

# Pediatric Cerebral Vascular Malformations : Current and Future Perspectives

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Intracranial vascular malformations typically encountered by pediatric neurosurgeons include arteriovenous malformations, vein of Galen malformations and cavernous malformations. While these remain amongst some of the most challenging lesions faced by patients and caregivers, the past decade has produced marked advances in the understanding of the pathophysiology of these conditions, with concomitant innovations in treatment. This article will highlight present and future perspectives relevant to these diseases, with a focus on an emerging approach utilizing disease-specific mutations to develop a novel taxonomy for these conditions.

**Key Words :** Arteriovenous malformations · Stroke · Pediatrics.

## INTRODUCTION

Historically, the treatment of pediatric cerebrovascular disease, particularly structural lesions such as arteriovenous malformations (AVMs), vein of Galen malformations (VOGMs) and cavernous malformations (CMs), was largely predicated on surgical techniques that had remained nearly unchanged for decades. Although cures were possible, many outcomes were devastating, such as attempts to operate on VOGMs. However, the advent of several disparate technologies within a short window of time has led to a revolution in the management of these conditions. Advances in neuroimaging, endovascular access, and molecular biology – among others - have been critical to improving the outcomes of affected patients.

The pioneering work in cerebrovascular disease has inspired

progress in other fields of medicine, but the converse is also true. One example is the complete restructuring of the classification of brain tumors from histology to mutational profiling. In neuro-oncology the use of molecular genetic markers has not only improved diagnostic and prognostic accuracy, but it has created opportunities for the development of targeted therapeutics. The profound success of this novel classification methodology, coupled with a surge of reports defining mutations in AVM, VOGM, and CM, has led to attempts to recapitulate this taxonomy schema in cerebrovascular neurosurgery<sup>25)</sup>. In combination, the widespread array of advances in the treatment of pediatric cerebrovascular disease has fundamentally changed the field and this manuscript will highlight the impact of these innovations for AVM, VOGM, and CM.

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## ADVANCES IN INTERVENTIONAL RADIOLOGY

The advent of the modern era of interventional radiology has ushered in a sea-change in the ability to visualize and treat AVMs and VOGMs. High-quality three-dimensional angiography can now be performed safely in the pediatric population, employing catheters and devices that are small enough for superselective access to individual pedicles in children<sup>30,50</sup>. The creation of detachable-tip and steerable microcatheters have been seminal to this progress, enabling interventional radiologists to reach crucial regions of vascular malformations for diagnostic and therapeutic access<sup>13,27,32</sup>. Complementing this newfound access is the ability to deliver agents capable of shutting down blood supply to the AVM/VOGM. These embolic agents include detachable metal coils (used commonly in the setting of short pedicle catheterization) and liquid embolic agents, n-butyl cyanoacrylate and ethylene-vinyl alcohol (EVOH or EVAL), with the well-known Onyx (EVOH dissolved in dimethyl sulfoxide), with tantalum added as a marker to make it radio-opaque) commonly used in North America, Europe, and Asia<sup>14,39,60,61</sup>.

Endovascular approaches can assist with the treatment of AVMs through better visualization for operative or radiation planning, perioperative reduction of high-flow pedicles to make surgery safer or – in some cases, such as VOGMs – complete cure through embolization alone<sup>1,55,62</sup>. Innovation continues in this field, including transvenous access and embolization, flow modulation (in which cardiac output can be altered pharmacologically or via cardiac pacing to attempt safer delivery of embolic agents) and the use of single or multiple intravascular balloons to regulate flow during procedures<sup>15,18,24,28,38,40</sup>. These advances also come with risk, including injury to unaffected vessels during the procedure, off-target embolization, radiation exposure (especially important in smaller children/infants) and the risk of unexpected hemorrhage resulting from re-routing of blood flow post-embolization<sup>4</sup>.

Stand-alone embolization as definitive treatment of high-flow vascular lesions has increasingly been reported. While this approach is often successful for VOGM (typically requiring multiple rounds of embolization), or single-hole fistulae, it is more controversial with nidal AVMs<sup>4,41,47,48</sup>. Initial data suggests that attempts to cure complex nidal AVMs with embolization alone may actually worsen the bleeding risk and outcomes rela-

tive to natural history – and, as such, it is increasingly discouraged in many high-volume centers<sup>20,22,48</sup>.

One of the most radical advances in the treatment of VOGM has been the recent report of percutaneous transuterine fetal cerebral embolization<sup>36,37,51</sup>. *In utero*, the fetus is largely protected from deleterious effects of VOGM shunting due to the presence of maternal blood supply, and the loss of this support at birth with the division of the umbilical cord results in immediate adverse effects to the newborn child. Treatment of the VOGM prior to birth obviates this dangerous transition and – in an initial case – has successfully achieved the goal of establishing normal cardiac and cerebral physiology<sup>37</sup>. While this technique will require further validation and refinement, it serves as an encouraging proof-of-principle to stimulate continued innovation in the field.

## ADVANCES IN SURGERY

### AVMs

One of the most important advances in the surgical treatment of pediatric cerebrovascular lesions has not been technical, but rather has consisted of clarification of operative indications based on data-driven guidelines. For AVMs, the controversial ARUBA (A Randomised trial of Unruptured Brain Arteriovenous malformations) trial had previously discouraged treatment of asymptomatic lesions, but recent analysis of the pediatric patients in this study actually strongly supports operative intervention – markedly reversing the initial consensus<sup>20,22,34,48</sup>. Additional studies, citing the expected long lifespan of children, the plasticity of pediatric neural pathways in recovering from treatment side effects and the improvement in surgical outcomes, have increasingly supported surgical treatment of pediatric AVMs in an expanding number of clinical scenarios, including many asymptomatic lesions (of note, radiosurgery, including Gamma Knife, remains an additional, well-documented treatment option for many AVMs)<sup>10,20,22,48</sup>.

Good surgical outcomes of pediatric AVMs are predicated on complete resection of the lesion and careful assessment of operative risk using scoring algorithms<sup>23,43,59</sup>. Recent data has increasingly demonstrated the utility of high-quality intraoperative angiography to confirm complete resection prior to concluding the case, given the risk of recurrence in chil-

dren<sup>3,10,21</sup>). As detailed in the prior section, the evolution of interventional radiology-related treatments has served as a powerful adjunct to surgical management of AVMs, with the best outcomes reported when treatment is provided at high-volume centers with multidisciplinary teams<sup>10,45,46</sup>.

## VOGMs

While VOGM remains a condition treated primarily by interventional radiologists, there have been recent reports that suggest that surgeons may be able to assist in the management of VOGM through the provision of improved endovascular access and – in select cases – treatment of refractory hydrocephalus. The high flow of VOGMs can occasionally result in compensatory jugular bulb stenosis, limiting endovascular access to the venous side of VOGMs. In these cases, direct access to the cerebral venous system can be provided by open surgical exposure of the transverse sinus<sup>44</sup>. An additional role for pediatric neurosurgeons in the management of VOGM centers on the treatment of refractory hydrocephalus secondary to occlusion of the cerebral aqueduct from the malformation. In these cases of obstructive hydrocephalus, it may be possible to perform an endoscopic third ventriculocisternostomy for treatment, with awareness of the risk of bleeding from perforators located subjacent to the floor of the third ventricle<sup>49</sup>.

## CMs

Operative indications for CMs are also undergoing reassessment, with generally broader recommendations encouraging surgical resection, including asymptomatic lesions in selected cases<sup>10,19</sup>. Growing recognition of the impact of chronic seizures on the developing brain has led to studies supporting the benefit of early resection of epilepsy-related CMs rather than medical management alone<sup>26,54,66</sup>. In addition to open surgical resection of CMs, there has also been a growing literature on the use of minimally invasive approaches, such as laser interstitial thermal therapy to access small, deep CMs or to assist with the treatment of adjacent epileptogenic tissue in controlling seizures<sup>5,35,64</sup>.

## Operative techniques applicable to multiple pathologies

In addition to disease-specific techniques, several technical advances in pediatric neurosurgery have applicability to

AVMs, VOGMs and CMs. The use of novel imaging and 3D printing for pre- and peri-procedural visualization and simulation have reduced procedure times and improved outcomes<sup>17,63</sup>. Intraoperative tools to enhance visualization, such as the exoscope and high-fidelity ultrasound, have added to the armamentarium available to surgeons managing these conditions<sup>31,33</sup>. Lastly, the growing field of augmented and virtual reality offers surgeons and interventional radiologists a new way of interacting with imaging to better plan and perform treatments which is particularly germane to the complex three-dimensional anatomy of cerebrovascular lesions<sup>9,29</sup>.

## ADVANCES IN MOLECULAR BIOLOGY

While neuro-oncology has led the way in translating benchtop discoveries in molecular biology into clinical practice with genetic classification of tumors and development of targeted therapeutics, cerebrovascular neurosurgery is now positioned as the next frontier most likely to reap the benefits of this approach<sup>8,11,16</sup>. Historically, neurosurgeons, neurologists and interventional radiologists have acted independently, characterizing diseases according to their own observations and practices. However, with the recent growth of multidisciplinary care teams in neurosurgery – arguably most common in pediatric cerebrovascular disease – the identification of shared phenotypes and radiographic features has accelerated the pace of translational research. In particular, cohorts of patients with structural vascular lesions – AVM, VOGM, and CM – have been subjected to intense study, providing insight about the genetic foundations underlying these conditions and laying the groundwork for a novel taxonomy to better illuminate the lineage and development of these malformations<sup>25</sup>.

It is becoming increasingly apparent that many AVMs and VOGMs are vein-based lesions, arising in association with mutations affecting one of two canonical pathways – ephrins (*EPHB4*) and *HHT* (*HHT1*, also called *ENG*; and *HHT2*, also called *ACVRL1*) – that direct endothelial differentiation in development<sup>6,16,25,67,68</sup>. In contrast, while CMs also have dysfunctional endothelial cells, there is a distinct family of genes related to capillary formation that drive their growth, including the related *CCM* genes (*CCM1*, *CCM2*, and *CCM3*), with only limited overlap with the ephrin pathway<sup>12,25,53</sup>. Categoriz-

ing the malformations within these separate pathways and connecting specific mutations with sporadic and familial forms of these diseases has helped to improve diagnostic and prognostic capabilities of clinicians.

Familial forms of inherited AVMs – as are found in hereditary hemorrhagic telangiectasia (HHT) – often have germline mutations in *ENG/HHT1* or *ACVRL1/HHT2*<sup>8,11,25,65</sup>. However, many of the sporadic lesions – the most common in pediatric neurosurgical practice – arise from somatic mutations in the ephrin pathway, usually *KRAS* or *BRAF*; downstream drivers of cell invasion and proliferation<sup>25</sup>. Given that ephrin is the cell surface-based receptor upstream of a pathway that subsequently controls the downstream intracellular molecules *RASA1*, *KRAS*, *BRAF*, and *RAS*, there is now basis for a biological connection between ephrin and *RAS* mutations in VOGM, *RASA1* mutations in AVM and AV fistulas and the aforementioned *KRAS* and *BRAF* mutated nidus AVMs – demonstrating how mutations in interrelated molecules in a specific pathway can manifest similar phenotypes<sup>7,16,25,67,68</sup>.

Similar to AVM, CM has both familial and sporadic forms. The *CCM* genes – *CCM1*, *CCM2*, and *CCM3* – can combine as a trimeric complex and can also work independently to affect the cellular pathways driven by *MEKK3* and *ROCK* that are critical to cell-cell adhesion and proliferation<sup>12,25,53</sup>. Given the interaction between these molecules, there are similarities in presentation across mutational profiles, but the unique roles of each gene product helps to explain the clinical heterogeneity of disease seen by physicians and patients. For example, *CCM3* has outsized impact on the regulation of *MEKK3* through a pathway independent of the *CCM* trimeric complex. In patients with *CCM3* mutations, this manifests clinically as more severe disease, with greater lesional burden and hemorrhages. Consequently, awareness of a *CCM3* mutation in a patient provides the clinician with important and potentially actionable prognostic information, while also offering a specific molecular target for developing therapeutics. This clinical scenario presents an excellent example of how genetic characterization in a formal taxonomy can inform clinical practice.

In addition to the value of mutational profiles helping patients and families better understanding the course of disease and the potential role of screening other family members, knowing the underlying molecular driver of disease may help with creation of targeted drug therapies – such as the current

trials with mammalian target of rapamycin (*mTOR*) and *KRAS* inhibitors for AVM, and *ROCK* inhibitors for CCM<sup>12,25,42,58</sup>. The pharmacologic treatment of vascular lesions – including inhibition of growth, better control of existing malformations and possible prevention of recurrence after therapy – are exciting future areas of research in pediatric cerebrovascular neurosurgery.

Finally, there may be a role for future prognostic and theranostic tools derived from this taxonomic knowledge, such as the emerging field of non-invasive biomarkers<sup>2,52,57</sup>. Proof-of-concept data in clinical studies with these types of biomarkers support the premise that CMs and AVMs can be detected through urine sampling and that levels of biomarkers reliably change in response to treatment<sup>8,53</sup>. If validated in larger trials, non-invasive testing could potentially help to reduce cost and risk of CM, AVM, and VOGM care<sup>2</sup>. An example of case use might be to reduce the number of imaging studies needed (along with the concomitant fees and sedation often needed in children) while providing a complementary method of ascertaining treatment response after surgery or radiation. It is exciting to consider the use of biomarkers and targeted therapeutics within the context of an emerging molecular taxonomy as the next step in the evolution of care for pediatric cerebrovascular lesions<sup>2,8,52,56,57</sup>.

## CONCLUSIONS

Pediatric cerebrovascular lesions such as AVM, VOGM and CM remain among the most challenging conditions in neurosurgery. Collaboration across clinical disciplines coupled with dedicated translational research are vital to the development of better outcomes for children afflicted with these diseases. Consequently, this issue of the *Journal of Korean Neurosurgical Society* is vitally important as it creates a forum to share and promote knowledge critical to the advancement of this field.

## AUTHOR'S DECLARATION

### Conflicts of interest

No potential conflict of interest relevant to this article was reported.

## Informed consent

This type of study does not require informed consent.

## Author contributions

Conceptualization : ERS; Data curation : ERS; Writing - original draft : ERS; Writing - review & editing : ERS

## Data sharing

None

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