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Guest Editorial

Advances in neurointervention for pediatric neurovascular disease

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This issue of the Journal of Pediatric Neuroradiology is dedicated to pediatric neurovascular conditions and their interventional management. With some exceptions, this category of pediatric disease is constituted by rare and exotic conditions, which remain obscure and poorly understood entities. Our understanding of these conditions, their pathogenesis, and natural history has improved in recent decades thanks to advances in neuroimaging technologies, epidemiological studies and a steady growth of the literature. Our ever-increasing fund of knowledge in this field is founded on the meticulous observations and records of early pioneers, and their contemporaries, some of who have contributed to this issue. Topics covered in this issue include childhood arterial ischemic stroke, cerebral aneurysms and neurovascular arteriovenous (AV) shunt lesions.

Watkins and Heran review the role of diagnostic cerebral angiography in modern clinical neuropediatric practice. They remind us that even in the era of advanced computed tomography and magnetic resonance imaging (MRI), catheter based digital subtraction angiography (DSA) remains an irreplaceable diagnostic tool for the evaluation of numerous pediatric neurovascular conditions including vasculitis, cerebral aneurysms, and vascular malformations of the craniospinal axis. The essential role of catheter based DSA in the diagnostic evaluation of all children with hemorrhagic stroke, and many children with ischemic stroke is emphasized. The authors highlight major technical differences in peri-procedural patient care and catheter technique that are relevant to patients less than 50 kg. Watkins and Heran affirm the noted safety of neuroangiography in children, when performed by experienced specialists. The higher complication rate observed in patients less than 10 kg is addressed, and procedural modifications that have been adapted for this challenging group of patients are discussed. In their review, Watkins and Heran also discuss the continued importance of the Wada test in modern neuropediatric practice. Despite major advances, a number of challenges encountered in children with epilepsy may render functional MRI inadequate for pre-operative lateralization of language and memory. The authors address specific challenges encountered in the pediatric population undergoing Wada testing, and describe techniques they have adapted to address these challenges.

Shakur and Lee give a concise update on pial AV malformations (AVMs) of the brain presenting in childhood.

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As the most common cause of hemorrhagic stroke in the pediatric population, cerebral AVMs are familiar problems to most neuropediatric specialists. Shakur and Lee review the common presentations of pediatric pial AVMs. Congestive cardiac failure, and macrocephaly are reported as unique manifestations of cerebral AVMs in neonates. Cerebral hemorrhage, though uncommon in neonates, is the most common presentation of older children.

Complex venous drainage patterns are more commonly expressed in pediatric brain AVMs. Cerebral AVMs associated with familial patterns of expression also present more commonly during childhood. Consequently, unusual clinical phenotypes and angioarchitectural characteristics associated with these conditions are also seen more commonly in children.

Shakur and Lee reinforce the traditional concept that definitive treatment with the intent to cure should be pursued for most un-ruptured cerebral AVMs found in children, due to the high cumulative risk of disease related morbidity and mortality. Nonetheless, despite significant advances in multimodal AVM therapy, children with unusually large and/or complex lesions intimately involving eloquent brain structures remain exceptions to this paradigm. Functional outcomes after cerebral AVM surgery are better in children than in adults regardless of clinical presentation or angioarchitecture. This has been attributed to some degree to the greater potential for recovery after neurological injury. Transarterial embolization remains an important preoperative adjunct to microsurgical excision of large and complex cerebral AVMs. Advances in interventional neuroradiology have improved our ability to achieve angiographic cure by embolization alone, but procedure related risks are not insignificant when an aggressive approach is taken to embolotherapy. Moreover, the rate of clinically significant late recurrences after a presumed curative embolization in the pediatric population remains to be seen. The pediatric brain AVM literature indicates that the highest rate of long-term angiographic cure is achieved after microsurgical excision. Even in patients who undergo apparently curative microsurgical excision, careful angiographic follow-up is needed to exclude recrudescence of dormant AVM nidus years later. The immature and developing cerebral vasculature seems to be particularly prone to such recurrence patterns. The importance of careful long-term follow up in this group must be recognized. Shakur and Lee emphasize the advantages of staging pediatric brain AVM embolizations, including a reduced risk of normal perfusion pressure break through hemorrhages, contrast and fluid related complications and radiation related complications.

Stereotactic radiosurgery has become an important treatment option for pediatric cerebral AVMs that are not readily amenable to curative treatment with endovascular and microsurgical approaches. Although many pediatric specialists continue to have concern over the long-term risks of radiation-induced malignancies and late AVM recurrences in children under the age of 12 yr, stereotactic radiosurgery is a reasonable option for small pediatric brain AVMs in deep or eloquent brain regions. Pediatric clinical outcomes seem to correlate with the radiosurgery-based AVM score. There is general consensus that DSA is necessary for confirmation of cure, and that long-term DSA follow up is needed to exclude late recurrences.

Gross et al. provide an excellent review of pediatric dural AV shunt lesions, differentiating the major angioarchitectural subtypes according to Lasjaunias. They remind us of the mysterious nature of dural sinus malformations, (DSMs) which seem to represent a primary overgrowth of the venous sinuses and secondary arterialization of the dysplastic vessels. As the majority of presenting patients are infants less than 6 mo of age, macrocrania, developmental delay and less commonly congestive cardiac failure are the primary presentations. Jugular bulb DSMs are noted to be an exception, usually presenting in older children when a bruit is detected by a caregiver. Larger case series indicate that overall, slightly less than half of DSM patients have unfavorable progression of their condition due to worsening cerebral venous hypertension and associated neurological injury. Features that correlate with unfavorable progression of DSM include torcular involvement, failure of cavernous capture and retrograde flow in the straight sinus, sagittal sinus or pial veins.

Gross et al. affirm that jugular bulb DSMs are distinguished by a relatively benign course, and that conservative management is not unreasonable when unfavorable features are absent. Unfortunately, mortality seems to be very high (>90%) among DSM patients with unfavorable progression. Embolization of the mural shunt seems to be associated with better outcomes, however the role of selection bias is unclear from the literature. The authors emphasize that therapeutic closure of mural AV shunts in DSM patients may lead to thrombosis of dysplastic venous sinuses, and secondary thrombosis of functional venous outflow pathways. The outcome of this process will strongly depend on the existing venous collateral reserve. As the authors have stated, the first management priority

is to eliminate retrograde flow in pial veins and the midline venous sinuses by staged reduction of mural AV shunts. The role of staged embolization with adjunctive anticoagulation is nicely discussed. The greatest challenge involved with interventional management of such cases is achieving a controlled thrombosis of the dysplastic sinuses without interrupting vital venous drainage pathways. It is somewhat counterintuitive that spontaneous lesional thrombosis is a predictor of good outcome among patients who are not treated. The authors share their experience with two DSM patients, emphasizing the important role of embolotherapy, both as a curative treatment and for palliative management.

Gross et al. review the bimodal progression of infantile dural AV shunts and emphasize the important role of embolotherapy, both as a means of definitive cure and for palliation. In comparison with DSMs, these lesions have similar clinical presentations, but are characterized by an absence of dysplastic sinus overgrowth, and a uniquely marked degree of multifocality. Gross et al. discuss the unique aspects of adult type dural AV shunts presenting in the pediatric age group. As in the adult population, the clinical behavior of these lesions is dictated by their venous drainage pattern. Treatment is indicated when the patient is symptomatic, or when leptomeningeal venous drainage is present. In contrast to the former two types of dural AV shunt lesions, a high rate of endovascular cure is possible using modern embolotherapy techniques, and embolization has become the first line treatment. Microneurosurgery and radiosurgery are complementary approaches that may play a role in the management of complex lesions, however experience with radiosurgery of these lesions in the pediatric population is not well known. The authors report their excellent results in five patients who were angiographically cured of their disease, primarily using endovascular techniques.

Keenan and Hetts discuss recent advances in the diagnosis and management of non-Galenic pial arteriovenous fistulae, (NGAVF) highlight emerging innovations and propose directions for future research. They begin by defining and disambiguating a series of terms used to describe these lesions, and then give a detailed review of the modern literature, picking up where Hoh et al. left off in 1999. Their review affirms that NGAVF are primarily a disease expressed in the pediatric population. Keenan and Hetts show that NGAVF manifest a range of age related phenotypes: newborns with congestive cardiac failure, infants with seizures or macrocephaly, and older children with seizures. As with other types of neurovascular lesions, the adult phenotype is distinct. Neurodevelopmental deficits in the group have not been described, so little is known. Hemorrhagic presentation, which is thought to result from a cumulative damage process, was uncommon in neonates and infants. The authors confirm that these lesions have a poor natural history and that treatment is indicated unless severe irreversible brain damage is already present.

The authors describe a trend toward endovascular treatment, which has emerged rapidly over the last decade. Keenan and Hetts give an excellent account of the evolution of modern treatment techniques, and discuss the preferred modern approaches in detail. The authors give a balanced discussion of the pros and cons of detachable coils versus liquid embolic agents. The recent use of balloon catheters for flow control during embolization with liquid embolics has enabled less difficult embolization of high flow fistulae.

The authors report that neonates and infants are more likely to have complex multihole fistulae, incomplete endovascular occlusion and poor clinical outcomes both in their own experience and in the literature. Keenan and Hetts inform us that the data from various series cannot be aggregated due to the absence of reporting standards, a methodological flaw which has thwarted clinical research in many fields. In order to facilitate future research, the authors propose several reporting standards, some of which can be applied to the endovascular treatment of any pediatric neurovascular condition, in particular the Pediatric Stroke Outcome Measure. The authors report that treatment related cerebral hemorrhages due to "normal perfusion pressure breakthrough" in patients with NGAVF are not as common as in the past. They suggest that many cases of post-embolization venous sinus thrombosis were incorrectly diagnosed as normal perfusion pressure breakthrough in the past, and that adjunctive post-operative anticoagulation has reduced the incidence of this phenomenon. The need for long-term angiographic (DSA and/or magnetic resonance angiography [MRA]) follow up, despite angiographic cure is recommended given reports of de novo AV shunt lesions, in particular dural AV shunts in the drainage pathway of the lesion.

Also in this issue of the journal, we review advances in the diagnosis and management of vein of Galen malformations (VGAM). The spectrum of age related clinical phenotypes expressed by the VGAM lesion are discussed with an emphasis on anatomical, neuroradiologic and pathophysiologic

characteristics. Different patterns of clinical expression associated with the VGAM lesion in fetuses, neonates and infants are contrasted, highlighting modern approaches to diagnostic evaluation and management at each of these stages. The central role of endovascular techniques in the definitive management of VGAM lesions is presented, and modern concepts of surgical and radiosurgical management are discussed. The advantages and disadvantages of specific neurointerventional techniques are reviewed, emphasizing the importance of patient oriented treatment strategies directed at optimizing cardiovascular and neurodevelopmental outcomes.

In our review, we report that less than half of all VGAM lesions are diagnosed prenatally, and that antenatal diagnosis is most commonly made after the 34th wk of gestation. We found recent studies showing that more than 70% of VGAM lesions diagnosed prenatally are associated with a lethal outcome. These studies show that predictors of poor prognosis on prenatal ultrasound imaging include cardiomegally and cerebral ventriculomegally. Our review discusses the role of fetal MRI, modern concepts of obstetric management and novel approaches to "pre-natal" digitialization of neonates.

Our review of the VGAM literature confirms that recent advances in interventional technology and technique have led to improved therapeutic success. Nonetheless, modern procedure related morbidity and mortality is not insignificant, especially in neonates. Even at the most experienced centers, the majority of VGAM patients presenting as neonates with congestive cardiac failure still have poor neurological outcomes after endovascular treatment. These results likely reflect the early and irreversible cerebral damage that occurs in the setting of a neonatal presentation. In contrast, the majority of VGAM lesions presenting in older infants with macrocephaly have good neurological outcomes after endovascular therapy, provided that definitive therapy is not excessively delayed.

In neonates presenting with VGAM, management strategies are directed at controlling cardiopulmonary dysfunction. Historically, endovascular therapy in this medically fragile population has been associated with significant procedure related morbidity and mortality. Such experience has shaped traditional approaches to VGAM management that focus on first line medical therapy until the patient is better able to tolerate endovascular surgery at 4 to 6 mo of age. In many patients this treatment paradigm may lead to irreversible and life threatening pulmonary hypertension. More recent experience suggests that earlier intervention may enable better outcomes in properly selected cases.

In older infants, management issues concern cerebral hydrovenous dysfunction. Prompt definitive treatment in this group is necessary to avoid the poor neurodevelopmental outcomes that are observed in late presenting children who escape early diagnosis.

In this issue of the journal, Moftakhar and Hetts give an excellent overview of pediatric spinal vascular malformations and provide an overarching contextual framework for the complex and varied spectrum of conditions that constitute this group of lesions. Using traditional classification schemes that are based on anatomical, topographical and hemodynamic characteristics, the authors highlight additional genetic and pathophysiologic features that contribute to specific pediatric clinical phenotypes, and contrast these with the more common clinical patterns seen in the adult population. In particular, the specific role of heritable and non-heritable mutations as an underlying cause of spinal vascular malformations in the pediatric population is emphasized. The authors report that genetic defects are responsible for as many as 2/3rd of all pediatric spinal vascular malformations. The authors remind us of the strong association between hereditary hemorrhagic telangectasia and large single-hole AV macrofistulae of the spinal cord. The authors include the parachordal AV fistulae in their review because of their close anatomical relationship to the spinal vasculature, and potential for the development of spinal vascular complications. The authors detail their approach to the diagnostic evaluation of pediatric spinal vascular lesions and describe the essential role of DSA, which remains the cornerstone of clinical diagnosis even in the era of advanced cross-sectional imaging.

Moftakhar and Hetts outline modern lesion specific therapeutic concepts. Pediatric endovascular techniques are emphasized, and anatomical variants commonly encountered in young children are discussed in relation to neuroangiographic decision-making. The roles of curative and palliative interventions are differentiated, emphasizing the importance of staged interventions in the management of complex lesions. Treatment outcomes in children are contrasted with those in the adult population, noting a greater potential for neurological recovery in young children, particularly neonates and infants. The authors remind us that the potential for neurological recovery can be lost if definitive treatment is excessively delayed, regardless of the patient's age.

In this issue of the Journal, Akgoz et al. highlight the lack of therapeutic guidelines for the management of pediatric arterial ischemic stroke in general. The authors reference the ongoing thrombolysis in pediatric stroke trial which will play an important role in the establishment of guidelines for intravenous thrombolytic therapy (IVT) in pediatric stroke. The critical role of pediatric stroke teams with specialized expertise in the evaluation and management of children with stroke, and the importance of adopting a cautious approach to rTPA dosing until TIPS trial data becomes available is emphasized.

Akgoz et al. articulate the experimental nature of endovascular ischemic stroke therapies in the pediatric population, and express the importance of a conservative approach to this new frontier in medicine. The authors correctly assert that the proper role of endovascular therapy in the management of arterial ischemic stroke in children is unknown. As with all surgical treatments, the risk of procedural morbidity must not exceed the probability of equivalent morbidity from disease natural history or alternative medical treatments such as IVT. The recently revealed results of large randomized clinical trials in the adult population have left us with uncertainty regarding the role of intra-arterial therapy in early presenting patients who are eligible for IVT [1–3]. The natural history of arterial ischemic stroke in children is often characterized by a more favorable course and by better clinical outcomes relative to adults. Consequently, the bar for endovascular stroke therapies must be set somewhat higher in children than in adults. The authors have eloquently summarized the unique aspects of pediatric stroke pathogenesis, developmental neurovascular anatomy and age-related changes in fibrinolytic physiology. They have used this knowledge to build a rational approach to stroke intervention in the pediatric population. Akgoz et al. also point out that only a small minority of pediatric stroke patients are likely to be eligible for IVT, and emphasize the great potential for neurointerventional therapies in this population. As the authors report, there is no clinical trial data addressing neurointerventional therapies for ischemic stroke in the pediatric population. The importance of arteriopathy is highlighted, especially in early school age children. It is noted that such children are at significant risk for recurrent stroke and that dedicated vascular imaging studies are critical in the initial management of such cases.

The review by Akgoz et al. shows that even with the beneficence of reporting bias in case reports and series, complications occur frequently in children undergoing endovascular intervention for arterial ischemic stroke. In particular, there is a relatively high rate of intra-cerebral hemorrhage in children who are administered intra-arterial thrombolytic drugs. Unfortunately, meaningful conclusions are difficult to derive from such reports due to variability in technique, and a wide range of unconventional temporal windows applied to treatment. Nonetheless, the suggestion is that pediatric endovascular stroke therapies should favor mechanical techniques, and emphasize decreased use of intra-arterial thrombolytic drugs. Consideration must be given however to the higher incidence of cerebral arteriopathies in the pediatric stroke population. The safety of some mechanical interventions (i.e. balloon angioplasty and stentrievers) in "arteriopathic" intracranial vessels, dissected arteries in particular, is unknown and significant vascular injuries could be anticipated.

This issue of the journal includes a detailed review of intracranial arterial aneurysms (IAAs) in children and young adults. The review categorizes pediatric IAA according to mechanisms of pathogenesis, and presents modern approaches to diagnosis and management in each category. The major categories of pediatric IAA considered in this review include idiopathic, traumatic, flow-related, arteriopathic, infectious, non-infectious inflammatory, oncotic and familial. The categories are characterized on the basis of published case series and a large original multi-institutional clinical database contributed by three regional tertiary referral hospitals. The data indicate that the majority of IAAs in the pediatric population are idiopathic, but that trauma, abnormal hemodynamic stresses, infection and arteriopathy represent important risk factors for cerebral aneurysms in children. The most common pediatric aneurysmal arteriopathies are discussed in our review, and recent advances in their medical management are highlighted.

Modern approaches to the diagnostic evaluation of children suspected of having IAAs are outlined. The authors favor computed tomography angiography as an initial study in children presenting with hemorrhage, but report that catheter based DSA remains the diagnostic gold standard. MRA is the preferred screening study in pediatric populations at significant risk of developing IAA, i.e. children with previously treated IAA and children with aneurysmal arteriopathies. Although screening MRA has been advocated for adult first-degree relatives of patients with familial intracranial aneurysms, screening of children from

familial intracranial aneurysm families is not currently recommended, especially in the pre-teen years.

Management strategies for pediatric IAAs are reviewed, emphasizing age related differences in cerebrovascular pathophysiology that influence treatment selection. Modality specific results in children are discussed and compared. The pediatric IAA literature suggests that microsurgery is generally associated with more major morbidity than endovascular treatment. Nonetheless, there continues to be debate over the best approach to pediatric IAA treatment, with experienced surgical centers arguing strongly in favor of microsurgery and experienced endovascular centers promoting interventional techniques. Proponents of microsurgery point out that aneurysm clip ligation is a more durable treatment than selective endovascular aneurysm occlusion, and that long-term durability is critical in the pediatric population. Interestingly, pediatric patients who undergo microsurgical treatment of an IAA continue to be at significant risk of aneurysm related morbidity and mortality 1 to 30 yr after surgery. Controversies aside, there seems to be a general consensus that children with IAAs often require a multidisciplinary management strategy and that the best outcomes are achieved in centers that offer a comprehensive range of expertise encompassing both endovascular intervention and microsurgery. The review in this issue of the journal points out that robust collateral networks in children enable well-tolerated parent artery sacrifice in most cases, but that the increased vulnerability to de novo aneurysm formation in all children with IAAs favors reconstructive therapeutic approaches. Recent experience with newer techniques in children, including liquid embolic agents and flow diverting stents is discussed.

The authors review pathology specific treatment considerations that play an important role in the management of pediatric IAAs. Modern concepts of infectious and traumatic aneurysms as pseudoaneurysms requiring parent artery sacrifice are discussed. While many un-ruptured infectious IAAs in children can be successfully treated with antibiotics alone, recent literature suggests that severely immunosuppressed children, and children requiring anticoagulant therapy should undergo early definitive aneurysm occlusion. The authors introduce the concept of dissecting aneurysms as a structural variant that clinically behaves like a pseudoaneurysm. As such, reconstructive techniques are prone to failure and parent artery sacrifice or flow reversal may be favored when feasible. The therapeutic challenges associated with giant aneurysms, which account for at least 10% of pediatric IAAs, are discussed. While parent artery sacrifice and flow reversal remain the primary approaches to fusiform IAAs in children, the authors note that flow-diverting stents have recently shown promising results in well selected cases. The review of pediatric IAAs in this issue of the journal highlights the problem of congenital aneurysmal arteriopathies. The authors emphasize the unusual propensity of this population to experience rapid de novo aneurysm formation when therapeutic parent artery sacrifice is performed and discuss emerging treatment strategies for this group of children. Some centers have adopted a watchful waiting approach to children with aneurysmal arteriopathies, and only perform focused aneurysm therapy using reconstructive endovascular approaches if there is evidence of aneurysmal instability on sequential imaging studies. While endovascular intervention in patients with some arteriopathies such as Ehlers Danlos type IV, is associated with very high morbidity and mortality, recent experience has shown that endovascular intervention can be performed with a high margin of safety in patients with other types of arteriopathies such as Loeys Dietz syndrome. Current concepts guiding the management of flow related cerebral arterial aneurysms in children with cerebral AVMs are discussed. The best approach is strongly dependent on aneurysm location. When aneurysms are located on distal vessels beyond the circle of Willis, there is a high probability of regression when at least 50% of the AVM nidus is obliterated. The literature suggests that targeted embolization of nidal compartments supplied by the aneurysm bearing artery is often sufficient to promote aneurysm regression in such cases. In contrast, aneurysms located within or proximal to the circle of Willis do not usually regress, even if curative AVM treatment is performed.

Although the traditional view is that post-hemorrhagic cerebral vasospasm is not a significant clinical problem in children with ruptured IAAs, there is sufficient evidence that even very young children can suffer significant vasospasm related morbidity. Consequently, it is prudent to aggressively monitor pediatric patients with aneurysmal subarachnoid hemorrhage in an intensive care unit setting, orally administer prophylactic calcium channel blockers, and obtain daily transcranial Doppler studies. In children with vasospasm, induced hypertension is proposed as an initial therapeutic approach. Initial experience suggests that intra-arterial calcium channel blocker infusions are safe and technically efficacious in the pediatric population. The role

of cerebral balloon angioplasty in the pediatric population has not been defined.

All children with IAA have a significantly higher risk of aneurysm recurrence and de novo aneurysm formation relative to adults with IAA. Specific risk factors for de novo aneurysms in children with IAA include fusiform index aneurysm, multiple aneurysms at presentation and pro-aneurysmal vascular risk factors such as arteriopathy or family history of aneurysms. Recurrent or de novo lesions can emerge within 6 mo, or may take longer than 10 yr to develop. Consequently, close long-term imaging follow up is recommended for all children with IAA. The authors discuss guidelines for imaging follow up for children with IAAs. The importance of early follow up (3–6 mo) in particular high-risk sub-groups, and ultra-early follow up (4 wk) in children with infectious IAAs that are being managed with antibiotics is emphasized.

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