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Pediatric Central Nervous System Vascular Malformation : Pathological Review with Diagram

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Pediatric central nervous system (CNS) vascular malformations are a group of abnormal blood vessel formations within the brain or spinal cord in children. The most crucial point of pediatric CNS vascular malformation is that no golden standard classifications exist. In addition, there is a big gap in knowledge and the viewpoint of clinicians, radiologists, and pathologists. In addition, many genes associated with pediatric CNS vascular malformation, such as Sturge-Weber-Dimitri syndrome with guanine nucleotide-binding protein G(q) subunit alpha (GNAQ) gene mutation, and cavernous malformations with cerebral cavernous malformations 1 (CCM1), CCM2, and CCM3 gene mutation, were recently revealed. For proper therapeutic approaches, we must understand the lesions' characterizations in anatomical, morphological, and functional views. In this review, the author would like to provide basic pediatric CNS vascular malformation concepts with understandable diagrams. Thus, the author hopes that it might be helpful for the proper diagnosis and treatment of CNS pediatric vascular malformations.

Key Words : Central nervous system vascular malformations · Pediatrics · Pathology.

INTRODUCTION

Pediatric central nervous system (CNS) vascular malformations are a group of abnormal blood vessel formations within the brain or spinal cord in children. The terminology of "malformation" has some presumptions, such as "presence at birth" and "tendency to develop" regardless of clinical onset time.

The International Society for the Study of Vascular Anomalies (ISSVA) proposed the updated classification of vascular anomalies in 2018[1]. Functionally vascular malformations are divided into the low flow (e.g., capillary, venous, and lymphatic malformations) or high flow (e.g., arteriovenous malformation [AVM] and fistulas and vein of Galen malformations [VOGMs])[3]. Privately, the most crucial point of pediatric CNS vascular malformation is that no golden standard classifications exist. In addition, there is a big gap in knowledge and the viewpoint of clinicians, radiologists, and pathologists. According to a textbook[6], an acceptable classification scheme, 'Developmental vascular anomalies and malformations in infants and children' (Table 1) was suggested.

Recently, many genes associated with pediatric CNS vascular malformation, such as Sturge-Weber-Dimitri syndrome[7] with guanine nucleotide-binding protein G(q) subunit alpha (GNAQ) gene mutation, and cavernous malformations (CMs)[5] with cerebral cavernous malformations 1 (CCM1),

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CCM2, and CCM3 gene mutations, were revealed.

For proper therapeutic approaches, we must understand the lesions' characterizations in anatomical, morphological, and functional views.

Especially, pathologists could not experience all areas of pediatric vascular malformations in CNS because neurosurgeons could submit specific lesions through a surgical approach. Thus, the vascular lesions, which could be requested for the pathological examinations, will be discussed, especially with pathological aspects.

Table 1. Developmental vascular anomalies and malformations in infants and children

Berry ("saccular") aneurysm
"Hemangioma"
- Arteriovenous malformation (parenchymal or dural) → high flow
- Mesencephalic-oculofacial angiomatosis (Wyburn-Mason syndrome)
- Cavernous malformations → low flow
- Developmental Venous anomalies → low flow
- Capillary telangiectasia including with Rendu-Osler-Weber disease → low flow
Vein of Galen malformations → high flow
Meningioangiomatosis
Proliferative vasculopathy with hydranencephaly (hydrocephaly) – Fowler syndrome
Meningocerebral angiodysplasia and renal agenesis
Sturge-Weber-(Dimitri) syndrome (encephalotrigeminal angiomatosis)
COL4A1 mutation-associated small vessel disease

Modified from Magaki et al.,[6] 2018

BERRY ("SACCULAR") ANEURYSM

This lesion is prevalent in adults. In the pediatric range, it is very rare, especially symptomatic. According to the textbook[6], it might be incidental findings at autopsy. If it is not ruptured, it shows a balloon-like lesion (Fig. 1A). If it is ruptured, it evokes intraparenchymal or subarachnoid hemorrhage. Clinically, the specific medical conditions that could result in collagen or elastic fiber abnormalities, such as polycystic kidney disease, neurofibromatosis type 1, Marfan syndrome, Ehlers-Danlos syndrome, and fibromuscular dysplasia, etc. can be associated[4]. The big aneurysms, so-called "giant" aneurysms (greater than 25 mm), may commonly occur on the basilar artery in children and adolescents[2].

Histologically, a focal thinning wall in the rupture site is noted. Notably, the loss of elastic fiber (Fig. 1B) around the rupture site is very prominent.

AVMS

AVMs are typical high-flow lesions. With CMs, these lesions could be encountered more in surgical specimens than in autopsy. They can be found in the brain parenchyma or dura.

Microscopically, they show two representative histological findings : 1) arterialized veins and 2) intervening and sur-

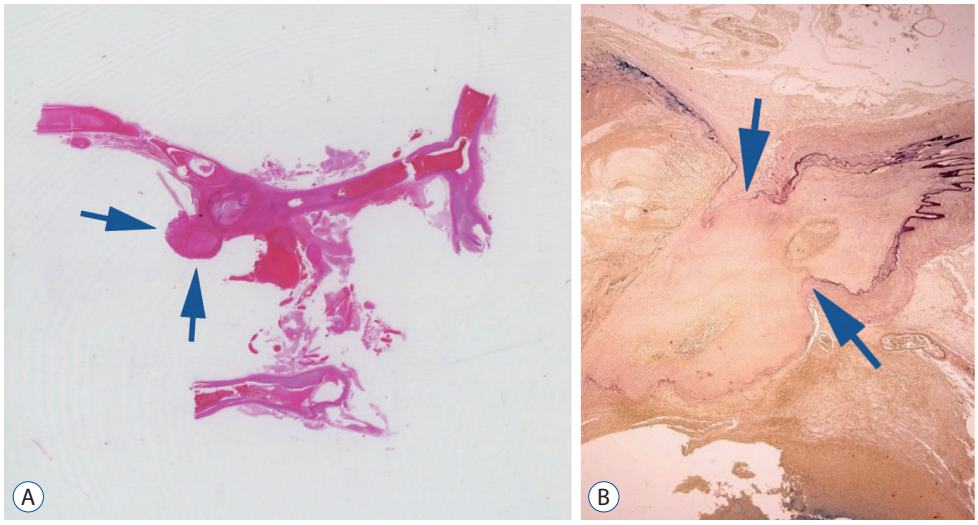

Fig. 1. A : The balloon-like protruding vascular lesion with hemorrhage (arrows) is noted (Hematoxylin and Eosin, ×1). B : The elastic Van Gieson's (EVG) staining shows abrupt loss of elastic fibers (black colors) (arrows) in the aneurysmal lesion (EVG, ×12).

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rounding gliotic tissues in the vessels (Fig. 2).

The arterialized veins show variable-sized thick-walled vessels but have incomplete or fragmented elastic fibers. And then, the gliotic tissues intervene in the vascular channels and surround the lesion. There are reactive astrocytes, microglia, macrophages, or red blood cells (RBCs) in the gliotic brain tissues. These two typical findings are significant key findings comparing CMs.

CMS

It is a typical example of a low-flow lesion. The terminology of cavernous hemangioma, CM, or cavernous angioma (hemangioma) is mixed. CMs comprise hyalinized blood vessels (Fig. 3). Most vessels are located closely, like "back to back." It means that there is no definite intervening brain parenchyma, unlike AVM. It is a histological differential point. When the pathologists meet the lesion, it has more secondary or degenerative changes, such as rupture, hemorrhage, and thrombosis, than AVM. Surrounding lesions, there are prominent histological changes, for example, altered blood pigments, hemosiderin-laden macrophage, or reactive gliosis, like AVM.

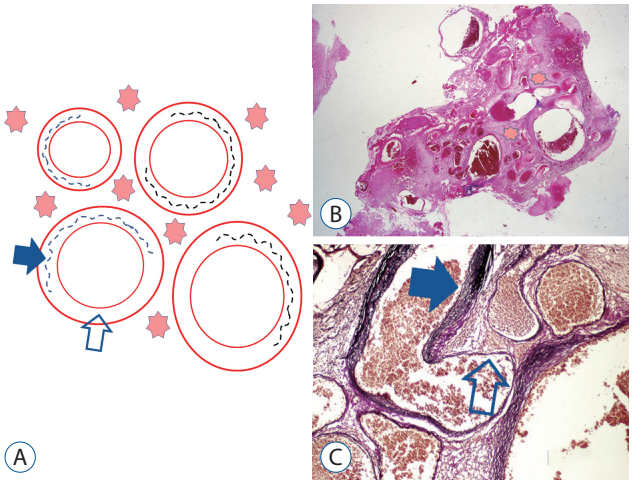

Fig. 2. A : The diagram of arteriovenous malformation (AVM). Variable-sized arterialized vessels with incomplete elastic fibers (black line) are seen. The gliotic tissues (pink stars) are in between the vessels and the surrounding lesion. The blue solid arrow indicates the presence of elastic fibers, and the open arrow indicates the absence of elastic fibers. B : The microscopic findings of AVM (Hematoxylin and Eosin, ×12). The intervening gliotic tissues (pink stars) are noted. C : The elastic Van-Gieson staining (EVG, ×100). An arterialized vein shows an incomplete elastic layer (blue solid arrow : presence; open arrow : absence).

DEVELOPMENTAL VENOUS ANOMALIES (DVA) AND CAPILLARY TELANGIECTASIAS

Unlike AVM and CM, DVA and capillary telangiectasias are rare in surgical specimens. Almost always, they are incidental findings at autopsy. Macroscopically, they present as a small "blush of hemorrhage" in any brain area[6]. The capillary telangiectasias are known to be in the basis pons.

Histologically, DVA comprise thin-walled dilated vascular channels, intervening normal brain parenchyma. (Fig. 4) There are no surrounding secondary histological changes, unlike AVM and CM. The histological difference between DVA and capillary telangiectasias is the vessels' diameters. (Fig. 4A) Comparing DVA, capillary telangiectasias show multiple small sized vessels (capillaries).

DURAL ARTERIOVENOUS FISTULAS

These involve an abnormal connection between arteries and veins within the dura. It is very difficult to experience these lesions for pathologists because dural arteriovenous fistulas are treated by endovascular embolization. They are presented in diagram and histological findings (Fig. 5).

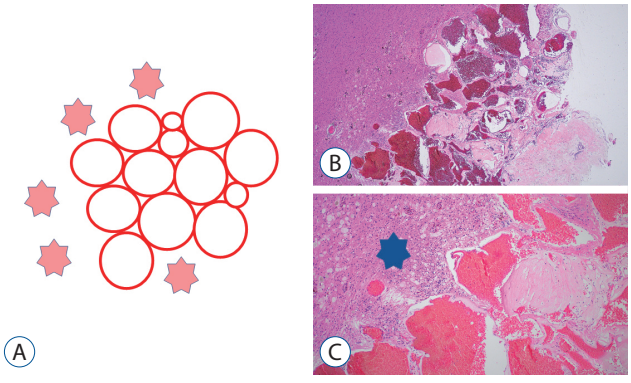

Fig. 3. A : The diagram of cavernous malformations (CMs). Hyalinized vessels are located closely without any intervening brain parenchyma. Surrounding the lesion, the gliotic tissues (pink stars) are noted. B : The microscopic findings of CM (Hematoxylin and Eosin [H&E], ×40). The hyalinized vessels are closed without intervening gliotic tissues. C : Surrounding the lesion, there are extensive hemosiderin-laden macrophages and reactive gliosis. (blue star) (H&E, ×100).

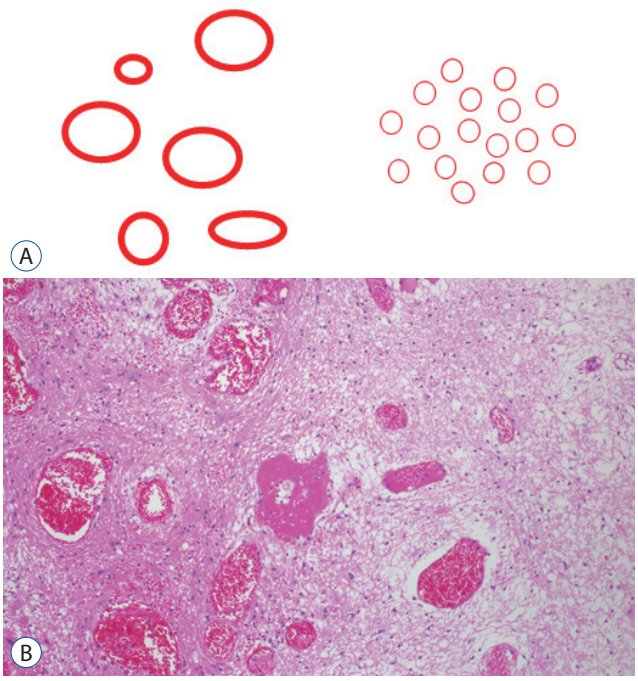

Fig. 4. A : The diagrams of developmental venous anomalies (DVA) (left) and capillary telangiectasias (right). There are dilated vessels with intervening normal blood parenchyma. The calibers of DVA between capillary telangiectasia are different. B : A typical histological finding of DVA (Hematoxylin and Eosin, ×100).

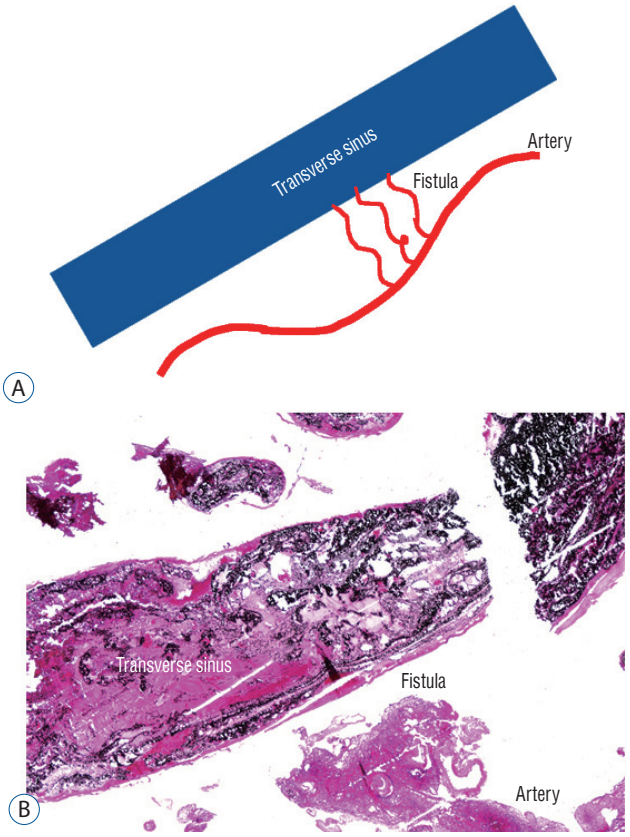

Fig. 5. A : The diagram of dural arteriovenous fistulas. In dura, there are abnormal connections between arteries and veins (transverse sinus). B : The embolized transverse sinus with arteries and fistulas is noted (Hematoxylin and Eosin, ×12).

VOGMS (OR VEIN OF GALEN ANEURYSMAL/ ARTERIOVENOUS MALFORMATION AND DILATATION)

It is a typical vascular malformation that pathologists could not encounter in the surgical specimen because the treatment may be endovascular embolization. It can cause abnormal hemodynamics (so-called "steal"), resulting in ischemia and an atrophic hemisphere. According to the textbook[6], the basal feeding arteries are usually dilated and hypertrophic, and VOGM shows a thickened venous wall structure (Fig. 6).

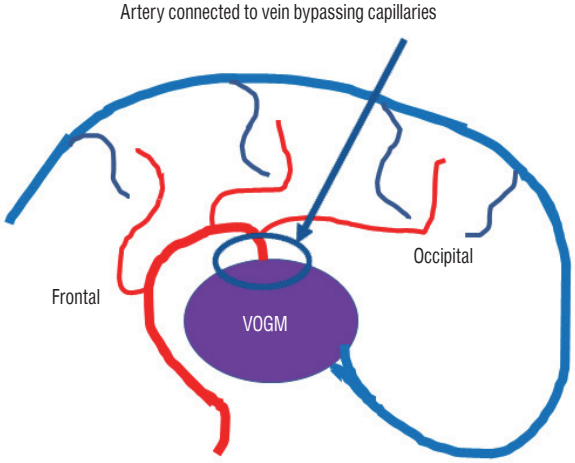

Fig. 6. The diagram of vein of Galen malformations (VOGM).

CONCLUSIONS AND PROSPECT

Nowadays, it is getting hard to encounter the classical histological features of CNS pediatric vascular malformations because there are advanced treatment modalities, especially endovascular treatment and gamma knife radiosurgery. From the pathologist's perspective, they should be aware of the secondary histological changes of vascular malformation resulting from several treatment modalities. Otherwise, it may be confused with other disease situations.

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Meanwhile, from the perspective of clinicians, especially neurosurgeons, it becomes essential to provide various aspects of clinical information to colleagues, radiologists, or pathologists for proper diagnoses and treatments of CNS pediatric vascular malformations.

The author believes these cooperations could give the patients the dream and hope for life.

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 : SHK; Data curation : SHK; Formal analysis : SHK; Funding acquisition : SHK; Methodology : SHK; Project administration : SHK; Visualization : SHK; Writing - original draft : SHK; Writing - review & editing : SHK

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