-111 labeled octreotide, 18F-DOPA-PET [1] 18F-Fluorodihydroxy-phenylalanine-PET [44], or 18F-fluoro-2-deoxyglucose-PET [5] can demonstrate accumulation within the tumor with varying degrees of sensitivity [45]. Scintigraphy

using 123-I-MBIG is also useful to detect extraadrenal tumors and metastatic disease [45]. Not all tumors identified using 123-I-MBIG are confirmed as tumors at the time of surgery.

2.3 Treatment

Embolization serves as a preoperative adjunct for PCCs and EAPGs, to eliminate feeding vessels and minimize intraoperative blood loss, with surgery 1–2 days after embolization to prevent the development of collateral blood supply [43, 74]. Some studies have suggested that preoperative embolization of spinal paragangliomas is unnecessary, as the well-encapsulated mass typically arises from a distinct vascular pedicle within the intradural extramedullary compartment that can be isolated and controlled [73]. Surgical resection is the management of choice, with gross total resection being curative. Prior to surgical resection, both alpha-adrenergic and beta-adrenergic blockade are required in pheochromocytomas and biochemically active EAPGs [50]. See details under Treatment of HNPs. Complete surgical resection should result in the resolution of hypertension. Delayed return of hypertension may indicate residual, multiple, or metastatic tumor. In patients with widely metastatic disease, debulking with continued medical management with alpha-adrenergic and beta-adrenergic blockade for symptom management is indicated. For PCCs and EAPGs, there is increasing evidence for the use of external beam radiation therapy at doses greater than 40 Gy for local control, though progression outside of the field of radiation eventually occurs [76].

3 Pathology

The World Health Organization classifies paragangliomas by location and secretory status (sympathetic or parasympathetic) [3]. The classic appearance is a "Zellballen" pattern of nests of chief cells surrounded by sustenacular cells. Paragangliomas arise from the chief cells. The Zellballen pattern is more common in parasympathetic than sympathetic paragangliomas [19]. There is also a sclerosing subtype; rare variants include gangliocytic (most common in the duodenum) and pigmented paragangliomas, and composite tumors (combined with ganglioneuroma, ganglioneuroblastoma, neuroblastoma, or peripheral nerve sheath tumor, more common in PCCs than other paragangliomas) which represent diagnostic dilemmas because of their rarity [19].

There are no histopathological criteria for the diagnosis of malignancy; malignancy is diagnosed by metastasis to non-neuroendocrine tissue [2, 3, 9, 43, 69, 77]. Metastases are most often found in the cervical lymph nodes (68.6%), with 31.4% to the bone, liver, and lung [1, 2]. Less than 10% of HNPs are malignant. 16–19% of vagal tumors, 5–6% of carotid body tumors (Economopoulos) [36], and 2–4% of jugulotympanic tumors are malignant [2, 78]. Various scoring systems and

indicators of malignancy have been proposed, but the best predictors of metastasis are the SDHB mutation and an extra-adrenal location [5]; notably, SDHB protein is lost in tumors with SDHA, SDHAF3, SDHB, SDHC, and SDHD mutations so demonstration of SDHB protein loss serves as a screening tool for any SDHx mutation [19]. Up to 50% of malignant EAPGs have a SDHB mutation [5]. Overall, 50% of patients with malignant HNPs survive more than 5 years [67, 79]. Lee's 2002 survey of the National Cancer Data Base found a 0.017% rate of malignancy in HNPs [2]. Malignancy has been reported to be 2–3 × more common in women than men [80], but the incidence was equal in Lee's series. Those with carotid body metastatic paragangliomas had spread to the regional lymph nodes only in 95%; 57% of other malignant HNPs had regional metastases only. The frequency with which only regional metastases are diagnosed suggests either an indolent course or early detection. 76.8% of patients with metastases to the lymph nodes were alive five years after diagnosis, while only 11.8% of those with systemic metastases were alive after five years. Resection of metastases is recommended whenever possible, and radiation has been used to prolong survival from 12 to 45 months [2]. There were fewer deaths after surgery alone (40%) for malignant paraganglioma than for surgery with adjuvant RT, but the survival time was nearly 4 × as long for those undergoing radiation therapy also, likely because adjuvant radiation therapy was pursued for the more difficult cases, and because it was effective [2].

4 Genetics and Paraganglioma Syndromes

Thirty percent of HNPs are estimated to be familial [4, 81] and 45.5% of patients with PCCs and paragangliomas have genetic mutations [82]. All known paraganglioma syndromes, which include the paraganglioma (PGL) syndromes 1–5, multiple endocrine neoplasia (MEN) type 2, von Hippel Lindau (VHL), and neurofibromatosis (NF) type 1, have autosomal dominant inheritance [1]. Up to 80% of pediatric pts have germline mutations in one of these genes [4, 14, 15]. Syndromic patients develop paragangliomas an average of 15 years earlier than those with sporadic paragangliomas [4], and those with malignant tumors present earlier than those with benign tumors [83]. Multiple tumors are far more common (occurring in 10–50% of patients) [84], as is malignancy. PCCs and sympathetic paragangliomas are more commonly seen in MEN2, NF1, and VHL, but HNPs are seen in <0.8% of patients with these syndromes [1]. Germline mutation are most likely in PCC with early onset, bilateral, extra-adrenal or malignant paragangliomas [85].

Sporadic carotid body paraganglioma cases are more common in people living at high altitudes and with chronic obstructive lung disease, so there may be a role for chronic hypoxia in the development of head and neck paragangliomas [8, 86, 87]. Patients with cyanotic congenital heart disease have an increased incidence of PCCs and paragangliomas, even many years after correction of hypoxemia, at a younger age (mean 31.5 years) and increased rate of multiplicity (39%) [88]. Interestingly, the protein implicated in the PGL syndromes induces a pseudo-hypoxic state at the

cellular level. Succinate dehydrogenase (SDH), with four subunits (A, B, C, and D), forms the mitochondrial complex II. It is important in the mitochondrial respiratory chain and the tricarboxylic acid cycle. Subunits B, C, and D are tumor suppressor genes. Mutations in one of these three genes (or SDHA or SDHAF2) leads to complete loss of SDHB protein [19] and loss of the function of SDH, resulting in a pseudo-hypoxic state and inducing the production of hypoxia-inducible factors that lead to tumorigenesis [16, 81, 89]. Over 100 SDH germline inactivating heterozygous mutations have been reported [82, 84]. Ninety percent of the mutations are in SDHB, SDHD, VHL, RET (the gene for MEN2), or NF1. Ten percent are in SDHC, SDHA, SDHAF2, TMEM127, or MAX [5]. Hypoxia and cigarettes should be avoided by mutation carriers [5].

PGL1 syndrome is caused by a SDHD mutation, and is the most common PGL syndrome. The mean age at diagnosis is 33 years [14]. Patients with this syndrome develop multiple paragangliomas (60%), as well as HNP with concurrent PCC in 18.1% [4]. Ninety-one to 97% of these patients have been diagnosed with HNPs [14, 82]. of which 86% are carotid body paragangliomas [16], and 79% develop multiple HNPs [14]. Over 50% develop PCCs [16]. Malignant paragangliomas have been reported in 3–9.6% of patients [4, 6, 14, 82]. This syndrome is inherited in a parent-of-origin-dependent fashion, meaning that it is only phenotypically apparent if the gene is inherited from the father [67, 89, 90]. though a single case of maternal transmission has been reported [91]. The maternally derived gene is inactivated during oogenesis by DNA methylation and histone modification, allowing the paternally derived gene to act unopposed [16]. There is high penetrance in this syndrome, with 61% having a positive family history, 50% penetrance by age 31, and 85% by age 50 [4].

PGL2 syndrome is secondary to a mutation in SDH complex assembly factor 2 (SDHAF2/SDH5). This rare syndrome, with only two families having been reported, is characterized by the development of benign HNPs only with a high rate of multifocality at an early age [19]. There is parent-of-origin -dependent inheritance and high penetrance, similar to PGL1.

PGL3 is defined by a SDHC mutation. The median age at diagnosis has been variously reported as 38 and 46 years [14, 84]. This rare syndrome, less common than PGL 1 and 2, is characterized by unifocal (73%) [14] and benign HNPs in 87% of diagnosed patients [82]. Only 3% are malignant [14]. The penetrance is estimated to be low, at 11.5% [4], and 62.5% have positive family history [14].

PGL4 is characterized by a SDHB gene mutation. The median age at diagnosis is 32 years [14, 84]. This genetic syndrome is the one most often diagnosed in pediatric patients [13]. Patients with this syndrome develop HNPs with EAPGs, with EAPGs being the most common tumors, and only 33% having multiple HNPs with or without EAPGs [14]. These tumors frequently recur, and malignancy occurs in 20.6–41% of cases [4, 13, 41, 89, 92]. Fifty-five to 60% of vagal paragangliomas occur in patients with this syndrome [82]. The penetrance is slightly lower than PGL1 but higher than PGL3, with 1/3 having a positive family history [14], 50% penetrance by age 35, and 77% by age 50 [4]. There is an increased risk of kidney

cancers (14% by age 70), gastrointestinal stromal tumors, papillary thyroid cancer, and neuroblastoma with SDHB mutations [89].

Several gene mutations have been grouped together as PGL5 (SDHA, TMEM127, MAX, HIF2A) [19]. SDHA mutations have no location predisposition nor familial tendency, low penetrance and a higher age at onset [19, 82]. TMEM mutations are found in 2–4% of familial cases. TMEM is a negative regulator of mTOR, a growth and proliferation protein [16]. Patients with MAX mutations tend to present at a younger age with bilateral PCCs. EAPGs are fairly common as well, though all that developed these had been diagnosed with PCCs first [82]. There is a low risk of malignancy with this mutation [82]. There may be a parent-of-origin effect with MAX mutations [5]. MAX encodes a transcription factor that functions with myc to regulate proliferation, differentiation, and apoptosis [16]. One percent of patients who test negative for SDHx and TMEM have MAX mutations [16].

Familial PCC occurs in 30–50% of patients with MEN 2 [6, 67], but there are only a few case reports of HNPs in this syndrome. Ten to 20% of patients with VHL syndrome have PCCs [67],and <1% have HNPs. MEN2 and VHL are statistically significantly more often diagnosed in children with paragangliomas than adults [13]. The risk of PCC is 1–5% for patients with NF1 and 1% for MEN type 1 [6, 93]. Interestingly, sporadic PCCs often have loss of NF1 function [82, 94]. Patients previously diagnosed with Carney triad (gastrointestinal stromal tumors (GISTs), PCCs, and pulmonary chondromas [95, 96] (also other paragangliomas, adrenocortical adenoma, and esophageal leiomyoma) [19], and Carney-Stratakis syndrome (GIST, paragangliomas and PCCs) [97] have mostly been diagnosed with PGL 1,3, or 4 in retrospect [14]. Thus, there may be an increased risk of GIST in patients with PGL 1,3, and 4. A subset of Carney patients, however, have not been diagnosed with any mutation, though this subset is still accepted to have a genetic etiology [19].

More than half (59–80%) [4, 13–15] of paragangliomas diagnosed in children are associated with germline mutations, and the frequency of such a diagnosis increases as age decreases, with 70% of children under age 10 years being diagnosed with a germline mutation [4]. In contrast, only 36% of adult paraganglioma patients are diagnosed with a genetic syndrome [13]. The average age at paraganglioma diagnosis in pediatric patients is 13.8 years, the most common genetic syndrome is PGL4, and the most commonly diagnosed paraganglioma in children is the HNP [13]. The youngest patient diagnosed with a paraganglioma to date was a 7 month-old boy with a massive carotid body tumor [97]. The most common tumor type reported in the literature in children is the carotid body paraganglioma [7, 12, 79, 95, 96, 97–107] though PCCs [13, 15] and EAPGs [4, 12, 13, 92, 108] have been reported as well. Takautz reported on 8 pediatric nonfamilial paragangliomas [12]. Despite four having local invasion and three having unresectable disease, only the one patient who also had lymph node involvement succumbed to her disease, 11.5 years after diagnosis. Two patients initially deemed to have unresectable disease underwent complete resection after external beam radiation therapy. It appears that those children diagnosed with genetic syndromes may be more likely

to have a surgical cure and higher rate of survival in comparison to those with spontaneous paragangliomas [109].

Genetic screening is useful as it predicts recurrence, multiplicity, and tumors in other locations for the patient, and genetic risk for their family members. All patients with multiples of the same tumor type or multifocal tumors (synchronous or metachronous), recurrent tumors, onset earlier than age 45 (thus, all pediatric patients), or a paraganglioma in the setting of a positive family history should be screened [5]. SDHB is an excellent screening tool for a genetic paraganglioma syndrome, as SDHB protein is lost in PGL1-4. Additionally, it is the most common mutation in pediatric patients [13, 92]. Patients with multiple HNPs, solitary HNP with a family history, and HNP and PCC should initially be screened for SDHD, then B and C, and then AF2. Patients with a solitary HNP and no family history should be screened for SDHB, D, and then C. Those with malignant HNP should be screened for mutations in SDHB, D, and then C. If transmission can be established to have been from mother to child, then the patient should be screened for SDHB first, followed by C [1]. Patients with solitary EAPGs should be screened for SDHB, then D, then VHL, then SDHC [41]. Patients with solitary PCCs must be considered for MEN2 and VHL, then SDHB and D, TMEM127, and MAX [4, 6, 41]. Those with bilateral PCCs should be assessed for VHL (these PCCs secrete norepinephrine and normetanephrine) and MEN2 (these PCCs secrete epinephrine and metanephrine) [5, 93, 110].

Standard initial screening of mutation carriers should include a physical exam, MRI of the head, neck, chest and abdomen with contrast, and plasma free metanephrines or 24 h fractionated urine metanephrines and normetanephrines [1, 40]. The age at which screening should begin is debatable, but certainly the use of radiation in screening children should be limited [84]. Screening should begin at least 10 years before the earliest diagnosis in the family [5, 111]. Instituting screening at age 10 would identify all tumors in patients with SDHD mutations, and 96% of those with SDHB mutations [6]. The most conservative recommendation is to initiate screening exams in patients with SDHD and SDHB mutations at age 6, since 8.7% of these patients developed a tumor before the age of 18 [82]. Even so, the youngest reported case occurred in a 7 month-old, though no genetic testing was done in this case [97].

Patients with SDHB mutations should undergo a clinical evaluation annually after the initial screening, MRI of the chest, abdomen, and pelvis every two years, and MRI of the head and neck and nuclear medicine study every four years [5]. Patients with SDHD mutations who have had a paraganglioma should undergo annual clinical evaluation, MRI of the head and neck every two years, and nuclear medicine study and MRI of the chest, abdomen and pelvis every four years [5]. Patients with SDHD mutations without a tumor history should be evaluated clinically every 3 years, and the screening tests spaced out as well. Patients with SDHC mutations should have follow-up screening with MRI of the head and neck, annually for those who have had a tumor and every 3–5 years for those who have not, as well as an MRI of the chest, abdomen, and pelvis every four years along with a nuclear medicine study [5]. Because of parent-of-origin transmission with

SDHD and SDHAF2, children of affected females need not be screened as frequently as those of males, though a single case of transmission from the mother has been reported [91]. Grandchildren of an affected female must be screened [84]. Prenatal testing is available if the gene variant is known.

5 Pearls

The majority of paragangliomas in children occur in the head or neck. They are far more likely to be associated with a genetic syndrome, and to be malignant. Surgery is the best, and the only curative, option for treatment of paragangliomas. In cases of unresectable, partially resected, or multiple tumors, radiation or stereotactic radiosurgery can be useful. Five autosomal dominant paraganglioma syndromes (PGL 1–5) have been identified, and paragangliomas also occur in MEN2, VHL, and NF1. PGL1 and 2 have parent-of-origin inheritance. A genetic cause should be sought for any paraganglioma in a child or young adult.

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Glomus Jugulare and Carotid Body Tumors

Badih Daou and Pascal Jabbour

1 Introduction

Paragangliomas are neuroendocrine tumors derived from the extra-adrenal paraganglia of the autonomic nervous system [1]. Paragangliomas of the head and neck are rare and constitute around 3% of all paragangliomas [2]. Furthermore, paragangliomas make up only 0.6% of head and neck neoplasms [2]. The main paragangliomas occurring in the head and neck region include carotid body tumors and glomus jugulare tumors. Other less common locations include the glomus tympanicum, glomus vagale, larynx and nasal cavity. Although, these tumors occur most commonly in the adult population, there have been many case reports that identified the occurrence of glomus jugulare and carotid body tumors in the pediatric population [3–8]. When they occur, they are most commonly benign [3]. Paragangliomas are most likely to be sporadic tumors; however, in 10–50% of cases they can be familial [2]. Although carotid body and glomus jugulare tumors represent two separate neoplasms, they share many similar biochemical, histological and clinical characteristics.

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1.1 Carotid Body Tumors

The carotid body is a chemoreceptor located in the adventitia at the level of the bifurcation of the common carotid artery. Carotid body tumors are the most frequent type of paragangliomas arising in the head and neck (60%), with a prevalence of 1–2 per 100,000 people [2]. There are three types: sporadic which is the most common form, familial which usually present at a younger age and may be bilateral, and hyperplastic that is associated with hypoxia (e.g. high altitude) [9, 10]. Sporadic carotid body tumors are bilateral in 4% of cases whereas they can be bilateral in as high as 31% of familial tumors [2, 11]. Malignancy is rare, approximately in 6% of tumors [12].

1.2 Glomus Jugulare Tumors

Glomus jugulare tumors arise from the paraganglion cells situated within the adventitia of the jugular bulb in the jugular foramen [13]. These tumors are rare, but constitute the second most common location of paragangliomas in the head and neck and represent the most common tumor of the middle ear [2]. Glomus tumors occur at an incidence of 8.6 per 100,000 people and glomus jugulare tumors have an incidence of 1 in 1.3 million people per year [14, 15]. Glomus jugualre tumors can be multicentric in about 10% of patients with sporadic neoplasms and in up to 50% of patients with familial tumors [2, 16]. Malignancy is rare.

2 Clinical Presentation

2.1 Carotid Body Tumors

These tumors are usually slow growing and remain clinically silent for years. For this reason, the occurrence of carotid body tumors in the pediatric population might be more frequent than reported but diagnosis might be delayed until older age. A high degree of clinical suspicion is required for diagnosis in children. The most common presentation is an asymptomatic neck mass situated in the antero-lateral neck. The mass is usually fixed in the superior-inferior axis but can be moved laterally because of the tumors' location within the carotid sheath (Fontaine's sign) [3]. Similarly, compression of cranial nerves IX, X, XI, and XII or involvement of the sympathetic chain can lead to related symptoms including hoarseness, dysphonia, dysphagia, shoulder and toungue dysfunction. A bruit is commonly heard on auscultation [2]. Familial carotid body tumors can present in association with multiple endocrine neoplasia II, neurofibromatosis 1, tuberous sclerosis and von Hippel-Lindau disease [10].

2.2 Glomus Jugulare Tumors

Glomus Jugulare tumors have a slow growth and a delayed occurrence of symptoms. The main presenting symptoms include pulsatile tinnitus and conductive hearing loss [17]. Local invasion and intracranial extension can accompany the progression of the tumor and result in erosion of bone and dura and symptoms related to dysfunction of cranial nerves VIII, X, X, XI including symptoms of facial weakness, hoarsness, and dysphagia [15]. Glomus paragangliomas are also referred to as chemodectomas or nonchromaffin paragangliomas since they have the ability to secrete catecholamines. Symptoms related to catecholamine release are uncommon (1–3%) [2], but seem to occur more commonly in children and include headache, palpitations, hypertension, tachycardia and sweating [4]. Jugulotympanic paragangliomas might be masked in children by symptoms of otitis media and recurrent obstructive infection that fails medical treatment [4].

3 Diagnosis

The workup of a suspected paraganglioma should begin with a thorough history and physical exam for initial characterization of the tumor and its extension. Patients with suspected functional tumors should undergo biochemical testing for urinary catecholamines and a 123I-MIBG (Iodine 123-labeled metaiodobenzylguanidine) scan or a somatostatin receptor scintigraphy [18, 19].

3.1 Carotid Body Tumors

Carotid body tumors can be identified by Doppler ultrasonography with color flow imaging which will show a solid, well-defined, highly vascularized mass at the carotid bifurcation [20]. Magnetic resonance imaging (MRI) with gadolinium contrast represents the imaging modality of choice for the diagnosis of carotid body tumors and for the evaluation of the vascularity, relationship to nearby structures and extension of the tumor [21]. MRI is especially useful in the pediatric population since it does not use ionizing radiation or nephrotoxic contrast agents that might lead to complications in young patients [3]. Carotid body tumors have a characteristic salt and pepper appearance on T2-weighted MRI imaging due to the presence of flow voids within the tumor [22]. Head and neck CT scan is less preferred but can be used to better characterize the bony anatomy. MR arteriography can be performed to evaluate the tumor's vascularity but conventional angiography remains the gold standard since it can accurately map the vascular tree and collateral circulation, and identify multicentric tumors [20]. On angiography, carotid body tumors result in widening of the carotid bifurcation (Lyre sign) [3, 20]. Incisional or fine needle aspiration biopsy of the mass is not required to establish

the diagnosis and should not be attempted routinely since it can lead to significant hemorrhage, cranial nerve injury and fibrosis at the operative site [23, 24].

3.2 Glomus Jugulare Tumors

Otologic examination may show a pulsatile red-bluish mass behind the tympanic membrane. On audiometric testing, a conductive hearing loss pattern is seen [17]. CT and MRI are complimentary diagnostic strategies that are both implemented in the diagnosis of glomus jugualre tumors. CT scanning will better demonstrate the presence and extent of bone involvement while MRI will allow superior characterization of soft tissue involvement, intracranial extension and tumor delineation [25]. Similarly, a salt and pepper appearance on T2-weighted MRI imaging is observed. On CT scan, bony distortion of the jugular fossa and erosion of the cortico-jugular spine lead to a "moth eaten pattern" involving the walls of the jugular fossa and the inferior temporal bone [26]. An angiogram is required in the presence of a large tumor and with intracranial extension and will also help in identification of multiple tumors.

For glomus jugulare and carotid body tumors, histopathological examination should only be obtained postoperatively. Grossly, the tumor appears as a well demarcated polypoid mass. Under light microscopy, two types of cells, chief cells (type I) and sustentacular cells (type II) are seen with individual homogenous tumor cells arranged in distinctive cell balls or Zellballen separated by fibrovasscular stroma [2]. Immunohistochemistry is positive for chromogranin,synaptophysin, neuro-specific enolase and neurofilament [2].

4 Staging

The classification of carotid body tumors described by Shamblin et al. in 1971 is the most widely used system to assess the resectability of this neoplasm. There are 3 groups in the Shamblin classification (Table 1) [27]. The morbidity, blood loss and surgical time associated with resection of the tumors increases with advancing stage [28].

Table 1 The Shamblin classification of carotid body tumors [27]

Class	Description
I	Tumor has little attachment to the carotid vessels. Tumor is easily dissected from adjacent vessels. Tumor resected with minimal morbidity
II	Tumor partially surrounds internal and external carotid arteries and is more adherent to vessel adventitia. Dissection is more difficult but still possible
III	Tumor is intimately adherent to the carotid and completely surrounds carotid bifurcation. Surgeon is unable to dissect tumor without entering the vessel lumen

Table 2 The Glasscock/Jackson classification of glomus jugulare tumors [29]

Type	Description
I	Small tumor involving jugular bulb, middle ear, and mastoid
II	Tumor extending under internal auditory canal; may have intracranial canal extension
III	Tumor extending into petrous apex; may have intracranial canal extension
IV	Tumor extending beyond petrous apex into clivus or infratemporal fossa; may have intracranial canal extension

Glomus jugulare tumors are often classified according to the Glasscock/Jackson classification (Table 2) [29]. Another widely used system for jugulotympanic paragangliomas is the Fisch classification [30].

5 Treatment

5.1 Carotid Body Tumors

Surgical resection is the main treatment of carotid body tumors in young patients. Other options include radiation therapy or clinical observation but these are reserved for older patients, those with large tumors in anatomically difficult locations, patients not fit for surgery and patients with multifocal paragangliomas. The primary objective of surgery is to achieve complete resection of the tumor with the lowest possible morbidity. This is best achieved with an experienced vascular surgeon. Although these tumors are slow growing, early surgical resection should be the aim in pediatric patients as larger and more advanced tumors carry higher morbidity and make surgical resection more difficult [3]. Furthermore, carotid body tumors have an unpredictable malignant potential in children and should be managed early. Preoperative evaluation is critical to determine tumor size, spread, multiplicity and functional status. Preoperative embolization has been advocated by many surgeons to improve the overall safety of carotid body tumor surgery by decreasing the size and vascularity of the neoplasm and minimizing intraoperative complications and blood loss [31, 32]. However, this is not performed on all cases but has been preferred for the management of large tumors (>4 cm) [33, 34]. Furthermore, the role of preoperative embolization is still uncertain in pediatric patients [3]. A temporary balloon occlusion test should be performed in patients who are at high risk of injury to the internal carotid artery including those with large tumors adherent to the carotid vessels causing stenosis, and irregularity of the vessel walls and extreme widening of the carotid bifurcation [35]. Surgery is performed through a transcervical incision. Proximal and distal vascular control should be established. Neurovascular structures should be identified including the ascending pharyngeal artery which is the main blood supply, other feeder vessels and cranial

nerves IX, X, XI, and XII. Periadventitial dissection of the carotid artery should be performed to preserve the vessel's integrity [36]. If an injury to the carotid artery occurs, partial heparinization and temporary clamping should be performed followed by vascular reconstruction [35].

5.2 Glomus Jugulare Tumors

Surgery is the standard management strategy of jugulotympanic paragangliomas, however, radiation therapy and stereotactic radiosurgery including gamma knife radiosurgery have shown to be safe and effective treatment modalities and are becoming more popular as the initial treatment of glomus jugualre tumors [37]. The tumor size and extent play a crucial role in determining treatment preference. Surgical management should be considered initially with low grade tumors. Surgical resection of more advanced tumors is still possible but is more complex with increased risk of neurovascular compromise, mainly cranial nerve deficits [37]. Similar to carotid body tumors, preoperative embolization can be used to facilitate surgical resection and decrease blood loss. In patients with catecholamine secreting tumors, preoperative management with alpha and beta blockers is required to prevent a hypertensive crisis following resection [38]. A systemic analysis by Suarez et al. that compared surgery and radiotherapy found that both methods offer comparable rates of tumor control and that patients treated with radiotherapy further had lower morbidity [37]. The best treatment approach has not been established in children but surgery remains the most common treatment of choice in the pediatric population because of the potential of complete and immediate resection [4].

6 Complications and Follow-Up

6.1 Carotid Body Tumors

Carotid body tumors usually encase adjacent neurovascular structures. Surgical morbidity is related to compromise of these structures. Large (>4 cm), higher grade tumors (Shamblin III), multicentric or bilateral tumors carry significantly higher operative risk. Cranial nerve injury represents the most common cause of postoperative morbidity [39]. Injury to cranial nerves IX, X, XI, XII occurs in as many as 40% of patients who undergo surgical resection [40]. Injury to the superior laryngeal nerve has been reported to be the most common injured structure during dissection of the tumor [40]. Patients can present with voice changes, hoarseness, shoulder dysfunction, difficulty swallowing, aspiration and tongue weakness. In a review of pediatric patients with carotid body tumors, the rate of postoperative cranial nerve deficits was lower than what was reported in adults (15.8%) [3]. The rate of cranial neuropathy is significantly lower with radiation therapy [39]. Injury to the common or internal carotid vessels, hemorrhage, stroke, infection and death

are less common but potential complications. Resection of bilateral carotid body tumors may result in compromise to the baroreceptor reflex and manifests as dramatic variations in blood pressure [2, 40]. The rate of recurrence after total resection is low (3%) [39]. There is a high rate of long-term control of the tumor after surgical resection or radiation therapy, more than 90% [39].

6.2 Glomus Jugulare Tumors

The rate of cranial nerve deficits observed with surgical management of glomus jugulare tumors is higher than surgery for carotid body tumors, as high as 59% [2]. Symptoms include facial weakness, hearing loss, aspiration, and difficulty swallowing and tongue weakness. Other complications include cerebrospinal fluid leakage, meningitis, stroke, bleeding and death [37]. Patients treated with radiation therapy have a lower rate of cranial neuropathy but can develop necrosis of bone and brain, secondary tumors and hearing loss [37]. Furthermore, the rate of long term tumor control is slightly lower (80–90%). Tumor recurrence may occur in about 7% of patients after total resection [37].

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Juvenile Nasopharyngeal Angiofibromas

Amanda M. Carpenter, Wayne D. Hsueh, Jean Anderson Eloy, and James K. Liu

1 Introduction

Juvenile nasopharyngeal angiofibroma (JNA) is a rare, benign sinonasal tumor that almost exclusively affects adolescent and young males, 14 to 25 years old. Its incidence has been cited to be 0.05 to 0.5% of all head and neck neoplasms, with reports suggesting that it is more common in India than the West [1–3]. The site of origin is the posterolateral wall of the nasal cavity, in the region of the sphenopalatine foramen, near where the palatine bone, vomer, and pterygoid process of the sphenoid meet [4]. The tumor grows in the submucosa of the nasopharyngeal roof and eventually can reach the nasal septum and posterior part of nasal space. It can erode and invade the sphenoid bone, and extend to the anterior and middle cranial fossae, the orbit, the optic chiasm, and the cavernous sinus [5]. Intracranial extension is seen in about one of five cases, but dura is usually not invaded [1]. JNA does not invade the skull base by cellular infiltration like malignant lesions, but rather leads to bone resorption through relentless expansion [6]. They can become very large, but the mean size is four centimeters [7].

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2 Clinical Findings

JNA is a histologically benign lesion, but it can have a potentially malignant course due to its prominent vascularity and propensity for aggressive local growth. The most common presentation is recurrent or profuse epistaxis and progressive nasal obstruction in an adolescent boy [4]. As disease progresses, patients can have cranial nerve II through VI palsies, facial deformities (broadening nasal bridge, cheek swelling), proptosis, and blindness [8].

Diagnosis of JNA is made clinically and radiographically. On nasal endoscopy, a large, hypervascularized, lobulated mass extending into nasopharynx is seen [9]. Biopsy is usually not necessary, but can be considered if the tumor is atypical or the history is unusual. If biopsy is warranted, it is advised to be done in an operating room under general anesthesia due to the high vascularity of the tumor. Mimickers of JNA include fibrous dysplasia, lymphoepithelioma, and rhabdomyosarcoma [6]. Other different diagnoses include: pyogenic granuloma, choanal polyp, angiomatous polyp, chordoma, and esthesioneuroblastoma. Prognosis is very good with early diagnosis; however, the relatively innocuous presentation frequently leads to diagnosis in later stages of disease.

3 Imaging

CT scan of the head and neck is indicated to evaluate the bony architecture of the sinonasal tracts, skull base, and orbit. On axial CT, the Holman-Miller sign, characterized by anterior bowing of the posterior maxillary wall due to invasion of the pterygomaxillary space, is pathognomonic for JNA[10]. MRI is useful to evaluate the soft tissue planes and is essential for operative planning. JNA demonstrates low intensity on T1 and intermediate intensity on T2. The tumor avidly enhances with contrast administration, and flow voids are seen secondary to the highly vascular nature of the tumor (Fig. 1) [9].

4 Tumor Biology

The exact etiology of JNA is unknown—proposed theories question whether the tumor has a vascular or fibrous origin. Some suggest that a vascular etiology is due to incomplete regression of the first branchial arch artery [11]; others postulate that the excess vessel growth is driven by deregulated stromal cells [12].

The gender selectivity and young age at diagnosis suggest that JNA is hormone dependent. Studies are generally positive for tumor tissue androgen receptor positivity [13, 14]. The anti-androgen drug, Flutamide, has been used in the past to shrink the tumor pre-operatively, with variable success [9].

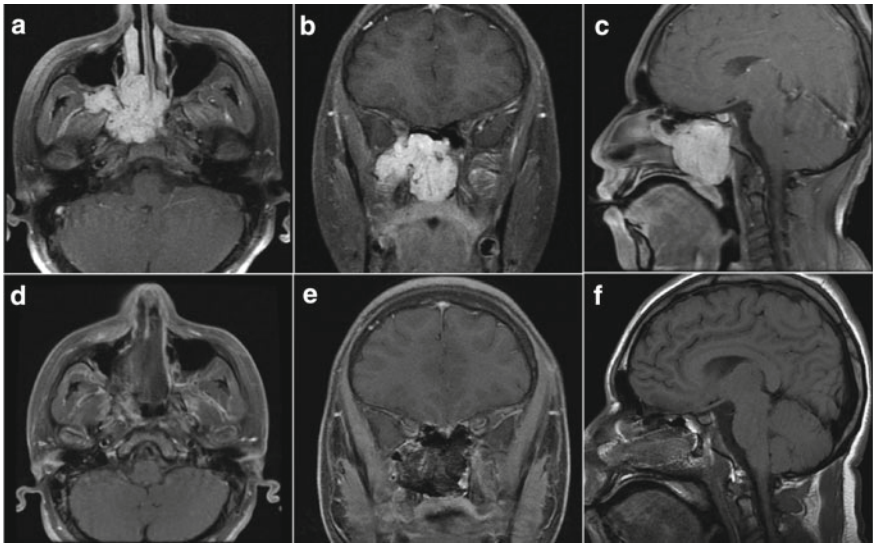

Fig. 1 **a**, **b**, **c**: Preoperative post-gadolinium T1-weighted MRI (**a**: axial, **b**: coronal, **c**: sagittal) demonstrating an enhancing, hypervascular, juvenile nasopharyngeal angiofibroma in the right nasal cavity, bilateral nasopharynx, right pterygopalatine fossa, and right infratemporal fossa. The tumor was removed using a combined endoscopic endonasal and sublabial transmaxillary approach. **d**, **e**, **f**: Postoperative post-gadolinium T1-weighted MRI (**d**: axial, **e**: coronal, **f**: sagittal) showed no evidence of residual tumor

There are mixed results of estrogen receptor positivity [15–18]. Anti-estrogen therapy has also been given to patients in the past, but the small benefit of shrinkage was not deemed greater than the negative side effects of feminization in a teenage male population [9, 14]. Despite the many reports of hormone receptors on JNA tumor tissue, there is no evidence of altered serum hormone levels in these patients, and steroid therapy has fallen out of favor [12]. At this time, there is no single theory that can explain the predilection for the male sex.

The highly vascular nature of JNA has prompted many investigators to evaluate the tumor for proangiogenic growth factors. Vascular endothelial growth factor (VEGF) is a prominent proangiogenic growth factor and is consistently positive on immunohistochemical studies of JNA[14, 17]. Other growth factors that may contribute to JNA pathogenesis include transforming growth factor-β1 (TGF β1), basic fibroblast growth factor, and insulin-like growth factors (IGFs) [12, 17, 19–21].

Several studies have identified numerous chromosomal alterations in JNAs, specifically, gains at chromosomes 4, 6, 7, and X; and losses at 17, 22, and Y [22–24]. In addition, there is an increased incidence of JNA in families with familial adenomatous polyposis, which is caused by a mutation in the adenomatous polyposis coli gene that regulates beta-catenin protein. β-catenin acts as both a cell–cell adhesion component and as a downstream transcriptional activator in the WNT

signaling pathway, and there is evidence that a mutated β-catenin gene increases androgen receptor expression [22]. Although APC mutations were not found in JNA, genetic alterations of other WNT-pathway members have been identified in JNA: CNNB1 (encodes β-catenin), GSK3β (glycogen synthase kinase 3-β), and Axin2 (Axis inhibition protein) [25].

5 Histopathology

On gross pathology, JNA is smooth, often lobulated, nonpedunculated, unencapsulated, firm, and rubbery [4]. It is grey-tan in color, although it is frequently pink-red upon inspection secondary to bleeding during resection. Microscopic histology demonstrates vascular proliferation in a fibrous stroma. Vascular channels vary from capillary size to venous size and are lined by endothelial cells that lie directly against stromal cells; many are characteristically staghorn shaped [7]. Lack of intervening smooth muscle between these two cell types contributes to the capacity of JNA to bleed easily [4]. Mast cells are occasionally seen.

6 Staging

Several staging systems have been developed to classify JNA lesions, largely based on tumor site and extension. The most commonly used grading systems are the Radkowski and the Andrews-Fisch, but the older Chandler and newer Onerci and UPMC scales are described in Table 1 [26–31].

Table 1 Outline of most widely used grading scales to assess Juvenile Nasopharyngeal Angiofibroma

	Chandler 1984	Andrews-Fisch 1989	Radkowski 1996	Onerci 2006	UPMC 2010
1	Tumor limited to NP	Tumor limited to NP, nasal cavity; bone destruction negligible or limited to sphenopalatine foramen	IA: Nose and NP IB: Nose and NP with extension into > = 1 sinus	Nose, NP, ethmoid and sphenoid sinuses or minimal extension into PMF	Nasal cavity, medial ptergopalatine fossa

(continued)

Table 1 (continued)

	Chandler 1984	Andrews-Fisch 1989	Radkowski 1996	Onerci 2006	UPMC 2010
II	Extension into nasal cavity and/or sphenoid sinus	Invasion of pterygopalatine fossa or maxillary, ethmoid, or sphenoid sinus with bone destruction	IIA: Minimal extension into medial PMF MB: Full occupation of PMF, displacing posterior wall of maxilla, orbit erosionbranches IIC: ITF and cheek extension	Maxillary sinus, full occupation of PMF, extension into ACF, limited extension into ITF	Paranasal sinuses, lateral pterygopalatine fossa, no residual vascularity following embolization
III	Tumor extending into one or more of the following: antrum, ethmoid sinus, PMF, ITF, orbit, and/or cheek	IIIA: Invasion of ITF or orbital region without intracranial involvement IIIB: Invasion of ITF or orbital region with intracranial extradural involvement	MIA: Erosion of skull base; minimal intracranial extension IIIB: Extensive intracranial extension	Deep extension into cancellous bone at pterygoid base or body and greater wing of sphenoid, significant lateral extension into ITF or pterygoid plates, orbital, cavernous sinus obliteration	Skull base erosion, orbit, ITF; residual vascularity following embolization
IV	Tumor extending into cranial cavity	IVA: Intracranial intradural tumor without infiltration of cavernous sinus, pituitary fossa, or optic chiasm IVB: Intracranial intradural tumor with infiltration of cavernous sinus, pituitary fossa, or optic chiasm	N/A	Intracranial extension between pituitary gland and ICA, tumor localization lateral to ICA, MCF extension, extensive intracranial extension	Intracranial extension, residuality vascularity following embolization

Abbreviations: Nasopharynx (NP); pterygotnaxillary fossa (PMF); infratemporal fossa (ITF); internal carotid artery (ICA); anterior cranial fossa (ACF); middle cranial fossa (MCF)

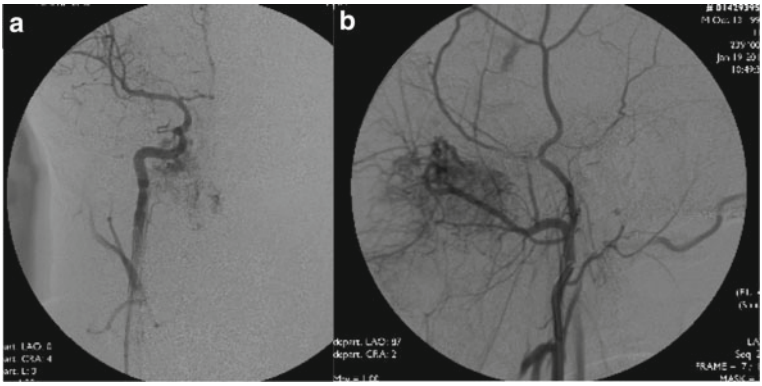

Fig. 2 Cerebral angiography (**a** right internal carotid artery injection, AP view; **b** right external carotid artery injection, lateral view) of patient in Fig. 1 shows hypervascularity of the tumor fed by both intracranial and extracranial carotid feeders. Preoperative embolization of the extracranial carotid artery feeders was performed prior to surgical resection

7 Management

Surgical resection is the mainstay of JNA treatment. Surgery is generally preceeded by embolization of feeding vessels to reduce intraoperative bleeding, preferably within 24 to 48 hours before surgery due to rapid revascularization of the tumor (Fig. 2) [32]. The major arterial supply of JNA is typically the ipsilateral internal maxillary artery, but the sphenopalatine artery, the ascending pharyngeal artery, the ipsilateral internal carotid artery, and even the contralateral external carotid artery can contribute to the blood supply, as well [4, 33, 34]. On angiogram, JNA has a characteristic dense, homogeneous blush [4].

Several different approaches to resect JNA have been described in the literature, such as transcranial, transfacial, endoscopic endonasal, and endoscopic transmaxillary. The optimal surgical approach should be selected based on tumor size, location, and extension of the tumor. A combined approach from above and below may also be necessary, especially if intracranial extension is observed.

8 Endoscopic Surgery

Endoscopic endonasal techniques are increasingly being utilized to resect JNA (Fig. 3). It is the preferred modality for small and intermediate sized tumors limited to the nasal cavity, nasopharynx, paranasal sinuses, and pterygopalatine fossa [32]. Advantages of this approach compared to open procedures include minimal soft tissue and bony disruption, lack of external incisions, shorter hospital stays, and less

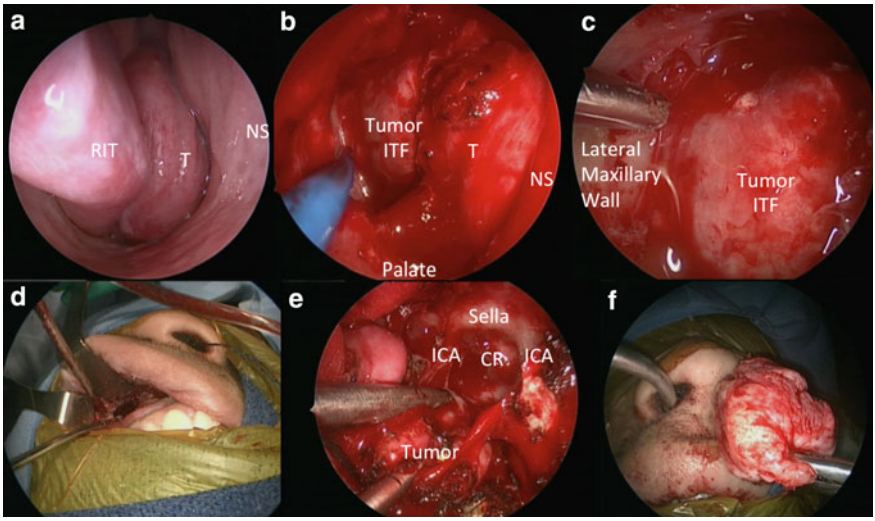

Fig. 3 Intraoperative photographs of patient in Fig. 1. **a** Endoscopic view of the tumor (T) in the nasal cavity between the nasal septum (NS) and the right inferior turbinate (RIT). **b** Endoscopic endonasal view of the tumor (T) in the right nasal cavity and right infratemporal fossa (ITF). **c** Endoscopic view through the sublabial transxmaxillary corridor showing the tumor in the ITF and the lateral maxillary wall. **d** View of the right sublabial transmaxillary exposure. **e** The tumor is being peeled off of the sella and clival recess (CR). Both paraclival internal carotid arteries (ICA) are visualized. **f** The tumor is delivered from the nostrils

intraoperative blood loss [32]. A disadvantage of this technique is a limited lateral exposure, although this can be optimized with adding a sublabial transmaxillary (anterior maxillotomy) corridor (Figs. 3 and 4) [35, 36].

9 Open Surgery

Many of the open transfacial approaches have been largely replaced by the endoscopic endonasal approaches. Nonetheless, we will briefly discuss them here. The transpalatal approach is effective for tumors limited to the nasal cavity, nasopharynx, and sphenoid sinuses. However, exposure is limited for tumors with significant lateral extension. One major complication is the potential for a palatal fistula [35].

Medial maxillotomy through a lateral rhinotomy or midfacial degloving approach provides a broad exposure for JNA without intracranial involvement. This approach is appropriate for tumors in the nasopharynx, nasal cavity, paranasal sinuses, pterygopalatine fossa, and medial infratemporal fossa [37]. Lateral rhinotomy has an undesirable scar and these approaches risk retardation of facial growth in young patients [35].

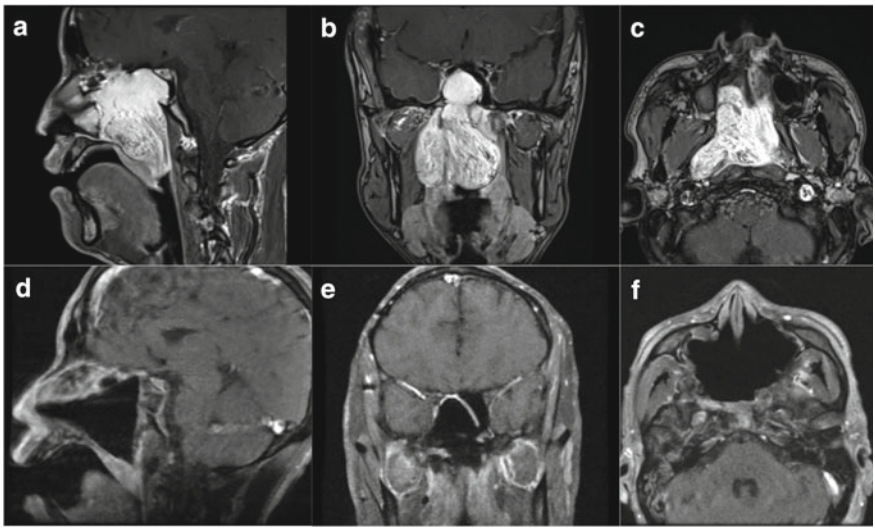

Fig. 4 **a**, **c** Preoperative post-gadolinium T1-weighted MRI (**a** sagittal, **b** coronal, **c** axial) demonstrating a large enhancing, hypervascular, juvenile nasopharyngeal angiofibroma in the nasal cavity, nasopharynx, sphenoid sinus, ethmoid sinus, and right infratemporal fossa. The tumor was removed using a pure endoscopic endonasal approach. **d**, **f** Postoperative post-gadolinium T1-weighted MRI **d** sagittal, **e** coronal, **e** axial) showed no evidence of residual tumor

The Le Fort I osteotomy is a well-described approach that allows access to tumors in the nasal cavity, nasopharynx, paranasal sinuses, pterygopalatine fossa, and to lesions with minimal extension into the infratemporal fossa [38]. A medial maxillotomy through a unilateral Le Fort has been described [39]. Cons to this approach include potential malocclusion post-operatively [39].

The facial translocation approach provides excellent exposure of tumors that have reached the infratemporal fossa and/or the maxillary sinus, if combined with a medial maxillotomy [38]. It can also be combined with a craniotomy to expose the skull base and cavernous sinus. Visible facial scars can be eliminated by the use of midfacial degloving [40].

Combined endoscopic and open approaches may be required for tumors that extend into multiple compartments. Tumors that extend into the lateral infratemporal fossa may warrant a sublabial, endoscopic-assisted transmaxillary CaldwellLuc approach. For tumors that extend intracranially, it may be necessary to do an orbitozygomatic, transcavernous, infratemporal fossa approach, in addition to an endoscopic endonasal approach (Fig. 5) [36].

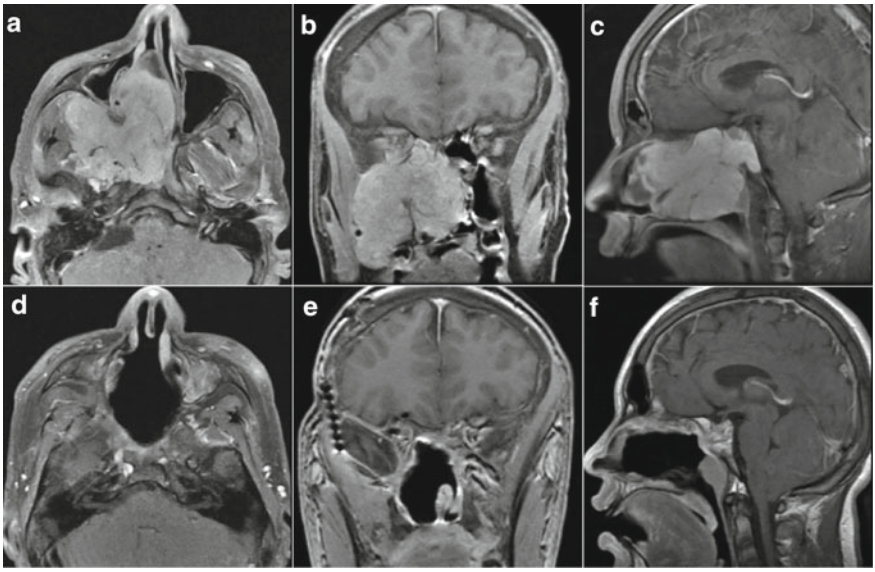

Fig. 5 **a**, **c** Preoperative post-gadolinium T1-weighted MRI (**a** axial, **b** coronal, **c** sagittal) demonstrating an enhancing, hypervascular, juvenile nasopharyngeal angiofibroma in the right nasal cavity, nasopharynx, right infratemopral fossa with intracranial extension into the right cavernous sinus. The patient underwent a staged resection. The lateral component was removed with through a first stage combined orbitozygomatic transcavernous infratemporal fossa approach with a sublabial transmaxillary endoscopic endonasal approach. The midline component of the tumor was removed at a second stage endoscopic endonasal approach. **d**, **f** Postoperative post-gadolinium T1-weighted MRI (**d** axial, **e** coronal, **f** sagittal) showed no evidence of residual tumor

10 Recurrence

It is imperative to aim for total resection at the time of surgery, because recurrence is inexplicably linked to subtotal resection. Reports of recurrence after surgery range from 0 to 40%, higher if there was intracranial extension and if there was significant bony involvement [25, 32]. Treatment of recurrent tumor is generally surgery, although it is reasonable to closely watch and wait [4]. If the recurrent lesion is small, there have been reports of spontaneous regression, especially in post-pubertal patients [10, 33]. Post-operative surveillance with MRI is imperative, even very early in the post-operative course.

11 Radiation and Chemotherapy

Radiation has been used to treat JNA, but it is largely reserved for patients with extensive intracranial extension and for patients who are poor surgical candidates. It is generally advised to avoid radiation in this young patient population due to risk of malignant transformation. In a patient with significant disease, risk of more extensive surgery must be weighed against the risk of radiation induced neoplasms.

There is a lack of evidence regarding chemotherapy use to treat JNA and it is rarely done. Bevacizumab, a humanized monoclonal antibody that inhibits VEGF-A, could potentially be a therapeutic agent [9].

12 Conclusion

JNA is a histologically benign, but locally aggressive tumor of the nasopharynx, which can invade into the paranasal sinuses, pterygopalatine fossa, infratemporal fossa, intracranial cavity, cavernous sinus, and orbit. The gold standard treatment is preoperative embolization followed by surgical resection. The endoscopic endonasal approach can access the majority of JNA. Combining this approach with an open transcranial approach may be necessary to access more extensive tumors extending into the intracranial cavity and cavernous sinus. Complete resection is the goal to prevent tumor recurrence.

Pearls

- Classic presentation of JNA is recurrent epistaxis and progressive nasal obstruction in an adolescent male
- JNA is histologically benign, but can have a potentially malignant course due to its prominent vascularity and its propensity for aggressive local growth
- Etiology of JNA is unknown—endothelial versus fibrous origin is under debate
- Surgery is mainstay of treatment, with endoscopic techniques used very frequently
- Histology is significant for vascular proliferation within a fibrous stroma
- Combined endoscopic and open procedures are useful for patients with JNA lesions in many compartments, especially intracranially
- Radiation is reserved for unresectable lesions or for patients who are very poor surgical candidates
- Recurrence is common, but some lesions spontaneously regress, especially in post-pubertal patients

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Pre- and Postoperative Care for Neurosurgery Procedures

Avital Perry, Christopher Salvatore Graffeo, and Fredric Bruce Meyer

1 Preoperative Care—General Considerations

Overwhelmingly, the management principles of preoperative care for the pediatric patient with cerebrovascular disease closely parallel those for adults, with several noteworthy departures. For most entities, these basic principles are manifest in either the management of acute cerebral hemorrhage, or preoperative planning for a semi-elective intervention or surgery.

The dominant themes of preoperative management in the setting of acute hemorrhage have previously been described in "Chapter 8—Neurocritical Care in Children," however we will expand upon the concepts pertinent to pre- and postoperative care in the specific context of pediatric cerebrovascular surgery. Following patient stabilization, the primary thrust of preoperative management is accurate identification of the underlying lesion, followed closely by operative or interventional planning. Notwithstanding, the essential strategies of acute management are dependent on the severity and etiology of hemorrhage, and it is critical to determine if early intervention is necessary to decrease the risk of secondary neurologic injury due to mass effect, cardiopulmonary failure, or hydrocephalus [2–4, 83].

Treatment of hydrocephalus is a key component of preoperative management, and cerebrospinal fluid diversion should be expeditiously undertaken where indicated, either by placement of an external ventricular or lumbar drain [5, 15, 29]. Blood pressure control is also paramount, and intravenous therapy should be instituted with age-appropriate systolic and mean arterial pressure goals—generally limited to 100 mmHg and 70 mmHg, respectively [50, 57, 58]. We favor labetalol

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and nicardipine in children, and avoid hydralazine, due to the potential lability of pediatric blood pressure, and the liability for imprecise titration with hydralazine [7, 19]. Similarly, euvolemia should be targeted with isotonic colloid, and requires careful attention to both shifting maintenance goals and pathologic derangements in fluid output [3, 61]. Above all, close neurologic monitoring is preferred in pediatric patients, and we strongly recommend serial neurologic examinations and avoidance of sedation whenever possible [3, 36].

Preoperative planning for elective surgery requires somewhat less alteration to the dogma of adult management. Medication management is disease-specific, but anticoagulation is almost universally held or transitioned to a reversible agent such as heparin, and nonsteroidal anti-inflammatory drugs are to be avoided. The role of prophylactic antiepileptic drugs is controversial, with no clear evidence supporting their use outside the setting of head trauma in children. Notwithstanding, the limited adult data demonstrating a decrease in early (but not late) seizures after craniotomy for any indication has been extrapolated to children by some clinicians—a decision we defer to surgeon preference [24, 41, 43, 55, 77].

Optimal imaging studies may require sedation or general anesthesia—particularly among children under ten years of age [8, 10, 26, 32, 78]. Angiography, although unavoidable in certain acute conditions, incurs substantially higher risk in children due to radiation sensitivity and the challenges of obtaining vascular access, and should be used sparingly [10, 20, 47, 74]. The adequacy of the recently-developed fast-brain MRI may be considered to spare additional risk in appropriately selected individuals, particularly prior to elective surgery [65]. However, this modality should be employed with trepidation in the acute setting, as it has been shown to under-diagnose venous sinus thrombosis, subdural hematoma, and extra-axial fluid collections—including acute blood products [6, 18, 65].

Perhaps most importantly, pediatric specialization at every echelon is crucial, and the team should ideally involve pediatric and neurocritical care colleagues, as well as pediatric anesthesiologists [2]. Treatment at a tertiary care center with the experience and expertise to manage these sophisticated diseases and their potential complications is essential to patient safety, and should only be foregone in the most critical of circumstances.

2 Preoperative Care—Special Circumstances

Aneurysm development and rupture is rare in the pediatric population, yet it presents a number of important considerations that distinguish it from the conventions of adult aneurysm surgery. The durability of endovascular coiling has not been definitively established, and current retrospective evidence suggests that open clipping may be preferable among children [1, 27, 37, 66, 67]. This possibility is further supported by the fact that pediatric patients develop aneurysms in unusual locations, with a peculiar preponderance of carotid bifurcation lesions—which tend to be large, complex, and more amenable to microsurgical treatment [11, 31, 51, 62,

71]. Similar perspectives remain true for pediatric aneurysms at other unusual locations, including the P3 segment of posterior cerebral artery, where surgical treatment may require complex microvascular reconstruction to preserve parent vessel patency [51].

Arteriovenous malformations, like aneurysms, are prone to uniquely aggressive presentations when they occur in children: complex lesions with a very high likelihood of rupture and/or epilepsy [68, 83, 84]. In childhood, AVM's can have a racemose configuration without a clearly defined nidus [38].They also may occupy significant brain topography, including functional cortex and white matter tracts. Broad, hemispheric AVM's are often untreatable without undue neurological risk, and palliative measures may be attempted, including partial embolization of both the nidus and any pedicle artery aneurysms that may be present, or adjunctive radiation therapy such as the proton beam [21, 69, 72, 73, 76]. The long term efficacy of these alternative treatments remains unproven, but may be the only safe course available for large, diffuse lesions involving elegant cortex.

In potentially resectable AVM's, it is important to understand the three-dimensional anatomy of the lesion and its relationship to functioning brain. Cerebral angiography is requisite, and MRI with tractography may be helpful [34, 56]. Most often these evaluations will require general anesthesia and overnight observation in an ICU post-procedurally [8, 32]. In the young child, careful fluid management is important to protect renal function following angiography—a consideration that is particularly relevant in the context of staged embolization-resection strategies [12, 14].

Vein of Galen malformations require another set of unique permutations to the anticipated algorithms for preoperative treatment of neurovascular disease. Definitive cardiovascular work-up—typical via echocardiogram and formal Cardiology consultation—is emphasized in the subacute or elective setting, due to the risk of high-output heart failure at the time of presentation, particularly in neonates [13, 28, 64]. Additionally, the prominence of venous stasis in the pathophysiology of hydrocephalus and the heightened risks of shunt predispose patients to significantly increased morbidity and mortality, and CSF diversion should only be considered under emergent circumstances, or if hydrocephalus fails to resolve following treatment of the lesion [22, 44, 85]. At present, endovascular occlusion of the vascular abnormality is the treatment of choice, and works well to normalize cerebrovascular hemodynamics (20–23) [9, 17, 45, 53]. During and after intervention, key ICU management considerations include maintenance of normotensive and normovolemic parameters, with the possible use of diuretics in high-output cardiac failure; prolonged intubation may be required if periprocedural pulmonary edema ensues [64].

Moyamoya disease is unique among cerebrovascular diseases for its high prevalence among pediatric patients, as well as the efficacy of treatment with intracranial indirect or direct revascularization surgery—particularly for ischemic-type disease [79]. The preoperative management of moyamoya is not complex. Although aspirin is the mainstay of early treatment for moyamoya disease, an index of suspicion for Reye syndrome is appropriate, and the agent may be held

during periods of suspected viral illness [4, 59, 63]. If possible, preoperative evaluation should quantify cerebral hemodynamics including regional measurements of cerebral blood flow, oxygen extraction fraction, and cerebral blood volume, which are best established via positron emission or single photon emission tomography (PET/SPECT), CT perfusion, or by acetazolamide challenge [3]. Intracranial vascular imaging is also required, either via MRA or formal cerebral angiography.

3 Postoperative Care—General Considerations

As with preoperative care, the fundamentals of postoperative care for pediatric cerebrovascular entities hem close to those for their adult variants—and for pediatric intensive care in general. The cornerstones of a multidisciplinary team and a nuanced approach to the management of blood pressure, fluid status, seizure prophylaxis, and other key concepts in neurocritical care, ensure that each patient the best chance at a neurologically meaningful recovery.

Blood loss and replacement presents a much more demanding concern in pediatric patients, due to their diminutive blood volume and the potential for catastrophic intraoperative hemorrhage. Total blood volume reaches a nadir in infancy as low as 70 mL/kg, and may remain below 80 mL/kg until puberty, placing all pediatric patients at considerable risk [46, 52, 70]. Unless a massive transfusion protocol is initiated, resuscitation goals outside the sphere of trauma are not clearly established; however, 20 mL/kg represents a 25% volume loss in most children, heralding the onset of shock [16, 33]. Physiologic compensatory mechanisms may support up to 25-30 mL/kg of acute blood loss, but resuscitation should be instituted quickly and aggressively, as poor outcomes are strongly associated with age-specific hypotensive events in children [42, 60]. The elevated risk of ischemia in pediatric cerebrovascular disease further underscores the importance of maintaining euvolemia and adequate oxygen delivery. Surgical type and crossmatch is of particular importance before higher risk operations including aneurysm or AVM surgery, whereas in moyamoya prophylactic preparation of blood products can be foregone.

When risk factors for a lowered seizure threshold are present—including cavernous malformation, cortical resection, use of sevoflurane or enflurane for inhalational anesthesia, or postoperative cerebral salt wasting—short-term seizure prophylaxis is recommended, with typical preference for levetiracetam, extrapolated from its efficacy in the pediatric tumor population and generally favorable side effect profile [23, 25, 35, 40, 75, 80]. Refractory postoperative seizures or suspicion for subclinical epileptiform discharges may warrant continuous EEG monitoring, and consultation with a pediatric epileptologist [3, 39].

Pain control is a challenging topic postoperative care for children, and while acetaminophen is the staple therapy, morphine, hydromorphone, and ketamine should all be components of the armamentarium, when appropriately employed. Related, postoperative constipation is very common among children, and a

multi-agent prophylactic regimen is essential, ideally employing both a stimulant such as polyethylene glycol and a stool softener such as docusate sodium [3, 81]. Dexamethasone use is controversial in general, but certainly less relevant to cerebrovascular than oncologic operations, and its utility in the present discussion is more limited to postoperative nausea—which may be better managed with ondansetron.

As important as the acute postoperative period is the road to long-term recovery, along which a multidisciplinary rehabilitation team will guide the patient. Physical and occupational therapists, child life specialists, educators, psychologists, and social workers all play a role in the chronic, coordinated efforts to achieve the child's best functional status, as well to facilitate their reintegrating with family, social, and educational milieus—particularly in the presence of persistent neurologic deficits [2, 3, 36]. We recommend early, team-based involvement of these ancillary services, often during the early postoperative period. Further, it is essential for the health care team to be mindful of the parental and family stress these disease and operations levy, and offer support services as necessary [2].

4 Postoperative Care—Special Circumstances

With respect to aneurysms and other etiologies of subarachnoid hemorrhage, vasospasm remains a feared sequela, although it occurs at a decreased prevalence in children relative to adults, with fewer long-term sequelae [27, 82]. Serial transcranial Doppler studies are preferred to angiography for diagnosis and longitudinal follow-up in the ICU setting, and nimodipine is frequently used as prophylaxis; of note, no safety or efficacy data have been demonstrated regarding nimodipine use in children, but it is generally thought to be a reasonable clinical indication [4, 57, 58, 83]. As with adults, maintenance of euvolemia, hemodynamic augmentation, and cerebrospinal fluid diversion are treatment pillars, and we recommend appropriate central monitoring as necessary to supplement neurologic examination, as the symptoms of vasospasm are often more obscure in children than adults [83]. Perhaps comfortingly, permanent ischemic changes are less likely to occur as a consequence of pediatric vasospasm, though long-term data on outcomes in children are limited [57, 58].

Early postoperative care after bypass for moyamoya is routine in children, with aspirin given to promote graft patency when a direct bypass was performed, and bedside Doppler studies can be useful in the perioperative period as well as follow-up clinic evaluations. Postoperative care for the more commonly performed indirect procedures such as encephalomyosynangiosis or encephaloarteriosynangiosis is routine. Aspirin should be discontinued in the early postoperative period, unless the patient has persistent ischemic symptoms. Follow-up imaging is recommended to ensure collateral formation and monitor the status of the donor vessel, and 3D time-of-flight MRA is our preferred pediatric modality notably when a direct bypass is performed. Additional studies to evaluate changes in postoperative

cerebral hemodynamics may also be warranted, with either CT perfusion, PET or SPECT. Reoperation for moyamoya presents a particular challenge in clinical decision making, and is only warranted when treatment failure is demonstrated clinically and radiographically, with both insufficient collateralization, and no improvement in cerebral perfusion [30, 48, 49, 54, 79].

5 Pearls

1. In acute hemorrhage, once the patient has been stabilized, identification of the underlying lesion and planning for appropriate intervention is the preoperative priority.
2. Early and aggressive surgery is recommended in children, and thought to decrease the risk of secondary neurologic injury.
3. Currently open clipping of ruptured aneurysms is preferred over endovascular intervention for most pediatric patients, due to the established durability of surgical clipping, and the unusual and often complex anatomy and location of pediatric lesions.
4. The key principles of both pre- and postoperative pediatric cerebrovascular management mirror those for adult neurosurgery, and rest on the central pillars of close neurologic examination, blood pressure control, euvolemia, treatment of intracranial hypertension, and management of hydrocephalus.
5. A multidisciplinary approach to care is essential, and as the team leader, the neurosurgeon should actively seek input from pediatric critical care, neurocritical care, and anesthesia.
6. Intimate familiarity with pediatric cerebrovascular disease and treatment in an experienced tertiary center is strongly recommended.
7. Vein of Galen Malformations Incur a Substantial Risk of Cardiovascular Complications, and Preoperative Cardiology Consultation Should Be Sought
8. Imaging pediatric patients presents an array of unique challenges. Angiography is to be avoided where possible; however, MRA and fast-brain MRI modalities must be employed with sensitivity to their limitations, and awareness of the potential need for anesthesia.

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Pre and Post Care After Neuro-Interventional Procedures

Lucy He, Christopher S. Ogilvy, and Ajith Thomas

Neuro-interventional procedures have gained prominence over the last two decades in the treatment of neurovascular diseases due to improved imaging technology and rapid development of access catheters and intravascular devices. While a mainstay in the treatment of vascular disease in adults, there continues to be a dearth of information regarding the care of pediatric patients undergoing neuro-interventional procedures. Significant differences are present from both a pre- and post-procedural management standpoint.

1 Pre-Procedural Care

The pediatric patient brings unique challenges to any neuro-interventional procedure. While in older children, routine diagnostic angiograms may be done with light conscious sedation and cooperation from the patient; the majority of endovascular procedures in pediatrics are done under general anesthesia [1]. As such, adequate preparation for the patients and their families is necessary for success.

For families, discussion about what to expect from the procedure and post-procedure will be important to set expectations and alleviate anxiety. For older patients that will be awake for procedures, walking the patient through the steps of the procedure and/or visiting the interventional room may be helpful for coopera-

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tion. In older children undergoing angiography with additional participation, such as for Wada procedures or balloon test occlusions, simulation prior to the procedure may be crucial. Furthermore, discussion between the neuro-interventionalist and anesthesia team regarding pre and intra-procedural sedation is critical for timing of the testing.

Fasting for several hours prior to any procedure involving conscious sedation or general anesthesia is standard across all institutions. In the case for pediatric patients, this may be challenging secondary to patient discomfort. As such, many institutions have protocols in place that allow for clear liquids until two hours prior to procedure time, while breast milk and solids will need to be stopped anywhere from four to six hours prior to the procedure.

Consideration should be given for pre-procedural admission for IV fluid hydration in certain disease states where hypovolemia may place the patient at risk, such as in moyamoya [2]. In these patients, prolonged NPO status and dehydration coupled with any hypotension during induction may have catastrophic consequences. In these situations, admission to the hospital prior to the procedure may be warranted for volume status monitoring and regulation.

For cases where intervention is planned, such as for aneurysm coiling or stent placement, pre-procedural medication with antiplatelet medication and any testing for medication efficacy should be undertaken as appropriate.

2 Post-Procedural Care

The biggest challenge for pediatric interventional patients is hemostasis at the femoral artery access site after the procedure. Patients will need to lay flat for several hours after the femoral arterial sheath is removed to prevent bleeding and avoid potential groin complications [3, 4]. Discussion should be had between the interventionalist and anesthesiologist prior to the start of the case about whether a wake up exam at time of extubation is needed. In cases where a deep sedation is acceptable, this may allow several hours of rest for the patient in the recovery area while allowing the groin to seal. However, in situations where a neurologic exam is necessary, additional medications, such as dexmedetomidine or low dose narcotics, may need to be employed prior to leaving the interventional suite along with parental presence to help keep the patient cooperative from a behavioral standpoint [1, 5].

Nurses in the recovery area or ICU should be educated to perform neurovascular checks for distal dorsalis pedis and posterior tibialis pulses bilaterally and also to check the groin site for evidence of hematoma formation. Hemodynamic instability with tachycardia or hypotension should also be monitored as harbingers of potential superficial or retroperitoneal hematoma formation.

Close monitoring of the neurologic exam is crucial after even simple procedures like diagnostic angiograms. It is easy to overlook changes in neurologic function if recent pain medication or sedation was given to keep the patient comfortable from a

groin standpoint. While the risk for thromboembolic complications after pediatric angiography is exceedingly low [6–8], we would advocate for the judicious use of narcotic medications as these may mask other symptoms of neurologic decline from a hemorrhagic or thromboembolic event after intervention. Titration of medications like dexmedetomidine is more ideal as there can still be careful monitoring of the neurologic exam.

Blood pressure management is another key point for careful observation. For patients who have undergone treatment of high-flow vascular pathology, such as arteriovenous malformations or arteriovenous fistulas, avoiding abrupt changes in blood pressure will help minimize risk of hemorrhage [9]. Antihypertensive medications may need to be utilized as necessary. It should be noted, that in general, hypertension in this age group is rare and increasing blood pressure or escalation of antihypertensive medications should allow for consideration of additional pathology, such as hemorrhage or ischemia, that may be present.

As with the pre-procedural considerations, in patients at risk for neurologic sequelae due to hypovolemia, IV fluid hydration should be maintained to help with euvolemia and also clearance of the iodinated contrast material [1, 10]. Conversely, in patients with high flow arteriovenous shunt pathology and heart failure secondary to increased pre-load, post-procedure careful fluid status monitoring is necessary to prevent fluid overload. In all neuro-endovascular procedures, heparinized saline is given through the catheters throughout the case and this fluid volume should be accounted for.

Post-procedurally, initiation of any new medications or continuation of prior medications should be discussed with the interventionalist. Common medications include antiplatelets or IV drips such as heparin. If the patient has an external ventriculostomy for intracranial pressure measurement, careful monitoring of ICP and changes in color of CSF output may help to evaluate for hemorrhage.

2.1 Extracranial Embolization

Embolization for epistaxis or other extracranial lesions are generally done through vessels of the external carotid artery. Despite this, there are numerous known anastomoses between the external and internal carotid circulation [11]. Due to this, unintended embolization or delayed thromboembolic events are possible and in the post-operative setting, vigilance should be maintained with serial neurologic examinations.

2.2 Intracranial Embolization

Direct thromboembolic complication can usually been observed during the interventional procedure for lesions involving the intracranial circulation. Post operatively, delayed thromboembolic complication can occur as well as hemorrhagic complication—especially after the treatment of high flow shunting states like dural

arteriovenous fistula or arteriovenous malformation. Close monitoring of neurologic examination and often tight blood pressure control is critical in these situations.

When patients are ready for discharge, education for families about any activity restrictions and instructions for how to manage any potential delayed groin issues should be given.

3 Conclusions

Pre and post management of neuro-interventional patients should be guided according to the disease pathology. Children often need additional medication to help keep still after removal of a femoral artery access and subsequent manual pressure, but this should be balanced against the need to obtain serial neurologic examinations.

4 Pearls

- Neuro-interventional procedures have gained prominence in the treatment of pediatric vascular pathologies
- Most endovascular procedure require participation from anesthesiologists and careful preoperative discussion is needed
- Adequate consultation with family for both the pre-, peri-, and post-intervention plans is necessary to help set adequate expectations and help parents and children
- Post operative management of sedative medications must be weighed against the masking of the neurologic examination
- Groin closure devices cannot be routinely used in pediatric patients and titration of appropriate medications to help achieve groin hemostasis should be discussed with the anesthesiologist prior to the procedure
- Multi-disciplinary approach for the management of pediatric neuro-interventional patients between anesthesia, neuroendovascular service, and the PICU is recommended.

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Parent Expectations and Counselling in Pediatric Neurosurgery

Silky Chotai and Abhishek Agrawal

1 Introduction

The evolution of pediatric neurosurgery as a subspecialty has witnessed steady and tremendous improvement in outcomes following most common surgical procedures. This has resulted in a higher survival rates and improved quality of life. Nonetheless, the pediatric neurosurgical patients often have associated medical co-morbidities and chronic lifelong conditions such as hydrocephalus or spina bifida, which often mandates special healthcare needs. Children with special health care needs are estimated to account for 13% of all children, yet they represent 70% of health care expenditures [1–3]. As a sole diagnosis, hydrocephalus in children accounts for nearly 40,000 admissions, up to 433,000 inpatient days, and cumulative hospital charges of 2.0 billion US dollars each year [4]. The total lifetime cost of care for a child with spina bifida is estimated to be $560,000 [5, 6].

To rein in the increasing costs and as a part of Affordable Care Act (ACA), the healthcare systems are rapidly transitioning from fee-for service into pay-for-performance model, where providers are rewarded for quality of care rather than volume of care [7]. More specifically, in addition to other outcome measure, the satisfaction metrics are considered important patient-centered measures of health-care service, and are commonly used as determinants of quality of care. There is a close relationship between patient satisfaction and their expectations. In child healthcare, parents, as legal guardians, serve as patient proxy to rate the quality of care [8]. It is imperative that expectations can be matched if they are known during the early stages of physician-parent conversations regarding the child's health. To achieve this goal it is important to communicate and counsel with

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parent and child to build a rapport and truly involve them in the decision-making. This chapter discusses the issues on parent expectations, satisfaction, counseling and challenges and barrier to shared-decision making in pediatric neurosurgery.

1.1 Shared-Decision Making and Parent Expectations

SDM is defined as "involving the patient and provider, both parties participating in the treatment decision-making process, requiring information sharing, and both parties agreeing to the treatment decision made" [9]. The concept of SDM was first popularized in a report issues by President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research in 1982 [10]. SDM is core of the patient-centered care and the shared decision between patients and providers is often facilitated by decision and communication aids. The concept of shared-decision making include that the patients be involvement in the discussion regarding the nature of the disease problem, decision about care delivery, treatment monitoring and follow-up [11]. In pediatric practice, this encompasses involving parents and children where appropriate, in decisions that affect their child`s health care [12]. Numerous studies have demonstrated that shared-decision making provides an opportunity to set patient and parents expectations and is associated with improved patient satisfaction following surgery [9, 13–20].

"Expectations" in clinical setting is defined as the "beliefs about future clinical confrontations" [21]. Satisfaction is "meeting the expectations and experiencing the clinical procedures not far from the expectations" [22]. Therefore, the identification of the parents' expectations and meeting the care requirements in accordance with their expectations truly affect their level of satisfaction. Berna Eren Fidanci et al., in their survey of 56 parents whose child was hospitalized in the pediatric clinic for at least one day, reported that all the mothers expected the doctors to be equipped and diagnose and perform treatment in a reasonable period of time, inform them about the implementation and prognosis. The authors reported that those expectations were satisfied in about 86% of mothers [23]. Suhonen R et al. reported that the expectations of parents from nurses includes that the nurses provide necessary information and options, they acknowledge parents and provide support during the periods of initial processing, diagnosis, changes in the treatment methodology, available to learn about the children's pre-hospital daily routine and personality traits so as to provide care accordingly, comforting both parents and children in adaptation to the new environment and supporting them to ease the feeling of loneliness, providing necessary information on the child's status or any changes in a timely and appropriate manner and to show proper respect to the parents and seriousness to the situation with opportunity to express ideas [24].

1.2 Parent Expectation Varies in Different Clinical Scenario

Children with neurosurgical problems span a wide spectrum of conditions, from mild involvement leading to limited physical function in daily life to extreme involvement of mental, physical and cognitive faculties requiring total care. In each of these situations expectations of parent–child from providers is different. When a child presents with potential shunt malfunction, the priority is to establish the diagnosis rather than offer a treatment plan. In this clinical scenario, the parents have previous knowledge due to chronic clinical course and their previous experiences with shunt related issues might be valuable information for further treatment course decisions. Smith J et al. [25] reported that in the event of shunt malfunction, the parents' and professionals' struggled with the concept of shared decision making as in this clinical context surgery to revise the shunt is the only realistic option. Parents' satisfaction when seeking health-care advice for suspected shunt malfunction was linked to the way professionals' engaged and involved them in decisions about the likely cause of illness symptoms. The authors reported that for providers the concept of shared-decision making varied in this clinical context. For some providers, working with parents was primarily about ensuring they understood the child's care requirements to obtain consent for treatments; in contrast, other providers were considerate of the value parents added to care decisions and the need to build effective and lasting relationships with the child and the family.

Children with neurological diseases often require multidisciplinary care in acute as well as chronic settings. The consultations from other specialties, including pediatric pulmonologists, urologists, orthopedics or critical care specialists are required at different stages of patient care during the pre and perioperative period. Each provider consults parent and child at different stage during pre and postoperative period and often times bring-in different perspectives on patient care and prognosis. This scenario is commonly encountered in patients with spina bifida [26]. During the course of diagnosis and treatment the parents consulted by gynecologist, fetal surgery experts, neonatologist, urologist and neurosurgeon. Parents can feel overwhelmed with information overload and at times can confuse the information coming from different physicians. A care coordinator or a designated nurse practitioner can perhaps act as a bridge to ensure smooth communication between providers and parents. In acute care setting, the shared decision-making is challenging. Most parents lack knowledge about the severity of children's primary injuries, or the early preventative goals in scenario such as traumatic brain injury or non-traumatic subarachnoid and parenchymal hemorrhage. Parents require a unified and balanced communication regarding the child`s responses to the primary injuries, subsequent treatments, and potential outcome trajectories. Roscigno C et al. in there survey of parents whose child had moderate to severe traumatic brain injury reported that the different perspectives on outcomes from multiple providers had negative effect on clear understanding of child's prognosis. The parents expected all providers to work together to optimize the synthesis of prognostic information and allow the parent to cope with the information and hence participate in shared-decision making [27].

Mitchell-Dicenso et al. [28] pointed out that parental satisfaction is highly dependent on the amount and quality of communication between the care providers and the parents. Hsiao JL et al. studied parents and children perspective on physician communication and reported that relationship building, demonstration of effort and competence, information exchange, availability and appropriate level of child and parent involvement were highly influential and salient in quality of care perception [29]. The pediatric neurosurgeon's ability to communicate with the child, parent and other family members plays key role in child`s health care recovery and management. Nonetheless, the parents' involvement in decision making, expectations and perception of care varies based on the parent-specific factors such as socioeconomic status, educational level of the family, language barriers, interpersonal relationships, accessibility of services, duration of hospitalization of the child and willingness to involve in the decision making [30]. In addition, the diagnosis and health-state of the child at the time of presentation plays a major role in parent involvement in shared-decision making.

1.3 Counseling and Informed Consent

The American Academy of Pediatrician recommends that the decision-making involving the health care of a child should flow from responsibilities shared by physicians and parents. Pediatric health-care providers should not necessarily treat children as rational, autonomous decision makers, but they should give serious consideration to each patient's developing capacities for participating in decision-making, including rationality and autonomy. The informed consent of parents includes all of the elements of a standard informed consent.

The bioethics committee of American Academy of Pediatrics has published recommendations on informed consent in pediatrics [31, 32]. In brief, "in most cases, physicians have an ethical (and legal) obligation to obtain parental permission to undertake recommended medical interventions. In many circumstances, physicians should also solicit a patient assent when developmentally appropriate." The process of obtaining informed consent and involving parent and or child in the shared decision-making process differs based on the age and development of the child [33]. The academy recommends providers to seek the informed consent from parents in the cases involving the care of infants and young children. The informed permission should be sought for, even in the pressing situations as performing lumbar puncture to evaluate the possibility of meningitis and obtain permission from the parents to initiate treatment based on reasonable clinical judgment, rather than delaying care or risking liability for performing the lumbar puncture without appropriate authorization. For the care involving older school-age children, the Academy encourages physicians to seek the assent of the patient as well as informed permission of the parents. In the cases involving care of the adolescents and young adults, the Academy encourages to obtain informed consent from the patient, as such patients are considered to have decision-making capacity and the legal authority to accept or reject interventions. Effective parent-patient-physician

communication is the core of informed consent. Therefore, it is important to understand the challenges encountered in the effective communication in the pediatric neurosurgery practice.

1.4 Approaches to Increase the Effective Physician-Parent–Child Communication

Several approaches to improve the physician-parent–child communications and relation have been proposed and utilized by the pediatric health-care providers. The key to prevent communication complications is establishment of a relationship between the child-parent-family-members of the pediatric neurosurgical team and other specialists involved in childcare. Positive changes occur when families and professionals work together to support families in their central role as caregivers. In addition, it is vital to counsel and support the patient and family throughout the clinical course. The modeling and counseling approach provides an opportunity for parents and family to learn from those who are in similar circumstances and situations [34]. A number of support groups for most common and morbid neurosurgical diseases are advocated to provide support and information to parents of children with the idea of *perceived sameness* among parents where families can share similar daily experiences [35–39]. One such group is parental advisory group; as reported by Martin J et al. [39] this groups primary function to foster collaborative relationships and communication, increase a sense of social support among families, increase the family-knowledge of community-based resources, and increasing families sense of efficacy and involvement in the care of their own and others children with chronic health conditions. In this era of patient-centered care there is increased emphasis on formulating patient expectations and determining avenues that meet those expectations. To set a realistic expectation it is important to provide patients and parents with tangible prognosis and outcomes and involve them in "true-shared decision making". One such avenue is the ability to predict prognosis and to provide information on outcomes based on the individual patient-specific factors. Predictive modeling based on the preoperative variables can be used as a potential tool, which will empower the patients to have an intellectual and concrete discussion about the expectations after surgery that is tailored to their particular risk profile. These models will empower a surgeon to have a substantive discussion with a patient about expectations after surgery that is particular to him/her, so that a truly informed decision can be made. Several predictive models are available to predict the outcomes by various sub-specialties. Nonetheless, this concept is still in the infancy phase and needs maturation with meticulous strategically planned methods before it can be integrated and utilized as a decision-making tool.

1.5 Key Points

- Effective parent-patient-physician communication is the core of informed consent in pediatric practice.
- The key to prevent communication complications is establishment of a relationship between the child-parent-family-members of the pediatric neurosurgical team involved in childcare.
- The consultations from other specialties, including pediatric pulmonologists, urologists, orthopedics or critical care specialists are required at different stages of patient care during the pre and perioperative period. Care coordination and unedified information delivery to child and parent is vital in the multidisciplinary setting.
- The expectations of parent–child from providers vary based on the acute versus chronic clinical scenario, which should be considered during parent-child counselling.

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