De novo cerebral arteriovenous malformation in a child with previous cavernous malformation and developmental venous anomaly

Case report

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Although cerebral vascular malformations are traditionally considered to be congenital lesions, they often become clinically evident in the 3rd to 4th decades of life, leading to the assumption of a long silent clinical period. Unlike vein of Galen malformations, antenatal diagnosis of cerebral arteriovenous malformations (AVMs) is highly uncommon. Postnatal development of an AVM is an emergent concept supported by more clinical observations. Genetic and biological studies demonstrate that an environmental trigger (“second hit”) in addition to genetic predisposition may be a key in understanding the pathophysiology of AVMs and other cerebral vascular lesions such as cavernous malformations (CMs). The authors describe a 6-year-old boy in whom a giant CM was diagnosed and a de novo AVM was detected 25 months after initial resection of the CM. This case seems to support the second-hit hypothesis. (http://thejns.org/doi/abs/10.3171/2011.12.PEDS11312)

Key Words • de novo arteriovenous malformation • cavernous malformation • developmental venous anomaly • vascular disorders

Case Report

Despite the fact that only a few patients with de novo AVMs have been reported, there is genetic and biological evidence that postnatal cerebral blood vessels maintain angiogenic capacity.10,12,17 Clinical observations showing differences between AVMs found in adults and those found in children have led to questioning of the classic assumption that these lesions are congenital in origin.1 We present the case of a patient with a de novo AVM found 2 years after the resection of a giant cystic CCM associated with a deep DVA and discuss recent evidence that cerebral vascular malformations may be acquired and are not congenital.

Abbreviations used in this paper: AVM = arteriovenous malformation; CCM = cerebral cavernous malformation; DVA = developmental venous anomaly; HHT = hereditary hemorrhagic telangiectasia.

History and Examination. A 6-year-old boy presented to our hospital with seizures and underwent head CT and MR imaging studies revealing a large heterogeneous mass with cystic changes and hemorrhage, surrounding edema, and mass effect (Fig. 1). The mass was thought to be a giant CM, a fact supported by the presence of a large adjacent DVA (Fig. 2), and thus it was decided not to perform catheter angiography. The boy’s family history was negative for any vascular anomaly or malformation, and for that reason no genetic tests were conducted.

Operation. Surgery allowed for total resection of the lesion.

Postoperative Course. Neurological examination was unchanged postoperatively. Histopathology confirmed that the lesion was a CCM. Light microscopy examination
showed loose to dense fibrous tissue with vascular channels of small to large size and thin or very thick fibrous walls. We also noted organizing hemorrhage, chronic inflammation, cholesterol granulomas, and fibrosis in multiple areas. No arteriovenous shunts or arterialized veins were seen. The AVM was not visible on preoperative CT or MR imaging. The first postoperative MR image was obtained at 24 hours and showed postsurgical changes and no AVM. Three-month and 18-month follow-up MR imaging and MR angiography revealed postoperative changes, no residual CCM, the previously noted DVA, and no AVM. Repeat follow-up MR imaging at 25 months after surgery showed subtle abnormal flow voids, and subsequent MR angiography studies at 33 months (Fig. 3) showed a network of new vessels in the third ventricle and an enlarged vein of Galen and straight sinus. Subsequent catheter angiography (Fig. 4) revealed a diffuse lesion fed by posterior choroidal arteries and drained by a dilated vein of Galen. A choroidal and intraventricular shunt consistent with an AVM draining into a dilated vein of Galen, distinct from an embryonic vein of Galen malformation (or persistence of the median vein of the prosencephalon), was diagnosed.

Discussion

Pial AVMs are focal abnormalities of pial cerebral or spinal medullary blood vessels characterized by a vascular network not directly contributing to normal function of the brain or spinal cord parenchyma fed and drained by dilated vessels. The molecular mechanisms and developmental sequences that lead to their development are still unknown. Arteriovenous malformations are thought to be congenital, but there is no clear clinical, biological, or genetic evidence to support this classic assumption. Unlike vein of Galen malformations, antenatal or neonatal diagnosis of pial AVMs is exceptionally rare. Moreover, untreated pial AVMs in newborns and infants are associated with rapid cerebral destruction and disturbances in postnatal brain maturation. A delay in psychomotor development is a common symptom in infants in whom an AVM is diagnosed during the first years of life. Older children and adults show no brain morphological defects or developmental anomalies associated with AVM, leading to acceptance of the concept that no neuronal disorganization or functional disturbances occur with an AVM in the developing brain. Population-based demographic studies show a peak in detecting cerebral AVMs around the 3rd and 4th decades of life, leading to the assumption that a long period of silent coexistence must occur. On the other hand, only a few cases of de novo cerebral AVMs have been identified and published. In an interesting article, Park et al. showed real-time images in the birth and growth of a de novo subdermal AVM in an adult mouse model of HHT with an ALK1 mutation and demonstrated that in addition to the genetic defect (first hit), a second hit (a vascular injury in Park and colleagues’ article) is required to induce a morphologically visible AVM.

Hereditary hemorrhagic telangiectasia, also known as Osler-Weber-Rendu syndrome, is a genetic disorder inherited as an autosomal dominant trait characterized by AVM in different organs including the brain and spinal cord. Mutations in 2 different genes, ENG and ALK1 (HHT Type 1 and HHT Type 2, respectively), were identified more than a decade ago, and more recently two new loci on chromosomes 5 (HHT3) and 7 (HHT4) have been found. ENG and ALK1 are TGFβ receptor–associated proteins involved in the process of vasculogenesis, developmental and postnatal angiogenesis, and vascular remodeling. Loss of function in those genes is associated with aberrant arteriovenous communications. Patients affected with HHT do not exhibit a complete phenotype at birth. Typical skin and mucosa telangiectasias in patients with HHT are uncommon, even exceptional in childhood, and they usually appear late in adolescence or adult life.

Fig. 1. Axial T2-weighted MR image showing a complex mass of varying signal intensities in the right temporooccipital region compatible with a giant CCM with cysts. There is hydrocephalus.

Fig. 2. Left: Axial postcontrast T1-weighted MR image showing parts of the CCM enhancing. Note the small DVA (arrow) anterior to the CCM. Right: Parasagittal postcontrast T1-weighted MR image showing the large CCM again and the small DVA (arrow) anteriorly.
supporting the hypothesis that a second-hit mechanism must occur during this relatively long period of time. The mechanism for the second hit is also invoked for other cerebral vascular malformations such as CCM. Some authors underline the likelihood of somatic epigenetic changes involved in sporadic lesions. Cerebral cavernous malformations are venous malformations composed of sinusoidal vascular spaces lined by a single layer of endothelial cells. They can occur in sporadic or familial forms. Familial CCMs are linked to mutations in 3 different genes (KRIT1 for CCM1, MGC4607 for CCM2, and PDCD10 for CCM). Mutations of KRIT1 are found in more than 40% of CCMs. Sporadic forms display single lesions, whereas familial forms tend to multiple lesions. De novo CCMs with and without prior radiotherapy have been described.

In our patient the AVM was first detected on MR imaging 2 years after initial surgery for a sporadic CCM. Previous contrast-enhanced CT, MR angiography, and MR imaging studies showed no evidence of either abnormal vessels in the choroidal region or an increased size of the vein of Galen. No angiogram was obtained in the preoperative period, and thus the existence of a previous choroidal shunt cannot be completely excluded. A preexisting AVM could have been masked or compressed by the large size of the CCM; however, an AVM was not seen at surgery, and tissue samples failed to demonstrate arteriovenous shunts or arterialized veins. Thus, the clinical evolution of our patient is similar to that of those with CCM and HHT in whom a period of time elapses before the development of the brain AVM. The nature of the second hit is not possible to determine.

Recurrences of AVMs after angiographically confirmed complete resections have been described. Reasons for these recurrences were compression by adjacent hematoma, thrombosis, or undetectable size. Andaluz et al., in their retrospective review of 36 patients with ages 4–16 years who had undergone complete resection of AVMs documented on angiography, found 2 patients (5.5%) in whom recurrence developed 3 and 5 years later.
These authors recommended the use of intraoperative or early postoperative angiography to document complete resection and delayed angiography 1 and 5 years after resection. Codd et al. stated that AVM recurrence should be considered in the setting of recurrent neurological symptoms or new intracranial hemorrhage even after angiographically proven complete resection.

A CCM (a malformation with no function) and a DVA (an anomaly adapted to the function of normal venous drainage) were first diagnosed in our patient. Both are a part of the spectrum of venous abnormalities. Their relationship with AVM, which is not a pure venous lesion, is unclear. Angiogenetic activity is known to occur in both CCM and AVM, but published data show that both exhibit different levels and patterns of expression for structural and functional proteins. Their origin and progression seem to follow different molecular mechanisms, and the association between AVM, CCM, and DVA in our patient could therefore be coincidental.

An association of CCM with DVA is seen in 14%–30% of patients. Developmental venous anomalies are extreme anatomical variants of venous drainage without significant pathological importance. It has been shown that DVAs lack angiogenesis activity and have a normal expression of structural wall proteins. Petersen et al. in a retrospective review of 112 patients with 2212 CCMs, found that an association with DVA occurred in 44% of patients with sporadic forms but in only 1 patient with familial CCM. In our patient, although no genetic test was performed, a family survey for CCM was negative.

Disclosure

The authors report no conflicts of interest concerning the materials or methods used in this study or the findings specified in this paper.

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