Abhishek Agrawal
Gavin Britz *Editors*

Pediatric Vascular Neurosurgery

Principles and Practice of Neurovascular Disorders (Part 1)

Springer

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ISBN 978-3-319-43634-0 ISBN 978-3-319-43636-4 (eBook)
DOI 10.1007/978-3-319-43636-4

Library of Congress Control Number: 2016961819

Printed on acid-free paper

This Springer imprint is published by Springer Nature
The registered company is Springer International Publishing AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

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.

October 2016

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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 Vascular Neurosurgery*.

Houston, TX, USA

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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, Ms. Morton, Ms. Megginson, Mr. Hacket Pain, Ms. Kayalvizhi, and the entire team from Springer Publishers for their collegiality.

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

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Evolution of Endovascular Treatment in Pediatric Population

1

Silky Chotai and Abhishek Agrawal

Introduction

Endovascular neurosurgery has witnessed a dynamic evolution over the past several decades. With advancing techniques and constant refinement of the neurointerventional tools the endovascular therapies are increasingly sought for. The cerebrovascular pathologies including intracranial aneurysms, arteriovenous malformations (AVMs), dural arteriovenous fistulae (AVFs), acute stroke, carotid artery disease, vasospasm, carotidcavernous fistulae (CCFs) and vascular tumors are effectively treated using endovascular therapies. Numerous studies fueled by the national and international trials for various cerebrovascular pathologies have increased the scope of endovascular neurosurgery. These advances in adults are applied to pediatric population with varying degrees of success.

Management of neurovascular diseases in pediatric population is challenging and standardized recommendations for endovascular management in this group of patients is still evolving. When treating a child, factors such as growth and development of the child, psychological and social factors, and longer life span needs to be considered in addition to the vascular pathology [1]. Furthermore, the nature and biology of the vascular pathology differs in this population compared to adults. Intracranial aneurysms, vein of Galen malformations, dural AVFs and AVMs are the common cerebrovascular conditions found in children. Endovascular treatment is considered the primary treatment modality for dural AVFs or vein of Galen

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A. Agrawal, G. Britz (eds.), *Pediatric Vascular Neurosurgery*,
DOI 10.1007/978-3-319-43636-4_1

malformations, while it is often used as adjuvant therapy for AVMs and tumors [1–4]. The focus of this chapter is to describe history and evolution of endovascular neurosurgery in pediatric population.

History of Endovascular Techniques and Tools

Egaz Moniz, in 1927, was the first to successfully perform cerebral angiography after a direct surgical exposure of the carotid artery, in a 20-year-old man with a pituitary adenoma, the angiography demonstrated displacement of anterior and middle cerebral arteries [5]. This attempt was followed by a successful cerebral angiography including arterial and venous phases, in 1931 [6]. Another major milestone in the history of endovascular neurosurgery is the development, of flow-directed balloon [7]. In late 1960s Serbinenko used a non-detachable flow-directed balloon to treat cavernous carotid fistulae while preserving carotid artery. Later, he developed a detachable balloon that was used to occlude "cavities of arterial aneurysms" [8, 9]. Balloons have found a variety of neurointerventional applications, including extracranial and intracranial angioplastly, thrombectomy and thrombolysis, balloon-assisted coiling, balloon test occlusion and balloon-expandable stent placement.

Guglielmi constructed a microwire with a small magnet that could be introduced endovascularly within an aneurysm. In 1991, Guglielmi developed the concept of detachable coil, which was based on his observation of accidental electrolytic detachment of steel electrode when trying to induce aneurysmal electro thrombosis [10–12]. The Guglielmi detachable coil (GDC) became a revolutionary technique for aneurysm embolization. The GDC functions by occluding the aneurysm and simultaneously ensuring the flow within the parent artery. In present practice, GDC embolization is commonly used and is the primary approach in the treatment of adult patients with intracranial aneurysm.

Several studies have reported successful application of neurointervention tools in the treatment of pediatric cerebrovascular diseases [13, 14]. The rates of complications are comparable to the published studies in adult population. Despite of the comparable complications rates, the concern exist on the safety of using devices in pediatric population that are approved for use in adults. In a recent study, He et al., demonstrated that. For patients <5 years old, even though the microcatheters and endovascular devices used in adults are compatible, even in distal vasculature; a smaller guide catheter may be necessary to minimize the risk of vasospasm [15]. Beyond the age of 5 years the majority of adult endovascular devices are compatible with arterial sizes.

Aneurysm

Intracranial aneurysms are rare in pediatric population, accounting for less than 5 % of the total aneurysms treated. Similar to adult population, the current management strategies include expectant management, surgical clipping and endovascular

therapy [16]. Among the endovascular therapies standard coiling, flow-diversion devices and pipeline embolization devices are used [29, 30, 33, 52].

The application of endovascular therapies in pediatric population is influenced by the results of a randomized multicenter trial, International Subarachnoid Aneurysm Trial. In 2002, the trial reported that for patients with ruptured intracranial aneurysms suitable for treatment with endovascular coiling and surgical clipping, the coiling is significantly more likely to result in survival free of disability at 1-year after subarachnoid hemorrhage (SAH) [17]. In 2009, the trial published long-term follow-up and reported a small but increased risk of recurrent bleeding from a coiled aneurysm compared to a clipped aneurysm. This raised the concern that, given the longer life span in pediatric population, the long-term durability of treatment is crucial [18].

In pre-GDC decade 1980 and 1990s selected aneurysms were treated using detachable balloon embolization techniques [19, 20]. After Guglielmi developed GDC in 1991, several authors reported their experience in using GDC for intracranial aneurysms in adults and pediatric population [21, 22]. Beez et al. conducted a literature review of 135 studies, accounting for total 573 children and 656 aneurysms, published between 2000 and 2015 [23]. The authors reported that 53 % of the children were treated surgically and 35 % underwent endovascular treatment with coiling, stent assisted coiling and flow-diverters. They demonstrated a gradual shift of trend from surgical to endovascular therapies. Vasan et al. analyzed the national trend in management of pediatric intracranial aneurysms using healthcare cost and utilization project (HCUP) Kid's inpatient dataset. The authors reported increase utilization of endovascular treatment for aneurysm from 10 to 19.8 % between 2006 and 2009 and the cost for surgical procedure rose by 6 % and for endovascular procedures rose 50 % during these 3 years [3]. Sanai et al., in a single large series of 32 children with 43 aneurysms, compared the surgical clipping and endovascular coiling. The authors reported microsurgical aneurysm obliteration rates of 92–93 % compared to endovascular obliteration rates between 79 and 82 % and recurrence rate of 14 % for endovascular treatment (mean follow-up 4.9 years) and 0 % for microsurgical treatment (mean follow-up 6.1 years) [4]. In their study, the giant and fusiform lesions were disproportionately represented. The children often presents with complex aneurysmal morphology [24]. Posterior circulation complex aneurysms are more common in pediatric population compared to adults [3, 14, 16, 25–28]. These morphologically challenging aneurysms, and deemed as difficult surgical candidates, require innovative treatment strategies in order to achieve complete occlusion of the aneurysm and preserve the patency of the parent circulation. Even if, complete or near-complete occlusion is achieved after initial embolization, the risk of coil compaction and recanalization is high, requiring additional treatment and retreatments. The flow-diverter stents have demonstrated promising results in treating complex aneurysms in adult patients. Few authors have reported the use of flow-diverter stents, including SILK flow diverters (Balt, Montmorency, France) [29] and Pipeline™ embolization devices (PED, EV3-MTI, Irvine, CA) [29, 30], in pediatric population with complex intracranial aneurysms. In 2009, Lylyk et al. published their experience in using PED in patients' age range 11–77 years. The authors reported that PED is a safe, durable and curative treatment option

for selected wide-necked, large and giant cerebral aneurysms, with 100% rate of complete occlusion and no angiographic recurrences observed during their maximum follow-up of 1-year. However, no specific details in pediatric patients can be derived from that publication [31]. Navarro et al. reported the use of PEDs in three children with vertebro-basilar big aneurysm, ICA segmental disease (multiple small aneurysm), posterior communicating artery-small neck recurrent aneurysm and demonstrated total occlusion at 12-month follow-up [32]. Similarly, Vargas et al. reported their experience in treating five children with coiling and flow-diverter stents [34]. In their series of 23 pediatric patients treated with endovascular therapies, Saraf et al reported one stent-related complication in giant basilar artery aneurysm treated with telescoping stents; the patient had stent thrombosis and posterior circulation stroke [35]. Even though, an overall favorable response with use of flow-diverter stents has been reported the longer life span in pediatric population raises the concerns regarding the vessel response to growth in presence of an endoluminal device, and long-term durability of flow-diverters and stents. Furthermore, safety of deploying a potentially thrombogenic material is not well documented.

Finally, endovascular therapies are recommended as adjuvant to microsurgery as in adult population. Kakarla et al. [16] reported three children who underwent adjuvant endovascular treatments. The authors treated one patient for a residual after clipping of a traumatic basilar apex aneurysm, and two other patients underwent endovascular treatment for recurrence following surgical clipping. Further multicenter randomized trials focusing on endovascular treatment of pediatric intracranial aneurysm is treated.

AV Malformation

In 1932 Bergstand et al. reported the first total removal of cerebral AVMs in five patients [36], followed by reports from Norlen et al. [37], Pool et al. [38], French et al. [39] and Sano et al. [40]; it was accepted that total excision of AVMs is the preferred treatment modality. In late 1960, Seljeskog et al. published a first pure pediatric series reporting successful surgical removal of an AVM involving the inferior sagittal sinus in an infant [41]; following which several authors have reported their experience in endovascular embolization.

The early endovascular treatment of intracranial AVMs was influenced by interventional techniques pioneered with control of GI bleeding and uterine AVMs. In 1960, Leussenhop and Spence reported the concept of direct embolization of enlarged, abnormal feeding arteries using a nonselective use of injectable beads [42]. The nonselective technique raised concerns associated with collateral penetration, and lack of sufficient nidal penetration. In 1974, Serbinenko et al. reported a direct catheterization delivery of detachable balloons to occlude feeding arteries for AVMs and AVDFs [7]. The early therapeutic devices and agents used in AVMs included detachable balloons, liquid embolic agents, particulate PVA beads and embolic acrylic or gel nanospheres. The agents used in current endovascular neurosurgery practice are primarily cyanoacrylates like NBCA (N-butyl cyanoacrylate) (Codman) agents and less adhesive more gelatinous ethylene-vinyl alcohol

copolymers dissolved in DMSO with tantalum powder for radio-opacity like the commercial agent Onyx-(EV3) [43]. The ongoing refinements include graded viscosities of Onyx and variety of mixes of NBCA and innovative detachable tip microcathers.

The endovascular embolization of AVMs is lagging behind than that in adult population. The size of the parent vessel and the AVM is typically small in children; even the finest of sub-selective catheters may not be optimal. Furthermore, AVMs most commonly presents with subarachnoid hemorrhage or hemorrhagic stroke in children, mandating surgical intervention more to preserve life or neurological function.

Nonetheless, as in adults, the embolization of AVMs is more often used, as an adjunct with microsurgery or radiosurgery, in reducing the size of large lesions or eliminating deep feeding arteries. Several authors have reported the efficacy of embolization as a part of multimodality therapy for AVMs [44–46]. In 1990s, Lasjaunias et al. reported 179 cerebral AVMs in children (77 vein of Galen malformations with 102 pial AVMs). Fifteen of 28 patients who harbored pial AVMs in which embolization was complete demonstrated no neurological deficits, whereas death occurred in five. Three patients had transient neurological impairment and two had permanent neurological change. Thirteen patients who had undergone partial embolization later were treated with open surgery. Three patients were treated with SRS after partial embolization [47]. This followed by reports from Humphrey [48] and Kondziolka [49] and several other authors [3, 50] recommended that endovascular embolization is a potentially useful adjunct to microsurgical or radiosurgery excision of pediatric AVMs.

AVFs

The primary goal of treatment of dural or pial AVF is disconnecting the fistulous point via surgical, endovascular or radiosurgical approach, which results in eventual regression of the associated venous varies and hence results in long-term cure. Compared to adults, pediatric cerebral AVFs are often high-flow lesions with aberrant anatomy, which results in difficult microcatheter access to the fistula increasing the risk of iatrogenic injury, unintended deployment of embolic agent, prolonged period of general anesthesia, and/or multistage therapy increasing the management challenges in these population.

The treatment paradigm for pediatric intracranial AVFs had paralleled the technological advances in the field of neurosurgery and neurointervention. In the pre-endovascular era surgical disconnection of fistulae was the primary treatment modality. The current surge in endovascular treatment for AVFs is influenced by numerous reports on safety and efficacy of the neurointervention compared to surgery. Lv et al., in a series of ten pediatric pial AVFs treated between 1998 and 2008, noted that endovascular therapies were considered the primary mode of treatment in all cases and open surgical treatment was discouraged in all series [11]. In a series of five pial AVFs in pediatric patients treated with endovascular embolization between 2000 and 2012, Madsen et al. reported a complication rate of 60% [51]. Similar

complication rates with microsurgery and radiosurgery have been reported. Although, endovascular embolization is well accepted as a primary treatment modality, pediatric AVFs often require multimodal approach. In a recent review, Zaidi et al. treated 17 children with AVFs, one was treated with open surgery alone, more than one-third (n = 6) required a multimodal approach, and other (n = 10) patients were treated with endovascular embolization (Onyx, NBCA or coil embolization) with or without balloon assistance [2]. The authors reported a case of 12-year old boy, who presented with a 2-day history of persistent headaches and left-eye proptosis. Cerebral angiography revealed non-Galenic AVF fed by the left PCA and a large varix drained by the vein of Galen. The AVF was treated by a transarterial balloon-assisted embolization of AVF using a combination of Onyx-18 and Onyx-34. The residual AVF was treated by microsurgical obliteration. The post-obliteration vertebral artery angiography revealed complete obliteration of the fistula. Post-operative 3-month MRI demonstrated a thrombosed varix without obvious residual fistula, which was then treated by gamma knife radiosurgery. This case example reiterates that multimodal (endovascular, microsurgery and radiosurgery) treatment approach may be needed for some AVFs. Therefore, a careful evaluation and close follow-up is necessary in children with AVFs who undergo endovascular embolization as primary treatment.

Key Points

- Endovascular treatment has substantially evolved as a primary and/or adjuvant treatment modality for children with cerebrovascular pathologies.
- There is a substantial need for evidence-based guideline for endovascular treatment of pediatric aneurysms, AVMs and AVFs.
- Current treatment decisions are driven by generalization of endovascular treatment experiences from adult trials, few case series and reports in pediatric population and parental tendency to avoid open brain surgery.
- Clearly, an interdisciplinary multicenter trial focusing on pediatric cerebrovascular diseases is needed.

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Cranial Vascular Anatomy and Its Variations

2

Petros Zampakis

Arterial Cranial Anatomy and Variations

The internal carotid arteries (ICAs) supply the so-called anterior cerebral circulation while the vertebral forming the basilar artery supply the posterior circulation. Those systems meet at the Circle of Willis (COW).

Anterior Circulation

The ICA consists of seven embryonic segments and this "embryonic" classification can explain the configuration and distribution of segmental agenesis and other anatomic variations [1].

ICA enters the cranial cavity through the carotid canal of petrous bone. For clinical purposes, the seven anatomical segments classification system by Bouthillier, is currently widely accepted -C1 cervical, C2 petrous, C3 lacerum, C4 cavernous, C5 clinoid, C6 ophthalmic and C7 communicating [2].

Two small but important branches arise from the cavernous ICA (C4). The tentorial and inferior hypophyseal artery may arise as a meningohypophyseal trunk. The inferolateral trunk supplies adjacent cranial nerves and anastomoses with the external carotid (ECA).

A very important anatomic landmark and a subject of great surgical attention, is the "transitional" or clinoid area of ICA. The vessel passing this area goes through the so-called distal dural ring and becomes intradural-subarachnoid. This transition is critical, because aneurysms past the aforementioned point are located in the subarachnoid space, and their rupture leads to subarachnoid hemorrhage. In the

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A. Agrawal, G. Britz (eds.), *Pediatric Vascular Neurosurgery*,
DOI 10.1007/978-3-319-43636-4_2

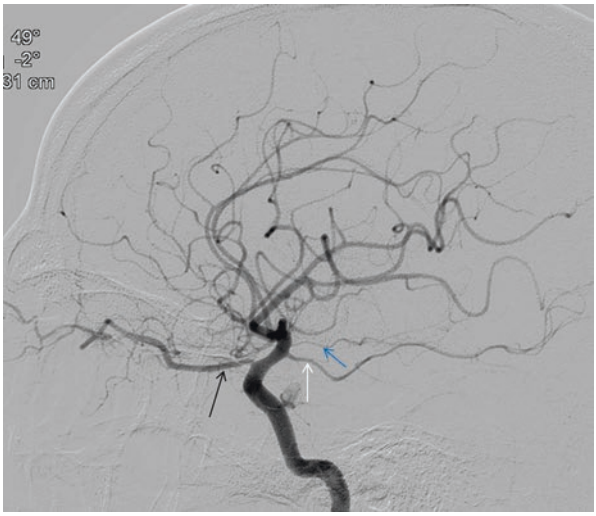


Fig. 2.1 Cerebral angiogram of the ICA (oblique view). *Black arrow* shows the ophthalmic artery (*OA*), the first major branch of ICA, which is the anatomic landmark of the distal dural ring. Anterior choroidal artery (*blue arrow*) and fetal type of posterior communicating artery (*white arrow*) are also seen

majority of people (~90 %) the ophthalmic artery which is the first major branch of ICA, is usually located distal to the distal dural ring (Fig. 2.1).

The C7 segment of ICA gives rise to two important branches, the posterior communicating artery (pCom) and the anterior choroidal artery. The former is part of the COW anastomotic network, varying in size and sometimes occurring as a fetal-type posterior communicating artery. The latter supplies the posterior limb of internal capsule, cerebral peduncle and optic tract, medial temporal lobe and choroid plexus (Fig. 2.1).

The main anatomic variations of ICA include course deviations [3] and segmental agenesis of the vessel, where each of these embryonic vessels represents the potential point of vascular reconstitution of flow into the distally preserved ICA. The aberrant course of ICA is such a configuration. In children, the diagnosis of course variations (especially the retropharyngeal course of ICA) must always be predicted, especially prior to adenotonsillectomy, in order to avoid catastrophic complications [4, 5]. Generally, knowledge of these variations is crucially important for neck surgery.

The terminal ICA is divided into the anterior (ACA) and middle cerebral arteries (MCA).

The ACA is divided into four segments: horizontal segment (A1), vertical segment (A2), genu segment (A3) and terminal portions (A4-A5) (Fig. 2.2a). The A1 segment is connected to the contralateral A1 segment by the anterior communicating artery (AcomA). The A1 segment gives rise to small perforating branches, the medial lenticulostriate arteries (LS). The recurrent artery of Heubner is the largest of the perforating branches, arising from the A1 or A2 segment (in 80 %).

The A2 segment gives rise to orbitofrontal artery and frontopolar artery, while A3 segment gives rise to pericallosal and callosomarginal arteries (Fig. 2.2b).

Surface branches supply the cortex and white matter of the inferior frontal lobe, the medial surface of the frontal and parietal lobes, as well as the anterior corpus

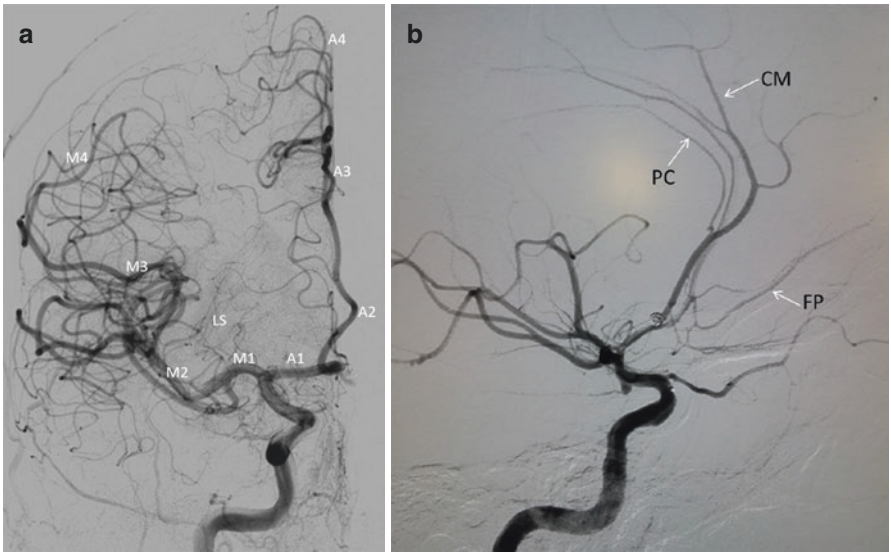


Fig. 2.2 (**a**) Cerebral angiogram of the R ICA (AP view). The segments of middle cerebral artery (MCA/M1-M4) and anterior cerebral artery (ACA/A1-A4) are annotated. *LS* lenticulostriate arteries. (**b**) Cerebral angiogram of the R ICA (lateral view). Branches of anterior cerebral artery are annotated. *CM* callosomarginal art, *PC* pericallosal art, *FP* frontopolar art

callosum. Penetrating branches supply the deeper cerebrum, diencephalon, the limbic structure, and head of caudate as well as the anterior limb of internal capsule.

Anatomic variations are very common in the first two segments of anterior cerebral artery, including hypoplasia, absence or fenestration of A1, variations of recurrent artery of Heubner (Accessory middle cerebral artery) and unpaired ACA configuration (including azygos artery and bihemispheric ACA) (Fig. 2.3a, b), as well as triplicated ACA.

The most common variant (~27 %) is the presence of hypoplastic A1 segment of ACA (Fig. 2.4), while aplasia of A1 is less common (Fig. 2.5a–c) [6].

Aplasia of A1 is an important variation in cases of Acom aneurysms, where the neurointerventionist must be aware that possible compromisation of the neck of the aneurysm (either endovascular or surgical), could lead to bilateral frontal lobe ischemic events. The same applies to the presence of an unpaired ACA (short or long segment) [7].

Although aplasia or hypoplasia of A1 is constantly seen in the vast majority of patients with Acom aneurysms, their role in the formation of aneurysms is unclear.

MCA, which is the phylogenetically youngest of all cerebral vessels, is divided into four anatomical segments: horizontal segment (M1), insular segment (M2), opercular segment (M3) and cortical branches (M4 segments) (Fig. 2.2a). The M1 segment gives off medial and lateral lenticulostriate arteries (perforating branches supplying basal ganglia and capsular regions), as well as anterior temporal artery for the anterior temporal lobe. Then, it divides as a bifurcation or trifurcation. Cortical branches supply the lateral surface of the cerebral hemispheres (Fig. 2.6).

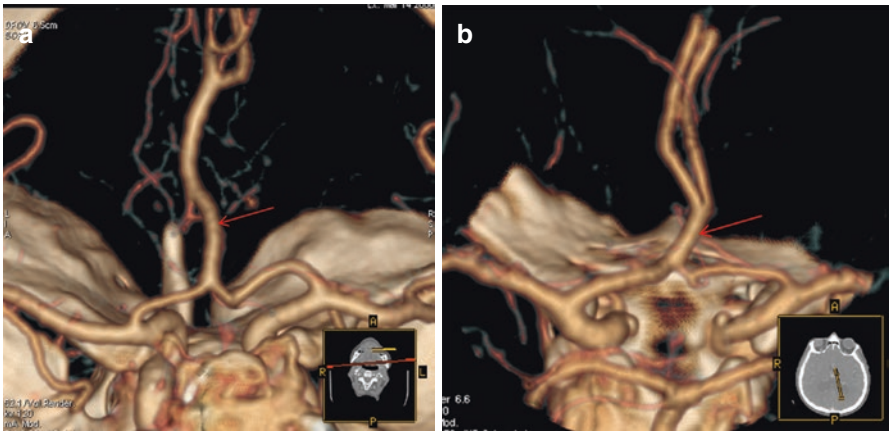


Fig. 2.3 (**a**) CTA (VRT 3D reconstructions) reveals the presence of an unpaired ACA (conventional type, long segment) (*red arrow*) (Reproduced from Zampakis et al. [6]) (**b**) CTA (VRT 3D reconstructions) shows an unpaired ACA (conventional type, short segment) (*red arrow*) (Reproduced from Zampakis et al. [6])

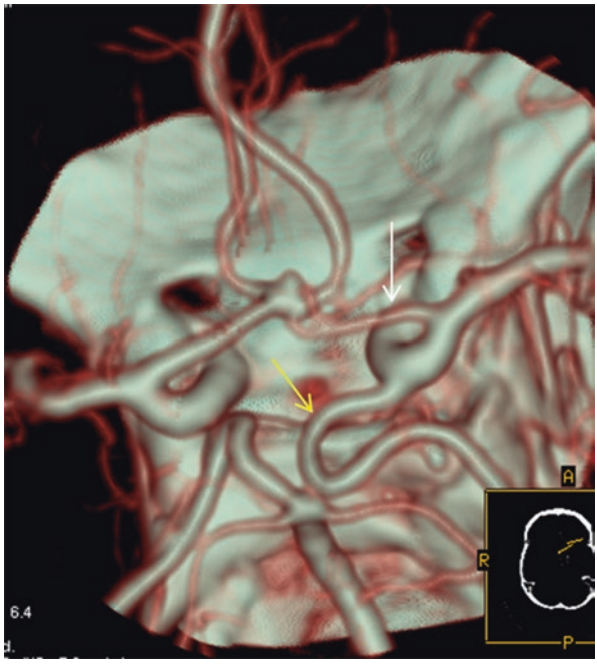


Fig. 2.4 CTA (VRT 3D reconstructions) shows a hypoplastic right sided A1 segment of anterior cerebral artery (*white arrow*), in a patient with an Acom aneurysm. Note the presence of a fetal Pcom on the same side (*yellow arrow*) (Reproduced from Zampakis et al. [6])

Relatively few MCA variants are present, the Accessory MCA (AccMCA) being the most important one. Other less clinically significant variants include early disposition of cortical branches (from M1 segment), duplication and fenestration of various segments [8].

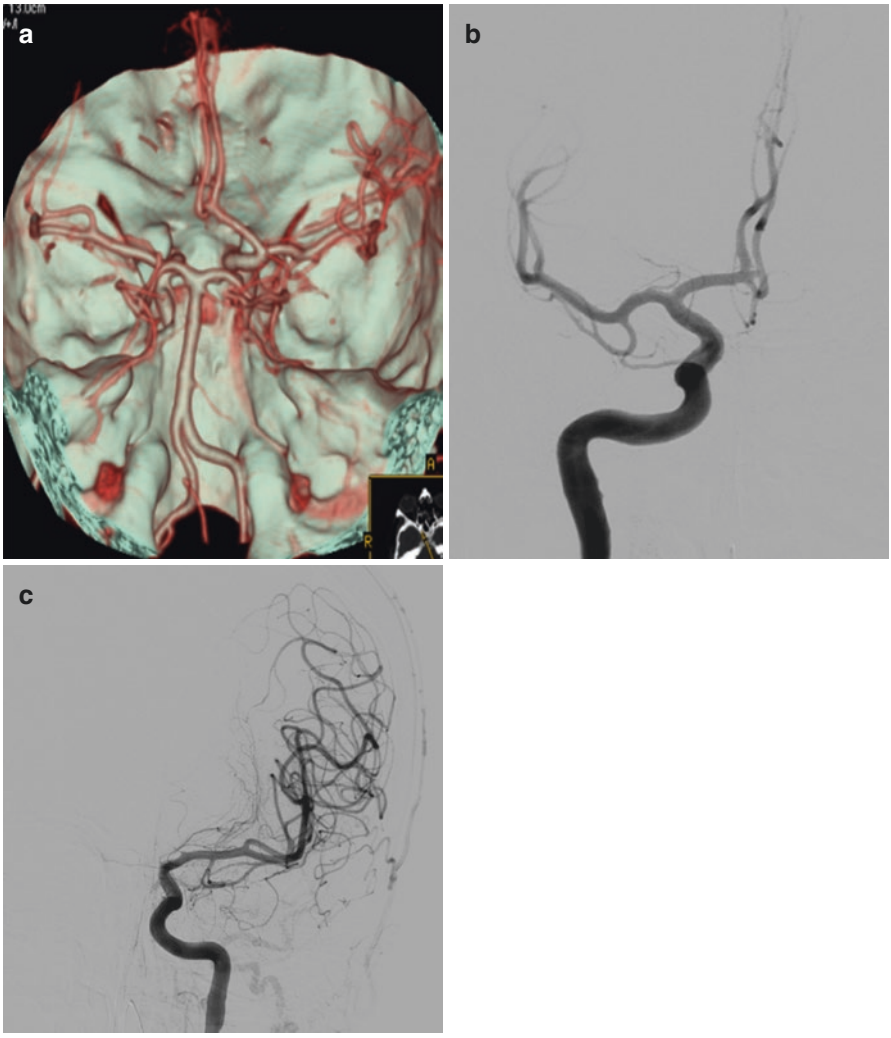


Fig. 2.5 (**a**) CTA (VRT 3D reconstructions) reveals aplasia of left A1 segment of anterior cerebral artery, in a patient with an Acom aneurysm (Reproduced from Zampakis et al. [6]). (**b**) Digital substraction angiography (AP view) of the right ICA, verifies the presence of a small Acom aneurysm. Both A2 segments are opacified, from this single injection (Reproduced from Zampakis et al. [6]). (**c**) Digital substraction angiography (AP view) of the left ICA. The left A1 segment is absent (Reproduced from Zampakis et al. [6])

The variations of the AccMCA express the phylogenetic origins of the MCA from a group of vessels with similar potentials in the early stages of evolution, including the recurrent artery of Heubner (RAH). Therefore, a distal ACA origin of the AccMCA corresponds to an enlarged RAH. This has been described by Manelfe

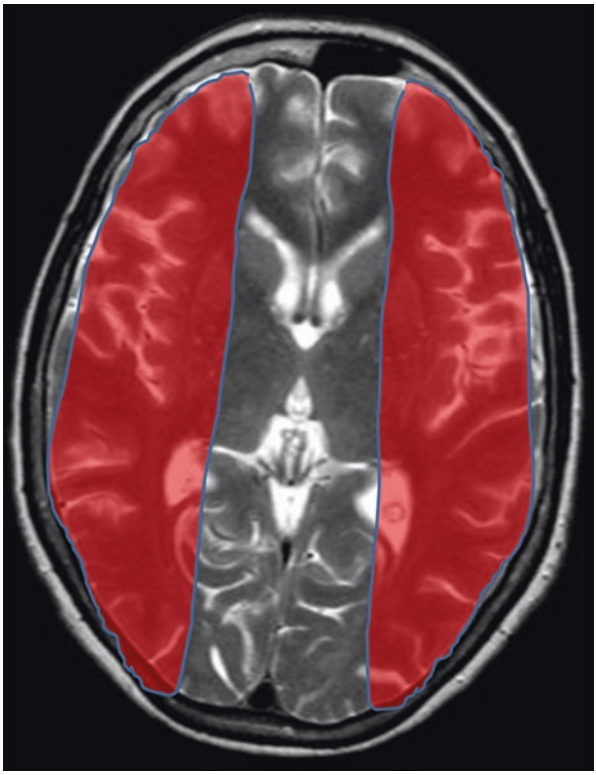


Fig. 2.6 Brain MRI. Axial T2 image at the level of lateral ventricles. *Red areas* indicate the vascular territory of cortical branches of MCA

in 1977 as type 3, where AccMCA is a Heubner artery with an extensive cortical supply, arising from the proximal part of A2 segment [9].

The most important clinical role of AccMCA is in cases of severe stenosis/occlusion of proximal carotid, where this vessel is actually a natural by-pass [10, 11] (Fig. 2.7a–e).

Posterior Circulation

The vertebral arteries (V4 segment) enter the cranial cavity, via foramen magnum. The vessel gives rise to the posterior inferior cerebellar artery (PICA) supplying the brainstem, inferior cerebellar hemisphere, vermis and the choroid plexus, before it forms basilar artery.

The latter runs superiorly on the anterior surface of the pons giving off anterior inferior cerebellar (AICA), superior cerebellar (SCA) and posterior cerebral arteries (PCAs) on both sides as well as perforating branches for brainstem (Fig. 2.8a, b).

The AICAs supply the anterior inferior part of cerebellum, as well as the internal auditory meatus nerves. Its cerebellar branches anastomose with those of the PICA. The SCAs arise right below the basilar tip and supply the superior part of the cerebellar hemispheres.

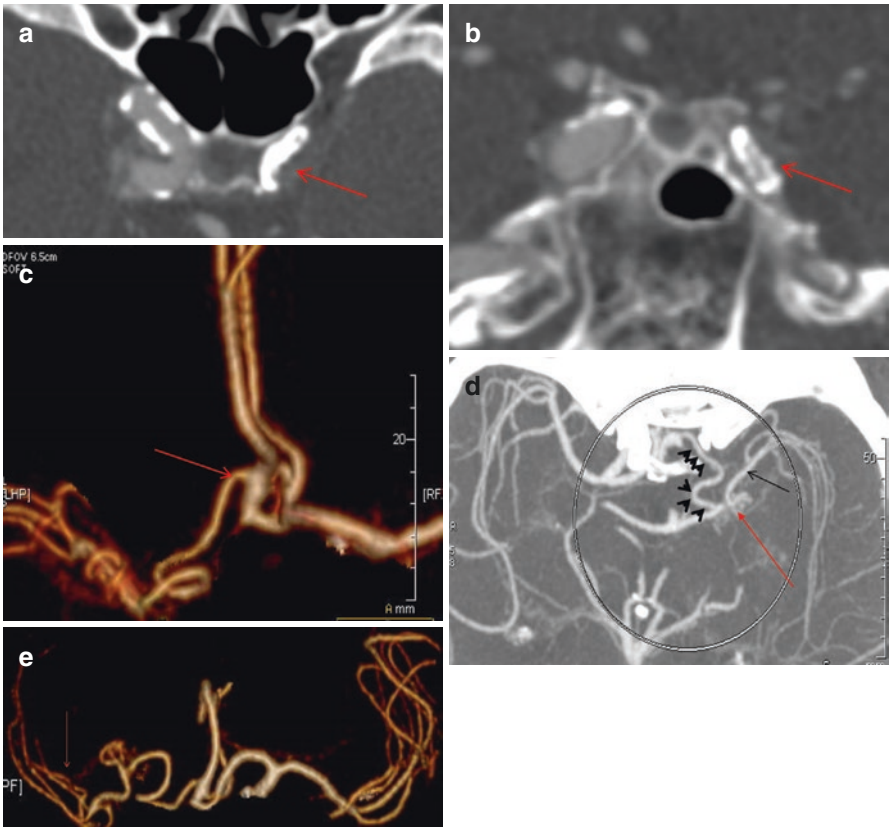


Fig. 2.7 (**a**) Axial CT image at the level of cavernous carotids shows occlusion of the left ICA (*red arrow*), due to atherosclerotic disease (Reproduced from Zampakis et al. [6]). (**b**) Coronal reconstruction at the level of cavernous carotids verifies the occlusion of the left ICA (*red arrow*), as well as the atherosclerotic disease (Reproduced from Zampakis et al. [6]). (**c**) CTA (VRT 3D reconstructions) shows the accessory MCA as a vessel coming from the A2 segment of ipsilateral anterior cerebral artery (*red arrow*) (Reproduced from Zampakis et al. [6]). (**d**) Axial MIP image shows the course of AccMCA (*black arrowheads*), the anastomotic network (Moya-Moya type) at the level of left mid M1 segment (*red arrow*), as well as the patent peripheral left MCA (*black arrow*) (Reproduced from Zampakis et al. [6]). (**e**) CTA (VRT 3D reconstructions) reveals the same configuration and patent peripheral MCA (*red arrow*) (Reproduced from Zampakis et al. [6])

The posterior cerebral arteries are the terminal branches of the basilar artery, each of which has four segments. These are the precommunicating (P1), ambient (P2) quadrigeminal (P3) and finally P4 segment which is the terminal segment including the occipital and inferior temporal branches (Fig. 2.9).

There is diversity in caliber of the P1 segment of the PCAs and pComs. One edge of this diversity is the so-called fetal origin of the posterior cerebral artery, where the P1 segments may be hypoplastic and even invisible on vertebral angiography. The posterior communicating arteries and P1 segments give off the thalamoperforating

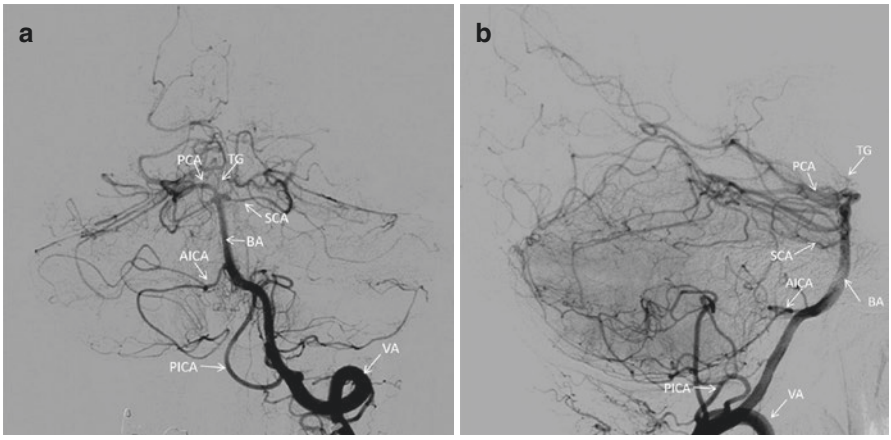


Fig. 2.8 (**a**) Selective angiogram of the L vertebral artery (AP view). Vertebral artery (*VA*), basilar artery (*BA*), posterior inferior cerebellar artery (*PICA*), anterior inferior cerebellar artery (*AICA*), superior cerebellar artery (*SCA*), posterior cerebral artery (*PCA*), thalamogeniculate (*TG*) perforating arteries. (**b**) Selective angiogram of the L vertebral artery (lateral view). Vertebral artery (*VA*), basilar artery (*BA*), posterior inferior cerebellar artery (*PICA*), anterior inferior cerebellar artery (*AICA*), superior cerebellar artery (*SCA*), posterior cerebral artery (*PCA*), thalamogeniculate (*TG*) perforating arteries

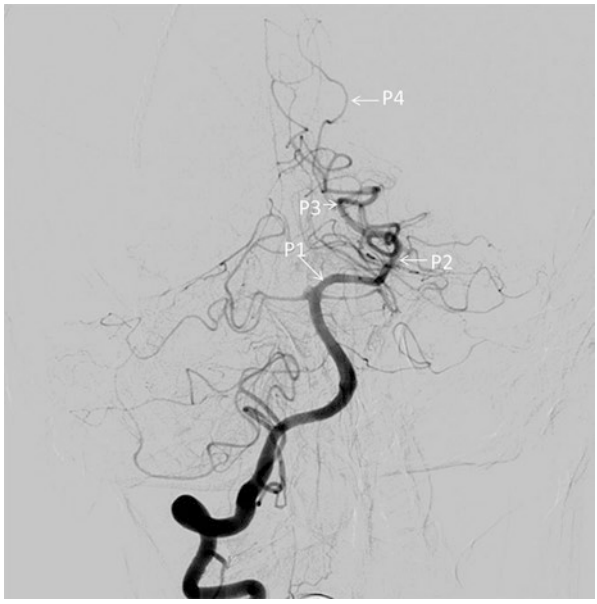


Fig. 2.9 Selective angiogram of the R vertebral artery (AP view). The segments of posterior cerebral artery (PCA/P1-P4) are annotated

arteries and thalamogeniculate arteries. Medial and lateral posterior choroidal arteries arise from the P2 segment and seem to be the main arterial feeders to Vein of Galen malformation or other arteriovenous malformations located in this area (Fig. 2.10a, b). Temporal branches (anterior, posterior, inferior), parieto-occipital

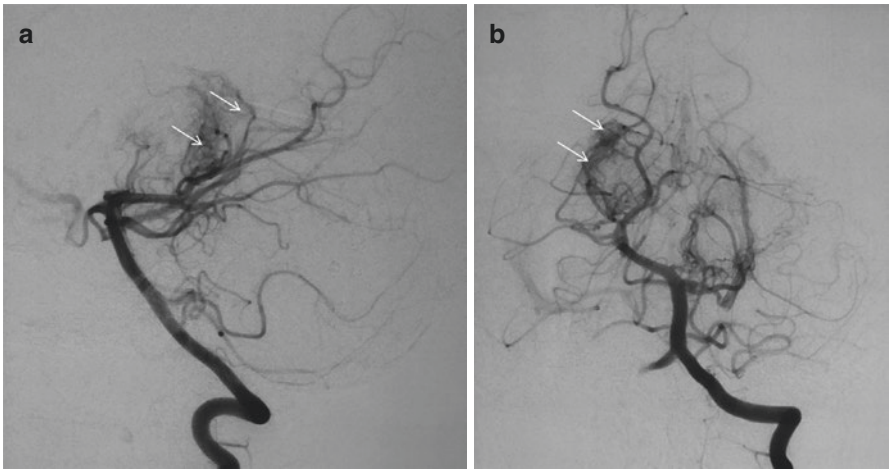


Fig. 2.10 (**a**) Selective angiogram of the L vertebral artery (Lateral view). Posterior choroidal arteries (*white arrows*) are the arterial feeders of a diffuse type arteriovenous malformation in a 7 year old girl. (**b**) Selective angiogram of the L vertebral artery (AP view). Posterior choroidal arteries (*white arrows*) are the arterial feeders of a diffuse type arteriovenous malformation in a 7 year old girl

artery and calcarine artery, are cortical branches supplying a large part of the inferior surface of the temporal lobe and the medial surface of the occipital lobe, including the visual cortex.

Most clinically important anatomic variations of posterior circulation system include "fetal" arrangement of PCA, other persistent carotid-basilar anastomosis and symmetric or asymmetric caudal fusion of the tip of basilar artery. Other variants include hypoplastic or aplastic V4 segment and fenestrations of basilar artery.

Persistent carotid-basilar anastomoses are actually developmental connections between the anterior (carotid) and posterior (vertebrobasilar) circulation that may persist into adult life.

By far the most common and clinically important persistent carotid-basilar anastomosis is the presence of fetal type of posterior communicating artery (Figs. 2.11 and 2.12) [6]. In this case, practically the PCA comes from the ICA.

Its knowledge plays an important role in patients with Pcom aneurysms, where this vessel comes out of the aneurysmal sac. If this variation occurs, the neurointerventionist should definitely protect the fetal pcom, in order to avoid occipital lobe infarct (Fig. 2.13a–d). Another important clinical significance is that carotid pathology may cause a "posterior circulation" stroke (Fig. 2.14a–c).

Other anastomoses include persistent hypoglossal artery (Fig. 2.15a–c), persistent trigeminal artery (Fig. 2.16) and proatlantal intersegmental arteries [6].

Asymmetric caudal fusion of basilar artery is clinically important for any neurointerventionist, in cases of basilar tip aneurysms treatment, where the major network of perforators derives from the P1 segment which has the most cranial position (Fig. 2.17) [12].

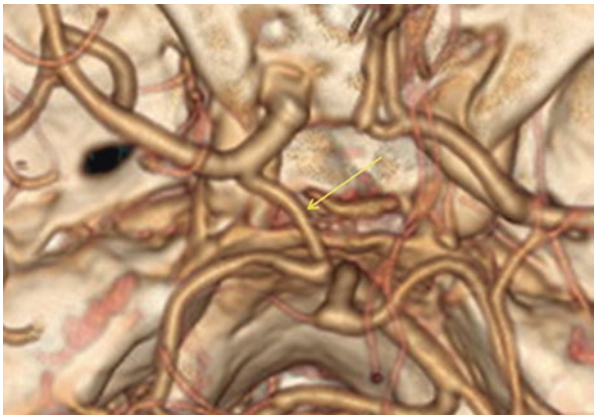


Fig. 2.11 CTA (VRT 3D reconstructions) shows a left sided Fetal Pcom (*yellow arrow*) (Reproduced from Zampakis et al. [6])

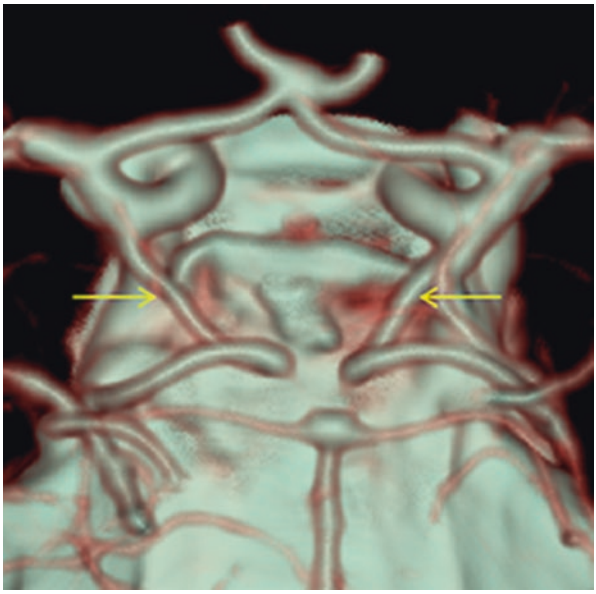


Fig. 2.12 CTA (VRT 3D reconstructions) shows bilateral Fetal Pcom (*yellow arrows*) (Reproduced from Zampakis et al. [6])

Anastomotic Pathways

Collateral supply to the brain comprises of three elements: The COW, leptomeningeal collaterals and extracranial–intracranial anastomoses.

COW plays an important role as a collateral supply in cases of acute or chronic cerebrovascular occlusive disease. It is best seen in CT or MR angiograms, ideally in 3D reconstructions. Anatomic variations of COW are the rule, since a complete COW is seen only in ~40 % of the people (Fig. 2.18) [13]. It is important to realize that COW collateral supply and morphologic changes, is a dynamic process that is influenced by several hemodynamic changes (Fig. 2.19).

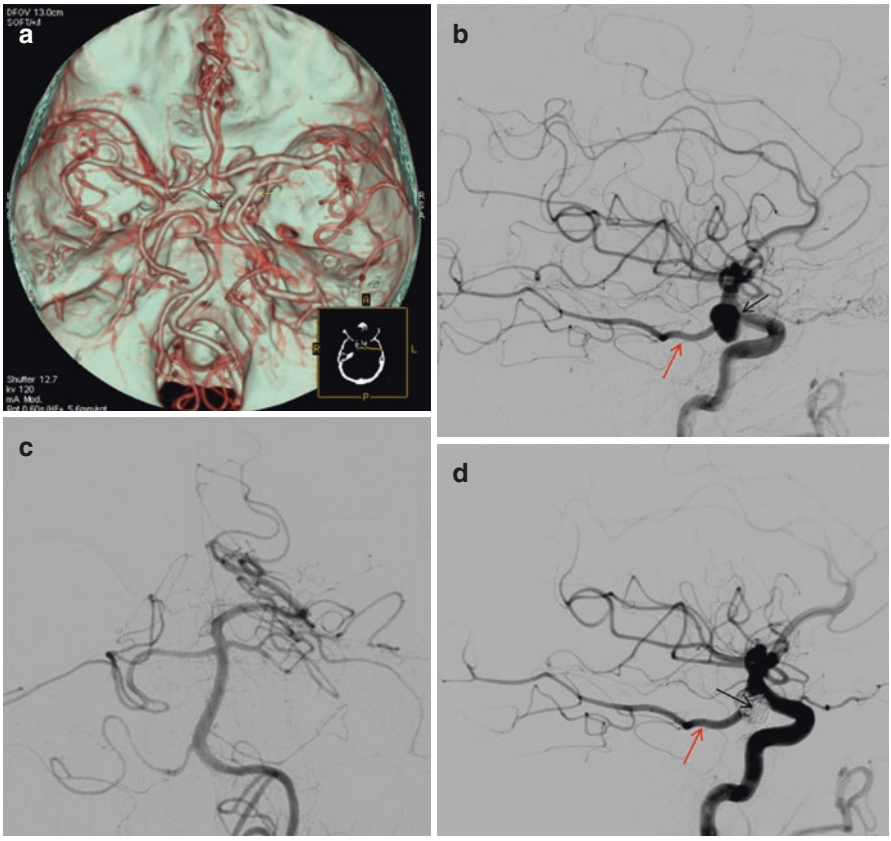


Fig. 2.13 (**a**) CTA (VRT reconstructions) shows a right sided Fetal Pcom (*black arrow*) with a large aneurysm at the origin of the vessel (*yellow arrow*) (Reproduced from Zampakis et al. [6]). (**b**) Digital substaction angiography (lateral view) of the right ICA, shows Fetal Pcom (*red arrow*) and large aneurysm at the origin of the vessel (*black arrow*), which cannot be compromised (Reproduced from Zampakis et al. [6]). (**c**) Digital substaction angiography (AP view) of the left vertebral artery. The posterior cerebral artery on the right is not opacified (definition of Fetal Pcom) (Reproduced from Zampakis et al. [6]). (**d**) Post-embolisation digital substaction angiography (lateral view) of the right ICA, shows good patency of Fetal Pcom (*red arrow*) and complete obliteration of the aneurismal sac (*black arrow*) (Reproduced from Zampakis et al. [6])

The extracranial—intracranial anastomoses are potential or actual anastomotic connections between branches of the external carotid artery and the internal carotid or vertebral arteries. They can play a role in chronic cerebrovascular occlusive disease (Fig. 2.20), but most importantly their knowledge is crucial for interventional endovascular procedures, in order to avoid hazardous complications, when injecting liquid material to ECA branches [14].

Finally, pial collaterals are end-to-end anastomoses between distal branches of the intracerebral arteries that potentially provide collateral flow across vascular watershed zones. These collateral networks play an important role in cases of stroke [15].

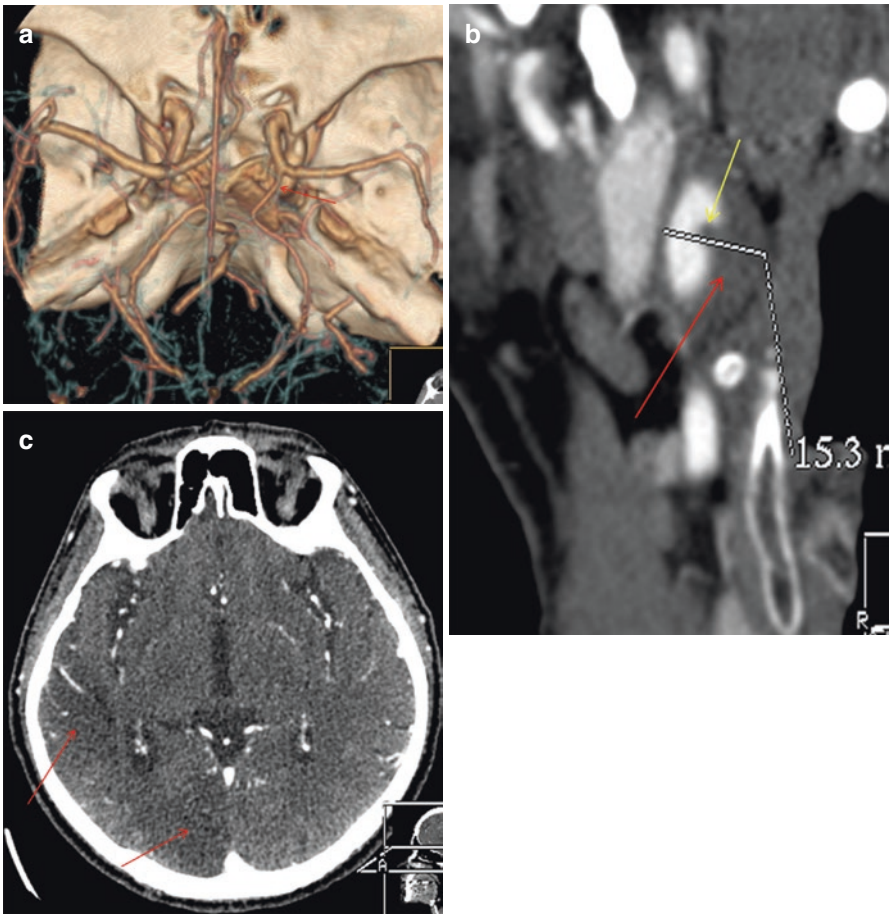


Fig. 2.14 (**a**) CTA (VRT reconstructions) shows a right sided Fetal Pcom (*red arrow*) (Reproduced from Zampakis et al. [6]). (**b**) CT oblique MPR image shows increased wall thickness (*red arrow*) and intimal flap (*yellow arrow*) of a dissected right ICA (Reproduced from Zampakis et al. [6]). (**c**) Axial CT image at the level of 3rd ventricle shows right sided occipital and posterior parietal lobe infarcts (*red arrows*) (Reproduced from Zampakis et al. [6])

Venous Cranial Anatomy and Variations

The cerebral venous system comprises of dural sinuses and cerebral veins and is divided into deep and superficial.

The main dural sinuses include the cavernous sinus, superior and inferior petrosal sinus, the superior sagittal sinus, the inferior sagittal sinus, the sphenoparietal sinus, the straight sinus, the transverse sinus and the sigmoid sinus.

Superficial cerebral veins collect the blood from the cortex and subcortical white matter. They join the superior sagittal sinus which along with the straight sinus

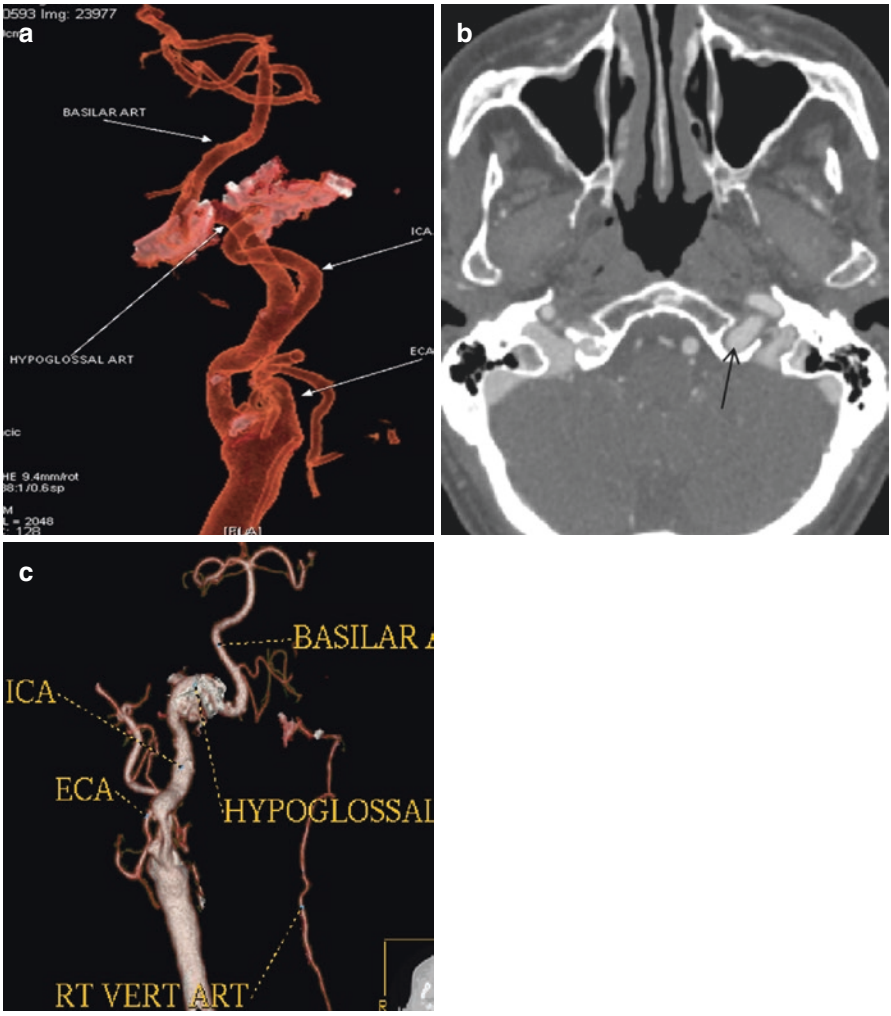


Fig. 2.15 (**a**) CTA (VRT 3D reconstructions) shows a vessel connecting the ICA with the basilar artery (annotations) (Reproduced from Zampakis et al. [6]). (**b**) Axial CT image at the level of hypoglossal canal shows an enlarged vessel piercing the skull base on the left, through the hypoglassal canal, which has been also enlarged (*black arrow*) (Reproduced from Zampakis et al. [6]). (**c**) CTA (VRT 3D reconstructions) reveals absent proximal vertebral artery and hypoplastic contralateral vertebral artery (annotations) (Reproduced from Zampakis et al. [6])

drains into the torcular herophili, where the lateral sinuses end up as well (Fig. 2.21a, b). Other major superficial cerebral veins include the anastomotic veins of Labbe and Trolard, as well as the middle cerebral veins.

The deep cerebral veins collect the blood from the deep white matter and basal ganglia. They consist of medullary and subependymal veins and the most important are the thalamostriate veins, the basal vein of Rosenthal and internal cerebral veins.

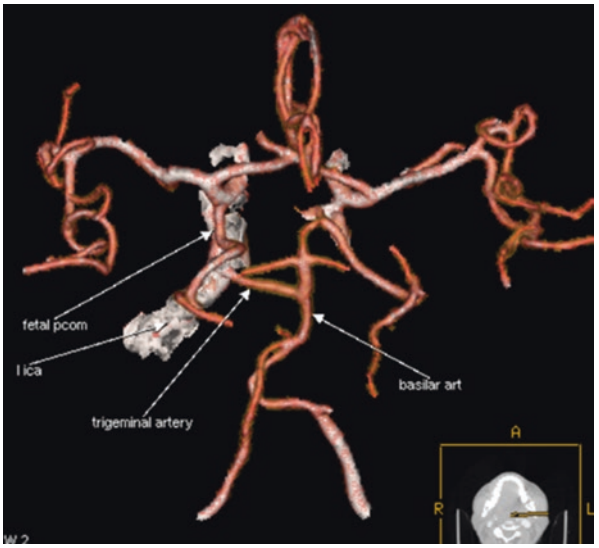


Fig. 2.16 CTA (VRT 3D reconstructions) shows a left-sided trigeminal artery joining the basilar artery. The basilar artery (which is relatively hypoplastic, proximal to the connection site) gives rise to the right PCA while the left PCA arises from the ICA (fetal PCom) (Saltzman's type II or Weon's type 3) (annotations) (Reproduced from Zampakis et al. [6])

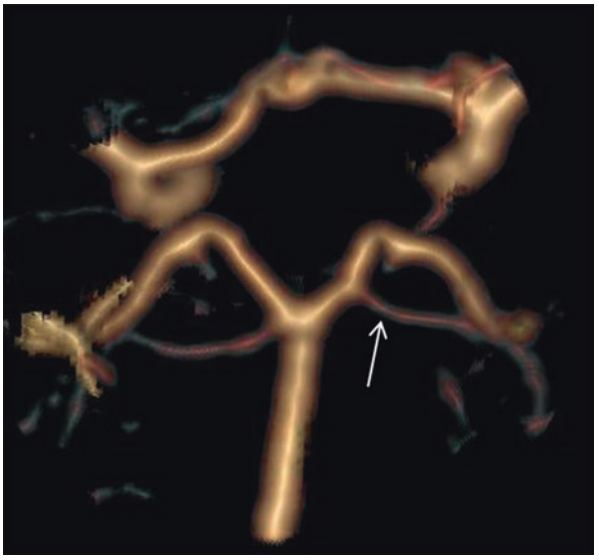


Fig. 2.17 CTA (VRT 3D reconstruction) shows a right-sided asymmetrical caudal fusion of the basilar artery. *White arrow* indicates the origin of the R SCA from the ipsilateral P1 segment of PCA

Fig. 2.19 (**a**) 3 T MRA in a 10y old girl with a vertebrovertebral fistula (VVF) on the right side (*black circle*). Note the enlargement of both posterior communicating arteries (*white arrows*) as part of the COW reconstitution due to the arterial steal from the fistula. (**b**) Axial CT image at the level of carotid canals shows a hypoplastic right ICA, along with the hypoplastic ipsilateral carotid canal (*white arrow*). (**c**) CTA of the brain (MIP reconstruction-Superior view). Note the enlargement of right posterior communicating artery (*white arrow*) as part of the COW reconstitution due to the ipsilateral carotid hypoplasia

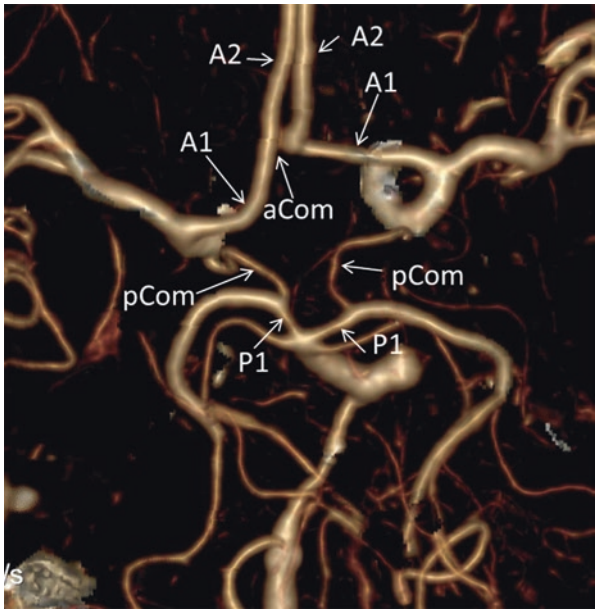
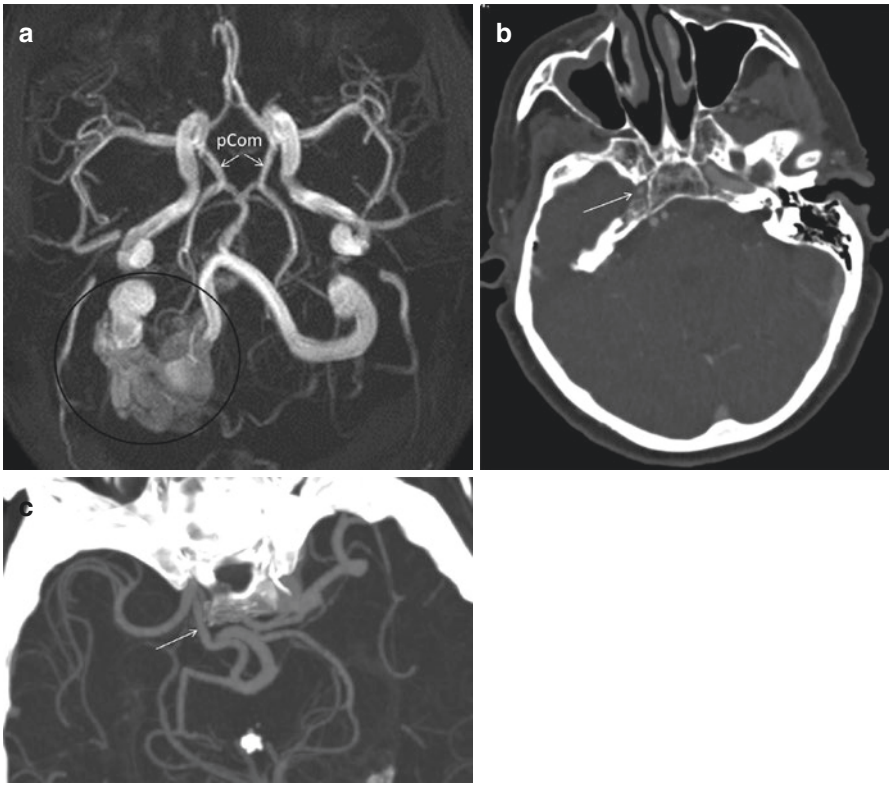


Fig. 2.18 CTA (VRT 3D reconstruction) A complete COW is seen. All parts of COW are annotated



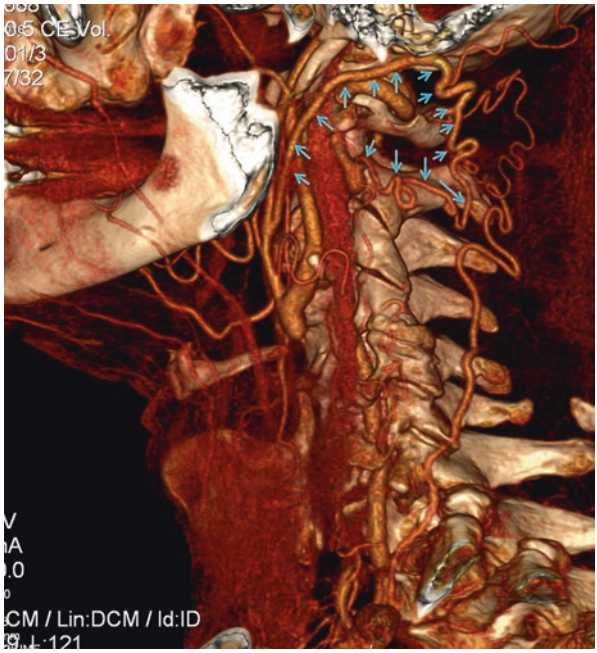


Fig. 2.20 CTA (VRT 3D reconstruction) *Blue short arrows* indicate the profound VA-ECA anastomosis between temporal artery and vertebral artery, due to total occlusion of the ipsilateral common carotid artery

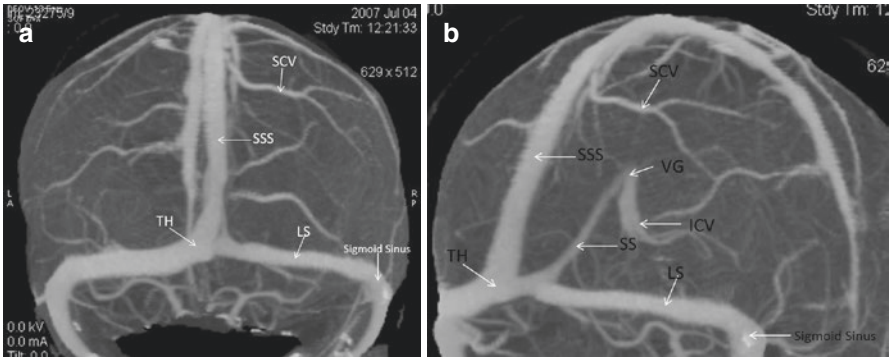


Fig. 2.21 (**a**) CT Venography of the brain (MIP reconstructions-AP View). *White arrows* indicate main venous sinuses and veins. *SSS* superior sagittal sinus, *SCV* superior cerebral vein, *LS* lateral sinus, *TH* torcular herophili, (**b**) CT Venography of the brain (MIP reconstructions-Oblique View). *White arrows* indicate main venous sinuses and veins. *SSS* superior sagittal sinus, *SS* straight sinus, *SCV* superior cerebral vein, *LS* lateral sinus, *TH* torcular herophili, *VG* vein of galen

The confluence of internal cerebral and basal veins of Rosenthal gives rise to the midline great vein of Galen, which enters the straight sinus (Fig. 2.21a, b).

The superior petrosal sinuses connect the cavernous sinus to the sigmoid sinuses, while the inferior petrosal sinuses connect the cavernous sinus to the jugular vein.

The deep sub-ependymal veins are rather constant, while the superficial cortical veins are extremely variable.

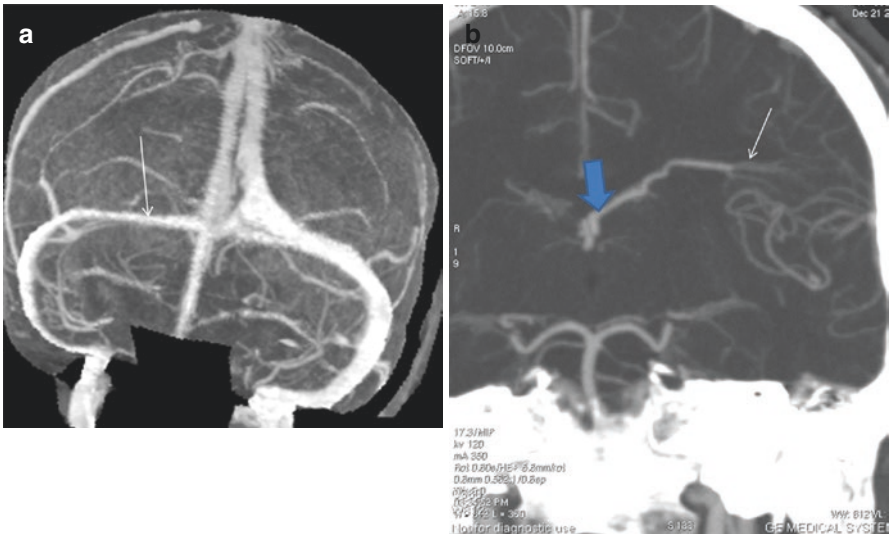


Fig. 2.22 (**a**) CT Venography of the brain (MIP reconstructions-AP View). *White arrow* indicates the hypoplastic left lateral sinus. (**b**) CT Venography of the brain (coronal MPR reconstruction) shows a left-sided developmental venous anomaly (DVA). *White arrow* indicates the characteristic "medusa-head" appearance of the DVA, while the *thick blue arrow* shows the deep venous drainage into the unilateral internal cerebral vein

Finally, the anatomy of the posterior fossa veins is quite variable, but the main drainage pathways include a superior (Galenic), an inferior (petrosal) and a posterior (tentorial) group of veins.

Although true anomalies of the deep and superficial venous system are quite rare, anatomic variations are not. The most common include asymmetric transverse sinuses (the left being more often hypoplastic than the right, due to pulsations of the right atrium and larger capacity of the right jugular system) and developmental venous anomalies (DVAs) (Fig. 2.22a, b).

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Spinal Vascular Anatomy with Variations

3

Yi Jonathan Zhang and Sean Barber

Arterial Anatomy of the Spinal Cord and Spinal Column

Embryological Considerations of Spinal Arterial Anatomy

The primitive neuraxis achieves nutrient and waste exchange via simple diffusion. Starting at approximately 4 weeks of gestation, with neural tube closure and acceleration of neural development, increasing metabolic demand exhausts diffusion capacity and stimulates formation of **transverse metameric segmental (radiculomedullary) arteries** that perfuse the developing spinal cord and nerve roots. These segmental vessels originate from the paired **primitive dorsal** and **ventral aortae**.

Further metabolic demand induces longitudinal anastomoses (e.g. **ventral midline longitudinal anastomoses** and **dorsal paramedian anastomoses**) to form between adjacent segmental arteries. The confluence of these ventral midline longitudinal anastomoses and paired dorsal paramedian anastamoses lead to the formation of the anterior spinal artery and posterior spinal arteries, respectively. These high-flow longitudinal arteries decrease the hemodynamic need for medullary perfusion at each segmental level, and subsequently, the majority of the segmental radiculomedullary arteries regress to become purely radicular arteries [1].

Spinal Extradural Arterial Anatomy

The arterial supply to the fully-formed spinal column consists of transversely oriented segmental arteries, longitudinally oriented feeding arteries and a variety of anastomoses between the two, together forming a rich and complex grid-like network of arterial supply. Each individual metameric segment of the spinal column,

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A. Agrawal, G. Britz (eds.), *Pediatric Vascular Neurosurgery*,
DOI 10.1007/978-3-319-43636-4_3

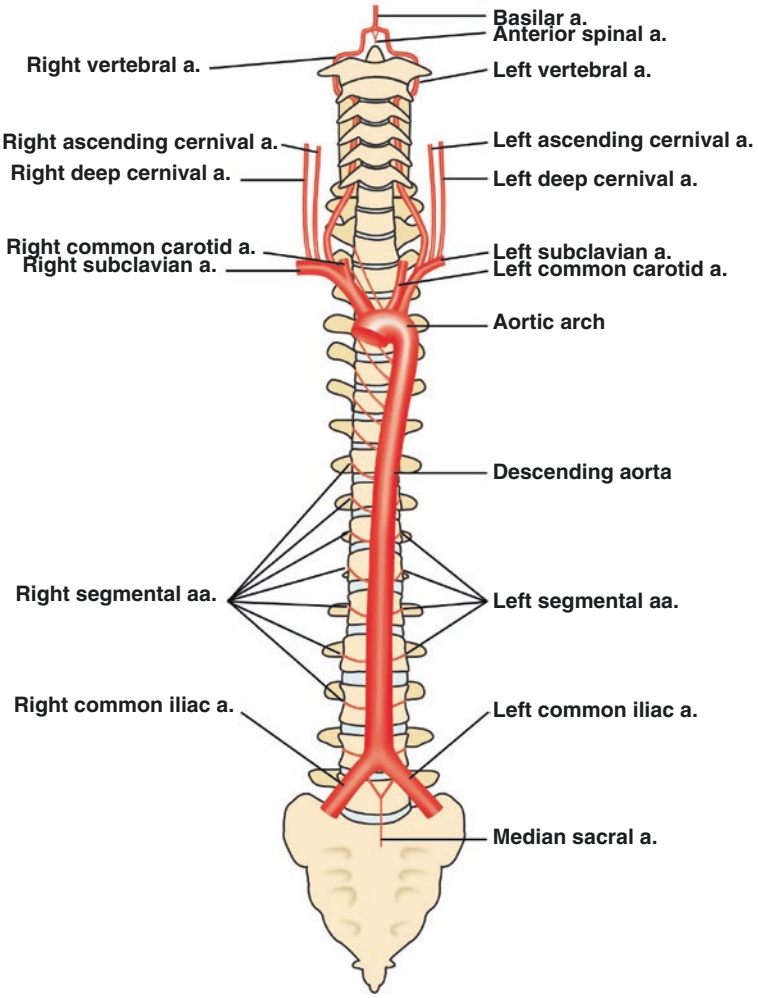

Fig. 3.1 Illustration depicting the major contributors to spinal extradural/extravertebral arterial supply

spinal cord, nerve roots and dura are supplied with arterial blood via a dedicated pair of **segmental arteries** arising dorsally from a larger feeding artery.

- Segmental arteries supplying the cervical spine originate from the vertebral arteries and branches of the subclavian artery (e.g. the costocervical trunk and thyrocervical trunk).
- Segmental arteries supplying the thoracic spine and first four lumbar vertebral segments originate from the descending aorta.
- Segmental arteries supplying the L5 vertebral segment and sacral region originate from branches of the internal iliac artery (e.g. iliolumbar, median sacral and lateral sacral arteries) (Fig. 3.1).

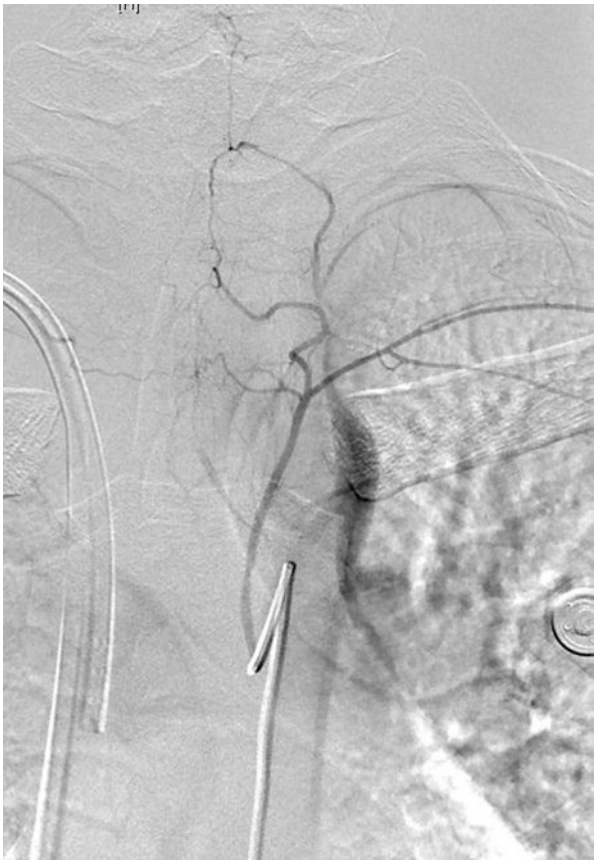

Fig. 3.2 Spinal digital subtraction angiographic image (AP projection) of an injection of a single ostium near the left T3 level supplying multiple segmental branches in the upper thoracic spine. Such a vessel is known as the **supreme intercostal artery**

The segmental arteries supplying the upper thoracic spine (often above the level of T3) frequently arise from a single pedicle and are together referred to as the **supreme intercostal artery** (Fig. 3.2).

Each of the paired segmental arteries courses laterally around its respective vertebral body before it branches into **lateral (ventral)**, **middle (dorsal)** and **medial (spinal) trunks**, which supply the adjacent rib (or adjacent soft tissues), paraspinous myocutaneous tissues/posterior spinal elements, and dural/epidural tissues, respectively. The medial (spinal) trunk branches further at the level of the intervertebral foramen into a **radicular** artery (which supplies the dura and nerve root of its respective segment) and **retrocorporeal** and **prelaminar** branches that supply the epidural vertebral and ligamentous structures. Occasionally, a radicular branch will maintain its embryologic communication with the anterior or posterior spinal arteries and provide arterial supply to the spinal cord, in which case it is referred to as an anterior or posterior **radiculomedullary artery**, respectively [2–4].

The largest of the radiculomedullary arteries – the *artery radiculomedullaris magna*, also known as the **great anterior radiculomedullary artery of**

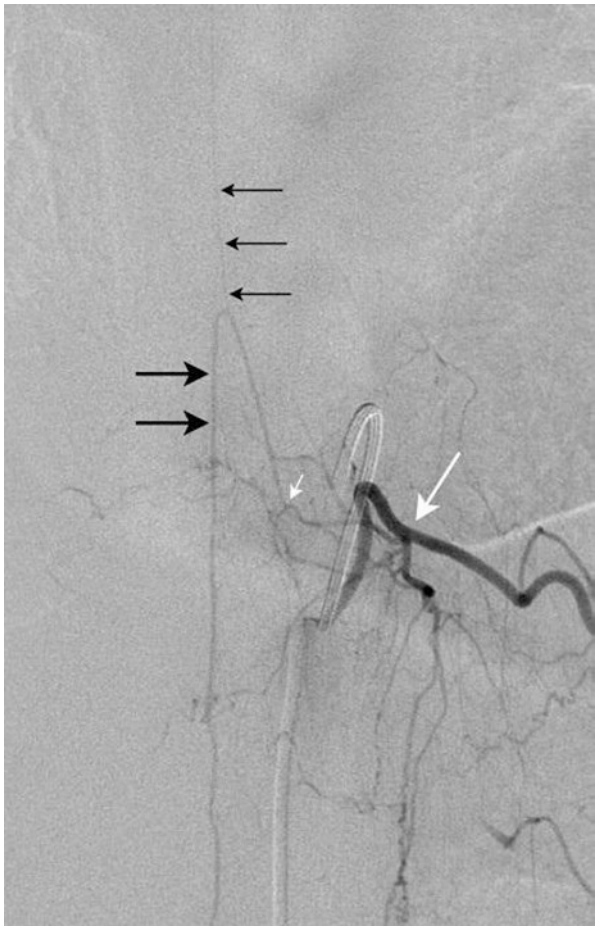

Fig. 3.3 Spinal digital subtraction angiographic image (AP projection) of an injection of the left T10 segmental artery which – in this patient – also supplies the anterior spinal artery. The branching of the segmental artery into lateral (ventral), middle (dorsal), and medial (spinal) trunks can be seen (*large white arrow*) as well as the branch point of the radiculomedullary artery of Adamkiewicz (*small white arrow*) which forms a characteristic "hairpin loop" prior to supplying the anterior spinal artery through a small ascending (*small black arrows*) and a large descending (*large black arrows*) branch

Adamkiewicz – is a significant source of spinal cord parenchymal arterial supply with infrequent collaterals arising below its communication with the anterior spinal artery, such that its sacrifice frequently leads to clinically-significant spinal cord ischemia or infarct. The artery of Adamkiewicz is typically 0.5–1 mm in diameter [5] and arises between T8 and L2 in 75 % of cases. In 80 % of cases it arises from the left segmental artery [6–9] (Fig. 3.3).

Spinal Cord Extrinsic and Parenchymal Arterial Anatomy

The extrinsic arterial system of the spinal cord is composed of three main longitudinal channels, a single **anterior spinal artery** (which supplies arterial blood to the anterior 2/3rds of the spinal cord) and the paired **posterior spinal arteries** (which supply arterial blood to the posterior 1/3rd of the spinal cord).

The anterior spinal artery (0.2–0.8 mm diameter) [4] forms as the union of two small branches of the vertebral artery, originating at the level of the foramen magnum. As the anterior spinal artery descends inferiorly, it resides in the anterior median fissure and receives intermittent arterial supply via several anterior radiculomedullary arteries.

The posterior spinal arteries (<0.5 mm diameter) also originate at the level of the foramen magnum from branches of the vertebral arteries or posterior inferior cerebellar arteries. As the posterior spinal arteries descend inferiorly, they reside just medial to the dorsal root entry zones [7] on the posterior aspect of the spinal cord and receive arterial supply through posterior radiculomedullary arteries [4].

The parenchyma is perfused by peripheral (centripetal) and central (centrifugal) arterial systems supplied by the ASA and PSAs. The peripheral system consists of a vast transverse anastamotic network of surface pial feeders from the anterior and posterior channels – known as the **pial plexus** or **vasocorona** – which supply the majority of the superficial white matter. The central system consists of deep perforators, known as the **sulcal** or **sulcocommisural** arteries, which originate only from the anterior spinal artery, travel in the anterior median fissure, and supply the deep gray and white matter [1].

Because of the relative paucity and variability of arterial supply to the anterior spinal artery from radiculomedullary arteries, several "watershed" areas of relatively low-volume arterial supply often exist within the spinal cord. These watershed regions occur most commonly at the junction of the three primary regions of radiculomedullary arterial supply; namely: the cervicothoracic, midthoracic, and thoracolumbar regions. Thus, in the event of systemic hypotension, for example, the regions of the spinal cord most likely to incur ischemia or infarct lie at the borders of these areas of arterial supply.

Venous Anatomy of the Spinal Cord and Spinal Column

The spinal venous drainage systems are vast, complex, and highly variable. While infrequently visualized with non-invasive imaging techniques, the spinal venous drainage pathways are thought to serve a critical role in the maintenance of cell viability within the spinal cord, a fact made clear by the often catastrophic clinical consequences of spinal venous hypertension and/or occlusion.

Spinal Cord Intrinsic Venous Anatomy

The venous drainage system within the spinal cord parenchyma consists of both axially- and longitudinally-oriented components which may be subdivided into **sulcal** (central) and **radial** (peripheral) veins. Whereas the arterial supply is predominantly through the anterior spinal artery (which supplies the anterior two-thirds of the spinal cord), the venous drainage of the spinal cord is divided roughly in half, with both ventral (anterior) and dorsal (posterior) components contributing equally.

The **ventral sulcal veins** (100–200 μm diameter) arise from capillaries supplying the bilateral medial halves of the anterior horns, anterior funniculus white matter and anterior commissure [4, 11, 12]. The **radial (peripheral) veins** arise from capillaries supplying the lateral horn gray matter, the dorsal nucleus of Clarke and the posterolateral peripheral spinal cord white matter and course towards the surface of the spinal cord where they drain into a venous ring surrounding the spinal cord which anastomoses with the pial venous network and extrinsic venous drainage system.

A rich network of anastomoses exists between the radial, sulcal, central and peripheral intrinsic venous drainage systems, including multiple large caliber (100–400 μm) **transmedullary anastomotic veins** connecting the ventral and dorsal spinal cord surfaces and a series of longitudinal intrinsic anastomic veins, including various longitudinal **intersegmental bridges** between the axially-oriented radial veins as well as median and paramedian longitudinal veins [1, 12].

Spinal Cord Extrinsic Venous Anatomy

Intrinsic sulcal veins within the spinal cord parenchyma drain into a system of pial collecting veins (400–500 μm diameter) with a predominant longitudinal orientation, most prominent ventrally in the lumbosacral region and dorsally in the high cervical and thoracic regions.

Intersegmental bridges between radial veins within the spinal cord parenchyma drain into longitudinal **ventral (anterior)** and **dorsal (posterior) median veins** (400–2000 μm diameter), further contributing to the pial venous networks. The ventral (anterior) median vein continues along the course of the filum terminale as the **terminal vein**.

A number of **radiculomedullary veins** receive blood from the ventral (anterior) or dorsal (posterior) median veins and travel alongside both dorsal and ventral nerve roots before exiting the dura before draining into the extradural vertebral venous plexus [1, 4, 12, 13]. The largest of these radiculomedullar veins travels with the anterior or posterior nerve root between T11 and L3 and is known as the **great anterior radiculomedullary vein** (up to 2 mm diameter) [12, 14].

The connection between the spinal cord and the systemic venous drainage systems provided by the radiculomedullary veins is a potential source of disease spread – whether neoplastic, infectious or inflammatory [17, 18, 19–23]. Cadaveric dissections by Batson [15] and others provided evidence that metastatic spread into the vertebral column commonly occurs via the vertebral venous plexus, a fact thought to be explained by the extensive connectivity and bi-directional flow capabilities of this system [15, 16].

Spinal Extradural Venous Anatomy

The vertebral venous plexus – also referred to as “Batson’s plexus” in reference to the Danish anatomist who described vertebral venous anatomy in 1940 – is a valveless network of veins consisting of three interconnected venous components: [10]

- The internal vertebral venous plexus,
- The external vertebral venous plexus, and
- The basivertebral plexus

The **internal vertebral venous plexus** is located within the epidural vertebral canal and anastomoses superiorly with the intracranial venous drainage systems. The **anterior internal vertebral venous plexus** lies just dorsal to the posterior longitudinal ligament and is connected via transverse branches to the **basivertebral plexus** – which courses transversely within each vertebral body. The **posterior internal vertebral venous plexus** lies just anterior to the ligamentum flavum and anastomoses with the **external vertebral venous plexus** that surrounds the vertebral column.

Drainage pathways of the vertebral venous plexus vary by spinal region, wherein:

1. The vertebral venous plexus of the cervical region drains into vertebral, deep cervical and jugular veins, eventually draining into the superior vena cava [10, 12].
2. The thoracic vertebral venous plexus drains via intervertrebral veins into the azygos, hemiazygos and accessory hemiazygos veins, eventually draining into the superior vena cava [10, 12].
3. The upper lumbar vertebral venous plexus drains into the ascending lumbar veins, which communicate with both the azygos system (the right and left ascending lumbar veins become the azygos and hemiazygos veins, respectively, at the level of the subcostal vein) and the inferior vena cava (the ascending lumbar veins communicate with the inferior vena cava via transversely-oriented lumbar segmental veins).
4. The sacral vertebral venous plexus empties into the lateral sacral veins, which then drain into the internal iliac veins [10, 12] (Fig. 3.4).

Highlights of Spinal Vascular Anatomy

- The arterial supply to the spinal cord originates from various major longitudinal feeding arteries, including the vertebral arteries (cervical region), aorta (thoracolumbar region) and iliac arteries/median sacral artery (lumbosacral region).
- These major londitudinal feeding arteries branch into a series of segmental arteries which provide arterial supply to the spinal cord, spinal column and surrounding myoligamentous tissue.
- The primary arterial supply to the spinal cord itself arises from a single anterior spinal artery (which supplies the anterior 2/3rds of the spinal cord) and paired posterior spinal arteries (which supply the posterior 1/3rd of the spinal cord).
- The anterior and posterior spinal arteries are supplied by radiculomedullary arteries originating from the paired segmental arteries.
- The largest of the radiculomedullary arteries – the artery of Adamkiewicz – originates most commonly on the left side between T8 and L2. Very few – if any – radiculomedullary arteries exist below the artery of Adamkiewicz, such that

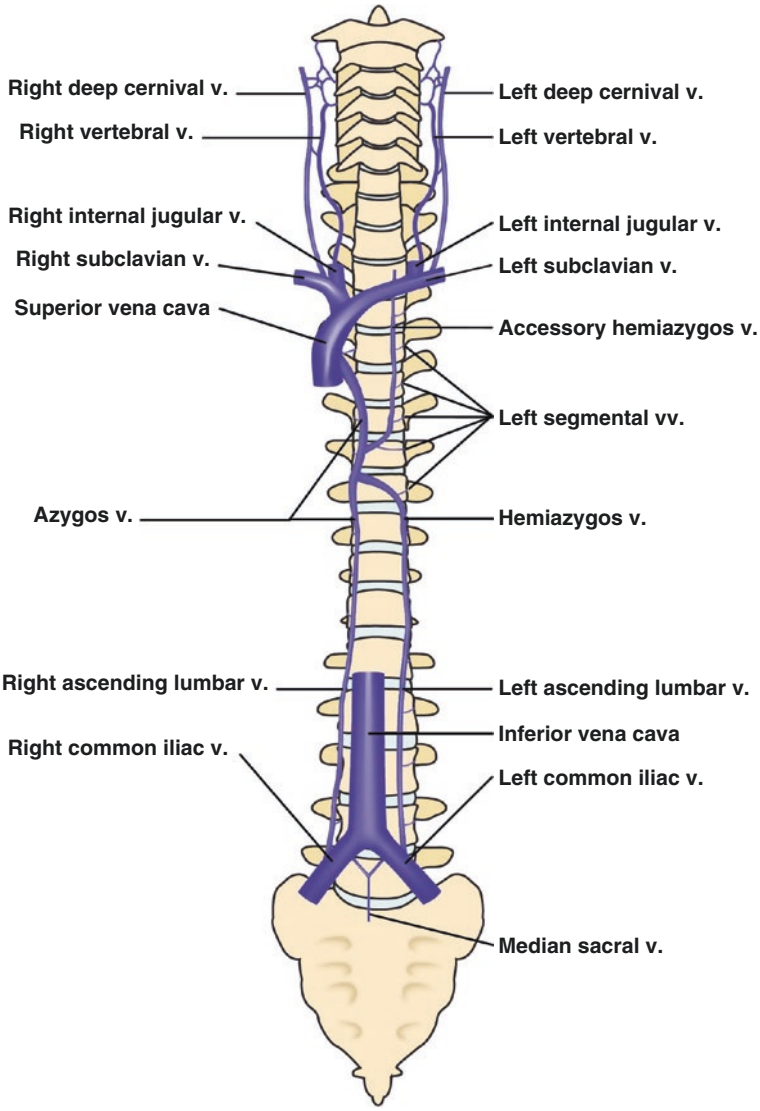

Fig. 3.4 Illustration depicting the major contributors to spinal extravertebral venous drainage

occlusion and/or sacrifice of this artery almost invariably leads to clinically-significant spinal cord infarction.

- Multiple "watershed areas" exist within the arterial supply to the spinal cord parenchyma, such that systemic hypotension may result in preferential ischemia and/or infarct between the borders of the major radiculomedullary arteries.
- The venous drainage of the spinal cord and spinal column is highly complex and variable.

- "Batson's" vertebral venous plexus is a valveless system – and although it possesses certain measures to prevent undue reflux or venous hypertension – it still provides a gateway for the bidirectional movement of venous blood (and any pathogens or neoplastic cells contained within) between the systemic and central nervous system venous drainage pathways, thus allowing for the spread of neoplastic and/or infectious disease from systemic to spinal circulation.

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Pediatric Vascular Neurology and Syndromes

4

Lisa R. Sun and Ryan J. Felling

The clinical diagnosis of stroke requires a thorough knowledge of vascular anatomy with particular emphasis on recognizing the deficits that occur with pathology of different vascular territories. Localization of neurologic deficits allows for rapid identification of the affected neurologic structures as well as the likely etiology and mechanism of the injury, even prior to obtaining neuroimaging. Children present an additional layer of complexity because of the normal process of neurodevelopment that occurs throughout childhood. Being able to put neurologic presentations into the context of the age spectrum is essential.

Pediatric vascular neurology is an emerging field. The epidemiology, pathophysiology, and optimal management are just beginning to be elucidated in a growing body of literature. For now, sufficient data on perinatal stroke (that occurring between 28 weeks gestation and 28 days of life) and childhood stroke (that occurring between 29 days of life and 18 years of age) are lacking. The approach to pediatric stroke is largely borrowed from the adult literature which can be problematic given the physiological differences between the developing child's brain and the mature adult brain [1].

While the same general principles of stroke management apply to adults and children, there are important differences to keep in mind. First, in adults, neurologic deficits correlate well with the area of infarct on imaging. The correlation is more difficult in children, in part because of the challenges inherent in the neurologic examination of children, but also because the presentation is often nonspecific. Seizures, headache, and altered mental status are uncommon presenting signs of stroke in adults but are common in neonatal and childhood stroke. In neonates, arterial ischemic stroke most commonly presents in the first week of life, with seizures by far the most common presenting sign in 72 %, followed by loss of consciousness and diffuse tone abnormalities in 39 % and 38 % of neonates, respectively [2]. Focal neurologic

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A. Agrawal, G. Britz (eds.), *Pediatric Vascular Neurosurgery*,
DOI 10.1007/978-3-319-43636-4_4

deficits are rare in neonatal stroke at onset and typically emerge at several months of age due to brain maturation and myelination [3]. In contrast, childhood arterial ischemic stroke presents in a focal manner in about 82–85 % of cases [4, 5]. However, seizures and diffuse neurologic signs remain common features, with seizures occurring in about a third of patients and diffuse signs such as decreased level of consciousness and headache occurring in 61–64 % of patients [4, 5]. In one study, children were 18 times more likely than adults to have a seizure within 24 h of stroke onset [6]. The reason seizures are so much more prevalent in pediatric stroke is unclear but likely related to transient hyperexcitability of the immature brain [7].

The mechanisms of stroke are quite different between children and adults, with the usual adult risk factors of hypertension, hyperlipidemia, diabetes mellitus, and atrial fibrillation being largely irrelevant in children. Adults who suffer from chronic hypertension and diabetes are at risk for small-vessel lacunar infarctions due to lipohyalinosis. Strokes in children are more likely to be large-vessel or embolic strokes, with common mechanisms being non-atherosclerotic vasculopathies (such as dissection, infectious vasculitis, and moyamoya syndrome) and embolism (for example from congenital heart disease).

The clinical diagnosis of stroke relies on recognition of distinct syndromes that are characteristic of pathology in an affected cerebrovascular territory. Strokes occurring in children can be either hemorrhagic or ischemic. Intracranial hemorrhage is more likely to have associated signs of increased intracranial pressure from mass effect, such as vomiting and diminished level of consciousness, although the ability to differentiate between ischemic and hemorrhagic stroke on a clinical basis alone is challenging. Cerebrovascular pathology can be broadly localized to the anterior cerebral circulation, the posterior cerebral circulation, or the spinal cord. In general, anterior circulation pathology can present with hemiparesis, hemisensory changes, visual field cuts, and cortical signs such as apraxia, aphasia, and agnosia. Posterior circulation strokes may instead present with nausea, vomiting, obtundation, cranial neuropathies, visual field cuts, vertigo, ataxia, and crossed sensorimotor deficits.

Anterior Circulation Syndromes

The anterior, or carotid, circulation supplies the motor and somatosensory cortices, with the anterior cerebral artery supplying superior medial frontal and parietal regions that control the leg and the middle cerebral artery supplying the lateral brain regions that control the face and arm, thus leading to their classic presentations, as described below. Both arteries supply both subcortical and cortical structures, so infarcts in these territories can produce weakness, sensory changes, and cortical signs.

Anterior Cerebral Artery

An anterior cerebral artery (ACA) stroke typically presents with a contralateral hemiparesis involving the leg more than the arm, and this can also be accompanied

by distal crural sensory loss, which is usually mild [8]. Importantly, frontal lobe signs may be prominent in ACA syndromes, including behavioral abnormalities, urinary incontinence, gait apraxia, and frontal release signs. Behavioral abnormalities may include impaired judgment, flat affect, and abulia. An infarct in the ACA territory can cause re-emergence of grasp and other previously extinguished primitive reflexes. Occlusion of the ACA proximal to the anterior communicating artery (Acom) will produce mild symptoms, as distal flow can be reconstituted from the contralateral ACA via the Acom. Notably, occlusion of the recurrent artery of Heubner, a branch of the ACA, will result in infarction of portions of the head of the caudate, putamen, and anterior limb of the internal capsule, which would produce a predominantly faciobrachial instead of crural hemiparesis [9].

Middle Cerebral Artery

In most people, the middle cerebral artery splits into two secondary divisions, with occlusion of each producing a distinct clinical syndrome.

An infarct of the superior division of the MCA classically presents with contralateral hemiparesis and sensory loss affecting the arm and face more than the leg. Involvement of the frontal eye fields produces a gaze preference toward the side of the lesion. Cortical signs differ depending on laterality of the stroke. If the dominant hemisphere is affected, infarction of the inferior frontal gyrus may cause a Broca's aphasia, in which speech production is impaired with intact comprehension. Involvement of the non-dominant hemisphere, in contrast, produces visuospatial defects and neglect.

If instead the MCA inferior division is affected, a patient may present with contralateral homonymous hemianopia due to involvement of the optic radiations traveling from the thalamus to the occipital lobes. Sensorimotor functions are typically spared. In the dominant hemisphere, the MCA inferior division supplies the superior temporal gyrus; an infarct of this territory may produce a Wernicke's aphasia, in which speech comprehension is impaired and speech production is fluent but nonsensical. In the non-dominant hemisphere, an MCA inferior division territory infarct instead results in a contralateral hemineglect. A profound hemineglect can make the motor, sensory, and visual field examinations difficult and can mimic hemiparesis, hemianesthesia, and homonymous hemianopia.

The deep MCA territory is supplied by lenticulostriate arteries that branch off of M1. Lenticulostriate occlusion may produce a lacunar syndrome without cortical signs. Lacunar infarcts, which commonly occur in older adults as a result of chronic diabetes and hypertension, are comparatively unusual in children. One exception is an entity of striatocapsular infarction that can often occur in infants less than a year of age, frequently associated with mineralizing lenticulostriate vasculopathy [10, 11]. These infarcts can cause a contralateral pure motor or pure sensory syndrome and frequently involve the face, arm, and leg equally because of the proximity of the corticospinal tracts as they pass through the internal capsule.

A proximal MCA occlusion will affect the territory of both the inferior and superior divisions in addition to the deep lenticulostriate territory. This will produce a global aphasia (dominant hemisphere) or anosognosia (non-dominant hemisphere), contralateral hemiparesis and sensory loss, contralateral homonymous hemianopia, and gaze preference toward the side of the lesion.

One syndrome caused by occlusion of distal MCA branches or borderzone territories that is worth mentioning is Gerstmann's syndrome, which causes the clinical tetrad of agraphia, acalculia, left-right disorientation, and finger agnosia [12]. Gerstmann's syndrome has traditionally been described in association with pathology of the left angular gyrus.

Anterior Choroidal Artery

Anterior choroidal artery (AChA) infarcts are rare in children, but in adults can produce a classic triad of contralateral hemiparesis, hemisensory loss, and visual field deficits, to variable degrees [8]. Aphasia and other cortical signs are absent. Case reports of children with infarcts in the AChA territory suggest the primary clinical manifestation is contralateral hemiparesis [13–15], though there is one report of contralateral motor neglect without weakness [16].

Posterior Circulation Syndromes

The posterior, or vertebrobasilar, circulation supplies the occipital and mesial temporal lobes, the thalamus, the brainstem, and the cerebellum. The blood supply to the thalamus is particularly complex, with four major arterial distributions that are highly variable between individuals. Vascular pathology in these territories produces an array of deficits dependent upon which specific thalamic nuclei are affected [17].

Posterior Cerebral Artery

Infarction of the posterior cerebral artery (PCA) territory typically entails a contralateral homonymous hemianopia due to involvement of the primary visual cortex. If the thalamus and/or posterior limb of the internal capsule are affected, contralateral hemiparesis and sensory loss may be seen, mimicking an MCA territory infarct.

The interesting syndrome of alexia without agraphia can be seen in PCA infarcts of the dominant hemisphere when the splenium of the corpus callosum is involved. In this syndrome, due to ischemia of the corpus callosum, visual information processed by the functional non-dominant occipital lobe cannot be transmitted to the language areas of the dominant hemisphere, causing an inability to read. However, the ability to write, which is not altered by PCA territory pathology, is unaffected.

Paramedian Artery

The paramedian arteries, also known as the thalamoperforators, branch off of the P1 segments of the PCA to supply the medial thalamus with variable contribution to the rostral midbrain [18]. The artery of Percheron is an anatomic variant in which the paired paramedian arteries share a common trunk arising from a single P1. Paramedian artery infarcts can cause difficulties with learning and memory, but present more severely with impaired consciousness and ophthalmoparesis (especially vertical gaze palsy) in cases of bilateral infarction, typically due to the artery of Percheron anatomic variant [19–27]. Bilateral paramedian artery infarcts due to artery of Percheron occlusion in children can present similarly to as in adults [28], though may present with seizures in the perinatal period [29].

Tuberothalamic Artery

The tuberothalamic artery, also known as the polar artery, branches off the posterior communicating artery and supplies the rostral thalamus. Vascular lesions here may cause personality changes and impairments in executive function, arousal, orientation, learning, and memory [17]. Dominant side lesions can produce language deficits while non-dominant side lesions can cause hemineglect.

Inferolateral Artery

The inferolateral artery, also called the thalamogeniculate artery, branches off P2 and supplies the lateral thalamus. An infarct in this territory may result in Dejerine-Roussy syndrome, which is characterized by hyperalgesia and allodynia, as well as contralateral hemianesthesia, hemiataxia, and choreoathesosis [30, 31]. A transient contralateral hemiparesis can also be seen secondary to compression of the internal capsule by thalamic edema that subsequently resolves [31].

Posterior Choroidal Artery

The posterior choroidal artery branches off the distal PCA and supplies the geniculate bodies, medial nuclei, and the pulvinar. Infarcts in this territory produce visual field deficits, variable contralateral sensory loss and weakness, and sometimes movement abnormalities such as tremor or dystonia [17].

Vertebrobasilar Syndromes

Occlusion of the vertebrobasilar system is a feared syndrome due to the devastating consequences and often subtle or prodromal presentations that are easily missed.

Table 4.1 Vetebrobasilar syndromes

Syndrome	Anatomic location affected	Vascular supply	Clinical presentation
Weber's syndrome	Ventromedial mibrain	Branches of PCA and basilar artery	Ipsilateral 3rd nerve palsy Contralateral hemiparesis
Claude's syndrome	Dorsal midbrain tegmentum	Branches of PCA and basilar artery	Ipsilateral 3rd nerve palsy Contralateral hemiataxia
Benedikt's syndrome	Paramedian midbrain	Branches of PCA and basilar artery	Ipsilateral 3rd nerve palsy Contralateral hemiparesis, hemiataxia, and tremor
Foville's syndrome	Inferior medial pons	Paramedian branches of basilar artery	Contralateral hemiparesis Ipsilateral face weakness Dysarthria Ipsilateral horizontal gaze palsy
Millard-Gubler syndrome	Ventral pons	Paramedian branches of basilar artery	Contralateral hemiparesis Ipsilateral face weakness
Locked in syndrome [32, 33]	Ventral pons	Basilar artery	Quadriplegia and anarthria Preserved consciousness Preserved vertical gaze and upper eyelid movement, with preservation of other cranial nerve functions to variable degrees
Wallenberg's syndrome	Lateral medulla	PICA or vertebral artery	Ataxia, nausea, vertigo, nystagmus Decreased pain and temperature of ipsilateral face and contralateral body Ipsilateral Horner's syndrome Hoarseness, dysphagia
Dejerine syndrome	Medial medulla	Vertebral artery, anterior spinal artery, or their branches [34]	Contralateral arm/leg weakness and decreased vibration and proprioception Ipsilateral tongue weakness
Top of the basilar syndrome	Visual cortex, midbrain, thalami, cerebellum	Basilar artery	Oculomotor/pupil abnormalities Visual disturbances Memory disturbances Alteration of mental status Hallucinations Ataxia

Occlusions of these arteries produce deficits of the brainstem and cerebellum. Specific deficits depend on the specific area of occlusion, and numerous syndromes have been described (Table 4.1). In general, dysfunction of the vertebrobasilar system presents with crossed findings (involving the ipsilateral face and the contralateral hemibody), nausea, vertigo, ataxia, nystagmus, cranial neuropathies (such as diplopia, dysarthria, and dysphagia), and somnolence. Hemiparesis or quadriparesis is caused by involvement of descending corticospinal tracts.

Watershed Syndromes

Watershed syndromes occur with infarction at the junction between two major arterial territories. Infarcts in this watershed territory or border zone typically result from decreased global perfusion, for example with systemic hypotension or cardiac arrest. Clinical presentation is variable, but can present with proximal arm and leg weakness ("person in a barrel" syndrome), difficulties with higher order visual processing if the MCA-PCA border zone is affected, and transcortical aphasias if the dominant hemisphere is involved.

Spinal Cord Syndromes

The vascular supply of the spinal cord is comprised of a single anterior spinal artery and two posterior spinal arteries. There are numerous and highly variable radicular arteries that supply various levels of the cord, making specific patterns of injury also quite variable. The upper spinal cord is primarily supplied by the vertebral arteries while the mid to lower cord is supplied by a large radicular branch artery from the aorta, classically termed the artery of Adamkiewicz. This creates a borderzone territory in the midthoracic cord that is vulnerable to ischemia due to decreased perfusion [35]. A spinal cord lesion produces deficits below the level of the lesion; however, it is important to remember that the localization of physical examination findings at a certain level signifies pathology at either that level or any level more rostral. Therefore, for example, a sensory level in the lumbar region can be due to a lesion in the lumbar, thoracic, or cervical cord.

Anterior Spinal Artery

The anterior spinal artery typically branches off the vertebral arteries and supplies the anterior two-thirds of the cord. Traumatic dissections of the vertebral arteries can thus involve the anterior spinal artery [36]. An infarct in this vascular distribution presents with pain and temperature loss, weakness, and autonomic dysfunction below the level of the lesion. Disruption of blood flow to the spinothalamic tracts but not the dorsal columns (which are supplied by the posterior spinal arteries) is responsible for the characteristic loss of pain and temperature with preservation of vibration and position sense in anterior cord syndrome. Initially, patients present with acute flaccid areflexic paralysis, but after the acute phase, an upper motor neuron pattern of spasticity and hyperreflexia may emerge. Autonomic symptoms including urinary retention and sphincter dysfunction are common.

Posterior Spinal Artery

Infarction in the posterior spinal artery territory is less common due to the dual blood supply of the posterior third of the cord. An infarct in this territory would

cause dysfunction of the dorsal columns, resulting in proprioception and vibration deficits. Motor function and pain/temperature sensation are typically spared.

Pearls

1. Perinatal stroke most commonly presents in the first week of life, with seizures being the most common presenting sign, followed by loss of consciousness and diffuse tone abnormalities. Focal neurologic deficits typically do not emerge until several months of age.
2. Children are more likely than adults to have seizures and diffuse neurologic signs at stroke presentation.
3. Anterior cerebral artery strokes present as contralateral hemiparesis more prominent in the leg than in the arm, behavioral abnormalities, urinary incontinence, gait apraxia, and frontal release signs.
4. Middle cerebral artery strokes present as contralateral hemiparesis, often with arm and face being more involved than the leg, and cortical signs including aphasia in the dominant hemisphere or neglect and visuospatial deficits in the nondominant hemisphere.
5. Anterior choroidal artery infarcts can produce a classic triad of contralateral hemiparesis, hemisensory loss, and visual field deficits without cortical signs in adults. Case reports suggest that contralateral hemiparesis is the most common presentation in children.
6. Pathology in the posterior cerebral artery territory typically presents with a contralateral homonymous hemianopia, with weakness and sensory changes being present to a variable degree depending on if the thalamus and/or internal capsule are affected.
7. The blood supply to the thalamus is complex, with four major arterial distributions that are highly variable between individuals. Presentation of thalamic infarcts is dependent upon which specific thalamic nuclei are affected but may present as a pain syndrome or with deficits of learning, memory, arousal, attention, language, and visual fields.
8. Dysfunction of the vertebrobasilar typically presents with crossed sensorimotor findings, nausea, vertigo, ataxia, nystagmus, cranial neuropathies, and somnolence. Subtle or prodromal symptoms are not atypical early in the course.
9. Spinal cord infarcts present with sensorimotor deficits below the level of the lesion. Though variable radicular supplies make localization to the anterior versus posterior spinal artery territories difficult, anterior spinal artery infarcts typically present with pain and temperature loss, weakness, and autonomic dysfunction, while posterior spinal artery infarcts cause deficits in proprioception and vibration.

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Pediatric Neuroanesthesia

5

Huy Do and David L. McDonagh

Introduction

Pediatric anesthesiologists involved in the care of children undergoing neurosurgical procedures require a thorough knowledge of the age-dependent anatomic and physiologic development of children, the impact of anesthetics on the developing nervous system, and the consequences of these surgical procedures to children. As the specialties of pediatric neurosurgery and neurointerventional radiology evolve with newer innovations and techniques, so must the pediatric neuroanesthesia team evolve to meet new challenges.

Developmental Changes

The newborn cranial vault is dynamic. Unlike adults, neonates and infants have open fontanelles and expandable cranial sutures, which allow for a compliant intracranial space. Slow increases in intracranial volumes can be accommodated and present with an increase in head circumference in young children [1, 2]. However, acute increases in intracranial volume or pressure commonly result in detrimental

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A. Agrawal, G. Britz (eds.), *Pediatric Vascular Neurosurgery*,
DOI 10.1007/978-3-319-43636-4_5

intracranial hypertension despite open fontanelles [3, 4]. These fontanelles close at different stages with the last fontanelle closing by 2 years in healthy children [5].

Cerebral blood flow (CBF) varies with age, reflecting changes in neural development. It is lower in premature infants and term neonates (40–50 ml/100 g/min) [6–8] and higher in infants and older children from 6 months to 7 years (70–110 ml/100 g/min) [9–11] of age as compared to adults (50 ml/100 g/min) [12]. CBF is coupled tightly with cerebral metabolism and cerebral metabolic rate of oxygen consumption ($CMRO_2$). $CRMO_2$ mirrors age-related changes in CBF. In children, $CRMO_2$ is higher (5.5 ml/100 g/min) than in adults (3.5 ml/100 g/min) [13]. Neonates have lower $CRMO_2$ (2.3–3.5 ml/100 g/min).

Unlike adults where the cerebral autoregulation is thought to be preserved in a mean arterial pressure (MAP) between 60 and 160 mmHg [14, 15], the autoregulatory limits are unclear in infants and children. Data from animal [16, 17] and preterm infants [18] postulate the lower limit for autoregulation to be a MAP of 30–40 mmHg. The lower limit of autoregulation for children aged 6 months and older may be similar to adults at 60 mmHg [19]. The autoregulatory range is poorly defined but is suspected to be lower and narrower than adults [2, 20].

Management of Anesthesia

Preoperative Evaluation and Preparation

Neonates and infants have a higher risk for perioperative morbidity and mortality than any other age group [21, 22]; therefore, a thorough history and physical examination should be performed in preparation for surgery. The preoperative evaluation requires a focused approach depending upon the indication for the surgical procedure. Particular considerations in the neurologic exam should include assessing for increased intracranial pressure (ICP), depressed level of consciousness, and focal neurological deficits. In infants and young children signs of intracranial hypertension can be subtle, such as irritability, lethargy, and failure to feed [23]. More obvious symptoms include full fontanelle, cranial enlargement, and cranial nerve palsies. Older children may present similarly to adults with headaches, vomiting, diplopia, and abnormal gait or coordination [23].

Preoperative laboratory testing may be indicated in pediatric patients for neurosurgical cases, such as craniotomies, where the risk of significant blood loss may occur. Hemoglobin or hematocrit levels, coagulation profile and typed and crossmatched blood should be ordered for these cases. Other preoperative labs may be tailored depending upon coexisting diseases (i.e. electrocardiogram or echocardiogram for congenital heart disease) or concurrent symptoms (i.e. electrolytes for diabetes insipidus or protracted vomiting). Identifying coexisting and concurrent diseases may prompt more extensive evaluations, which may require optimization prior to elective surgery. This may not be feasible for urgent and emergent cases.

Judicious use of oral or intravenous sedative premedications may be beneficial for small children to ease transition to the operating room [24]. Over-sedation may

decrease ventilation, resulting in hypercapnia and further worsening ICP. These medications should best be avoided in all children with symptomatic intracranial hypertension. For children who do not have an IV catheter yet demonstrate symptomatic intracranial hypertension, an IV catheter may need to be started in the preoperative area.

Induction

The fundamental goal of anesthetic induction is to maintain cerebral perfusion pressure (CPP) by preventing increases in ICP and decreases in MAP. During induction, ICP can increase secondary to tracheal intubation, hypoxia, or hypercapnia; furthermore, certain anesthetic agents can influence MAP. For the patient with an IV catheter, induction with intravenous anesthetic and a paralytic agent is ideal. Pediatric patients that are at risk for aspiration (e.g. due to recent oral ingestion) require a rapid-acting paralytic agent such as rocuronium or succinylcholine. Succinylcholine is contraindicated for neurosurgical patients with spinal cord injuries, paretic extremities/denervating diseases, or suspected muscular dystrophy because of concerns for life-threatening hyperkalemia [25, 26] with its use.

For scheduled or elective surgical procedures in a neurologically stable patient who comes from home, commonly such a patient does not have an IV catheter. In children without (or having difficult) IV access, a smooth inhalational induction by facemask with sevoflurane and nitrous oxide with oxygen is preferred. This technique facilitates obtaining an IV in children and allows for a smooth tracheal intubation.

Airway Considerations

Because of the relatively short trachea in the pediatric population, the endotracheal tube can easily migrate with positional changes of the head. Neck flexion may result in endobronchial intubation or intraoral kinking of the tube. Conversely, excessive extension may result in extubation of the endotracheal tube especially in neonates and infants. Minimal movements may result in significant changes of the respiratory dynamics affecting oxygenation and/or ventilation, which may worsen during surgery. Reevaluation of the airway parameters is crucial after final positioning of all children.

Vascular Access

For neurosurgical procedures where the risk for significant blood loss may occur, attaining appropriate intravenous access is paramount. In most of these cases, two relatively large-bore IVs are sufficient. Due to the size of infants and neonates, the option may be limited to two 24-gauge venous cannulae. Placement of central

venous access is reserved for pediatric patients with difficult/inadequate IV access or an increased risk of air embolism (e.g. sitting position). When surgeries involve risk for sudden hemodynamic swings due to hemorrhage, venous air embolism, and cranial nerve manipulation, an arterial line is also required for continuous blood pressure monitoring and blood chemistry sampling. In common neurosurgical cases that involve minimal blood loss (e.g. ventriculoperitoneal shunting, angiography), a single IV catheter alone is usually suitable.

Positioning

Neurosurgical procedures are performed in various positions to facilitate surgical access. Children with supratentorial lesions are often placed in supine or modified lateral positions. Surgeries for posterior fossa or spinal cord lesions commonly require the prone position. The placement of supportive rolls under the chest and pelvis is needed in this position to minimize abdominal and thoracic pressure, thereby, aiding in ventilation and venous drainage. The sitting position is seldom utilized in the pediatric population because of increased likelihood of venous air embolism (VAE) with risk for hemodynamic collapse and/or paradoxical systemic arterial embolization in the setting of a right to left cardiopulmonary shunt [27, 28]. The increased risk of VAE also occurs with any position where the head is slightly elevated above the heart (i.e. reverse trendelenberg). Similar to adults, head pinning is usually reserved for older infants and children when the skull is denser. Head pinning is avoided in neonates and infants because of an increased risk of skull fracture, dural tear, and hematoma. Due to the prolonged duration of many neurosurgical procedures, general considerations for all positions include proper padding, and prevention of pressure or traction on nerves.

Maintenance Anesthesia

The primary goal during maintenance anesthesia during neurosurgery is to optimize cerebral perfusion and minimize brain bulk (and/or ICP). This can be achieved with volatile agents, intravenous anesthesia (TIVA), or a combination of these agents along with opioids and controlled ventilation. There is no evidence to suggest that any particular anesthetic agents lead to better neurologic outcomes [29]. The technique of low dose volatile agent and opioid is commonly used for pediatrics patients of all ages. Nitrous oxide should be avoided in endovascular neurosurgical procedures as well as in procedures with risk for VAE due to nitrous oxide's rapid diffusion into and enlargement of intravascular air bubbles.

Neuromuscular blockade is maintained during most neurosurgical procedures to prevent spontaneous movements. Neuromuscular blockade is avoided during motor testing or cortical mapping. Potent titratable opioids, such as remifentanil, can be very useful in cases where neuromuscular blockade is contraindicated.

Intraoperative Fluid and Temperature Management

Crystalloid solutions such as normal saline or lactated ringers are recommended for maintenance fluids. Excessive amount of the former results in hyperchloremic acidosis [30]. Colloids (5 % albumin) are acceptable intravenous fluids but the available data has not shown improvement in outcomes when compared to crystalloids [31]. In the setting of cerebral ischemia, hyperglycemia is injurious and normoglycemia should be maintained; however, neonates and young infants are at risk for hypoglycemia due to their limited glycogen reserve and hepatic glucose production. Dextrose-containing solution may be judiciously used and the serum glucose should be periodically checked throughout the case. Similarly, hyperthermia exacerbates acute brain injury and should be avoided. There is no proven benefit to therapeutic hypothermia outside of the setting of anoxic brain injury. Therefore, the goal in most neurosurgical procedures should be controlled normothermia.

Brain Bulk Reduction

The multifaceted stepwise approach to reducing brain bulk (in order to avoid retraction injury or tissue herniation through the craniotomy) during pediatric neurosurgery includes:

1. CSF drainage via external ventricular or lumbar drains (if present).
2. Mild head elevation and avoidance of jugular compression to facilitate venous outflow.
3. Mild hyperventilation to reduce cerebral blood volume ($PaCO_2$ target ~30 mmHg)
4. Hyperosmotic therapy with mannitol or hypertonic saline (generally titrated to an serum osmolality limit of ≤320 mOsm/L).
5. Corticosteroids for vasogenic edema due to tumor
6. Metabolic suppression with propofol, etomidate, or barbiturates, ideally guided by EEG.
7. Therapeutic hypothermia in select cases.

Adequate cerebral perfusion pressure (as a surrogate for cerebral blood flow) must be maintained throughout, in addition to any of the above measures.

Neurophysiologic Monitoring

The increased use of intraoperative neurophysiological monitoring for the pediatric population has allowed for more aggressive neurosurgical resection of brain and spinal cord lesions while assessing and maintaining the functional integrity of sensorimotor pathways during surgery. Common monitoring modalities include somatosensory evoked potentials (SSEPs), motor evoked potentials (MEPs), electromyography (EMG), auditory brainstem evoked responses (ABR), and

electroencephalography (EEG). Certain anesthetic agents can affect these modalities. In general, volatile agents have the most impact and are often used in lower amounts while intravenous agents (e.g. propofol) have lesser effects. Muscle relaxants should be avoided when monitoring MEPs or EMG. Open communication with the neurophysiologic technician is important in order to provide optimal anesthetic care without ablating the monitoring signals.

Anesthetic Neurotoxicity in the Developing Brain

No one topic has garnered more current interest in pediatric anesthesia than the effects of general anesthesia on developing brains. In animal models, prolonged anesthesia with gamma-aminobutyric acid (GABA) agonists (e.g. volatile anesthetics, midazolam, propofol) as well as N-methyl-D-aspartate (NMDA) antagonists (e.g. ketamine and nitrous oxide) produce accelerated neuronal apoptosis and altered synaptic plasticity [32–34]. Extrapolating these data to the human model is dubious. Ongoing human observational studies [35–37] are investigating the association between general anesthesia and neurocognitive development in children. Presently there is inadequate evidence to change the approach in anesthetizing children for neurosurgical procedures based on concerns over anesthetic induced neurotoxicity. What is clear is that insufficient anesthesia and analgesia during surgery are associated with poor neurologic outcome [38–42].

Pediatric Vascular Neurosurgery

There are unique aspects to the anesthetic management of the vascular neurosurgical patient.

1. Aneurysm Surgery: Attention to blood pressure control during periods of noxious stimuli (endotracheal intubation, Mayfield head frame placement) is paramount, especially in the setting of aneurysmal subarachnoid hemorrhage. The use of adenosine arrest or rapid ventricular pacing to produce controlled hypotension and facilitate aneurysm clip placement has only occasionally been described in the pediatric neuroanesthesia literature, but remain options in select cases [43].
2. Moyamoya disease: These patients have very tenuous cerebral perfusion and are at risk for ischemia with hypotension, and at risk for cerebral hemorrhage with hypertensive surges. Tight hemodynamic control is essential, targeting preoperative blood pressure levels. Blood pressure goals should be established after communication with the neurosurgeon regarding patient specific factors [44]. There is theoretical concern for cerebral steal (also called the ‘reverse Robinhood

syndrome') with the use of inhalational anesthetic agents due to nonspecific cerebral arterial dilation. However, there is no evidence to suggest that propofol TIVA is preferred/superior and either inhalational or intravenous anesthetics remain acceptable [45].

3. Endovascular Neurosurgery: As with other neurovascular interventions, open communication with the surgical team is essential to determine the predicted susceptibility for injury from hypo- or hypertension in the individual patient. Nitrous oxide should be avoided due to its potential to exacerbate any intra-arterial air emboli (which are a known risk in endovascular surgery) [46].

Conclusions

A pediatric anesthesiologist who specializes in neuroanesthesia best meets the unique and evolving needs of children undergoing neurosurgical procedures. Such specialization will facilitate thorough attention to the preoperative assessment, perioperative management, and interdisciplinary communication that will minimize morbidities and maximize outcomes.

Pearls

- The cerebral autoregulatory range in neonates and young infants is unclear but suspected to be lower and narrower than adults.
- A detailed history and physical, addressing any neurologic pathology and coexisting conditions or concurrent illnesses, reduce perioperative patient risk and morbidity.
- The clinical presentation of the child guides the need for preoperative anxiolytic medication.
- Airway reassessment is important with all position changes, especially when involving the head and neck.
- Neurosurgical procedures with the potential risk of significant blood loss require appropriate intravenous, arterial, and possible central access.
- Neonates and young infants may require dextrose-containing solution during surgery. Close monitoring of blood glucose prevents hypoglycemia and hyperglycemia.
- There is no evidence that any particular anesthetic agents provider better neurologic outcomes in pediatric patients.
- Preoperative and intraoperative communication with the neurophysiologic technician allows for optimal anesthetic tailoring.
- The long-term effects of various anesthetic agents on developing brains are unknown. At this present time, there is a lack of evidence to change the approach to anesthetizing children for neurosurgical procedures.

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Pediatric Neurocritical Care

6

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Introduction

Pediatric Neurocritical Care is an emerging multidisciplinary field of clinical and experimental medicine. While there are challenges to implementing specialized units for pediatric neurologic critical care, and limited evidence on which to base clinical practice, several models now exist for pediatric neurocritical care programs in centers that are contributing to the development of treatment guidelines and protocols; including multimodal neuromonitoring [1, 2]. Recent multi-center studies investigating pediatric brain injury in stroke, status epilepticus, and hypothermia after cardiac arrest and traumatic brain injury have served to promote the feasibility of accomplishing brain-directed research in children [3–7]. Several organizations, such as the Pediatric Emergency Care Applied Research Network (PECARN) and the Pediatric Neurocritical Care Research Group (PNCRG) are working on advancing care in highly specialized training programs across the United States. Pediatric neurocritical care exists thanks to technological advances in pediatric critical care, neurology, neurosurgery, and anesthesiology. The main goal of pediatric neurocritical care is to improve outcomes in infants and children with life-threatening

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A. Agrawal, G. Britz (eds.), *Pediatric Vascular Neurosurgery*,
DOI 10.1007/978-3-319-43636-4_6

neurologic injuries, and to prevent the development of secondary neurologic and non-neurologic injuries. This chapter briefly covers some of the most common neurologic conditions encountered in the pediatric intensive care unit (PICU).

Traumatic Brain Injury

Traumatic brain injury (TBI) remains a leading cause of disability and mortality in infants, children and adolescents across the United States, and constitutes a significant portion of PICU admissions [8, 9]. In the United States alone, TBI affects over half a million children ages 0–19 annually, including 630,000 emergency department visits, 60,000 hospitalizations and over 6100 deaths [10]. It is estimated that five times as many children will succumb from the devastating effects of acute brain injury (hypoxic-ischemic or traumatic) than childhood neoplasias [9]. Guidelines for the care and management of pediatric severe traumatic brain injury were first published in 2003 and updated in 2012 [11, 12].

TBI pathophysiology occurs in two known different phases of care: primary and secondary injury. Currently, there is little that can be done to reverse primary injury, which is the damage resulting at the moment of trauma. Secondary or delayed injury is most commonly caused by physiologic insults such as hypotension and hypoxia. Inflammatory, metabolic, and excitotoxic mechanisms also represent a wide spectrum of potential secondary insults, leading to cerebral edema and intracranial hypertension. Fortunately, secondary injury is a potentially preventable and treatable condition.

The Kennard principle proposes the idea that pediatric recovery after TBI would be enhanced due to a higher degree of neural plasticity in the developing brain [13]. For years, it was thought that children had a greater ability to recover from TBI. However, the Kennard principal referred to localized or focal lesions, not diffuse brain injuries; and outcome following TBI in children may not be better than in adults [14, 15]. Children suffering from TBI classified into favorable outcome groups still may exhibit long-term underappreciated cognitive and behavioral impairments [16, 17]. Moreover, in comparison with their peers, TBI leads to decreased academic achievement, lower scores on intelligence testing, reduced ability to focus, and other neurocognitive deficits [18, 19].

TBI has special connotations in the pediatric population as the impact of the injury may not be entirely evident until many years later as developmental stages are acquired. Falls, bicycle, motor pedestrian and motor vehicle collisions are the most common causes of injury in young children and adolescents. However, inflicted or abusive head trauma (AHT)- also termed non-accidental trauma (NAT)- deserves special mention as one of the leading causes of TBI in infants <2 years [20], as this is frequently associated with significantly worse outcomes than accidental mechanisms [21, 22]. Abusive TBI is typically defined by a triad of physical and radiologic findings including, hyperdense and hypodense subdural collections, retinal hemorrhages, and some degree of encephalopathy [23]. Brain injury in these patients is associated with repetitive trauma, delay in seeking medical care and

high incidence of hypoxic-ischemic injury and seizures, which all may serve to worsen neurologic outcomes [24]. Seizures have been reported to occur in as many as 77 % of AHT patients who had continuous EEG monitoring, significantly higher than rates of older children and adults with accidental mechanisms. Of particular importance is the high frequency of subclinical events. In a report by Arndt et al., subclinical seizures occurred in 16 % of children with TBI; however all of the children with only subclinical seizures were < 1 year old and subclinical status epilepticus occurred in 45 % of AHT infants [25]. In this study subclinical seizures and subclinical status epilepticus were associated with worse hospital discharge outcome scores. Thus AHT and young children may benefit from additional EEG monitoring to detect subclinical seizure activity [25]. Every year, 3 million cases of child abuse and neglect are reported to child welfare systems in the USA, and of these one-third are substantiated [26]. Despite well described injury patterns, NAT is a difficult and serious diagnosis due to the widespread implications beyond the patient [27]. Currently, serum and cerebrospinal biomarkers are under investigation to determine differences between accidental and NAT [28].

As compared to adolescents, children have a higher incidence of diffuse axonal injury (DAI), SDH, and cerebral edema [29]. In turn, adolescents show a higher incidence of DAI and contusions compared to the adult population [30]. There are also reports of a higher magnitude of cerebral edema after TBI in pediatric populations, likely due to a more heterogeneous vascular and inflammatory response [31, 32]. Also, a child's skull is more susceptible to suffer a higher degree of deformity before reaching its compliance limit [33, 34].

Animal data suggests that immature and developing cerebral tissue is at higher risk of apoptotic cell death [35]. In fact, increased levels of apoptosis-related proteins such as cytochrome c, Fas, and caspase-1 have been observed in children after TBI [36]. In addition, increased CSF levels of neuron-specific enolase which is a pro-apoptotic protein have been found after TBI [37].

Pediatric TBI Management

Cervical Spine and Airway Management

Although not as frequent as in adults, associated cervical spine (C-spine) injury can be seen after sustaining severe blunt cranial trauma. It is estimated that up to 25 % of patients suffering C-spine injury develop neurologic deficits caused by pre-hospital manipulation [38]. C-spine evaluation in children must take into consideration the anatomic development (Table 6.1). Any child at risk of having a C-spine injury must be immobilized in a neutral position until injury is ruled out. Patients less than 8 years of age are more susceptible to injury of the upper cervical spine as the maximal motion occurs at C1–C3. After 12 years of age, maximal movement occurs around C5–C6. C-spine clearance should follow the current pediatric guidelines for children with either reliable or unreliable physical examinations. In children, spinal cord injury may occur without radiographic evidence (SCIWORI) necessitating reliance on the clinical exam or magnetic resonance imaging to detect injuries that

Table 6.1 Pediatric C-spine anatomic considerations

Large head size in comparison to neck and trunk- causes increased flexion and extension in the cervical spine
Weaker cervical musculature results in greater mobility of the upper cervical spine
Horizontally inclined facet joints facilitate sliding of the upper cervical vertebrae
Increased elasticity of facet joint ligaments
Incompletely ossified vertebrae
High water content & elasticity of intervertebral disks, increases vertical loading effect

may not be evident on conventional radiographic imaging. Patients with severe TBI (i.e., TBI with coma; GCS <9), or worsening mentation should have a definitive secure airway established [39]. Initially, the airway can be opened with a jaw thrust and chin-lift maneuver while maintaining cervical immobilization (by an assistant). Endotracheal intubation is always a potentially challenging scenario in trauma patients. It is recommended to perform orotracheal intubation with in-line manual stabilization to prevent further spinal cord injury. In-line manual stabilization should be performed by an experienced provider. Nasotracheal intubation should be avoided in patients with facial trauma and/or signs of skull base fracture.

Endotracheal intubation is best achieved using rapid sequence induction/intubation with application of gentle cricoid pressure. Etomidate is frequently used for this purpose as it decreases ICP without significant reductions in mean arterial pressure [40]. There is no definitive evidence showing that succinylcholine increases ICP in humans with brain injury [41, 42]. Therefore, the use of succinylcholine vs. rocuronium for rapid sequence induction should be based on other clinical factors and provider expertise. Prolonged hyperventilation during mechanical ventilation should be avoided as it may cause cerebral tissue ischemia resulting from oligemia [43]. Arterial $PaCO_2$ should be monitored and normocapnea, $PaCO_2$ 35-40 mmHg, should be targeted except in the setting of reversal of clinical herniation syndrome where lower $PaCO_2$ levels can be temporarily used. The head should be elevated, either at 30° (or equivalent reverese trendelenburg tilt) to improve cerebral venous drainage. Studies performed in adults suggest that head elevation to 30° improves CPP and reduces ICP [44]. Also, the head should be maintained in a neutral position to avoid obstruction of jugular venous outflow.

As in adults, children who are hypotensive during the first hours of hospital care have worse outcomes [45, 46]. The lower limit of systolic blood pressure should be maintained greater than the 5th percentile for age (estimated by 70 mmHg + (2 × age in years). Evidence supports that better outcomes are achieved in children who receive early fluid resuscitation [47]. Therefore, it is imperative to urgently initiate resuscitation with isotonic fluids to correct hypotension and hypovolemia.

Current guidelines for the management of pediatric TBI recommend the use of intravenous agents such as analgesics, sedatives, and neuromuscular blockers as adjuvants to prevent or minimize secondary brain injury and intracranial hypertension [12, 43]. There are few studies addressing the choice of agent, however the use of these agents should be limited to patients who are hemodynamically stable with a secure

airway. Decompressive craniectomy and barbiturate therapy are also used to reduce ICP and improve CPP. While there are currently few studies that would lend support to adopting a standard of care recommendation, these therapies may be consider using effective in "control of refractory ICP" or "treating refractory ICP" control and should be considered in children with a salvageable or recoverable injury [12]. Contrary to adult guidelines, pediatric use of propofol infusion is not FDA approved due to its associated morbidity [11]. The incidence of early post-traumatic seizures in children ranges from 5 to 43 %; risk factors include young age (<2 years), AHT, skull fracture and severe head injury [25, 48, 49]. In a randomized trial of 102 children with acute TBI, Young et al., found empiric phenytoin versus placebo did not affect the incidence of post-traumatic seizures (7 % vs. 5 %) or outcome [48]. Prophylactic anticonvulsant use varies widely among centers (10–35 %), current recommendations state that prophylactic treatment with anti-seizure medications can be considered and might decrease the onset of post-traumatic seizures in children, and improve outcomes [50, 51].

It is well known that hyperglycemia is associated with worse outcomes after TBI in adults and children. This may be secondary to worsening of lactic acidosis at a brain tissue level [52]. Sharma et al. [53] in 2009 observed that predictors of hyperglycemia were children <4 years old, GCS ≤ 8, and multiple traumatic injuries including SDH. Currently, it is not completely clear what the upper cutoff for hyperglycemia in children should be [43]. The majority of centers recommend that hyperglycemia should be corrected in acute childhood TBI. Of note, steroid administration in children following TBI has not been associated with additional benefit or improved outcomes [11]. In fact, evidence suggests increased morbidity and mortality after its use [54].

Intracranial Hypertension Management (See Also Table 6.2)

Multiple clinical trials have shown the beneficial effect of hyperosmolar therapy (mannitol or hypertonic saline) in decreasing ICP in children [55, 56]. Potential concerns with using hypertonic saline include dehydration, natriuresis, central pontine myelinolysis, and the theoretical concern for rebound intracranial hypertension in the setting of a disrupted blood brain barrier [57]. The 2012 severe pediatric TBI guidelines recommend that either bolus or infusion therapy is effective in reducing intracranial pressure in children [11]. The use of mannitol in children has not been well studied. Several potential complications have led to a decrement of its use, i.e. volume depletion, hypotension, acute renal injury particularly in hypovolemic patients, a lower reflection coefficient than sodium chloride, and the potential reverse osmotic effect leading to an increase in ICP.

Hyperventilation therapy linearly reduces CBF and ICP due to hypocapnia via cerebral vasoconstriction; sustained hyperventilation ($PaCO_2 < 30$ mmHg) has been associated with regional cerebral ischemia in up to 73 % of patients and poorer long-term outcomes [58, 59]. Current guidelines recommend against *routine* use of hyperventilation to a $PaCO_2$ less than 30 mmHg. If used, concomitant advanced neuromonitoring should be provided [11, 43].

CSF drainage works by reducing the amount of intracranial fluid and achieves immediate reductions in intracranial pressure. An external ventricular drain can be

Table 6.2 Pediatric ICP management

Evacuation of intracranial mass lesions/hematomas
Cerebrospinal fluid drainage with an external ventricular drain
Sedation ± neuromuscular blockade
Maintain adequate cerebral perfusion pressure
Hyperosmolar therapy with hypertonic saline
Mild hyperventilation $PaCO_2$ 35–40 mmHg
Hyperventilation for acute ICP spikes
Decompressive craniectomy to accommodate cerebral edema without herniation
Profound sedation- burst suppression with pentobarbital
Therapeutic hypothermia (32–34 °C) to control ICP refractory to medical management

used to both remove CSF and to monitor ICP. CSF drainage is highly effective until cerebral edema produces ventricular collapse.

Barbiturate coma is recommended in the hemodynamically stable patient when maximal medical and surgical therapy has failed to manage elevated ICP. Barbiturates decrease the cerebral metabolic rate (~50 % at the point of burst suppression), with concomitant decreases in CBF, brain bulk, and subsequently ICP [60]. Ionotropic and vasopressor support to avoid hypotension and maintain adequate mean arterial pressures are commonly required after starting barbiturate coma. Continuous EEG monitoring is used to guide therapy, both to maintain a burst suppression profile as well as to monitor for subclinical seizures (Fig. 6.1).

Decompressive craniectomy should be considered in pediatric patients who are experiencing signs of cerebral herniation or in those with intracranial hypertension refractory to medical treatment. The ideal timing for performance is still a debate (early vs. late/rescue). Decompressive craniectomy can clearly be life-saving with good neurologic outcome in select cases. However, the application and timing of this surgery is debated as the evidence base is limited, particularly in children. Decompressive craniectomy has been reported in small pediatric case series and retrospective studies to be effective in lowering ICP in children with refractory ICP elevation with reports of good outcomes [61, 62]. Recommendations are limited by the small sample size, single center and retrospective design and lack of adequate case controls for comparison. Taylor et al., randomized 27 children with severe TBI and refractory ICP to early bitemporal decompressive craniectomy (mean 19.2 h form injury) versus maximal medical therapy. The mean ICP was lower in the craniectomy group 48 h after randomization and outcome appeared to be improved (normal or mild disability 54 % in craniectomy group versus 14 % in the medical group) [63]. The Decompressive Craniectomy in Diffuse Traumatic Brain Injury (DECRA) trial did not show benefit to bifrontal craniectomy in comparison to medical therapy in adults (Median age ~24 years) [64]. ICP was reduced, along with length of stay in the intensive care unit, but neurologic outcomes at 6 months were worse. The rescueICP (Randomised Evaluation of Surgery with Craniectomy for

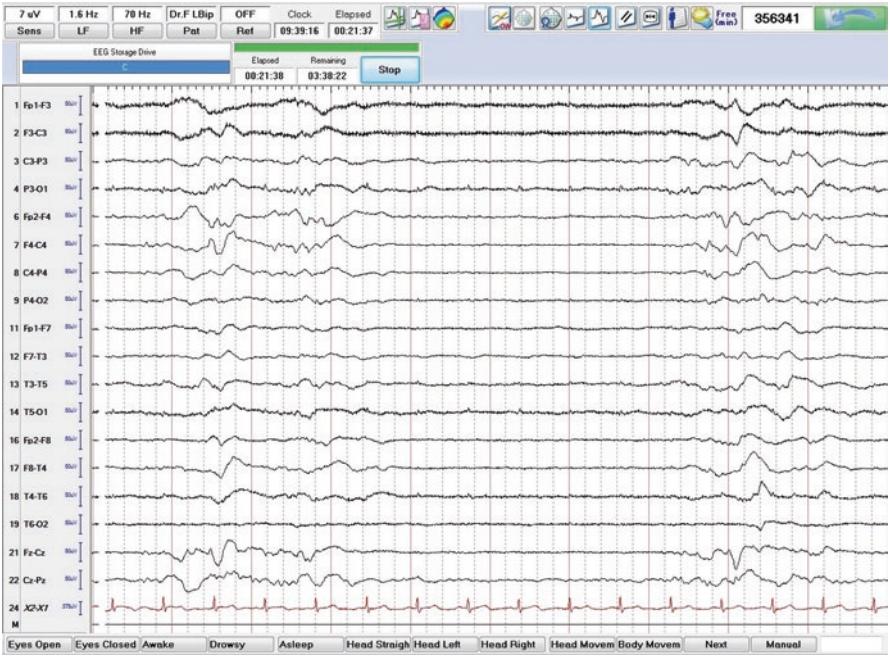

Fig. 6.1 Typical burst-suppression pattern observed during EEG recording while in pentobarbital coma

Uncontrollable Elevation of Intra-Cranial Pressure) trial has finished enrollment but results have not yet been published [65]. Randomized trials are needed in children to determine the safety, efficacy, timing, and optimal patient population for decompressive craniectomy in pediatric TBI patients.

Therapeutic hypothermia can be used to lower ICP (decreases cerebral metabolic rate ~6 % per degree Celsius) and it remains a therapeutic option for controlling refractory ICP [66], however 2 prospective randomized clinical trials have failed to demonstrate a benefit of early prophylactic hypothermia on neurologic outcome [3, 4]. In these studies, children with severe TBI were randomized to hypothermia 32–34 °C within 6–8 h of injury for either 24 or 48–72 h, versus normothermia 36.5–37.5 °C, with slow rewarming. The authors found no difference in the proportion of children with unfavorable outcomes at 3 or 6 months. *Hyperthermia* is thought to be injurious in the setting of acute brain injury of any etiology. Therefore, 'targeted temperature management' is becoming standard of care in the patient with acute neurologic injury [67]. A prospective multi-center international trial is ongoing, Approaches and Decisions for Acute Pediatric TBI (ADAPT) trial that will use a comparative effectiveness strategy to test intracranial hypertension therapies, brain tissue oxygenation monitoring, hyperventilation, and nutrition on neurologic outcome in severe pediatric TBI. With a proposed enrollment of 1000 children, this will be the largest prospective dataset in pediatric TBI obtained to date.

Hypoxic Ischemic Brain Injury

Neonatal asphyxia remains a common cause of hypoxic brain insults in the pediatric population. Unlike TBI, high level evidence exists for the efficacy of therapeutic hypothermia in this setting. Standard of care in neonatal resuscitation is the induction of moderate hypothermia for the treatment of moderate-severe hypoxic ischemic encephalopathy [68]. American Heart Association Guidelines [68] recommend a target temperature of 33.5–34.5 °C (initiated within 6 h of birth) for 72 h followed by a controlled rewarming period, avoiding overshoot hyperthermia. Neonates seem particularly sensitive/vulnerable to hyperoxia, so FiO_2 should be minimized with pulse oximetry guidance.

Unlike adults, the primary mechanism for cardiac arrest in children is secondary to respiratory failure, thus establishment of an airway, oxygenation and ventilation with bag mask ventilation (BMV) or endotracheal intubation should be rapidly instituted. Standard therapy for post-anoxic cerebral resuscitation should be targeted at optimizing systemic hemodynamic and physiologic variables and avoiding secondary insults. Poor prognostic factors include myoclonic status, non-reactive or burst suppression pattern on EEG, absent pupillary reflex at 72 h and abnormal somatosensory evoked potentials.

The role of induced moderate hypothermia in neuroprotection of children beyond the neonatal period is less clear. Pediatric Advanced Life Support (PALS) guidelines suggested that the immediate induction of therapeutic hypothermia (Temperature 32-34 °C) may be beneficial but that further study is needed [69]. In a multicenter study of Therapeutic Hypothermia after Pediatric Cardiac Arrest (THAPCA) trial, 295 comatose children were randomized within 6–8 h of return of spontaneous circulation after cardiac arrest to either a target temperature of 33.0 for 48 hours vs. 36.8. I am not sure if it is important but in this study normothermia was also controlled for 5 days after the injury or 36.8 °C [5]. In this study, which first published the out-of-hospital cohort, there was no difference in 1-year neurologic function or survival in the hypothermia group vs. the controlled normothermia group. Analysis of the in-hospital arrest cohort and subgroup analysis may provide additional insight data. Hyperthermia should be avoided after cardiac arrest as it increases cellular energy metabolism and release of excitotoxicity chemicals and accelerates apoptotic pathways. In neonates after HIE, the odds of death or disability are increased 3.6–4 fold for each 1 °C increase above 38 °C [70]. Additionally, hypotension and hyperventilation should be avoided in these patients to avoid cerebral hypoperfusion and oligemia.

Stroke

Although more common in the elderly, arterial and venous strokes also occur in neonates, infants, and young adolescents, and result in significant mortality and long-term disability [71]. Overall, the occurrence is at least as frequent as the number of pediatric tumors [72]. Reported incidence is variable, ranging from 0.9 to 13

Table 6.3 Causes of acute ischemic stroke in children [76, 78, 79]

Source	Most common cause	Other potential causes
Cardiac	Congenital heart disease	PFO, MVP, endocarditis
Hematologic	Sickle cell disease	Anemia, antiphospholipid, Protein C and S deficiency, AT III deficiency
Vasculopathy	Focal cerebral arteriopathy of childhood [78]	Moyamoya, traumatic dissection, vasculitis, post-varicella arteriopathy
Metabolic		CADASIL (cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy)
		Fabry disease
		Menkes disease
		Homocystinuria
		Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS)
Illicit drug abuse	Cocaine and methamphetamine	Heroin, marijuana, opiates

cases per 100,000 children [73, 74]. Neonates represent the group at the highest risk, with an incidence for ischemic and hemorrhagic stroke of 1 per 3500, and 1 per 16,000 live births respectively [73, 75]. Whereas in adults ischemic stroke is more common, hemorrhagic stroke is more equally distributed in children due to the higher prevalence of vascular malformations.

Common causes of acute ischemic stroke in children include embolic sources from congenital cardiac defects, sickle cell disease, and head and neck infections (Table 6.3). Venous strokes can be due to dehydration, infection, and hyperosmolar states. Etiology varies again in young adults, with vasculopathy, cardiac defects, smoking, pregnancy, drug use, hypercoagulable states, and premature atherosclerosis among the most common [76]. Hemorrhagic strokes are most commonly due to arteriovenous malformations, cavernomas, tumors, and coagulopathy [77].

Clinical Presentation

Diagnosis of stroke in children is frequently delayed, with an average time to establish a diagnosis of >24 h [80–82]. The delay in diagnosis may be related to the community misperception that children are not at risk for strokes and that pediatric patients are likely to manifest more subtle non-focal signs such as seizures or altered mental status [83]. Also, a low clinical suspicion for acute ischemic stroke by healthcare providers plays an important role in the diagnostic delay as stroke symptoms are often attributed to other more common diagnoses [84]. Even with more classic signs such as hemiparesis and aphasia, presentation to a tertiary pediatric facility is delayed; advanced stroke centers and evidence based protocols are lacking for children. Whereas in neonates seizures often are the presenting symptom, the most common clinical presentation of stroke in older children is hemiparesis, with the middle cerebral artery territory being most frequently affected [85].

Evaluation and Management

Neuroimaging is a cornerstone of stroke diagnosis in children. CT is no longer recognized as the gold standard initial test in children. Current United Kingdom guidelines recommend performing MRI as soon as possible after admission, as MRI is more sensitive than CT in detecting ischemic stroke [86]. Also, MRI will help differentiating clinical conditions mimicking stroke (migraine, seizure, encephalitis, other intracranial lesion) which may be seen in a significant proportion of patients.

As stroke etiology in children can encompass a broad spectrum of conditions, beyond a general laboratory and toxicology screens, patients should be evaluated for hypercoagulable states (i.e. Protein C and S deficiency, homocysteine, Lupus, Factor V Leiden), intracardiac lesions, vasculitis, and mitochondrial disorders.

Pediatric stroke management closely follows the guidelines adapted for adults (https://www.rcplondon.ac.uk/sites/default/files/documents/stroke-in-childhood-guideline.pdf) [87]. However, anticoagulation and thrombolysis therapy may differ. Currently, alteplase (rt-PA) is not FDA approved for use in children less than 18 years of age with ischemic stroke, and endovascular thrombolysis/mechanical thrombectomy are not routinely used in children <14 years of age [88]. For adolescents >15 years, thrombolytic use should be considered on an individual basis. Now in 2015, with 5 prospective randomized trials [89] demonstrating the superiority of stent-like retrievers over intravenous rt-PA in improving the outcome of adults with acute large vessel stroke, the application of mechanical thrombectomy to pediatric acute ischemic stroke is likely to expand.

Currently, there are no trials showing the efficacy of anticoagulation or antithrombotic therapy in children with acute arterial ischemic stroke. The American Heart Association considers reasonable the use of LMWH or unfractionated heparin until full work-up is completed [88]. The Royal College of Physicians recommends the use of aspirin as initial therapy (https://www.rcplondon.ac.uk/sites/default/files/documents/stroke-in-childhood-guideline.pdf) (Table 6.4).

Intensive care unit management of pediatric stroke patients largely follows adult treatment goals. Intubation is instituted for airway protection due to depressed level of conciousness or for maintenance of oxygenation and ventilation. Euvolemia and adequate mean arterial systemic pressure should be maintained. Anticonvulsant medications may be considered in individual cases, and patients should have their temperature controlled to prevent fever. Depending on the stroke etiology pediatric neurosurgery, neurology and neuro-interventional radiology consults may be required. Management of intracranial hypertension may require ICP monitoring, sedatives, hyperosmolar therapy and barbiturate therapy. Decompressive craniectomy is reserved for children presenting with large stroke(s) involving the middle cerebral artery territory causing malignant (i.e., life threatening) cerebral edema with intracranial hypertension, midline shift, and decline in neurologic exam [90].

Table 6.4 Recommendations vary for management of specific causes of ischemic stroke

Cause	Royal college of physicians[a]	AHA [88]	American academy of chest physicians [87]
Unknown etiology	Aspirin 3–5 mg/kg	UFH or LMWH (1 mg/kg every 12 h) up to 1 week until cause determined	UFH or LMWH or aspirin until cardioembolic and dissection sources are excluded
Cardiac source *(Embolic, arterial dissection, hypercoagulable state)*	Individualized based on provider expertise	Goal directed therapy towards specific cardiac pathology	LMWH for >6 weeks *Cervical arterial dissection:* UFH or LMWH as a bridge to oral anticoagulation
Sickle cell disease	Exchange transfusion to HbS <30 % of total Hgb	Hydration, correction of hypoxemia and hypotension Exchange transfusion to HbS <30 %	Intravenous hydration and exchange transfusion to HbS <30 %

Recommendations [87, 88] based on source of stroke
NS normal saline, *PFO* patent foramen ovale, *MVP* mitral valve prolapse
[a]https://www.rcplondon.ac.uk/sites/default/files/documents/stroke-in-childhood-guideline.pdf

Status Epilepticus (SE)

SE is one of the most common pediatric neurologic emergencies. Traditionally, SE is defined as a seizure that lasts more than 30 min, or occurs frequently enough that the patient does not recover consciousness in between episodes [91]. However, some experts suggest that SE definition should include those patients with seizures lasting more than 5–10 min [92], as the risk for a worse outcome and the potential for seizures to be refractory to anti-seizure medications increases with longer ictal duration [93].

The highest incidence of SE is observed during the first year of life due to febrile seizures [94]. Risk factors identified with recurrent SE are symptomatic established epilepsy [91], young age at onset, and genetic syndromes (i.e. Angelman syndrome, Dravet syndrome) [95]. SE may also be the manifestation of metabolic abnormalities, CNS infections, tumors, illicit drug abuse, hypoxic-ischemic injuries, child abuse, heat stroke, TBI and fever, among others [94].

Of great importance is to diminish secondary complications associated with SE, including hypoxia, acidosis, myoglobinuria, hyperkalemia, intracranial hypertension, and hemodynamic instability [96]. SE can be fatal in some cases, accounting for mortality close to 10 % [95, 97–99]. Long-term outcomes depend on the underlying cause, the duration of event, and the child's age [98].

Management

In patients with epilepsy, it is crucial to know the response to previous antiepileptic drugs to guide the treatment approach, and to obtain a focused history from parents or caregivers. Common causes for SE in children are intercurrent infection, recent changes in medications, missed medications, or inadequate antiepileptic medication dosing. The approach should include an assessment of respiratory and circulatory status, intravenous access, and neurologic examination to determine type and possible precipitants. Laboratory workup should include screening for infection, level of current AEDs, sodium, and glucose levels. Neuroimaging studies (CT and/or MRI) are used to exclude other pathologies (such as hematoma, tumor, or stroke) and should be used in patients who have new onset SE, focal neurologic deficits or have not responded to initial therapy by regaining consciousness. Continuous video EEG may also be appropriate for SE management for patients with persistent encephalopathy, especially if the child's neurologic status is impaired beyond baseline making clinical correlation difficult or for assessment for non-convulsive SE.

Pharmacologic management is based on the guidelines published by the Neurocritical Care Society in 2012 [100]. Benzodiazepines (lorazepam, midazolam, or diazepam) are first-line treatment as they can quickly achieve seizure control. If seizures persist for 10 min after at least 2 doses of BDZ, fosphenytoin should be loaded at a dose of 20 mg/kg IV. If seizures persist, a third-line drug is initiated (phenobarbital, valproic acid, levetiracetam, lacosamide) and placement of a secure airway should be considered. For refractory SE (RSE) cases not responsive to standard therapies treatment options are multiple. Intravenous anesthetics are administered with continuous EEG guidance. Intravenous infusions of midazolam at high doses may be used to achieve seizure control; or pentobarbital infusion to produce burst-suppression pattern. Severe hypotension and or respiratory depression may occur with initiation of IV infusions requiring mechanical ventilation or vasopressor support, thus airway and continuous hemodynamic monitoring should be available when starting these therapies. After 24-48 h of seizure control, the infusion is slowly titrated to off (over many hours) and the patient is monitored for seizure recurrence. Ketamine infusions have been reported in small case series to be effective in RSE in children who failed to respond to barbiturate therapy [101]. Propofol is infrequently used in pediatrics, due to the risk of propofol infusion syndrome [102].

Multimodal Cerebral Monitoring

A fundamental goal of neurocritical care is to prevent the development of secondary neurologic injury after the initial (and typically irreversible) cerebral insult. In the brain-injured child multiple physiologic parameters need to be simultaneously managed and optimized in order to achieve the best posible outcome. In addition to standard physiologic monitors (pulse oximeter, EKG, blood pressure), patients with neurologic conditions frequently require specific cerebral monitoring to avoid and promptly recognize the occurrence of secondary injuries. Such monitors include ICP measurement devices (Fig. 6.2), measures of global and regional cerebral

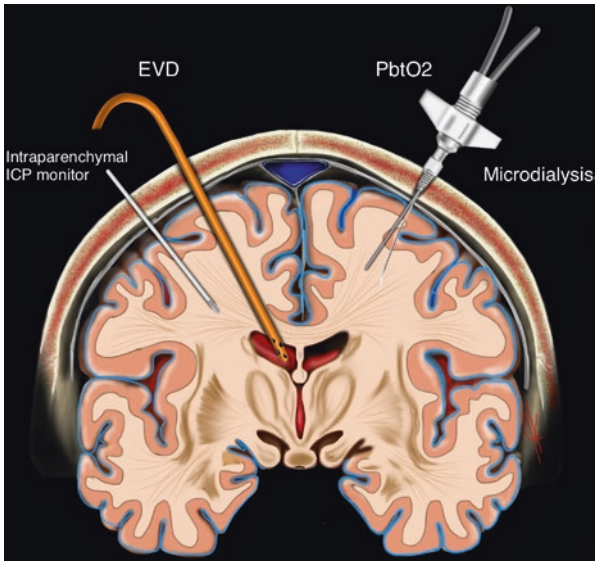

Fig. 6.2 Diagram demonstrating multimodal monitoring

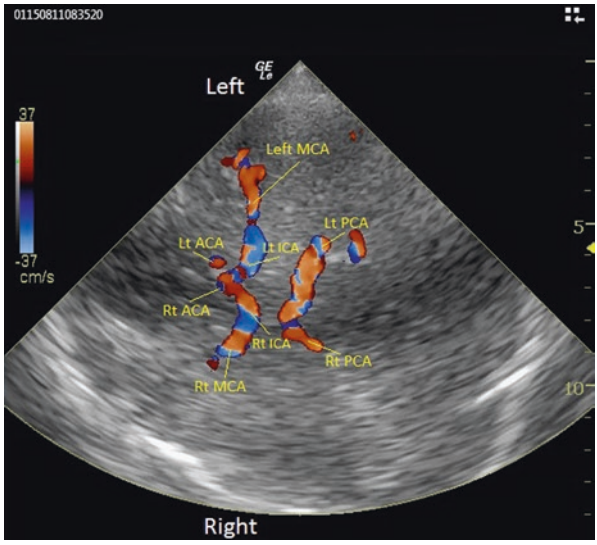

Fig. 6.3 Circle of Willis defined by color-coded transcranial Doppler ultrasound

oxygenation [near infrared spectroscopy (NIRS), jugular venous oxygen saturation ($SjvO_2$), or partial brain tissue oxygen tension ($PbtO_2$)], measures of cerebral metabolism (cerebral microdialysis), continuous EEG monitoring (discussed above), transcranial Doppler ultrasound (Fig. 6.3), and cerebral blood flow (CBF) measurements [103]. Multimodal neuromonitoring involves understanding not only displayed numbers, but also data acquisition, informatics challenges, device interoperability-related issues, and longitudinal data analysis, among others. Observational

studies suggest that multimodal neuromonitoring provides accurate and unique information when used to individualize management of severe head injured patients. Clinical outcome data are sparse.

Partial Brain Tissue Oxygen Tension ($PbtO_2$)

$PbtO_2$ can be measured by inserting an oxygen electrode into the brain parenchyma. Cerebral blood tissue oxygen tension is continuously measured and threshold values for treatment are generally to maintain $PbtO_2 > 15–20$ mmHg [11, 104]. Most of the current pediatric data is focused on TBI, however, there are some other potential applications for this technology including pediatric stroke, and management of cerebral edema during diabetic ketoacidosis [105, 106]. Low levels have been associated with poor outcomes after TBI [107].

Jugular Venous Oximetry ($SjvO_2$)

Through retrograde cannulation of the internal jugular vein, $SjvO_2$ can be measured at the level of the jugular bulb. Normal values in adults are considered to be between 55 and 75 mmHg [108]. There is limited evidence for the utility of its use in pediatric or adult population.

Cerebral Microdialysis

Cerebral microdialysis allows the determination of the metabolic state of the brain. An intraparenchymal probe is inserted into the brain tissue to determine levels of extracellular pyruvate, lactate, glucose, glutamate, and glycerol [109]. In adults, elevation of lactate, and/or a lactate:pyruvate ratio >40, are suggestive of anaerobic metabolism which could exacerbate secondary cerebral injury [110]. Currently, there is limited evidence for its application in children. A small pilot study by Richards et al., in 2003, showed that decreased glutamine:glutamate ratio could be an outcome predictor after brain injury [111]. Overall, its current use can be considered experimental [112].

Thermal Diffusion Cerebral Blood Flow and Cerebral Oximetry

Point-of-care continuous cerebral blood flow monitoring at a regional (such as lobar) or *global* level is a holy grail in neurocritical care but beyond currently available technology. Quantitative CBF can be obtained with CT perfusion, MR perfusion, or positron emission tomography (PET), but not in a frequent or continuous manner that would allow titration of hemodynamic and intracranial pressure therapies. *Focal* cerebral blood flow can be monitored continuously with thermal diffusion technology using a parenchymal probe inserted through a cranial bolt. However, whether such data allows optimization of outcome, or simply exposes the patient to added risk, requires further study. Trancutaneous near-infrared cerebral oximetry can be used to monitor cerebral oxygen saturation in a continuous manner in the intensive care unit. While new monitors are being developed, data to support widespread use in neurocritical care is very limited [103].

Transcranial Doppler Ultrasound

Doppler ultrasound (typically 2 MHz) insonated through the temporal bone 'windows', foramen magnum, and orbits can be used to assess cerebral blood flow velocity and direction. Coupled with B-mode sonography, transcranial Duplex can be performed (Fig. 6.3) in order to obtain some information regarding vascular anatomy [103]. TCD is routinely used for vascular screening in sickle cell disease but has not seen widespread adoption in pediatric neurocritical care; however, it is extremely low risk and can be used to assess pediatric cerebrovascular disease including vasospasm, TBI/post-traumatic vasospasm, and for the assessment of cerebral blood flow (ie, global oligemia vs. hyperemia) [113, 114].

Conclusion

In summary, pediatric neurocritical care is an emerging field in which providers must be able to integrate multiple neurologic specialties in the care of the brain-injured child. Neurologic injury and disorders are common in the PICU, representing approximately 20% of all admissions, and are associated with a longer length of stay and higher mortality than general ICU patients [1, 115]. Pathways into pediatric neurocritical care are less established than adult neurocritical care programs and need to be matured. Finally, an ever expanding evidence base, both for neurocritical care pharmacotherapeutics and advanced cerebral monitoring technologies, is shaping the field and will warrant the need for increased numbers of subspecialized pediatric neurointensivists.

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Pediatric Neurovascular Imaging (CT/MRI/Ultrasound)

7

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Abbreviations

2D	two dimensional
3D	three dimensional
ACA	Anterior cerebral artery
ADC	Apparent diffusion coefficient
ASL	Arterial spin labeling
AVM	Arterio-venous malformation
CBF	Cerebral blood flow
CBV	Cerebral blood volume
CE-MRA	Contrast enhanced magnetic resonance angiography
CNS	Central nervous system
CSF	Cerebrospinal fluid
CT	Computed tomography
CTA	Computed tomography angiography
CTV	Computed tomography venography

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A. Agrawal, G. Britz (eds.), *Pediatric Vascular Neurosurgery*,
DOI 10.1007/978-3-319-43636-4_7

DSA	Digital subtraction angiography
DTI	Diffusion tensor imaging
DVA	Developmental venous anomaly
DWI	Diffusion weighted imaging
ECMO	Extracorporal membrane oxygenation
EDV	End diastolic velocity
FLAIR	Fluid attenuated inversion recovery
ICA	Internal carotid artery
ICH	Intracerebral hemorrhage
MCA	Middle cerebral artery
MELAS	Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes
MMD	Moyamoya disease
MMS	Moyamoya syndrome
MRA	Magnetic resonance angiography
MRV	Magnetic resonance venography
MRI	Magnetic resonance imaging
MTT	Mean transit time
PC	Phase contrast
PSV	Peak systolic velocity
PWI	Perfusion weighted imaging
RI	Resistive index
US	Ultrasonography
SAH	Subarachnoid hemorrhage
SCD	Sickle cell disease
SNR	Signal to noise ratio
STOP	Stroke Prevention in Sickle Cell Disease
SVT	Sinovenous thrombosis
SWI	Susceptibility weighted imaging
TAP	Time average maximum mean velocity
TOF	Time of flight
TTP	Time to peak
VGAD	Vein of Galen aneurysmal dilatation
VGAM	Vein of Galen aneurysmal malformations

Introduction

Many intracranial vascular lesions that are seen in adults are also encountered in children. However, the incidence of lesions, clinical symptoms, imaging presentation and especially the behavior may differ significantly [28]. Hemorrhages in intracerebral cavernous angiomas, for example, are more likely in children than in adults [58]. In addition, several vascular lesions are unique to the child's age. Vein of Galen aneurysmal malformations (VGAM) are typically diagnosed in the neonatal

period [5]. Moreover, vascular malformations may interfere with the normal anatomical and functional development of the central nervous system (CNS).

Neuroimaging plays a key role in the early, sensitive and specific diagnosis of intracranial vascular lesions. Nowadays, a large "toolbox" of various neuroimaging diagnostic tests is available to the clinicians. Depending on the age of the child, clinical presentation, urgency, location, and availability, ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MRI) or digital subtraction angiography (DSA) may be used [28]. The goal of each neuroimaging study is to obtain as much detailed and specific information as possible using the least invasive diagnostic technique. The collected information is used to make decisions about treatment options, monitor progression of disease or success of intervention, predict outcome, and counsel patients and their parents.

In this book chapter, we aim to (1) review the currently available non-invasive "toolbox" of neuroimaging techniques to evaluate intracranial pediatric vascular lesions and (2) summarize the neuroimaging findings of the most common vascular lesions of the pediatric brain.

Neuroimaging Techniques

Various non-invasive techniques are currently available to study the pediatric brain. They may be classified based on (1) the technique used to generate tissue contrast, US (ultrasound waves) versus CT (X-ray attenuation) versus MRI (T1 and T2-relaxation times) or (2) the character of information that is obtained. US, CT and MRI may provide purely anatomical images next to functional maps that localize functional processes in two-, three- or four-dimensional space. The functional data may be related to blood flow (Duplex sonography and MR-angiography (MRA)), blood products (susceptibility weighted imaging (SWI)), brain perfusion (resistive index of major brain vessels and perfusion weighted imaging (PWI)) or diffusion within the brain (diffusion weighted or tensor imaging (DWI/DTI)). The anatomical and functional techniques are complimentary, not competitive. Frequently, the initial diagnostic work-up starts with US or CT followed by MRI with MRA, PWI or DWI as second line neuroimaging techniques. DSA is usually considered if the US, CT or MRI findings do not explain the neurological presentation or if an interventional neuroradiological procedure is planned.

Ultrasonography

Ultrasonography (US) is limited to the first months of life while the cranial fontanelles are open and can be used as acoustic windows to the cranial vault [49]. Based on the different acoustic impedance of the brain structures (gray matter, white matter, cerebrospinal fluid within the ventricles) high resolution images are generated typically in the coronal and sagittal planes. The diagnostic quality and accuracy depends on various factors including the use of an up-to-date, state-of-the-art

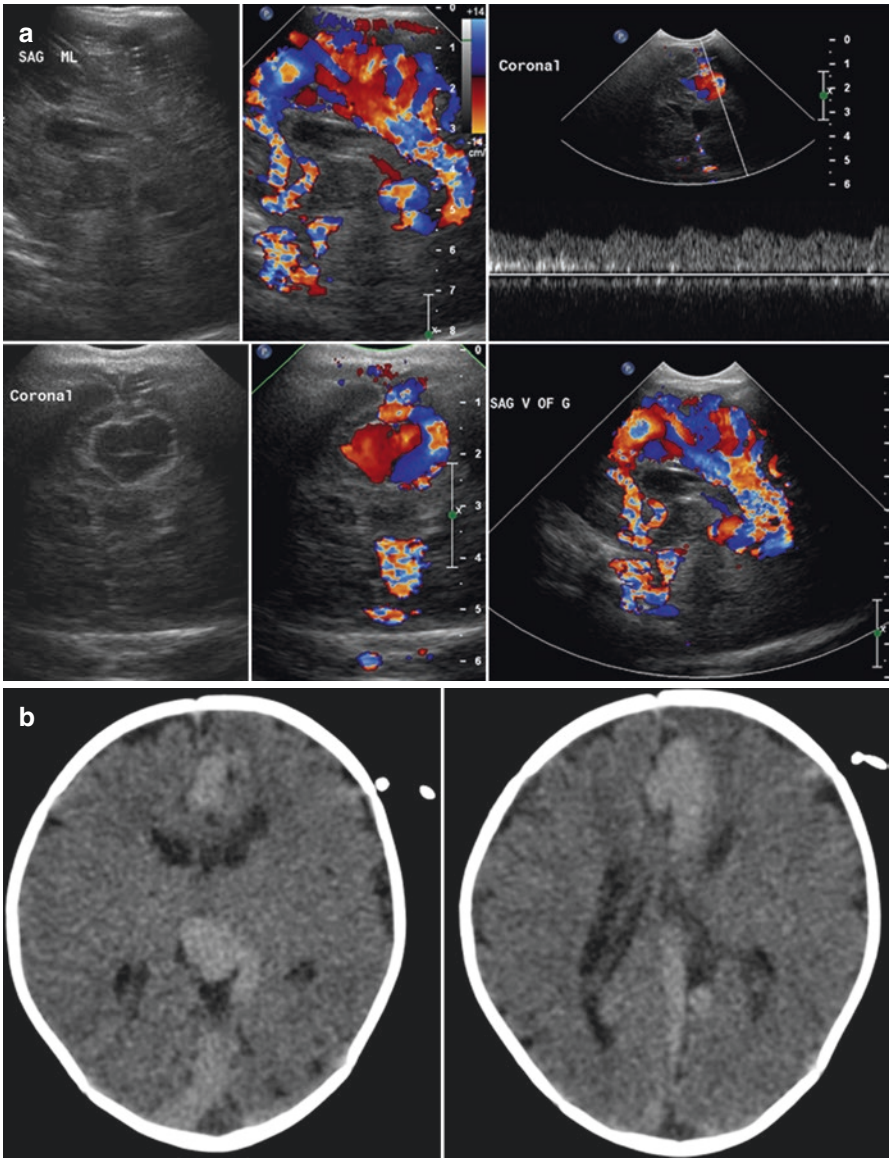
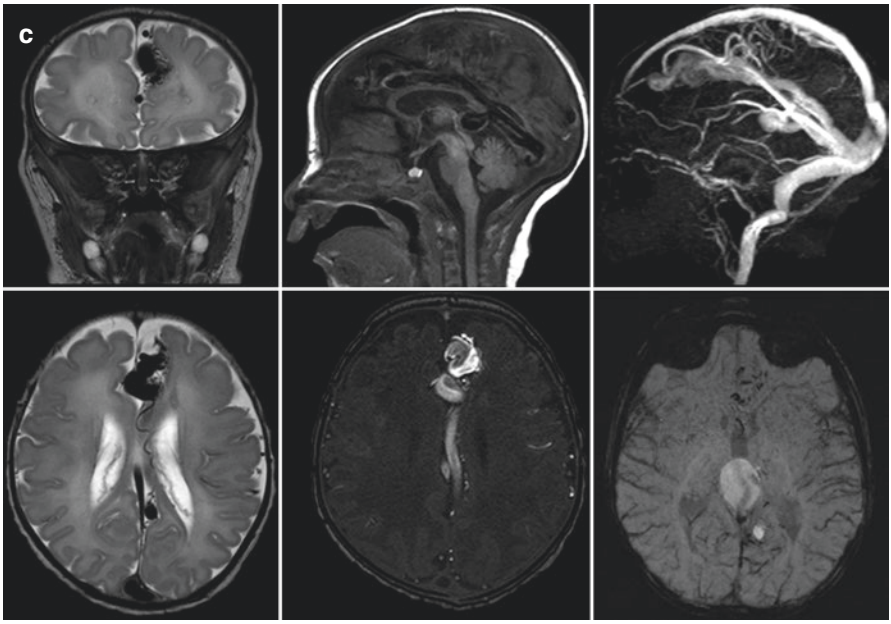


Fig. 7.1 One-month-old girl with a complex left frontal parasagittal arteriovenous fistula with multiple large feeding arteries and diffuse moyamoya like collateral supply. Direct arteriovenous shunting into an enlarged midline supracallosal vein, which drains into an aneurysmally enlarged vein of Galen. Sagittal and coronal US images including color-coded duplex sonography (**a**) reveal a significantly dilated anterior cerebral artery, which drains into a dilated vein of Galen. Significant turbulence and a propagated arterial waveform are noted within the vein of Galen. Axial non-contrast enhanced CT (**b**) shows the mildly hyperdense, elongated and tortuous draining vein within the midline. No intracranial hemorrhage or focal stroke is seen. Multi-sequence MR (**c**) including coronal and axial T2, sagittal T1, axial source MRA, sagittal MIP MRV, and axial SWI MR images allow to localize and characterize the vascular malformation in detail. Coronal and sagittal MRA and contrast enhanced dynamic MRA and MRV (**d**) display the various feeding arteries and draining veins. The 3D TOF MRA shows the arterial side in detail, the contrast enhanced MRA and MRV show the draining veins in better detail. Both studies are complementary. Conventional DSA in lateral and anterior-posterior projection (**e**) confirm the complex angio-architecture of the vascular malformation as seen by MRA and MRV



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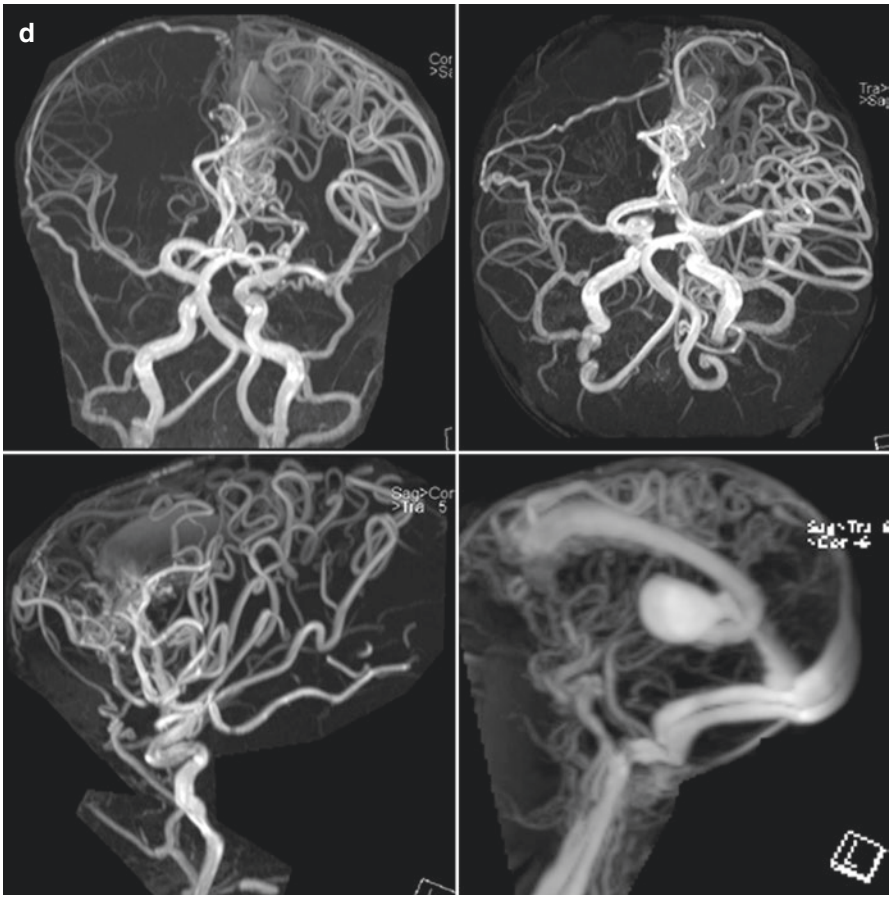

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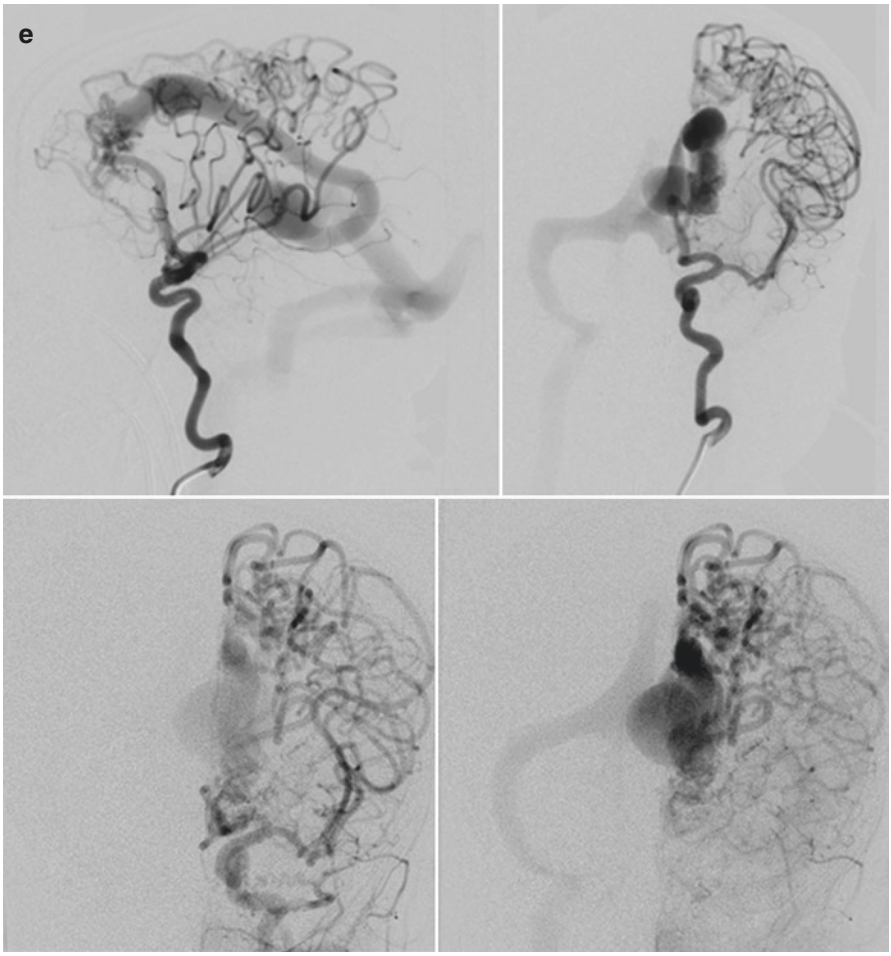


Fig. 7.1 (continued)

equipment, a meticulous scanning technique with optimized imaging settings and high resolution, multi-hertz US transducers, and last but not least, an expert investigator who is familiar with neonatal brain pathologies [14, 37]. In addition to the anatomical information, Doppler US techniques with simultaneous color and spectral Doppler interrogation of the major cerebral arteries and veins render valuable functional, hemodynamic information (Fig. 7.1) [39]. Spectral analysis of the arterial flow signals allow quantifying the peak systolic velocity (PSV), end diastolic velocity (EDV), and time average maximum mean velocity (TAP). In addition, a resistive index (RI) can be calculated (RI = PSV-EDV/PSV) which gives important functional information related to brain autoregulation, brain edema, and intracranial pressure. For term neonates the normal RI ranges between 0.65 and 0.75 while premature infants have a slightly higher RI value (0.77) [74]. By the age of 2 years the

RI value decreases and ranges between 0.43 and 0.58 [14, 37, 39]. Decreased RI values are seen in brain edema. A relative increase in the EDV may result from a loss of autoregulation or a compensatory response to hypoperfusion and/or hypoxia [14]. An increased RI is usually due to a reduction in EDV secondary to an increased intracranial pressure. Color-coded Doppler sonography is especially helpful in the non-invasive bedside evaluation of a neonate with a VGAM. The angioarchitecture of the VGAM can be evaluated with depiction of the dilated feeding vessels and the enlarged vein of Galen. Furthermore, the degree of brain edema, hydrocephalus, and possible thrombosis can be assessed. Color-coded Doppler sonography may be used to evaluate the success of neuro-interventional treatment [39]. Color-coded Doppler sonography can also detect presence or absence of venous flow within the major venous sinuses. Venous sinus thrombosis may be caused by dehydration, coagulopathy, infection, or arterio-venous malformations (AVM) [39].

Computed Tomography

Computed tomography (CT) is usually used as the primary neuroimaging modality of choice in children with acute onset of neurological deficits to rule out acute focal hemorrhage or ischemia (Fig. 7.1) [25]. CT is also used as a screening imaging modality in children with various minor or major neurological disorders. The current generation of high-speed multislice, dual source CT scanners allow examining the pediatric brain in seconds, frequently obviating the need for sedation in young children. Non-contrast enhanced CT is sufficient to identify most intracranial vascular lesions and their complications (Fig. 7.1). Intracranial hemorrhages appear as focal mass lesions with evolving densities depending on the age of the hemorrhage [25]. Cerebral ischemic stroke typically presents as a focal area with reduced density and, depending on the size and age of the ischemia, with different degrees of mass effect [73]. Occasionally a hyperdense intravascular thrombus is encountered. CT may also be helpful to identify intracranial calcifications. The sensitivity and specificity of CT can be further increased by the simultaneous injection of intravenous contrast agents. Vascular lesions including arterial aneurysms, cavernomas, developmental venous anomalies (DVA), and AVM can be evaluated in better detail after injection of contrast. Three-dimensional (3D) reconstructions of the 3D-data sets are particularly helpful to understand better the angio-architecture of vascular lesions and their relation to the intracranial vasculature. High-end post-processing programs allow arterial (CT-angiography, CTA) and venous (CT-venography, CTV) reconstructions with subtraction of the overlying, obscuring bony structures (Fig. 7.2). In addition to anatomical data, high-speed CT scanners can also acquire functional data like brain perfusion. However, high-end CT applications result in a substantial radiation dose to the brain limiting their use in children. The pediatric brain and eye lens are more sensitive to ionizing radiation compared to adults. Consequently, MRI should be considered as an important alternative for the primary, but particularly for the secondary detailed anatomical and functional work up of complex intracranial vascular lesions.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) revolutionized the non-invasive diagnosis of intracranial vascular lesions [28]. MRI provides non-invasively, multiplanar two- and three-dimensional (2D/3D) anatomical and functional data (Fig. 7.1). Anatomical MR images are generated based on intrinsic differences in the T1- and T2-relaxation phenomena of different brain tissues, while functional sequences are based on various physiological and functional processes like intracranial blood flow (MRA/MRV), diffusion (DWI/DTI) or perfusion (PWI). Because MRI does not use any ionizing radiation, it is exquisitely well suited for examining the pediatric patient group.

Conventional T1- and T2-weighted sequences are essential in the anatomical examination of intracranial vascular processes. Intracranial vessels are typically T1- and T2-hypointense due to flow related signal loss (Fig. 7.1). Intravenous injection of gadolinium based contrast agents increases the sensitivity and specificity of conventional MRI sequences. A detailed knowledge of the signal characteristics of intra- and extracranial blood products is essential for the correct interpretation of focal hemorrhages or thrombosis. The signal intensities of intracranial hemorrhages change over time [25]. Different sequences provide different quality of information. Consequently, the pediatric neuroradiologist should use the sequences which best show the extent and characteristics of the studied vascular lesion. In the pediatric brain, high-resolution T2-weighted sequences are particularly helpful to study the anatomical details of the developing brain, anatomical configuration of the vascular lesion, and potential complications such as perilesional vasogenic edema or ischemia. T1-weighted images show best different blood products (intra- versus extracellular meth-hemoglobin, oxy- and deoxy-hemoglobin) and can depict an interrupted blood–brain-barrier after the intravenous injection of gadolinium.

Different "dry" and contrast enhanced (peripheral intravenous contrast injection) MR angiographic techniques are currently available to evaluate the intracranial vasculature [6, 23]. Typically, 2D and 3D angiographic images are generated from 2D or 3D MRA data sets using various post-processing algorithms. The acquired MRA data sets allow the reconstruction and study of the intracranial vasculature from multiple viewing angles without the need for additional measurements (Fig. 7.1). In addition, the post-processing programs allow to "cut away" overlying, obscuring vessels if needed. Depending on the used techniques and applied acquisition parameters, different arterial (MRA) or venous (MRV) "phases" can be acquired. Unenhanced, "dry" MRA techniques rely solely on blood flow related signal variations [6]. Two completely different "dry" MRA techniques are used: Time-of-Flight (TOF) and Phase contrast (PC) MRA/MRV (Fig. 7.3). In the 2D or 3D TOF angiographic techniques, the signal of stationary tissue is suppressed/saturated while the signal of flowing, intravascular blood is preserved. Consequently, on the resulting source images (Fig. 7.3), the brain itself has no or only a minimal MR signal intensity while the perfused blood vessels appear bright with high signal intensities ("bright-blood" MRA). The TOF technique has proven to be robust, provides high quality images of the intracranial vessels, and is considered to be the "work horse" in the MR angiographic evaluation of the brain. PC MRA and MRV belong to the "bright blood" techniques. Typically two data sets are acquired

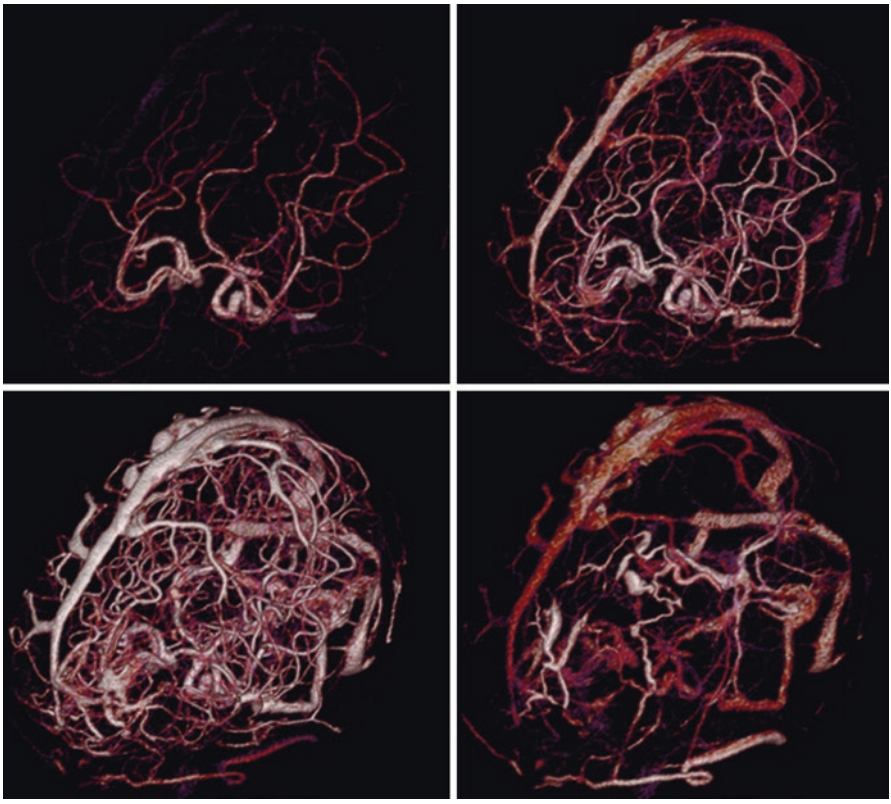
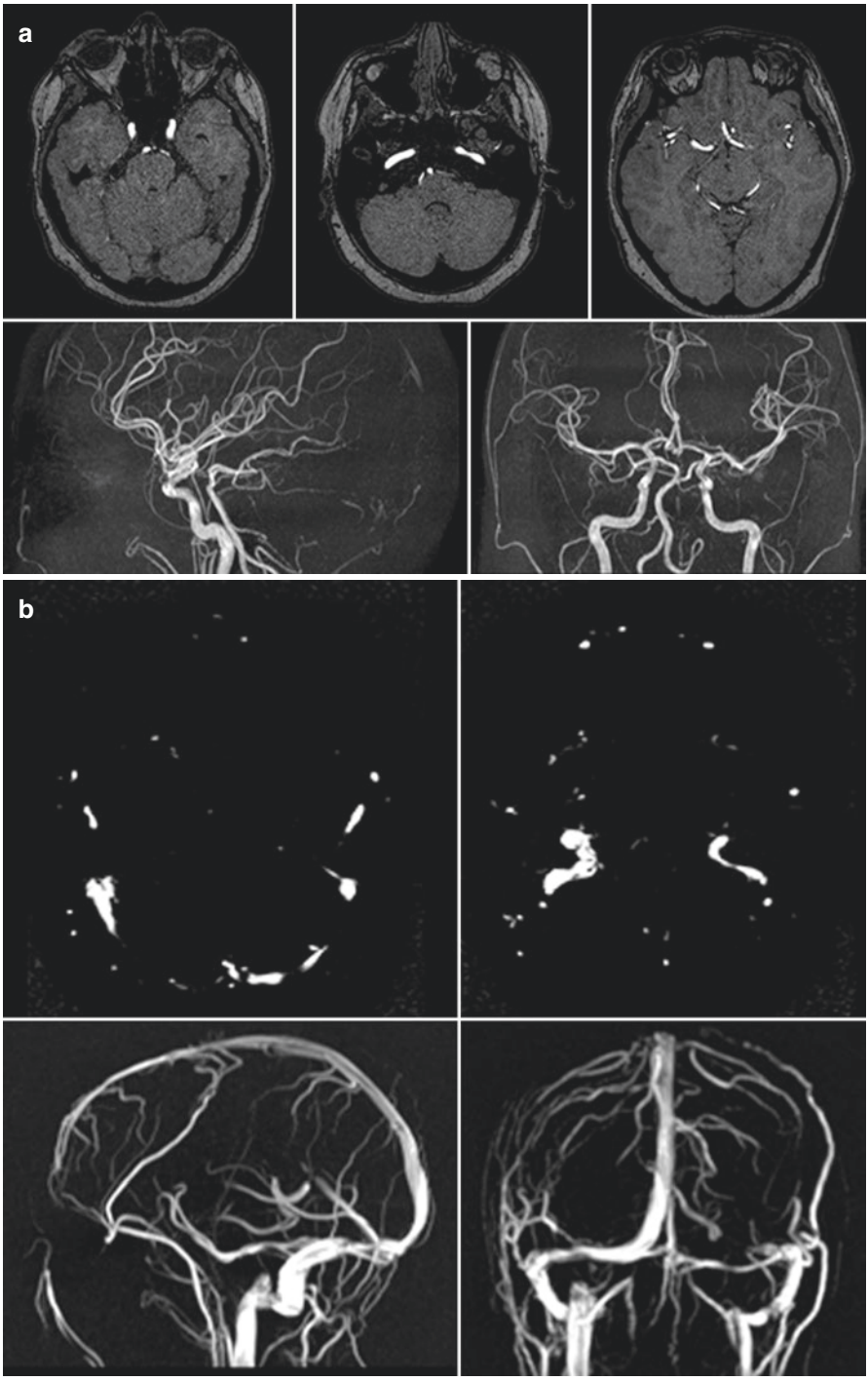


Fig. 7.2 Sagittal oblique multiphase, 3D reconstruction of the cerebral vasculature using a rapid contrast enhanced, 3D volume CT acquisition of the brain. The arterial phase is well separated from the venous phase

(flow rephrased and dephased) and then subtracted. Flow related phase shifts result in a signal increase of the flowing blood in the vessels, while the signal of stationary tissue is effectively suppressed. PC angiographic techniques can be used in a 2D or 3D modus and may be sensitized for different flow velocities (velocity encoding). Consequently, PC-MRA does not suffer from saturation effects like TOF MRA in slow flow lesions (Figs. 7.3 and 7.4). In addition, PC MRA allows absolute flow quantification and measurement of flow direction. Because the acquisition time is longer and the spatial

Fig. 7.3 Axial source 3D TOF and sagittal/coronal MIP MRA images (**a**) are highly sensitive for the anatomical evaluation of the circle of Willis. The signal of stationary brain tissue is suppressed while the signal intensity of the moving blood within the arteries is enhanced. Axial source 2D PC and sagittal/coronal MIP MRV images (**b**) can based upon the selected velocity encoding be optimized for the evaluation of the cerebral veins without the necessity to inject intravenous contrast agents


a
b

resolution is lower compared to TOF MRA, PC-MRA is less frequently used for standard imaging.

Contrast-enhanced MRA (CE-MRA) is a more recent development in which T1-shortening gadolinium based contrast agents are injected intravenously as a bolus during rapid T1-weighted image acquisition (Fig. 7.1) [23]. Bolus tracking techniques allow the imaging of target vessels during their peak contrast filling. For

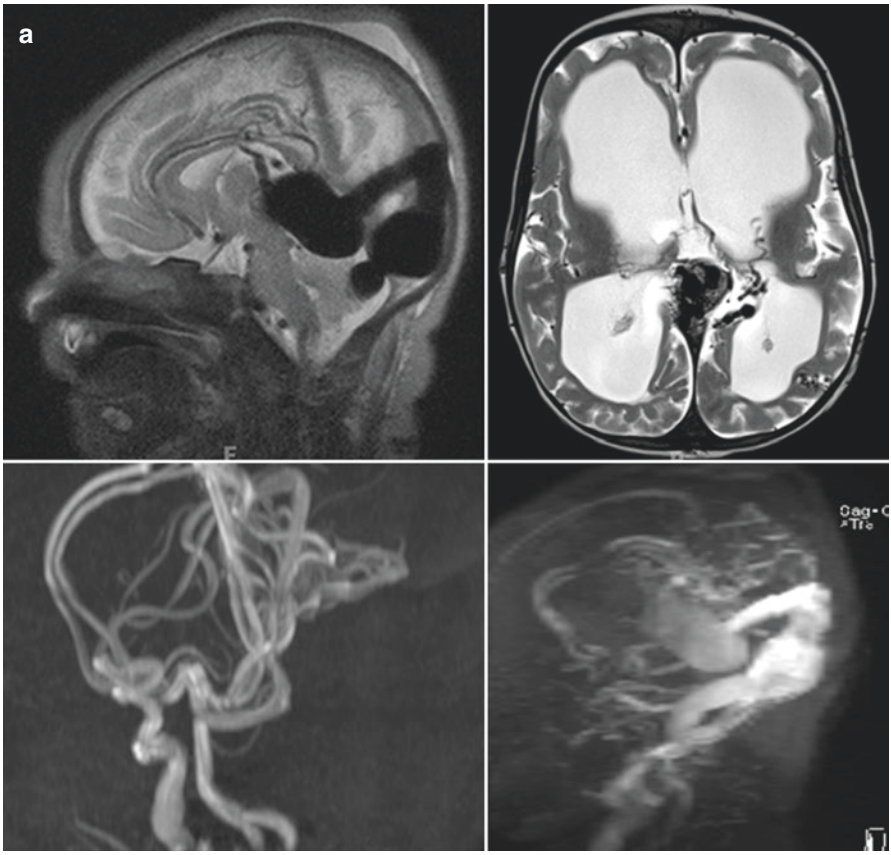


Fig. 7.4 Twenty-day-old boy with a vein of Galen aneurysmal malformation with congestive heart failure. The VGAM is supplied by multiple bilateral posterior medial and posterior superior choroidal arteries. Primary venous drainage over an aneurysmally dilated superior vermian vein into the torcular Herophili. Sagittal and axial T2-weighted MR and sagittal MRA and MRV MIP images (**a**) shows the complex angioarchitecture of the vascular malformation. The veins appear T2-hypointense due to the blood flow related signal loss. Significant periventricular white matter volume loss with enlargement of the ventricles is noted. Color-coded duplex US (**b**) confirm the turbulent flow within the malformation with an arterial waveform within the draining veins. Matching sagittal MRA, contrast enhanced MRA, and DSA (**c**) allow to study the various arterial and venous components of the malformation. The contrast enhanced MRA partially obscures the malformation due to the multiple vessels displayed

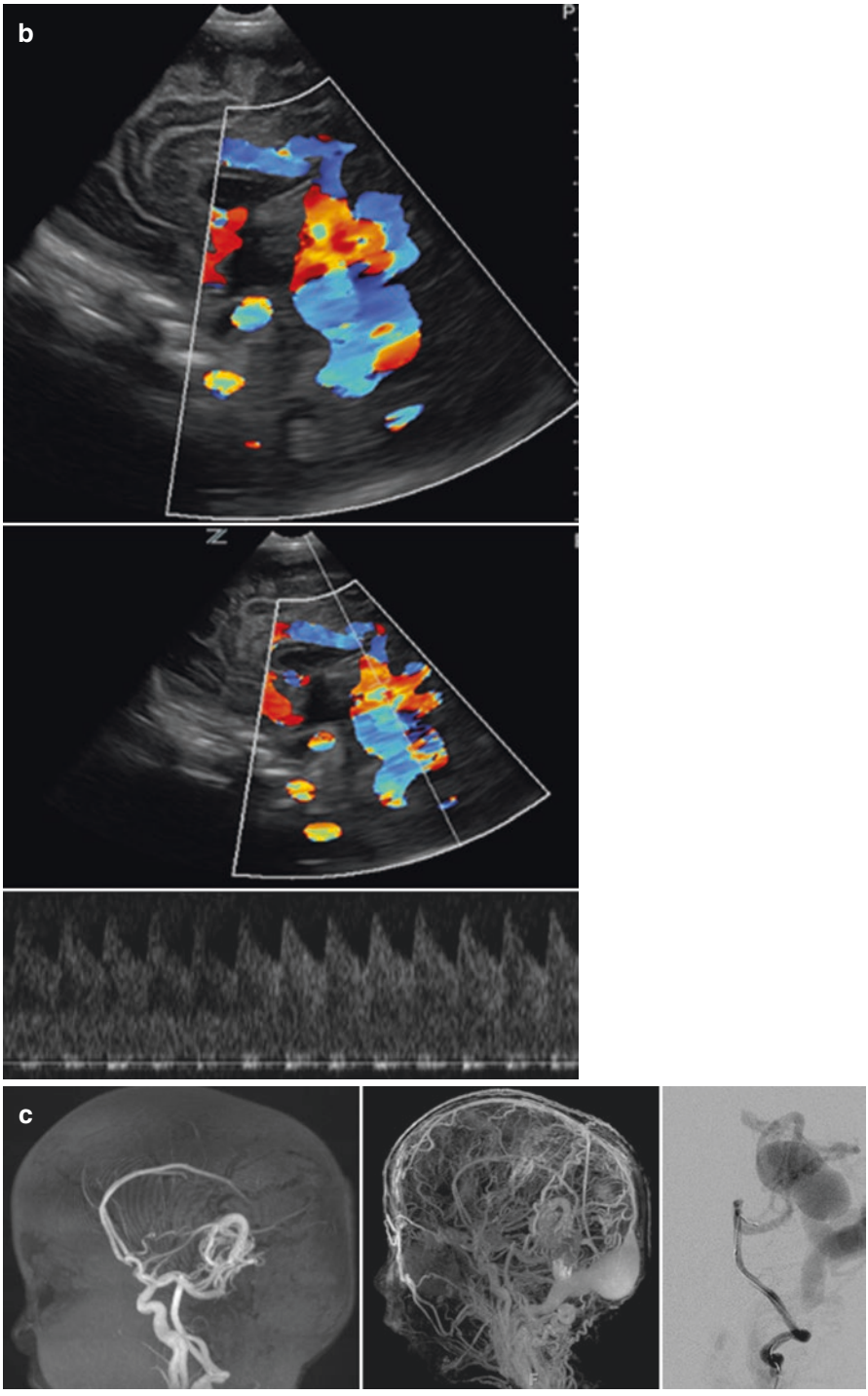


Fig. 7.4 (continued)

arterial phases, the imaging is centered on the period of the arterial bolus passage, while for venous phases, imaging is performed after the contrast has cleared from the arteries. The temporal alignment of maximal intravascular enhancement and rapid image acquisition allows angiographic reconstructions in which veins do not obscure arteries and vice versa. Further soft- and hardware developments allow time resolved imaging in which multiple phases are generated within one acquisition during a single contrast injection (time resolved CE-MRA) [51, 76]. The brain is exquisitely well suited for these contrast enhanced techniques because the blood–brain barrier prevents contrast from leaking into the brain tissue. The disadvantage of this technique is the need for contrast injection, which may be troublesome in young children or in children with sickle cell disease or renal disease.

Finally, one major advantage of MR angiographic techniques is that angiographic images and anatomical images of the brain may be acquired during the same examination. This may allow the localization of vascular lesions with high anatomical accuracy, the identification of vascular lesions that go undetected on MRA (e.g. thrombosed vessels and slow flow lesions like cavernomas), and the detection of vascular-hemodynamic complications such as vasogenic or cytotoxic brain edema, venous stasis, or ischemia.

In addition to anatomical and angiographic MR sequences, non-invasive functional MR sequences may provide important information about the impact of vascular lesions on the brain. DWI and DTI generate tissue contrast based on differences in the diffusion of protons within the brain [24, 27]. DWI with calculation of apparent diffusion coefficient (ADC) maps (Fig. 7.5) allows the differentiation between vasogenic edema (increased ADC values) and cytotoxic edema (restricted diffusion, low ADC values). Vasogenic edema is frequently reversible and may be seen in the periphery of an acute/subacute hematoma, result from the compression of brain tissue by large, adjacent vascular malformations, or occur as a complication from altered brain hemodynamics (e.g. VGAM with venous stasis). Cytotoxic edema is usually irreversible and indicates ongoing ischemic tissue injury, possibly due to chronic hypoperfusion (steal phenomenon in AVM) or thrombo-embolic events. In addition, DWI and DTI may detect a lesion before it becomes apparent on conventional T1- and T2-weighted sequences. DWI and DTI should be part of the MRI protocol to completely and accurately evaluate neurovascular lesions and their impact on the pediatric brain. DWI and DTI play a key role in the early identification of vascular complications and, hence, in the planning and monitoring of treatment.

PWI represents an additional functional sequence, which provides important information about the impact of vascular lesions on brain perfusion [29]. PWI generates multiple hemodynamic maps such as cerebral blood flow (CBF), cerebral blood volume (CBV), mean transit time (MTT) and time to peak (TTP) (Fig. 7.5). Several techniques are currently available to generate these hemodynamic maps. The most frequently used and robust method is the “dynamic susceptibility contrast technique”. This approach uses principles of indicator dilution methods in which a decrease of T2 or T2* MR signal intensity is related to the passage of paramagnetic gadolinium based contrast derivates through the capillary bed of the brain. The drop

in MR signal intensity is related to brain hemodynamics. Since no blood sampling is performed, the CBF and CBV maps are relative maps (rCBF, rCBV). The second technique is called "arterial spin labeling" (ASL) and relies on the use of inversion pulses that label blood spins before moving into the brain slice of interest [71]. In ASL, the resulting MR signal drop in the brain is directly related to the CBF and CBV. ASL has some important advantages that makes it well suited for imaging children: it does not require injection of contrast media, can be repeated as often as necessary, and allows the study of different vascular territories by selectively labeling separate blood vessels. The low signal-to-noise ratio (SNR) and low flow-related signal drop, however, makes ASL less reliable.

New anatomical and functional MR techniques are continuously being developed. One of the most recent techniques that has proven to be especially helpful in the diagnostic work-up of intracranial vascular lesions is susceptibility weighted imaging (SWI) [10]. SWI is a high-spatial-resolution 3D gradient-echo MR imaging technique with phase post-processing that strongly accentuates the paramagnetic properties of

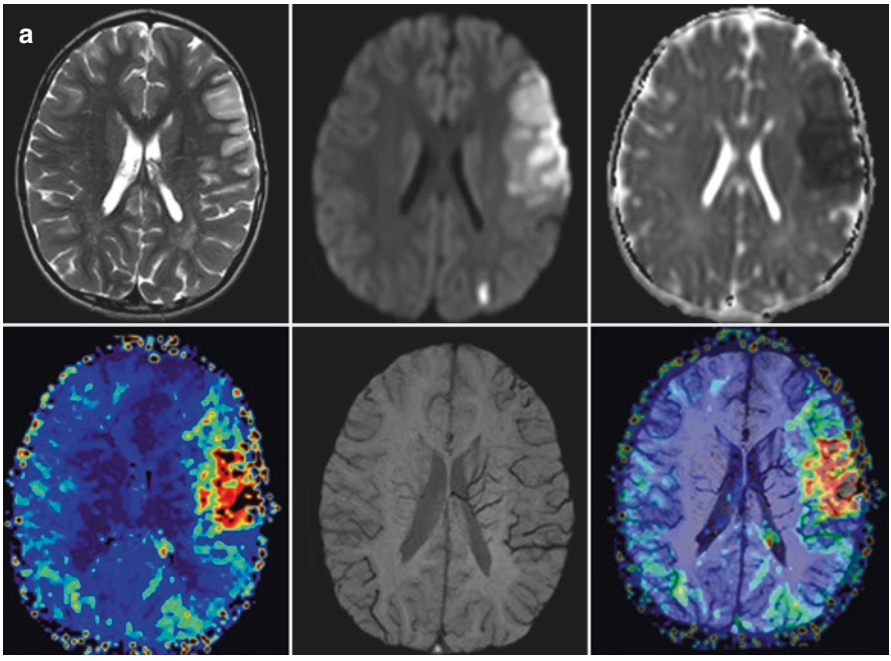


Fig. 7.5 Six-year-old boy with right sided facial weakness, slurred speech and facial droop related to moyamoya vasculopathy. Multisequence anatomical and functional MRI (**a**) reveal a focal area of restricted diffusion (DWI-hyperintense, ADC-dark) with matching area of abnormal perfusion on perfusion weighted MR. The area of restricted diffusion is larger than the area of signal abnormality on the T2-weighted image. Prominent, SWI hypointense veins are noted to drain the ischemic tissue into the deep venous system. The SWI/PWI overlay image combines the information of PWI and SWI. Coronal and axial 3D TOF MRA images and conventional DSA (**b**) show the characteristic bilateral distal internal carotid artery occlusion with "moyamoya" collaterals along the expected course of the lenticulostriate arteries

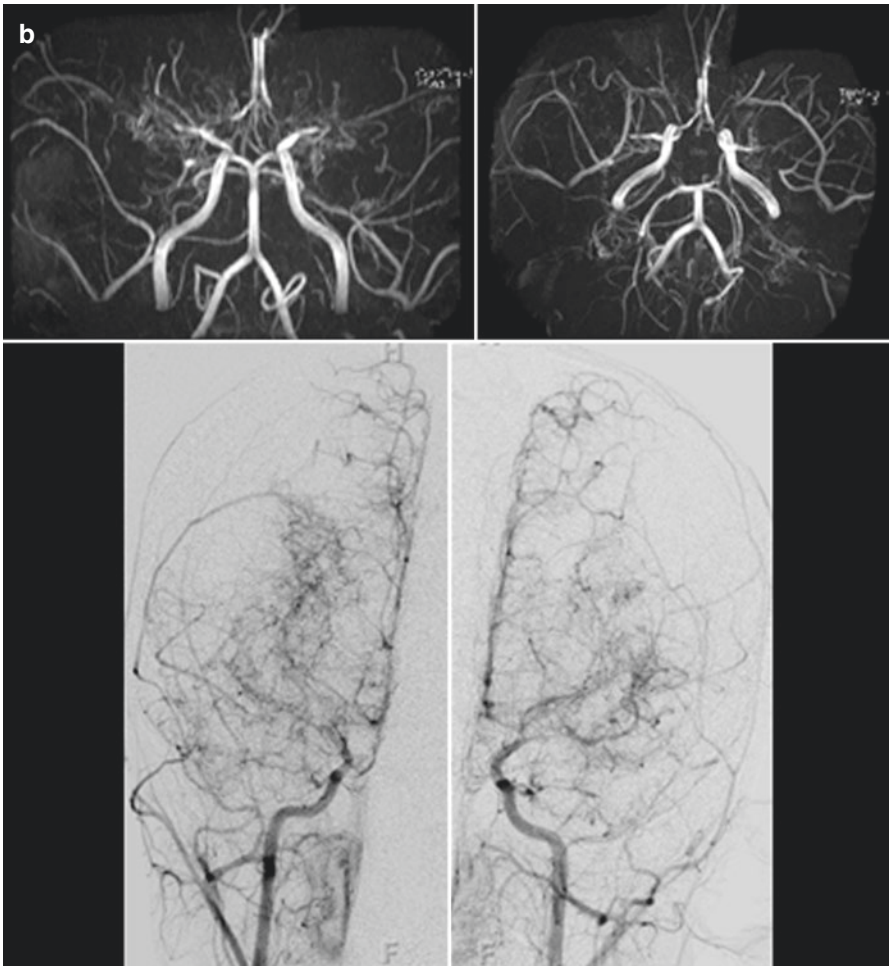


Fig. 7.5 (continued)

blood, blood products, iron, and calcium in the brain. SWI is very sensitive in the detection of intravascular venous deoxygenated blood as well as extra-vascular blood products such as deoxy-hemoglobin, intracellular meth-hemoglobin, hemosiderin, and calcifications (Fig. 7.5). SWI has proven its value in studies of AVM's, cavernomas, pial angiomas in Sturge-Weber syndrome, occult venous disease, trauma, tumors, stroke, and functional brain imaging [10]. It has also been shown to facilitate identification of venous thrombosis [68]. SWI is rapidly becoming a standard sequence in examining intracranial vascular lesions [64, 65].

Next to ongoing MR hard- and soft-ware developments, continuing research in the field of MR contrast agents (e.g. higher concentration, intravascular contrast media) will continue to increase the diagnostic value of MRI/MRA.

Intracranial Vascular Lesions in Children

A wide variety of vascular lesions may be encountered in children. The following paragraphs will discuss the typical US, CT and MR imaging findings of focal ischemia, hemorrhage, and a variety of vascular malformations that can be seen in children including cerebral aneurysm, cavernoma, DVA, and AVM, in particular, VGAM. This book chapter cannot cover the complete range of intracranial vascular lesions in children; consequently, multiple, less frequent pediatric vascular lesions will not be discussed.

Focal Cerebral Ischemia in Children

For many decades ischemic stroke was considered to be rare in children. For clinicians, the recognition of arterial ischemic stroke in children may be challenging: the presentation is varied and nonspecific and encompasses a broad spectrum of differential diagnoses. Acute neurological symptoms caused by arterial ischemic stroke may be incorrectly attributed to other conditions such as migraine or epileptic seizures with which physicians are more familiar [8]. In addition, clinical presentation of ischemic stroke varies with age. Neonates typically present with focal seizures or lethargy, infants tend to present with an early side preference, while later in childhood acute focal neurologic deficits such as hemiparesis or hemiplegia may be observed. This may result in a delayed diagnosis of pediatric arterial ischemic stroke [42, 57]. With continuing technical advances in neuroimaging and increasing clinical awareness, arterial ischemic stroke is being more frequently diagnosed in children [19]. Schoenberg et al showed in a study done in 1978 an incidence of ischemic and hemorrhagic stroke of 2.52 cases per 100,000 children per year [62], deVeber showed an incidence of 3.3 cases per 100,000 children per year in a study performed 2002 [16], while Lynch reported an even higher incidence ranging up to 7.9 per 100,000 children per year in a study done in 2004 [40]. In addition, it became obvious that knowledge collected from adult ischemic stroke cannot be directly translated to children. The etiologies of ischemic stroke differ significantly between children and adults. Most adult strokes result from arteriosclerotic occlusive disease, while in children the causes of ischemic stroke are varied and often multifactorial [41]. In the majority of cases (up to 80 %), a specific cause for the ischemic stroke can be found. Congenital heart disease (embolic infarctions), arteriopathies (infectious and non-infectious arteritis with focal or segmental stenosis), and prothrombotic disorders (inherited or acquired) are the most commonly recognized risk factors in children [41]. In addition, stroke may result from spontaneous (mostly intracranial) or traumatic (mostly extracranial) dissections of arterial vessels [50]. Chabrier reported dissections in 20 % of children with arterial ischemic stroke [11]. Moyamoya vasculopathy and sickle cell disease (SCD) are two other etiologies that may result in chronic, recurrent ischemic infarctions in childhood. Moyamoya vasculopathy is characterized by progressive stenosis/occlusion of the supraclinoid internal carotid arteries (ICA) and proximal anterior or middle cerebral arteries

(MCA) [9]. Moyamoya vasculopathy may be idiopathic (so called moyamoya disease (MMD)) or associated with other clinical conditions and risk factors such as SCD, Down syndrome, neurofibromatosis type 1, and post radiation treatment (so called moyamoya syndrome (MMS)) [12, 63]. SCD is the most common hematologic disorder associated with arterial ischemic stroke in children [66]. Symptomatic and silent strokes result from occlusive vasculopathy with a predilection toward the distal ICA's, proximal MCA's, and anterior cerebral arteries (ACA) [75]. The prevalence of arterial ischemic infarctions has been reported to be 4 % with an incidence of 0.6 per 100 patient years [66]. The Stroke Prevention in Sickle Cell Disease (STOP) trial showed that blood transfusions greatly reduce the risk of arterial ischemic stroke in children who have two abnormal transcranial Doppler US studies, done at least 1 week apart based on the STOP study criteria [35]. Many other, rare disorders may result in pediatric stroke [21]. A detailed clinical work-up and state-of-the-art neuroimaging is needed to identify arterial ischemic stroke as early as possible, rule out potential mimickers such as hemiplegic migraine or mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome, and detect the specific etiology of the stroke.

In children, venous strokes is caused typically by cerebral sinovenous thrombosis (SVT) [15]. In addition, approximately 20 % of ischemic cerebral vascular disease in children is due to SVT with an incidence of 0.67 cases per 100,000 children per year. The majority of SVT cases occur in neonates and infants [15]. Well-known risk factors for SVT in children include head and neck disorders, particularly infections (29 %), acute systemic illnesses such as dehydration, perinatal complications, and sepsis (54 %), chronic systemic diseases such as connective-tissue disorders, cancer, and cardiac diseases (36 %), and prothrombotic states (41 %) [15]. SVT may also result from head trauma with skull fractures that cross dural sinuses. Symptoms can vary from minimal with non-specific symptoms to lethargy and coma [15].

Transcranial US is especially helpful in the neonatal period [49]. Acute ischemia presents as focal hyperechoic areas within the white and gray matter. In addition, mass effect by the ischemic brain tissue may cause effacement of the adjacent sulci and ventricles. On follow-up neuroimaging, the infarcted brain tissue is progressively resorbed, filled with cerebro-spinal fluid (CSF), and, hence, becomes hypoechoic. Color-coded duplex sonography can be especially helpful to rule out SVT [56]. The superficial and deep intracranial veins are easily accessible for color-coded duplex sonography.

CT is frequently used in the acute work up of a child with sudden onset of neurological symptoms. Hyperacute and acute ischemic stroke may be difficult to identify on CT: the lesion may be isodense or slightly hypodense compared to normal brain tissue. Frequently the cortico-medullary differentiation is reduced and the adjacent sulci may be effaced. In the subacute phase, the infarcted brain tissue becomes progressively hypodense and better delineated. Intracortical hemorrhages may be seen as gyriform hyperdense lesions. A hyperdense thrombus may be seen within the affected arterial vessel. In the acute phase, contrast enhancement of the injured brain tissue may obscure depiction. CT is very helpful to rule out intracranial hemorrhage as the underlying cause of the acute neurologic symptoms. CTA

and CTV can depict thrombosed vessels. In moyamoya vasculopathy, the distal ICA's and proximal MCA's may be absent with simultaneous display of multiple collaterals within the basal cisterns [9].

MRI and MRA have proven to be the most sensitive and specific neuroimaging modalities for an early identification of arterial ischemic stroke in children [19]. Acute ischemic stroke typically presents as a T2-hyperintense, T1-iso- or hypointense focal lesion within the vascular territory of one or more intracranial arteries (Fig 7.5). Multiple small lesions may be observed in a thrombo-embolic stroke. In contrast, venous stroke is characterized by areas of signal abnormality that crosses arterial vascular territories. Infarcted brain tissue may show intralesional hemorrhages and contrast enhancement. On follow-up neuroimaging, the ischemic lesion typically becomes CSF-isointense with resolution of the infarcted brain tissue and ex vacuo enlargement of the lateral ventricles. MRA can show a paucity of vessels within the ischemic brain and segmental narrowing or occlusion of the supplying arteries. In moyamoya vasculopathy, multiple T2-hypointense vessels are typically seen within the basal cisterns along the circle of Willis [9]. DWI has revolutionized the imaging of acute arterial ischemic stroke [24]. DWI may detect areas of restricted diffusion/cytotoxic edema within minutes after vessel occlusion, well ahead of any signal abnormality on T1- and/or T2-weighted imaging. This opens up the therapeutic window for early/acute treatment of arterial ischemic stroke. In children, thrombolytic protocols have not yet been as widely established. However, the Chest and American Heart Association guidelines support the use of anticoagulation in acute pediatric arterial ischemic stroke [45, 60] and a prospective treatment trial on thrombolysis in acute pediatric stroke was recently funded by the NIH [59]. On DWI, an acute ischemic stroke is characterized by an area of restricted diffusion (low ADC values) (Fig. 7.5). After 8–10 days, the ADC values typically normalize (pseudonormalization) before they increase above the norm due to progressive tissue loss/disintegration [24]. In venous ischemia, the thrombus within the dural sinuses is frequently seen as hyperintense lesion on DWI with matching low ADC values [68]. However, the neuroimaging appearance of thrombi in SVT is variable and MRI sequences individually are not sensitive enough to provide the diagnosis [68]. DWI has proven to be especially helpful in combination with PWI. By matching the area of signal alteration on DWI with the area of hypoperfusion on PWI, two different compartments of ischemia can be depicted. The area of restricted diffusion, which matches an area of hypoperfusion on PWI, is believed to be the irreversible core of infarction. The area of hypoperfusion, which does not match the area of restricted diffusion, represents the so called penumbra. The penumbra is an area of oligemic brain in which the neurons are still viable, but not functional. The penumbra is considered to be potentially salvageable by e.g. acute thrombolysis. If hypoperfusion persists, however, the core of irreversible tissue injury may progressively extend and grow into the penumbra [29]. Consequently, the combined DWI/PWI information may help in the selection of patients who may benefit from aggressive, thrombolytic or revascularization treatments. In children, however, the routine application of PWI outside research protocols and tertiary care centers is still limited. DSC-PWI requires a rapid bolus injection of intravenous paramagnetic contrast agents that

may delay acute antithrombotic therapy. ASL is a non-contrast-enhanced PWI method capable of measuring tissue perfusion by using blood as an endogenous "contrast" agent. ASL is not routinely performed in the acute setting because of the low signal-to-noise ratio and limited spatial resolution. In addition, changes in signal intensity on ASL may be determined by factors other than reduced flow or ischemia, and knowledge of ASL-related artifacts is crucial for accurate interpretation. Recently, SWI was shown to be a valuable alternative to PWI for the noninvasive evaluation of altered cerebral hemodynamics in children with acute ischemic stroke (Fig. 7.5). The SWI-DTI mismatch has been shown to predict stroke progression in children with arterial ischemic stroke [55]. In addition, SWI has been increasingly shown to detect hemorrhagic components within infarcted tissue with higher sensitivity than other MRI sequences or imaging modalities [72], detect acute occlusive arterial thromboemboli [44, 67], quantify microhemorrhages and predict hemorrhagic transformation before thrombolytic therapy is initiated [4], and detect early hemorrhagic complications after intra-arterial thrombolysis [44].

Intracerebral Hemorrhage

Intracerebral hemorrhage (ICH) is a common cause of death and long-term neurodevelopmental disability in children [38]. The most frequent risk factors for "spontaneous", non-traumatic ICH in children are intracranial vascular anomalies, congenital heart disease, ischemic infarction, and brain tumors. Under intracranial vascular malformations, ICH are most frequently caused by AVM's and cavernomas [13]. Extracorporal membrane oxygenation (ECMO), cardiosurgical procedures, and transplantations are also risk factors for ICH because of the needed anticoagulation. Finally, ICH may be also observed as a complication of arterial and venous ischemic infarctions [70]. High morbidity and mortality results from the fact that in many children ICH are associated with sepsis, leukemia, malignancy, or other systemic diseases. ICH also frequently results from traumatic brain injury [53, 54].

Familiarity with the neuroimaging features of ICH is essential for correct diagnosis. In addition, the exact etiology of ICH has to be determined. The spontaneous evolution of ICH on neuroimaging is complex and may be confusing [25]. ICH follows a well-known evolution including five distinct phases: hyperacute (<12 h); acute (12 h to 2 days); early subacute (2–7 days); late subacute (8 days to a month), and chronic (more than 1 month). US, CT, and MRI appearance vary with the stage of hematoma resolution [25].

Only few studies have systematically studied the evolution of hematomas using US. Exact differentiation between the phases of hematoma evolution is limited. Acute hematomas typically appear as an iso- or hyperechoic focal mass lesion. On follow-up, the retracting hematoma typically becomes progressively centrally hypoechoic with decreasing mass effect. In the chronic stage, the hematoma may dissolve completely, frequently leaving a hypoechoic CSF-filled brain defect [25].

On CT, early hyperacute hematomas are isodense to normal brain. Progressive blood clot retraction increases the density of the hematoma during the acute and

early subacute phases, while progressive red blood cell lyses decreases the hematoma's density in the late subacute phase. Hypodense edema may develop surrounding the hematoma. In the chronic phase, progressive hematoma resorption results in a hypodense, CSF filled brain defect. Intravenous contrast injection may increase the conspicuity of hyperacute isodense hematomas [25].

The complex MRI signal is caused by the MR susceptibility effects of the evolving blood products and the different oxidation states of the iron within the hemoglobin molecule in the hematoma, magnetic field strength, and applied MRI sequence. Hyperacute hematomas are T1- iso/hypointense and T2-hyperintense, acute hematomas are T1-iso/hypointense and T2-hypointense, early subacute hematomas are T1- and T2-hypointense, late subacute hematomas are T1- and T2-hyperintense, and chronic hematomas are T1-hypointense and T2-hyperintense with a T2-hypointense hemosiderin ring. The paramagnetic properties of blood products such as deoxy-hemoglobin, intracellular methemoglobin and hemosiderin are well demonstrated on SWI due to the magnetic susceptibility effects. This makes SWI exquisitely sensitive to identify blood and small blood products. The detectability of microbleeds on SWI is significantly higher compared with T2*-weighted and conventional T1- and T2-weighted MR sequences [4, 46, 48]. Hematomas also follow a well reported temporal evolution on DWI [25]. Transient disruption of the blood–brain barrier causes peripheral enhancement during hematoma evolution [25].

As mentioned previously, neuroimaging should not only detect ICH and the related complications, but also identify the cause of ICH. Contrast enhanced sequences as well as MRA/MRV sequences and various functional sequences may be necessary to exclude AVM's or neoplasms as the underlying cause of ICH.

Cerebral Aneurysm

Pediatric intracranial aneurysms differ significantly in their incidence, location, morphology, etiology, and clinical presentation from adult aneurysms, particularly in the neonatal and infantile period [3]. Overall, intracranial aneurysms are rare in children: less than 5 % of all aneurysms occur in childhood [33]. Children may present with subarachnoid hemorrhage (SAH), mass effect, headache, cranial neuropathy, and, less frequently, seizures or stroke. The reported incidence of findings differs in the literature. In older studies, SAH was the most frequent presentation (up to 70 %) with a decreasing incidence progressively with age [2]. Recent studies showed that children with intracranial aneurysms present more commonly with neurologic deficits with or without infarction (45 %), followed by headaches (33–45 %), and SAH or intracerebral hemorrhage in 27–32 % of children [2, 22]. In the majority of cases, the cause remains unknown. Well described etiologies include trauma (5–39 %), infection (5–15 %), connective tissue diseases such as Ehlers-Danlos syndrome and Loeys-Dietz syndrome, and other disorders including tuberous sclerosis complex and moyamoya vasculopathy [2]. Large autopsy studies showed no evidence for so-called "congenital"

aneurysms [3]. The so-called "idiopathic" aneurysms are classified according to their morphology into saccular or fusiform/dissecting aneurysms. In the pediatric population, dissecting aneurysms are four times more common compared to adults. The location of childhood aneurysms differs significantly from adults. Children aneurysms are five times more common at the level of internal carotid artery bifurcation [20]. In addition, in children the posterior circulation is more frequently involved, while the anterior communicating artery is rarely affected [20]. Moreover, giant aneurysms are four times more frequent in children (incidence between 20 and 45 %) compared to adults. They frequently present with focal neurologic deficit (e.g. cranial neuropathy) due to mass effect [34]. Finally, the simultaneous, "spontaneous" appearance of multiple aneurysms is significantly rarer in children compared to adults.

In pediatric cerebral aneurysms, neuroimaging has multiple roles: identification and characterization (shape, size, location, thrombosis) of the aneurysm, collection of information about the possible etiology, identification of cerebral complications, ruling out of additional vascular lesions or multiplicity of aneurysms, and evaluation of accessibility for neurosurgical or endovascular treatment options [2, 20].

US is of limited value in the evaluation of intracranial aneurysms. CT is frequently the first line neuroimaging in the work-up of children to rule out an aneurysm. The location and distribution of a SAH or ICH may point towards the location of the aneurysm. On postcontrast images, an aneurysm may be hyperdense or isodense due to thrombosis. Dedicated CTA studies may directly reveal the location and shape of the aneurysm. MRI with MRA is however the best non-invasive neuroimaging technique to study intracranial aneurysms and their complications [20]. MRI, MRA, and functional sequences like DWI, SWI, and PWI allow a one-stop diagnosis. Because of flow related signal void, cerebral aneurysms are typically T1- and T2-hypointense (Fig. 7.6). Turbulent flow within larger aneurysms or partial thrombosis may show, however, a heterogeneous MR signal (Fig. 7.7). It may be difficult to distinguish flow related enhancement from partial thrombosis. Accurate correlation of pre- and postcontrast enhanced MR sequences may answer this important question. Pulsation artifacts along the phase encoding direction may also point out patency of the aneurysm. Subarachnoid blood is frequently best seen on fluid attenuated inversion recovery (FLAIR) sequences, where the blood stained CSF appears hyperintense. The intracranial vasculature is most frequently evaluated with a 3D TOF MRA sequence due to its superior spatial resolution. MRA provides images that are comparable to catheter angiography and can be viewed from multiple angles in order to study the exact 3D architecture of the aneurysm (Figs. 7.6 and 7.7). There are, however, some pitfalls and the radiologist should be aware of them: (1) a fresh, T1-hyperintense thrombus within the aneurysm may mimic patency of the aneurysm, (2) an adjacent T1-hyperintense ICH may obscure the aneurysm, and (3) non-enhanced MRA tends to overestimate stenosis. Dynamic contrast enhanced MRA partially solves these limitations. Its spatial resolution, however, is not comparable to 3D TOF MRA.

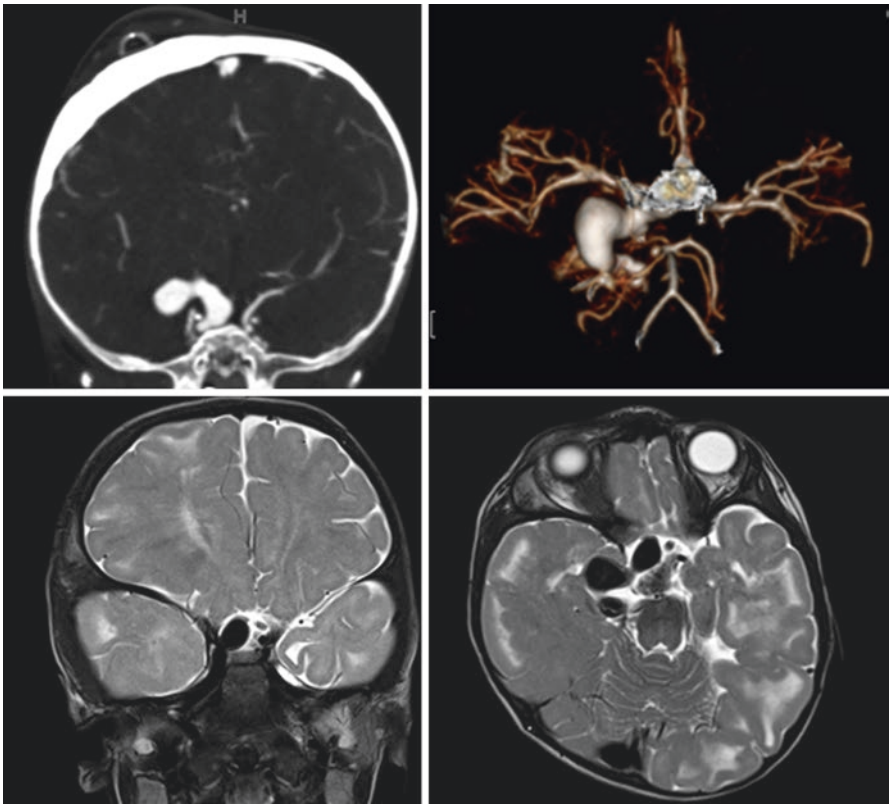


Fig. 7.6 Nineteen-month-old girl with confirmed tuberous sclerosis complex. A large lobulated/fusiform distal internal carotid artery aneurysm is seen extending into the region of the proximal right middle cerebral artery. The aneurysm is well demarcated on the contrast enhanced CTA and on the matching contrast enhanced 3D CTA-reconstruction. On T2-weighted MR images the aneurysm appears hypointense due to the flow void. The characteristic stigmata of tuberous sclerosis complex are noted within the brain parenchyma bilaterally

Cavernous Angioma and Developmental Venous Anomaly (DVA)

Cavernous angiomas or cavernomas are slow-flow, low-pressure sinusoidal malformations with an estimated incidence of 0.37–0.53 % in children [47]. About 25 % of all cavernomas are found in children [1]. Clinically, most children present with seizures (up to 70 %), followed by headache or acute focal deficits resulting from ICH. Cavernomas may be seen at every age, but they are more common between 1 and 3 years and 13 and 16 years of age, respectively [1]. The mean age at diagnosis is between 9 and 10 years of age. The majority of pediatric intracranial cavernomas occur in the supratentorial brain (79.4 %), while the infratentorial brain (20.6 %) and spinal cord (5 %) are less common locations. In the supratentorial brain, the majority of cavernomas are found in the frontal lobes, while infratentorial cavernomas are

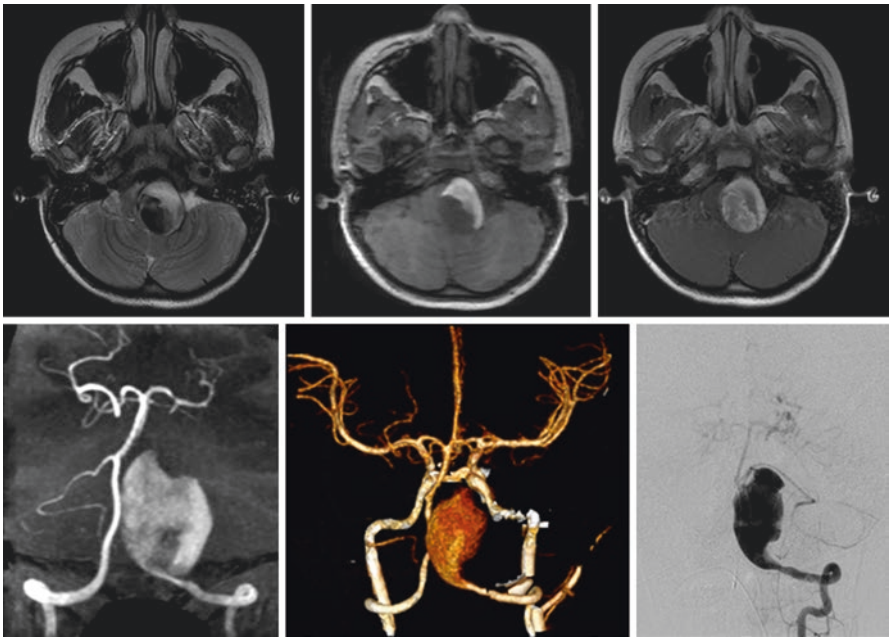


Fig. 7.7 Eight-year-old girl with headache, vomiting and left partially thrombosed vertebrabasilar junction aneurysm. The left posterior inferior cerebellar artery originates from the aneurysm. The partially thrombosed aneurysm appears heterogeneous T2-hypo and hyperintense, the thrombosed part is T1-hyperintense, with contrast enhancement of the patent component after contrast injection. MRA and DSA images assist in characterizing the large aneurysm in detail

predominantly located within the brainstem, particularly in the pons. Intraventricular cavernomas are uncommon (4 %) [1]. Pediatric cavernomas have a more aggressive natural history compared to adult cavernomas, grow faster, and bleedings form cavernomas are about 2–3 times more common [1]. In children, symptomatic hemorrhages from cavernomas occur in 27.3–78 % of patients, while affect only 8–37 % of adult patients [1]. In addition, pediatric cavernomas are frequently larger (giant cavernomas) at the initial presentation. The exact etiology of spontaneous cavernomas is still unknown. Spontaneous cavernomas may present as an isolated variant or in a familial form. Multiple cavernomas are noted in 30 % of isolated forms, but in up to 80 % of the familial forms [1]. CNS radiotherapy because of brain tumors is a major risk factor for development of cavernomas in children [1]. The occurrence of radiation-induced cavernomas is not related to the radiation dose. The latency period between radiation therapy and radiological diagnosis of cavernomas may range up to 23 years. Therefore, it is important to perform neuroimaging follow-up up to 15 years after completion of CNS radiation [1]. In addition, the risk of hemorrhage in radiation-induced cavernomas is high (up to 50 %) [1]. Finally, cavernomas are frequently seen in combination with DVA's.

DVA's are thought to represent a variation of the cerebral venous angioarchitecture in which multiple medullary veins drain into a dilated collector vein which

drains into the superficial and/or deep venous system. DVA's are usually asymptomatic and are typically found as an incidental finding on neuroimaging with a prevalence of 2.5–9 %. DVA's occur at all ages without a gender predilection. Rarely, DVA's may present with hemorrhage. Most frequently, the true cuase for the hemorrhage is an adjacent cavernoma. The simultaneous occurrence of DVA's and cavernomas is present in 13–40 % of patients [61]. It is unknown whether DVA's and cavernomas have the same etiology or DVA's are a complication of the altered venous hemodynamics due to the cavernoma. Indeed, cavernomas may obstruct the normal venous drainage of adjacent brain tissue [30]. Rerouting of the venous flow into non-obstructed, superficial or deep medullary veins may cause a DVA. The recruited medullary veins may drain via pre-existing transcerebral veins into the deep or superficial venous system. These recruited veins may dilate due to the encountered venous overflow mimicking a DVA-like collector vein. The risk of bleeding from an isolated DVA is low (0.22–0.68 % per year) [18, 43]. Acute thrombosis of the DVA may cause a hemorrhagic venous infarction. In addition, a stenosis is commonly seen where the collector vein joins the superficial or deep venous system. This may explain venous stasis/ischemia [61]. DVA's should not be resected or occluded because they have a key role in the venous drainage of the brain. Resection or occlusion of a DVA maty result in venous ischemia. In children with cavernomas, a detailed preoperative work-up is mandatory to rule out "associated" DVA's. In rare cases, a DVA may drain into a sinus pericranii. If a surgical resection of the sinus pericranii is planned, the functional dependence of the DVA to the sinus pericranii needs to be evaluated.

US has no reported value in the detection of cavernomas [1]. Cavernomas may be missed on non-enhanced CT (30–50 %), if intralesional calcifications (40–60 %) or hemorrhages are not present. After intravenous contrast injection, cavernomas usually show mild and/or delayed enhancement and appear as "blueberry" or "popcorn" like, focal white matter lesions with occasional extension into the overlying cortex [58]. The low venous pressure within the cavernoma causes the slow and delayed contrast enhancement. There is no brain tissue within the cavernoma. Because hemorrhages occurs repetitively within a cavernoma, blood products of different stages of evolution may be present. The typical hemosiderin staining of the adjacent brain cannot be identified on CT. Small cavernomas usually have little or no mass effect, while larger lesions may significantly displace adjacent brain structures. Hypodense perifocal edema may be seen in cavernomas that enlarged acutely due to a bleeding. MRI can identify cavernomas with high accuracy (Fig. 7.8). T2*-weighted and particularly SWI sequences have proven to be have high sensitivity in the detection of cavernomas due to the susceptibility artifacts (blooming artifacts) of the intralesional blood products [10]. In addition, SWI depicts easily the hemosiderin staining of the adjacent brain tissue. The sensitivity of SWI in detecting cavernomas increases at 3 T compared to 1.5 T MR scanner [52]. In addition, SWI detects small cavernomas that have not bled and may not be visible on conventional MRI sequences. Due to recurrent intralesional hemorrhages, cavernomas are heterogeneous T1-hypo/hyperintense and T2 hypo/hyperintense. As in CT, a mild/delayed contrast enhancement is noted. Perifocal vasogenic edema may be seen

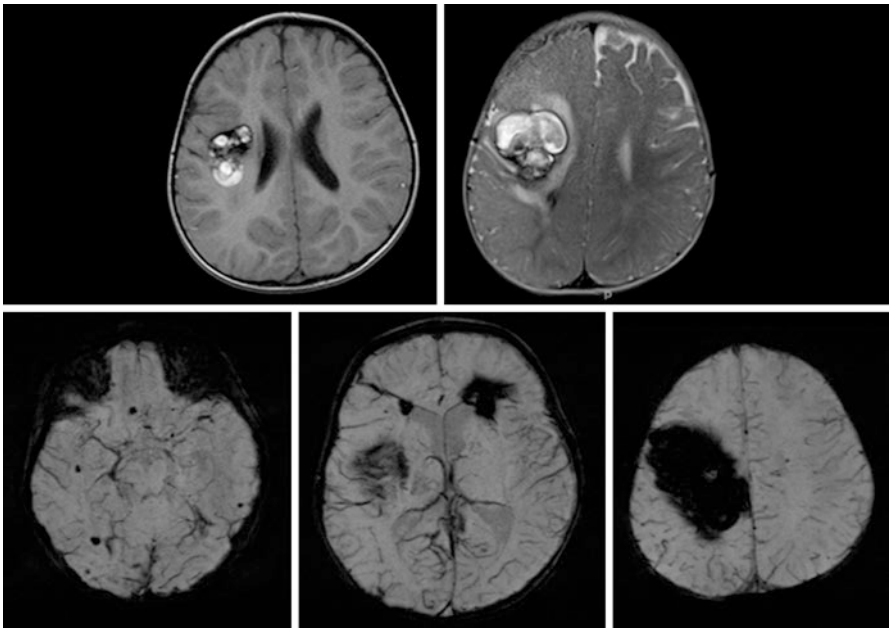


Fig. 7.8 Nineteen-month-old girl with seizures and history of cerebral cavernous angiomas. Axial T1-weighted, T2-weighted, and SWI images reveal a large T1/T2-heterogeneous cavernoma within the right hemispheric white matter. The cavernoma is surrounded by a mild amount of white matter edema. On SWI multiple additional hypointense cavernomas are noted as well as a transmantel DVA in the right frontal lobe

after recent hemorrhage. Because cavernomas are slow flow venous malformations, MRA/MRV are frequently negative, unless delayed contrast enhanced MRA/MRV techniques are used. Identification of cavernomas may also be limited due to acute hemorrhages that may obscure or compress cavernomas. T2*-weighted images or SWI should be used to rule out additional cavernomas, especially in the familial forms (Fig. 7.8).

Imaging of DVA's relies predominantly on contrast enhanced CT or MRI. US is of no diagnostic value. On contrast enhanced CT and MRI, multiple, contrast-enhancing medullary veins are typically seen draining into an enlarged collector vein that may drain either into the superficial or deep venous system (Fig. 7.9) [61]. On T2-weighted imaging, the medullary veins and collector vein may be hypointense due to flow related signal void [61]. DVA's are usually invisible on MRA, but may become apparent on MRV or delayed contrast enhanced MRA/MRV sequences (Fig. 7.9) [31]. Recently, SWI has been shown to have a higher sensitivity in depicting DVA's compared to conventional MR sequences including T2*-weighted images [36]. DVA vessels are well shown on SWI images as hypointense vessels due to the presence of deoxy-hemoglobin in the slow flowing veins. Some DVA's with relatively higher flow, however, may reduce the amount of deoxy-hemoglobin resulting in less obvious DVA veins on SWI [17]. As mentioned previously, combined occurrence of cavernomas and DVA's should be excluded.

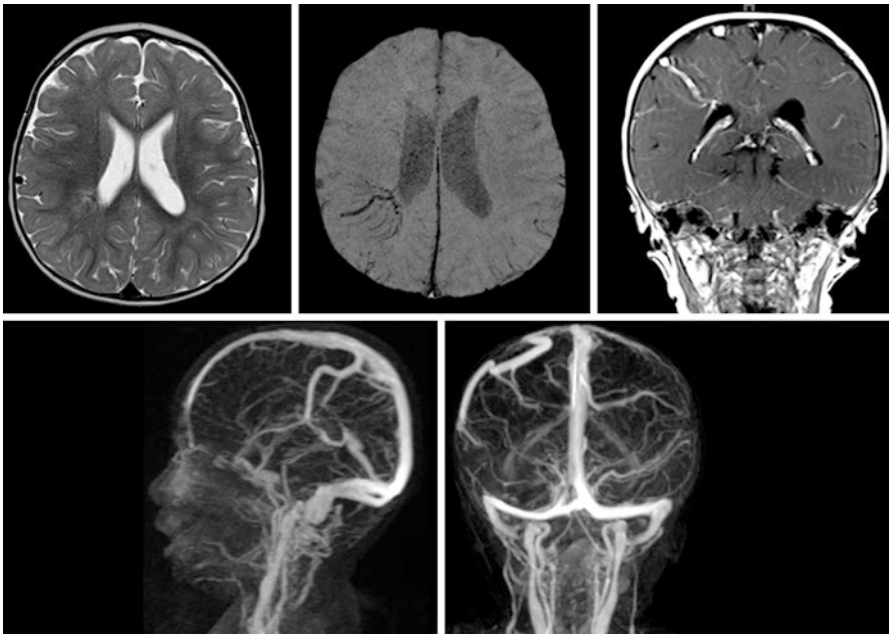


Fig. 7.9 Two-year-old girl with a large right parietal DVA. The DVA is faintly visible on the T2-weighted MR images, well seen on SWI with display of the hypointense caput medusa of veins that converge to the draining collector vein, and prominently enhancing on the T1-weighted coronal MR image. The DVA is also well seen on the contrast enhanced sagittal and coronal MRV. The DVA is draining into the superficial venous system

Arteriovenous Malformation (AVM) and Vein of Galen Aneurysmal Malformation (VGAM)

Pediatric AVM's differ significantly from adult forms in their angioarchitecture, clinical presentation, systemic hemodynamic impact, and overall functional outcome [7]. In children, AVM's are typically fistulous or multifocal, often exercise a hemodynamic effect on the entire venous system, and rarely present with high-flow related vasculopathy. Furthermore, the feeding arteries rarely bear flow-related aneurysms. Systemic manifestation with cardiac overload may be a key clinical feature that increases morbidity and mortality. Chronic venous stasis and ischemia associated with a steal phenomenon and chronic cardiac insufficiency may cause irreversible brain damages. The so called "melting brain" is a well-known devastating complication of a VGAM. Finally, the functional impact of the AVM on the developing brain is difficult to assess. The neonatal and infant brain are more vulnerable to injury, but the functional plasticity of the developing brain may improve the final functional outcome. Treatment options as well as the challenges and goals of treatment are significantly different between pediatric and adult AVM's. Complete anatomical cure is rarely the primary goal of treatment. The main aim of each treatment should be the regulation of the hemodynamic impact of the AVM on the developing brain in order to optimize functional, neurological outcome.

Pediatric AVM's may be classified based on their morphology, primary location, functional impact, or natural history [7]. Various vascular lesions may involve the vein of Galen [5]. Differentiation between "true" and "false" VGAM's is essential. The "true" VGAM is a choroidal type AVM in which choroidal arteries drain directly into a dilated, persisting median prosencephalic vein (Markowski vein). During normal vasculogenesis, this prosencephalic vein becomes the vein of Galen after communications with the thalamo-striate and internal cerebral veins develop. In children with "true" VGAM these communications do not form. The persisting embryonic vein does not connect with the deep venous system. In "false" VGAM, subpial AVM's adjacent to the cerebellum, brainstem, or deep supratentorial territories drain into a normally developed vein of Galen, which may dilate due to the venous overload. Consequently, the correct terminology would be "vein of Galen aneurysmal dilatation" (VGAD). The degree of dilatation is also caused by associated, flow-related stenosis or partial thrombosis at the junction between the vein of Galen and the straight sinus. In contrast to VGAM, the draining vein is not only draining the AVM, but also the adjacent deep cerebral structures. In addition to the VGAM and VGAD, a varicose dilatation of the vein of Galen without an underlying AVM or dural lesions that develop in the wall of the vein of Galen (frequently after straight sinus thrombosis) have been reported [5]. Correct differentiation between the different entities is essential. True VGAM may result in high output cardiac failure, pulmonary hypertension, and various neurologic complications resulting from hydrocephalus due to direct compression of the Sylvian aqueduct, impaired CSF-resorption at the Pacchionian granulations, and chronic venous hypertension, which may lead to the so called "melting brain". In less severe cases, sequelae of impaired brain maturation may result in developmental delay.

US is an important non-invasive imaging tool in the perinatal period, which allows the direct visualization of the dilated vessels of the VGAM as well as possible complications like brain edema and hydrocephalus [49]. Color-coded duplex sonography and spectral analysis of the blood flow curve within the supplying and draining vessels can give important hemodynamic information before and after treatment (Fig. 7.4). CT and MRI allow a detailed study of the angioarchitecture of VGAM and potential complications. CT may show calcifications with higher sensitivity compared to MRI. MRI and in particular advanced sequences like DWI, PWI, and SWI, however, may provide specific information about ongoing tissue injury (cytotoxic versus vasogenic edema), altered brain perfusion (PWI), and possible thrombosis of vessels and hemorrhages (SWI). In addition, SWI may be helpful in differentiating between low- and high-flow abnormalities of the Vein of Galen: high-flow abnormalities are SWI-hyperintense, while low-flow abnormalities are SWI-hypointense [32]. MRA and MRV provide a fast, non-invasive overview of the malformation. A detailed study of the exact angio-architecture, however, requires a selective digital subtraction angiography.

If prenatal US studies raise the possibility of a VGAM, fetal MRI should be considered (Fig. 7.10) [69]. Ultrafast fetal MRI does not require sedation of the mother or fetus, allows the study of the fetal brain in high detail, and can reliably identify CNS complications like brain edema, hydrocephalus, or hemorrhage.

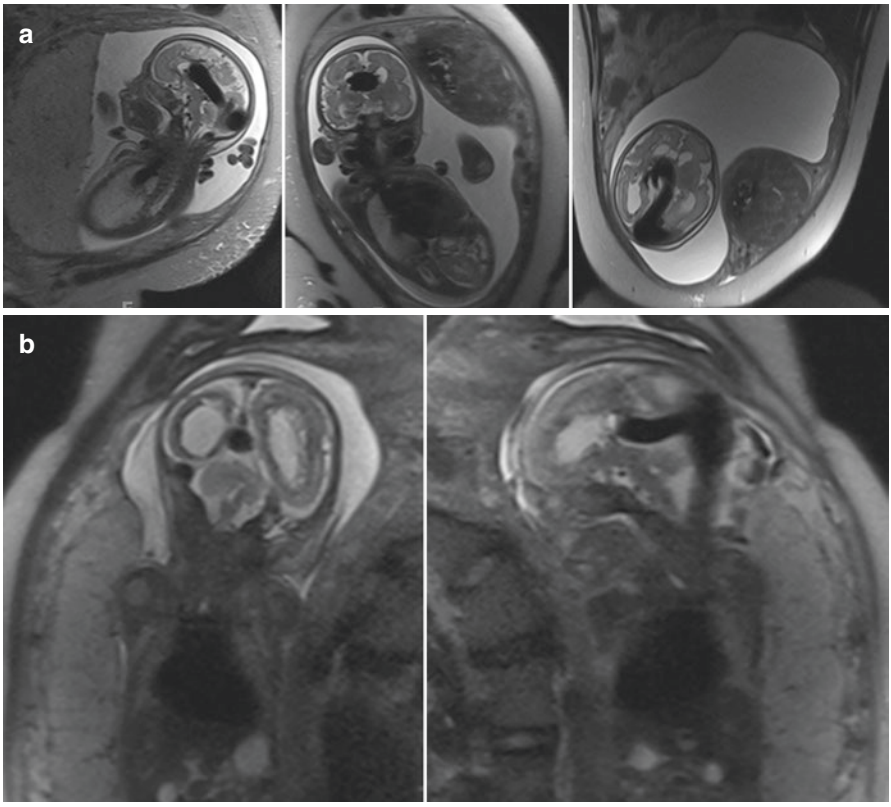


Fig. 7.10 Serial fetal T2-weighetd MR images of a fetus with a VGAM. On the initial MRI (**a**) the dilated, elongated vein is noted in typical location. First signs of periventricular leukomalacia are seen which progress ("melting brain") on the follow up fetal MRI (**b**). In addition, fetal cardiomegaly and fetal hydrops with subcutaneous edema and ascites are noted

Fetal MRI performed late in pregnancy or shortly before delivery should be considered as a valuable alternative to postnatal MRI examinations. The maternal uterus serves as a "maternal incubator", in which the child is in a very safe and controlled environment [26].

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Vascular Interventional Neuro-angiography

8

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Introduction

Digital subtraction angiography (DSA) is the gold standard for diagnosis and treatment of many intracranial cerebrovascular pathologies. With a growing recognition of pediatric cerebrovascular disorders and advances in endovascular treatments, there has been an increasing number of DSAs performed in children [1]. Although the safety profile of DSA has been well studied in adults, emerging data on the safety of DSA in children shows a relatively strong safety profile [1–5]. DSA in children poses unique challenges for neurointerventionalists, including the small size and fragility of pediatric vessels, limited application of devices designed for adults to the pediatric population, reduced radiation and contrast dosage, and specific anesthetic considerations. Further, children have unique cerebrovascular pathologies with specific vulnerabilities that may make errors more consequential [6]. Here we discuss the indications, alternatives, and potential complications of DSA in children. We provide suggestions on how to tailor anesthesia, contrast, radiation exposure, femoral access, catheterization, and closures during DSA for the pediatric population.

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A. Agrawal, G. Britz (eds.), *Pediatric Vascular Neurosurgery*,
DOI 10.1007/978-3-319-43636-4_8

Indications and Alternatives

It is important to know when a DSA study is indicated. In a recent study of 697 consecutive DSA procedures in children, arteriovenous malformations (extracranial and intracranial), vein of Galen malformations, and dural arteriovenous fistulas were the most common pathologies diagnosed and treated with DSA [5]. Other less common pathologies appropriate for DSA included tumors, vascular occlusion, and aneurysms (Table 8.1) [1, 3, 5, 7, 8] (Figs. 8.1, 8.2, 8.3, and 8.4). In contrast, in adults, DSA is performed more frequently in atherosclerotic cerebrovascular disease, tumors, aneurysms and subarachnoid hemorrhage [4].

With the recent advances in diagnostic radiology, there are less invasive diagnostic imaging alternatives that can provide a sufficient amount of information in children with cerebrovascular pathologies without the need for a DSA. A MRA time of flight is a quick study that requires no contrast, no gadolinium, and provides visualization of AVMs, aneurysms, dural sinus thrombosis, congenital vascular abnormalities, arterial dissections, and moya moya [9–14]. It can, however, exaggerate stenosis and occlusions, and is difficult to see small vessels and collateral flow in ischemic disease [9]. CT angiography is another alternative to DSA that is quick, requires no sedation, with 3D rendering capabilities that can well characterize vascular abnormalities. However, there is a high radiation dose required, with technical issues such as the volume of contrast, injection rates, breath-holding, and timing that need to be adjusted for the pediatric population [15, 16].

Clinicians often ask at what point in a diagnostic workup s a DSA indicated. This depends on a case-by-case basis. An interdisciplinary team that includes both neurosurgeons and radiologists should review every case to weigh surgical and endovascular options. When a DSA is indicated, cross-sectional imaging can be thoroughly evaluated to avoid unnecessary catheterization and angiographic runs [5].

Table 8.1 Pathologies in pediatric population undergoing angiography

	Recent Studies								Total	
	Lin et al. (2015) [5]		Hoffman et al. (2014) [7]		Wolfe et al. (2009) [3]		Burger et al. (2006) [1]			
Pathology	No.	%	No.	%	No.	%	No.	%	No.	%
Vascular malformation	194	0.72	3	0.03	20	0.43	93	0.42	310	0.50
Tumor	42	0.16	77	0.89	2	0.04	4	0.02	125	0.20
Normal	0	0	0	0	13	0.28	80	0.37	93	0.15
Stroke/vascular occlusion	3	0.01	4	0.05	5	0.11	23	0.11	35	0.06
Aneurysm	19	0.07	0	0	1	0.02	13	0.06	33	0.05
Other	10	0.04	0	0		0	0	0	10	0.02
Intracranial hemorrhage/ Trauma	0	0	3	0.03		0	6	0.03	9	0.01
Moya – moya	0	0	0	0	5	0.11	0	0	5	0.01
Total	268		87		46		219		620	

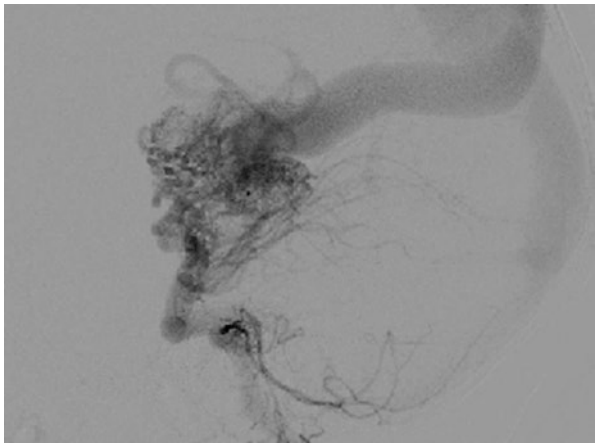

Fig. 8.1 Vein of Galen malformation: 10 month old female with a vein of galen malformation who was monitored secondary to only mild cardiac abnormalities

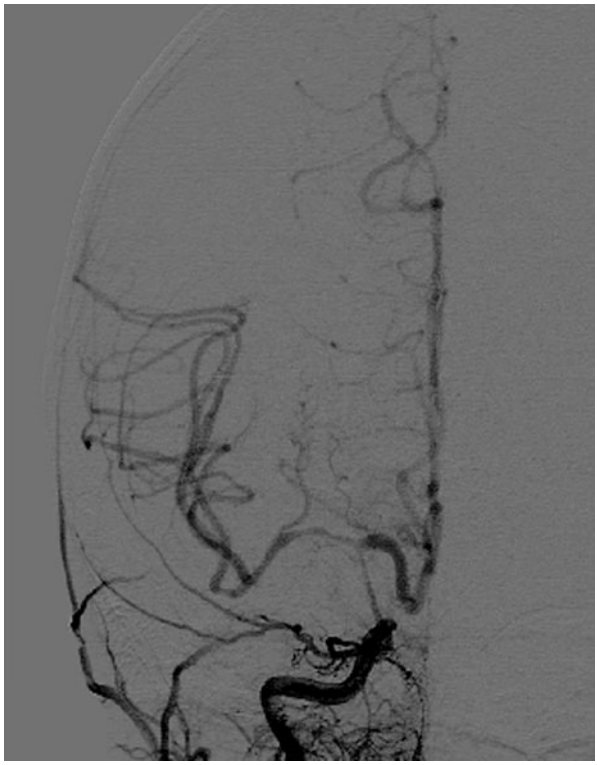

Fig. 8.2 Moya moya: 4 year old female with moya moya, treated with EDAS (encephalo-duro-arterio-synangiosis)

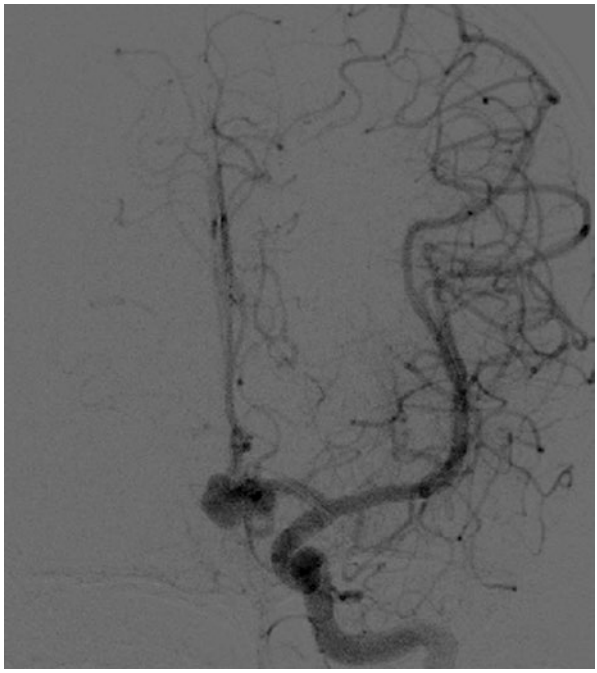

Fig. 8.3 Pseudoaneurysm: 10 year old male with a TBI (traumatic brain injury) and a left A1 pseudoaneurysm, treated with craniotomy and clip ligation

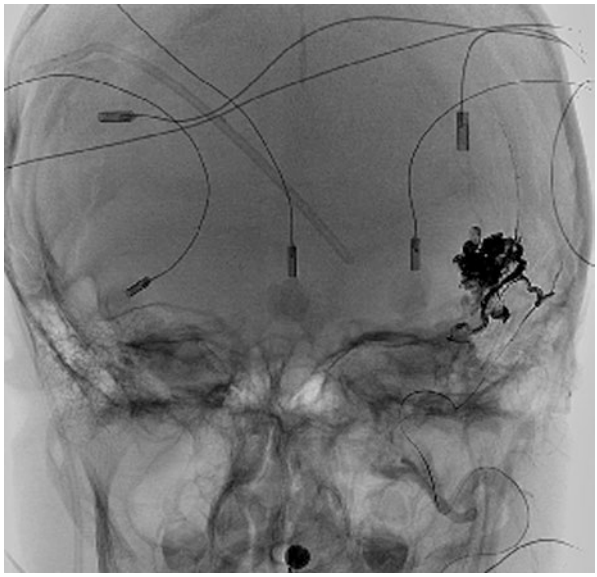

Fig. 8.4 AVM (arteriovenous malformation): 8 year old male with a hemorrhagic AVM, treated here with onyx embolization

Complications

DSA is a relatively safe procedure, with complications in the adult population occurring in less than 5 % of the population. In 19,826 consecutive cerebral angiograms in adults, the most common complications were a groin site hematoma (4.2 %), followed by a neurologic events such as a stroke or TIA (2.63 %), and nausea, vomiting, and/or transient hypotension (1.2 %) [4].

Although DSA in the pediatric population may appear high risk, four major recent studies show a relatively low complication rate, comparable to or even less than adults, especially when performed at high volume pediatric DSA centers (Table 8.2). Lin et al. reviewed 697 consecutive pediatric DSAs, and found a total of 3 complications (0.7 %, 2 with contrast allergies, 1 with post-procedural hair loss) in diagnostic DSAs. All complications resolvesd with no long-term consequences [5]. More complications occurred in the embolization group (6.7 %), with most of these non-neurologic (5.6 % – 15 with contrast allergy, 4 with groin site bleeding, 2 with coil or onyx migration), only 1 short term neurological event (0.4 % – cranial nerve palsy), and 2 long-term neurologic events (0.7 % – ischemic stroke, intracranial hemorrhage). Hoffman et al. reviewed 309 consecutive pediatric DSA in patients <3 years old. There were no neurologic complications, 2.9 % non-neurologic complications (7 with contrast allergy or bronchospasm, 1 groin hematoma, 1 transient femoral artery occlusion), and 1.3 % radiographic complication (1 transient asymptomatic intra-arterial dissection, 3 asymptomatic vasospasm) [7]. They concluded that rates of complications were comparable to older children, and less than adults. Burger et al. reviewed 241 consecutive DSA with no intra-procedural complications, 2 minor post-procedural complications (groin site bleeding) and 1 post-procedural hemorrhage (0.4 %, a dAVF rehemorrhage secondary to a posterior fossa varix rupture 3 h after DSA) [1]. Fung et al. reviewed 176 DSAs with no neurologic complications. Local complications occurred in 4.5 % of children (5 groin hematoms, 2 bleeding at puncture site, 1 reduced pedal pulse distal to site of catheterization, but Doppler was normal) [2]. Wolfe et al. reviewed 46 cerebral angiograms with no peri-procedural complications [3]. Although these studies are not as well powered as the adult population, DSA in the pediatric population appears relatively safe.

Factors that increase the risk of a complication include being female [5, 17], an intracranial embolization [5], and the initial DSA procedure compared to a repeat DSA [5]. Even given the anatomic and physiological differences in the younger pediatric population, age [5, 7], and catheter size [7] were not risk factors for complications

Anesthesia

Anesthesiology during DSA should be performed by an anesthesiologist specializing in the pediatric population. The type of anesthesia employed depends upon the individual and planned procedure. Generalized endotracheal anesthesia (GETA)

Table 8.2 Pathologies in pediatric population undergoing angiography

	Recent studies									
	Lin et al. (2015) [5]		Hoffman et al. (2014) [7]		Wolfe et al. (2009) [3]		Burger et al. (2006) [1]		Total	
Complication	No.	%	No.	%	No.	%	No.	%	No.	%
Contrast allergy	2	0.007	7	0.023	0	0.000	0	0.000	9	0.010
Groin site bleeding	4	0.015	1	0.003	0	0.000	0	0.000	5	0.006
Vasospasm (asymptomatic)	0	0.000	4[a]	0.013	0	0.000	0	0.000	4	0.005
Hair loss	3	0.011	0	0.000	0	0.000	0	0.000	3	0.003
Bradycardia	3	0.011	0	0.000	0	0.000	0	0.000	3	0.003
Decreased pulse at groin site	1	0.004	1[b]	0.003	0	0.000	0	0.000	2	0.002
Coil/Onyx migration	2	0.007	0	0.000	0	0.000	0	0.000	2	0.002
Hemorrhage	1[c]	0.004	0	0.000	0	0.000	1[d]	0.004	2	0.002
Retained catheter	1	0.004	0	0.000	0	0.000	0	0.000	1	0.001
Numb patch after facial embolizatoin	1	0.004	0	0.000	0	0.000	0	0.000	1	0.001
CN palsy (transient)	1	0.004	0	0.000	0	0.000	0	0.000	1	0.001
Vessel perforation	0	0.000	1[e]	0.003	0	0.000	0	0.000	1	0.001
Ischemic stroke	1[f]	0.004	0	0.000	0	0.000	0	0.000	1	0.001
Hypothermia at end of procedure (resolved)	0	0.000	0	0.000	0	0.000	1	0.004	1	0.001
Heparin hypersensitivity	1	0.004	0	0.000	0	0.000	0	0.000	1	0.001
Contrast nephrotoxicity	0	0.000	0	0.000	0	0.000	0	0.000	0	0.000
Procedures	268		309		46		241		864	

[a]Three patients with vasospasm that was resolved with verapamil during the case

[b]Transient femoral artery occlusion. The next day, the limb was cooler. Patient was given aspirin with repeat ultrasound showing resolution of occlusion

[c]Uncomplicated right frontal AVM in 16 year old female who had an intraparenchymal hemorrhage overnight requiring craniotomy with resection of AVM (which is associated with a 4–12 % post-embolization hemorrhage rate in adults)

[d]Posterior fossa hemorrhage 3 h at the site of the dural AVF varix

[e]Balloon microcatheter dissection in the supraclinoid ICA using a HyperForm balloon for intra-arterial chemotherapy treatment. The dissection was not flow limiting. After 30 min, the balloon was deflated and removed with no evidence of vessel injury. The patient was placed on aspirin and asymptomatic after the procedure

[f]14 kg patient with moya moya who underwent coil embolization of a posterior communicating artery neurysm with intra-procedural parent vessel thrombosis

allows the anesthesiologist to administer paralytics, and hold the breath during the angiogram. This allows for optimal imaging for a roadmap, for example, to assist the neurointerventionalist in navigation through a difficult vessel. GETA is also appropriate if the procedure is painful (e.g., when Onyx (ev3 Neurovascular, Irvine, CA) or polidocanol is utilized), prolonged, or the patient has failed conscious sedation in the past [8]. Conscious sedation with local lidocaine may be approriate for a diagnostic cerebral angiogram on a teenager who is calm, cooperative, and willing to stay still and participate throughout the procedure [3]. Using local lidocaine can reduce overall vasospasm, and lessen post-procedural discomfort. EMLA® crème (lidocaine and prilocaine) can also be administered 30–45 min before the procedure to numb the skin, followed by local lidocaine (6 mg/kg) [18, 19].

To minimize the risk of aspiration during induction, children are made NPO (nothing per oral) depending upon their age and type of food most recently ingested. In general, no milk or solid foods for >4 h in infants, and 6–8 h in older children. Clear liquids are allowed up to 2 h for oral sedation medications, and up to 4 h before parental medications.

Especially on small children it is very important to have a clear communication with the inventionalist, anesthesiologist, and the radiology staff in the room to account for all the fluids that are infused through the femoral line, and continuous flush. This is not an insignificant amount of crystalloids and heparin. Further, the urinary output has to be monitorized strictly, either by a Foley catheter or when applicable, weighing the diaper before and after the procedure.

Contrast

An allergy to contrast is one of the most common non-neurologic complications in the pediatric DSA population [5, 7]. Although many of these patients experience an allergic reaction to contrast for the first time during a DSA, those with known contrast allergies can be prepped with a combination of diphenhydramine benadryl (1.5 mg/kg) and hydrocortisone (10 mg/kg). Many institutions use the Broselow-Luten color zone charts, which categorize children into eight color zones based on weight and height. These charts contain appropriate pediatric doses for commonly used medications for allergic reactions, and are integrated into anesthesia and/or crash carts with easy to use reference cards. Table 8.2 provides common mediation doses for allergic reactions.

Contrast induced nephropathy (CIN) can occur secondary to transient renal ischemia, direct renal toxicity, or changes in local glomerular capillary permeability. This can be minimized by peri-procedural hydration and minimizing contrast load. Adequate hydration can be achieved with initiation of IV fluids up to 6 h before a DSA (4 mL/kg for an infant or 6 mL/kg for children) [20]. Low-osmolar contrast media (LOCM, eg, Omnipaque 300 (GE Healthcare) or isovue 300) can reduce the risk of an allergic reaction, as well as nephrotoxicity and osmotic overload [21]. There are no systematic studies on the appropriate dose of contrast for DSA in children; however, there are widely accepted norms for dose limits used by radiology [22]. Based on a recent review of 2321 pediatric cardiology interventional cases, a total dose limit of

Table 8.3 Injection rates [23]

Vessel	Weight (kg)	Volume
Common carotid artery (CCA)	0–10 kg	2–5 mL
Common carotid artery (CCA) Internal carotid artery (ICA)	10–20 kg	5–8 mL
	20–40 kg	8–10 mL
	75 % of CCA injections	
External carotid artery (ECA)	50 % of CCA injections	
Vertebral artery (VA)	0–10 kg	2–4 mL
Vertebral artery (VA) Subclavian artery (SCA)	10–20 kg	4–6 mL
	20–40 kg	6–8 mL
	0–10 kg	0.75–1 mL/kg
Subclavian artery (SCA) Aortic arch	10–20 kg	0.5–0.75 mL/kg
	20–40 kg	0.25–0.5 mL/kg
	0–10 kg	1.5 mL/kg
Aortic arch	10–20 kg	1.5 mL/kg
	20–40 kg	1.2–1.5 mL/kg

7 ml/kg has been extrapolated to minimize the risk of contrast neuropathy and neurotoxicity [5]; however, other protocols use as low as 2–3 ml/kg [7] and 5 ml/kg [3]. For a 3 vessel angiogram, others have set a target goal of 9 mL of contrast (0.5 cc of contrast as a test dose, followed by 2.5 mL per vessel) [6]. Strategies used to minimize contrast injection include performing fewer vessel angiograms using half saline and half contrast during angiographic runs, and injection of only 1–2 ml of contrast per vessel. Wasted contrast needs to be strictly accounted for, to have an accurate account of the actual amount of contrast injected in the pediatric patient. Another strategy is to pre-load a Tuohy-Borst valve system and catheter dead space with 2.5 mL of contrast. During an angiogram run, inject with a 5 mL syringe full of saline. Injection rates adapted for weight and vessel size is available on Table 8.3.

Radiation

Children are more vulnerable to the effects of radiation compared to adults [24]. Manufacturers often have settings optimized to sell the best looking image, with less concern for radiation exposure [6]. Before the pediatric patient enters the room, the machine can be turned to a customized “pediatric mode” by removing the grid, reducing the frames per second during angiography, and reducing the dose per second, pulse rate per second, and maximizing the use of copper filtration during fluoroscopy. At the start of the case, a conscientious team effort can be verbalized during “time out” to keep the radiation dose to as “low as reasonably achievable” (ALARA principle). During the procedure, the neurointerventionalist can minimize the source image distance, use tight collimation, position frame angles as close to ideal without fluoroscopy, and perform only those runs deemed necessary [2, 25, 26].

Access

Children have a relatively smaller common femoral artery compared to adults, making initial access and maintenance of distal flow challenging. Although the pediatric common femoral artery tends to be straight and non-atherosclerotic, it is more mobile and may be difficult to feel the pulse. Therefore access with an ultrasound is highly recommended [5]. For patients who undergo re-treatment, using the contralateral femoral artery is recommended [5]. Once the vessel has been manipulated, it is more vulnerable to occlusion, vasospasm, and thrombosis.

Once access is obtained with a micropuncture device, the smallest available sheath to insert is 3 F in size. Once this sheath is inside a small vessel, pulses may be lost, which occurs in 6 % of pediatric catheterizations [27]. 3 F sheaths are manufactured, but not widely available at many institutions. If the vessel size to sheath ratio is too large to allow for distal flow, the dilator that comes with the 4 F sheath can be used for access [6]. However, a 4 F sheath is preferred in cases with multiple manipulations, interventional procedures, and/or catheter exchanges [28, 29]. Hoffman et al. used 3 F sheaths for IA-chemotherapy, 4 F sheaths for diagnostic DSA, and 5 F sheaths for complex interventional cases [7].

It is difficult to tell whether a loss of pulses is due to thrombosis or vasospasm. Thrombosis is more common in patients <15 kg [30], and can be prevented with a continuous flush of heparinized saline after access is obtained, with the flow rate minimized to prevent fluid overload [5, 20, 31]. Children have a lot of collateral circulation in response to arterial occlusion. However, ischemia at the femoral artery can be as consequential as a loss of a limb, or can be more subtle such as development of leg length discrepancies over time [32]. Treatment for a cold limb involves warming of the limb for 2–4 h with IV heparin (bolus 75–100 U/kg, followed by an infusion titrated to a PTT 2x normal) until pulses return or for 24 h [27, 33]. It if does not return in 24 h, thrombolytics are recommended.

If the pulse is present, but diminished, there may be a concern for vasospasm. Vasospasm can limit access and require abortion of the DSA before even getting started [33, 34]. Strategies to prevent vasospasm include using an ultrasound, a short micropuncture needle while an assistant passes a wire, and injection of verapamil 0.01 mg/kg or nitroglycerin 2–3 mg/kg upon access. If there is persistent vasospasm, wait 20 s, then retry [6].

Alternative access arteries include the brachial, axillary, carotid, or vertebral arteries. The umbilical artery has been accessed in the neonate or premie which spares the peripheral vasculature, and can accommodate a larger sheath and catheter [20]. In cases of large arteriovenous fistulas in neonates, it is useful to have these children come from the neonatal unit with both umbilical artery and vein catheterized. The umbilical artery is patent for up to 5 days after birth, and can be checked with a small contrast injection [8].

Table 8.4 Needle guide wire catheter compatibility [37]

Patient weight (lb)	Needle (gauge)	Wire size (in)	Catheter size
<15	21 butterfly	0.018	4
<15	21 thin-wall art	0.018, 0.021	4
15–35	19 butterfly	0.025	5
35–60	18 thin-wall art	0.035	5

Catheterization

Intracranial target vessels are smaller than their analogous counterparts in adults. This make them more fragile and vulnerable to thrombosis from partial obstruction [5]. Catheterization of pediatric sized vessels has become less challenging with the development of microcatheters in adults. As a general rule, a 3–4 F diagnostic catheter is used in patients <10 kg, 4 F catheter in patients 10–20 kg, and 5 F catheter in patients >20 kg [35, 36]. In small children, there may be too much flimsy catheter outside of the patient, making navigation difficult. One suggestion is to place the diagnostic catheter inside a shorter 60–90 cm constraining outer catheter [6]. A standard glidewire can be used, the neurointerventionalist must be conscientious to turn on the fluoroscopy before getting close to the end of a glidewire. One strategy is to remember to place the torque in the mid-section of the glidewire to minimize the changes of advancing too far without fluoroscopic guidance [6]. A needle-guide wire-catheter compatibility chart is available on Table 8.4.

The risk of vascular trauma secondary to the small size of vessels is extremely rare in both adults and children [1, 5, 7]. Hemorrhage secondary to vessel perforation is treated with protamine (1 mg/1000U heparin) [23], and an external ventricular drain if there is mass effect. Inadvertent embolization rates are similar to adults (0.9 %) [36], with most traveling to the MCA. IA-thrombolysis in children have been achieved with IA-tPA (0.2 mg/kg with a maximum of 12 mg) or mechanical thrombectomy with stent retrievers or aspiration devices [38].

Closure

Closure devices have not been evaluated in the pediatric population [8]. To save contrast, no femoral arteriogram is necessary because it would not impact closure [3]. One strategy described to maintain the ideal amount of groin hemostasisis to place the right hand on the distal pedal pulse while the left hand applies light pressure on the femoral artery [6]. Further, deep extubation techniques performed by the anesthesiologist have been used to minimize coughing and limb movement for 4 h after the procedure [3, 5].

Pearls/Summary [8–10]

1. Digital subtraction angiography (DSA) is the gold standard for diagnosis and treatment of many intracranial cerebrovascular pathologies
2. Cross sectional imaging such as MRA with time of flight and CTA may provide sufficient information for diagnosis of many pediatric cerebrovascular disease, obviating the need for DSA.
3. Complications can be minimized with appropriate adjustments for the unique cerebrovascular pathologies, anatomic, and physiologic differences in children.
4. Contrast reactions and groin site hematoma are the most common complications associated with pediatric DSA.
5. Contrast reactions can be minimized with diphenhydramine and hydrocortisone pre-procedurally, and reaction specific drugs intra-procedurally.
6. Contrast induced nephropathy can be minimized by use of low-osmolar contrast media (LOCM) with a total dose limit of 7 ml/kg.
7. Radiation dosage should be set to as "low as reasonably achievable".
8. Femoral access is limited secondary to available sheath sizes on the market, as well as inherent vessel vulnerability to vasospasm and occlusion.
9. Catheterization of small intracranial vessels should proceed with caution secondary to their fragility and vulnerability to thrombosis from partial obstruction.
10. Closure and hemostasis should be achieved with manual compression, followed by deep extubation.

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Pediatric Arteriovenous Malformations

9

Karam Moon and Robert F. Spetzler

Abbreviations

AVM	Arteriovenous malformation
CT	Computed tomography
CTA	Computed tomography angiography
DSA	Digital subtraction angiography
HHT	Hereditary hemorrhagic telangiectasia
MRI	Magnetic resonance imaging
VEGF	Vascular endothelial growth factor

Introduction

Arteriovenous malformations (AVMs) are part of a spectrum of vascular malformations of the central nervous system that affect the brain and the spinal cord in both adults and children. They are extremely heterogeneous in location, morphology, and presentation, all of which can be unique to the pediatric population. Because children with AVMs are frequently symptomatic, they are often diagnosed at an early age. AVMs represent the most common lesion causing intracranial hemorrhage in this age group. Since AVMs present a lifelong risk of hemorrhage and an often debilitating spectrum of symptoms in the pediatric population, treatment is crucial whenever possible. This chapter discusses the fundamental characteristics of AVMs in children and treatment strategies based on current evidence and data.

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A. Agrawal, G. Britz (eds.), *Pediatric Vascular Neurosurgery*,
DOI 10.1007/978-3-319-43636-4_9

Epidemiology

AVMs are the most common symptomatic high-flow intracranial vascular lesion in adults and children alike [1]. Pediatric AVMs are often considered the most common abnormality of the intracranial circulation in children, accounting for 12–18 % of all AVMs in the general population, and an overall prevalence in children of about 0.02 % [2–6]. About 20 % of symptomatic AVMs occur in patients younger than 15 years of age [7]. There is no sex predilection for AVMs.

Familial subtypes of AVMs also exist in children, and these are associated with genetic conditions. The *RASA1* gene mutation, typically related to familial AVMs of the musculoskeletal system and to cutaneous capillary malformations, has been shown to be associated with intracranial AVMs [8]. More commonly, hereditary hemorrhagic telangiectasia (HHT) is a genetic condition that predisposes both children and adults to the development of AVMs. Approximately 35 % of children with AVMs develop lesions secondary to HHT [9].

Pathophysiology

The histopathology of AVMs involves direct arterial-to-venous connections without intervening capillaries or functional neural tissue (Fig. 9.1). AVMs may exhibit growth over time by several mechanisms. Increased flow and shunting in the venous system can lead to dilatation of existing vessels and recruitment of more arterial feeders. Concurrent molecular mechanisms around pathways of angiogenesis are regulated by a wide range of proteins and factors, including metalloproteinases and vascular endothelial growth factor (VEGF) [10–16]. Furthermore, as the patient ages, AVMs may undergo dynamic changes in morphology and develop associated arterial and venous aneurysms and venous stenoses, all of which can change the natural history and hemorrhagic risk profile of the lesion.

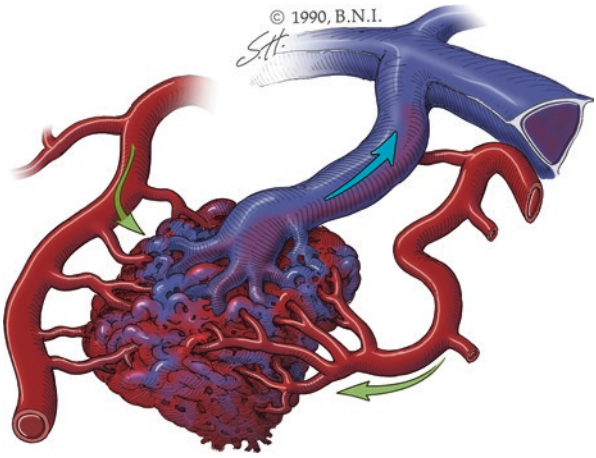

Fig. 9.1 Illustration of an arteriovenous malformation depicts multiple arterial pedicles feeding a nidus that drains directly into a single large vein (Used with permission from Barrow Neurological Institute, Phoenix, Arizona)

The natural history of AVMs has not been prospectively studied in pediatric-only cohorts, although a recent retrospective analysis of 120 pediatric patients with AVMs found an annual hemorrhage rate of 4 % [17]. Hemorrhage has been associated with a mortality risk of approximately 25 %, with an annual hemorrhage risk of approximately 2 % [6, 18, 19]. Moreover, children must bear the psychological burden of carrying a lesion that may cause significant neurological morbidity or even death at any time in their lives. Given these reasons and the often-resilient capacity of the developing brain to recover from and to compensate for injury, all children with an AVM should undergo evaluation for potential treatment.

Presentation

The presentation of children with AVMs is similar to that of adults with AVMs, in that it often correlates with the intracranial location. Seizures are the most common symptom of an unruptured lesion; other less common symptoms include headache, cognitive decline, progressive ischemia due to steal phenomenon, and focal neurological deficits. However, unlike the presentation of AVMs in adults, the presentation in children may also depend on age. For example, AVMs can produce symptoms at birth or soon after birth, with patients presenting with high-output cardiac failure due to the presence of a high-flow lesion, such as a vein of Galen malformation, which is a closely related pathological entity. The presence of substantial shunting may also result in other cardiac manifestations, such as tachycardia, cardiomegaly, or even cardiac overload [19].

Patients with lesions may also present with hemorrhage, the likelihood of which probably depends on multiple factors. Although some data support a correlation between AVM size and risk of hemorrhage in children, other series have not found an association [2, 20]. Other variables may include the number and location of arterial feeders/pedicles, the venous drainage pattern, and the overall hemodynamic profile, all of which are poorly understood in the pediatric population. Compared to adults with AVMs, children with AVMs are much more likely to present with hemorrhage, with rates as high as 60–85 % [2, 21]. Hemorrhage is most commonly intraparenchymal, but it can also be subarachnoid or intraventricular. In general, a nontraumatic intraparenchymal hematoma in a child should immediately raise a high level of suspicion for presence of an AVM or neoplasm.

Physical examination findings for pediatric AVMs vary by the morphology and location of the lesion. Systolic bruits over the eyes or fontanels have been found in 15–40 % of patients [19]. Patients with lesions that involve branches of the external carotid circulation may present with large, pulsatile vessels in the scalp, face, and neck, as well as with other vascular anomalies in the retina. Focal neurological deficits such as cranial neuropathy or motor findings should also correlate with localization of the lesion.

Imaging and Diagnostics

Unless AVMs are found incidentally, imaging should be based on symptomatology or suspicion of hemorrhage. Screening for hemorrhage should start with computed tomography (CT) for immediate visualization of possible blood products or space-occupying hematomas. Given the likelihood of a vascular lesion in the setting of a non-traumatic pediatric intracranial hemorrhage, further workup should be carried out without delay. CT angiography (CTA) is typically preferred, given its speed and availability in the acute setting. When possible, magnetic resonance imaging (MRI) should be performed for better delineation of the normal anatomy surrounding the lesion. AVMs are easily identifiable by a characteristic network of flow-voids on T2-weighted sequences, which facilitates accurate localization within potentially eloquent territories. Susceptibility sequences are useful for identifying blood products or hemosiderin staining as a dark bloom or artifact around the lesion. Even when angiography is planned, MRI should be performed first while considering possible interventions.

Digital subtraction angiography (DSA) is the gold standard for definitive characterization of the angioarchitecture of the lesion. DSA allows for accurate characterization of arterial feeders and pedicles and venous drainage patterns, all of which are crucial for surgical planning. Circulation throughout the lesion is characteristic, with rapid shunting from the arterial system into the venous system and early venous opacification. Diagnostic angiograms should be performed with injections of contrast media into both the internal and external carotid systems, as well as into the posterior circulation.

Treatment

The indications for treatment of an AVM center on the reduction or elimination of hemorrhage risk, as well as the alleviation of symptoms such as seizures. The primary modalities used in the treatment of AVMs include surgery, embolization, and stereotactic radiosurgery. Complete excision by open microsurgery has the potential to cure the patient, thereby avoiding the risk of future hemorrhage. Given the high likelihood of hemorrhage in the pediatric population, most centers advocate for a surgery-first approach because of the advantages of immediate therapeutic cure and the high rate of surgical obliteration (Fig. 9.2). This approach contrasts with the typically unknown long-term impact of cranial radiosurgery in children, both with regard to the AVM obliteration rate and radiation-associated complications and side effects.

Immediate therapeutic cure is particularly advantageous and desirable in cases of ruptured AVMs, because these patients face a greater risk of rerupture [22, 23]. While this is also true of AVMs in adults, surgical results and clinical outcomes in children may be better than those in adults, as discussed below [24]. Given that most pediatric patients with AVMs in nearly all series have presented with hemorrhage, a more aggressive and expedient cure via microsurgical excision, as opposed to

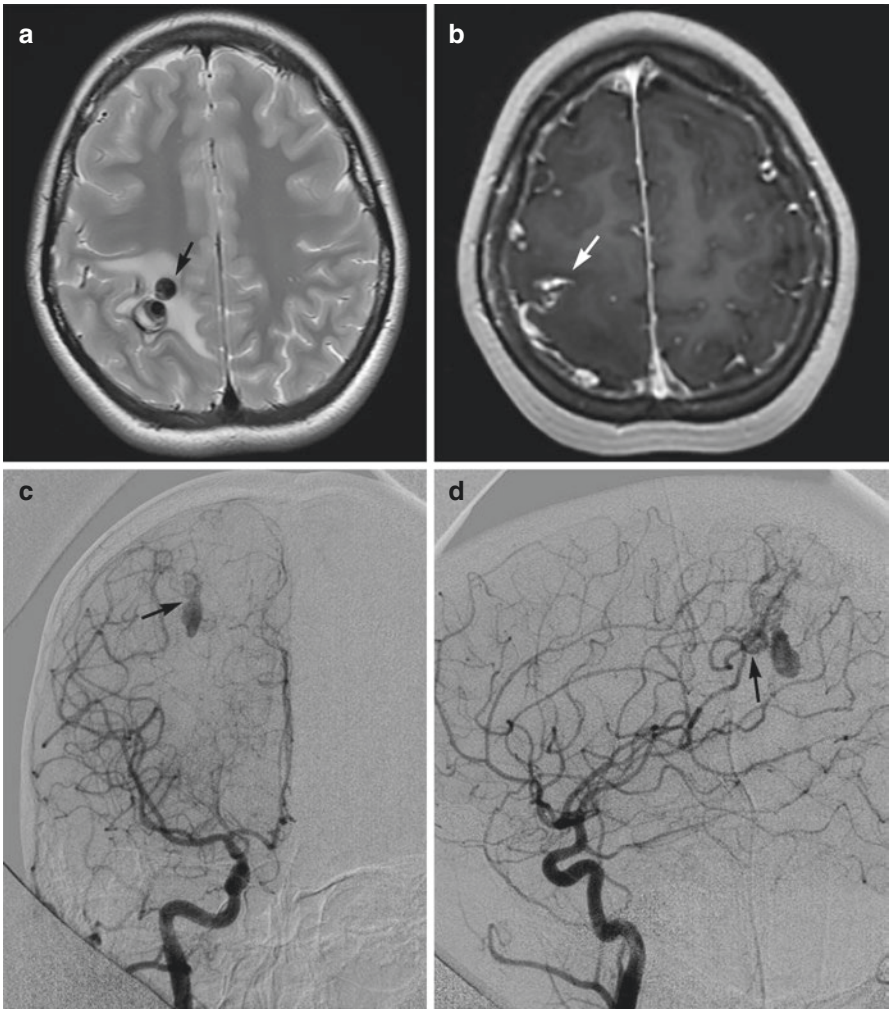

Fig. 9.2 A 16-year-old female patient presented with seizures, and imaging demonstrated a Spetzler-Martin grade II arteriovenous malformation (AVM). She underwent preoperative embolization followed by craniotomy for resection. (**a**) T2-weighted axial magnetic resonance imaging (MRI) demonstrates large venous dilatations, secondary to an AVM, with surrounding cerebral edema (*arrow*). (**b**) Gadolinium-enhanced axial MRI demonstrates superficial cortical drainage of the AVM (*arrow*). (**c**–**d**) Preoperative digital subtraction angiography with a right internal carotid artery injection demonstrates the AVM with superficial drainage (*arrow*). (**e**–**f**) Postoperative digital subtraction angiography of the right internal carotid artery injection demonstrates obliteration of the AVM with no evidence of early venous drainage (Used with permission from Barrow Neurological Institute, Phoenix, Arizona)

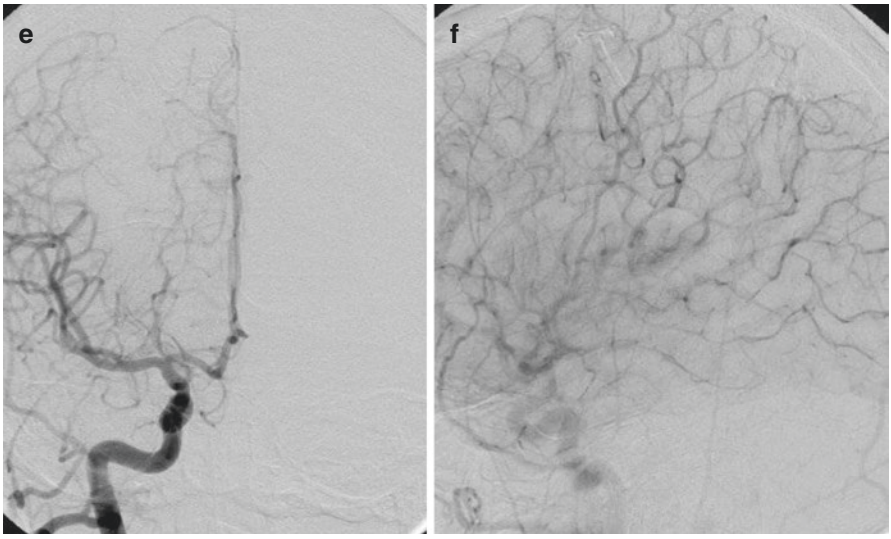

Fig. 9.2 (continued)

radiosurgery, should typically be sought. Furthermore, in the most recent iteration of radiosurgical grading schemes, hemorrhage was considered an adverse factor for radiosurgical success in contrast to its impact on microsurgical outcomes [25, 26].

Surgical outcomes for low-grade lesions in pediatric series reported in the medical literature are sparse but generally acceptable. Overall obliteration rates range from 65 to 100 %, with complication rates ranging from 5 to 33 % [6, 17, 20, 21, 23, 24, 27–32]. The complexity of lesions that are treated also varies widely, but most treated AVMs are Spetzler-Martin grades I-III. While high-grade AVMs are typically observed, proper patient selection can lead to successful resection, with Bristol et al. [20] reporting an 86.4 % rate of good or excellent outcomes in grade IV or V lesions at long-term follow-up. However, most of these lesions were in patients who presented with hemorrhage or worsening neurological deficits. Moreover, data suggest that the brain of a pediatric patient has inherent plasticity that allows for better recovery than that of an adult, with one series reporting an initial postoperative morbidity rate of 24.2 %, which improved to 7.8 % over a mean of 3.8 years [33].

Radiosurgical outcomes are highly variable and depend on factors such as AVM size and location, margin dose, patient age, and history of prior embolization. While conventional fractionated radiation therapy is not indicated for most AVMs, stereotactic radiosurgery can achieve cure rates of 62–90 % in small lesions less than 3 cm in size. This modality is especially useful in deep lesions that are surgically inaccessible [19, 34]. Although no randomized clinical trials have evaluated stereotactic radiosurgery in comparison to surgical resection, aggregate class III data seem to support use of the Gamma Knife (Elekta AB) for small deep-seated lesions. For larger lesions, one-year obliteration rates range from 27 to 71 %, whereas overall obliteration rates range from 35 to 83 % [35–43]. Shortcomings include a delay of

up to 3 years to achieve obliteration, during which bleeding rates of 2–25 % have been reported. The risk of side effects in a long-term cohort followed for 25 years was 3.6 %; these included radionecrosis, new motor deficits, cerebral edema, cognitive problems, and cranial neuropathy [44]. Regardless, the effects of radiotherapy on neurocognitive ability in the developing brain are poorly understood and warrant further rigorous studies and research.

Optimal management paradigms are somewhat controversial. In general, surgical excision of AVMs that are Spetzler-Martin grades I-III, whether symptomatic or not, likely remains the best option. Low-grade lesions in highly eloquent territories with a high risk of permanent neurological deficits should be considered for radiosurgery as the primary therapy if they feature a compact nidus that is amenable to radiosurgery. Stand-alone primary embolization should not be used as a definitive treatment because it is often difficult to fully penetrate angiographically occult vessels and recurrence rates are high. High-grade lesions are a therapeutic challenge without an accepted gold standard of treatment, especially given that most patients will not be cured with radiosurgery or embolization alone. Surgery should be considered if the AVM has bled. Otherwise, any other intervention that is considered should involve a multimodal approach; for example, any plan to surgically resect a high-grade lesion should involve preoperative embolization. Emerging data suggest that volume-staged radiosurgery is capable of achieving overall obliteration rates of 41–62 % at 5 years, with significantly higher rates of obliteration observed in patients undergoing >17 Gy per stage [25, 45]. Given the modest obliteration rates, the use of staged radiosurgery may be better suited for downgrading a lesion for salvage therapy. This approach can be especially useful for AVMs with deeper components that are not surgically accessible. Finally, observation should be considered a reasonable option for most high-grade lesions, given the high risk of morbidity with intervention. In some cases, embolization of obvious high-risk features (i.e., intranidal or proximal flow-related aneurysms) can be considered as a palliative measure.

Technique

The goals of surgery should be complete excision of the lesion, including any components that have been embolized. Preoperative embolization, when utilized, can reduce blood loss and operative time. Its use has been shown to be safe and efficacious in many series [46–49]. All children with AVMs should be evaluated for potential preoperative embolization prior to resection. In most cases, embolization can be performed the day before surgery, with the patient monitored overnight in the intensive care unit. All embolizations should be performed under general anesthesia. The goal of embolization is deep penetration of the nidus, most commonly with a liquid embolic agent such as Onyx (ev3 Neurovascular) and with careful avoidance of occlusion of venous drainage. Arterial pedicles are chosen by location and on the basis of the access they provide to the AVM nidus. Deep pedicles, especially those that are not expected to be encountered along the surgical track from the periphery to the AVM, are systematically embolized.

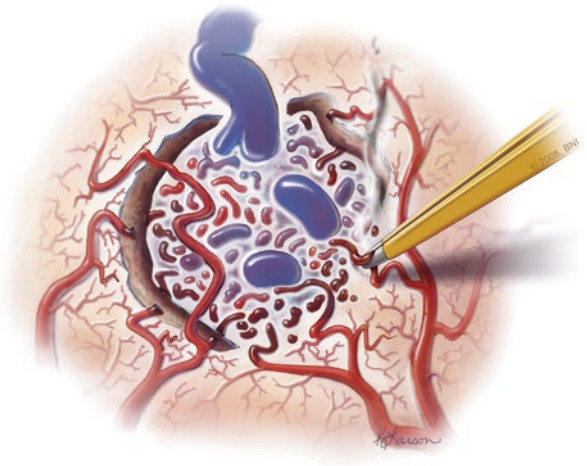

Fig. 9.3 Illustration of cortical lesions shows how easily they can be delineated by identifying superficial venous drainage and arterial feeders leading into the nidus. Note en passage vessel, which should be preserved during resection (Used with permission from Barrow Neurological Institute, Phoenix, Arizona)

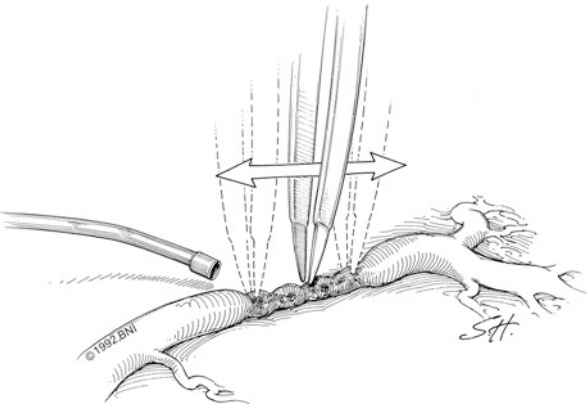

Fig. 9.4 Drawing shows coagulation technique for arterial feeders proximal to the nidus, which often require prolonged coagulation along an extended segment of the vessel prior to ligation (Used with permission from Barrow Neurological Institute, Phoenix, Arizonay)

Prior to incision, matched blood products should be available in the operating room. Special equipment, such as the microscope and temporary aneurysm clips, should be prepared and ready to use. The craniotomy should ensure that the margins of the lesion lie well within the margins of the operative exposure, and the dissection should be performed under the operating microscope once the dura is opened. When feasible, a superficial draining vein identified early on can be followed proximally to localize the nidus. Easily identifiable major arterial feeders are then coagulated. Before the venous drainage is disconnected, an anatomical, circumferential cortical and subcortical dissection is performed, with serial coagulation of supplying arterial pedicles (Figs. 9.3 and 9.4). Indocyanine green angiography is particularly helpful in distinguishing arterial feeders from arterialized veins, in identifying en passage vessels, and in confirming resection. Formal angiography should be performed to confirm total AVM obliteration. Angiography can be performed

intraoperatively, but many centers prefer to keep the pediatric patient intubated to obtain a full angiogram in a dedicated angiography suite. If residual AVM is detected, the patient can be returned to the operating room for resection of the residual AVM; otherwise, anesthesia is reversed and extubation performed.

Pearls

1. AVMs are the most common abnormality of the intracranial circulation in children and are extremely diverse in morphology and presentation.
2. Because of a potentially devastating natural history over the course of a child's life, all pediatric AVMs should be evaluated for potential treatment.
3. Digital subtraction angiography and MRI scans should be obtained as part of the preoperative work-up for any patient being considered for surgery.
4. Surgical excision should be considered as the first-line therapy for all low-grade AVMs because of its curative potential, with or without preoperative embolization.
5. Most high-grade AVMs (Spetzler-Martin grades IV and V) should be observed, although a subset may be amenable to multimodal therapy.
6. Radiosurgery is most effective for small and surgically inaccessible AVMs.
7. Emerging data support staged radiosurgery as an adjunct to help downgrade large lesions.
8. Modern advances, such as indocyanine green angiography and microscope technology, have made AVM surgery safer and should be used whenever possible.
9. Immediate postoperative angiography should be performed to confirm total AVM resection; if residual lesions are found, they should be resected.

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Vein of Galen Aneurysmal Malformations

10

Christopher J. Stapleton, Collin M. Torok, Matthew J. Koch, and Aman B. Patel

Introduction

Vein of Galen aneurysmal malformations (VGAMs) are rare vascular malformations involving the median prosencephalic vein of Markowski, the precursor of the vein of Galen and the embryonic drainage of the choroid plexus. Although reported to comprise 30 % of pediatric vascular and 1 % of pediatric congenital anomalies [1], the exact incidence of VGAMs is difficult to quantify given the array of vascular pathology causing dilation of the median prosencephalic vein of Markowski or the vein of Galen [2]. In this chapter, we review relevant VGAM vascular anatomy and embryology, classifications schemes, clinical features and pathophysiology, and treatment strategies.

Anatomy and Embryology

During normal neurovascular development, the choroid plexus forms before the brain parenchyma is penetrated by vessels and is still nurtured by the surrounding vascularized mesenchymal covering of the brain from which the pia, arachnoid, and

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A. Agrawal, G. Britz (eds.), *Pediatric Vascular Neurosurgery*,
DOI 10.1007/978-3-319-43636-4_10

dura mater later develop. As the choroid plexus expands on the roof of the diencephalon, the arteries and veins supplying and draining the choroid plexus begin to form. The arteries include the anterior cerebral, anterior choroidal, and posterior choroidal arteries. The vein consists of a midline dorsal vein that drains the bilateral choroid plexuses, known as the median prosencephalic vein of Markowski. The median prosencephalic vein of Markowski is the first vein to drain an intracerebral structure and remains functional through weeks 5–10 of gestation. As intracerebral vascularization progresses by week 11 of gestation, the basal ganglia develop and the paired internal cerebral veins form. The internal cerebral veins become the dominant route of venous drainage for the choroid plexuses, leading to the regression of the median prosencephalic vein of Markowski except for its most caudal portion, which in turn becomes the vein of Galen [3]. It is estimated that formation of VGAMs occurs between weeks 6–11 of gestation, when arteriovenous shunts form between the choroidal circulation and the median prosencephalic vein of Markowski [4]. By definition, VGAMs do not involve the vein of Galen proper and the term "vein of Galen malformation" is a misnomer.

With VGAMs, the normal deep cerebral structures utilize alternate routes of venous egress, typically through a vein with an epsilon (ε) shape on the lateral projection of a cerebral angiogram [5, 6]. VGAMs drain in most cases through the embryonic falcine sinus to the superior sagittal sinus, as the straight sinus is usually absent. The presence of a straight sinus, however, does not preclude the existence of a VGAM. Persistence of other embryological sinuses, including the occipital and marginal sinuses, is also frequently observed [4].

Classification Schemes

It is important to distinguish VGAMs from other vascular lesions that lead to dilation of the true vein of Galen, such as vein of Galen aneurysmal dilations (VGADs) and vein of Galen varices (VGVs). VGADs are a group of vascular malformations that drain pial or dural arteriovenous shunts into the vein of Galen or its tributaries. VGVs represent dilated veins of Galen without arteriovenous shunting.

Several classification schemes exist for VGAMs based upon their angioarchitecture. Lasjaunias and colleagues distinguished between choroidal and mural VGAMs. The choroidal VGAM consists of many fistulas located within the subarachnoid space of the choroidal fissure that communicate with the anterior aspect of the median prosencephalic vein of Markowski (Fig. 10.1). The arteries involved are the bilateral anterior and posterior choroidal and anterior cerebral arteries, with additional occasional arterial involvement from the quadrigeminal and thalamoperforating arteries. The mural VGAM consists of a single (or multiple) fistula located in the wall of the dilated median prosencephalic vein of Markowski, most commonly along its inferolateral margin. The arteries involved are usually the quadrigeminal or posterior choroidal arteries [7–9]. Yaşargil and colleagues proposed a four-tiered classification scheme for VGAMs. Type I VGAMs consist of one or more direct cisternal fistulas between the pericallosal and posterior cerebral arteries and the

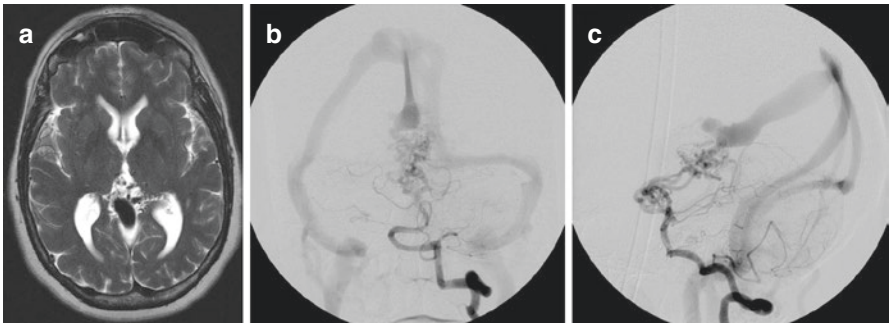

Fig. 10.1 (**a**) Axial T2-weighted magnetic resonance image showing an enlarged venous structure within the velum interpositum posterior to the third ventricle in approximation to numerous arterial structures. (**b**) Frontal and (**c**) lateral left vertebral artery cerebral angiograms demonstrating the Lasjaunias choroidal type vein of Galen aneurysmal malformation, with arterial supply from enlarged bilateral posteromedial and posterolateral choroidal arteries, venous drainage into the median prosencephalic vein of Markowski, and a persistent falcine sinus

median prosencephalic vein of Markowski. Type II VGAMs are made up of thalamoperforator networks that lie between the arterial feeders and the median prosencephalic vein of Markowski. Type III VGAMs have multiple fistulous connections from different arterial feeders, and have characteristics of Yaşargil type I and II VGAMs. Type IV VGAMs are not true VGAMs, and are characterized by the presence of adjacent arteriovenous malformations that drain into the vein of Galen leading to secondary aneurysmal dilation [10].

Clinical Features and Pathophysiology

Cardiac as well as neurological symptoms are common in patients with VGAMs. Each age group, neonate versus infant, and each VGAM subtype, choroidal versus mural, has characteristic presenting clinical symptoms. In neonates, high-output cardiac failure is a frequent clinical feature, while in infants hydrodynamic macrocephaly and neurological complications are more common. Choroidal VGAMs typically cause high-output cardiac failure in newborns as a result of multiple high-flow fistulas with less outflow restriction. Mural VGAMs, on the other hand, have fewer fistulas and more outflow restriction and usually cause macrocephaly or failure to thrive in infants [2, 3].

High-output cardiac failure is almost exclusively the presenting symptom in the neonate. In fact, given the high-flow nature of the arteriovenous shunt, cerebral blood flow can at times comprise 80 % of the cardiac output. The high-flow, low-resistance arteriovenous shunting present in VGAMs results in increased venous return to the right heart. In neonates, this is poorly tolerated and leads to right heart overload, pulmonary arterial hypertension, increased pulmonary blood flow, left heart overload, and decreased myocardial perfusion. This cascade of events culminates in biventricular heart failure. The presence of a patent ductus arteriosus or

patent foramen ovale in the neonate can also increase venous return, exacerbating pulmonary hypertension and precipitating left heart overload. Given the lack of cardiopulmonary reserve capabilities, cardiogenic shock results rapidly and may eventually lead to additional end-organ failure, including hepatic and renal dysfunction [1, 3, 11].

Unlike neonates, infants typically present with symptoms from hydrodynamic disorders related to hydro-venous disequilibrium, although these disorders can also be seen in fetuses, neonates, and infants. When a VGAM is present, there is increased pressure in the torcula herophili and superior sagittal sinus, which impedes normal cortical and deep venous drainage of the brain. Venous hypertension results in brain edema and hypoxia, leading to impaired cortical development and mental retardation, and in reduced cerebrospinal fluid reabsorption, resulting in communicating hydrocephalus [1, 2, 12].

Evaluation and Treatment

Complete evaluation of a patient with a suspected VGAM should include a clinical history and physical examination, including weight and head circumference; renal and liver function tests; a cardiac ultrasound to assess cardiac function; a transfontanelle ultrasound (US) to evaluate the size of the ventricles; and magnetic resonance imaging (MRI) of the brain to obtain information regarding the VGAM and surrounding brain parenchyma. Treatment decisions are guided by careful analysis and assessment of the patient's growth and development, any associated neurological symptoms, and the presence of cardiac and other systemic manifestations. Radiologic data obtained from US and MR imaging yields information regarding the VGAM and brain parenchyma [1, 3, 9, 13, 14]. In general, if a patient is clinically stable, treatment is delayed until 5–6 months of age to reduce the risk associated with intervention at a younger age. Medical, surgical, and/or radiosurgical treatment can be used alone or in combination with endovascular therapy.

For patients with VGAMs, there are both immediate or short-term and long-term treatment goals [8, 13, 15]. Regardless of age, the long-term goal of VGAM treatment is complete closure of the lesion, in an effort to afford the patient the chance of a normal neurological development without deficits. The immediate or short-term goal of intervention, however, may be different and depends largely on the age of the patient at the time of presentation. For neonates, since the presenting symptom is usually cardiac failure, the primary treatment goal is occlusion of the fistula to a degree that allows for resolution of the congestive heart failure. In the absence of life-threatening cardiac failure, the presence of neonatal macrocephaly or hydrocephalus is not an indication for urgent treatment. If significant brain damage is discovered, with or without cardiac failure, treatment is typically not indicated because the clinical outcome, even with complete closure of the VGAM, is likely to be poor [16]. Given the concomitant occurrence of compromised cardiac and renal function in neonates with VGAMs, the extent of angiographic evaluation prior to endovascular treatment should be limited, secondary to intolerance to significant

contrast and volume loads. For infants and children, the immediate or short-term goal of intervention is to restore normal hydrovenous equilibrium to allow for normal development. Within this age group, urgent embolization is classically performed when there is a rapid increase in head circumference, intracranial pressure, or developmental delay. It is recommended that embolization be performed before the onset of symptomatic hydrocephalus, even if the endovascular treatment is only partial. Unfortunately, in these instances, the effect of even complete endovascular closure of the VGAM is usually not sufficient to preclude the need for permanent cerebrospinal fluid diversion once frank hydrocephalus develops.

Once a treatment decision is made, it can take the form of medical management or endovascular embolization, surgical resection, and radiosurgical lesional therapy. The most critical feature of medical management for VGAMs is controlling cardiac failure in newborns. Provided the congestive heart failure can be medically managed, curative treatment should be delayed until 5–6 months of age, when endovascular treatment is technically safer. The management of cardiac failure consists of diuretic and pressor medications and supplemental oxygenation, tailored to the severity of the patient's symptoms. If a neonate in heart failure does not respond to these conservative measures, then emergency endovascular embolization of the VGAM is warranted. Even if only a partial endovascular closure is achieved, the cardiac status of the patient usually drastically improves following a reduction in the high-flow arteriovenous shunt [3, 14].

The endovascular treatment of VGAMs can be performed by occluding the fistula sites via the transarterial approach or by closing the ectatic vein via a transvenous approach. Berenstein and colleagues advocate for the transfemoral transarterial approach when feasible [2, 3], though the transumbilical artery approach is an option in newborn patients if the femoral artery is prohibitively small [17]. From a technical standpoint, a 4 Fr sheath is used for transfemoral access and a 4 Fr diagnostic catheter is used to conduct pre-treatment angiography, with nonionic contrast material utilized. To minimize the amount of radiation, contrast, and fluid volume given to the patient, the right or left vertebral artery is catheterized and injected first. Most often, a frontal projection is sufficient to identify the largest fistula, which should be the target of the first embolization, given that the goal of this treatment is management of the patient's cardiac or neurological symptoms and not necessarily complex closure of the VGAM.

Following diagnostic angiography and identification of the target fistula, embolization can be performed with a flow-directed microcatheter through the 4 Fr guide catheter. For Berenstein and colleagues, the first choice embolic agent is N-butyl-cyanoacrylate (NBCA) [2, 3], although ethylene vinyl alcohol copolymer (Onyx) is also an option [18]. As with dural arteriovenous fistulas in adults, with adequate penetration of embolic material into the site of fistulation, progressive thrombosis of the fistula and dilated vein occurs over several weeks post-procedurally. If the arterial supply is complex, the embolization procedure can be staged, with different arterial pedicles targeted at each staged intervention. Transvenous embolization of the VGAM can be accomplished either via a percutaneous transfemoral or a transtorcular approach [19, 20]. The transtorcular approach may require surgical

exposure of the torcula. For transvenous embolization, a reduction in arteriovenous shunting is achieved by packing the venous pouch with coils, nylon, and/or balloons [2, 3, 21]. As during embolization of carotid-cavernous fistulas, the extent of embolization may be monitored during the procedure by injection of contrast transarterially. In the experience of Berenstein and colleagues, the transvenous approach is reportedly technically easier, but leads to fewer favorable clinical outcomes than with transarterial embolizations [2, 3].

Khullar et al. recently reviewed outcomes following treatment of VGAMs reported in the literature between 1983 and 2010. In total, 22 papers and 615 patients with VGAMs were reviewed, 557 of whom underwent endovascular therapy. While untreated patients had a 76.7 % mortality rate and patients undergoing microsurgical therapy had an 84.6 % mortality rate, 84.3 % of patients undergoing endovascular therapy had a good or fair outcome with only a 15.7 % mortality rate. Neonates were found to have the worst outcomes with a mortality rate of 35.6 %; infants and children fared better with mortality rates of 6.5 % and 3.2 %, respectively [22].

Historically, surgical management of VGAMs was the primary treatment modality [1, 22]. However, given that surgical outcomes are poor, it has been supplanted by endovascular therapy as the primary form of treatment [13]. Radiosurgery has a limited role for VGAMs, as its latency of closurecan be prohibitive in achieving the timely occlusion needed for restoration of normal cardiac and neurological function [2].

Summary

VGAMs consist of abnormal arteriovenous shunts between choroidal and anterior cerebral arteries and the median prosencephalic vein of Markowski, the precursor to the vein of Galen. The presenting symptoms vary depending on the type of VGAM and the age of the patient at presentation. Treatment of VGAMs has historically been conservative or surgical. The advent of endovascular therapies has improved treatment efficacy and neurological outcomes.

Conflicts of Interest The authors have no conflicts of interest, sources of financial support, or industry affiliations to disclose relevant to this investigation.

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Capillary Telangiectasias

11

Matthew R. Reynolds, Joshua W. Osbun,
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Abbreviations

AVM	Arteriovenous Malformation
BCT	Brain Capillary Telangiectasia
CM	Cavernous Malformation
CT	Computed Tomography
DVA	Developmental Venous Anomaly
MRI	Magnetic Resonance Imaging

General

Classically, intracerebral vascular malformations have been categorized into four main types based upon their angioarchitecture: arteriovenous malformations (AVM), cavernous malformations (CM), developmental venous anomalies (DVA), and brain capillary telangiectasias (BCT) [21, 24]. The latter cerebrovascular malformation will be the focus of discussion in the present chapter.

While the precise natural history of BCTs is currently unknown, these lesions have long been regarded as the most benign vascular malformation in the brain and, with few exceptions, are small, solitary, asymptomatic lesions of unknown origin that are discovered incidentally on routine neurological imaging or at autopsy [34]. Anatomical and pathological reports of BCTs in the literature date back to the early 1940s [5]. These are relatively rare lesions, with a reported prevalence between 0.4 and 0.15 % in large autopsy studies [15, 38]. BCTs represent 16–20 % of all

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A. Agrawal, G. Britz (eds.), *Pediatric Vascular Neurosurgery*,
DOI 10.1007/978-3-319-43636-4_11

intracerebral vascular malformations at autopsy [28]. BCTs are typically diagnosed in the adult population and reports in pediatric patients (particularly symptomatic lesions) are infrequent [4, 8].

BCTs are considered by most authorities to be congenital lesions occurring most commonly in the striate pons [18]. However, they have also been reported to occur in other regions of the brain as well, including the posterior fossa (e.g., cerebellar hemispheres, middle cerebellar peduncle, medulla), cerebral hemispheres, basal ganglia, and spinal cord [19, 29]. While BCTs are most often solitary lesions, multiple lesions have also been described [25]. Furthermore, BCTs can also coexist with sporadic or syndromic cerebrovascular malformations of the central nervous system including Osler-Rendu-Weber syndrome (Hereditary Hemorrhagic Telangiectasia), Sturge-Weber syndrome, ataxia-telangiectasia, and Wyburn-Mason syndrome.

In some circumstances, cerebrovascular malformations can occur in pairs, or triads (most commonly a CM with a DVA) [32]. This has led some authorities to hypothesize that these malformations may not represent separate entities, but more likely encompass a spectrum of more aggressive vascular lesions resulting from progressive venous outflow obstruction and venous hypertension [32]. This theory is supported by the finding that some BCTs can develop in de novo fashion [36] or following radiation therapy [13]. In cases such as these, it is also feasible that some BCTs could be acquired as well.

With improvements in magnetic resonance imaging (MRI) capabilities during the past decade (e.g., increased field strength and utilization of T2*/gradient echo and susceptibility weighted sequences), these slow-flow lesions are being increasingly detected on neuroimaging studies. While BCTs rarely require neurosurgical intervention, it is important to differentiate these cerebrovascular malformations from more serious neuropathologies such as intracerebral neoplasm, acute demyelinating disease, infection, inflammation, subacute infarction, and central pontine myelinolysis.

Histological Features

While the diagnosis of BCT rarely requires histopathological confirmation, the hallmark histopathological appearance is that of multiple, dilated, irregular, thin-walled capillary spaces intermixed with normal brain parenchyma [9]. This distinguishes BCTs from CMs, which are identical in microscopic appearance but have no intervening normal brain parenchyma [9]. Typically, the capillary walls of BCTs lack smooth muscle and elastic fibers [22]. Oftentimes, these lesions are associated with an enlarged venous draining vessel.

Radiographic Features

Computed Tomography (CT)

Standard CT imaging (both with and without iodinated contrast) is generally not helpful in the diagnosis of BCT. Contrasted CT scans occasionally detect the lesion on high resolution, thin-cut studies. Also, in the rare event that a BCT

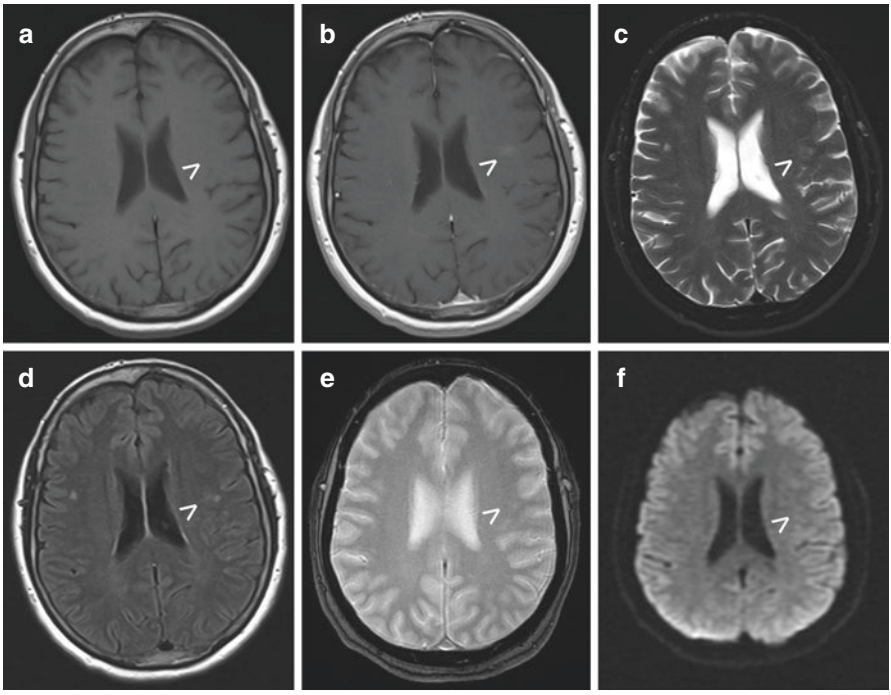

Fig. 11.1 An incidentally-diagnosed, left frontal (centrum semiovale) BCT is demonstrated in a 14-year-old boy. Non-contrast head CT showed no clear abnormality (not shown). Axial MR imaging demonstrates a lesion that is isointense to gray matter on T1-weighted sequences (**a**; *arrowhead*) with faint, brush-like, gadolinium enhancement (**b**; *arrowhead*), slightly hyperintense on T2-weighted (**d**; *arrowhead*) and fluid-attenuated inversion recovery (FLAIR) (**e**; *arrowhead*) sequences, and exhibits a subtle, punctate area of hypointensity on T2*/gradient echo sequences (**f**; *arrowhead*). MR angiography (time-of-flight) was normal (not shown). This abnormality was noted to be stable on serial MR imaging studies over a period of 10 years

induces a spontaneous intraparenchymal hemorrhage, the acute blood products and surrounding vasogenic edema can be easily seen on non-contrasted CT studies.

Magnetic Resonance Imaging (MRI)

Review of the literature reveals substantial inconsistency of the MR features of BCTs. BCTs exhibit considerable variability on standard MR sequences including unenhanced T1-weighted, T2-weighted, and fluid-attenuated inversion recovery (FLAIR) imaging [19, 33]. Following gadolinium contrast administration, BCTs may demonstrate faint, brush-like patterns of enhancement on a background of unenhanced brain parenchyma [19] (Fig. 11.1). In most cases, an enlarged venous channel—likely representing a draining vein—can be observed [19]. There is rarely associated mass effect, gliosis, or focal edema. Hemorrhage, hemosiderin, and calcifications are infrequent findings. On T2*/gradient echo

sequences and susceptibility weighted imaging, however, BCTs have a more stereotyped and diagnostic appearance. These lesions appear hypointense (e.g., signal loss) on these MR sequences given the presence of increased local deoxyhemoglobin in the stagnant, low-flow venous channels [2] (Fig. 11.1). Some recent evidence suggests that susceptibility weighted imaging may increase the frequency of detection of BCT as compared to T2*/gradient echo imaging [11]. The stability of these MR imaging findings over time further supports the diagnosis of BCT.

Cerebral Angiography

Traditionally, BCTs (as well as CMs) belong to the category of "angiographically-occult" intracerebral vascular malformations [39]. Due to the stagnant, low-flow hemodynamic state of most BCTs, there are no conspicuous findings on diagnostic cerebral catheter angiography. Tiny capillary vessels may occasionally be observed in the late venous phase. In the setting of a mixed vascular malformation that includes a BCT, and AVM or DVA may be appreciated on angiographic studies.

Clinical Presentation

Asymptomatic

Based upon their frequent incidental discovery on routine neurological imaging studies and at autopsy in subjects without clear neurological manifestations, BCTs have been considered by most authorities to be benign lesions with an innocuous clinical course. In 1968, McCormick and colleagues [23] published an autopsy series of 157 subjects harboring 164 cerebrovascular malformations within the posterior fossa. In these specimens, they discovered 60 pathologically-verified BCTs: 38 BCTs were located in the posterior fossa and 22 BCTs were located in the supratentorial compartment. No BCT demonstrated any evidence of remote or current hemorrhage. The authors concluded that BCTs represent a benign lesion with a low risk of hemorrhage. More recently, Lee et al. [19] and Barr et al. [4] reported on the MR imaging appearance and clinicohistopathologic findings of 15 and 12 subjects with BCTs, respectively, followed over a period ranging from 1 month to 4 years. These authors also found no instance of spontaneous hemorrhage resulting from a BCT in any patient. Finally, in a population-based analysis of intracerebral vascular malformations in a defined population (Mayo Clinic Database, Olmstead County, Minnesota) over a 27-year observational period, the authors did not observe any spontaneous hemorrhage referable to a BCT [7].

Symptomatic Without Hemorrhage

While the vast majority of BCTs are discovered incidentally, some BCTs do exhibit a more aggressive clinical course and can produce clinical signs and symptoms either with or without evidence of frank hemorrhage. Scaglione et al. [34] presented a series of 3 young patients with transient or intermittent focal neurological symptoms suggesting brainstem involvement due to pontine BCTs. In this report, they also performed a literature review of 20 additional cases of unruptured BCTs presenting with a myriad of neurological signs and symptoms compatible with lesion location including: headache, nausea/vomiting, vertigo, tinnitus, speech disturbance, visual alteration, sensorineural hearing loss, cranial nerve palsies, weakness, numbness, and/or myelopathy. The age at presentation ranged from 15 months to 71 years, but was most common in the third and fourth decade. They also found that symptomatology in some female patients corresponded with changes in hormonal cycles (e.g., pregnancy or menstruation). Because of this, the authors proposed that steroid receptors present in the capillary endothelium of BCTs may be responsive to local changes in estrogen and/or progesterone.

Sayama et al. [33] retrospectively reviewed 105 patients with MR imaging findings suggestive of a BCT. Seven (6.7 %) patients were found to have BCT > 1 cm in size, and two of these patients were identified as having symptoms likely related to their BCT. No patient with a BCT < 1 cm was suspected of having symptoms due to their BCT. The authors concluded that unruptured BCTs are infrequently symptomatic, but that large size may positively correlate with clinical symptoms. While most symptomatic unruptured BCTs are small in size, Tan et al. [37] reported on a patient with a giant unruptured pontine BCT measuring 3.0 × 2.7 × 2.5 cm causing symptoms of headache, vertigo, and bilateral upper extremity numbness. This lesion was managed conservatively with complete resolution of symptoms.

Focusing on symptomatic, unruptured BCTs in the pediatric population, Huddle and colleagues [14] reported on an exceptionally aggressive BCT in a child which resulted in progressive neurological deterioration, and, eventually, death. The patient was an infant who experienced febrile seizures, strabismus, gait ataxia, and speech deterioration before 2 years of age. At 4 and ½ years of age, the symptoms progressed to involve multiple cranial nerves without affecting sensation or motor strength. On MR imaging, there were large areas of gadolinium enhancement in the pons and upper medulla. The child died in her sleep at the age of 5 years. Autopsy confirmed a large, diffuse BCT replacing much of the normal basis pontis and pontine tegmentum. No evidence of recent or remote hemorrhage was noted on histopathological examination. Pozzati et al. [30] described an unusual case of a giant, unruptured BCT in the right frontal lobe of a 10-month-old child causing symptoms of progressive neurological decline. The child underwent surgical evacuation of the lesion with satisfactory clinical results. Moreover, Smith et al. [35] presented a case of a brainstem BCT in a child resulting in neurological decline. Serial MR imaging studies demonstrated lesion progression prior to the child's death. The authors

proposed that intravascular coagulation within the BCT leading to localized ischemia might be responsible for the radiographic progression and growth of the lesion.

Possible pathogenic mechanisms for how non-ruptured BCTs produce neurological symptoms include (1) focal mass effect from the lesion and/or (2) local and/or regional hemodynamic alterations (including true arterio-venous shunting and vascular steal phenomena) in the brainstem leading to insufficient cerebellar perfusion and ischemic injury [3, 10, 14]. In addition, small microhemorrhages within, or adjacent to, the brainstem that are not detectable on routine neuroimaging studies may produce primary and secondary neuronal injury that directly cause clinical symptoms [14].

Symptomatic with Hemorrhage

While surgical evacuation of spontaneous pontine intraparenchymal hematomas in children and young adults have been reported [1, 12, 17], few instances of hemorrhage resulting from a BCT have been documented. In general, hemorrhage seen in association with a BCT is far more likely to arise from an accompanying, more aggressive vascular malformation (e.g., AVM or CM) rather than from the BCT itself [6, 20]. However, symptomatic pontine BCTs have been reported in the pediatric neurosurgical literature.

Katsuzo and colleagues [16] reported on a young female who presented with a symptomatic intraparenchymal hemorrhage (~1 cm) in the right pontine tegmentum. This lesion demonstrated some enhancement on contrasted CT and was angiographically-occult during catheter vertebral angiography (fenestration of the left distal vertebral artery was observed). Craniotomy and microsurgical resection was performed with a histopathological diagnosis of BCT.

Bland et al. [6] also reported a single case of a large, acute cerebellar hemorrhage secondary to a BCT in a 4-month-old infant. This lesion required prompt intervention via craniotomy and surgical evacuation of the hematoma. Histopathology confirmed the presence of a BCT. The patient went on to have an excellent neurological outcome after surgery.

While hemorrhage from a BCT is exceedingly rare, some authors have speculated that these lesions could alter the local hemodynamics and promote a vascular remodeling process that leads to a more aggressive vascular malformation. Small hemorrhages within a BCT could also induce angiogenic factors that promote a more extensive and disorganized vascular structure [3, 31]. Moreover, vascular shunting through BCTs could cause arteriolization of some vessels, perhaps leading to the formation of an AVM [10]. Finally, hemodynamic stresses on BCTs may lead to thickening and hyalinization of the vascular channel walls, which, combined with progressive venous outflow obstruction, may result in a lesion with a greater risk of hemorrhage [3].

Development

The precise etiopathogenesis of BCTs remains enigmatic. The brain has numerous capillary channels that involute during normal cerebrovascular development. Any type of aberrant physiological signal that prevents this normal involution process may ultimately result in a BCT [3, 26, 27].

Neurosurgical Management

Conservative Therapy

As mentioned above, the vast majority of BCTs are small, solitary, clinically-benign lesions that will never require neurosurgical intervention. In the case of a suspected BCT, serial MR imaging studies (including T1-weighted post-gadolinium and T2*/gradient echo or susceptibility weighted sequences) verify stability of the lesion over time may be entertained.

Neurosurgical Resection

In rare cases of BCT that cause overt or progressive neurological symptoms referable to an unruptured or ruptured lesion, craniotomy and surgical resection may be appropriate. However, one must always consider the presence of an underlying mixed vascular malformation (e.g., AVM or CM) that could accompany a BCT. In these cases, the latter malformation should be the target of surgical resection.

Clinical Pearls

1. BCTs are most often small, solitary, asymptomatic, incidentally-discovered, clinically-benign lesions.
2. Cerebral angiography is often not helpful in diagnosing BCTs given the low flow state of blood within the lesion (e.g., angiographically-occult), but can exclude other forms of vascular malformations.
3. BCTs appear best on MR imaging studies that include T1-weighted post-gadolinium sequences, T2*/gradient echo sequences, and susceptibility weighted sequences.
4. Size, location, MR signal characteristics, and lack of progression on serial neuroimaging studies are all features that are highly suggestive for a BCT.
5. In rare cases of symptomatic ruptured or unruptured BCTs, surgical resection may be appropriate.
6. In the absence of overt neurological signs and symptoms referable to the BCT a conservative management strategy is recommended.

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Developmental Venous Anomaly

12

Spyridon Kollias and Iris Blume

Introduction

The term developmental venous anomaly (DVA) was suggested by Lasjaunias [1] based on the fact that DVAs are more likely to be embryologic venous drainage variants. DVA is a well-established synonym replacing the term venous angioma or cerebral venous malformation. The cerebral vascular malformations are categorized in four major types by the standard classification of Russel and Rubinstein's: (1) Developmental venous anomaly; (2) cavernous malformations; (3) arteriovenous malformations (AVM) and (4) capillary telangiectasia. DVAs are considered to be low flow congenital cerebral vascular malformations and are the most common type of vascular malformation.

The incidence of DVAs is reported to be between 00.5 and 3 % in the general population and they compose up to 42–63 % of all cerebral vascular malformations [2]. The etiology of DVAs is unclear and different theories have been postulated. The most accepted theory is that a DVA develops as a result of compromised venous drainage of normal developing brain due to stenosis, thrombosis and maldevelopment of the embryonic venous system [3]. The other theory suggests an abnormal fetal angiogenesis with consequent vessel regression leading to the development of a DVA [4]. There have been very few documented cased of postnatal development of DVAs and they are considered congenital lesions.

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A. Agrawal, G. Britz (eds.), *Pediatric Vascular Neurosurgery*,
DOI 10.1007/978-3-319-43636-4_12

A DVA drains normal brain parenchyma and is composed of linear branching veins, the "caput medusae", draining into a single larger collecting vein. The collecting vein crosses a variable length of brain parenchyma to drain into the superficial or deep venous system, or in up to 10 % of cases into both [1] DVAs can involve a variable territory of the brain parenchyma ranging from tiny lesions to massive ones, with a very complex venous architecture, involving up to an entire hemisphere. The role of DVAs in the venous drainage of normal brain parenchyma (both supra- and infratentorial) should not be underestimated and surgical resection can lead to dramatic complications such as venous infarction and hemorrhage.

Most DVAs are localized in the frontal lobe and the caput medusae most often drains the deep brain parenchyma followed by the subcortical layer or a combination of both [5]. Coexistence of two or more DVAs is reported in up to 1.2–16 % of cases [6, 7]. Focal stenosis of the collecting vein can be observed at the point where the vein crosses the dura to drain into the sinus. Ampullary dilatation of the proximal vessel segment [8] can be observed and is due to a focal thickening of the collecting vein. These findings can lead to chronic venous congestion [9, 10].

Clinical Presentation

DVAs are typically incidental findings. They are mostly asymptomatic and show a benign course [11, 12]. Headaches, dizziness and ataxia have been thought to be possibly associated with DVAs but it's difficult attributing such generalized symptoms to such common lesions. They are associated with other vascular malformations predominantly with cavernomas [13]. When isolated a DVA has a very low complication rate (0.15 % per year) mainly from spontaneous thrombosis of the collecting vein leading to venous infarction or hemorrhage. If associated with another lesion the risk of complication is elevated to risk of the associated lesion (Fig. 12.1). More complex forms of DVA's such as the arterialized DVAs though can lead to complications. In cases of suspected arterialized DVA a DSA is necessary to further characterize the lesion. Ruiz et al. classified arterialized DVAs into three different groups: (1) DVAs with opacification of the caput medusae in the mid to late arterial phase but without a visible feeding artery or AVM nidus; (2) DVAs with a dilated arterial feeder but without a detectable AVM nidus; (3) DVAs draining an AVM. A possible continuum exists from a simple DVA to an arterialized DVA eventually leading to the formation of an AVM. Thrombosis and partial recanalization of the DVA may induce arterialization of the DVA creating the basis of newly formed AVMs [14] (Fig. 12.2a, b).

There are few reports suggested associations of DVAs with focal cortical dysplasia's and epilepsy [15–17], hydrocephalus due to aqueduct obstruction [18], ophthalmoplegic migraine [19], tinnitus [20], nerve root compression [21] and possible even brain tumors [22].

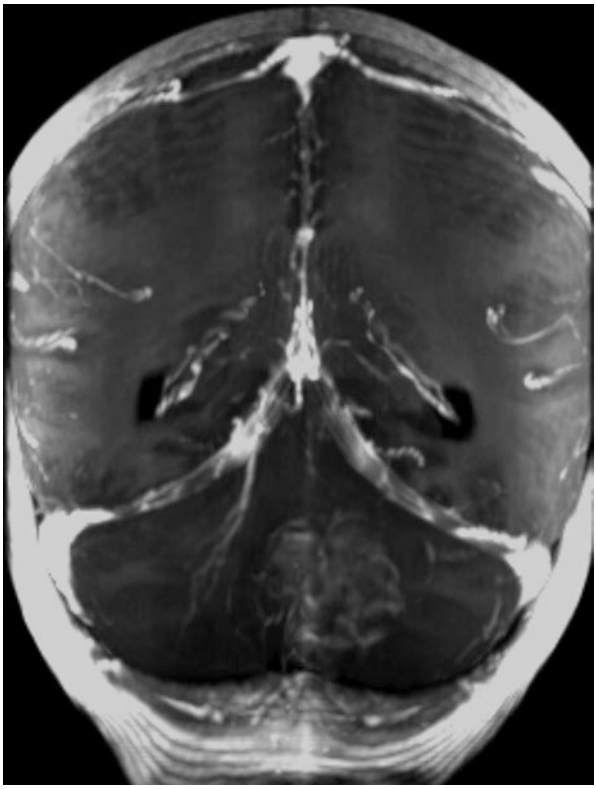

Fig. 12.1 Hemorrhage in the left temporal lobe due to a cavernoma. The cavernoma is in close approximity with a large DVA

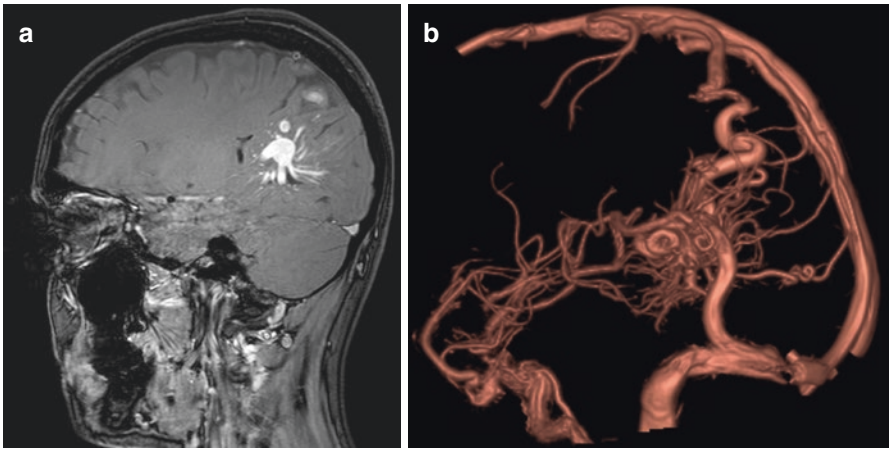

Fig. 12.2 Sagittal Phase contrast MRA (**a**) and 3D volume reconstruction (**b**) demonstrate a large arterialized DVA in the left parietal lobe with a prominent collecting vein

Neuroimaging of Developmental Venous Anomalies

On non-contrast enhanced CT (NECT) the collecting vein may be slightly hyperdense or in case of thrombosis distinctly hyperdense. NECT can demonstrate associated hemorrhage, calcifications and atrophy [8]. Flow-voids and phase-shift artifacts may be noted on unenhanced T1 and T2 weighted imaging.

In CT and MRI the likelihood of depicting the caput medusae is increased by contrast administration. MRI is superior in detecting associated parenchymal abnormalities and small DVAs. An increased detection rate of DVAs is achieved by higher field strength MR Scanners with improved image quality and by the standardized use of susceptibility weighted imaging.

Susceptibility-weighted imaging is a high-resolution 3D gradient-echo technique enhancing paramagnetic properties of blood products (deoxyhemoglobin, intracellular methemoglobin and hemosiderin), which makes this sequence sensitive to the presence of small amounts of hemorrhage. The T2* gradient echo sequences is less sensitive in detecting DVAs compared to SWI. Using these sequences is a helpful tool to screen patients for associated Cavernoma [14].

A DVA exhibiting typical imaging characteristics on CT or MRI needs no further evaluation by digital subtraction angiography (DSA) but DSA remains the gold standard characterizing the micro- and macrovascular structure and the hemodynamics of a DVA. A DSA needs to be performed only when a DVA presents with atypical bleeding, ischemic complications or when associated with vascular malformations [23].

Association with Other Vascular Malformations

A high number of DVAs (13–40 %) are associated with cavernous malformations [8, 13]. In the literature simultaneous cavernoma and DVA are more common in adults but there are also reports in the pediatric literature. The cavernomas are typically found adjacent to the caput medusae suggesting their close relationship and may represent an embryologic continuum (Fig. 12.3a–c).

DVAs and cavernomas are though to present responses of a compromised venous drainage with elevated venous pressure in the DVA leading to recurrent microhemorrhages [4, 24]. The risk of hemorrhage associated with DVAs was found to be 0.22 % per year in a retrospective study [25] and even as high as 0.68 % in a prospective study [15]. Acute thrombosis of the collecting vein can lead to hemorrhage and ischemic venous infarctions [11, 26, 27].

De novo formation of Cavernomas in the drainage territory of DVAs has been documented [28, 29] due to a reactive angiogenesis caused by venous hypertension with subsequent microhemorrhage from fragile vessel walls resulting in relative tissue hypoxia [30, 31]. These neovascular structures lack a regulatory capacity making them prone to bleeding, which again increases angiogenesis with abnormal vessel formation eventually leading in the formation of a cavernoma [17, 32].

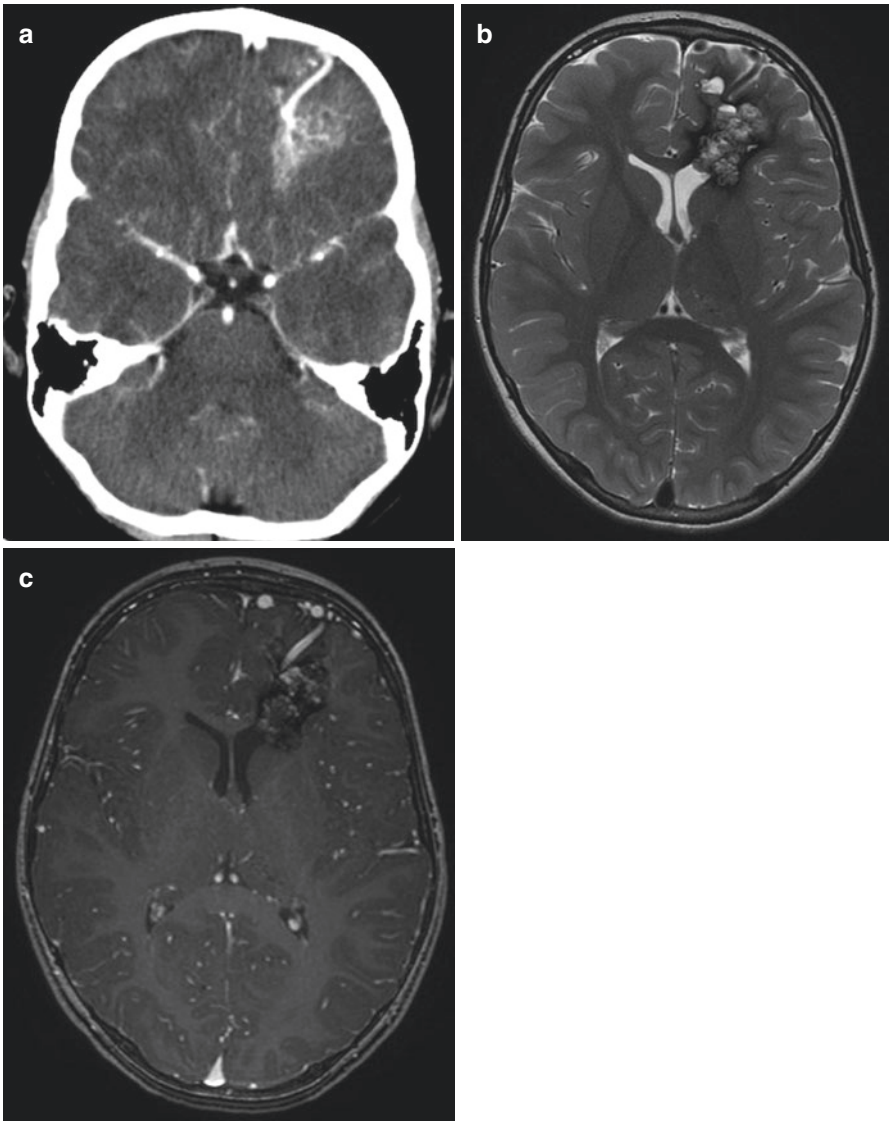

Fig. 12.3 Axial CT (**a**), axial T2w (**b**), axial T1w post contrast MRI (**c**) demonstrade a large cavernoma in the left frontal white matter associated with a DVA draining in the superficial cortical vein with a caput medusae intimatly related to a cavernoma

Follow up of DVAs with signs of hemorrhage may be warranted to screen for cavernoma development.

DVAs are associated with other malformations of the head especially with large superficial venous malformations [33]. In patients with lymphatic or venolymphatic malformations a DVA is found in up to 60.6 % of the cases but other associated

intracranial vascular lesions such as Cavernomas (6.1 %), dural arteriovenous fistulas (12.1 %), pial arteriovenous malformations (3 %) or sinus pericranii (3 %) have also been reported [34] [35]. Sinus pericranii is an abnormal extracranial drainage of the intracranial circulation via a diploic emissary vein into a superficial venous pouch connected to the subgaleal venous system. Sinus pericranii can be the major drainage of the DVA. These correlations suggest that a solitary DVA may be due to a focal abnormality in the venous drainage but also may be a sequel of a widespread perturbation in vascular development. DVAs may also be associated with the blue rubber bleb nevus syndrome ([36]) which is a vascular phakomatosis.

Adjacent Brain Parenchymal Changes

Concurrent brain parenchymal signal abnormalities are described in up to 11.6 % of examined children [37] and in 12.5–28.3 % of the adult population [8, 38]. In a series of adults, parenchymal abnormalities were reported in up to 65 % of the patients including regional atrophy (29.7 %), dystrophic calcifications (9.6 %) and non-specific white matter lesions (28.3 %) [8].

A study showed that white matter lesions occurred with a higher prevalence in young children and were decreasing over time with brain maturation [37]. This finding suggests that white matter lesions in children are possibly due to delayed myelination in the DVA drainage territory. With aging irreversible gliotic changes are thought to be the predominant process. In the mentioned study the children were found to have a higher incidence of cavernoma (6.2 %). Additional parenchymal abnormalities such as focal atrophy were less frequent in the pediatric age group (4.1 %) as compared to the adult population (29.7 %).

White matter lesions on T2/FLAIR weighted images occurring in the drainage territory of the DVA lead to a diagnostic dilemma with regards to their significance and relationship to the presenting symptoms. The pathologic correlation and etiology of white matter lesions remains uncertain but may reflect edema, demyelination and gliosis due to chronic venous hypertension caused by the abnormal venous drainage with subsequent ischemia and microhemorrhage. The hyperintense white matter lesions can coexist with hypointense foci on T2-and FLAIR weighted imaging. Coexistence with hypointense foci may indicate microhemorrhage or cavernoma [39].

In MR perfusion studies, evaluating the hemodynamics of DVAs, an altered cerebral blood flow in the drainage territory of DVAs was noted regardless of lesion size. The typical perfusion pattern is an increased cerebral blood flow and blood volume with a slightly increased mean transit time [40].

DVA in the Neonatal Period

Even though assumed to be a congenital lesion very little is known about DVA in the neonate. A recent study evaluated neonates by sonography and MRI with incidentally found DVAs on imaging performed for other reasons [41] 41]. The

ultrasonographic appearance of a DVA is a uniform area of hyperechogenicity. On doppler US blood flow is depicted in the center of the lesion corresponding to the collecting vein. Serial evaluation of the DVA showed marked changes in its imaging appearance and on the surrounding parenchyma in MRI and US without a clear pattern. This is a surprising finding since DVAs are usually considered stable over time. In the neonates there was a higher incidence of arterialized DVAs (29 %) compared to adults suggesting that an arterialized phase could be a point in the evolution of DVAs with subsequent loss of the arteriolization once they reach hemodynamic stability [41].

DVA in the Pediatric Tumor Patients

In a recent publication a higher prevalence of DVAs in children with brain tumors was reported [22]. A concomitant DVA was diagnosed in 10.17 % of the pediatric tumor patients compared to 5.32 % in children without a tumor. There was no significant difference in the incidence among various tumor types and no correlation was found between the location of the DVA and the tumor. The reason and the clinical significance of DVAs being more prevalent in children with brain tumors is uncertain. A direct causative link of DVAs and brain tumors is unlikely since the DVAs were not draining the tumor territory in the reported cases. The hypothesis of a DVA being the result of a vascular compromise leads to the assumption that a concomitant damage elsewhere in the brain could result in a higher risk for tumor development (Fig. 12.4a, b).

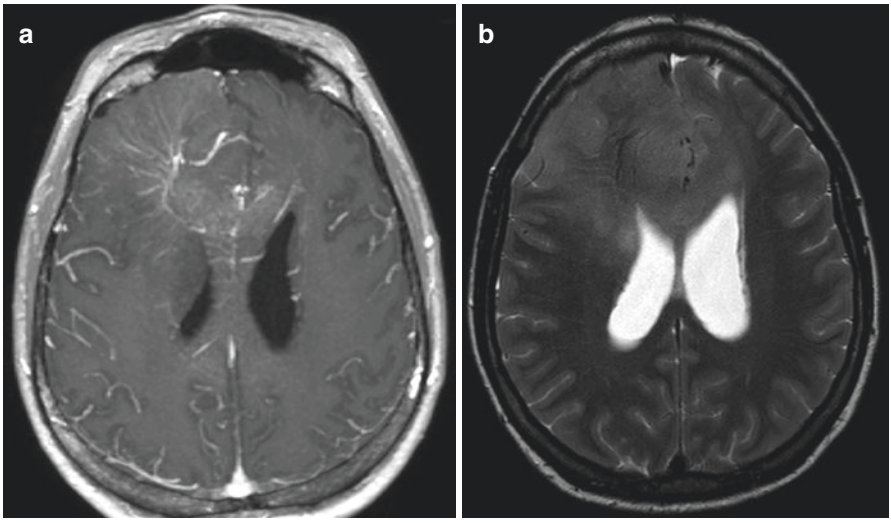

Fig. 12.4 Axial T1w post contrast (**a**) and T2w (**b**) demonstrade a diffuse infiltrating mass in the right frontal lobe and corpus callosum with a huge associated DVA in the right frontal lobe

DVA Associated with Other Diseases

There are unusual presentations associated with DVAs such as aqueductal stenosis in children. Usually the obstruction of the aqueduct is caused by a tumor, post-inflammatory gliotic atresia or congenital disease and very rarely by a vascular malformation. An obstruction of the ventricular system due to a DVA is extremely rare with very few reported cases in the literature [42]. In these cases the DVA should not be treated, rather the treatment should target decompression of the hydrocephalus.

An association with migrational abnormalities has been described but DVAs are rather thought to be a manifestation of an underlying disease than being the cause of it.

There are a few reports in the pediatric literature regarding the association of DVAs with seizures in children [43]. In most reports the children were thought to be symptomatic due to associated hemorrhage. In children with epilepsy a DVA is often an incidental finding, which in most cases is not correlated with the seizure focus in the electroencephalography.

Rare reports exist of DVAs draining in the veins of the cerebellopontine angle cistern and internal auditory canal leading to a unilateral sensorineural hearing loss in children [44].

Treatment

Acute thrombosis of the collecting vein can lead to hemorrhage and ischemic venous infarctions which shows that DVAs play an important role in the venous drainage of normal brain parenchyma. Management of these complications is usually conservative and surgery is only necessary in cases of significant hematoma or in the setting venous infarctions with significant mass effect. Surgical removal of DVAs can lead to a devastating venous infarction and hemorrhagic complications [45] [46]. In order to prevent such complications the surgeon must preserve the collecting vein of a DVA when surgery becomes necessary. If the DVA is an isolated lesion no further treatment is necessary. If the DVA is associated with another vascular malformation the treatment of the other lesion is guiding further therapy.

Pearls

- DVAs are usually asymptomatic and an incidental finding on MRI/CT.
- Often associated with other malformations most commonly cavernomas.
- Complications are not related to the DVA but rather to the risk of the associated lesion
- Rarely venous infarctions due to thrombosis of collecting vein.
- Higher incidence in children with brain tumors.
- Rare association with focal cortical dysplasia's, epilepsy, hydrocephalus, ophthalmoplegic migraine, tinnitus, nerve root compression.

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Sinus Pericranii

13

Carlos Zamora and Mauricio Castillo

Sinus pericranii (SP) are rare venous anomalies characterized by epicranial blood-filled pouches that communicate with the intracranial venous system. These lesions can be spontaneous, congenital, or traumatic, although their precise pathogenesis remains elusive. They may be found incidentally by imaging or come to clinical attention as scalp soft tissue masses and they are rarely symptomatic. SP can occur in isolation or with other intracranial vascular anomalies and have also been described in the setting of certain syndromes and systemic processes. Here we offer a brief review of these lesions.

Embryological and Anatomical Considerations

Development of the veins of the head lags behind that of the arteries and begins shortly after closure of the neural tube. Starting at week 5 of embryonic life, the neural tube becomes embedded the *meninx primitiva*, a mesenchymal covering that later gives rise to the meninges [1]. During weeks 5 and 6, an early vascular meshwork develops within the *meninx primitiva* and subsequently divides into deep and superficial layers, which will respectively form the future deep cerebral and

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A. Agrawal, G. Britz (eds.), *Pediatric Vascular Neurosurgery*,
DOI 10.1007/978-3-319-43636-4_13

superficial (dural) venous systems, with their remaining anastomoses constituting the precursors of the bridging veins [1, 2]. At around week 8, development of the calvarium further separates what becomes the extracranial superficial system from the dural system. The small intervening connections form the emissary veins, which ultimately play a decompressive role by equalizing intracranial pressures [2, 3]. Lack of valves in these veins allows bidirectional flow [3].

Accordingly, albeit rather simplistic, the veins of the head can be classified into a superficial system draining the integumentary tissues; a dural system, between the inner and outer layers of the dura; and a cerebral system [2]. Communication of a SP with the dural system occurs via single or multiple emissary veins crossing the calvarium, either directly or less commonly through cortical veins [4]. Aside from those probably related to trauma, the pathophysiology of SP has not been elucidated, but their association with other venous anomalies has led some to believe that transient venous hypertension in the late embryonic period may play a role [5].

Clinical Presentation and Natural History

For practical purposes, a SP may be categorized as being spontaneous (probably the most common type), congenital or traumatic [6]. Regardless of its cause, a SP presents as a fluctuant and compressible soft tissue mass generally of small size and adherent to the underlying bone as it is subperiosteal in location. Most SP are found in the frontal bones (40 %) along the metopic suture [7]. They do, however occur in other regions (parietal: 34 %, occipital: 22 %, and temporal: 4 %) [7]. SP may or may not pulsate and the overlying skin may show blue or red discoloration and be hairless. Tortuous and dilated veins may accompany the bump and larger SP may show superficial ulcerations and infection. A SP changes in size in accordance with intracranial pressure and enlarges with Valsalva maneuver, laying down, coughing and/or compressing the jugular veins [8]. Otherwise, SP tend to be asymptomatic. When symptoms occur they include headaches, vertigo, nausea, hearing loss, and ataxia; other symptoms are extremely uncommon. SP tend to grow very slowly. At presentation, most patients are young (<30 years) and most are males (since they are more prone to trauma than females) [6]. Congenital SP do however present earlier in life and probably occur equally in both genders [6].

From a clinical standpoint, the differential diagnosis mainly includes: dermoid/epidermoid, hematoma, encephalocele, growing fracture (leptomeningeal cyst), AVM, hemangioma, lipomas, and eosinophilic granuloma [8]. Diagnostic imaging generally confirms the diagnosis of SP and no histological examination is needed. If histological examination is performed, congenital ones show walls that have endothelial lining similar to that of normal veins but post traumatic ones do not show these features but rather just a fibrous wall [9].

As stated previously, most SP grow slowly and have a favorable prognosis. Although some disappear spontaneously many require some type of treatment. Treatment is generally done for cosmetic reasons, to prevent infection and

hemorrhage, and to avoid air embolism and underlying venous thrombosis. Treatment is done only after a normal intracranial venous anatomy has been documented (see below). Spontaneous thrombosis may be induced by non-steroidal anti-inflammatory drugs and warm compresses [10]. Larger SP may have negative psychological impact on patients and may have to be treated solely for this reason [6].

Special mention should be made of congenital SP as it may be associated with other intracranial vascular anomalies (this does not happen with traumatic and spontaneous ones). In one series the most common associated anomalies were: vein of Galen hypoplasia, vein of Galen malformation, dural sinus malformation, developmental venous anomalies, and arteriovenous malformation (AVM) [7]. Systemic associated anomalies include meningocele, esophageal atresia, facial hemangioma, von Hippel Lindau disease, blue rubber bleb nevus syndrome, and cerebrofacial arteriovenous metameric syndrome [6].

Although anecdotally, some very large SP have been associated with consumption coagulopathy (Kasabach Merritt syndrome), most of these have been accompanied by hemangiomas elsewhere in the body and these have probably been the cause of the coagulopathy, not the SP. Some authors have termed these "malignant SP", a term which we do not use. Additionally, it is important to remember that many so-called lateral SP are actually emissary veins (especially at the mastoid level) and that misinterpretation and occlusion will result in consequences for the patient.

Imaging Features

Computer Tomography

Due to its use of ionizing radiation, CT in general is discouraged in children if alternative modalities such as MRI and/or ultrasound are available. However, SP can be found incidentally on CT scans performed for other reasons. Depending on the size of the pericranial varicosity, noncontrast CT will show a homogeneous soft tissue density mass [11] that may be confused with a solid neoplasm. These lesions have also been misinterpreted as soft tissue venous malformations (cavernous hemangiomas) and AVM [10, 12, 13]. Because of its excellent demonstration of osseous structures, CT is very good at delineating the calvarial channel [4], although this can be small and its identification may require close attention and the use of thin slices (0.5–0.75 mm) and multiplanar reconstructions (Fig. 13.1). The appearance of multiple diploic holes in a "honeycomb" pattern has also been described [14], and there may be scalloping of the outer table reflecting their slow growth [4, 11, 15]. When intravenous contrast is administered, CT can characterize the vascular nature of the lesion, its intra-osseous course, communication with dural sinuses or cortical veins, and its relationship with other vascular malformations if present (Figs. 13.2, 13.3, and 13.4) [7, 10]. Unless thrombosed, SP will appear as subgaleal varicosities with avid, vascular-type enhancement, although this will vary depending on the timing of the scan after injection and the amount of contrast material present within the

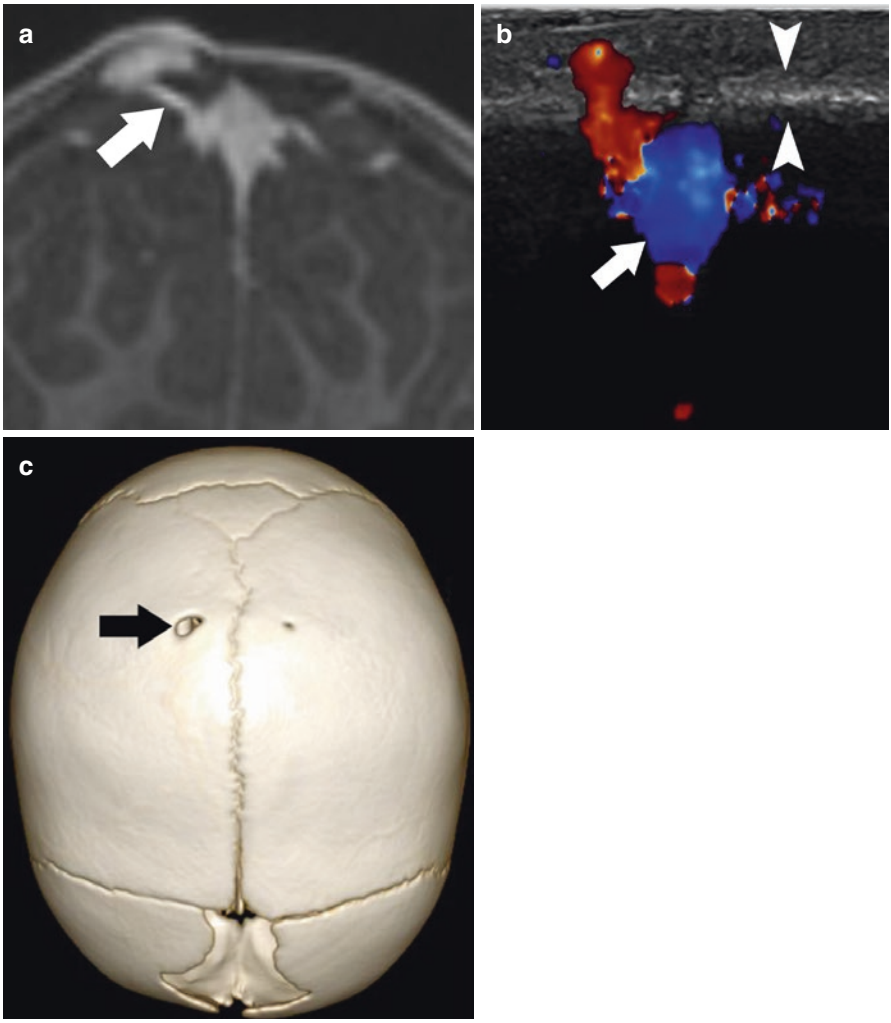

Fig. 13.1 Sinus pericranii in a 13-month old. (**a**) Coronal thin post contrast T1 weighted image shows a right parietal epicranial venous pouch communicating with the superior sagittal sinus through a small intra-osseous vein (*arrow*). (**b**) Coronal color Doppler ultrasound shows the intraosseous course of the vein and the superior sagittal sinus (*arrow*). Note the hyperreflective calvarium (*arrowheads*). (**c**) Volume-rendered 3DCT shows an enlarged osseous channel (*arrow*) associated with the sinus pericranii (compare with the normal parietal foramen on the left)

venous system [10]. Importantly, however, pericranial varicosities with slow flow may not enhance early and can be missed on conventional CT angiography, and delayed imaging (in the venous phase – about 40 s after injection) may be needed [10]. As with other imaging techniques, Valsalva maneuvers can help fill the varicosities, and positioning of the head below the level of the heart has also been proposed [10].

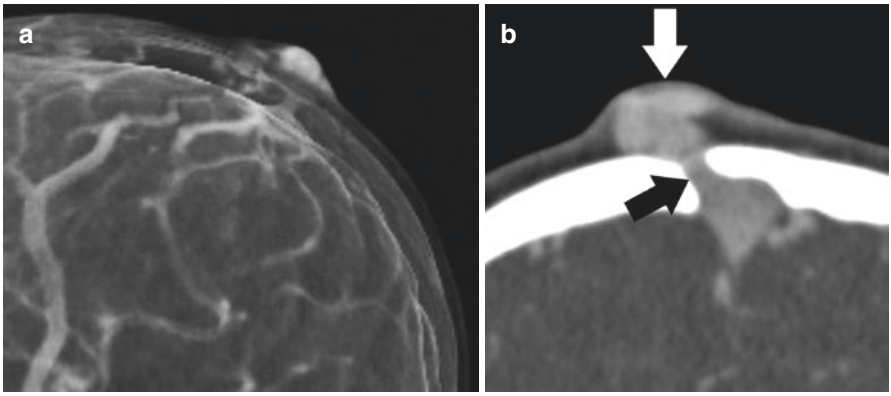

Fig. 13.2 Six month old with parietal sinus pericranii. (**a**) Lateral view of a volume-rendered 3DCT reconstruction shows an epicranial pouch and an osseous channel in the subjacent parietal calvarium. (**b**) Coronal CT angiography shows the epicranial venous pouch (*white arrow*) to communicate directly with the superior sagittal sinus through the calvarial defect (*black arrow*).

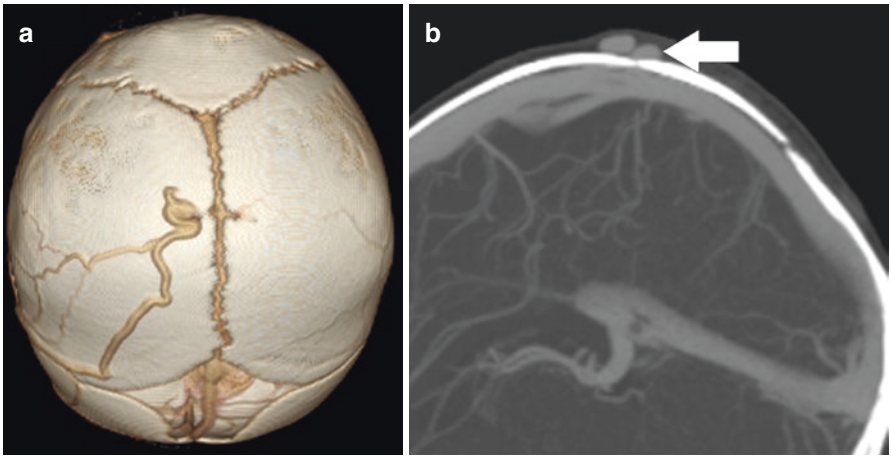

Fig. 13.3 Sinus pericranii in a 5-month old. (**a**) Volume-rendered 3DCT shows a prominent and tortuous vein in the right parietal region. (**b**) Thick slab sagittal maximum-intensity projection (MIP) reconstruction shows the epicranial pouch (*arrow*) to communicate with the superior sagittal sinus through a tiny calvarial defect

Color Doppler Ultrasound

Ultrasound does not involve ionizing radiation and can be performed at the bedside in real time. High-frequency transducers (we use between 7.0 and 10 MHz) can provide excellent spatial resolution in superficial tissues, which is advantageous in the evaluation of the epicranial pouch; frequency may be increased as long as it provides enough depth of visualization. SP, as veins in general, are

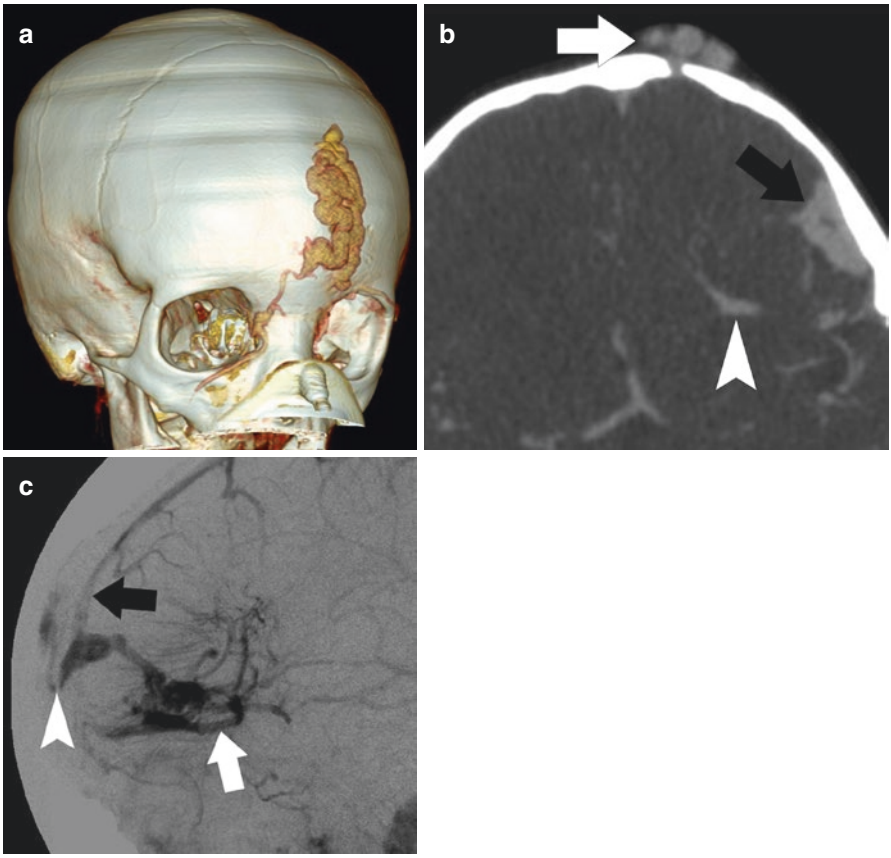

Fig. 13.4 Three month old with a frontal sinus pericranii. (**a**) Volume-rendered 3DCT angiography shows a tangle of vessels in the frontal soft tissues. Communications with right frontal and angular veins and left supraorbital vein are partially seen. (**b**) Axial CT angiography shows the epicranial pouch (*white arrow*) with a small vein crossing the calvarium. Note a developmental venous anomaly (*arrowhead*) and a prominent varicosity in the left frontal region (*black arrow*). (**c**) Lateral digital subtraction angiogram shows a complex developmental venous anomaly with two collecting vessels (*white arrow*). There is drainage to both the superior sagittal sinus (*black arrow*) and veins in the frontal soft tissues through a trans-osseous channel (*arrowhead*)

hypoechogenic and easily compressible with the transducer unless they are thrombosed [12]. The major drawback of ultrasound is its poor penetrance through bone, which limits the ability to visualize the intracranial components of a SP, particularly in older children and adults. However, in young infants, ultrasound can provide a good depiction of the intracranial compartment if the fontanelles are open. Even in older patients, ultrasound can usually show the osseous defect and depict the trajectory of the vessel through the hyperechogenic calvarium with the use of Doppler, which superimposes a color-coded map on structures with flow (Fig. 13.1) [7, 12, 15]. Color Doppler also adds hemodynamic information in

terms of flow directionality and turbulence and may also be able to depict filling defects in thrombosed SP [12]. Spectral Doppler waveforms can also help differentiate between venous and arterial flow.

Magnetic Resonance Imaging

Apart from the lack of ionizing radiation, MRI allows for a complete evaluation of the epicranial, intraosseous, and intracranial components of SP as well as associated intracranial anomalies (vascular and otherwise). At our institution we employ a routine contrast enhanced MRI protocol with thin sections through the lesion. Time-of-flight, non-contrast MR angiogram and venogram in addition to a contrast enhanced time-of-flight, time resolved MR angiogram are obtained. Thin section, post contrast T1 images (VIBE) through the suspected SP are very helpful in its assessment. While most SP are bright on T2 images, their signal intensity on T1 sequences is complex and depends on their size, flow, and thrombosis (lack of contrast enhancement suggests the latter) [11]. However, contrast enhancement is present on nearly all patent SP (Figs. 13.1, 13.5, and 13.6). In older patients, the post contrast study may be done in quiet respiration and using rapid sequences during Valsalva maneuver which will show enlargement of the SP (we generally do not find this necessary) [11]. The enhancing mass also shows an enhancing stalk (bridging vein) crossing the skull and communicating with a dural sinus (more common) or a cortical vein (less common) [4].

Angiography

The use of digital subtraction angiography (DSA) is controversial especially if US, CT, and MRI have been done and the diagnosis is certain [16]. Some surgeons still prefer the detailed anatomy provided by DSA and of course for lesions that are treated via endovascular or transcutaneous approaches, DSA is very useful. DSA shows SP during the venous phase once the cortical veins and superficial venous sinuses have been opacified [16]. Drainage is towards scalp veins and the neck of the SP can be readily identified (Figs. 13.4, 13.5, and 13.7). Intracranial and/or cervical venous stenoses/occlusions preclude the occlusion of the SP. SP drainage is of two types: accessory or dominant [6]. In the accessory type, the cerebral venous drainage is not predominantly via the SP and treatment may be done generally without complications. However, in the dominant type, the SP is the main outlet of cerebral venous drainage and bypasses other venous structures. Thus, occluding it will result in congestion and even in venous infarction and hemorrhage [17]. On DSA, the arterial phase of the study is almost always normal unless a lesion such as an AVM is associated. Direct puncture and opacification of the SP is reserved for equivocal DSA studies. Percutaneous puncture of an SP carries a risk of infection [6]. Direct venography serves to opacify the epicranial pouch and its trans-osseous connection but does not demonstrate the entire intracranial venous anatomy as DSA does.

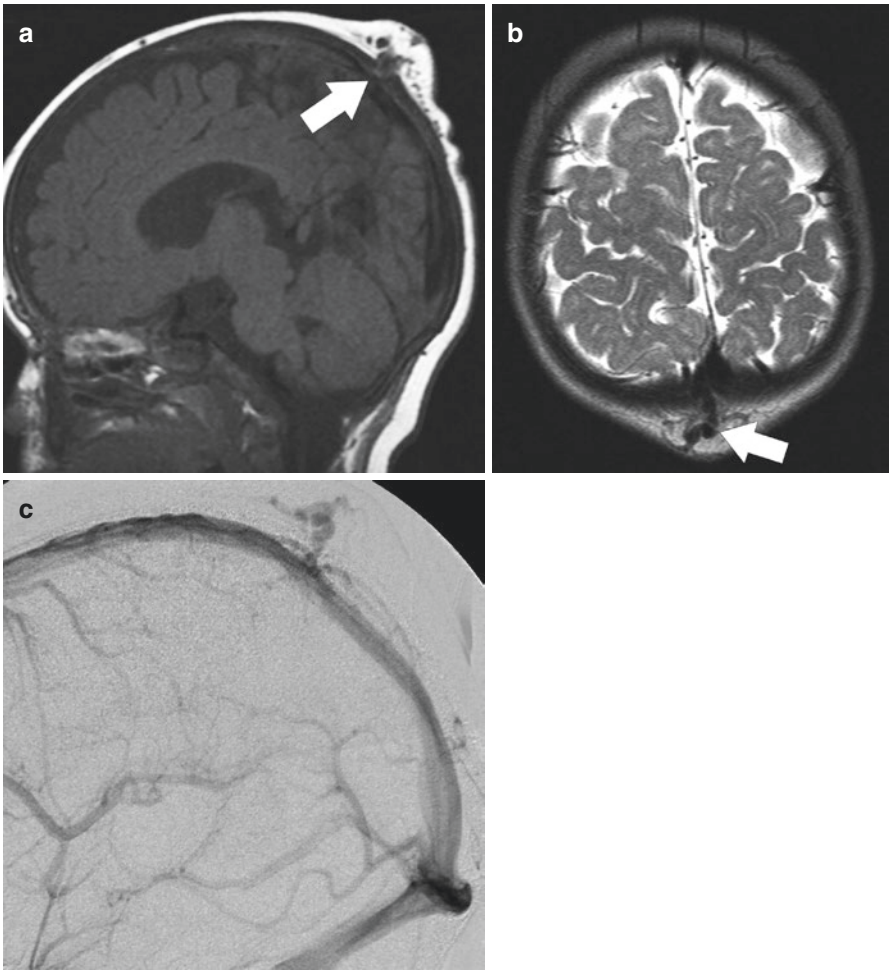

Fig. 13.5 Sinus pericranii in a small child. (**a**) Sagittal noncontrast T1 shows a bulge in the parietal soft tissues. There are small dark foci within it and tissue projecting into the calvarium (*arrow*). (**b**) Axial T2 image shows these foci to represent vascular flow voids (*arrow*). (**c**) Lateral view digital subtraction angiography clearly depicts the connection of the epicranial pouch with the superior sagittal sinus through a trans-osseous channel

Treatment

Treatment of SP may include surgical eradication, endovascular or percutaneous embolization, or a combination of these. While surgery is the established modality, no widely accepted guidelines exist [15]. Treatment requires discrimination between accessory and dominant drainage patterns, as obliteration of the latter is contraindicated (see above) [7]. Surgery can be curative and is aimed at obliterating the trans-osseous communication and removing the epicranial vessels (SP can recur if these

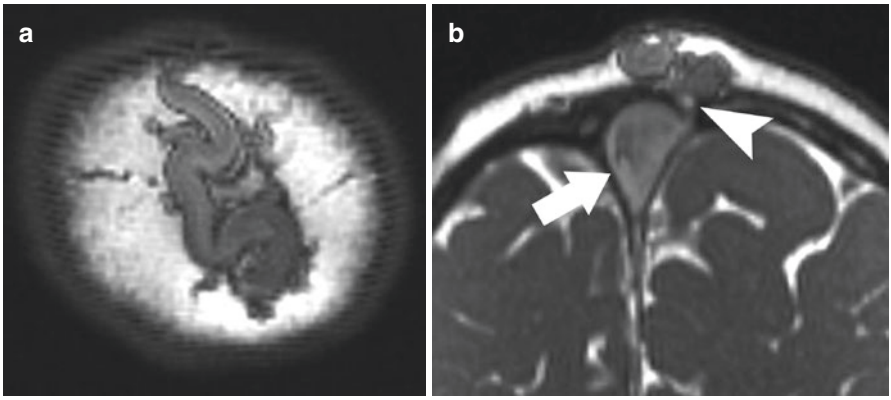

Fig. 13.6 Heavily T2-weighted CISS images in a 1-month old with a scalp mass. (**a**) The axial image shows a prominent subgaleal varicosity with small venous tributaries. (**b**) The intra-osseous vein (*arrowhead*) and its connection with the superior sagittal sinus (*arrow*) are well demonstrated on the coronal image

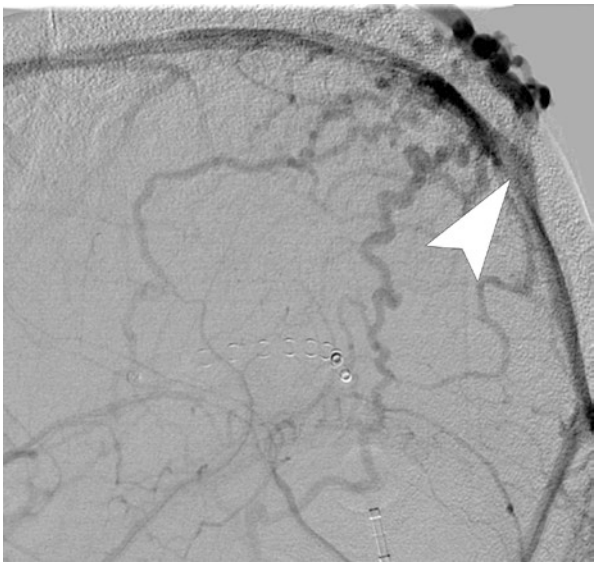

Fig. 13.7 Angiographic appearance of sinus pericranii. Digital subtraction angiography shows prominent varicosities in the parietal soft tissues communicating with the superior sagittal sinus through a trans-osseous venous channel (*arrowhead*)

are incompletely excised) [13, 15]. Bleeding, while usually low-pressure, can be significant [13]. Patients with craniosynostosis merit special consideration. It has been postulated that SP can be the result of venous hypertension and that correction of the craniosynostosis may lead to secondary improvement or even regression in some patients [15]. Recently, endovascular and percutaneous occlusion of the trans-osseous channel have been advocated with different embolic materials [16–18]. A recent case series showed no recurrence with such approach up to 24 months after treatment, but long-term results beyond this point are lacking [15]. Catheter-guided

or percutaneous obliteration with acrylics should aim at obliteration of the neck of the SP and not the filling of the entire pouch. The latter may result in a hard scalp bump whose overlying skin may become eroded with time (especially in girls as they tend to brush their hair more than boys) with subsequent extrusion of the glue and infection.

Pearls

- SP can be congenital, spontaneous, or traumatic.
- Most SP are asymptomatic but they may present with headaches, vertigo, nausea, hearing loss, and ataxia.
- Congenital SP may be associated with other intracranial vascular anomalies.
- A high index of suspicion for SP must be maintained for vascular masses in the scalp, particularly in young patients.
- Ultrasound and MRI constitute the mainstay of imaging diagnosis.
- The most important aspect in the management of SP is discrimination between dominant and accessory drainage patterns, as only the latter is amenable to treatment.
- Indications for treatment include cosmesis, thrombosis, and prevention of infection, hemorrhage, and air embolism.
- Surgery is the established treatment modality; endovascular/percutaneous obliteration has provided good results, but data on long-term follow up are lacking.

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Infectious Aneurysms

14

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Introduction

Infectious intracranial aneurysms (IIAs) are relatively rare, but associated with comparatively higher morbidity and mortality rates to their other intracranial aneurysm counterparts. The first description of an IIA was published in 1869 and is credited to Church [10]. He presented the case of a 13 year-old boy with mitral valve endocarditis and onset of left hemiparesis that subsequently died from rupture of a right middle cerebral artery (MCA) aneurysm. In 1885, Sir William Osler first used the term *mycotic aneurysm* to describe a patient with sub-acute bacterial endocarditis, who at autopsy was found to have a ruptured aortic aneurysm. He made comment that the debris visualized within the aortic arch aneurysm seemed similar to that found on the valves of the heart in cases of *malignant (mycotic) endocarditis* [7]. At the end of the nineteenth century, the misnomer *mycotic aneurysm* was frequently used to describe any aneurysm resulting from infection, irrespective of the microbial etiology [7, 17, 36]. Its more contemporary term infectious intracranial aneurysm was initially used by Ojemann in 1984 [35] and represents a more accurate and widely accepted denomination.

Regardless of the source of infection, IIAs are not true aneurysms. Rather, they are pseudoaneurysms that develop in response to an inflammatory reaction within the adventitia that spreads into the muscularis layer ultimately resulting in disruption of both the internal elastic membrane and the intima [14]. They are frequently symptomatic at presentation with a mortality rate that has been reported to be as high as 80 % in patients with bacterial endocarditis whose aneurysm hemorrhaged during their acute hospitalization [7]. High clinical suspicion, prompt diagnosis,

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A. Agrawal, G. Britz (eds.), *Pediatric Vascular Neurosurgery*,
DOI 10.1007/978-3-319-43636-4_14

and adequate treatment are of paramount importance to prevent devastating neurological consequences.

This current chapter will discuss important aspects of the epidemiology, the diagnosis, and the management of IIAs in the pediatric population.

Epidemiology

Intracranial aneurysms are relatively rare during childhood, with an estimated prevalence of 0.5–4.5 % [6, 9, 15, 20–22, 29, 40, 43, 44]. However, despite the fact that IIAs account for only 0.7–6.5 % of all intracranial aneurysms in the general population [12, 18, 25, 26], their prevalence in the pediatric population may actually be higher. Of the 75 pediatric aneurysms (59 patients) reported by Lasjaunias et al., 15 (8 patients) were infectious [30]. Other contemporary series have demonstrated similar results [8, 20, 21, 40]. In contrast, Huang et al., in an exhaustive review of published series, identified 706 aneurysms reported within the pediatric literature from 1939 to 2005, of which only 14 (2 %) were attributed to an infectious etiology [22]. It is important to note, that this particular literature review did not include isolated case reports and small case series. It seems that isolated case reports and small case series account for most of the IIAs within the published literature. In addition, the true incidence of pediatric infectious aneurysms may further be underestimated due to either the limited use of advanced neuroimaging in the commonly treated bacteremic child or the fact that IIAs are often asymptomatic with a low rupture rate (~2 %) [13]. In general, it appears that IIAs account for approximately 15 % of all pediatric intracranial aneurysms [29].

There appears to be an overall male predominance in pediatric aneurysms [21, 22, 29, 30, 40]. When stratifying for different age groups, however, the overall predominance is reversed in the first 2 years of life (male/female = 1:4), becomes most significant between ages 2 and 5 (male/female 4:1), and then stays constant from ages 5 to 16 (male/female 3:2) [29].

Several authors have described a bimodal distribution of age at presentation for all pediatric aneurysms. The early childhood group is characterized by a peak within the first 6 months with the majority of cases occurring within 2 years of life. The second peak occurs during adolescence [4, 8]. Others have argued that the majority of aneurysms occurring in children are identified in teenagers and are exceptionally unusual in infants [6]. These numbers are all based on the entire pediatric aneurysm population. Caution should be taken before generalization to the case of IIAs. If one assumes, though, that the majority of the IIAs are secondary to infective endocarditis (IE) [7, 12, 14, 39], the demographics data for the latter should represent an accurate estimate. Large institutional review studies have shown that the mean age at diagnosis for children with IE in the US ranges from 8 to 12 years [23, 33, 42]. These findings are similar to the ones published by Hetts et al., who described 12 IIAs (12 % of study population) in a 27-year single institution experience, with a mean age at presentation of 9 ± 3.5 years [21]. On the other hand, a recent study analyzing seven decades of IE data from a single institution has demonstrated a

clear shift in the mean age at diagnosis towards the early toddler years. Between the years 1930 through 1992, the mean age of those affected was 8 years, while a change occurred between 1992 and 2004 with the mean affected age dropping to 1.5 years [42]. In 2006, a systematic review of the literature on intracranial aneurysms in children under 1 year of age identified 110 articles with 131 aneurysms; 10 % of those were IIAs [8]. Those findings together would corroborate the validity of a similar bimodal distribution for the IIA population.

Like the situation observed in the adult population, the majority of pediatric IIAs are located within the anterior circulation, with an estimated prevalence of 75–93 % [8, 21, 30]. Aneurysms involving the middle cerebral artery (MCA) are nearly three times more frequent than on any other vessel [8]. A systematic review of the literature demonstrated that 57.4 % of the IIAs are located on the MCA, and 17.6 % on the posterior cerebral artery or its distal branches [12].

Infectious intracranial aneurysms are multiple in 15–25 % of cases, especially in the immune-deficient patient and in the face of inadequate antibiotic coverage [5, 7, 29, 36, 39, 40]. While the multiplicity of intracranial aneurysms in children is low compared to their adult counterparts, an exception is seen in those children with aneurysms of infectious etiology [15]. This multiplicity of IIAs does not necessarily translate into worse clinical outcomes when compared to patients with solitary IIA [36]. Analysis of the IIA literature has demonstrated that 41 % are saccular and 52.5 % fusiform [12].

Pathogenesis

Infectious aneurysms have been grouped by Karsner into three types based on their pathophysiology [27]. The first, and most common, forms as a result of embolization from bacterial endocarditis and, thus, are of intravascular origin. Included in this category is the hematogenous infection of the *vasa vasorum.* The second type of IIA occurs by extension of a neighboring infection resulting in vessel wall invasion from the contiguous infected anatomical structure and centripetal migration towards the elastic intimal layer. This extravascular origin of infectious aneurysms may arise from meningitis, cavernous sinus thrombophlebitis, adjacent osteomyelitis of the skull, sinus infection, or postoperative infection. The third form of IIA is the so called *primary* or *cryptogenic mycotic aneurysm* that develops in the absence of an obvious inflammatory lesion elsewhere in the body [5, 27, 31]. Independent of the pathophysiology, all three groups appear to have in common some degree of infective arteritis with profound inflammatory reaction in the arterial wall, especially the adventitia. This arteritis leads to the development of arterial weakening and eventual aneurysmal formation [5].

It appears that the initial infectious mechanism correlates with IIA location. Aneurysms resulting from septic emboli and infective endocarditis tend to be located on the distal intracranial vasculature (primarily on the distal anterior circulation), while cases secondary to contiguous spread or meningitis tend to involve the more proximal vessels that are closer to the skull base [1, 3, 7, 9, 12, 13, 18, 25, 26].

Regardless of the infectious source, IIAs are not true aneurysms, but rather, as was noted earlier, pseudoaneurysms. They appear secondary to an acute inflammatory reaction of the adventitia that spreads into the muscular layer resulting in disruption of both internal elastic membrane and intima [14, 36, 45]. Grossly, the aneurysm appears friable, has a thin-wall, and is frequently without an obvious neck. This pathological pseudoaneurysm formation is the main reason why the morphological characteristics of saccular aneurysms are not common amongst IIAs [9]. It also helps explain why these lesions can be so dynamic in terms of growth. The time interval between the release of infectious emboli and the development of an IIA, including its rupture, has been estimated to be as short as 24–48 h [24, 37].

Infective intracranial aneurysms are clinically recognized in 3–15 % of patients with infective endocarditis. At the same time, up to 65 % of patients with IIAs present with bacterial IE. Other less common sources of infection include bacterial meningitis, cavernous sinus thrombophlebitis, septicemia, cerebral abscess and subdural empyema [12]. However, given that IIAs are often clinically silent and discovered in 5–10 % of autopsy cases, their incidence may be higher than current estimates [7, 12, 39].

The most common causative organisms in IIAs are *Staphylococcus* (*aureus, epidermidis*) and *Streptococcus* (*viridans, sanguis, morbidiformis, pneumoniae*) species [9, 12, 16, 24, 36]. Among those, *Staphylococcus aureus* is the most commonly cultured pathogen [16]. It is estimated that *Streptococcus viridans* and *Staphylococcus aureus* are responsible for 57–91 % of IIAs. HACEK (*Haemophilus spp, Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, and Kingella spp*) organisms, Gram-negative rods, and fungi are less commonly reported to cause intracranial aneurysm formation [36]. Among fungi, *Aspergillus* accounts for half of the cases, followed by *Candida albicans* [24]. These fungal aneurysms tend to occur more proximally on the intracranial vessels than do their bacterial counterparts. They involve the large arteries at the skull base and they occur almost exclusively in immunocompromised patients [5].

Another important but, frequently under-recognized cause of IIAs in the pediatric population, is HIV infection. The acquired cerebral arteriopathy of HIV infection typically occurs in children 8–11 years of age, who acquire the HIV infection through vertical transmission or perinatal blood transfusion [1]. These lesions meet histologic criteria for an infectious aneurysm, and they tend to resolve following antiretroviral treatment. HIV-related IIAs tend to occur in the anterior circulation, are characteristically multifocal, and, most often, assume a fusiform configuration involving the proximal basal cerebral arteries [1, 6, 12, 21, 30]. Other CNS opportunistic infections such as Cytomegalovirus, *Herpes simplex*, *Varicella zoster*, *Salmonella*, *Mycobacterium tuberculosis*, *Treponema pallidum*, and Cryptococcus have all been implicated in intracranial aneurysm formation. Characteristic pathologic changes include medial fibrosis with loss of the muscularis layer, disruption or destruction of internal elastic lamina, and intimal thickening in the setting of sparse or absent vascular inflammation [38].

Clinical Presentation

The signs and symptoms associated with an IIA are diverse and, frequently, nonspecific. The clinical presentation can be directly associated with the IIA or with its initial causative agent. The most frequent neurological symptoms associated with IIA include headaches, lateralizing motor or sensory deficits, ophthalmoparesis, visual loss, and seizures. Other nonspecific findings are related to the primary infectious etiology and include malaise, fevers, nuchal rigidity, photophobia, chest pain, symptoms of systolic or diastolic heart failure, or sepsis. In their case series of 16 patients with IIAs, Phuong et al. reported that the most common presenting symptoms were fever and chills (87.5 %). Almost half of their patients had a nonspecific headache, and 37.5 % presented with lethargy and confusion.

The diagnosis of IIA requires a high index of clinical suspicion. In fact, Bohmfalk et al. suggest that patients with murmurs or other suggestions of endocarditis whom are found to have peripheral aneurysms should be considered to have IIAs until proven otherwise [7]. The constellation of infection, fever, heart failure and focal neurological symptoms should immediately prompt a thorough investigation that necessarily involves the exclusion of an infectious intracranial aneurysm. Neurological complications are frequent and can occur in up to 30 % of infectious endocarditis patients, with stroke complicating 12 % of those IE cases [36]. Septic emboli leading to intracranial ischemic strokes are found in up to 20 % of patients with IE. Of these, 12–20 % can have a significant hemorrhagic event resulting from either rupture of a IIA or a weakened arterial wall [13].

The natural history of untreated mycotic aneurysms is ominous; they demonstrate a high incidence of spontaneous rupture. In fact, the most common presentation for an IIA is intracerebral and/or subarachnoid hemorrhage [1, 5, 6, 8, 12, 18, 25, 43]. In patients with bacterial endocarditis, the aneurysm rupture may be the first clinical manifestation of the illness [6]. In his literature review of IIAs in the adult and pediatric population, Ducruet et al. found that 72 % of patients with IIA presented after a hemorrhagic event. Intraparenchymal hemorrhage tends to occur more commonly with IIA than with noninfectious intracranial aneurysms. In contrast to berry aneurysms, size does not appear to be a reliable predictor of potential rupture [12]. The presence of multiple IIAs appears to correlate with a higher incidence of an initial hemorrhagic presentation though as previously discussed, this does not necessarily portend a worse outcome compared to isolated single IIA cases [37].

There is divergence in outcome when specifically analyzing aneurysms within the pediatric population. Lasjaunias et al. reported 75 aneurysms in 59 children under the age of 15. Of those, eight patients harbored 15 IIAs. Hemorrhage was the most frequent presentation for saccular aneurysms. Headaches and nonhemorrhagic deficits were the most common presenting complaints in infectious aneurysms [30]. Hetts et al., describing their 27-year institutional experience on the management of intracranial aneurysms in childhood, reported that hemorrhage was twice more likely to result from a saccular aneurysm rupture than from fusiform or infectious aneurysmal disease. Similar to the findings of Lasjaunias,

more than 80 % of their pediatric IIAs presented with headache or non-hemorrhagic deficits [21]. The rupture incidence in these two institutional series was 17 % and 13 %, respectively.

Infectious aneurysms of the cavernous segment of the internal carotid artery may present initially as an infectious process with low-grade fever, malaise, and fatigue along with signs and symptoms of orbital cellulitis, cavernous sinus thrombophlebitis, meningitis, sinusitis, periodontitis, or facial abscess. The classic cavernous sinus syndrome is often seen and manifests clinically with severe orbital or retro-orbital pain, proptosis, chemosis, ptosis, and ophthalmoplegia [16].

Despite this wide variety of signs and symptoms associated with an infectious intracranial aneurysm, silent IIAs are not uncommon and can be present in up to 10 % of autopsy cases [45].

Diagnosis & Imaging

The initial workup of the IIA is directed towards investigation of the primary source of infection. Complete blood count will frequently demonstrate marked leukocytosis with neutrophilia and predominance of immature cells (*left shift*). Inflammatory indices, such as c-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), are invariably elevated; they are both useful markers of adequate response to antibiotic therapy and should be trended appropriately. Transthoracic and transesophageal echocardiogram are indispensable tests for the diagnosis of infective endocarditis, to estimate the degree of valvular and systolic dysfunction, and to identify the presence and location of valvular vegetations.

Blood cultures should be mandatory in all patients with suspected infective endocarditis and IIAs. A significant number of patients, however, will have persistently negative cultures, either because of prior antibiotic therapy or in cases of cryptogenic infectious aneurysms [31]. Bohmfalk et al. reported a 10 % incidence of negative blood cultures in their series of bacterial intracranial aneurysms on patients with confirmed IE [7] while others have described a much lower percentage of microbial isolation. Kannoth et al. could isolate a causative organism in only 28 % of cases despite routine sampling for bacterial, tuberculous and fungal etiologies [25]. A systematic review of the literature showed that blood cultures were positive in only 35.6 % of patients screened, although the authors noted that many of the blood samples were obtained following initiation of antibiotic therapy [12].

Examination of the cerebrospinal fluid (CSF) does not aid in identifying the organism in patients with IIAs caused by septic emboli. Cerebrospinal fluid cultures are frequently negative even in the setting of positive blood cultures. In the study by Pruitt et al., only 11 of 69 patients with infective endocarditis who underwent lumbar puncture had positive CSF cultures [41]. In the cases where the etiology of the IIA is thought to be secondary to meningitis, CSF studies may reveal elevated opening pressure, neutrophilic elevated white cell count with neutrophilia, elevated protein and various degrees of hypoglycorrachia [16].

Computed tomography (CT) is considered the screening intracranial imaging modality of choice, even in the pediatric population. It is easily accessible, has fast image acquisition times, and is very sensitive for even small areas of subarachnoid or intraparenchymal hemorrhage. It also eliminates the need for intravenous sedation and Monitored Anesthesia Care or total ventilator support, as seen even with rapid sequence magnetic resonance imaging (MRI). Computed tomography angiography (CTA) is frequently obtained at the same time as the noncontrast enhanced CT. Due to its lower risk profile compared to digital subtraction angiography (DSA), CTA is frequently the initial intracranial vascular imaging of choice. Twenty to 33 % of IIAs are centrally located (proximal to the first bifurcation of the circle of Willis) and can be difficult to differentiate from berry aneurysms. CTA features that may help differentiate a centrally located infected cerebral aneurysm from a berry aneurysm include arterial stenosis or occlusion close to the aneurysm, rapid change in aneurysm morphology, or multiplicity. A combination of these features increases the likelihood of a diagnosis of an IIA. The diagnostic performance of CTA is comparable to that of two-dimensional DSA for detection of cerebral aneurysms. The mean sensitivity and specificity of 64-row multidetector CTA are 92.8 %–94 % and 90.2 %–100 %, respectively. The performance of CTA in detection of aneurysms <3 mm is less optimal, with a sensitivity of 70.4–91.7 % [16, 32].

Magnetic resonance imaging provides a detailed evaluation of the cortical structures and their relationship to an adjacent intraparenchymal hematoma if present. It is especially helpful in cases where surgical evacuation of an intraparenchymal hematoma is planned, because it can easily identify areas of cortical presentation that would minimize injury to already ischemic perilesional cortex. A diffusion-weighted imaging (DWI) sequence is frequently indicated in cases where an ischemic event – resultant from septic emboli – is suspected based on the neurological examination. T2-weighted or Fluid Attenuation Inversion Recovery (FLAIR) sequences may provide essential information in cases where a partially thrombosed, large or giant aneurysm is suspected. Gadolinium-enhanced MRI provides important anatomical information in cases of cavernous sinus thrombophlebitis. The sensitivities of contrast-enhanced magnetic resonance angiography (MRA) and three-dimensional time-of-flight MRA for detection of cerebral aneurysms are 95 %–100 % and 82 %–96 %, respectively. The ability of contrast-enhanced MRA on a 3 T scanner to detect cerebral aneurysms is comparable to that of CTA.

Since the majority of the IIAs are located peripherally on the intracranial vasculature, some authors have developed specific MRI/MRA-based frameless stereotactic protocols for intraoperative navigation [19]. This technique reportedly removes the hemorrhagic component signal from the navigation image, preventing it from obscuring the IIA. Other authors have reported no utility to the use of intraoperative navigation in their surgical practice [9].

Digital subtraction angiography remains the gold standard imaging modality for detection of IIAs. It should be obtained in all patients with suspected IIA but no obvious vascular lesion on non-invasive CTA or MRA. Some limitations that should be specially considered in the pediatric population include difficult vascular access and lower dose-limits for both intravenous contrast administration and radiation exposure.

Treatment

In general, three questions should guide the management decisions for patients with IIAs [9]:

1. Is the aneurysm ruptured or unruptured?
2. Is there a hematoma or other space occupying lesion causing elevated intracranial pressure (ICP)?
3. Does the parent artery supply eloquent brain tissue?

The answers to those three questions should orient the treating physician's decision into either antibiotic therapy alone or the use of antibiotics in combination with surgical intervention, either microsurgical or endovascular. The application of aneurysm clips or the endovascular delivery of coils or liquid embolic agents to aneurysms whose walls are acutely inflamed and friable is potentially catastrophic. Thus, the definitive management of IIAs may differ from that of the more well-known scenario of saccular aneurysms. It may involve the elimination of long aneurysmal segments from the circulation [9]. In the past decade, there has been a gradual shift from traditional microsurgical treatment toward endovascular treatment [44]. This trend has also been seen in the pediatric population [15]. Conclusions on the best management of pediatric IIAs remain limited to small series and anecdotal reports.

Antibiotics

Adequate, broad-spectrum antibiotic therapy should be initiated promptly at diagnosis and continued until blood, CSF, or specimen cultures are resulted. As emphasized before, IIAs tend to be dynamic lesions with the interval between septic emboli release and the development and rupture of the aneurysm as short as 24–48 h. Except in the cases of unruptured IIAs, the introduction of intravenous antibiotics should not be delayed even if obtaining cultures at the time of initial presentation is not possible [24, 37]. In the majority of IIAs secondary to IE, optimal treatment duration is typically 4–6 weeks [16, 32, 33]. Aneurysms secondary to fungal infection frequently require longer treatment courses [28, 34], sometimes followed by lifelong maintenance oral antifungal therapy [32]. The natural history of unruptured IIAs treated with antibiotics alone is limited to anecdotal reports. Nonetheless, multiple series have shown an effective response with medical management and no direct open or endovascular intervention [5, 7, 9, 12, 13, 16, 25, 36, 37]. Bartakke et al. demonstrated moderate success with medical management. The aneurysm disappeared in 29 %, decreased in 18.5 % and remained the same size in another 15 % of patients treated. Failure was defined by either an increase in the size of the treated aneurysm, 22 %, or the development of an additional IIA, 15 %. Corr et al. had similar results and described the disappearance of the aneurysms in 33 %, the reduction in size of IIAs in 17 %, and the stabilization of size in 33 % of patients followed. They reported an increase in size in 17 % of their 14 patients with infective

endocarditis who were medically managed. Follow-up was with serial angiography in both reports [12, 45]. And finally, in another relatively small series, 10 of 25 patients (40 %) demonstrated angiographic resolution of their IIAs on last follow up utilizing antibiotics alone [7].

It is important to recognize that the risk of rupture of an IIA is not reduced during antibiotic therapy [9, 13, 25]. In the cases where medical management is employed, serial angiography should be considered to monitor the stability of the aneurysm.

Microsurgical Treatment

The role of microsurgery in the management of infectious intracranial aneurysms has significantly changed throughout the last three decades. Taking into account only the pediatric population, there has been a gradual shift from traditional open surgical approaches towards endovascular treatment of intracranial aneurysms. This shift has been seen even in high volume, tertiary cerebrovascular referral centers [2, 21]. It may be possible to conclude that microsurgery has become a second-line treatment option for IIAs in the pediatric population.

Open techniques still have a role in the management of IIAs. The advantages of open surgery are the ability to evacuate an associated hematoma and relieve intracranial pressure concurrent to aneurysm treatment and its ability to better preserve the parent artery in hopes of avoiding an ischemic complication [5, 7, 9, 36]. Limitations do exist. There are co-morbidities in patients with infective endocarditis that may need to be respected. Many will not infrequently undergo cardiothoracic procedures for valve repair that, consequently, require systemic heparinization and long-term anticoagulation and ultimately affecting the decision to perform a craniotomy, when the risks of intracranial hemorrhagic complications are far from negligible [18, 45]. And, some authors have shown that cardiothoracic surgery following craniotomy procedures increases the risk of perioperative heart failure [45].

Three distinct surgical groups have been identified: (1) those individuals with ruptured IIAs associated with large intraparenchymal hematomas and/or elevated ICP; (2) those patients with ruptured aneurysms involving eloquent areas, where the endovascular parent artery occlusion (PAO) would be associated with prohibitive risks of neurological decline; and (3) those suffering from the dynamic or enlarging unruptured aneurysm in an eloquent area [9]. Open surgery has also been recommended for those aneurysms that enlarge or fail to resolve with antibiotic therapy alone [5, 20, 31].

Direct clipping of IIAs in the acute phase is thought to be associated with high morbidity rates. Clip erosion of the vessel wall and catastrophic rupture during aneurysmal dissection are frequently reported (Awad, comments in [9]). Some argue that direct open attack should be reserved for those unruptured or ruptured IIAs that have been treated with antibiotics for at least 2 weeks. It has been suggested that the interval between diagnosis and surgery allows time for the IIA to mature from a friable acute lesion to a more fibrotic, subacute or chronic lesion that

is more amenable to surgical clipping. The aneurysm is then felt to be less likely to tear or rupture during the operative dissection and the clip application [5, 9]. A ruptured IIA associated with a large intraparenchymal hematoma or one requiring parent artery occlusion in an eloquent area should be treated with open microsurgery, the former at the time of clot evacuation and the latter with the awareness of a potential extracranial-intracranial bypass [5, 9, 18, 20].

The most common microsurgical technique for the treatment of a pediatric IIA that is reported in the literature is microsurgical trapping with resection of the involved vessel wall segment and pseudoaneurysm. While this technique completely eliminates the pathological lesion, it is primarily limited to non-eloquent areas. Because the majority of the IIAs are distally located, the trapping of this small cortical branch is often associated with minimal morbidity and lower chance of postoperative deficit. In the rare event that a small perforator (e.g., lenticulostriate arteries) vessel is the source of hemorrhage and direct surgical clipping or trapping/bypass options are not available, a wrapping technique to reinforce the parent vessel wall has been reported with minimal procedural morbidity. Wrapping agents include muscle, gauze, cotton, muslin, Teflon, silastic sheet, adhesives (Biobond, fibrin glue, and polyglactin 910 + fibrin sealant), and collagen-impregnated Dacron fabric [11].

Open microsurgical treatment of pediatric IIAs remains useful in situations where the parent artery supplies an eloquent area of the brain as opposed to endovascular treatment, as will be discussed below, which may be associated with higher risk of vessel occlusion and ischemic events. A common procedure involves trapping/resection of the involved vessel segment followed by an extracranial-intracranial bypass using the superficial temporal or occipital arteries. Occasionally, when an IIA is located proximal to the MCA bifurcation, the wall segment can be surgically excised and a direct end-to-end bypass technique used for adequate revascularization. Independently of the bypass technique (extracranial-intracranial or intracranial-intracranial bypass), it is imperative to inspect the recipient intracranial vessel to exclude all signs of residual infectious involvement. The safety of those procedures can be enhanced by the methodic use of intraoperative neurophysiologic monitoring and anesthetic cerebral protection techniques, such as barbiturate or propofol burst suppression or mild intraoperative hypothermia.

Endovascular Treatment

Infectious intracranial aneurysms in the pediatric population present a challenge to the endovascular neurosurgeon because of the fact that these lesions are often irregular in shape and have wide or nonexistent neck, these lesions are often located in distal vasculature (thus making microcatheter navigation more challenging), and these lesions may involve arteries supplying eloquent brain, necessitating preservation of the parent artery [14]. The advancements in microcatheter technology, the wide variety of catheters currently available for intracranial navigation, and the development of better embolic agents have revolutionized the treatment of IIAs. In

fact, some institutions now utilize endovascular therapy of IIA as the first option for patients, especially children, with either unruptured or ruptured infectious aneurysms who are in stable condition and are not burdened by large hematomas [2, 13, 14, 17, 18, 21, 25, 30, 43–45]. And, as noted above there has been a gradual shift in the management of all types of pediatric aneurysms over the last 35 years, from 100 % of cases treated surgically before 1985 to 55 % of them treated with endovascular techniques (45 %) or observation (10 %) [21].

Despite the intrinsic fear of infection of the embolic materials used in the endovascular treatment of IIA, there has not been a report of persistent infection or abscess formation [12]. There has been no reported infectious complication as a result of stent placement, deployment of coils, or injection of N-butyl cyanoacrylate (NBCA) or Onyx [18].

There may be several advantages to endovascular therapy over the traditional open microsurgical treatments in the management of IIAs: a decreased risk of anesthesia (particularly in patients with impaired valve function), the ability for rapid institution of anticoagulation therapy, and the shortening of the time interval between aneurysm treatment and cardiac surgery (in the cases associated with IE). In those cases, the delay can be reduced from 2 to 3 weeks to as little as 1 day [12, 45]. In addition, multiple aneurysms, including bilateral IIAs, can be treated in one intervention. And, some cases have been performed under local anesthesia [9, 18].

Parent artery occlusion with detachable coils, particles, or liquid embolic agents is currently the most common endovascular strategy used for treatment of infectious aneurysms. Avoiding the need for aneurysm catheterization reduces intra-arterial manipulation and lowers the risk of aneurysm perforation [45]. In a meta-analysis of endovascular therapies for IIAs, Chun et al. concluded that endovascular treatment was more likely to involve PAO than surgical treatment. The parent artery was preserved in 35 % IIAs treated by endovascular means, compared to 63 % of the surgically treated aneurysms in their series [9]. That being said, for situations where parent artery supply of an eloquent area is suspected, intracranial temporary balloon occlusion or amobarbital injection testing on an awake patient may help predict the potential neurological consequences of PAO [14, 18]. The use of PAO for children may actually be safer than for adults. Takemoto et al. reviewed the locations and procedural results of 34 PAOs without bypass surgery from different case series. Despite the lack of bypass surgery, a symptomatic infarction occurred in only one patient who had a basilar artery trunk aneurysm [44].

Of the embolic agents currently available in the endovascular armamentarium, NBCA and Ethylene Vinyl Alcohol Copolymer (Onyx®) are the most frequently used for the treatment of IIAs. NBCA is a nonabsorbable, adhesive, and rapidly polymerizing embolic agent, with excellent durability and minimal inflammatory effect. Several of its characteristics are desirable for treating infectious aneurysms. For example, NBCA has the ability to chemically modify its polymerization properties such that vessels downstream of the catheterized vessel can be occluded rather than only at the site of deployment. On the other hand, the disadvantage of NBCA is its demand for extreme familiarity with its use and the risk of microcatheter retention if not removed expeditiously, due to its almost instant polymerization [14]. Onyx® is a newer, nonabsorbable, nonadhesive liquid embolic agent that permits

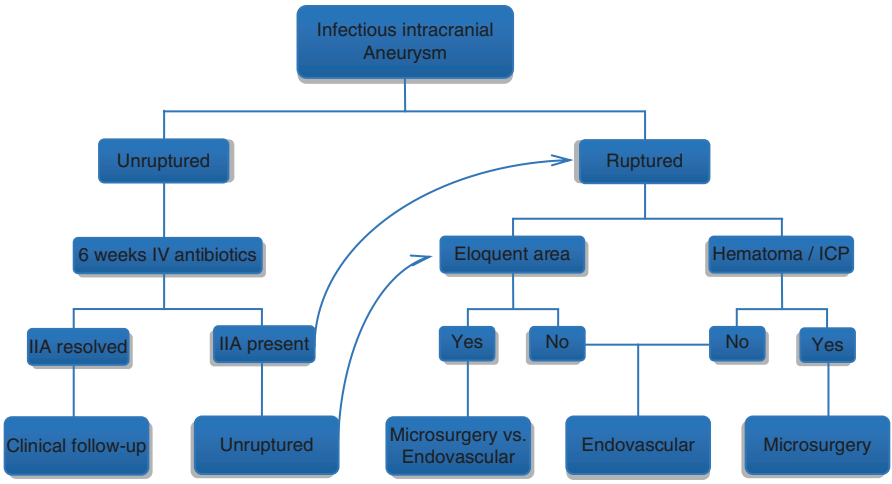

Fig. 14.1 Treatment algorithm for the management of infectious pediatric aneurysms

PAO under a more controlled fashion, as well as the allowance of multiple injections from a single catheterization. Its main advantage over NBCA is its long precipitation time, which is a result of its nonadhesive properties. This allows for more precise control that results in a more satisfactory embolization.

Several authors have published their experience with primary IIA coiling, with or without stent deployment [9, 13, 18, 30, 44]. This technique, however, appears to have been supplanted by the use of modern liquid embolic agents as described above. The experience with the use of flow diverters in the endovascular management of IIAs is limited and its use is generally still seen with caution. To our knowledge, the only case reported to date was published by Appelboom et al. in 2010. They describe the case of a 10 year-old girl that presented with streptococcal meningitis complicated by the development of cavernous sinus thrombophlebitis and a large infectious intracavernous aneurysm. The IIA was discovered upon the onset of facial edema, diplopia, ptosis, and mydriasis to the ipsilateral eye. She was initially managed with a 6 weeks course of intravenous antibiotics, but had progression of her ophthalmologic symptoms. The child had clinically failed a trial of temporary balloon occlusion. The cavernous ICA aneurysm was subsequently treated using a SILK® flow-diverting stent with complete aneurysmal occlusion and resolution of her ophthalmoplegia at 3 months follow-up [3].

Treatment Algorithms

A few authors have described their experience and institutional treatment algorithms for the management of IIAs [9, 12, 36, 37]. Many of those recommendations are very similar to the ones applied to the management of these lesions at our own institution (Fig. 14.1). A few aspects of this treatment algorithm deserve special attention.

There is general agreement that unruptured, asymptomatic IIAs should initially be treated with a 6 weeks course of intravenous antibiotics and close surveillance. At the University of Texas Southwestern Medical Center and the Children's Medical Center of Dallas, these patients are started on broad-spectrum intravenous antibiotics as soon as the IIA is recognized. The antibiotic therapy is tailored down to a specific antimicrobial based upon final culture results. Computed tomography angiography (CTA) has become the imaging modality of choice for both diagnosis and surveillance. The study is repeated every week until completion of the treatment course and resolution of the aneurysm. Digital subtraction angiography is now reserved for cases where the clinical suspicion is high, despite negative CTA, or when endovascular treatment is planned during the same procedure. Regardless of the size of the aneurysm, if the IIA does not resolve completely with antibiotics at the end of the 6 weeks, it is treated with either a microsurgical or endovascular approach. Again, the delay in the institution of a surgical treatment in some cases may be actually beneficial, since the resolution of the infection may allow for some degree of reparative fibrosis to occur facilitating the microsurgical reconstruction (Barrow, comments on [37]). Caution is used to attempt to avoid a primary aneurysm clipping in the acute infectious environment. The profound inflammatory process and the friable characteristics of the pseudoaneurysm capsule of vessel wall has been hypothesized to cause clip erosion of the parent artery and increase the risk of a catastrophic perioperative rupture (Awad, comments on [9]).

The child that presents with a ruptured IIA is treated with both intravenous antibiotics and aneurysm occlusion. Infectious aneurysms that do not involve an eloquent vascular distribution and that are not associated with a hematoma producing mass effect or increased ICP are primarily treated by endovascular means, notably PAO with liquid embolic agents. The cases with an associated intraparenchymal hematoma causing symptomatic mass effect and/or elevated ICPs, as well as those where the risk of an ischemic complication to an eloquent vascular territory are prohibitive, are treated with open microsurgical clipping or trapping with bypass. In situations where both ruptured and unruptured aneurysms are present, acute operative management is generally reserved for the ruptured lesion.

Outcome

Historically, the mortality rate associated with an infectious intracranial aneurysm has been high. Bohmfalk et al., in a frequently cited manuscript from 1978 [7], reported a mortality rate of 80 % in those patients hospitalized for the treatment of bacterial infective endocarditis whose aneurysms hemorrhaged during acute hospitalization. In the same study, the authors surprisingly noticed a much lower mortality rate in patients with subarachnoid hemorrhage at presentation (42 %), which they explained was probably the result of not capturing those patients who had died prior to hospital admission. No procedural-related mortality was seen in their group who underwent elective microsurgical treatment, and the mortality rates were similar independent of the number of IIAs. With the evolution of both intracranial imaging

and surgical treatment modalities, outcomes have improved. A subsequent literature review of IIA management has demonstrated better results. Approximately 36 % were managed with antibiotics alone, 45 % of the patients underwent microsurgical treatment and 17 % had an endovascular intervention [12]. Overall, 62 % of those patients had a positive outcome, while only 20 % had further neurological decline. The combined mortality rate was 17 % (5 % prior to and 12 % after definitive intervention). These improved results are similar to those now reported by others [9, 18, 37]. Specific types of IIAs may play an important role in outcome. Kannoth et al. reported significantly higher mortality rates in patients with fungal infections compared to bacterial equivalents and in those that developed IIAs secondary to meningitis as opposed to hematogenous spread [25]. The mortality for patients with IIAs in the vertebrobasilar territory is significantly higher than those arising from the carotid circulation. Size, morphology, and number of IIAs have not been shown to correlate with outcome [4, 8, 20–22, 30, 39, 44]. In one study exclusive to the pediatric population, Kaplan-Meier survival curves demonstrate little to no decline in outcomes after the initial few weeks following presentation suggesting that the initial hemorrhage and resultant neurological sequelae are the main cause of death in children [8].

Outcomes seem to be more favorable in those children treated via endovascular means as opposed to open surgery independent of clinical status at presentation and independent of PAO [2]. The rates of permanent procedural complications and favorable outcome range from 3.3 % to 6.7 %, and 77 % to 96 %, respectively [44]. Interestingly enough, both occlusion and complication rates in those treated by endovascular modalities appear to correlate highly with the particular embolic agent used. Gross et al., in a meta-analysis of endovascular treatment of IIAs, reported 88 % occlusion rates for coil embolization of IIAs, with permanent complications seen only in 9 % of the patients. In contrast, all aneurysms treated with NBCA or Onyx were successfully occluded without any reported permanent complication or procedure-related mortality. Notably, in all 3 reported cases where a stent-only technique was used (including one flow diverter), the aneurysm was occluded at last angiographic follow-up and there were no complications [18].

Conclusions

Infectious intracranial aneurysms of the pediatric population are rare. They represent a formidable challenge for the treating clinicians. They are often symptomatic and they frequently present with either intraparenchymal or subarachnoid hemorrhage. The diagnosis requires a high clinical suspicion with prompt intracranial vascular imaging. In children with a known diagnosis of infective endocarditis who develop new neurological manifestations, it is imperative to exclude the existence of an IIA as a cause for such. The prompt initiation of intravenous broad-spectrum antibiotics represents the mainstay of treatment, independent of the need for microsurgical or endovascular adjuvant treatments. Treatment with antibiotic therapy alone is reasonable for unruptured infectious aneurysms that remain stable in size as documented by frequent surveillance. However, ruptured IIAs or those that are persistent or progressive in the setting medical management require additional intervention to eliminate the high risk of rupture. Over

the last two decades, there has been a significant shift from primarily microsurgical treatments (either aneurysm clipping, trapping ± bypass or vessel sacrifice) toward endovascular techniques, namely PAO using liquid embolic agents. Microsurgical treatment still remains an important treatment modality for the patient with a large intraparenchymal hematoma that requires evacuation, for cases with associated elevated intracranial pressure, or in situations where endovascular PAO is contraindicated.

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Pediatric Stroke

15

Jorina Elbers and Gary K. Steinberg

Abbreviations

CA	Conventional angiography
CT	Computerized tomography
CTA	Computerized tomography angiography
DWI	Diffusion-weighted imaging
EEG	Electroencephalogram
IAT	Intra-arterial thrombolysis
IV	Intravenous
MCA	Middle cerebral artery
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
PVA	Post-varicella arteriopathy
SAH	Subarachnoid hemorrhage
SCD	Sickle cell disease
TCD	Transcranial Doppler
TIA	Transient ischemic attack

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A. Agrawal, G. Britz (eds.), *Pediatric Vascular Neurosurgery*,
DOI 10.1007/978-3-319-43636-4_15

TOF Time-of-flight
tPA Tissue plasminogen activator
TTE Transthoracic echocardiogram

Introduction

Pediatric stroke is an increasingly recognized cause of childhood mortality and disability. Stroke in childhood occurs in-utero, during the early neonatal period, during the early childhood years, or in adolescence. There are fundamental differences between stroke in childhood and stroke in adulthood. First, pediatric stroke is a relatively rare occurrence, resulting in frequent missed or delayed diagnosis by both parents and health care professionals. Second, multiple risk factors may exist simultaneously, resulting in complex etiologies and investigations. Alternatively, no cause may be apparent, resulting in uncertainty in both treatment and prognosis. Third, because of the low incidence of stroke, and stroke recurrence, there is limited evidence to support treatment practices and safety. Treatment and prognosis are often based on adult data, which may be inaccurate given developmental differences in coagulation and stage of brain development between children and their adult counterparts.

Whether a stroke is ischemic or hemorrhagic, or occurs in a newborn or an older child, the complexity of stroke in children necessitates a high index of suspicion to recognize the symptoms of stroke, knowledge of the necessary investigations, familiarity with treatment options, and the ability to counsel the family regarding prognosis.

Epidemiology

Incidence

The risk of stroke is highest within the first year of life, with a peak incidence of both ischemic and hemorrhagic stroke occurring in the perinatal period. The incidence of stroke in infants at <30 days of life is 26.4 per 100,000 live births per year, with rates of 6.7 for hemorrhagic stroke and 17.8 for ischemic stroke [1]. In children, the annual incidence rate is 2.3 per 100,000 children, 1.2 for ischemic stroke, and 1.1 for hemorrhagic stroke [2]. Advances in the recognition and care of children with stroke has reduced the 30-day case fatality from 18 % in 1988 to 9 % in 1999. Despite this, cerebrovascular disorders remain among the top ten causes of childhood death in the United States [3].

Ethnicity and Sex

Compared with white children, black children have a higher relative stroke risk of 2.12, while Hispanics have a lower relative risk of 0.76. Asians have a similar risk of stroke to white children. There are no ethnic differences in stroke severity or case

fatality. Sickle cell disease (SCD) is the most common cause of stroke among black children. Boys have a higher risk for all stroke types than girls, and have a higher risk of case-fatality after stroke even after controlling for trauma [2].

Arterial Ischemic Stroke

Perinatal Arterial Ischemic Stroke

Definitions

The term perinatal stroke typically refers to stroke occurring in-utero after the 20th week gestation up to the first 28 days of life [4]. An estimated 80 % of perinatal strokes are ischemic. Presumed perinatal ischemic stroke defines a sub-group of children who were asymptomatic at birth, but present later in life with seizures or motor-asymmetry and evidence of a chronic, focal infarction on neuroimaging.

Perinatal stroke may result from intracranial thrombosis or embolism from a distal site such as extracranial vessels, heart, umbilical vein, or placenta. Due to the multitude of risk factors, the precise timing of the ischemic event, whether pre-partum, intra-partum or post-partum, is seldom known.

Risk Factors

Perinatal arterial ischemic stroke is commonly associated with multiple risk factors, which include maternal, perinatal and neonatal conditions. Risk factors include infertility, primiparity, preeclampsia, chorioamnionitis, prolonged rupture of membranes, oligohydramnios, decreased fetal movement, prolonged second stage of labor, and fetal heart rate abnormalities [5, 6]. Maternal smoking [7] and cocaine use [8, 9] have also been identified as independent risk factors for perinatal stroke. While risk factors are commonly identified, most cases of perinatal stroke remain idiopathic.

Children with congenital heart disease have a high risk of stroke, and account for approximately one-quarter of all cases of perinatal stroke [6, 10]. Congenital cardiac lesions can lead to stroke through the development of intracardiac emboli, prolonged hypotension, and right-to-left shunting of systemic thrombi. In the setting of cyanotic heart disease, additional mechanisms of stroke include polycythemia and iron deficiency anemia, which increase blood viscosity thereby promoting the formation of thromboembolism [11, 12]. Ischemic stroke may also occur due to embolization after a cardiac procedure, including cardiac surgery or catheterization [13, 14]. Neuroimaging at baseline prior to cardiac surgery may reveal clinically silent ischemic strokes [15].

Coagulation abnormalities are frequently tested for and found, however the clinical significance of these abnormalities remains understudied. A recent meta-analysis determined the odds ratios of various prothrombotic conditions in the setting of neonatal arterial ischemic stroke and sinovenous thrombosis [16]. According to this study, the odds ratio of a first arterial ischemic stroke in children <18 years of age in the setting of a single thrombophillic risk factor is highest with protein C deficiency (OR 11.0; 95 % CI = 5.13–23.59), followed by antiphospholipid antibody syndrome (OR = 6.95; 95 % CI = 3.67–13.14) and elevated lipoprotein(a) (OR = 6.53; 95 %

CI = 4.46–9.55). This risk is further increased in the presence of two or more thrombophillic risk factors (OR = 18.75; 95 % CI = 6.49–54.14). While coagulation studies are frequently undertaken in the clinical setting, the significance of abnormal findings is unknown.

Infection is a frequently observed risk factor in perinatal stroke. Infection leads to a hypercoagulable state through pro-inflammatory cytokines, endothelial activation, and destruction of anti-thrombin III and protein C [10]. Maternal chorioamnionitis may increase hypercoagulable factors in-utero, and is a risk factor for perinatal stroke [17]. Infants with meningitis and sepsis are at increased risk for ischemic stroke [6, 18].

Clinical Presentation

Infants with stroke typically present after 12 h of life with focal motor seizures, apnea, hypotonia or neonatal encephalopathy [5, 19]. Motor asymmetry is less common in neonates, compared to older children. Children presenting with seizures or motor asymmetry after 4 months of age, including early handedness prior to 1 year of age, can be retrospectively diagnosed with a chronic infarct on neuroimaging, indicating presumed perinatal ischemic stroke [20].

Investigations

The evaluation of an infant presenting with stroke should include a detailed history regarding maternal medical history and exposures, pregnancy complications, labor and delivery history, placental pathology, neonatal history and family history of stroke before 55 years of age, hematologic disease and mental retardation.

While head ultrasound and computerized tomography can identify stroke in newborns, magnetic resonance imaging (MRI) is the gold standard imaging modality, and diffusion-weighted imaging (DWI) can provide important information regarding event timing and prognosis. The majority of strokes appear to be thromboembolic in nature. Neuroimaging commonly demonstrates exclusive involvement of the left middle cerebral artery (MCA) territory, or bilateral multifocal infarcts [6, 21]. Extension of the diffusion-weighted lesion down the corticospinal tract into the brainstem may be observed, and can be a poor prognostic sign indicating early Wallerian degeneration [22].

Further studies are necessary to investigate the stroke etiology and should include head and neck angiography, echocardiogram (ECHO), and assessment for coagulation abnormalities. While a standardized coagulation profile for perinatal stroke is not yet evidence-based, infants and their mothers may be tested for: homocysteine, protein C, protein S, anti-thrombin III, lipoprotein (a), antiphospholipid antibodies and plasminogen activator inhibitor. Inherited coagulopathies should be ruled out with Factor V Leiden, prothrombin G20210A gene mutation, and MTHFR in the setting of elevated homocysteine [23–25] (Table 15.1).

Management

Managing perinatal stroke entails supportive care, including blood pressure maintenance, and aggressive treatment of seizures and hyperthermia [23, 26].

Table 15.1 Hematological work-up for ischemic and hemorrhagic stroke

Primary Ischemic stroke work-up	Primary hemorrhagic stroke work-up
CBC with differential	CBC with differential
PT	PT
aPTT	aPTT
Anticardiolipin IgM/IgG	Fibrinogen
Lupus anticoagulant	Von Willebrand disease
β2 glycoprotein IgM/IgG	Factors VII, VIII, IX, X, XI, XIII
Protein C	Sickle cell screen
Protein S	Urine toxicology screen
Activated protein C resistance (APCR)	
Homocysteine	
Lipoprotein(a)	
Antithrombin III	
Factor VIII, IX, XI	
Prothrombin gene mutation G20210A	
Factor V Leiden	
MTHFR (if homocysteine elevated)	
Sickle cell screen	
Urine toxicology screen	

While therapeutic hypothermia has been widely used for hypoxic neonatal encephalopathy, its use after perinatal stroke remains unstudied. The safety and efficacy of thrombolytics and thrombectomy in the setting of perinatal stroke has not been established, and is therefore not recommended. Given the low risk of stroke recurrence in this population, secondary stroke prophylaxis is not necessary in the majority of cases, unless a cardiac abnormality is identified. Anticoagulation is safe, and should be considered in neonates with a cardioembolic ischemic stroke [26].

Outcome

Hemiplegic cerebral palsy is a common outcome in children following perinatal stroke, and is more frequently observed in children diagnosed retrospectively with presumed perinatal ischemic stroke. Motor deficits are present in 30–60 % of children, and are more likely to occur if the infarction extends to involve the motor cortex, basal ganglia, and internal capsule, or in the presence of a descending corticospinal tract sign on DWI [21, 22, 27, 28]. The risk of remote epilepsy ranges from 20–45 % [29, 30], and children with large MCA infarcts are at risk for developing infantile spasms [31]. Other outcomes include seizures, language delay, and cognitive difficulties [21, 27]. Seizures can interfere with brain development and are therefore associated with co-morbid cognitive difficulties [30, 32]. Stroke recurrence is exceedingly low following perinatal stroke, but may occur in patients with vascular or cardiac anomalies [33].

Childhood Arterial Ischemic Stroke

Definitions

Stroke is defined as a clinical syndrome characterized by a rapidly developing focal or global disturbance of brain functioning lasting >24 h or leading to death with no obvious nonvascular cause. Stroke in children is defined as occurring after 28 days of life, and extending into late adolescence. Arterial ischemic stroke in children is typically due to thromboembolism resulting in infarction of an associated vascular territory, or hypoperfusion resulting in watershed infarction between vascular territories. A primary ischemic infarct may result in hemorrhagic transformation, which can be scored according to the European Cooperative Acute Stroke Study (ECASS) scoring system [34]. ECASS subtypes include punctate petechial without space-occupying effect [HI1], confluent petechial [HI2], small parenchymal (≤30% infarcted area with mild mass effect) [PH1], or large parenchymal (>30% infarcted area with significant mass effect or hemorrhage remote from stroke location) [PH2] [35]. Transient ischemic attack (TIA) is defined as "a sudden, focal neurological deficit that lasts for less than 24 h, of presumed vascular origin, confined to an area of the brain or eye perfused by a specific artery" [36].

Mechanisms of Ischemic Stroke

Thromboembolism arising from within the cerebral circulation may be due to disease or injury of intra- or extra-cranial blood vessels, or from prothrombotic states. Endothelial damage from injury or disease causes a thrombogenic surface on which platelets and fibrin collect. Other factors such as flow rates, inflammation, cytokine activation, infection, and shear stress play a role in local thrombus formation.

Embolic sources for arterial ischemic stroke most frequently arise from the heart in children, however other sources, including the aorta and cerebral arteries, can cause artery-to-artery embolism. Venous emboli may reach the cerebral circulation in children with right-to-left shunting, which may occur in the setting of corrected congenital heart disease, a patent foramen ovale or a septal defect. A left-to-right shunt may reverse with a Valsalva or other maneuver that increases intrathoracic pressure, allowing for the temporary conduit of systemic venous emboli.

Infarction due to hypoperfusion of cerebral tissue is commonly due to a state of global hypoperfusion or cardiac disease, but may also result from severe stenosis of a supplying blood vessel, as in moyamoya disease. These infarcts appear as border zone, or watershed, infarcts in between the middle, anterior and posterior cerebral artery territories, and frequently involve the deep white matter and corona radiata.

Metabolic stroke is uncommon, yet important on the differential diagnosis for pediatric stroke. Metabolic stroke results from mitochondrial failure and impaired oxidative metabolism, in the absence of vascular occlusion or hypoperfusion. Neuronal swelling impinges on local capillary beds, resulting in further ischemia and early venous filling [37]. The pattern of metabolic stroke differs from arterial stroke, demonstrating diffusion restriction in a symmetric, bilateral pattern, or crossing multiple vascular territories. Spontaneous intracranial or subdural hemorrhage may also occur [38, 39], thereby making metabolic disease an important diagnosis to consider in the setting of a presumed non-accidental injury [40].

Risk Factors

It is increasingly recognized that stroke in children is often multifactorial. About half of the children who present with an acute arterial ischemic stroke have a previously identified risk factor, and the other half exhibit multiple risk factors [41, 42]. Several independent risk factors have been borne out of multiple studies and include infection, head trauma [43, 44], and cardiac disease [45]. Other important risk factors include arteriopathies, systemic inflammatory diseases, genetic disease, metabolic disease, neoplasms and hematological conditions. A complete list of risk factors can be found in Table 15.2.

Arteriopathies

With recent advances in neuroimaging, arteriopathies have been recognized as a major risk factor in childhood stroke, accounting for 53 % of acute stroke cases in a multi-centered study [46]. Several studies have implicated a post-infectious inflammatory mechanism underlying these disorders [47–49]. Childhood arteriopathies have been associated with a stroke recurrence risk of 66 % [33], and poorer long-term outcome compared to other stroke etiologies [50].

Current neuroimaging modalities impose significant limitations in the ability to determine the cause of an arteriopathy causing stroke in a child. Frequently, angiography will demonstrate unilateral steno-occlusive disease affecting the distal internal carotid artery, proximal MCA and proximal anterior cerebral artery. This appearance is non-specific, with a broad differential diagnosis including spontaneous intracranial dissection, unilateral moyamoya disease, and transient cerebral arteriopathy. The management and prognosis for these separate entities differ substantially, therefore care must be taken to establish the most probable diagnosis [51]. Follow-up angiography at 3 months, and again at 1 year is the most reliable way to arrive at a definitive diagnosis and counsel appropriate prognosis.

Arterial Dissection

Extracranial dissection of the carotid or vertebral arteries accounts for 5–25 % of childhood arterial ischemic stroke; and is often preceded by trauma [52]. Risk factors for arterial dissection include head or neck trauma, minor neck torsion, cervical chiropractic manipulation, or connective tissue disease [52, 53]. On angiography, a double-lumen, intimal flap, tapered stenosis (“string-sign”) or intramural hematoma on T1 fat-saturated MRI or high-resolution arterial wall MR imaging, are specific features suggesting arterial dissection. The most common location for extracranial carotid artery dissection is 2–3 cm above the carotid bulb (Fig. 15.1), while the vertebral artery is most vulnerable at C1–C2 due to its tortuous course through the transverse foramina. Children with vertebral dissections should be evaluated with additional neck imaging to assess for a cervical skeletal abnormality. Aneurysmal dilatation, also termed pseudoaneurysm, may occur as a complication of dissection secondary to impaired integrity of the vessel wall and persistent arterial pressure, therefore follow-up arterial imaging at 3–6 months is recommended [54, 55].

Table 15.2 Risk factors for arterial ischemic stroke in children

Infection
Varicella
Meningitis
Otitis media
Tonsillitis
Upper respiratory tract infection
Mycoplasma pneumonia
Dengue infection
Sepsis
Traumatic
Minor head trauma
Arterial dissection/transection
Carotid ligation
Arterial compression by hemorrhage or edema
Iatrogenic (ie. neurovascular interventional procedure)
Non-accidental trauma
Cardiac disease
Mechanical circulatory support (ECMO, ventricular assist device)
Left-sided cardiac catheterization
Single-ventricle palliative procedures (Norwood, Bi-directional Glenn)
Atrial or ventricular septal defects
Left-sided valvular disease
Endo/myocarditis
Cardiomyopathy
Heart transplantation
Atrial myxoma
Cardiac rhabdomyoma
Dysrhythmia
Arteriopathy
Acquired
Infectious vasculitis
Central nervous system vasculitis (primary or secondary)
Transient cerebral arteriopathy
Fibromuscular dysplasia
PHACES syndrome
Sturge-Weber syndrome
Bowhunter's syndrome
Idiopathic moyamoya disease
Premature atherosclerosis
Migrainous infarction
Ergotism
Reversible cerebral vasoconstriction syndrome
Stimulant drug use
Vasospasm associated with subarachnoid hemorrhage

Table 15.2 (continued)

Genetic
Ehlers-Danlos Syndrome
Marfan Syndrome
ACTA2 mutation
Moyamoya disease (RNF213)
Neurofibromatosis Type I
William's-Beuren Syndrome
Down syndrome
Homocysteinuria
COL4A1 mutation
Pseudoxanthoma elasticum (ABCC6 mutation)
CADASIL (NOTCH3 mutation)
CARASIL (HTRA1 mutation)
Alagille syndrome (JAG1 mutation)
Microcephalic osteodysplastic primordial dwarfism type II (PCNT mutation)
Schimke immune-osseous dysplasia
Aicardi-Goutièrs syndrome (SAMHD1 mutation)
Menkes disease (ATP7A mutation)
Arterial tortuosity syndrome (SLC2A10 mutation)
Metabolic disease
Fabry's disease
MELAS (Mitochondrial encephalopathy with lactic acidosis and stroke-like episodes)
MERFF (Myoclonic epilepsy with ragged-red fibers)
Kearns-Sayre syndrome
Homocysteinemia
Methylmalonic academia
Propionic academia
Glutaric aciduria type II
Isovaleric academia
Ornithine transcarbamylase deficiency
Carbamyl phosphate synthetase
Systemic inflammatory disease
Antiphospholipid antibody syndrome
Systemic lupus erythematosus
Takayasu arteritis
Polyarteritis nodosa
Dermatomyositis
Inflammatory bowel disease
Sarcoidosis
Neoplastic
Arterial compression by tumor
Hypercoagulable state (leukemia)

(continued)

Table 15.2 (continued)

Post-radiation arteriopathy
Medication-related (L-asparaginase, mitomycin)
Hematological
Acquired
Anti-thrombin III deficiency
Factor abnormalities
Protein C deficiency
Protein S deficiency
Plasminogen deficiency
Dysfibrinogenemia
Disseminated intravascular coagulation
Thrombocytopenic purpura
Hemolytic uremic syndrome
Polycythemia
Iron-deficiency anemia
Elevated lipoprotein (a)
Activated protein C resistance
Oral contraceptive
Pregnancy and post-partum
Genetic
Anti-thrombin III deficiency
Hemoglobinopathies (sickle cell disease)
Factor V Leiden mutation
Prothrombin G20210A gene mutation
Methyltetrahydrofolate reductase deficiency (thermolabile variant)
Miscellaneous
Fat or air embolism
Foreign body embolism
Traumatic/laceration

There is considerable variability in the treatment of arterial dissection, and recommendations are based on adult data. Recently published childhood stroke guidelines recommend treatment of extracranial dissection with anticoagulation, such as unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), or warfarin for 3–6 months. Anticoagulation is not recommended in patients with associated subarachnoid hemorrhage (SAH) [26]. Neuroimaging is typically repeated at 3 months, and if arterial abnormalities persist, treatment is extended to 6 months at which time the patient may be transitioned to aspirin 3–5 mg/kg. Given recent controversy regarding the benefits of anticoagulation in adults, aspirin may be substituted for anticoagulation [26]. Recanalization of the affected artery occurs in 60 % of children, and the risk of recurrent stroke or TIA is 12 % [56]. Aspirin therapy should be continued as long as arterial abnormalities persist on arterial imaging as

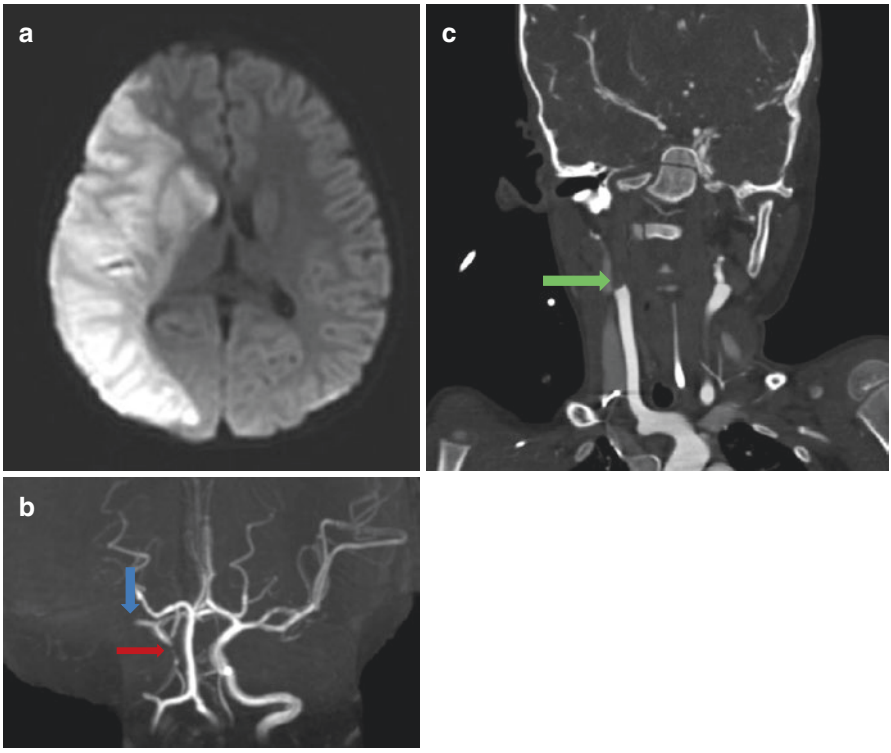

Fig. 15.1 A 3-year-old boy presents with acute onset left hemiparesis involving the face, arm and leg. Axial MRI diffusion-weighted imaging demonstrates complete right middle cerebral territory infarct (**a**); MR time-of-flight angiography demonstrates absent flow through the cavernous portion of the right internal carotid artery (*red arrow*), with reconstitution of flow at the supraclinoid internal carotid artery, and subsequent loss of flow signal in the proximal MCA (*blue arrow*), suggesting occlusion from artery-to-artery embolism (**b**); contrast-enhanced CT angiography demonstrates an abrupt cut-off at the carotid bifurcation *(green arrow*) suggesting arterial dissection (**c**)

this is a risk factor for stroke recurrence. In the event of recurrent stroke, a combination of aspirin and heparin is frequently utilized. Due to the dynamic nature of developing blood vessels, surgical stenting or balloon angioplasty is not recommended, and reserved for cases failing aggressive medical management [26].

Intracranial dissection is less common than extracranial dissection, and less understood. Given frequent non-specific MR angiography findings of steno-occlusion at the distal internal carotid artery, proximal MCA and proximal ACA, more detailed luminal imaging using conventional angiography (CA) or high-resolution arterial imaging on MRI is recommended [57]. Anticoagulation is not recommended for intracranial dissection because of the potential increased risk of SAH [26].

Moyamoya Disease and Moyamoya Syndrome

Moyamoya disease is an idiopathic steno-occlusive arteriopathy predominantly affecting the distal internal carotid artery bifurcation, proximal MCA or ACA, which

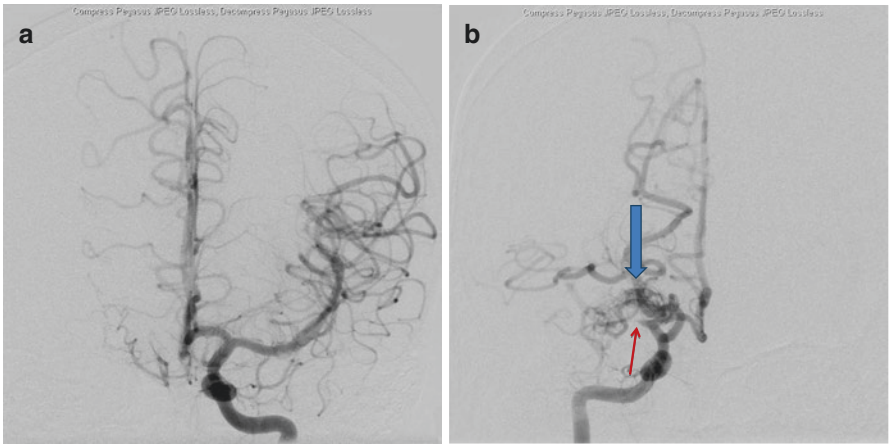

Fig. 15.2 Unilateral moyamoya disease in a 13-year-old girl affecting the right-sided anterior circulation. Conventional angiography demonstrates normal left anterior circulation (**a**), and abnormal right anterior circulation (**b**), with abrupt occlusion of the middle cerebral artery (*red arrow*), and an abnormal network of collateral vessels, or "moyamoya" (*blue arrow*)

may also progress to involve the posterior circulation. Classically, moyamoya disease implies an abnormal network of collateral vessels extending from involved arteries which likely compensate for impaired cerebral perfusion (Fig. 15.2). Arterial abnormalities may be unilateral initially, with bilateral progression in 30–40 % of patients over 2–5 years [58, 59]. Moyamoya disease is the term used when the arteriopathy is idiopathic, while moyamoya syndrome is used when the arteriopathy is secondary to an associated condition like cranial radiation or genetic syndromes such as neurofibromatosis type 1, trisomy 21, or Alagille syndrome. The recent identification of RNF213 as a susceptibility gene in patients of Japanese descent has expanded the role of genetics in patients with idiopathic moyamoya disease [60]. In addition to arterial ischemic stroke, moyamoya may also present with chronic headache, TIA, or hemorrhagic stroke. The location of ischemic strokes may involve large-vessel territories, basal ganglia or watershed regions. Given the progressive nature of this disease, follow-up imaging at regular intervals is performed. Surgical revascularization procedures are recommended in patients presenting with acute stroke or progressive cognitive decline, and are associated with a 2.6 % risk of deterioration [61], compared to the natural history rate of progressive decline in 50–66 % of untreated patients [62, 63]. Disease onset at a young age is associated with more rapid disease progression [62, 63]. Revascularization techniques include a direct anastomosis procedure, most commonly a superficial temporal artery to MCA anastomosis, or indirect revascularization procedures such as encephaloduroarteriosynangiosis (EDAS) and encephalomyoarteriosynangiosis [64].

Vasculitis

Central nervous system vasculitis in children may be idiopathic, termed primary angiitis of the central nervous system, or secondary to known causes such as infection or systemic auto-immune disease (Table 15.2) [65]. Vasculitis may also

be differentiated according to the distribution of affected vessels. Large-medium vessel vasculitis typically presents with acute focal neurological deficits and arterial ischemic stroke, while small-vessel disease manifests with sub-acute onset of headaches, encephalopathy, seizures or cognitive decline, with vasogenic edema on MRI [65]. Characteristic angiographic evidence of large-vessel vasculitis includes segmental stenosis, beading and occlusion. Aneurysmal formation may also occur [66]. Small-vessel vasculitis is by definition angiography-negative, and requires brain biopsy evidence of intramural, lymphocyte-predominant inflammation for diagnosis [67]. In the setting of angiographic abnormalities, vasculitis secondary to bacterial, viral, fungal or spirochete infection is treated with concomitant aspirin therapy. In contrast, primary large and small-vessel angiitis of the CNS, and systemic inflammatory conditions such as systemic lupus erythematosus or Takayasu's arteritis require aggressive immunosuppressive therapy to control inflammation and prevent recurrent stroke. Treatment protocols have been extrapolated from adult literature and commonly use combinations of aspirin 3–5 mg/kg/day, pulse methylprednisolone 30 mg/kg, intravenous (IV) immunoglobulin 2 g/kg divided over 2 days, and monthly IV cyclophosphamide [68, 69].

Transient Cerebral Arteriopathy and Post-varicella Arteriopathy

Transient cerebral arteriopathy (TCA) refers to a focal, unilateral intracranial arteriopathy involving the distal internal carotid artery and its proximal branches, with a stereotyped, monophasic course characterized by early progression over days to weeks, a plateau with non-progression by 6 months, and subsequent improvement, with nearly 25% demonstrating complete resolution [47, 48] (Fig. 15.3). Patients typically present with isolated basal ganglia, or more extensive MCA-territory infarction. Angiography at stroke onset may demonstrate beading, steno-occlusion, or may even be normal, with subsequent angiographic worsening over weeks to months. The etiology of TCA is as yet unknown, however given the natural history and association with upper respiratory tract infection, is presumed to be inflammatory. When arterial ischemic stroke with similar angiographic features occurs within 1 year of varicella infection, this is termed post-varicella arteriopathy (PVA) [49]. Like transient cerebral arteriopathy, PVA has a predilection for the carotid-T junction and basal ganglia stroke. There is little consensus on the treatment of transient cerebral arteriopathy or PVA at the current time. Some authors advocate for treatment with steroids, anticoagulation and acyclovir in the acute phase of the disease [49, 70], however no clinical trials have been performed.

Genetic Disease

There are several genetic diseases which may place a child at risk for either embolic or thrombotic stroke (Table 15.2). Genetic diseases may affect the coagulation system (Factor V Leiden, prothrombin gene mutation), while others may cause arteriopathy or induce premature atherosclerosis (homocystinuria, Schimke immuno-osseous dysplasia). Screening for arteriopathies with angiography has been recommended in children with SCD and neurofibromatosis type I [71].

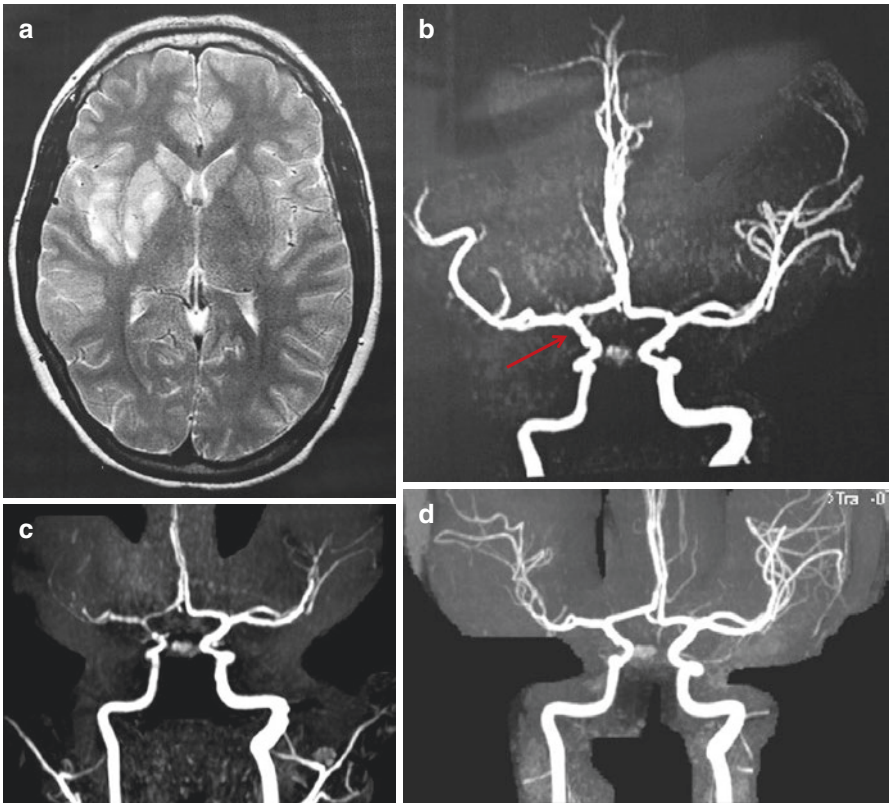

Fig. 15.3 Fourteen year-old girl presents with acute onset left hemiparesis affecting the face, arm and leg. Baseline T2-weighted MRI demonstrating right MCA infarction involving the basal ganglia and adjacent cortex (**a**). MRA at the time of stroke recurrence demonstrating irregular segmental narrowing of the distal ICA, M1 and A1 (*red arrow*) consistent with beading (**b**). MRA at 3 months post-stroke demonstrating progression with reduced flow in the distal ICA, and proximal MCA and ACA (**c**). MRA at 2 years post-stroke demonstrating near complete resolution of arterial abnormalities, consistent with transient cerebral arteriopathy (**d**)

Metabolic Disease

Metabolic disease increases the risk of stroke from multiple mechanisms: embolic formation, vascular proliferation, or non-vascular, oxidative failure. Elevated levels of homocysteine in the blood cause disruption of the endothelium, resulting in carotid artery stenosis, as well as a prothrombotic state [72]. Fabry disease is an x-linked lysosomal storage disorder that results in the accumulation of metabolic byproducts within endothelial cells, causing both large and small vessel vasculopathy [73].

Non-vascular metabolic diseases, however, are more likely to present with stroke-like episodes. Abnormalities within cellular organelles may impair a cell's ability to perform oxidative metabolism resulting in focal ischemia. Mitochondrial diseases, such as mitochondrial encephalopathy lactic acidosis

and stroke-like episodes (MELAS), commonly present with multifocal or bilateral occipital lobe strokes, with either decreased, increased or normal apparent diffusion co-efficient values on MRI suggesting both cytotoxic and vasogenic edema [74]. Suspicion of a metabolic cause of stroke should be raised when the pattern of ischemia does not conform to a vascular territory or border zone, involves the bilateral basal ganglia, or is associated with spontaneous intracranial or subdural hemorrhage.

Hematologic Disease

Although the risk of stroke from most prothrombotic states is relatively low, the risk tends to increase when a prothrombotic disorder occurs in combination with other stroke risk factors. Thus, it is reasonable to evaluate for common prothrombotic states even when another stroke risk factor has been identified. SCD is the most common hematologic disorder causing stroke in children. Other genetic conditions to look for include Factor V Leiden, prothrombin 2021A gene mutation and, in the setting of elevated homocysteine, MTHFR homozygosity (Tables 15.1 and 15.2). While prothrombotic abnormalities are frequently identified [75], their link to stroke causation is controversial as rates are often comparable to the general population [24, 76].

Patients with SCD are the population with the single-most highest risk of stroke. In a population-based study in the Baltimore-Washington, USA catchment area, the incidence of stroke in young persons with SCD was 285 per 100,000 persons compared to 1.29 per 100,000 in the general population [77]. Approximately half of strokes occurring in patients with sickle cell are ischemic, and occur as a result of local endothelial damage, vasculopathy or moyamoya syndrome, venous thrombosis and sludging of sickled red cells through penetrating small vessels. Young children between 2 and 5 years of age are at the highest risk for developing ischemic stroke, with an annual incidence rate of 1.02 % [78]. Annual screening with transcranial Doppler (TCD) offers an opportunity to identify those patients at high risk for first stroke. Children with TCD ultrasound evidence of high cerebral blood flow velocity rates (time-averaged mean velocity 200 cm/s) have a stroke rate of at least 10 % per year [79] Regular exchange transfusion in children identified with TCD velocities above 200 cm/s is an effective primary stroke prevention strategy [80], however it also carries the complications of iron overload. For the purposes of screening, normal TCDs may be repeated annually, while an abnormal study should be repeated in 1 month. Borderline and mildly abnormal TCD studies (time-averaged mean velocities between 170 and 200 cm/s) may be repeated in 3–6 months [81]. Following acute stroke, children with SCD require treatment with IV hydration and exchange transfusion to reach a sickle hemoglobin level <30 %, in addition to supportive care. If moyamoya syndrome is also present, surgical revascularization may reduce the risk of subsequent stroke. While arteriopathy is the most common cause of stroke in these patients, other causes of stroke, including sinovenous thrombosis, cardioembolism and infection, should be considered.

Clinical Presentation

As in adults, early recognition of stroke is a critical factor in obtaining a rapid diagnosis, instituting important supportive measures for neuroprotection, and implementing treatment. Pediatric stroke is commonly under-recognized by health professionals [82]. The recognition of stroke in children is particularly challenging when children are young, and the presenting features are non-specific, transient or subtle. The presenting clinical symptoms in younger children may include seizures, fever, headache or lethargy [83]. Hemiparesis is the most common presentation, observed in up to 80 % of children with stroke [84].

One of the reasons why stroke is often overlooked as a cause for focal neurological deficits in children is the high frequency of stroke mimics in children presenting with seizures, headache and focal neurological deficits. Approximately 20 % of acute stroke presentations are diagnosed with stroke mimics [85], which include tumor, posterior reversible encephalopathy syndrome, infection, Todd's paralysis, hypoglycemia, and conversion disorder.

Investigations

Baseline laboratory studies can be found in Table 15.1. Since congenital and acquired heart disease is a common cause of stroke in children, a transthoracic ECHO (TTE) is indicated in all children with stroke. This should be performed promptly following the diagnosis of stroke to evaluate for a cardiac thrombus or vegetation, or right to left shunt. A "bubble" or "contrast" study is indicated in children with recurrent strokes of unknown etiology to assess for patent foramen ovale or pulmonary arteriovenous malformation [86]. In rare cases, transesophageal ECHO may detect abnormalities not seen on TTE, particularly vegetations and left atrial thrombi [87]. In addition, an electrocardiogram should be obtained to rule out arrhythmias [88].

The high frequency of stroke mimics in children makes confirmation of stroke especially important [85, 89]. A computerized tomography (CT) scan will often miss early signs of ischemic infarction and is therefore not sufficient in ruling out stroke in a child. MRI with DWI, in addition to magnetic resonance angiography (MRA) of the head and neck, should be performed in a child suspected of having an acute ischemic stroke.

If an arterial abnormality is suspected on time-of-flight (TOF) MRA, a more specific angiography may be necessary to better define the arterial lesion and assess for additional lesions in the distal circulation. This can be performed with contrast imaging using MRA, MRI high-resolution arterial wall imaging, CT angiography (CTA) or digital subtraction angiography (DSA) [90]. While DSA is considered the gold standard for arterial imaging, it is invasive, and can be technically challenging in small children [91]. CTA is more widely available than DSA, and provides greater luminal detail than MR TOF angiography to characterize arterial lesions, such as dissection, vasculitis or moyamoya disease, although in most cases it does not add significantly to information obtained on contrast-enhanced MRA [88].

TCD may be useful for characterization of flow abnormalities on MRA, detection of circulating microemboli in patients with potential embolic sources, including dissection, and to monitor for vasospasm in patients with SAH. TCD is most frequently used in children with SCD for stroke risk stratification [79].

Management

Supportive Care

The prevention of secondary injury caused by pathologic changes in blood pressure, oxygenation, and temperature or impaired glucose regulation, is a fundamental principle of supportive care in a child presenting with acute stroke. Close observation is recommended for patients during the first 48 to 72 h from the time of their stroke to monitor for changes in neurologic exam, physiologic derangement, signs of raised intracranial pressure, recurrent stroke or hemorrhage, or treatment complications.

To maximize cerebral perfusion pressure, the head of the bed should be flat for at least 24 h and up to 72 h as tolerated, unless there are concerns about malignant infarct or raised intracranial pressure, in which case it should be placed at 30°. Children should be placed NPO (nothing by mouth) until their swallowing has been formally assessed. Adequate hydration is established with normal saline (with or without D5) at 1 or 1.5× maintenance for the first 48–72 h, to obtain euvolemia and normoglycemia (serum glucose level 60–200 mg/dL). Prevention of hyperthermia is essential, with liberal use of acetaminophen or a cooling blanket to maintain temperatures below 37.5 °C [88].

Patients with stroke often demonstrate a natural elevation in blood pressure, which is likely to be multifactorial, related to stress, anxiety, cerebral perfusion pressure, and increased sympathetic activity. This reactive hypertension serves to perfuse the penumbra, a potentially viable area of tissue surrounding the infarcted brain. Hemorrhagic conversion following pediatric ischemic stroke appears to be rare and associated with large infarct volumes [34]. Recommended blood pressure goals are between 50 and 95 percentile for age and height, with permissive hypertension up to 20% above the 95 percentile. If blood pressure lowering agents are used, care should be taken to avoid precipitous drops in blood pressure that may worsen cerebral ischemia.

Clinical and subclinical seizures are common in children with acute neurologic injuries [92]. Seizures may further compromise an already vulnerable ischemic penumbra, leading to progression of an infarct. Anticonvulsant medication is necessary in all patients presenting with seizures. In patients with reduced level of consciousness, electroencephalogram (EEG) or continuous EEG monitoring should be considered to rule out subclinical seizures [93].

Intravenous Thrombolysis

In adults, IV tissue plasminogen activator (tPA) is FDA-approved for use within 3 h of stroke onset, and recent American Heart Association/American Stroke Association advisory recommends extending the time window to 4.5 h [94]. When administered

within 4.5 h for arterial ischemic stroke, IV tPA is associated with symptomatic intracranial hemorrhage in 2.6% of adults [95]. A recent study of thrombolysis in young adults (16–49 years) showed that these patients benefited from IV tPA and may be at lower risk for intracranial hemorrhage than older adults [96].

The use and outcome of IV tPA in the setting of acute stroke in children is variable, and demonstrates that safety data are lacking [97–110]. Given the absence of safety data and the high rate of stroke mimics in children, tPA should only be considered in select patients presenting with a significant, persistent neurological deficit, with evidence of ischemic infarction and arterial occlusion on neuroimaging. Treatment contraindications and dosing should be within established safety guidelines for adults. The use of tPA in children under 2 years of age is not recommended due to the lack of safety data and the inability to firmly establish time of onset in most cases [88].

Intra-arterial Thrombolysis

Recent randomized controlled trials in adults have demonstrated superiority of endovascular intra-arterial thrombolysis (IAT) versus IV tPA when performed within 6 to 12 h from the onset of the stroke [111–113]. In children, several case reports and case series discuss IAT for MCA or basilar artery occlusion [114, 115]. Complications arising from the use of IAT in children include iatrogenic arterial dissection, intracranial hemorrhage, and recurrent stroke distal to the site of thrombosis, therefore such procedures should be performed by an experienced neurointerventional radiologist [88].

Stroke Recurrence and Secondary Stroke Prevention

Stroke recurrence in children ranges from 10–30%, and can occur in the immediate post-stroke period or several years later [33]. Recurrence risk is highest in children identified with underlying cardiac disease, affecting 27% [116], or cerebral arteriopathy, where the 5-year cumulative recurrence risk is 66% [33]. In the absence of a known cause or arterial abnormality, stroke recurrence is negligible [33, 117].

Current treatment recommendations are based on expert consensus, as trials to establish the most effective agent for secondary stroke prevention are impractical due to the required sample size [118]. Initial secondary stroke prophylaxis comprises either aspirin 3–5 mg/kg [26, 119] or heparin until cardioembolic stroke and dissection have been ruled out [119]. In patients with complete MCA territory infarcts, heparin may be contraindicated given the increased risk of hemorrhage, and the low benefit associated with preventing stroke recurrence in an already infarcted territory.

There are no clinical trials for the long-term treatment of stroke prevention in children, and clinical practice is largely based on adult data. Current practice suggests that children with persistent arterial stenosis on angiography require ongoing treatment with aspirin 3–5 mg/kg, as turbulent flow through narrowed arteries may precipitate clot formation leading to stroke recurrence. Similarly, children with congenital heart disease are frequently treated with long-term antiplatelet or anticoagulation due to the high risk of stroke recurrence associated with shunting and anomalous cardiac anatomy [116].

Outcomes

It is a widely held belief that children fair better than adults following an ischemic stroke. Reported outcomes following childhood stroke have ranged from full recovery in up to 37 % of patients, mild or moderate deficits in 29–50 %, and severe or unfavorable outcome in 15–44 % [27, 120, 121]. Functional status at 1 year post-stroke strongly predicts long-term outcome [122]. Despite functional deficits in over 60 % of patients, most young adults are independent in driving, relationships, and employment [122]. The risk of epilepsy following stroke is 13–24 %, most commonly occurring in children with seizures at the time of their stroke presentation [123, 124]. Pediatric stroke is also associated with a higher incidence of psychiatric illness, including attention deficit hyperactivity disorder, anxiety, mood disorder and personality change [122, 125].

Rehabilitation therapy is an important predictor of functional outcome, with increasing evidence for task-specific approaches, and constraint-induced therapy [126]. Infants and young children have additional challenges due to restricted growth of hemiplegic limbs. Hemiatrophy is commonly observed, and can create leg-length discrepancy and scoliosis. In addition, more subtle deficits in learning, communication, behavior and socialization can affect quality of life and education, and should be adequately assessed.

Hemorrhagic Stroke

Perinatal Hemorrhagic Stroke

Definitions

Perinatal hemorrhagic stroke refers to clinically evident intracerebral hemorrhage occurring within the 28th post-natal day. Hemorrhagic stroke in the newborn may involve parenchymal hemorrhage, intraventricular hemorrhage, subdural hemorrhage or SAH. Intraventricular hemorrhage is the most common type of hemorrhage in preterm neonates due to germinal matrix hemorrhage. In term neonates, the location can be more variable, and in some instances all compartments may be involved. Infratentorial subdural hemorrhage is the most frequent intracranial hemorrhage in asymptomatic term newborns [127]. As intraventricular hemorrhage is primarily a disorder of prematurity, its presence in a term neonate should raise the suspicion of sinovenous thrombosis, and prompt further investigation with venography [128].

Parenchymal hemorrhage may be primary, as in the case of a ruptured arterial vessel, cavernous malformation or coagulation abnormality, or secondary to ischemic stroke and arterial or venous occlusion. Common causes of hemorrhage according to their location can be found in Table 15.3 [129].

Risk Factors

Identified risk factors for hemorrhagic stroke are present in approximately 40 % of infants and include fetal distress, post-maturity, congenital heart disease and hematologic abnormalities [130, 131]. Birth trauma may result in tearing or direct laceration of

Table 15.3 Pathophysiology, relative frequency and causes of hemorrhagic stroke in the newborn according to location

Location	Pathophysiology	Relative frequency and causes
Epidural hemorrhage	Tearing of middle meningeal artery	Rare; significant birth trauma or fall
Subdural hemorrhage	Tearing of tentorial blood vessels	Common; idiopathic, birth trauma, congenital hemophilia
Subarachnoid hemorrhage	Tearing of bridging vessels and dural venous sinuses	Most common in term infants; birth trauma, aneurysmal rupture
Intraventricular hemorrhage	Germinal matrix hemorrhage in preterm infants; choroid plexus or extension of thalamic hemorrhage in term infants	Most common in premature infants; birth trauma, neonatal asphyxia, venous sinus thrombosis, cryptic hemangioma of choroid plexus
Intraparenchymal hemorrhage	Ischemia, venous congestion,	Uncommon; hemorrhagic transformation of arterial ischemic stroke, venous sinus thrombosis, rupture of arteriovenous malformation or aneurysm, birth trauma, hematological disorder

bridging vessels in the tentorium or dural sinuses. Hypoxic ischemic encephalopathy is a common factor in both term and preterm infants with intraventricular hemorrhage. Risk factors for hemorrhagic transformation of primary ischemic hemorrhage include sepsis, acidosis, acute systemic illness and bilateral ischemic lesions [6]. Subdural hemorrhage can be seen in asymptomatic newborns within 72 h of birth [132].

Hematologic abnormalities are present in 10–30 % of newborns with hemorrhagic stroke, and promote either hemorrhage or thrombosis. Hypercoagulable factors include deficiencies in protein C and S, and anti-thrombin III. Factors promoting hemorrhage are less common, and include neonatal alloimmune thrombocytopenia, hypofibrinogenemia, vitamin K deficiency and disseminated intravascular coagulation. Hereditary coagulopathies that promote hemorrhage include von Willebrand disease and factor deficiencies such as hemophilia A (factor VIII deficiency) and hemophilia B (factor IX deficiency) [130, 131]. Disseminated intravascular coagulation due to sepsis or other medical conditions may also cause hemorrhagic stroke in term newborns.

In multiple case series, arteriovenous malformations and aneurysms as a cause for perinatal hemorrhagic stroke are rare [130, 131, 133–137]. Previously documented vascular lesions causing hemorrhage in this age group include cavernous malformation [131], aneurysm [138], and vein of Galen malformation [139].

Clinical Presentation

Infants with hemorrhagic stroke present with encephalopathy, apnea, seizures or motor asymmetry [131]. Acute hydrocephalus may present as irritability, poor feeding, vomiting and a bulging fontanelle [130]. Children with infection may be at higher risk of developing hemorrhagic transformation of an ischemic stroke.

Investigations

The evaluation of an infant presenting with hemorrhagic stroke should include a detailed history regarding maternal medical history and medications, pregnancy complications, labor and delivery history including vitamin K supplementation, neonatal history and family history of stroke before 55 years of age, bleeding disorders and mental retardation.

Coagulation screening should include baseline CBC, prothrombin time, and activated partial prothrombin time. If hemorrhagic transformation of an ischemic stroke is suspected, labs should focus primarily on hypercoagulable factors. If primary hemorrhage is more likely, these labs can be curtailed. Coagulation work-up can be found in Table 15.1. Because congenital heart disease is a common cause of stroke, all infants with hemorrhagic stroke should undergo cardiac ECHO.

Neuroimaging is frequently initiated with head ultrasound, which demonstrates a hyperechoic mass suspicious of hemorrhage. Head ultrasound is effective at detecting intraventricular hemorrhage, however it may miss small lesions, and is unable to distinguish between parenchymal hemorrhage and ischemia. Subsequent imaging with CT or MRI is necessary to visualize the size and location of hemorrhage, associated ischemia, and concurrent subarachnoid or subdural hemorrhage. MR is preferable given the absence of radiation and greater anatomical detail, however it is often less readily available than CT. CT or MR angiography is frequently performed, and provides useful information on arterial abnormalities, such as aneurysm or arteriovenous malformation, however these are rare in newborn infants. Venous infarcts typically consist of ischemic lesions demonstrating both cytotoxic and vasogenic edema, and frequently include hemorrhage. Venography is recommended in term infants with intraventricular hemorrhage or hemorrhagic infarcts to rule out sinovenous thrombosis. In contrast, hemorrhagic transformation of arterial ischemic stroke is suspected when hemorrhage is within a significantly larger area of ischemia identified by restricted diffusion on MRI corresponding to an arterial territory. In the setting of intraventricular hemorrhage, assessment of ventricular size is important to note, and monitored with serial head circumference for the development of hydrocephalus.

Management

Management of infants with hemorrhagic stroke is primarily supportive, with the goals of providing adequate ventilation, preventing metabolic acidosis, and maintaining perfusion of vital organs, including the brain. Prompt treatment of platelet and factor deficiencies is necessary to prevent further hemorrhage. Vitamin K supplementation 1 mg IV should be considered if not previously administered, and larger doses may be necessary in mothers taking certain medications, such as warfarin, phenytoin or barbiturates during pregnancy [140].

Newborns with intracranial hemorrhage should be monitored closely for complications, including seizures, delayed cerebral edema or syndrome of inappropriate antidiuretic hormone. Aggressive seizure management with anticonvulsants is necessary to suppress both clinical and subclinical seizures. A loading dose of 20 mg/kg of phenobarbital, phenytoin or levetiracetam, followed by daily maintenance, is frequently required in such patients.

Due to the compensatory mechanism of the sutures and open fontanelle in the newborn, surgical evacuation of hematoma is rare, but may be necessary to reduce malignant intracranial pressure [135]. Ventricular drainage is appropriate for infants with hydrocephalus secondary to intraventricular hemorrhage, with subsequent peritoneal shunting as necessary [137].

Outcome

The outcome of infants with hemorrhagic stroke is variable, and depends on the etiology of hemorrhage, the location and size of the hemorrhage. Infant mortality ranges from 1 to 25 % [130, 134–136]. Not surprisingly, children with hemorrhagic stroke following birth trauma or hypoxic ischemic encephalopathy are more likely to have long term deficits. Adverse neurological outcomes occur in 9–57 % of children, and may include developmental delay, focal neurological deficits, vision abnormalities, seizures and cognitive impairment [130, 134–136].

Childhood Hemorrhagic Stroke

Definitions

Nearly half of stroke cases occurring in children are hemorrhagic [2]. Despite this, most of the knowledge pertaining to pediatric hemorrhagic stroke is based on small case series [34, 141–144], as large prospective cohort studies do not exist. The term hemorrhagic stroke refers to spontaneous subarachnoid or intracerebral hemorrhage, with intracerebral hemorrhages involving the parenchyma or the ventricles. In general, hemorrhagic stroke is not used to describe hemorrhage secondary to trauma, or hemorrhagic transformation of a primary ischemic stroke.

Risk Factors

Etiological risk factors can be identified in approximately 80 % of patients presenting with hemorrhagic stroke. These may occur as a result of vascular anomalies (arteriovenous malformation, aneurysm, and cavernous malformation), arteriopathy, tumor, disorders of coagulation, genetic-metabolic disorder or infection. A complete list of risk factors can be found in Table 15.4. Vascular anomalies account for nearly half of cases and include (in descending order of frequency): arteriovenous malformation, cavernous malformation, aneurysm, and venous angioma, although it is controversial whether venous angioma is truly responsible for hemorrhage (rather than an associated cavernous malformation) [142] Moyamoya disease can also occasionally cause hemorrhage (subarachnoid, intraventricular or intraparenchymal) in this pediatric age group. In some cases, multiple risk factors are identified; while spontaneous hemorrhage is more likely to occur with severe factor deficiency, bleeding from milder deficiencies are often precipitated by trauma [145].

Table 15.4 Risk factors for hemorrhagic stroke in children according to location

Epidural hemorrhage
Accidental trauma
Non-accidental trauma
Middle ear or sinus infection
Ventricular shunt complication
Langerhans cell histiocytosis
Hematologic disorder
Sickle cell disease
Subdural hemorrhage
Accidental trauma
Non-accidental trauma
Aneurysm
Arachnoid cyst
Glutaric aciduria
Galactosemia
Hypernatremia
Subarachnoid hemorrhage
Trauma
Intracranial aneurysm
Stimulant drug use
Sickle cell disease
Moyamoya disease
Intraventricular hemorrhage
Trauma
Arteriovenous malformation
Intraventricular extension of primary parenchymal hemorrhage
Moyamoya disease
Intraparenchymal hemorrhage
Trauma
Hemorrhagic transformation of arterial ischemic stroke
Venous sinus thrombosis
Brain tumor
Hematological disorder
Infection (systemic or primary CNS)
Mycotic aneurysm
Hypertension
Posterior reversible encephalopathy syndrome (PRES)
Stimulant drug use
Medications (warfarin)
Vascular Anomalies
Arteriovenous malformation
Dural arteriovenous fistula

(continued)

Table 15.4 (continued)

Aneurysm
Cavernous malformation
Venous angioma
Arteriopathy
Vasculitis
Reversible cerebral vasoconstriction syndrome
Moyamoya disease
Fibromuscular dysplasia
Genetic-Metabolic
Sickle cell disease
Glutaric aciduria
ACTA2 mutation
COL4A1 mutation
Fabry's disease
Ehlers-Danlos Syndrome
Alagille syndrome (JAG1 mutation)
Menkes disease (ATP7A mutation)
Pseudoxanthoma elasticum (ABCC6 mutation)
Aicardi-Goutièrs syndrome (SAMHD1 mutation)
Arterial tortuosity syndrome (SLC2A10 mutation)
Osler-Weber-Rendu syndrome
Autosomal-dominant polycystic kidney disease

Sickle cell disease is an important cause of intracerebral hemorrhage, and may present as epidural, subarachnoid or intraparenchymal hemorrhage. Patients with SCD may develop hemorrhage due to vascular fragility, aneurysm formation at vessel bifurcations or moyamoya disease. While regular transfusions have been observed to reduce the risk of arterial ischemic stroke, there is no evidence that this practice reduces the risk of intracranial hemorrhage [26].

Clinical Presentation

The classic presentation heralding an intracranial hemorrhage is abrupt onset of clinical symptoms followed by progressive neurological decline. Young children will present with irritability, vomiting, altered level of consciousness or seizures, while older children may report headache [34, 142, 143]. Thunderclap headache is a red flag for intracranial hemorrhage, therefore all patients with this character of headache require neurovascular imaging. Focal deficits, such as sensorimotor or aphasia, are present in half of patients presenting to the Emergency Department [34].

Investigations

Patients presenting with acute deterioration in mental status require urgent head imaging with CT scan.

In the setting of a primary parenchymal hemorrhage, intraventricular extension may be observed [146]. MRI with gradient ECHO or susceptibility-weighted

imaging are also sensitive for hemorrhage. Given the high rate of associated vascular malformations in these patients, noninvasive angiography with CT or MR angiography should be pursued in all cases of intracranial hemorrhage. CA is frequently pursued for surgical planning, or in the absence of an obvious explanation for a hemorrhage. The benefit of discovering a treatable vascular anomaly must be weighed against the risk of the procedure [26]. In the setting of mixed lesions with vasogenic edema, diffusion restriction and hemorrhage, venous imaging may demonstrate sinovenous thrombosis. The laboratory work-up for primary hemorrhagic stroke can be found in Table 15.1.

Management

The treatment of hemorrhagic stroke involves three categories for care: (1) general efforts to stabilize the patient, (2) measures to reduce the risk of rebleeding, and (3) attempts to treat the hemorrhage itself [26]. Stabilization of the patient requires respiratory optimization, treatment of clinical and subclinical seizures, control of systemic hypertension, and medical management of increased intracranial pressure. The head of the bed should be elevated to 30°, and patients should have nothing by mouth. Patients who have progressed to a severely compromised mental state should have intracranial pressure monitoring to maintain cerebral perfusion pressure between 50 and 70 mmHg [142]. Hypotonic fluids can contribute to cerebral edema, and should be avoided. Large, symptomatic intraparenchymal hematomas may require surgical evacuation.

Severe edema associated with mass effect should be suspected in a child with abrupt deterioration in level of consciousness, pupillary asymmetry, or periodic breathing. The physiological response to increased intracranial pressure, termed "Cushing's triad," manifests as hypertension, bradycardia and irregular respirations, and indicates impending herniation. When these clinical changes occur, a repeat CT scan is necessary to distinguish the effects of increasing cerebral edema from rebleeding or rupture of hemorrhage into the ventricles [142]. Hyperosmotic treatment with mannitol or hypertonic saline is frequently used to treat elevated intracranial pressure. While corticosteroids may be beneficial in patients with vasogenic edema, associated hyperglycemia can be detrimental [147]. Decompressive hemicraniectomy can be life-saving in children with ischemic stroke [148, 149], and may be considered in cases of severe hemorrhage and edema, to limit injury due to hypoperfusion and herniation [150].

Rebleeding

In adults, the risk of rebleeding following aneurysmal rupture is high, and associated with high mortality and poor neurological outcome in survivors [151]. The risk of rebleeding is highest in the first 12 h, with nearly half occurring within 6 h of symptom onset [152]. In children, the risk of rebleeding is poorly understood, with an incidence ranging from 0–41 % [141, 153]. Given the risk of rebleeding in the setting of congenital vascular lesions, surgical or endovascular management of these lesions should be pursued when feasible. Similarly, ruptured AVMs should be treated with surgery, endovascular embolization and/or stereotactic radiosurgery, while symptomatic cavernous malformations that have bled should be treated with surgical resection.

Treatment of Vasospasm

Children with SAH may benefit from additional measures to control cerebral vasospasm [26]. In adults, the risk of clinically significant vasospasm increases 3–5 days after the initial hemorrhage, and is highest in patients with moderate to severe SAH [151]. Adult trials for the treatment of vasospasm have demonstrated benefit with oral nimodipine to reduce the frequency and severity of neurologic deficits after SAH. While there is little published data on the use of nimodipine in children, treatment may be considered in the setting of moderate to severe hemorrhage [26]. In the event of symptomatic SAH, perfusion can be improved with volume expansion, moderate systemic hypertension, and hemodilution [142, 151].

Practice parameters have been established for children with hemorrhagic stroke, and can be found in Table 15.5 [26].

Table 15.5 Practice parameters for pediatric hemorrhagic stroke [26]

Class I recommendations
1. Children with non-traumatic brain hemorrhage should undergo a thorough risk factor evaluation, including standard cerebral angiography when noninvasive tests have failed to establish an origin, in an effort to identify treatable risk factors before another hemorrhage occurs (Class I, Level of Evidence C).
2. Children with a severe coagulation factor deficiency should receive appropriate factor replacement therapy, and children with less severe factor deficiency should receive factor replacement after trauma (Class I, Level of Evidence A).
3. Given the risk of repeat hemorrhage from congenital vascular anomalies, these lesions should be identified and corrected whenever it is clinically feasible. Similarly, other treatable hemorrhage risk factors should be corrected (Class I, Level of Evidence C).
4. Stabilizing measures in patients with brain hemorrhage should include optimizing the respiratory effort, controlling systemic hypertension, controlling epileptic seizures, and managing increased intracranial pressure (Class I, Level of Evidence C).
Class II recommendations
1. It is reasonable to follow-up symptomatic individuals who have a condition that predisposes them to intracranial aneurysms with a cranial MRA every 1–5 years, depending on the perceived level of risk posed by an underlying condition (Class IIa, Level of Evidence C). Should the individual develop symptoms that could be explained by an aneurysm, CTA or CA may be considered even if the patient's MRA fails to show evidence of an aneurysm (Class IIb, Level of Evidence C). Given the possible need for repeated studies over a period of years, CTA may be preferable to CA for screening individuals at risk for aneurysm (Class IIb, Level of Evidence C).
2. Individuals with SAH may benefit from measures to control cerebral vasospasm (Class IIb, Level of Evidence C).
Class III recommendations
1. Surgical evacuation of a supratentorial intracerebral hematoma is not recommended for most patients (Class III, Level of Evidence C). However, information from small numbers of patients suggests that surgery may help select individuals with developing brain herniation or extremely elevated intracranial pressure.
2. Although there is strong evidence to support the use of periodic blood transfusions in individuals with SCD who are at high risk for ischemic infarction (see Sickle Cell Disease), there are no data to indicate that periodic transfusions reduce the risk of ICH caused by SCD (Class III, Level of Evidence B).

Risk of Recurrence

In a population-based study of children with hemorrhagic stroke, recurrent hemorrhage occurred between 7 days and 5.7 years after the incident hemorrhage, with a 5-year cumulative recurrence rate of 10 %. Hemorrhage is more likely to recur acutely in patients with medical illness, while the recurrence rate is more prolonged in children with vascular lesions. Idiopathic intracranial hemorrhage has a low risk of recurrence [33]. Patients with aneurysm are also at risk for developing recurrent ischemic stroke [34].

Outcome

Non-traumatic hemorrhagic stroke in children is associated with a mortality rate of approximately 10 % [34, 143], with some rates as high as 25 % [154]. In survivors, the outcomes are variable, with large hemorrhage volume and presentation with altered mental status predicting poor outcome [34]. On average, 38 % of children have a good outcome with little clinical impairment, while 29 % have deficits ranging from moderate to severe [142]. Cognitive deficits are present in approximately half of patients [34, 155]. Other deficits include weakness, spasticity, dystonia, seizures, speech difficulties, and mood and behavior changes.

Conclusion

Recent advances in pediatric stroke research have resulted in an improved understanding of the incidence of stroke across the first two decades of life, as well as an awareness of the breadth of risk factors and frequency of their occurrence. The astute clinician may recognize that, in some cases, the etiology of stroke in a child may not be readily apparent, and that only with thorough work-up and the passage of time will the cause present itself. The more widespread availability of MRI with angiography has led to an appreciation of the dynamic nature of cerebral vasculature, and its vulnerability to injury and disease in children. While further prospective studies are necessary to establish more evidence-based treatment guidelines, current treatment practices with aspirin and heparin are safe, and are often sufficient to reduce the risk of stroke recurrence in children. Surgical, endovascular and stereotactic radiosurgical intervention is sometimes indicated for certain ischemic and hemorrhagic disorders.

Acknowledgments We thank Cindy H. Samos for assistance with the manuscript. This work was supported in part by funding from Bernard and Ronni Lacroute, the William Randolph Hearst Foundation, and Russell and Elizabeth Siegelman (to GKS).

Disclosure Dr. Steinberg serves on the Medtronic Neuroscience Strategic Advisory Board and is a consultant for Qool Therapeutics.

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Pediatric Moyamoya Disease: Indirect Revascularization

16

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Abbreviations

ACA	Anterior cerebral artery
CBF	Cerebral blood flow
CCA	Common carotid artery
CVRC	Cerebrovascular reserve capacity
DSA	Digital subtraction angiography
DWI + ve	Diffusion Weighted Image positive
ECA	External carotid artery
EDAMS	EncephaloDuroArterioMyoSynangiosis
EDAS	EncephaloDuroArterioSynangiosis
EGPS	EncephaloGaleoPeriosteoSynangiosis
EEG	Electroencephalography
EMAS	EncephaloMyoArterioSynangiosis
EMS	EncephaloMyoSynangiosis
ICA	Internal carotid artery
MCA	Middle cerebral artery
MMA	Middle meningeal artery
MMD	Moyamoya disease
MMS	Moyamoya syndrome
MBH	Multiple burr holes
MR	Magnetic resonance

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A. Agrawal, G. Britz (eds.), *Pediatric Vascular Neurosurgery*,
DOI 10.1007/978-3-319-43636-4_16

OA	Occipital artery
PCA	Posterior cerebral artery
SPECT	Single photon emission computed tomography
STA	Superficial temporal artery
TIA	Transient ischemia attack
Xe-CT	Xenon-enhanced computed tomography

Introduction

Moyamoya disease (MMD) is an idiopathic, chronic, occlusive cerebrovascular disease that involves bilateral stenosis or occlusion of the terminal internal carotid or proximal middle and anterior cerebral arteries. Development of basal collateral channels, including hypertrophy of the lenticulostriate and thalamoperforating arteries, results in characteristic "moyamoya vessels." It is from the angiographic appearance of these vessels that the name moyamoya is derived, meaning "haziness" or "puff of smoke" in Japanese [1, 2]. Patients with moyamoya syndrome (MMS) present with identical clinical and angiographic features as those with MMD, but have an underlying associated condition, such as Down's syndrome, neurofibromatosis, sickle cell disease, primordial dwarfism, or previous cranial irradiation [3].

Epidemiology

Although it was first described and is most prevalent in Asian populations, MMD occurs in people of diverse ethnicities, including Europeans, Americans, Japanese, Koreans and Chinese [4–6]. The reported incidence of MMD is highest in Japan, with an estimated incidence of 0.94 per 100,000 and prevalence of 6–10 per 100,000 population [4, 7, 8]. In Europe and North America, where the true incidence is still unknown, partly due to under diagnosis or misdiagnosis, a 2005 study estimated an incidence of 0.086 per 100,000 population in California and Washington [9]. However, a more recent 2012 study found a US prevalence of 0.57/100,000/year [7, 8]. The estimated incidence of pediatric MMD in France is 0.065 per 100,000 children per year [10]. There is a bimodal age distribution of MMD, with the first peak in the pediatric population around the ages of 5–9 years, and the second peak in mid-adulthood (ages 45–49 years). In the first decade of life, the diagnosis is equally common in males and females, but subsequently shows a strong female predominance with a ratio of 2–3:1 thereafter [11].

Presentation

In children, the most common presentation is cerebral ischemia. In a North American study [12] of 143 pediatric patients with MMD, nearly all presented with symptoms of either stroke or TIA; similar findings were also found in

European studies [13, 14]. In a large Asian population study, 40 % of those younger than 10 years of age presented with TIA and nearly 30 % with cerebral infarction [15]. Hemorrhagic presentation occurred in 3–9 % of pediatric patients in both Asian and North American series [12, 16]. Other less common presentations include seizures, movement disorders, learning difficulties and developmental delays.

Indications for Revascularization

With a morbidity rate of over 65 % in untreated and medically treated patients [17–19], surgical intervention has become the standard therapy in patients with MMD [20–22]. Neurosurgical techniques for the treatment of MMD have been grouped into two main categories: direct and indirect revascularization. The principal difference between the two strategies lies in the method of cerebral reperfusion. Whereas direct methods attempt to anastomose scalp arteries to intracranial arteries to perfuse affected areas of the brain, indirect methods aim to stimulate the development of a new vascular network over time. This can be achieved by using adjacent tissues (galea, muscle, scalp arteries, dura) or distant graft (omentum) to cover the brain surface to promote indirect collateralization.

Indirect Bypass Procedures

Indirect procedures for MMD tend to be reserved for pediatric patients where they have higher angioplasticity with successful collateralization in comparison to adult patients. Furthermore, direct bypass is more difficult in young children due to the extreme small size of the arteries. Repeat revascularization using the various indirect techniques is another indication for MMD patients with ongoing symptoms due to inadequate revascularization from the initial procedures.

Indirect procedures include encephalomyosynangiosis (EMS), encephalogaleo [periosteo] synangiosis (EGPS), encephaloduroarteriosynangiosis and pial synangiosis (EDAS), encephaloduroarteriomyosynangiosis (EDAMS), multiple burr holes (MBH), and omental transposition (encephalo-omental synangiosis). All are based on the observation that vascularized tissue placed on the brain induces vascular collateralization from the graft to the brain.

Indirect Bypass Techniques Using Adjacent Tissue

Encephalomyosynangiosis (EMS)

EMS was first applied to MMD by Karasawa and associates [23] in the late 1970s and has been widely used as an initial surgical intervention [24–28].

The principle is to place vascularized muscle on the brain's cortical surface. It usually involves a frontotemporal craniotomy with transposition of the temporalis muscle, due to its anatomical location, rich blood supply and potential for dense vascular collateralization.

For the frontotemporal craniotomy, a linear incision is used overlying the temporalis muscle, where the muscle is dissected from the bone. After the craniotomy, the dura is opened, and the muscle is placed on the brain and sutured to the dural edges. Hemostasis is obtained to avoid postoperative hemorrhage in the subdural and epidural space. The bone edges are removed, and the bone flap is thinned prior to securing it down to prevent compression of the muscle on the brain and skull edges.

Encephalogaleoperiostealsynangiosis (EGPS)

For ischemia of the anterior cerebral artery territory, bifrontal EGPS is recommended, preserving the superficial temporal artery (STA) branches for future procedures. Galea tissue with or without periosteum is placed on each side of the frontal area. A curvilinear scalp incision and bifrontal craniotomy crossing the midline is performed. The posterior margin of the craniotomy is placed at the coronal sutures to avoid disruption of large draining parasagittal veins during dural opening.

The galea tissue is harvested using anterior, posterior and midline incisions (H pattern). Some reflect and place the periosteum with galea as one layer, while others insert the galeal tissue only and leave the periosteum in situ. For very young children with very thin scalps, leaving the vascularized periosteum in situ may help to avoid the complication of postoperative ischemic scalp necrosis.

The dura mater is incised separately in both hemispheres, and arachnoid fenestration performed. The previously created dural flaps are inserted into each hemispheric fissure, and the galeoperiosteal flap sutured to the margin of the dura. This technique is well documented and illustrated by Park et al. [29] and Kim et al. [15].

Encephaloduroarteriosynangiosis (EDAS)

EDAS was first developed by Matsushima and colleagues [30] in 1980s and is our preferred technique for indirect revascularization in pediatric MMD. It is probably the most commonly performed indirect procedure for MMD, and many variants have been developed, including the EDAS + pial synangiosis and EDAS + split dural techniques.

One of the three main branch arteries of the scalp (frontal or parietal superficial temporal artery branch, or the occipital artery) is used, based on the area of ischemia and the configuration of the vessels. The artery is traced out using Doppler, and the skin incision to harvest the vessel is made either over the artery or as a scalp flap behind the hairline. The galea is cut with a fine tip monopolar electrocoagulator parallel to but 5–7 mm from the artery and the artery is dissected with a strip of galea from the underlying muscle and periosteum. It is then mobilized and carefully retracted so that the temporalis muscle incision and craniotomy can be performed underneath.

Two burr holes are made for the craniotomy, proximal and distal to the ends of the skeletonized artery, so that when the bone flap is replaced, the artery can enter and exit through these burr holes. A cruciate dural opening is performed, with care taken not to transect major meningeal arteries, and the arachnoid layer is fenestrated at multiple sites. The scalp vessel is then placed on the pia-arachnoid surface (Fig. 16.1). The dura is then approximated over the vessel, the bone flap is replaced, and a multilayer scalp closure is performed ensuring the patency of the bypass graft.

Modified EDAS + Pial Synangiosis

A slight modification to the EDAS technique was made by the Boston Children's Hospital group [12]. After the cruciate dural opening, the arachnoid layer is incised under surgical microscope to allow wide access to the pia. The superficial temporal artery is then placed on the pial surface and sutured to the pia using 10–0 monofilament sutures. This creates the synangiosis of the artery and the brain. As many sutures as possible are placed to encourage tight approximation of the artery to the brain surface. Hemostasis is obtained by gentle irrigation or judicious bipolar coagulation. The rest of the closure is as described for EDAS.

Modified EDAS + Split-dural Technique

This technique was described by Kashiwagi and colleagues [31], using a similar approach to EDAS until the bone flap is removed. The dural incision is made carefully through the outer layer of the dura, preserving the major middle meningeal artery (MMA). The outer layer of the dura is split from the inner layer, the inner layer is then incised along the same configuration and folded over into the subdural space so that this split surface is attached to the cortical surface. The outer dural layer is then approximated after the STA vessel is laid on the cortical surface. Ideally, bleeding from the dural incision or split surface should be controlled with minimal coagulation to maintain the dural blood supply.

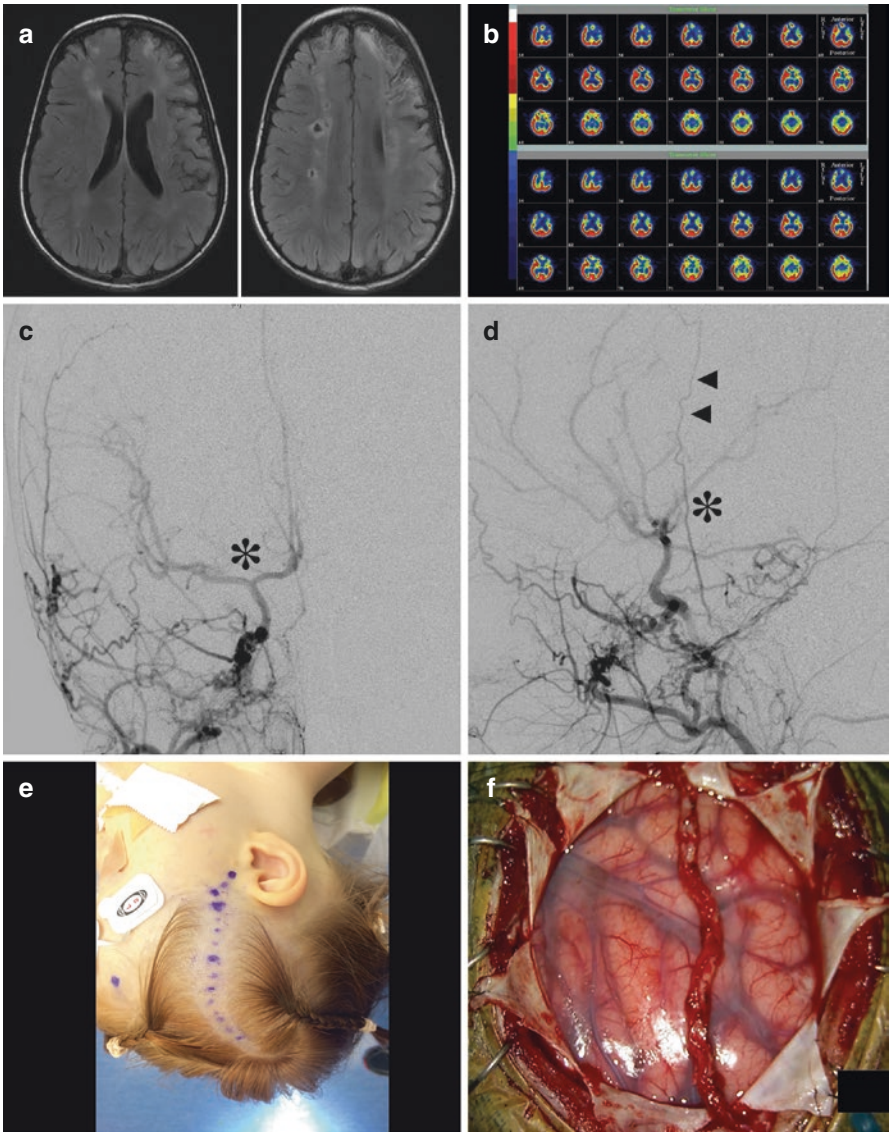

Fig. 16.1 A 6-year-old patient presented with intermittent episodes of speech disturbance and walking difficulty. (**a**) MRI brain (FLAIR) showing evidence of bilateral watershed ischemia. (**b**) Technitium-99 scan showing a bifrontal perfusion defect, worse on the left, with a Diamox induced steal phenomenon on the right frontal area in keeping with impaired cerebrovascular reserve. (**c**, **d**) Right CCA injection (AP & lateral views) showing moderate right supraclinoid ICA stenosis (*asterisk*) and a very thin right STA (*arrowheads*) branch for revascularization. (**e**, **f**) Intraoperative view of right EDAS, with a cuff of soft tissue left around the right STA branch, and laid on the exposed brain parenchyma, after stellate dural opening. (**g**, **h**) Right CCA injection (AP & lateral views) at 9 months post right EDAS showing progressive disease of the right supraclinoid ICA stenosis (*asterisk*), and indirect collateralization from the EDAS (*arrowhead*). (**i**, **j**) Left ICA injection (AP & lateral views) showing occlusion of the distal left ICA (*arrows*) with moyamoya collateralization resembling a "puff of smoke" (*block arrows*). (**k**, **l**) Left CCA injection (AP & lateral views) at 9 months post left EDAMS showing extensive collateralization supplying MCA territories (*block arrowheads*). She remained symptom free at 5 years follow-up

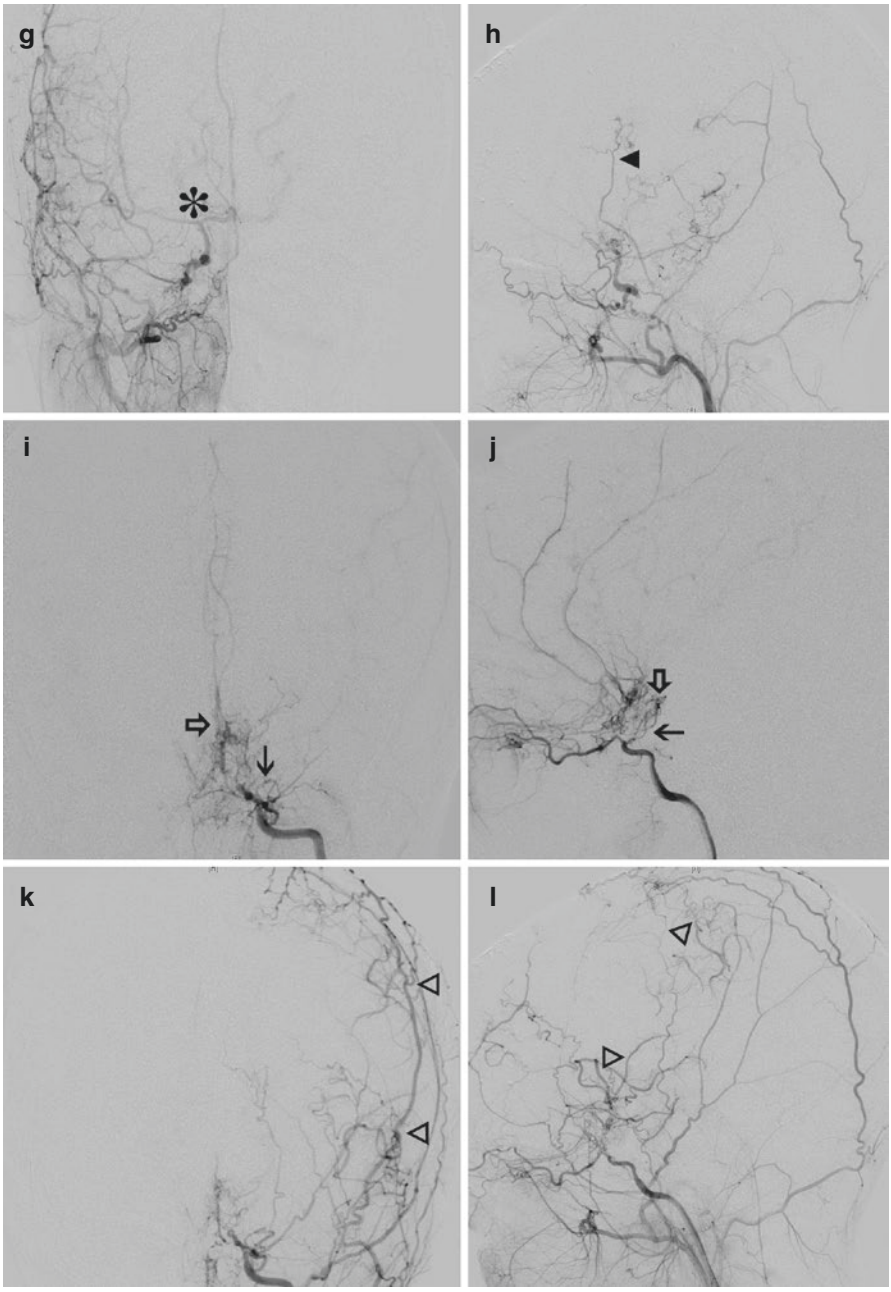

Fig. 16.1 (continued)

Encephaloduroarteriomyosynangiosis (EDAMS)

Another variation is the combination of both EDAS and EMS, where EDAMS [32] was developed with the hypothesis that increased neovascularization from the temporalis muscle, STA and dura would be more likely to fully perfuse the affected area. This procedure also requires the creation of dural flaps that are folded into the subdural/epiarachnoid space to allow the MMA to participate in angiogenesis.

Multiple Burr Holes (MBH)

This less technically challenging technique was developed after vasculogenesis was observed in patients with ventriculostomies requiring cranial burr holes [14]. Thus strategically placed burr holes in areas of cerebral hypoperfusion might aid in stimulating vascular formation between underlying cortex and dura matter, effectively providing an arterial supply to hypoxic brain areas.

Indirect Bypass Techniques Using Distant Tissue

Omental-Cranial Transposition

Karasawa and associates [33] dissected omental tissue with the gastroepiploic artery and vein for transplantation to the middle cerebral artery (MCA) and anterior cerebral artery (ACA) territories of the brain. They concluded that this procedure may be appropriate for MMD in ACA or posterior cerebral artery (PCA) territories, however it is technically challenging, as it requires harvesting of omental tissue via laparotomy, a large craniotomy to overlay the omental tissue on the cortical surface, and vessels grafted to the external carotid artery. In our own experience [34], although the revascularization obtained is quite effective, it has been infrequently performed owing to its associated morbidity with laparotomy and numerous graft complications, including torsion, necrosis and mass effect on the brain. We have since introduced modifications to the omental-cranial transposition technique in children, and found that it is especially effective in children with progressive neurological symptoms despite previous revascularization procedures [35]. The omentum is harvested using a minimally invasive laparoscopic technique by an experienced pediatric general surgery team, which minimizes the morbidity of the procedure. The right gastroepiploic artery is preserved to maintain the vascular pedicle to the omentum. Once the omentum is maximally mobilized, it is brought to the surface at the midepigastric level using a 3–4 cm incision for inspection ensuring the patency of its blood supply. The omentum is carefully divided between the epiploic arcades with step cuts, which then creates a thin, homogeneous omental flap that is long enough to reach the contralateral cerebral hemisphere, as required. A subcutaneous channel is then created between the

craniotomy wound and the midepigastric incision using blunt dissection, and the omental flap is thoroughly irrigated and lubricated with KY jelly to facilitate its tunneling to the cranial region (Fig. 16.2). Vascular patency is checked at the cranial end by direct inspection and use of a Doppler probe.

While the pediatric surgery team laparoscopically harvests the omentum, the neurosurgery team performs the craniotomy, designing the incision and bone flap away from the previous surgery to avoid damage to the previous revascularization (Fig. 16.2). The bone flap is shaped to allow ample room for the omentum to pass intracranially, and the inner table is then drilled off to prevent strangulation of the flap and its vasculature, and to reduce mass effect on the brain while bone flap is replaced. Two layers of scalp closure and abdominal wound incision are performed.

Gracilis Muscle- Cranial Transplantation

Touho et al. [36] described a technique for cerebral revascularization with gracilis muscle transplantation used in children who continued to suffer symptoms of ischemia in the ACA or PCA territory after omental transposition. Although technically feasible, it is very rarely performed in contemporary neurosurgical practice, and we have not found the need to do so in our own experience.

Combined Indirect Techniques

Multiple combined indirect procedures use many of the previously mentioned techniques to obtain the widest coverage of brain parenchyma to allow optimal revascularization. The commonly described techniques are EDAS + bifrontal EGPS [15], EDAS + EMS + EMAS [37], EDAS + EMS [38], and multiple burr holes + EMS [39]. The results for these procedures are variable depending on the specific combinations of techniques used.

Combined Indirect and Direct Procedures

Of the indirect/direct procedure combinations, the most common is STA-MCA anastomosis with an EMS using the same craniotomy. Other combinations include STA-MCA anastomosis with EDAS, MMA-MCA anastomosis with EDAS, and STA-MCA anastomosis with EDAMS [40–42].

It is generally believed that indirect revascularization techniques are less technically demanding than direct techniques, and have a decreased overall risk. However, a recent systematic review [43] showed no differences in the postoperative stroke rate between direct and indirect procedures. There was approximately double the number of published cases of indirect procedures over those treated by direct/combined procedures, with a recognized trend toward use of direct/combined procedures [44, 45].

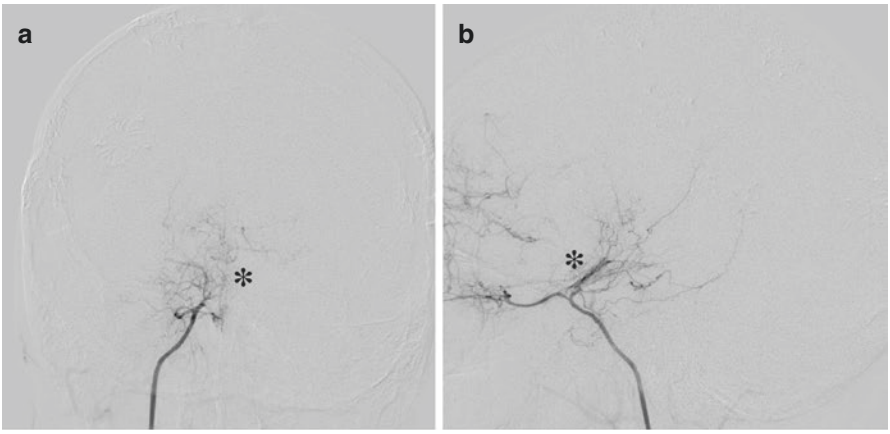

Fig. 16.2 A 12-year-old patient with bilateral moyamoya disease initially underwent bilateral STA-MCA direct bypass at age 7 when she presented with weakness and speech disturbance. She subsequently presented with left-sided weakness, and choreiform arm and leg movements after 5 years of being symptom free. (**a**, **b**) Right ICA injections (AP & lateral views) showing an occluded terminal ICA with moyamoya collateralization (*asterisks*). (**c**, **d**) Right CCA injection (AP & lateral views) post right direct STA-MCA bypass showing the patent bypass graft with collateralization of the right MCA territory (*arrows*), but with an area of reduced cerebral perfusion of the posterior MCA (*area outlined*). (**e**, **f**) Left ICA injections (AP & lateral views) showing an occluded left supraclinoid ICA/ACA/MCA with moyamoya vessels (*asterisks*). (**g**, **h**) Left CCA injections (AP & lateral views) post left direct STA-MCA bypass showing extensive collateralization to the left hemisphere, and patent bypass graft (*arrows*). (**i**) Repeat MRI of the brain showing no new evidence of cerebral ischemia, but with areas of old bilateral watershed infarcts. (**j**) SPECT cerebral blood flow studies showing impaired right hemispheric perfusion with poor cerebrovascular augmentation with Diamox. (**k**, **l**) Due to the large area of posterior MCA to be revascularized, she underwent right omental-cranial transposition with intraoperative position, exposure, and final wide omental coverage of the right hemisphere. Her choreiform movements and TIA symptoms resolved within 3 months postoperatively. (**m**, **n**) Postoperative angiogram with celiac trunk injection at 6 months showing the patent pedicle of the omental flap traveling through the upper abdomen, chest wall, and neck (*block arrows*), with perfusion to a large area of the right hemisphere. (**o**) Angiogram at 6 months, celiac trunk injection, lateral projection through the head showing the area of revascularization by the omental graft in keeping with the area of deficient cerebral perfusion marked in (**c**) block arrow. (**p**) Technetium 99 scan at 6 months postoperative showed areas of fixed perfusion defect in keeping with old infarcts. However, the baseline perfusion was improved showing bilateral symmetrical perfusion, with Diamox augmentation. She remained symptom free at 3 years follow-up after right omental-cranial transposition

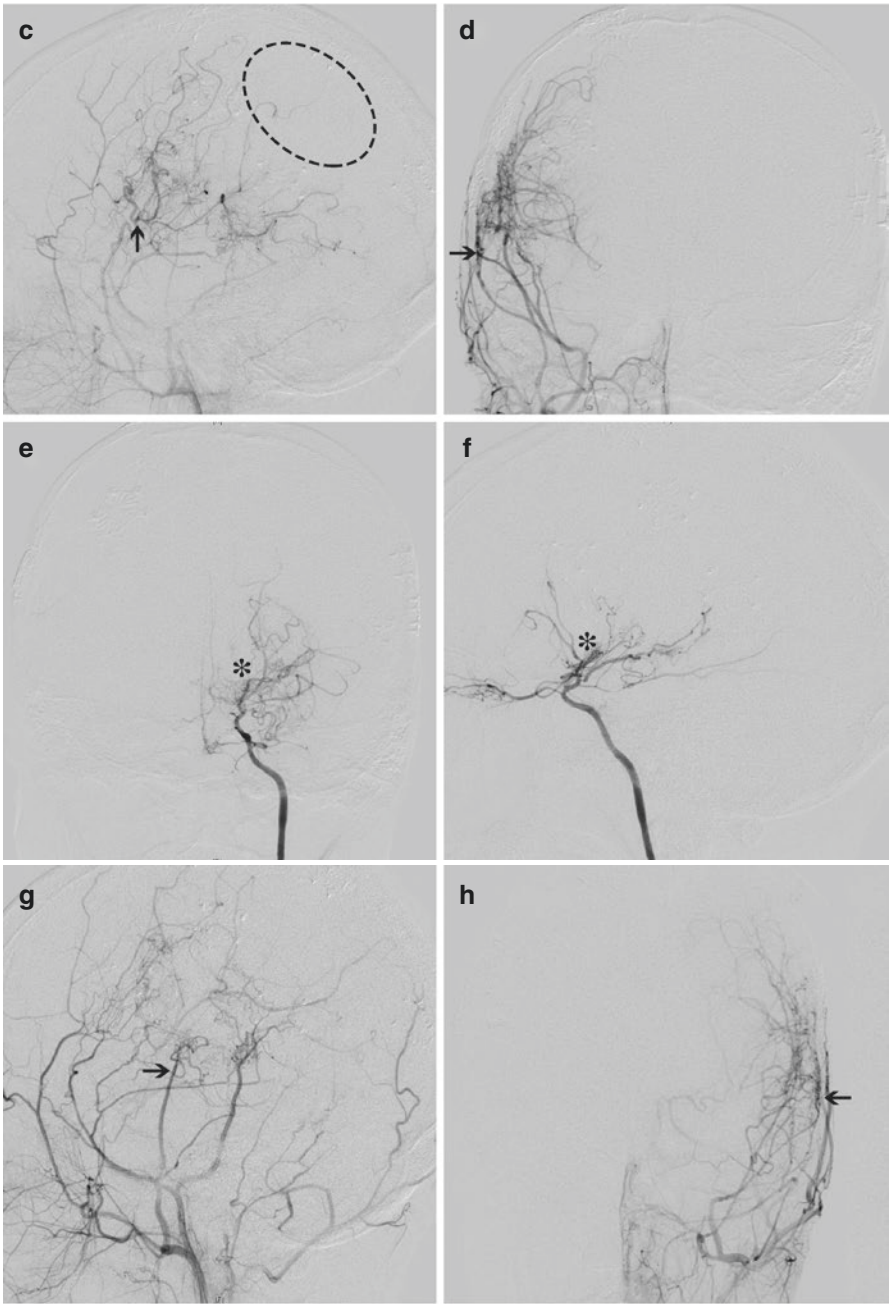

Fig. 16.2 (continued)

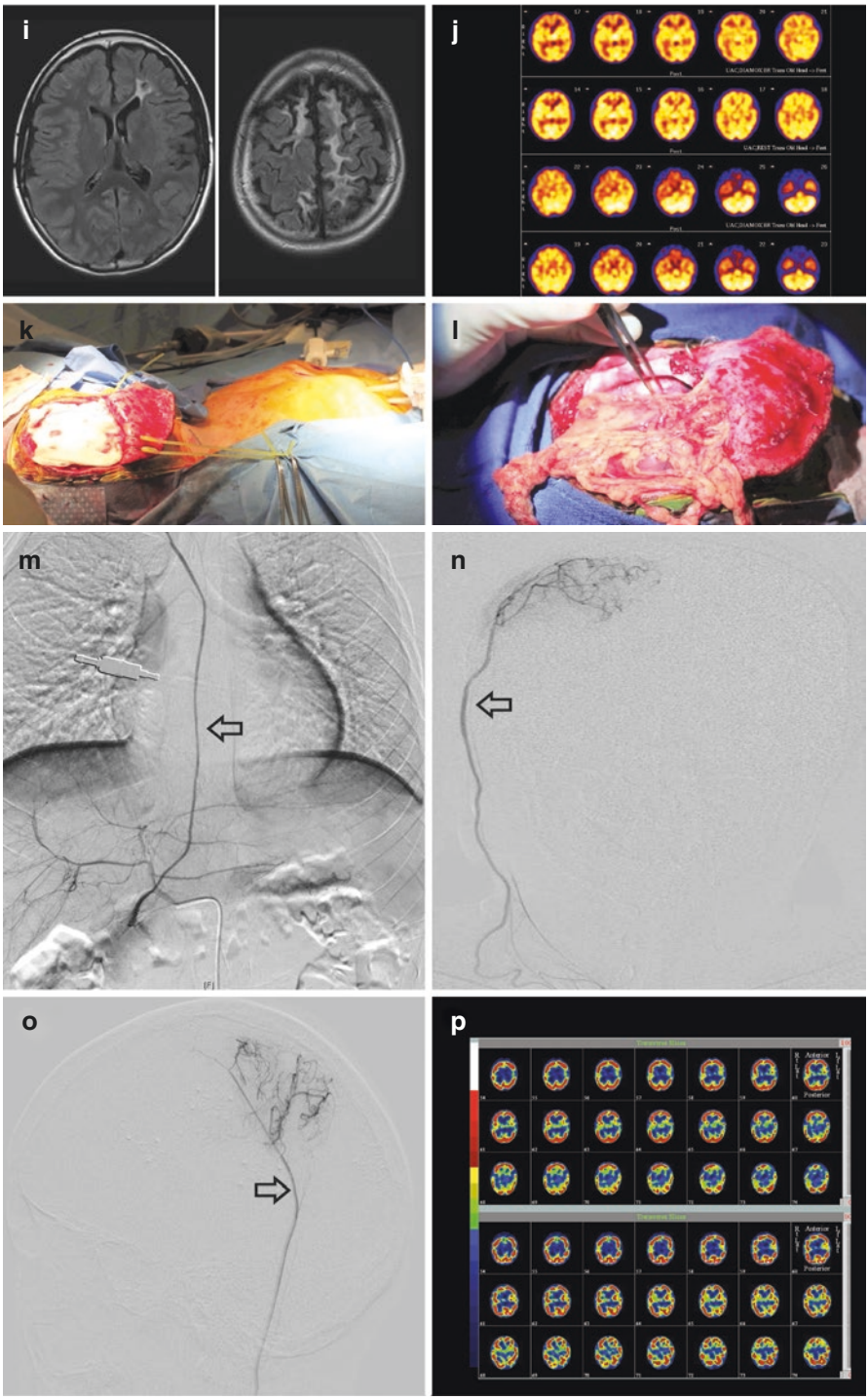

Fig. 16.2 (continued)

Outcome

Outcome of Indirect Techniques in Isolation

In a study by Scott et al. [12] representing one of the largest single-institution series of pediatric patients with MMD, 126 children underwent pial synangiosis (modified EDAS). Over a 17 years period, 11 patients suffered from postoperative stroke and three from severe TIA. Angiographic outcome revealed that 65 % of 195 hemispheres showed filling of at least 2/3 of the MCA territory; 25 %, 1/3-2/3 filling; and 10 %, 1/3 filling. Furthermore, the synangiosis-induced collateral vessels remained functional and intact for as long as 9 years postoperatively. They also concluded that 75 % of children who underwent this procedure continue to lead independent and normal lives. Similar EDAS procedures have been shown to yield comparable efficacy in pediatric patients in other parts of the world [46] (Table 16.1).

Another technique that is widely applied due to its technical ease is the sole use of multiple cranial burr holes. In a study by Sainte-Rose et al. [14], 14 children received 10–24 burr holes in the frontotemporoparietooccipital region of each hemisphere. They reported complete resolution of ischemic episodes and motor improvement in those with preoperative paresis.

The use of omental transplantation has been studied for the alleviation of ACA and PCA circulation symptoms. In a study by Karasawa et al. [33], 30 children with MMD underwent omental transplantation to the ACA, PCA or both the ACA and PCA territories. All of the 19 patients who received ACA transplants and 11 (85 %) of 13 who received PCA transplants experienced improvement in their preoperative neurological symptoms. The authors concluded that patients who demonstrate greater collateral vasculature from omental tissue showed more rapid and complete neurological improvement, although symptoms of the PCA territory often persisted. We performed a few cases of omental-cranial transplantation in the 1990s, but were disappointed with the associated morbidities, especially those associated with laparotomy and graft patency. We have since made modifications to the technique, and have to date performed seven cases in children with good outcome achieved. In our published series [35], blood loss ranged from 75 to 250 ml, patients immediately tolerated diet, and were discharged in 3–5 days. MRI at 1 year showed improved perfusion with no new infarcts, and angiography showed excellent revascularization of the targeted areas and patency of the donor gastroepiploic artery (Fig. 16.2). All patients also experienced symptom resolution within 3 months postoperatively.

Comparison Between the Different Indirect Techniques

The various indirect techniques have been compared in the literature. Isono and colleagues [47] found in their study of 22 pediatric hemispheres that EDAS resulted in greater revascularization than EMS or EDAMS (92 % vs 50 % respectively). However, this study had a small sample size, and none of the 11 patients experienced postoperative stroke, highlighting the distinction between angiographic and clinical outcomes.

Table 16.1 Literature review of studies on outcomes of indirect bypass (isolation or combined) for moyamoya disease in children

Authors & year	Study country	Intervention	No. of children (no. of hemispheres)	Outcome
Kashiwagi et al. (1997) [31]	Japan	EDAS - split DES	18 (25)	All patients symptom free by 1.5 years postop. Postop reversible ischemic neurological deficit and infarction seen in 12 % and 4 % (one patient) respectively
Scott et al. (2004) [12]	USA	EDAS (pial synangiosis)	126 (195)	11 strokes & three severe TIAs within 30 days postop; of 195 hemispheres studied, 65 % with 2/3 MCA filling (Grade A), 25 % with 1/3 -2/3 filling (Grade B), 10 % with less than 1/3 filling (Grade C)
Tripati et al. (2007) [46]	India	EDAS	8 (NA)	No postoperative stroke or TIA in any patient during 2-year follow-up
Sainte-Rose et al. (2006) [14]	France	MBH	14 (24)	No patients had further ischemic postoperative events, and angiogram showed excellent revascularization by ECA collaterals in select cases.
Navarro et al. (2014) [35]	USA	Omental transposition	3 (4)	All patients had symptoms resolution within 3 months. 6-month angiogram and MRI perfusion showed collateralisation and improved perfusion with patent donor vessel.
Matsushima et al. (1997) [38]	Japan	EMAS+EDAS+EMS; or EDAS alone	12 (16)	Increased collateral formation and greater reduction in ischemic events with combined treatment vs EDAS alone
Isono et al. (2002) [47]	Japan	EDAS; or EDAMS alone	11 (22)	12 of 13 sides treated with EDAS had well-developed neovascularization vs 3 of 6 treated with EDAMS/EMS
Kim et al. (2002) [15]	Korea	EDAS+bifrontal EGPS; or EDAS alone	159 (NA)	EDAS+bifrontal EGPS compared with EDAS led to more favorable outcomes (62 vs 36 %, $p<0.003$), revascularization on angiograms (79 vs 16 %, $p<0.001$), and hemodynamic changes on SPECT (70 vs 52 %, $p=0.002$)
Kim et al. (2003) [58]	Korea	EDAS+bifrontal EGPS; or EMS alone	67 (NA)	Excellent and good recovery rates of 57 % and 31 %, respectively; complete disappearance of TIA rate of 63 %

DES duroencephalosynangiosis, *EDAMS* encephaloduroarteriomyosynangiosis, *EDAS* encephaloduroarteriosynangiosis, *EGPS* encephalogaleoperiosteosynangiosis, *EMAS* encephalomyoarteriosynangiosis, *EMS* encephalomyosynangiosis, *MBH* multiple burr holes

In a study by Kim et al. [15], surgical results of EDAS were compared with those of EDAS + bifrontal EGPS. In their study of 159 pediatric patients, 67 underwent EDAS and 92 underwent EDAS + bifrontal EGPS. Their results showed that EDAS + bifrontal EGPS significantly improved ACA symptoms (81 % vs 40 %, $p < 0.015$), revascularization on angiograms (79 % vs 16 %, $p < 0.001$), and hemodynamic changes on single-photon emission computed tomography scans (70 % vs 52 %, $p < 0.002$). Despite these differences in radiographic outcomes, however, the incidence of postoperative infarction was not significantly different, and thus the final clinical outcomes were not related to the surgical modality chosen. This study again demonstrated that even though radiographic outcomes can differ significantly, clinical outcomes might not differ. In a smaller study by Park et al. [29], among 17 patients who underwent EDAS + bifrontal EGPS, ten patients had excellent outcomes, five good outcomes, and two poor outcomes. The overall morbidity rate was 5.9 % (one patient). Based on changes in the ACA and MCA territories after surgery, as shown on SPECT scans following administration of acetazolamide, 14 patients (82 %) demonstrated an improved vascular reserve capacity in both ACA and MCA territories. They therefore concluded that EDAS + bifrontal EGPS is an adequate surgical technique for revascularization of both the ACA and MCA territories, and highlighted the need for ACA territory prophylaxis, as some patients with advancing disease could suffer from frontal ischemia with cognitive decline.

Comparison Between Direct and Indirect Bypasses

The direct technique is generally accepted as providing immediate revascularization to the ischemic territory, and has been shown to be more effective in adult MMD patients in achieving greater angiographic collateralization, more symptomatic improvement, less recurrent ischemic risk, and more patients with stroke-free survival [43, 48, 49]. However, the role of direct bypass in children is more controversial. Here we review the outcomes of various studies in which various techniques (direct alone, combination or indirect alone) were employed and compared in pediatric MMD patients (Table 16.2).

In a study by Ishikawa et al. [50], 34 pediatric MMD patients underwent 64 hemispheric surgical bypasses. They performed STA-MCA + EDAMS in 48 sides (combined group) and indirect bypass alone (EDAMS) in 16 sides (indirect group). Outcomes were divided into perioperative and postoperative events. Perioperative ischemic events occurred in five indirect surgeries (31 %) and in six combined surgeries (13 %), though the difference was not statistically significant between the two groups. Postoperatively, the incidence of ischemic events was significantly reduced in the combined group (10 %) compared with the indirect group (56 %; $p < 0.01$). However, the long-term outcome was similar between the two groups regardless of the type of surgical intervention applied. They therefore concluded that despite reduced ischemic events, the direct bypass technique was not more efficacious than the indirect technique in preventing the deterioration of intelligence as measured using the Wechsler Intelligence Scale for Children–Revised.

Table 16.2 Comparative studies on outcomes of indirect versus direct bypass for moyamoya disease in children

Authors & year	Study country	Intervention	No. of children (no. of hemispheres)	Outcome
Matsushima et al. (1992) [54]	Japan	STA-MCA + EMS; or EDAS alone	16 (20)	Complete resolution of symptoms in 3 (23 %) of 13 hemispheres after EDAS & 7 (100 %) of 7 hemispheres after STA-MCA + EMS ($p < 0.01$)
Ishikawa et al. (1997) [50]	Japan	STA-MCA + EDAMS; or EDAMS alone	34 (64)	Incidence of postop ischemia significantly reduced in combined treatment group (10 %) vs indirect bypass group (56 %; $p < 0.01$)
Suzuki et al. (1997) [59]	Japan	STA-MCA + EDAS + EMS + MBH; EDAS + EMS + MBH; or STA-MCA + EDAS + MBH	36 (NA)	Frequency of TIAs reduced/resolved within 1 year in 25 (81 %) of 31 patients
Miyamoto et al. (1998) [60]	Japan	STA-MCA and/or EMS	113 (NA)	Resolution of stroke in 110 (97 %) of 113 patients; independent lifestyle achieved by 100 (89 %) of 113 patients
Matsushima et al. (1998) [40]	Japan	STA-MCA + EMS; or EMAS + EDAS + EMS; or EDAS	50 (72)	Postop collateralisation in >2/3 of MCA distribution in 74 %, 52 %, 44 % respectively; clinical symptoms resolution within 1 year in 74 %, 63 %, 56 % respectively
Houkin et al. (2000) [52]	Japan	STA-MCA; or EDAMS alone	34 (NA)	Patency of direct bypass verified in 15 sides (53 %); indirect bypass yielded neovascularization in >90 %
Kim et al. (2007) [51]	Korea	STA-MCA + EDAMS; EDAS alone; or EDAMS alone	7 (12)	EDAMS alone & STA-MCA + EDAMS radiographically superior; all indirect bypass techniques have similar clinical outcome
Czabanka et al. (2011) [55]	Germany	STA-MCA + EMS; or EMS alone	7 (14)	Medium or extensive revascularization in 86 % (6 of 7) of hemispheres with Indirect bypass, compared to 43 % (3 of 7) of hemispheres that received combined revascularization
Abla et al. (2013) [48]	USA	STA-MCA; or EDAS	24 (NA)	20 indirect bypass, 4 direct bypass; despite predominantly indirect bypass, outcome is similar to adult direct bypass group

EDAMS encephaloduroarteriomyosynangiosis, *EDAS* encephaloduroarteriosynangiosis, *EMAS* encephalomyoarteriosynangiosis, *EMS* encephalomyosynangiosis, *MBH* multiple burr holes, *STA-MCA* superficial temporal artery to middle cerebral artery

A similar study to determine the efficacy of a combined technique compared to an indirect procedure alone was conducted by Kim et al. [51] in seven children with 12 hemispheric bypasses. The goal was to determine if significant differences in the postoperative radiographic or clinical outcome were observed in patients managed with STA-MCA + EDAMS or with EDAS or EDAMS alone. Although the authors found that patients who had undergone EDAMS or STA- MCA + EDAMS were more likely to demonstrate greater angiographic revascularization, the clinical outcomes of the three procedures were not significantly different, a finding consistent with Ishikawa et al. [50].

EDAMS has been directly compared with STA-MCA bypass. In a study by Houkin et al. [52] 34 children underwent either EDAMS or direct STA-MCA bypass. The patency of the direct bypass was found to be more difficult to achieve, with only 15 sides (53 %) verified on postoperative digital subtraction angiography (DSA). The indirect procedure showed satisfactory neovascularization in over 90 % of hemispheres. It was also observed that direct techniques were far better in preventing perioperative ischemic complications, possibly due to the newly enabled immediate revascularization [53]. They also concluded that both techniques were similar at preventing long-term ischemic events.

The EDAS procedure has also been compared with STA-MCA + EMS. In a study with16 children by Matsushima et al. [54], 13 hemispheres were treated with EDAS and seven with STA-MCA + EMS. Complete resolution of symptoms was associated with 3 (23 %) of 13 EDAS-treated hemispheres and 7 (100 %) of 7 STA-MCA + EMS–treated hemispheres ($p < 0.01$). The STA-MCA anastomosis together with EMS was superior to EDAS alone in both the development of collateral circulation ($p < 0.05$) and postoperative clinical improvement ($p < 0.01$). At the authors' institution, EDAS led to a 20–30 % rate of failed collateral vascularization, which prompted the authors to begin using the STA-MCA + EMS procedure. They hypothesized that the narrow contact site of EDAS predisposed the ischemic area of the brain to incomplete collateralization. After their subsequent paper [40], which compared STA-MCA + EMS, EMAS + EDAS + EMS, and EDAS in 50 pediatric MMD patients (72 hemispheres), postoperative collateralization was observed in over 2/3 of the MCA distribution in 74 %, 52 %, and 44 % of patients, respectively; clinical symptoms resolved within 1 year in 74 %, 63 %, and 56 % of patients, respectively. The authors concluded that STA-MCA + EMS remains the most efficacious combination and should be considered as first-line therapy.

In a study from Germany, Czabanka et al. [55] showed that combined revascularization (STA-MCA + EMS) improved cerebrovascular reserve capacity (CVRC) significantly compared to preoperative measurements (preoperative: 16.5 ± 34.6 % vs postoperative: 60.8 ± 64.22 %; $p < 0.05$), whereas EMS alone showed a trend toward improved CVRC (preoperative: 21.8 ± 35.9 % vs postoperative: 34.8 ± 63.0 %; $p > 0.05$). However, in the pediatric population, medium or extensive revascularization was observed in 86 % (6 of 7) of hemispheres with indirect bypass, compared to 43 % (3 of 7) of hemispheres that received combined revascularization. These age-dependent revascularization results are thought to be due to the better arteriogenesis-inducing potential in young patients.

A recent paper from the United States [48] showed that in their institutional moyamoya series, despite children having undergone predominantly indirect bypasses, the modified Rankin score at last follow up was 1.29 ± 1.31, 1.09 ± 0.90, and 1.94 ± 1.51 (p = 0.04) in the pediatric, adult direct, and adult indirect groups, respectively. They concluded that due to their robust potential for angiogenesis, children with mostly indirect bypasses had similar outcomes to the adult direct bypass group.

Conclusion

Surgical revascularization has been shown to improve the cerebral blood flow and reduce ischemic events in pediatric MMD patients. However, there is currently no clear data to support the superiority of either direct or indirect revascularization techniques in the pediatric MMD population. Clinical decisions depend on patient age, extent of disease, anatomical size of the vasculature, and the surgeon's preference. Indirect vascularization leads to delayed collateralization, whereas direct bypass can immediately perfuse ischemic areas. Additionally, over time direct STA-MCA bypasses usually also develop significant indirect revascularization if a long length of STA is laid on the cortical surface and the dura is opened widely with multiple leaflets at the time of the direct graft. Some authors have asserted that indirect techniques do not lead to a predictable vascularization pattern and therefore may not resolve the associated moyamoya vascular formation, and may also carry an increased risk for postoperative stroke in the long term. Thus, some surgeons have suggested combining direct and indirect techniques to take advantage of immediate revascularization with the security of more diffuse neovascularization in the longer term [56, 57]. This approach has evolved to combining STA-MCA direct bypass with EDAS, EDAMS, or EMS.

Key Messages/Learning points

- MMD is a surgical disease with direct, indirect or combined methods of revascularization.
- Various indirect strategies are available, depending on whether using adjacent donor tissue (EDAS, EMS, EGPS, and EDAMS) or a distant graft (omental-cranial transposition).
- The clinical decision on the method of revascularization depends on patient age, extent of disease, anatomical size of the vasculature and surgeon preference.
- We prefer direct techniques laying a long length of STA on the cortical surface (to also promote indirect revascularization) in most patients with MMD, except in very young children with extremely small (or fragile) donor or recipient arteries, where we perform indirect revascularization.

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Moyamoya Bypasses

17

Virendra R. Desai, Robert A. Scranton, and Gavin W. Britz

Introduction

Moyamoya is a rare disease characterized by progressive stenosis of the distal internal carotid arteries and/or proximal anterior and middle cerebral arteries [1]. The resulting decrement in cerebral blood flow leads to cerebral ischemia and in turn, collateral blood vessel development via lenticulostriate arteries [2]. On angiography, these collaterals resemble a "puff of smoke", which is the meaning of the Japanese word "moyamoya" [1, 2].

Moyamoya can be either idiopathic (Moyamoya disease) or secondary to another underlying condition (Moyamoya syndrome) such as atherosclerosis, radiation, sickle cell disease, Down syndrome or neurofibromatosis I [2]. One of the first and largest reports of moyamoya examined 100 patients in Japan between 1961 and 1980 [2, 3]. A bimodal age distribution was seen with one peak in the first decade and another in the fourth decade, with a slight majority of females (60:40) [2, 3]. Younger patients usually presented with ischemia (79 %) while older patients usually presented with hemorrhage (42–58 %) [2]. While these characteristics are true of Japanese moyamoya patients, patients in North America and Europe are mostly adults between the third and fifth decades of life, mainly females (3:1 ratio), and typically adults present with ischemia (about 3/4 of patients) [2].

The natural history of moyamoya is poor with high recurrent ischemic and hemorrhagic stroke rates, even with medical management [2]. Suzuki and Takako designated six grades to the angiographic nature of moyamoya [4]:

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A. Agrawal, G. Britz (eds.), *Pediatric Vascular Neurosurgery*,
DOI 10.1007/978-3-319-43636-4_17

Grade I – narrowed internal carotid artery (ICA) apex without moyamoya collaterals
Grade II – ICA stenosis plus moyamoya collaterals
Grade III – progressive ICA stenosis with more robust moyamoya collaterals
Grade IV – development of external carotid artery (ECA) collaterals
Grade V – more robust ECA collaterals with diminished moyamoya collaterals
Grade VI – complete ICA occlusion, no moyamoya collaterals with only ECA collaterals

There is no proven medical treatment effective for moyamoya. Surgical treatment of moyamoya involves two basic techniques: indirect and direct revascularization. Indirect techniques include encephaloduroarteriosynangiosis (EDAS), encephalomyosynangiosis (EMS), encephalomyosynangiosis, among others [5, 6]. The direct technique involves an end-to-side anastomosis from the external carotid artery circulation, usually the superficial temporal artery (STA), to a cortical artery that is typically a branch of the middle cerebral artery (MCA) [1]. The STA-MCA technique was introduced by Donaghy and Yasargil in 1968 [7]. Relative to indirect revascularization, direct bypasses have the major advantage of providing immediate increase of cerebral blood flow, but this technique may be difficult in children given the small caliber of the donor and recipient vessels [1]. Moreover, many surgeons utilize indirect revascularization in addition to direct rather than solely performing the latter [8].

Operative Technique for Indirect Revascularization

At our institution, patients diagnosed with moyamoya syndrome are started on aspirin 81 mg daily at the time of diagnosis and continued on this peri-operatively, including the day of surgery and post-operatively. Patients undergoing either indirect or direct bypass are admitted the day prior to surgery for intravenous fluid hydration to avoid shifts in blood pressure during anesthesia induction.

In the operating room, after intubation, the patient is placed supine with head turned 90° contralaterally. A shoulder roll is placed under the ipsilateral shoulder if necessary. After clipping the hair on the ipsilateral scalp, a Doppler probe is used to identify and mark out the STA with a marking pen from the level of the zygoma superiorly at least 7–8 cm, past the superficial temporal line. A needle is then used scrape the skin along this marking so that the chlorhexidine or betadine preparation does not obscure the area of the planned incision. The ipsilateral scalp and ear are prepped and draped sterilely.

The microscope is then brought into the field. A small amount of ioban and sterile draping over the needle marking is removed to improve visualization of the needle scraping. A ~1 cm superficial incision halfway, but not completely through, the dermis is created with a 15-blade scalpel over the distal aspect of the needle scraping. The Colorado bovie is then used to cut through the remainder of the dermis, just into the subcutaneous layer. Tenotomy scissors are then used to dissect in the

potential space between the dermis and the subcutaneous tissue just proximal to the recently created incision. The blades of the scissors are then kept together by the primary surgeon while an assistant uses the cut setting on the Colorado bovie to incise the dermis and superficial tissue down to the blades of the scissors. Keeping the blades together serves as protection, preventing past-pointing of the Colorado bovie needle tip into the superficial temporal artery. A self-retaining retractor is placed, and at this point, the posterior, parietal branch of the superficial temporal artery may be visualized. Again the steps mentioned above are repeated, using the tenotomy scissors to dissect deep to the dermis and the Colorado bovie to incise the scalp, until the entirety of the incision is opened.

The Colorado bovie is then taken by the primary surgeon and using the adson forceps, the scalp is undermined in the layer just superficial to the galea about 2 cm in each direction away from the superficial temporal artery. Then the Colorado bovie is used to dissect through galea about 0.5–1 cm away from the STA till temporalis muscle fascia is seen. In this manner, a cuff of galea is created around the STA. This is then rotated laterally and protected with wet telfa.

The microscope is removed and under surgical loupes and headlight, the craniotomy is performed. Increased anterior-posterior exposure is achieved by using a regular bovie tip to cut the temporalis muscle and fascia in a T-shape, with the top of the "T" (aka the horizontal part) near the STA pedicle. A periosteal elevator is used to dissect the muscle off the skull. A perforating drill bit is used to create two burr holes, both in the middle of the exposed skull with one inferiorly near the root of the zygoma and the other superiorly near the distal aspect of the incision. A #1 penfield is used to dissect dura carefully away from the inner table – this step must be done carefully to avoid disrupting the dura and its vascular supply, as dural inversion is important to promote vascularization. A craniotome is then used to elevate the skull flap.

Hemostasis along the dura is obtained at this point with bipolar electrocautery, taking care to minimize cauterization of the middle meningeal artery (MMA), as it supplies the majority of the dural vasculature. The dura is opened in an H-shaped fashion, assuring that the MMA is not bisected. First, a 4–0 nurolon is placed superficially in the center of the exposed dura to elevate it off the underlying brain as an 11-blade scalpel is used to carefully make a small nick in the dura. Tenotomy scissors and adson forceps are used to create the dural flaps, which are inverted along the cortical surface.

The STA and galeal cuff are then laid onto the exposed cortical surface. Thus the STA travels from the scalp, down to the brain and then back up to the scalp in continuity. Duragen (Integra, Plainsboro, NJ) is placed over the dural defect. The bone flap is then prepared by removing a small area of bone along the inferior and superior aspects of the bone flap with a leksell ronguer with cranial plates secured, such that a small opening exists in the area of the STA proximally and distally. The wound is then irrigated with antibiotic irrigation and closed in layers with 2–0 vicryl to approximate the temporalis fascia and galeal layers and 4–0 nylon in vertical mattress manner to approximate the skin edges. During skin closure, great care is taken not to puncture or occlude the STA (Fig. 17.1).

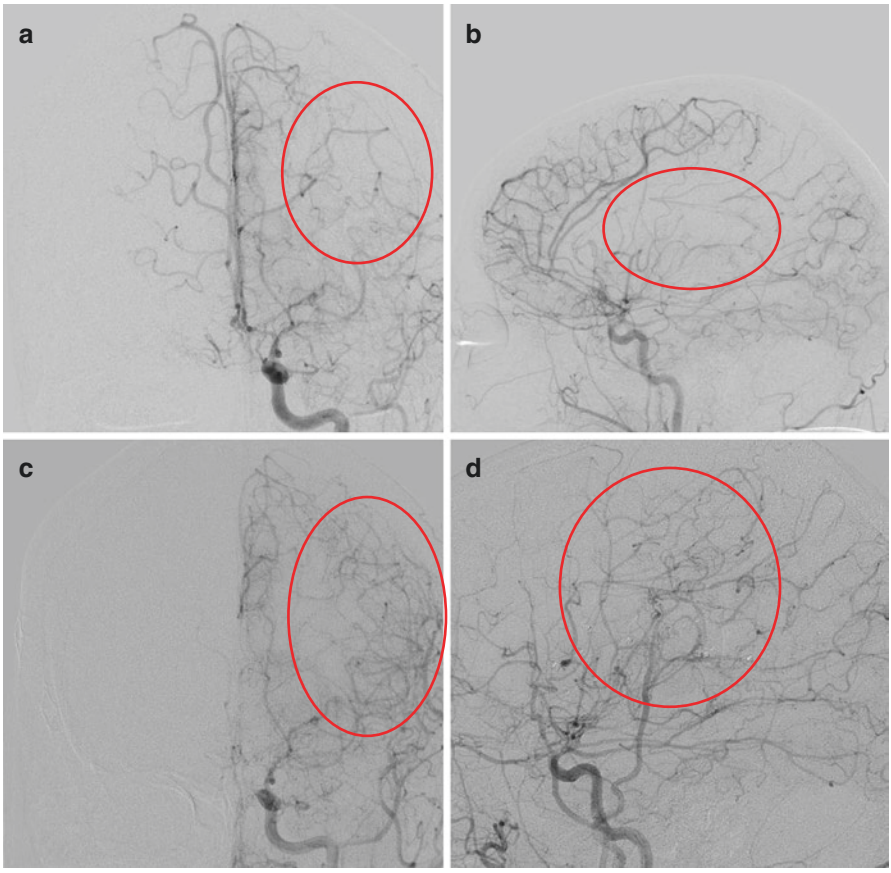

Fig. 17.1 (**a**) Pre-operative angiography image of left common carotid artery injection AP projection for patient who underwent indirect bypass. Note the area within the *circle*, denoting poor capillary staining. (**b**) Pre-operative angiography image of left common carotid artery injection lateral view for same patient. Again the *circle* represents cortical tissue with poor capillary staining. (**c**) Post-operative angiography image of left common carotid artery injection AP view after indirect bypass, 12 months after surgery. Note the robust capillary staining within the circle. (**d**) Post-operative angiography image of left common carotid artery injection lateral view of same patient after indirect bypass. Again note the robust capillary staining within the *circle*

Operative Technique for Direct Revascularization

Patients undergoing elective direct bypass are also admitted the day prior to surgery for intravenous fluid hydration and continued on daily baby aspirin. On the day of surgery, after intubation, a lumbar drain is placed, and just prior to the craniotomy, 30 cc of cerebrospinal fluid is drained for brain relaxation. The patient is then positioned similarly to the indirect method as described above, the Doppler probe is used to identify the STA and the STA is harvested as above.

Once the STA with galeal cuff is harvested, the distal end of the STA is then cauterized with the bipolar and cut. After confirming good flow through the cut end, a temporary vascular clip is placed at the base of the STA. Excess galea and adventitia is dissected off the distal end of the STA, until several millimeters of bare vessel is exposed. This is then cut in fish-mouth configuration and using a small flexible needle, heparinized saline is injected till all the blood has been flushed out. The Colorado bovie is again taken to cut all the way down to bone along the distal aspect of the STA. The STA along with its cuff of galea is then undercut and elevated with the Colorado bovie all the way down to the proximal part of the incision.

The STA is then flapped inferiorly and covered with a wet sponge, leaving the temporarily clip in place. The craniotomy and dural opening are performed as described in the indirect method above.

Then, the cortical surface is surveyed to identify a recipient vessel of appropriate caliber. Typically a vessel 2–3 mm in diameter is chosen. Two jeweler forceps are used to dissect arachnoid off the recipient vessel for a length of about 1–2 cm. Bipolar electrocautery is used to coagulate small branches off the isolated segment of the cortical vessel, and then two temporary vascular clips are placed on either end of the isolated segment. Periodically, we inject heparinized saline into the STA pedicle to assure that it does not form an intravascular clot. A small elliptical cut is made in the side of the cortical vessel, and the blood is flushed out with heparinized saline. Using 10–0 nylon, the STA is stitched to the cortical vessel in a step-wise manner:

1. First stitch is placed outside to inside on the apex of the fish-mouth end of the STA and then inside to outside on one end of the cortical vessel, thereby assuring the knot will be located extra-luminal. Three alternating knots are tied, and the suture is cut, leaving the tails several millimeters long.
2. Second stitch is placed in a similar fashion on the opposite end of the STA and cortical vessel.
3. Multiple stitches are then placed on the back/deep side of the anastomosis first, taking care not to grab the back wall of the vessels when throwing the stitch.
4. Multiple stitches are then placed on the front/superficial side of the anastomosis, and heparinized saline is injected into the STA and cortical vessel just prior to the last 1–2 stitches.

The temporary clips are then removed one at a time beginning with those on the cortical vessel. Any areas of the anastomosis that bleed after clip removal can be stitched closed. After removal of the clip on the STA pedicle, small branches off the STA that are bleeding are identified and cauterized with the bipolar. Several pieces of surgicel are then placed around the anastomosis site.

Some authors recommend opening the arachnoid widely at this point to promote vascularization, although this step is not undertaken at our institution. The bone flap is then prepared as described above in the indirect method, although only a small opening in the inferior aspect of the bone flap is necessary. The wound is then irrigated and closed in layers as described above (Fig. 17.2).

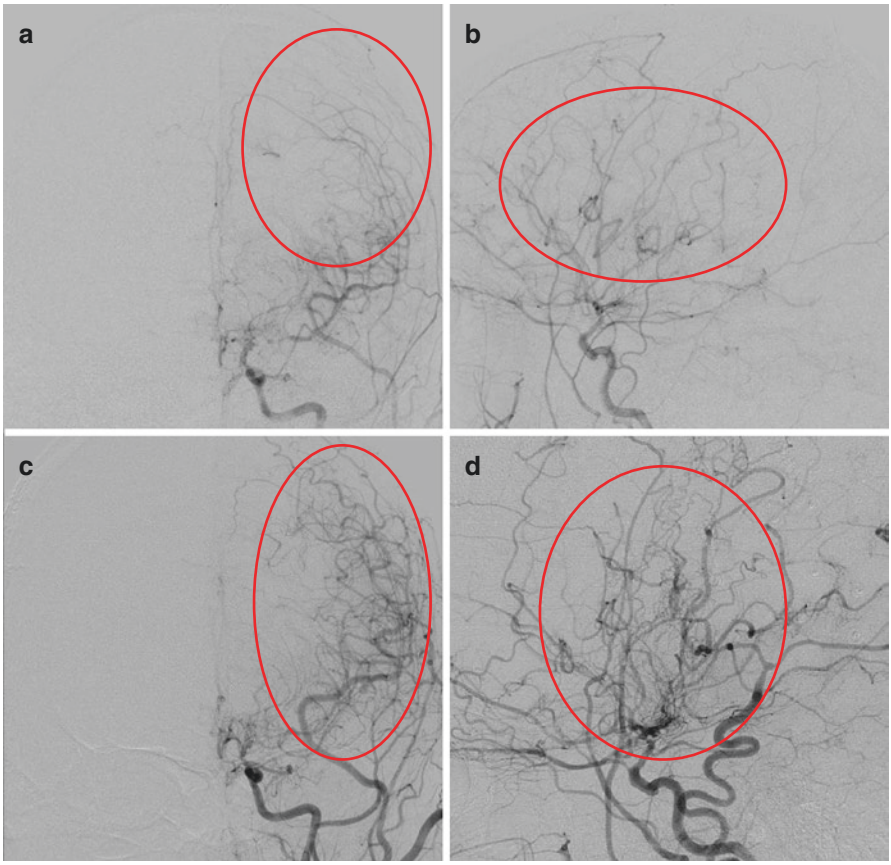

Fig. 17.2 (**a**) Pre-operative angiography image of left common carotid artery injection AP projection for patient who underwent direct bypass. Note the area within the *circle*, denoting poor capillary staining. (**b**) Pre-operative angiography image of left common carotid artery injection lateral view for same patient. Again the circle represents cortical tissue with poor capillary staining. (**c**) Post-operative angiography image of left common carotid artery injection AP view after direct bypass, 23 months after surgery. Note the robust capillary staining within the *circle*. (**d**) Post-operative angiography image of left common carotid artery injection lateral view of same patient after direct bypass. Again note the robust capillary staining within the *circle*

Anesthetic Considerations

Maintaining hemodynamic stability is of paramount importance during anesthesia induction, during the operation and during emergence from anesthesia, as moyamoya patients have such a tenuous cerebrovascular state [2]. Although no formal anesthesia routine has been proposed, several considerations exist. First, intravenous anesthetics are typically used as opposed to inhalational agents as the latter may reduce regional cerebral blood flow (CBF), increasing the risk of cerebrovascular steal phenomenon and ischemic complications [9]. Second, mean arterial blood pressure is maintained about 10 % higher than the pre-operative baseline

during the entirety of the operation [2]. Third, normocarbia is maintained, contrary to most intracranial operations in which hyperventilation is used to promote cerebral vasoconstriction and thereby, brain relaxation [2]. Fourth, no mannitol is administered in order to maintain sufficient intravascular volume during the operation [2]. Other considerations include somatosensory evoked potential and electroencephalogram monitoring to detect impaired cerebral perfusion that may require blood pressure adjustments and/or barbiturate usage to induce burst suppression and reduce metabolic demand during temporary cortical vessel occlusion while the anastomosis is performed [2].

Checking Graft Patency

Several methods exist to ascertain graft patency intra-operatively, including indocyanine green (ICG) usage, formal digital subtraction angiography and Doppler measurement [2]. ICG is injected intravenously and as it passes near-infrared light, it emits near-infrared fluorescence, which can be visualized as a green fluorescent glow on microscope imaging [2]. Doppler flow measurement uses ultrasound to detect direction and rate of blood flow and can be used in two ways. One method involves measuring flow through the STA after the anastomosis and dividing by the flow through the STA before the anastomosis to calculate a "cut flow index". An index <0.5 correlates with a poorly functioning bypass and requires revision [10]. The second method measures post-anastomotic MCA flow, with high flow correlating with increased risk of post-operative ischemia or hemorrhage [11].

Post-operative Management

Post-operatively, the patients are extubated and monitored in the intensive care unit post-operative day 1. Their systolic blood pressure is monitored and controlled to less than 120 mmHg. They are also maintained on 81 mg aspirin daily, with frequent Doppler ultrasound checks for graft patency. Post-operative day 2, they are transitioned to the floor if blood pressure is controlled with no need for intravenous drips. By post-operative day 3, they are typically discharged home.

Outcomes

Outcomes for revascularization surgery for pediatric moyamoya have generally been excellent, with significant decreases in ischemic symptoms and/or hemorrhage rates. Fung et al. 2005 performed a systematic review of revascularization for pediatric moyamoya and found 86.8 % of total patients becoming completely asymptomatic or having definite improvement, while only 2.3 % worsened [8]. These are in stark contrast to the relentless clinical deterioration in untreated or medically treated patients, with 50–66 % having a poor outcome or progressive symptoms [12–14].

While Fung et al. found no significant difference in outcomes between indirect and direct revascularization groups, a true comparison is difficult to establish as only 4 % of the cases were direct bypass only while the remainder were indirect only (73 %) or combined (23 %) [8]. However, Ikezaki et al. showed that re-operation rates were higher after indirect only procedures (18 %) compared to direct only (2.8 %) and combined (1.8 %), although this is difficult to interpret since the specifics of the initial and subsequent operations were not mentioned [15]. Matsushima et al. found that 70–80 % of those undergoing indirect bypass had good collateral formation and good clinical results, but that the direct bypass was significantly superior to EDAS and EMS in terms of collateral circulation and clinical improvement 1 year post-operatively [5, 6].

Pearls

- Patients are started on aspirin 81 mg daily when diagnosed with moyamoya syndrome and continued on this peri-operatively, including the day of surgery.
- They are admitted the day before surgery for intravenous fluid hydration to prevent shifts in blood pressure during induction.
- A lumbar drain is placed after intubation to allow brain relaxation after the craniotomy.
- A Doppler probe is used to identify the STA, which is marked out with a needle scraping.
- The STA is harvested under the microscope with blunt dissection and bovie electrocautery, taking care not to injure the vessel. It is harvested with a cuff of galea.
- The dura is opened in a cruciate fashion and meticulous hemostasis is obtained while taking care to minimize cautery of the middle meningeal artery.
- The donor STA vessel is cut in a fishmouth manner and 10–0 nylon interrupted stitches are placed beginning with the ends and such that the knots lie outside the lumen. Heparinized saline is injected into the donor and recipient vessels periodically to prevent any endoluminal clot formation.
- Post-operatively, the patients are monitored in the intensive care unit for at least one day with strict blood pressure control, daily ASA 81 mg use, and frequent graft patency checks via Doppler ultrasound.

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Anticoagulation and Thrombolysis in the Pediatric Population

18

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Abbreviations

CVT	Cerebral venous sinus thrombosis
GP	Glycoprotein
IA	Intra-arterial
ICH	Intracranial hemorrhage
IV	Intravenous
LMWH	Low-molecular weight heparin
UFH	Ultra-fractionated heparin

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A. Agrawal, G. Britz (eds.), *Pediatric Vascular Neurosurgery*,
DOI 10.1007/978-3-319-43636-4_18

Introduction

The incidence of stroke in the pediatric population has risen over the past decade as it has become a more recognized disease process. As the World Health Organization has defined it, a stroke is due to clinical signs from cerebral dysfunction caused by a lack of blood supply to the brain [1–3]. In the pediatric population, the annual incidence is 2–13/100,000 for ischemic stroke, 0.5–1/100,000 for cerebral venous sinus thrombosis (CVT), and 1–5/100,000 for hemorrhagic stroke [1, 4, 5]. With such limited populations having been studied, no definitive consensus for the management of stroke in children has been made, and management with anticoagulation and thrombolysis-thrombectomy is based on studies conducted in adults [6–9].

Ischemic Stroke

Ischemic stroke is characterized by sudden loss of neurologic function, and symptoms are based on the vascular distribution that is affected. Children with anterior circulation strokes tend to present with hemiparesis and facial palsy, whereas those with posterior circulation strokes tend to present with headache, nausea, and dysphasia and can sometimes be misdiagnosed in the pediatric population [6, 10, 11].

Children have significant risk factors that can help the clinician key into a diagnosis of ischemic stroke. These stroke risk factors include vasculopathy, occlusion, dissection, Moyamoya disease, congenital heart disease, metabolic disorders, genetic disorders, anemia, and infection [12–14]. Underlying conditions such as factor V Leiden deficiency and protein C or S deficiencies can help in raising suspicion of stroke as well as CVT.

Acute Therapy

Treatment of acute ischemic stroke and dissection leading to stroke in the pediatric population revolves around anticoagulation and antiplatelet therapy (Fig. 18.1). Antiplatelet therapy and anticoagulation by means of aspirin, ultra-fractionated heparin (UFH), and/or low-molecular weight heparin (LMWH) are key measures in the acute setting [2, 15, 16]. The risk of ischemic stroke from an acute or traumatic dissection tends to be embolic, and aspirin has been the mainstay to prevent clot formation [17]. Although anticoagulation therapy is aimed at increasing perfusion and improving brain viability, no studies have been done – aside from safety studies – to show which means of acute anticoagulation is best.

Several protocols for systemic anticoagulation have been developed. These therapies tend to aim at correcting antithrombin III deficiency using heparin and can be reversed (if necessary) with protamine. Ten to 20 % of institutions use dual therapy (systemic anticoagulation and antiplatelet therapy) to limit embolic phenomena and clot formation [4–6, 10]. Nearly 15 % of children do not receive therapy within

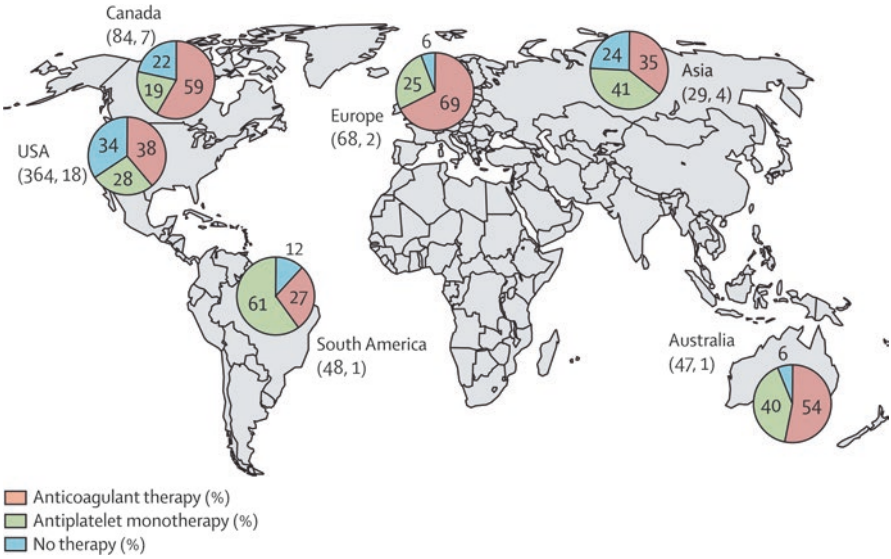

Fig. 18.1 Antithrombotic treatment practices in the International Paediatric Stroke Study. Acute antithrombotic therapy use in childhood-onset arterial ischemic stroke by geographical region (number of patients, number of centers). Anticoagulant therapy (red) includes patients who received anticoagulant therapy with or without antiplatelet therapy (With permission from Elsevier [17])

24–48 h of symptom onset because of late presentation, misdiagnosis, or poor hospital guidelines [4, 10].

Given the higher incidence of congenital heart abnormalities and cardiac emboli in the pediatric population, workup for cardioembolic sources and dissection should be paramount [2, 11]. Diagnosing both conditions allows for limiting further stroke burden and initiating antiplatelet agents as quickly as possible. The use of clopidogrel and warfarin is limited in the pediatric stroke population and has not been well studied [2, 11].

The American Heart Association has provided some independent guidelines to help with anticoagulation management [18]. For cardiac conditions, aspirin offers protection against thrombotic events [2]. For patients with iron deficiency anemia, or sickle cell anemia, exchange transfusions are suggested to decrease the likelihood of these events.

Secondary Prevention

Aspirin is the preferred agent for secondary stroke prevention in adults. Use of long-term antiplatelet therapy should be started with a window around when thrombolysis-thrombectomy may be planned in an acute setting [8]. Antiplatelet prophylaxis for at least 2 years after the initial ischemic event is recommended, whereas life-long antiplatelet therapy is suggested for adults [15, 17]. No studies have looked at

long-term outcomes associated with antiplatelet therapy in children. Some studies have suggested that children who have ischemic symptoms with neuroimaging documentation of normal vasculature will not have recurrent strokes but those who have abnormal vessels have a higher likelihood of recurrent stroke for which long-term antiplatelet therapy may be warranted [11, 15, 17]. Although clopidogrel is not in widespread use in pediatrics, dipyramidole has been increasingly used for those patients with cardiac problems [17].

Pharmacologic Thrombolysis

Pediatric pharmacologic thrombolysis (with intravenous [IV] or intra-arterial [IA] thrombolytic agents) remains a poorly studied therapy and is currently not recommended due to a paucity of data. Such therapy for stroke is clearly defined for adults with alteplase protocols and treatment windows. In situations where supratentorial vessels or clinically significant posterior circulation vessels are occluded, IV thrombolysis serves as a viable means to attempt recanalization [9, 19]. As the time frame to patient presentation increases in conjunction with greater rates of stroke diagnosis, an increasing number of studies are extending the window for treatment with IV or IA thrombolytic agents [7, 11].

Very few studies have demonstrated the efficacy of IV or IA thrombolytic therapy in children [8]. The International Pediatric Stroke Study is the only prospective study that has reported outcomes associated with alteplase administration [2, 19]. In that study, 15 of 687 patients received thrombolytic therapy (9 IV alteplase, 6 IA alteplase). The median time to treatment after the first signs of symptoms was nearly 3.3 h. Post-treatment, 25 % of patients had asymptomatic intracranial hemorrhage (ICH) and 2 patients died, although not from thrombolytic therapy. Pharmacologic thrombolysis is still an area of research for the pediatric population, and further studies are needed.

Cerebral Venous Sinus Thrombosis

Children with CVT present with diverse symptoms that tend to be nonspecific. The triad of headache, nausea, and changes in mentation are common. Patients frequently also present with seizures and that can sometimes be the first clinical sign. The management of CVT revolves around the cause. Systemic diseases and disorders such as infection, dehydration, anemia, and hypercoagulable states predispose children to sinus thrombosis, and reversal of the underlying condition is the best means of treatment [20, 21]. Given the many possible causes of sinus thrombosis and the nonspecific symptoms, many cases go undiagnosed. Most patients have more than one risk factor for CVT. The major cause of morbidity and mortality associated with sinus thrombosis is the development of venous infarction. After treatment of a CVT, the rate of recurrence is lower than 4–5 % [20–22].

Several guidelines are available that offer suggestions for the treatment paradigm of CVT in children [20, 22–26]. CVT without ICH is commonly treated with either LMWH or UFH until recanalization is noted or for at least 3–6 months. When no recanalization has occurred or the patient continues to have intermittent symptoms, thrombectomy or open surgical decompression is considered. The use of thrombolytic agents can also be considered, although no set protocol exists.

The use of heparin or LMWH is useful also to limit thrombus propagation in the setting of CVT. Survival and propagation studies have shown that anticoagulation with UFH is safe and effective in children. In patients with ICH, recommendations vary and clinical judgment should be used with respect to the size of the hemorrhage, but eventual anticoagulation therapy is recommended and has shown benefit in many studies that were conducted primarily in adults [22, 25, 27, 28].

Local Thrombolysis and/or Thrombectomy for Cerebral Venous Sinus Thrombosis and Acute Ischemic Stroke

Local (IA) thrombolysis was first described in 1988 by Scott et al. [28] who used urokinase for pharmacologic recanalization. Since that time, several techniques and outcome studies for local thrombolysis therapy have been reported. Wasay et al. [9] described the use of bolus doses with urokinase infusion therapy or systemic heparin anticoagulation for sagittal sinus thrombosis and found that urokinase thrombolysis was more efficient in terms of clinical outcomes (the thrombolysis group had better neurological function at the time of discharge). However, in their report, they reviewed the literature to provide a perspective on the application of this therapy, highlighting associated risks including ICH, worsening neurological deficit scores, distal emboli, and causing further stroke with mechanical disruption (i.e., mechanical disruption meaning thrombectomy versus pharmacologic thrombolysis; physically moving clot versus dissolving clot).

Currently, the most widely used endovascular therapy for CVT in adults is mechanical thrombolysis–thrombectomy in combination with local thrombolysis. The clot-disruption technique uses angioplasty balloons, microwires, snares, stents, and microcatheters to disrupt and evacuate the clot; and many new devices, including distal protection devices, have been used for protection from a shower of emboli [29, 30]. The theory is that mechanical clot disruption enhances pharmacologic thrombolysis by increasing the surface area for the local thrombolytic agent.

With the newer catheters being developed, there have been more case reports describing the treatment of ischemic stroke and CVT in children. The AngioJet rheolytic endovascular device (Boston Scientific, Marlborough MA) has been used for successful recanalization of sinus thrombosis, and some reports have shown a benefit from combination therapy with AngioJet mechanical clot disruption and IA abciximab [23, 24]. Along the same lines, the Penumbra system (Penumbra Inc., Alameda, CA) and the Merci clot retrieval device (Stryker Neurovascular, Kalamazoo, MID) apply the same theory of mechanical clot disruption in combination with thrombolysis [27]. The Penumbra system proved to be effective for partial

and complete revascularization in large vessel thromboembolic events with nearly 100 % recanalization rates [8, 27, 29]. The success of these thrombectomy systems comes from the separator facilitating fragmentation of the clot and suction devices reducing the clot burden along with distal protection devices.

Hemorrhagic Stroke

In children, the symptoms of hemorrhagic stroke are similar to those for ischemic stroke with sudden onset of symptoms including severe headaches, focal deficits, and seizures. Causes of hemorrhagic stroke include vascular abnormalities (such as arteriovenous malformations and aneurysms), tumors, and trauma. Up to 20 % of pediatric patients with hemorrhagic stroke do not have a diagnosed underlying cause [6]. Rates of recurrence, rebleeding, and morbidity and mortality are dependent on the type of vascular lesion that is found during the patient's workup. Patients should be screened for vascular abnormalities; and given the low rate of recurrent rebleeding from a vascular abnormality in the pediatric population, elective definitive treatment is generally recommended [4].

There are no specific anticoagulation recommendations for patients with vascular abnormalities, although some research has been conducted on the use of recombinant factor VII to promote hemostasis in the pediatric population with hemorrhagic strokes [1]. No pediatric studies to date have shown any changes in neurological function for these patients, although adult studies demonstrate smaller areas of hemorrhage albeit a slight increase in thromboembolic risk [1].

Other Therapies for Pediatric Stroke

Aside from ASA, thrombocyte aggregation inhibitors are not recommended in pediatrics. Glycoprotein (GP) IIb/IIIa receptor antagonists or radical scavengers should not be used as single agents outside the limitations of a clinical trial [25]. Although there are case reports showing good outcomes using abciximab with mechanical thrombolysis, there is no large scale trial or evidence to support its commonplace use in pediatrics [27].

Conclusion

Stroke and cerebrovascular abnormalities are increasingly diagnosed in children, and the incidence of these conditions is rising. As more studies are carried out in the adult population, a better understanding of antiplatelet, anticoagulation, and thrombolysis–thrombectomy outcomes has been acquired to suggest their benefits in the pediatric population. Pediatrics offers a unique situation where risk factors and causes for stroke as well as venous sinus thrombosis play a more significant role. Although antiplatelet and anticoagulation therapies play the largest role in treatment protocols, endovascular therapy for ischemic stroke and CVT is becoming more prevalent and may lead to improvement in outcomes.

Pearls

- Antiplatelet agents serve as the mainstay for ischemic stroke therapy in pediatrics. Dipyramidole may be more useful than aspirin; clopidogrel has not been recommended.
- CVT is most commonly treated with heparin or LMWH (which is weight based).
- Patients with CVT-related ICH benefit from anticoagulation despite the risk of hemorrhage propagation associated with this therapy.
- A combination of mechanical thrombolysis and endovascular therapy with clot-retrieval devices (mechanical thrombectomy) is playing an ever-increasing role in ischemic stroke and CVT.
- Patients with hemorrhagic stroke should undergo a comprehensive evaluation to look for underlying abnormalities. Treatment should be directed at the underlying pathology.

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Embolization of Pediatric Intracranial and Skull Base Vascular Tumors

19

Krishna Amuluru, Fawaz Al-Mufti, I. Paul Singh, Charles J. Prestigiacomo, and Chirag D. Gandhi

Introduction

Neurointerventional embolization has emerged as an important tool in the treatment of a variety of hypervascular head, neck, and spinal tumors. Recent improvements in catheter design, angiographic imaging and the development of novel embolic agents have all combined to make endovascular intervention safer and easier in the management of select pediatric tumors. However, endovascular therapy requires careful consideration of multiple patient- and tumor-related factors to achieve the greatest benefit while minimizing potentially dangerous complications. This chapter focuses on preoperative intracranial and skull-based tumor embolization, including indications, techniques and complications.

Specific Pediatric Neurological Tumors Amenable to Embolization

Primary malignant central nervous system (CNS) tumors are the second most common childhood malignancies, after hematologic malignancies, and are the most common pediatric solid organ tumors. They are the leading cause of death from

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A. Agrawal, G. Britz (eds.), *Pediatric Vascular Neurosurgery*,
DOI 10.1007/978-3-319-43636-4_19

childhood cancer [1, 2]. Although advances in microsurgical resection, radiotherapy, and chemotherapy have improved the survival rates in children with CNS tumors, mortality and morbidity associated with these disorders persist, especially with malignant brain tumors.

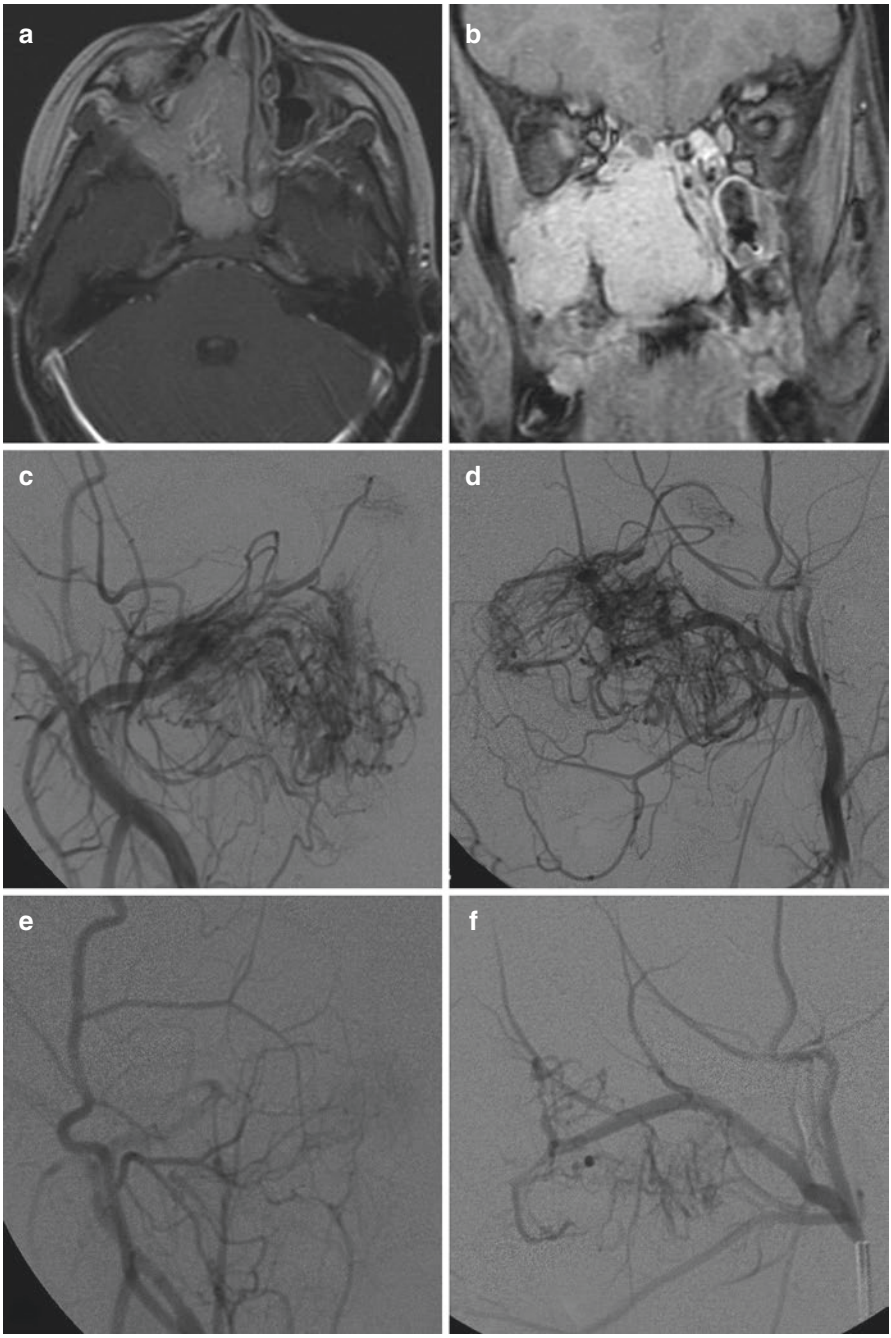
Microsurgical resection of hypervascular pediatric neurological tumors is challenging due to the potential for intraoperative bleeding and peri-neoplasm tissue injury [3]. This complication may have catastrophic effects in the pediatric population due to the potential loss of a significant proportion of a child's circulating volume [4]. Thus the identification and pre-operative treatment of these hypervascular tumors is vital in order to minimize risk in this age group.

In the adult population, preoperative embolization of intracranial extra-axial tumors, such as meningiomas, has been established as an effective adjunct in decreasing blood loss during surgical resection [5–7]. Among intra-axial tumors, hemangioblastomas of the brain and spine are among the most common CNS tumors embolized preoperatively [8–12].

However, large prospective trials examining the safety and efficacy of pediatric tumor embolization are lacking and thus each case must be evaluated on an individual basis in regards to the risks and benefits of embolization. With that in mind, hypervascular pediatric neurological tumors that may be potentially amenable for endovascular treatment include juvenile nasopharyngeal angiofibroma (JNA), choroid plexus papilloma, hemangioblastoma, hemangiopericytoma, meningioma, schwannoma and other neurogenic tumors, paraganglioma, esthesioneuroblastoma, bone tumors, and intra- and extracranial metastatic tumors (Figs. 19.1 and 19.2) [13–15].

JNAs are the most common primary tumor of the nasopharynx, tend to occur in adolescent males, and frequently present with recurrent epistaxis and nasal obstruction. They are highly vascular tumors typically supplied by the internal maxillary artery in addition to numerous external and internal carotid artery branches. Preoperative embolization is effective in reducing blood loss and improves visualization during endoscopic surgical resection [15]. However, although embolization reduces blood loss, some authors have suggested that embolization may lead to a suboptimal degree of tumor removal at surgery, particularly for those lesions that exhibit deep sphenoid invasion, potentially leading to increased recurrence rates [15, 16].

Fig. 19.1 This 11-year-old boy with recurrent epistaxis was found to have a juvenile nasal angiofibroma as seen on (**a**) axial and (**b**) coronal views of gadolinium-enhanced MRI of the brain. The lesion is centered in the nasopharynx with extension into the pterygopalatine fossa, sphenoid sinus, masticator space and cavernous sinus. Digital subtraction angiogram (DSA) in (**c**) frontal and (**d**) lateral views shows vascular tumor blush with arterial supply via distal sphenopalatine branches of the right internal maxillary artery. After PVA embolization, post-embolization DSA in (**e**) frontal and (**f**) lateral views shows markedly reduced tumor blush. Estimated blood loss at complete surgical resection 2 days after embolization was 300 ml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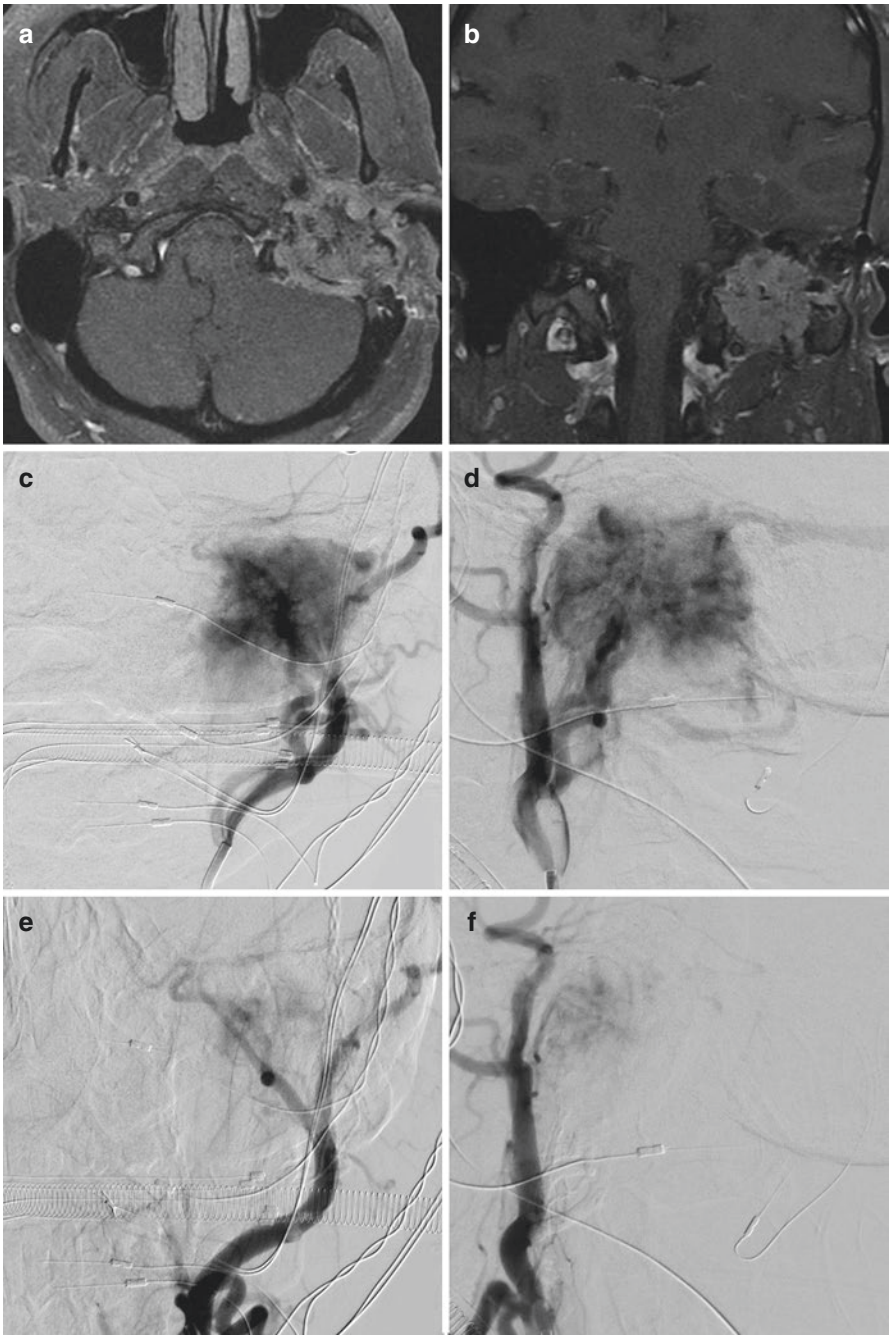
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Fig. 19.2 This 15-year-old boy with history of left sided conductive hearing loss and 7th cranial nerve palsy was found to have a left sided glomus jugulotympanicum tumor. MRI of the brain, gadolinium-enhanced T1 fat-saturated sequences in (**a**) axial and (**b**) coronal views showing enhancing lesion involving the left jugular bulb, left middle ear cavity with extension into the internal auditory canal and stylomastoid foramen. DSA in (**c**) frontal and (**d**) lateral views shows vascular tumor blush with arterial supply via the ascending pharyngeal, posterior auricular and occipital arteries. After embosphere and NBCA embolization, DSA in (**e**) frontal and (**f**) lateral views shows markedly reduced tumor blush. Estimated blood loss at surgical resection 24 h after embolization was 800 ml

Pediatric choroid plexus papilloma is another tumor in which there is a greater amount of evidence regarding preoperative embolization compared to other pediatric neurovascular tumors, although these reports yield conflicting results. A recent report on a cohort of pediatric choroid plexus papillomas demonstrated an 86.6% rate of successful embolization using histoacryl glue, suggesting that preoperative embolization is a useful adjunct that should be considered prior to surgical resection [14, 17].

Indications

In 2012, several members of the Society of Neurointerventional Surgery released a consensus report on the standards and guidelines for embolization treatment of vascular head, neck, and brain tumors [18]. This report dictated that the primary aim of tumor embolization is to aid in the successful surgical resection of the lesion, by minimizing blood loss through the tumor's devascularization, and/or to decreasing operative time [18].

Pertinent to the pediatric patient is not whether embolization is feasible, but rather whether it is necessary, especially in cases where the tumor is small, the major blood supply to the tumor is readily accessible or when the patient would safely tolerate the anticipated extra blood loss without embolization [15]. Tumor hypervascularity alone is not an indication to subject a pediatric patient to the risks of embolization and the overall combined risks of embolization and surgery should be less than that of surgery alone.

Embolic Agents

Particle Embolic Agents

Although a variety of embolic agents exist for adult tumor embolization including silk, gelatin sponge, fibrin glue and ethanol, the major classes of embolic agents used in pediatric cases include particles and liquid embolics [19].

Particles, such as polyvinyl alcohol (PVA) or spherical particles such as Embospheres (BioSphere Medical, Rockland, MA, USA), may be used to achieve distal tumor penetration. PVA particles are irregularly shaped embolic particles that are inexpensive, and both biocompatible and efficient as a semi-permanent embolic agent. However, because PVA particles are hydrophobic and irregular in shape, particles tend to cluster and create aggregates of an unpredictable size, which can occlude smaller sized microcatheters [20].

Embospheres are manufactured microspheres composed of trisacryl gelatin. They are hydrophilic, biocompatible, nonresorbable, and uniformly spherical. Embospheres have more uniform sizing and thus are less likely to clump and occlude the delivery microcatheter. Because of their uniform sizes, embospheres may travel more distally compared to PVA [20].

Particles, sizes 150–250 μm, are commonly used for penetration of tumor supply [13, 21]. Smaller particles penetrate more deeply but carry a greater risk of inadvertent embolization of normal adjacent arterial feeders. Thus in cases that involve embolization of the *vasa nervosum* of cranial nerves, such as the petrous branch of the middle meningeal artery supplying the facial nerve, the ascending pharyngeal or posterior auricular artery, which give rise to the neuromeningeal trunk supplying cranial nerves IX through XII, larger particles sized 100 μm and greater are used to avoid the risk of injury [13].

A disadvantage of all particle embolic agents is that they are radiolucent; therefore, the extent of tumor embolization must be determined by subsequent angiography. Furthermore, particles resorb over time, potentially allowing for vessel recanalization if the embolization is performed too far in advance of the planned surgical resection. Optimal timing for surgical resection is approximately 1–8 days after embolization. This period is sufficient for tumor necrosis to occur but insufficient for significant recanalization to develop [18]. However, in cases with significant pre-embolization mass-effect, surgical resection should be considered as promptly as possible to minimize the risk of tumor swelling and herniation.

Liquid Embolic Agents

The use of liquid embolics, such as *n*-butyl cyanoacrylate (NBCA; Trufill, Codman, Raynham, MA, USA) and Onyx (ev3 Neurovascular/Covidien, Irvine, CA, USA), has increased significantly in recent years. NBCA is a liquid adhesive glue that polymerizes rapidly on contact with ionic substances, such as blood, and can be injected to achieve permanent vessel occlusion. NBCA can be mixed with varying amounts of ethiodized oil to modify the rate at which it polymerizes and to customize the flow rate and depth during embolization [15]. NBCA injections must be performed rapidly and continuously and the microcatheter should be removed in a timely fashion to avoid microcatheter adherence to the glue cast or to the adjacent vessel wall, potentially resulting in catheter retention or vessel avulsion. Another limitation of NBCA is the possibility of inadequate tumor penetration when the

delivery microcatheter is wedged within the supplying vessel, thus inhibiting anterograde flow delivery of the embolic material.

Onyx is a cohesive polymer of ethylene vinyl alcohol (EVOH) dissolved in dimethyl sulfoxide (DMSO) that is used as a liquid embolic agent. In 2005, the Food and Drug Administration approved Onyx in the USA for embolization of brain AVMs in adults but cautioned that its safety for use in children had not been studied. Reports on Onyx used in pediatric neurointervention have been relatively scarce and limited to case reports or small series [22]. Currently, the safety and efficacy of Onyx in the pediatric population have not been firmly established.

Embolization

Anesthesia

General endotracheal anesthesia is preferred for all pediatric intracranial and head/neck embolization procedures. This minimizes patient anxiety, motion and allows for intermittent suspension of the patient's respirations, which greatly enhances angiographic visualization during embolization.

Radiation Protection in Pediatric Angiography

Special considerations are required to protect children, who are more sensitive to the harmful effects of radiation and because they have a longer remaining lifespan during which time radiation-related cancer might develop [23]. Total fluoroscopy exposure and arteriography run times must be minimized. Progressive pulse fluoroscopy, last image hold, use of filters, appropriate shielding (including gonadal protection), and optimal coning all help in reducing patient exposure, with reduction in distance between the image receptor and the patient allowing for reduction in scattered radiation. Removal of the grid is important when imaging neonates and small infants. If magnification is required, the consequent significant increase in radiation dose should be remembered, with consideration of digital magnification instead [24].

Contrast Media

All efforts should be made to reduce the risk of contrast agent–induced nephropathy in pediatric cases. The risk of nephrotoxicity is markedly less with the use of low-osmolar contrast medium and may be even further reduced with the use of iso-osmolar agents [24]. Low-osmolar, nonionic monomeric iodinated contrast medium (300–350 mgI/mL) is most commonly used for pediatric arteriography, with a reduction in nephrotoxicity and osmotic load.

Additional dilution of contrast medium (i.e. to half strength) can offer significant dose reduction without compromising image quality. Furthermore, the total volume

of contrast needs to be closely monitored given that pediatric patients tend to weigh less and will thus reach the maximum dose in a shorter time compared to typical injections. Smaller volume syringes may be used for injections as a means to better control administration volume.

Pre-embolization Angiography

Percutaneous transfemoral artery angiography is performed to evaluate all potential sources of tumoral blood supply, tumor flow dynamics, and to identify important normal vasculature. Any dangerous anastomoses between the external carotid artery (ECA) and internal carotid artery (ICA) or vertebral artery branches must be evaluated. Venous drainage and involvement is also vital, especially when a tumor is compromising a dural sinus or jugular vein.

In most diagnostic cases, 4-French systems can be used for patients larger than 10 kg, and 3-French catheters for those smaller than 10 kg [24]. Microcatheters can be advanced directly through 3- and 4-French arterial sheaths, or coaxially through catheters with an appropriate inner diameter (ID).

Anticoagulation

Once a decision is made to proceed with embolization, patients are fully anticoagulated. Intra-procedural heparinization can prevent vascular thrombosis and its use is well accepted, especially in infants smaller than 10–15 kg [24]. After a baseline Activated Clotting Time (ACT) is obtained, intravenous heparin is typically administered as a 50–100-IU/kg intravenous bolus dose to a target prolongation of two to three times the baseline ACT value. Care must be taken to achieve this goal, as pediatric patients may require a higher weight-based dose of heparin than adults to achieve the desired ACT. Additionally, the use of heparin in all flushes (2000 IU heparin in 1 l of normal saline) is critical.

Embolization Technique

Once the arterial supply to the tumor has been mapped and stable access has been achieved, embolization should be performed within an arterial feeder as close to the lesion as possible to achieve maximum tumoral penetration. In tumors with rapid arteriovenous shunting, injected embolic agents may inadvertently flow through the lesion and into the venous circulation. In these cases, protective microcoils may be deployed distally to the major arterial suppliers creating an iatrogenic sump into the tumor, subsequently making it safer to use the desired embolic agent.

For most pediatric embolization procedures, a 0.021 in. ID microcatheter such as a Prowler Plus (Codman, Raynham, MA, USA) or a Renegade (Boston Scientific Corporation, Natick, MA, USA) is sufficient for administration of 150- to 500- μm

particles. For 45- to 150-μm particles, a 0.013 in. ID Marathon microcatheter over a Mirage 0.008 in. microwire (both ev3 Neurovascular/Covidien) is preferable [13]. The microcatheter is tracked as distally as possible, beyond any vital collateral vessels. Once in place, superselective angiography is performed to study the microvasculature, intratumoral collaterals, and the possibility of reflux. Embolization is performed under continuous fluoroscopic mask, until stasis of contrast within the tumor is noted, or until unacceptable reflux along the supplying vessel is noted. Great care to flush the microcatheter with a saline flush under subtraction fluoroscopy should be undertaken as the microcatheter's intraluminal volume still contains particles that can inadvertently be embolized to normal circulation. If too much reflux is noted, the microcatheter must be removed without flushing to reduce this risk.

In cases in which NBCA is the desired embolic agent, the microcatheter is positioned in the target vessel and is then thoroughly flushed with 5 % dextrose solution in order to avoid precipitation in the microcatheter. NBCA is then mixed with ethiodized oil as well as tantalum powder for radio-opacity. This mixture is then slowly injected under fluoroscopic mask for tumoral penetration or for occlusion of arterial supply. Once the desired embolization has been achieved, or if there is any question of reflux or non-target embolization, the injection is stopped, aspiration is applied, and the microcatheter is briskly and smoothly withdrawn from the patient and discarded.

Complications

The data on the overall risk of embolization of both intra- and extra-axial brain tumors remains controversial. The overall rate of neurologic adverse events in adults has been cited to be between 6.5 and 12.6 %, with persistent deficit in 2.2–9.0 % and death in 0.5 % of patients following embolization [13, 15, 25]. However similar data on pediatric patients is scarce due to the lack of large prospective-based studies.

Minor complications of embolization include access site complications, localized pain, fever and allergic reactions to contrast media. Major complications include ischemic and hemorrhagic stroke, skin and mucosal necrosis, intratumoral hemorrhage and nontumor embolization from reflux or collateral anastomoses into the ICA, ECA or vertebral circulations [13, 15, 24].

Access site complications are primarily seen in the neonate or infant population and are the most common adverse events following arteriography [24, 26]. Puncture site complications include local hematoma, dissection, thrombosis/occlusion, pseudoaneurysm, and arteriovenous fistula formation. The incidence of hematoma varies from 0.3 % to as high as 25 % when arterial interventions are performed in patients smaller than 15 kg. The risk of pseudoaneurysms and arteriovenous fistulas has been cited at 0.3 % overall, with an increased risk in patients aged 3-years or younger and when 6-French or larger groin sheaths are used [24].

Inadvertent non-target embolization may lead to major complications such as stroke and damage to normal tissue. Blindness may result from non-tumor embolization to the central retinal artery by way of ECA to ICA anastomoses via the ophthalmic artery, or

via anatomic variants such as an ophthalmic artery origin from the middle meningeal artery. Other complications include skin necrosis, transient or permanent cranial nerve palsies due to embolization of the vasa nervosum, and pulmonary embolism [13].

Tumor swelling post embolization may compromise the airway or increase intracerebral mass effect. The potentially life-threatening consequences of post-interventional edema are significantly increased in cases involving posterior fossa tumors because of the risk of brainstem compression or herniation [13].

Radiation injury is another potential complication as children may be more sensitive to the effects of radiation. The average radiation dose to the pediatric brain during neurointerventional procedures ranges from 100 to 1300 mGy if exposed to non-collimated fields, and from 20 to 160 mGy in collimated, moving fields [23].

Clinical Pearls

- The primary goals of preoperative tumor embolization are to reduce intraoperative blood loss, shorten operative time, and decrease surgical morbidity.
- Pediatric neurological tumors that may be amenable for preoperative treatment include juvenile nasopharyngeal angiofibroma, choroid plexus papilloma, hemangioblastoma, hemangiopericytoma, meningioma, schwannoma, paraganglioma, esthesioneuroblastoma, bone tumors, and metastatic tumors.
- Optimal timing for surgical resection is approximately 1–8 days after embolization, which allows sufficient time for tumor necrosis, while avoiding the potential for significant recanalization to develop.
- The major classes of embolic agents used in pediatric cases include particles and liquid embolic agents.
- Particles, sizes 150–250 μm, are commonly used for penetration of tumor supply. Smaller particles penetrate more deeply but carry a greater risk of inadvertent embolization of normal adjacent arterial feeders.
- Liquid embolics, such as *n*-butyl cyanoacrylate, can be used for tumoral penetration or for occlusion of proximal arterial supply.
- Special radiation precautions are required to protect children, who are more sensitive to the harmful effects of radiation.
- Minor complications of embolization include access site complications, localized pain, fever and allergic reactions to contrast media.
- Major complications include ischemic and hemorrhagic stroke, skin and mucosal necrosis, intratumoral hemorrhage and nontumor embolization from reflux or collateral anastomoses into other circulations.

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Stereotactic Radiosurgery in Pediatric Neurovascular Diseases

20

Hannah E. Goldstein, Stephen G. Bowden, Sunjay M. Barton, Eileen Connolly, Richard C.E. Anderson, and Sean D. Lavine

Introduction

Stereotactic radiosurgery (SRS) is an evolving approach for the treatment of pediatric neurovascular diseases. To date, SRS has mainly been used in the treatment of arteriovenous malformations (AVMs), though there are some reports of successful use in cerebral cavernous malformations (CCMs) and dural arteriovenous fistulas (dAVFs). Our understanding of the utility of SRS as either primary or adjunctive therapy has improved with experience. With proper selection of lesions, empiric comparisons between SRS and microsurgery for the treatment of pediatric AVMs have shown

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A. Agrawal, G. Britz (eds.), *Pediatric Vascular Neurosurgery*,
DOI 10.1007/978-3-319-43636-4_20

comparable outcomes for obliteration and re-hemorrhage rates, making it a reasonable modality to add to the neurosurgeon's armamentarium of treatment options.

History

Stereotaxis was designed by Lars Leksell, a Swedish professor and neurosurgeon, in 1949 [1]. Originally intended for use with probes and electrodes, ionizing radiation was used shortly thereafter in the early 1950s. SRS was first used for the treatment of neurovascular disease in 1970 by Ladislau Steiner, in the treatment of an AVM [2]. This first approach to SRS AVM treatment included angiography to define the target, the use of a single isocenter, and delivery of 50 Gy over 30 min. The AVM was noted to be obliterated at follow-up angiography 19 months post-operatively. Several subsequent patients did not fare as well, but many technical modifications and improvements allowed for the expansion of SRS into a viable alternative to microsurgery in neurosurgical practices worldwide.

Use in the pediatric population followed shortly thereafter. Physicians at St. Anne Hospital in Paris, France began treating pediatric AVMs with SRS in 1984 [3]. Expansion into the United States occurred in 1987 with the establishment of the first Gamma Knife unit at the University of Pittsburgh in 1987. Altschuler et al. [4] published the first exclusively pediatric series on SRS for AVMs with a report of 18 patients treated from 1987 to 1989. Follow-up was poor, but three of the seven patients with angiography at 1 year had total lesion obliteration, showing potential for future use.

Patient Selection

When deciding which patients to treat with SRS, multiple factors should be considered, including AVM size, location, pattern of venous drainage, prior history of hemorrhage, surgeon experience, and patient/family preference. Outcome predictors have been developed retrospectively and validated prospectively in order to facilitate decision making. Additionally, five tiers of outcomes, from excellent to poor, have been defined by Pollock to allow for cross-comparison of treatment results in clear, straightforward terms (Table 20.1) [5]. These outcomes are tiered by complete versus incomplete obliteration, and the development of any new neurological deficits.

The Spetzler-Martin (S-M) grading system is a well-known grading system developed in 1986 to assess the risk of neurological complications following

Table 20.1 Outcomes following SRS for AVM [5]

Outcome	Obliteration	New neurological deficit
Excellent	Complete	None
Good	Complete	Minor
Fair	Complete	Major
Unchanged	Incomplete	None
Poor	Incomplete	Minor or major

microsurgical resection of an AVM. Dependent on AVM size (by maximum diameter), venous drainage (superficial versus deep), and location (eloquent or non-eloquent cortex) [6], the S-M system grades AVMs on a scale from I to V, with Grade I representing the lesions most amenable to resection, and V being those most likely to produce neurological deficits following surgery.

The AVM Score, originally developed by Pollock [7] in 2002, and modified in 2008, was developed as the radiosurgical corollary to the S-M grading system. It can be used to determine the likelihood of an excellent outcome, or complete obliteration with no new neurological deficits, following radiosurgery for a given AVM. Similar to the S-M Grade, the AVM Score accounts for AVM size, though in volume, rather than largest diameter; AVM location, though eloquence is defined differently; and finally, the AVM Score does not factor in venous drainage, but instead includes patient age. The AVM Score is calculated according to the following equation [8]:

$$AVM\ score = (0.1)(volume, mL) + (0.02)(age, yrs) + (0.5)\begin{pmatrix} location; hemispheric / corpus\ callosum / cerebellar \\ = 0, basal\ ganglia / thalamus / brainstem = 1 \end{pmatrix}$$

A score of ≤1.00 corresponds to an 89 % chance of obliteration with no new deficits after SRS, 1.01–1.50, a 70 % chance, 1.51–2.00 a 64 % chance, and ≥2.00 a 46 % chance [8]. Though originally developed for the adult population, the use of the AVM Score has been extended to the pediatric population [9–11], LINAC formats for radiosurgery [11–13], and deep-seated AVMs [13, 14]. It has also been validated in predicting outcomes after multiple radiosurgical procedures [15] and predicting the risk of neurologic decline after AVM radiosurgery [16, 17].

Though there is no direct relationship between radiosurgery-specific complications and S-M Grade, Kiran et al. found a greater incidence of permanent neurological complications in patients with S-M Grade IV or V lesions undergoing radiosurgery, as compared to those patients with lower S-M Grade lesions [18]. Other radiosurgical series include S-M Grades in their results, but none have reported a significant relationship with obliteration or complication rates [10, 19–22].

Generally speaking, cross-comparison between S-M grade with SRS outcomes and AVM Score with microsurgical outcomes may elucidate proper treatment selection. S-M grade I-II lesions undergoing SRS experience complications at a rate of 0–2.9 % (Table 20.2). In contrast, microsurgery in S-M grades I-III has reported complication rates of 3.2–10 % [23–25]. Therefore, SRS could be considered a viable option in this population for selected lesions, but ultimately the immediacy of

Table 20.2 SRS complication rates by Spetzler-Martin grade

Author	Date published	Complication rate by Spetzler-Martin grade (%)					
		I	II	III	IV	V	VI
Yen [41]	2010	0/23 (0 %)	1/55 (1.8 %)	3/87 (3.4 %)	2/20 (10 %)	0/1 (0 %)	n/a
Reyns [33]	2007	0/10 (0 %)	1/35 (2.9 %)	2/23 (8.7 %)	0/5 (0 %)	n/a	3/30 (10 %)

cure with microsurgery is often better in this group. SRS exhibits slightly higher complication rates in S-M Grades IV–V, between 0 and 10 % which offers substantially less morbidity than the complication rate of 12–38 % [25–27] incurred with microsurgery in this population, suggesting that SRS is a better approach for most patients in this group.

Integration of these two scores can be helpful in determining the optimal treatment modality for a given patient. Technical differences between the modalities must be discussed with the patient's family, as well as the latency versus immediacy of cure. If an AVM is completely obliterated immediately following a microsurgical procedure, any further risk of bleeding is also eliminated.. Obliteration following SRS, on the other hand, has been shown to take as long as 4–5 years in some cases [21, 28, 29], during which time there is still a risk of hemorrhage. While this latency period is often shorter in children relative to adults, likely due to greater radiosensitivity of pediatric lesions, there is also a greater tendency of the lesions to bleed [30, 31]. When risk between the two techniques appears comparable, a thorough discussion should be had with the patient and their family.

Timing

Timing of SRS treatment primarily depends on whether the patient presents with hemorrhage. Treatment timing is fairly elective in patients who have not bled. Conversely, treatment is often delayed in patients who present with hemorrhage to allow for hematoma reabsorption. Hematomas are responsible for up to 9 % of radiosurgical failures [5], likely due to compression and subsequent recanalization following treatment. The optimal timing of treatment has not been studied prospectively, but Maruyama et al. found no significant outcome differences in groups treated within the first three months, 3–6 months, or after 6 months following hemorrhage. However, the group treated at least 6 months later experienced significantly increased rebleeding rates prior to treatment [32], suggesting that SRS treatment within 6 months is preferred.

Technique

SRS for AVM was originally performed with Gamma Knife (GKRS), but many institutions use Linear Accelerator (LINAC) with comparable success [3, 9, 22, 33]. The focus of this discussion will be on GKRS, as this is performed at the authors' institution.

The decision regarding whether or not to use general anesthesia (GA) and endotracheal intubation is one that should be made with involvement of the patient's family. In prior studies, children receiving GA have generally been under 14 years old or unable to cooperate for the duration of the procedure [19, 21]. Local anesthetic for frame placement [10] and moderate sedation [20] can be used as an alternative to GA, particularly for more mature patients.

In preparation for GKRS, an MRI-compatible, stereotactic coordination frame (Elekta Instruments Inc., Norcross, GA) is placed on the patient's head. Imaging sequences involving a combination of post-contrast T1 volumetric MRI, MRA, and T2 weighted sequences as well as digital subtraction angiography are then obtained for stereotactic guidance [10, 19, 20, 34]. Treatment planning and dosage is determined by a multidisciplinary team, usually consisting of a neurosurgeon, radiation oncologist, and medical physicist, with the aid of software which calculates radiation dosages to surrounding regions and facilitates development of a three-dimensional treatment plan. Treatment planning is aimed at maximizing the mean treatment dose to the nidus of the AVM while maintaining tight conformality and limiting dosage to the adjacent normal brain tissues [29]. Radiation dosages vary between institutions, but rates of complete obliteration have been shown to be ten times higher when marginal prescription doses are 18 Gy or more, though at the cost of increased risk of neurological deficits [35]. See Treatment Plan and Case Example.

The length of the treatment session is dependent on the AVM size, but generally ranges from 30 to 60 min as radiation is delivered to the AVM nidus according to the pre-planned treatment protocol. Patients are monitored during the session to ensure no adverse reactions. Most patients tolerate the procedure well and are discharged home that evening.

Multi-stage Treatment

Staged treatment is a useful strategy for large lesions or those in eloquent areas that require a decreased dose of radiation. There are several strategies for staging, including repeat SRS, proton-beam SRS, fractionated SRS, dose-staged SRS, and volume-staged SRS. Nicolato et al. recently proposed an algorithmic approach to staged treatment having identified a low likelihood of success with lesions ≥10 mL and to which ≥16 Gy cannot be safely delivered following a single treatment [19]. Dose-staging has been evaluated in the treatment of large AVMs, with successful nidus obliteration in 16 of 21 patients after 6 years [36]. Seymour et al. reported an institutional comparison of volume-staged SRS between two groups following a change in technique to smaller treatment volumes per stage, shorter intervals between stages, and higher radiation doses. The new technique resulted in markedly improved outcomes, with particular significance granted to a dose of ≥17 Gy [37].

Outcomes

The goals of SRS treatment of AVMs are the same as those with microsurgery: complete nidus obliteration with elimination of the risk of hemorrhage without the development of any new neurological deficits. Together, these constitute an "excellent outcome" as defined by Pollock.

Nidus obliteration is commonly assessed with a combination of MRI, MRA, and neurological examination following SRS. Serial MRIs/MRAs are typically done every 12 months until obliteration is achieved, but may be deferred if general anesthesia is required for the study. Contrast-enhanced T1 and T2-weighted MRI images showing disappearance of the nidus should be confirmed by conventional digital subtraction angiography at 3–4 years after SRS, as MRI may overestimate obliteration during the follow-up period [21]. Obliteration is confirmed with disappearance of the nidus and absence of early venous flow on angiogram.

Additionally, delayed follow up angiography should be obtained even after complete obliteration is noted, as there is a risk of de novo AVM formation. Lang et al. reported a 14.3 % recurrence rate in a cohort of 28 patients. In their study, all recurrent AVMs were picked up on imaging obtained at 1 year after complete obliteration was noted; none of the patients with negative results at 1-year follow up were noted to have recurrence later on [38]. However, Klimo et al. report at 13 % recurrence rate, with lesions appearing up to 6 years post initial negative angio [39]. While the actual recurrence rate is likely underreported, it is clear that delayed follow up imaging is important in the pediatric population.

Several prognosticators of obliteration rate have been identified. Lesions that are ≤2.5 cm in diameter with a solitary draining vein as seen on angiography have been shown to have the highest likelihood of obliteration [40]. Similarly, smaller target volume [19, 41] has been shown to significantly correlate with higher obliteration rates, specifically ≤10 mL [33, 34]. Larger margin dose [3, 21, 41], usually considered to be ≥20 Gy, and no prior endovascular embolization [41] have also been shown to significantly correlate with higher obliteration rates. Notably, there have been no reports indicating a significant difference in obliteration rates between pediatric and adult populations or between GK and LINAC modalities [42].

Reported obliteration rates vary widely between 35 and 90 % (Table 20.3). However, most studies to date are relatively small with limited follow-up. In one of the largest studies to date, consisting of 80 patients, Potts et al. [35], showed a comparatively low obliteration rate (OR) of 59 % after first SRS, assessed with angiography at 3 years post-treatment. Of note, a lower margin dose (17.5 Gy) was used in this study, and the authors report an institutional preference to treat larger, more complex AVMs with SRS, and smaller, better-defined AVMs with surgical resection. Other large studies with long-term follow-up report ORs between 62.9 and 89.3 % after first SRS [19, 21, 33, 34, 41]. With additional SRS for persistent lesions, these ORs improve to 70–90 %. Nicolato et al. have reported the highest OR to date, with 90 % overall obliteration following SRS in 100 pediatric and adolescent patients. Notably, the majority of lesions treated in this series had volumes less than 3 mL, and while over 90 % of lesions treated were in eloquent or deep-seated brain regions, they were also almost entirely S-M Grade I–III, in which the likelihood of success with MS is equivalently high [19].

Rates of hemorrhage during the latency period following SRS for AVM vary widely, between 0 and 22.7 % (Table 20.3). Most reviewed case series report rates less than 5 %. However, studies in which patients received lower radiation doses at

the margins, had larger nidus volumes, or both, report bleeding rates higher than this common range (16.0–22.7 %) [11, 35, 43]. Findings by Potts et al. suggest a threshold margin dose of 18 Gy, with hemorrhage in 35 % of patients receiving <18 Gy but only 3 % of those receiving ≥18 Gy [35].

Rates of permanent neurologic deficits due to adverse radiation effects (ARE) have generally fallen between 0 and 1 % (Table 20.3). Higher rates have been reported with larger nidus volumes [41], particularly lesions greater than 10 mL [19]. Lower rates of ARE were observed in Potts' series with a low prescription dose, though at the cost of a lower obliteration rate and higher bleeding rate.

Complications

The complications of radiosurgical treatment of neurovascular disease are fairly well defined in the adult population, but long-term effects of SRS in the pediatric population are still poorly understood. In considering neurovascular disease in any population, the main concern is the rate of hemorrhage post-operatively. The latency period incurred by radiosurgery renders this a particular concern; however, several studies have shown that radiosurgery offers some protection against hemorrhage even prior to total obliteration, with annual hemorrhage rates comparable to those of microsurgical series [10, 20, 21, 33, 34, 44, 45].

Radiosurgery-specific complications include post-radiation edema, radiation necrosis, radiation-induced neoplasm, and the impairment of normal neurodevelopment. The majority of post-operative neurological complications can be attributed to post-radiation edema, which is of particular concern in large AVMs with surrounding eloquent cortex. These focal deficits are often temporary, however, and the edema can be managed with steroids in the acute period [29]. The frequency and character of neoplasms and developmental impairment are still poorly defined, with follow-up generally limited to 5 years or less in most outcome-driven case series. No radiosurgery related radiation-induced neoplasms have been reported in the literature despite the theoretical risk. The risk of long-term developmental complications has also been poorly studied, though a recent study by Yeon et al. reported a decline in school performance in 14 out of 32 patients (44 %) undergoing GKRS for cerebral AVMs. In their study, Yeon et al. found AVM volume and AVM score to be reliable predictors of a decline in school performance; re-bleeding and the use of antiepileptic medications were also associated with decreased school performance, though these associations were not statistically significant on multivariate analysis [46].

A recent study by Hanakita et al. examined long-term patient outcomes, with a median follow-up of 100 months and six patients followed up for 20 years. Ten of the 116 patients experienced adverse events, including hemorrhage and new radiation-induced neurological deficits after SRS. Interestingly, delayed-onset complications occurring between 9 and 20 years post-treatment included cyst formation, a chronically expanding hematoma, and radiation-induced edema, in four of the patients followed [28].

Table 20.3 Summary of literature results for SRS for pediatric AVM

Author (Year)	Platform	# Pts w F/U	Age	% p/w bleed	AVM volume (cm^3)	SM grade (%)						AVM score (* indicates modified)		
						I	II	III	IV	V	VI	<1	1–1.5	1.51–2
CUMC	GK	25	1–18	60	1.7 (0.12–8.69)	0	43.5	47.8	8.7	0	0	95.5	0	4.5
Nicolato (2015)	GK	100	3–18	70	2.8(M) (0.06–39.6)	4	30	58	8			76*	12*	7*
Zeiler (2015)	GK	11	7–18		2.2	9.1	36.4	54.5				7	2	
Potts (2014)	GK	80	12.7 (M)	56	8.4(M)	0	13	56	23	9				
Sheth (2014)	GK	42	12(M)	62	4.6(M)	0	10	48	38	7				
Borcek (2014)	GK	58	4–18	41.4	3.5 (0.42–23)	12.1	32.8	27.6	13.8	13.8		36	13	
Dinca (2012)	GK	220	1–16	80.2	1.57	6	27	48	18	2				
Kano (2012)	GK	135	2–17	64	2.5 (0.1–17.5)	2.2	25.2	43	12.6	0	17	99	26	8
Yeon (2011)	GK	39	3–17	64	1.5	12.8	15.4	46.2	15.4	10.3				
Yen (2010)	GK	186	4–18	71.5	3.2(M) (0.1–24)	12.4	29.6	46.8	10.8	0.5				
Pan (2008)	GK	100	2–18	78	11.7(M) (0.4–63)	5.7	21.9	46.7	19	5.7	1			
Buis (2008)	LINAC	22			1.8	27.3	40.9	22.7	9.1					
Kiran (2007)	GK	103	3–18	86	2.4(M) (0.04–23.3)	55.3		44.7						
Reyns (2007)	LINAC	100	2–16	69	1.7 (0.9–21.3)	9.7	34	22.4	4.9	0	29.1			
Zadeh (2007)	LINAC	30	4–19	65		15	35	35	15	0	0			
Nicolato (2006)	LINAC	62	5–20	70	2.9(M) (0.1–25)	4	30	58	8			76*	12*	7*
Cohen-Gadol (2006)	GK	38	7–18	53	3.4(M) (0.2–33)	28.9		50	21.1					
Zabel-du Bois (2006)	LINAC	22	4–16	59	4.2 (0.4–26.5)	4	32	56	4	4				
Maity (2004)	LINAC	17	5–18	82.4	6.9 (0.7–24.8)									
Nataf (2003)	LINAC	49	7–15	69.4	3.5 (0.6–16)	11	35	40	14	0				
Smyth (2002)	GK	31	3–17	58	1.6 (0.2–37.4)	0	16	68	10	6				
Shin (2002)	GK	100	4–19	79	1.8 (0.1–19.2)	8	36	42	10	0	4			

F/U follow-up, *% p/w bleed* % of patients with hemorrhage as initial presentation, *M* mean, *SM* rate, *LP* latency period

		Margin dose (Gy)	Rate after 1st SRS	Time to oblit (months)	Total oblit Rate (%)	F/U period (months)	Bleed during LP (%)	Complication rate		Permanent deficits
>2	Overall							General (%)	Radiation specific (%)	
		20 (15–22)		23.9 (8.7–189)	44	46.7 (8.7–189)	12	40	4	4
5*		22.6 (14–26.4)	89.3	27.4	90	82.2 (36.4–234.9)	9		11	2
1	0.9 (0.28–3.63)	20 (16–22)				36 months	0	18.2		0
	1.3(M)	17.5 (12–20)	59			36 months	20	48		
	1.5(M)	17 (12–20)	30		37	36	2.2			
	0.68*	22 (15–24)	68.9			32 (12–100)		15		
			71.3	32.4(M)	82.7		2.2	3.6	1.7	
2		20(15–25)	70	37	81	71 (6–264)	6		5.9	1.5
	0.94*(M)	20 (13–30)	44	23.2(M)	44	23.2(M)	7.7	8		
	0.88(M) (0.21–3.03)	21.9(M) (7.5–35)	62.9		73.7	98(M) (24–240)	9.1	13 (7%)	1.1	1.1
		18.5(M) (14.5–25)	65		81	25 (6–134)	4	8 (8%)		5
	0.76	19	68	25	68	29	4.5	1 (4.5%)	4.5	4.5
		24.4(M) (15–27)	87				2.9		3.8	
		23(M) (15–25)	65	25.5(M)	70	26 (11–126)	2.0	6.7%		5
			66.7			36(M)	3.3	5 (16.7%)		13.3
5*		22.6 (14–26.4)	88.1	25.7	85.5	29 (6.2–77.2)	1.3		11	2
	1.08 (0.36–4.08)	20 (16–25)	54		55	42 (12–131)	2.6		0	0
	1.07 (.61–3.55)	18	64	27.1	64	37 (19–87)	22.7	0	0	0
		18 (16–18)	53	16	53	21 (9.4–63.1)	0	4 (23.5%)		17.6
		25 (18–28)	61.2	30	61.2	34 (7–172)	8.2	0	0	0
		18 (12–19)	27		35	60 (6–99)	16			6
		20 (17–28)	71	21.5	71	71 (6–124)	4			2

grade Spetzler-Martin Grade, *Time to oblit* time to obliteration, *Total oblit Rate* total obliteration

Additionally, as with any neurological surgery, there is a risk of new neurological deficits post-operatively. Increased risk of permanent deficits has been associated in univariate analyses with deep-seated lesions [21], high Pollock-Flickinger AVM Score [21, 46], larger volume [18, 33, 46], S-M Grade IV or V [18], and male sex [33], though none of these carried through in multivariate analysis.

Cavernous Malformations

The use of stereotactic radiosurgery in treating cerebral cavernous malformations (CCM) in children has not been investigated, as they are still largely thought of as a surgical entity. Microsurgical excision has been shown to be lower risk if the lesion has recently bled and at higher risk if the lesion is located in the brainstem [47]. Smaller studies in adults with lesions deemed surgically inaccessible have shown promising results for SRS. One study in particular showed that SRS reduced annual hemorrhage rates in patients with surgically inaccessible CCMs from 17.3 to 4.5 % per lesion per year after a latency period of 2 years [48]. These data suggest a potential role for SRS in deep-seated CCMs in the future, following further study and extension to the pediatric population.

Dural Arteriovenous Fistulas

Pial or dural arteriovenous fistulas (AVFs) have long been disconnected via surgical clipping or endovascular embolization. One 55-patient series in adults used SRS as an adjunct to clipping or embolization, showing angiographic obliteration in 54–65 % of patients at 3 years with a 5 % annual hemorrhage rate during the latency period [49]. However, rates of surgical obliteration remain much higher, suggesting that the role of SRS may be as an adjunct treatment in the event of persistent flow. In the pediatric population, data is limited to case reports, which have demonstrated the use of SRS as a treatment adjunct to embolization alone, or embolization and surgical clipping [50] with promising results.

Conclusions

SRS for the treatment of neurovascular disease in children is a viable, even preferred, option in many clinical scenarios. Deep-seated, surgically inaccessible and small-volume AVMs treated with SRS have been shown to have comparable or superior outcomes when compared with microsurgical resection. The application of the Spetzler-Martin grade and Pollock-Flickinger AVM score provide valuable information to guide the clinician in the present day. Outcomes will continue to improve with greater radiosurgical experience and better knowledge of the implications of radiosurgery on the developing brain, unique to the pediatric population.

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Intra-arterial Delivery of Chemotherapeutic Agents

21

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Intra-arterial chemotherapy (IAC) has been described in the treatment of retinoblastoma [1–3], sarcoma [4, 5], and malignant glioma [6, 7]. Intra-arterial chemotherapy (IAC) in these settings has generally been considered adjuvant therapy along with systemic chemotherapy, surgical resection, and/or radiation therapy. IAC is appealing given the potential to limit systemic toxicity from chemotherapeutic agents while increasing the concentration in areas of active malignancy. Within the central nervous system, the blood brain barrier (BBB) has proven to be a hurdle to the delivery of chemotherapy agents with various protocols described to help breakdown the BBB to facilitate chemotherapy delivery [8]. Within the pediatric population, IAC for the treatment of retinoblastoma (Rb) has become well studied with a good safety profile and efficacy.

Retinoblastoma (Rb) represents approximately 6% of all childhood cancers occurring under age five in the United States [9]. Traditional treatment of Rb involved a combination of surgery (enucleation), systemic chemotherapy, radiation, and brachytherapy [10]. While the majority of these patients survive, there is significant morbidity and disability associated with traditional treatment options [11, 12]. The search for more targeted therapies started in 1958 with the first administration of intra-carotid triethylene melamine for Rb with mixed results (1). With advances in both imaging for fluoroscopy and intracranial access via smaller

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A. Agrawal, G. Britz (eds.), *Pediatric Vascular Neurosurgery*,
DOI 10.1007/978-3-319-43636-4_21

catheters, selective ophthalmic artery chemotherapy (chemosurgery) for Rb was trialed throughout the 1990s (2) and the first trials of US patients were published in 2008 (3). The results of these studies showed promise at slowing disease progression and avoiding enucleation of the affected eye. Since that time, multiple additional studies have attested to the efficacy of IAC in the treatment of advanced and/or refractory Rb [2, 13, 14].

Patient Selection

International Classification for Rb separates patients into five groups based on extent of disease spread, Group A-E (Table 21.1) [15–17]. This classification system represents the natural history of Rb disease progression with the most severe disease being Group E. Intra-arterial chemotherapy is generally considered for patients in the moderate to high risk, Group C or D, with select cases of the very high risk Group E [12]. Combining various studies, IAC has a globe salvage rate of between 58 and 100 % when used as primary treatment and 50–75 % when used as a secondary treatment [13, 14, 18, 19]. When looking at IAC efficacy by group, there is nearly 100 % globe salvage rate in Group C and D, but this drops off steeply to 33 % in Group E [12, 20].

Table 21.1 International classification for retinoblastoma classification, separates patients into five groups based on extent of disease spread and severity [14–16]

Group	Subgroup	Quick reference	Specific features
A	A	Small tumor	Rb ≤3 mm
B	B	Large tumor	Rb > 3 mm or
		Macula	Macular Rb ≤3 mm to fovela
		Juxtapapillary	Juxtapapillary ≤1.5 mm to disc
		Subretinal fluid	Clear subretinal fluid ≤3 mm from margin
C		Focal seeds	
	C1		Subretinal seeds ≤3 mm from Rb
	C2		Vitreous seeds ≤3 mm from Rb
	C3		Subretinal & vitreous seeds ≤3 mm from Rb
D		Diffuse seeds	
	D1		Subretinal seeds >3 mm from Rb
	D2		Vitreous seeds >3 mm from Rb
	D3		Subretinal & vitreous seeds >3 mm from Rb
E		Extensive retinoblastoma	Rb occupying 50 % globe
			Neovascular glaucoma
			Opaque media from hemorrhage in anterior chamber, vitreous, or subretinal spaces
			Invasion of postlaminar optic nerve, choroid (>2 mm), sclera, orbit, anterior chamber

Intra-arterial Chemotherapy Agents

The most commonly used agent is melphalan, which has some properties to disrupt the BBB. Other commonly used IAC agents include carboplatin, topotecan, methotrexate and etoposide [12]. With the exception of methotrexate and melphalan, the remaining agents can also be used in IV systemic chemotherapy. Melphalan, methotrexate and carboplatin can also be used in intravitreal chemotherapy. By in large, the majority of IAC is done with melphalan with topotecan or etoposide as additional chemotherapy agents in cases of bilateral disease or tumors resistant to melphalan alone [20].

General Procedure

Intra-arterial chemotherapy is generally undertaken at larger academic centers with access to pediatric experienced pediatric neuro-interventionalists, pediatric anesthesiologists, pediatric retinal ophthalmologists, and oncology pharmacists. The procedure is performed under general anesthesia with close monitoring of fluid status and hemodynamic stability.

Briefly, general anesthesia is induced and access to the femoral artery is obtained in the standard fashion. The room should be free from any cotton or lint debris as these may cause reactions with the chemotherapy agents. Systemic heparin is generally given to prevent thromboembolic issues. Angiogram from of the internal carotid artery ipsilateral to the tumor/treatment site is performed. Next, a catheter is used to navigate to the ophthalmic artery for selective injection of chemotherapy agents. Two major techniques have been described – direct access to the ophthalmic artery using microwire and microcatheter [3, 20] (Fig. 21.1) or indirect injection of chemotherapy to the ophthalmic artery via temporary occlusion of the distal internal carotid artery via balloon occlusion [2] (Fig. 21.2). In certain cases, the ophthalmic artery may be fed from branches off the external carotid circulation and indirect access may be gained to the ophthalmic artery for treatment [21, 22] (Fig. 21.3). Targeting the ophthalmic artery to minimize intracranial chemotherapy

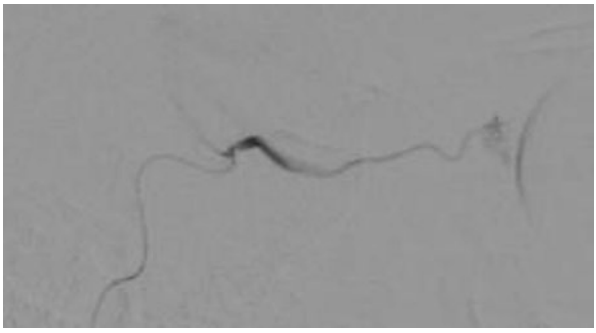

Fig. 21.1 Selective microcatheter injection of the ophthalmic artery, note the classic crescent shape of the choroid blush

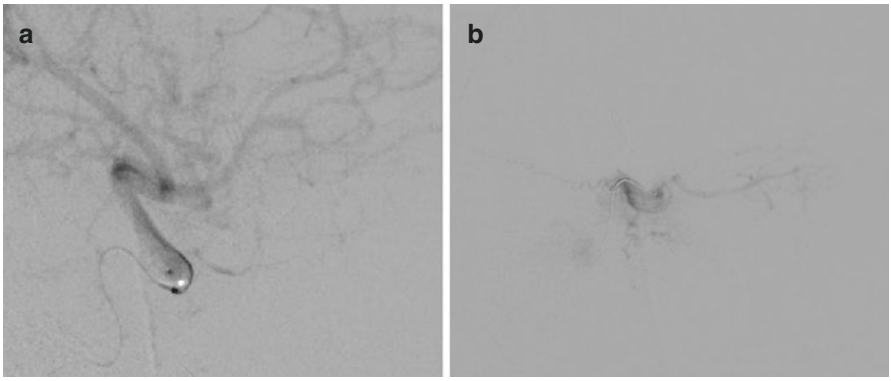

Fig. 21.2 (**a**) Left internal carotid angiogram shows acute angle of the ophthalmic artery not suitable for direct microcatheter selection. (**b**) After balloon inflation distal to the ophthalmic artery take off, repeat angiogram of the left internal carotid shows filling only of the ophthalmic artery. Targeted intra-arterial chemotherapeutic agent injection can then be undertaken at this point. The balloon should be deflated between the various drugs to allow for brain reperfusion

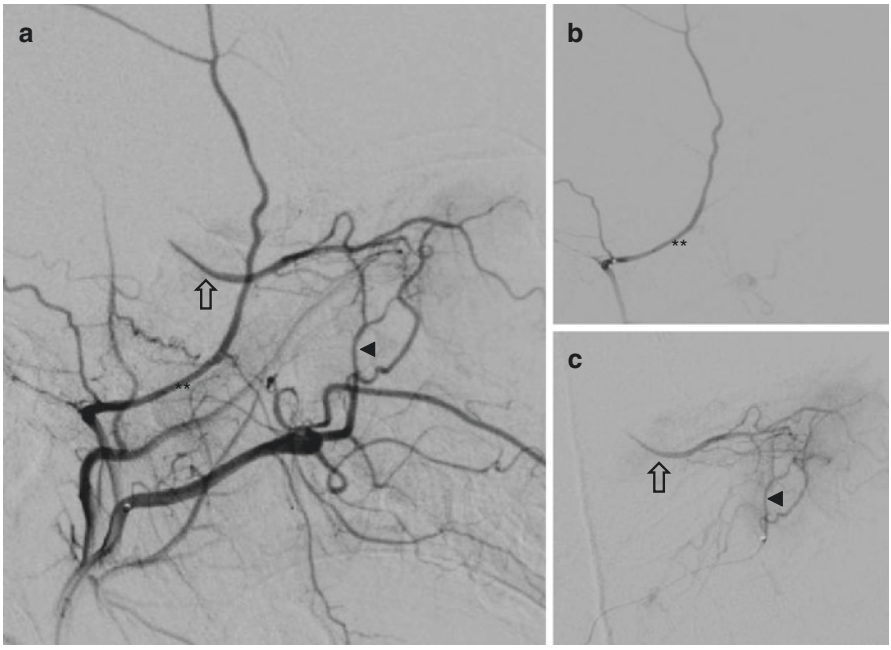

Fig. 21.3 Right external carotid artery selective angiograms. (**a**) Internal maxillary artery angiogram showing retrograde filling of the ophthalmic artery (*arrow*), the middle meningeal artery is also seen (*stars*) and a branch of the anterior deep temporal artery (*arrowhead*). (**b**) Middle meningeal artery angiogram (*stars*) demonstrates no filling of the ophthalmic artery. (**c**) Anterior deep temporal artery artery (*arrowhead*) angiogram demonstrates retrograde filling of the ophthalmic artery (*arrow*)

agent delivery and increase delivery to the tumor is desired. Adjuncts used during IAC include vasoconstrictive agents in the periorbital area including topical phenylephrine or Afrin [23].

The chemotherapy agents are generally delivered in a gentle pulsatile fashion at a rate of 1 cc/min. Afterwards, the catheter is flushed with heparinized saline to prevent any crystallization and minimize the risk for embolic complication. After all chemotherapeutic agents have been given, follow up angiogram is performed to ensure no thromboembolic or hemorrhagic (contrast extravasation) events have occurred. The catheters and any groin sheaths are removed and manual pressure is held for hemostasis.

Procedural Considerations

The majority of large medical centers performing IAC for Rb have dedicated oncology pharmacies that are able to mix the various chemotherapy agents at different concentrations into various volumes. It is critical that discussion with the oncology pharmacist prior to each procedure about drug dosing and concentration occurs so that the necessary volumes are on hand for the procedure. Furthermore, melphalan has a short half-life of 1.5 h and is generally mixed just prior to the start of the procedure. Communication between the pharmacy and intervention team is critical to avoid wasted medications.

Safety Considerations

Safety should be of the utmost concern given the risks for local and systemic side effects from IAC. Given the intricate navigation of small pediatric blood vessels with various catheters and microwires, IV heparin should be employed to minimize risk for thrombus formation. As is standard for angiography, having lines on a heparinized saline flush will further reduce risk of clot formation. Care should also be taken when selecting larger "guide" catheters for use in the pediatric circulation to minimize trauma to blood vessels and risk for dissection or stroke. Of the available literature on IAC for Rb, there have not been any reports of thromboembolic complication or intracranial hemorrhage related to selective catheterization for drug delivery [20]. There have been case reports of groin hematoma [24] and transient femoral occlusion [25, 26] without long term sequela.

A commonly seen side effect related to microcatheter selection of the ophthalmic artery include bronchospasm and bradycardia [20, 27, 28]. The rates of bronchospasm during IAC can be as high as a quarter of all patients, causing severe respiratory compliance changes [27]. The changes look clinically similar to acute bronchospasm and are characterized by decreases in tidal volume and hypoxia. The exact mechanism is unknown but is speculated to be related to autonomic reflex between the intracranial vasculature and airway. A child who previously has not had issues with bronchospasm can subsequently develop this issue in later treatment

sessions [27]. Bradycardia is seen in similar rates as bronchospasm and is thought likely secondary to the trigemino-cardiac reflex. Both bronchospasm and bradycardia are most likely to occur during selective catheterization of the ophthalmic artery, prior to injection of any contrast or chemotherapy agent [27, 28]. These events were generally transient and self-resolve in the majority of cases with supportive anesthetic care. However, it is prudent to have easy access to epinephrine and atropine to treat more prolonged episodes of bronchospasm and bradycardia, respectively. Furthermore, during the critical period of ophthalmic artery catheterization, communication between the neuro-interventional and anesthesia teams is crucial for patient care.

Additional common systemic complications from IAC include neutropenia and iodine allergy [20]. Periodic cell count checks should be obtained and discussion had with the oncologic pharmacist about any adjustments to IAC doses prior the initiation of the next treatment.

Common minor ocular side effects include eyelid edema, forehead erythema, thinning of eyelashes, bepharoptosis and transient ocular dysmotility [20, 24, 29]. These episodes generally resolve spontaneously, though they can take up to a few months. More concerning ocular side effects of IAC include vasculopathy of the retinal, choroidal or ophthalmic vessels generally thought to be due to chemotherapy toxicity side effects, catheter-related injury to the vessel, or foreign body embolization either from the catheter itself or pieces of cotton or dust [20, 30]. Careful follow up with retinal ophthalmology specialists who may help to identify early vasculopathy changes is imperative.

Ionizing radiation exposure should be carefully considered for any patient undergoing IAC given the cumulative effects of repeated treatment sessions. Care should be taken by the neuro-interventional to minimize the field of radiation exposure, to utilize low radiation modes in available angiography equipment and to carefully monitor radiation dose per treatment session. While overall radiation doses for patients undergoing IAC in large centers was below toxic levels, there is evidence that these children may still be exposed to catarctogenic or carcinogenic doses – the long term effects of this repeated ionizing radiation exposure is still currently unknown [31]. Minimizing radiation exposure in these children cannot be overstressed.

Post Operative Care

Post-operatively, manual pressure is held for hemostasis at the femoral artery access site. The patients are extubated and should be checked to ensure no deficits are concerning for stroke. Prior to extubation, discussion should be had with the anesthesia team regarding the preferred method for sedation after extubation as patients will need to remain still for several hours to prevent groin hematoma formation. At some centers, the patients may be observed overnight or may be discharged home the same day. The use of aspirin therapy after IAC has been described by some groups [20].

Summary

Retinoblastoma is the most common intra-ocular malignancy in children. Classic treatment options have included enucleation, radiotherapy, systemic chemotherapy or focal ocular therapy. Intra-arterial chemotherapy for the treatment of Rb has gained prominence over the last decades especially in cases of refractory or aggressive disease with good rates of salvage and tumor control. However, the use of IAC does carry the risk of ocular and systemic complications. Consideration of patients for IAC treatment should be done in a multidisciplinary manner at centers with access to experienced pediatric neuro-interventionalists, ophthalmologists, pharmacists, and anesthesiologists.

Pearls

- Retinoblastoma represents 6 % of all childhood cancers in children under 5 years of age
- Overall survival is good, but traditional treatments including enucleation and systemic chemoradiation can leave children with significant morbidity and disability
- Intra-arterial chemotherapy shows promise as a targeted therapy for retinoblastoma, controlling tumor growth and preventing spread
- Targeted delivery of the chemotherapy agents can occur through direct selection of the ophthalmic artery or via indirect routes through naturally found anastomotic vessel connections
- Bronchospasm and bradycardia are commonly report reactions during selective catheterization of the ophthalmic artery and should be carefully monitored for during the procedure
- Care multidisciplinary discussion and planning between ophthalmology, pharmacy, anesthesia, neuro-interventionalist, and ICU specialists is necessary for successful and safe treatment strategies

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Sclerotherapy

22

Ian A. Kaminsky

Pediatric Extracranial Vascular Anomalies

Pediatric vascular anomalies generally present at birth, or in early childhood. The head and neck are the most common sites of involvement [1]. Proper classification is crucial to guide treatment planning. These vascular anomalies can be divided broadly into two categories: vascular tumors and vascular malformations. This initial biologic classification was first devised in 1982 by Mulliken and Glowacki [2]. Several revisions of this initial classification have taken place over the years in an effort to remove confusion and misleading nomenclature, which can impede the proper diagnosis and subsequent therapy. The most updated classification by the International Society for the Study of Vascular Anomalies (ISSVA) was completed in 2014 [3].

The ISSVA further divides vascular tumors as benign, locally aggressive or borderline, and malignant. Benign vascular tumors include: infantile hemangioma (IH) and congenital hemangioma (CH), with rapidly involulting (RICH) and noninvoluting (NICH) varieties. Kaposiform hemangioendothelioma is an example of a locally aggressive or borderline lesion, and angiosarcoma is an example of a malignant vascular tumor. Sclerotherapy is not typically an option for lesions in the vascular tumor category.

The main categories in the vascular malformation group are simple or combined. Simple vascular malformations include: capillary malformations (CM), lymphatic malformations (LM), venous malformations (VM), arteriovenous malformations (AVM), and arteriovenous fistulae (AVF). AVM and AVF are high-flow lesions while CM, LM, and VM are low-flow lesions. Combined implies that two or more

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A. Agrawal, G. Britz (eds.), *Pediatric Vascular Neurosurgery*,
DOI 10.1007/978-3-319-43636-4_22

vascular malformations are found in one lesion, and entities in the combined group are a combination of the aforementioned anomalies. Anomalies of major named vessels and vascular malformations associated with other anomalies/syndromes also fall under the vascular malformation grouping. Sclerotherapy is quite useful in the treatment of VM, LM, and some combined lesions. CM are not well served by sclerotherapy, and high-flow lesions are typically best treated by trans-arterial preoperative embolization and surgery. Cyanoacrylate glue is an excellent option for the preoperative embolic agent. Ethanol can also be utilized in high-flow lesions by experienced operators.

Clinical presentation alone often identifies whether the lesion is a vascular tumor or vascular malformation. The addition of imaging provides crucial information and aids in follow-up, with a combination of imaging modalities proving to be most useful. Imaging helps determine the lesion size, location, extent, presence or absence of phleboliths, vascular anatomy, and proximity to adjacent vital structures [4]. Ultrasound and MRI are the most advantageous combination of modalities for these purposes in the pediatric population. CT and its associated ionizing radiation can generally be avoided.

Ultrasound is especially useful due to its portability, lack of ionizing radiation, no need for sedation in most cases, and image guidance if therapeutic intervention is pursued [5]. MRI has exceptional soft-tissue contrast, multiplanar capabilities, and excellent evaluation of the adjacent anatomic structures. Unfortunately, superficial lesions may be difficult to characterize on MRI, while ultrasound is excellent in evaluating superficial structures. The role of MRI for image-guided intervention is limited at the current time in most institutions. Conventional angiography remains the gold standard for diagnosis and in some instances, treatment of high-flow vascular lesions [6]. Angiography can also be useful to further evaluate atypical lesions and exclude high-flow components [4]. An in depth description of the imaging features of individual vascular anomalies is beyond the scope of this chapter.

Sclerotherapy Agents

Sclerotherapy is the use of physical, chemical, and biological properties of an agent to disrupt target tissue. Disrupted tissue becomes sclerosed or “hardened” with drastically changed or diminished functions. Sclerosing vascular malformations may limit recurrence, proliferation, or collateralization by permanently disrupting the endothelium of targeted vascular structures. The sclerosing effect extends beyond structures with an endothelium; the epithelial lining of true cysts, capillary beds, lymphatic structures, and bone cysts are examples of structures that have been targeted successfully with sclerotherapy agents [7].

Prior to injecting a sclerosant, a small volume of contrast should be injected under fluoroscopy to confirm that the needle or catheter is truly within the lesion. Attempts should then be made to aspirate the fluid within a vascular malformation. Only a small amount can typically be aspirated from a VM, but there should be at least a small amount of blood return. Fluid aspiration is more beneficial in LM. This

facilitates better contact with the agent and the wall of the lesion, in addition to providing an estimate of the internal fluid volume of the lesion to determine the approximate volume of sclerosant needed. After the agent has been injected and allowed to take effect for approximately 20 min, aspiration should again be attempted (aspiration may not be possible at this point, especially when using ethanol in VM). The more commonly used sclerotherapy agents will be discussed in detail.

Ethanol is one of the first sclerosants and continues to be highly effective in clinical practice [8]. The mechanism of action is a combination of cytotoxic damage induced by the denaturation and extraction of surface proteins, hypertonic dehydration of cells, and coagulation and thrombosis when blood products are present. All of these factors lead to fibrinoid necrosis [7, 9–11]. Ethanol is also one of the most potent agents with the lowest recurrence rate [4]. There is quite a pronounced inflammatory effect that results, so utilization near the airway or structures such as the orbit and tongue should be handled with caution to avoid potential complications. That is not to say that ethanol cannot be used in these locations, but significant swelling should be expected. Extravasation beyond the vascular malformation should be avoided to limit damage to adjacent structures. The total dose of ethanol should not exceed 1 ml/kg, and the volume administered should be given in small increments over time (0.1 ml/kg every 5 min) to avoid overwhelming the cardiovascular system [4]. Ethanol is an ideal agent for many VM. Given the total dose limitations, ethanol is not ideal for large lesions in smaller pediatric patients.

Sotradecol or sodium tetradecyl sulfate (STS), is an anionic surfactant that functions through the formation of organized thrombus, denudation of endothelium, inflammatory response, permanent luminal occlusion, and sclerosis [7]. The 3 % solution is one of the most commonly utilized concentrations for sclerotherapy of VM. Total dosing should generally be limited to 0.5–2 ml per session. STS can be utilized on its own, made into foam, or used in combination with other agents. Foam can be produced by mixing 1 ml 3 % STS with 4 ml of air across a 3-way adapter with 2 syringes. The foam is theorized to improve endothelial surface contact [12]. The use of foam also allows overall lower total doses of STS, that may reduce dose related complications. Ethanol can be used after STS has been injected and aspirated, with the theory that STS increases endothelial permeability to ethanol [13]. Some research has shown some sclerosants to cause elevated serum prothrombin time (PT) and D-dimer, with decreased platelets and fibrinogen in a dose–response fashion, particularly when ethanol and STS are used in combination [14].

Several studies have demonstrated the efficacy of doxycycline for LM of both the macrocystic and microcystic varieties [13, 15, 16]. The exact mechanism by which doxycycline functions as a sclerosant is unknown, but it is theorized that an inflammatory process results in fibrosis and involution of cysts [17]. It is associated with an inhibition of matrix metalloproteinases, which may be another cause of its effectiveness. Additionally, doxycycline suppresses the vascular endothelial growth factor induced angiogenesis and lymphangiogenesis [18]. The main risks associated with docycyline are local erythema, edema at the injection site, and pain [17]. Pain can be more significant than other agents and generally can last up to 3 h post

procedure. There may be long-term effects on tooth development in children, like dental staining. Concentrations for percutaneous injections range from 5 to 20 mg/ml with a maximum dose of 20 mg/kg [4]. In macrocystic and freely communicating microcystic LM, the maximum dose has anecdotally been exceeded, since the agent will be aspirated after 20 min.

Bleomycin is a cytotoxic antibiotic discovered in 1966, and is currently an established anticancer drug [19]. A specific sclerosing effect on vascular endothelium has been demonstrated, as well as destruction of lymphatic vessels and stromal fibrosis [20]. The exact mechanism of action in LM sclerotherapy is unknown, but inflammation is the proposed process [21]. The effectiveness of bleomycin for LM has been demonstrated in several studies [20, 22–24]. Bleomycin typically demonstrates less pronounced post procedural swelling than other agents, and may be beneficial in locations where significant mass effect should be avoided, such as the orbit and tongue. Complications include mild flu-like symptoms, erythema, edema, pigmentation of the skin, and transient hair loss [25]. Systemic complications such as lung toxicity have not been reported after intralesional treatment of LM. An initial dose of 15 IU is recommended, which is reconstituted with 2.5 ml of saline. Adding 2.5 ml of human serum albumin (25 %) allows the operator to agitate the solution to create foam. If 30 IU is desired, reconstitute with 5 ml saline and 5 ml albumin (25 %), and if 45 IU is desired, reconstitute with 7.5 ml saline and 7.5 ml albumin (25 %). A total lifetime dose should not exceed 400 IU, to avoid the theoretical complication of pulmonary fibrosis.

Conclusion

A multidisciplinary team approach is crucial to ensure that a proper diagnosis and classification of pediatric vascular anomalies is reached. This is essential to determine if treatment is necessary and to select the appropriate treatment type if indicated. Utilizing the ISSVA classification system should eliminate confusion and misleading nomenclature.

Disruption of target tissue via sclerotherapy is an effective and safe treatment modality for VM, LM, and some combined lesions when utilized in the correct setting. Treatment approaches including preoperative embolization and resection, surgical resection alone, laser ablation, and other modalities may better serve the patient, given the specific type of lesion, location, and adjacent anatomic structures. This point again serves to emphasize the importance of a multidisciplinary team approach.

Each individual sclerotherapy agent has specific benefits and drawbacks, and the ultimate agent selection tends to be based on operator experience and comfort level. Ethanol, doxycycline, and bleomycin were the typical agents used in this author's training and experience. Ethanol is an excellent, highly potent agent for treatment of VM if they are not too large to risk approaching the upper dose limit. Doxycycline and bleomycin are very safe and effective for treatment of LM, and bleomycin may be more beneficial in locations where significant post procedural swelling should be avoided.

Pearls

- ISSVA Classification for proper diagnosis and treatment planning
- LM and VM are the main lesions treated with sclerotherapy
- Combined multi-disciplinary team approach is crucial
- MRI and ultrasound are the primary modalities for diagnostic imaging
- Ultrasound combined with fluoroscopy for most image-guided interventions
- Ethanol for VM, except when too large
- Doxycycline for most LM
- Bleomycin for LM in areas where significant swelling should be avoided (Figs. 22.1, 22.2 and 22.3).

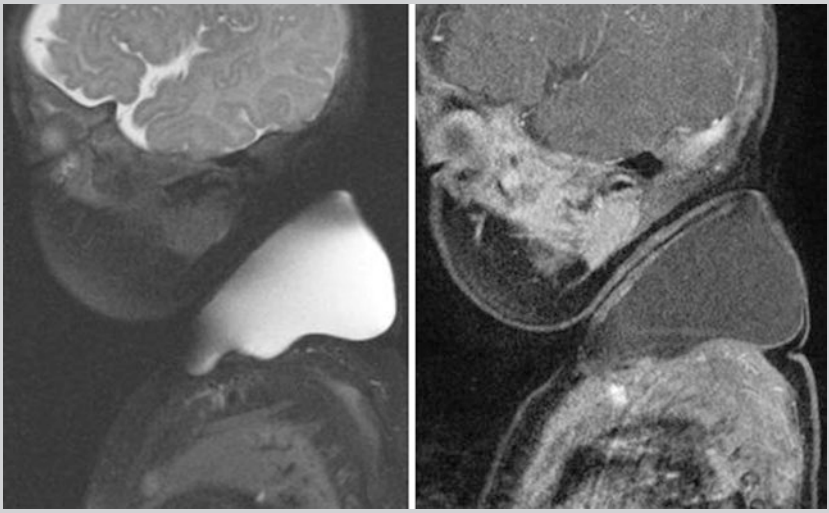

Fig. 22.1 Sagittal T2 and T1-post gadolinium weighted images show a T2 hyperintense, unilocular, peripherally enhancing left neck mass consistent with a macrocystic lymphatic malformation

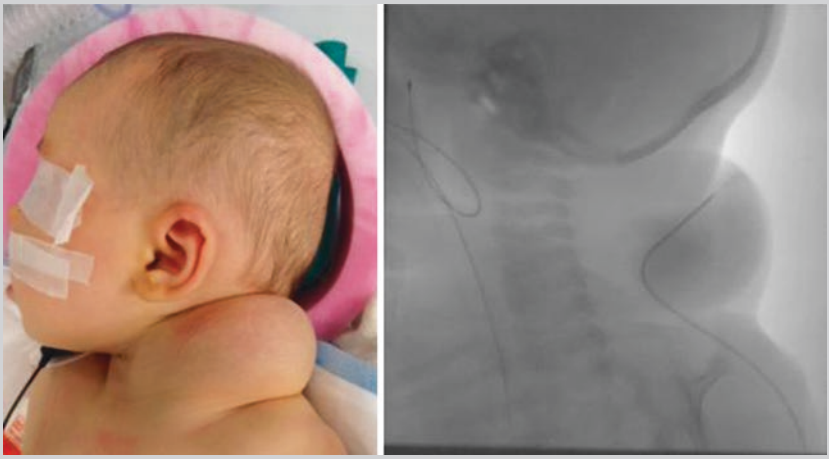

Fig. 22.2 Clinical photograph prior to sclerotherapy demonstrates the large left neck mass. Lateral/oblique fluoroscopic image after needle placement and injection of iodinated contrast to confirm intralesional access

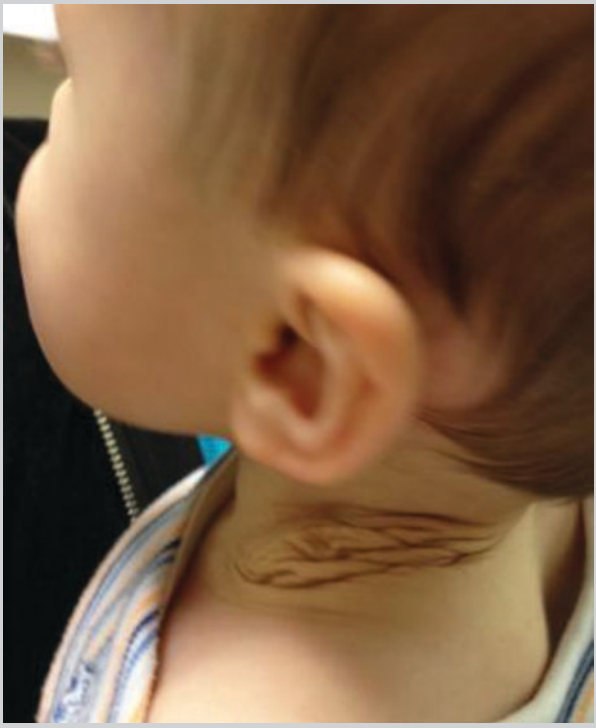

Fig. 22.3 Clinical photograph 2 weeks after the procedure shows no visible mass. The floppy skin overlying the left neck continues to involute. This baby was treated with a single sclerotherapy session with doxycycline at 3 months of age. Clinical and ultrasonographic follow-up at 1 year showed no recurrence. Images courtesy of Monica Pearl M.D.

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Index

A. Agrawal, G. Britz (eds.), *Pediatric Vascular Neurosurgery*,
DOI 10.1007/978-3-319-43636-4