Intracranial vascular malformations represent a heterogeneous group of lesions classically classified by McCormick into 4 major groups: arteriovenous malformations, cavernous malformations, venous angiomas, and capillary telangiectasia. These vascular anomalies were once considered uncommon. However, the routine use of MR imaging has demonstrated a higher incidence than originally considered. In addition, the observation that some of these malformations can occur in association has raised questions about a potential common genesis. Although the venous system was traditionally considered a “passive” component of vascular malformations, recent evidence suggests an increasing potential role of the venous system and its anomalies in the genesis of various intracranial vascular malformations, including dural arteriovenous fistulas, cavernous malformations, parenchymal arteriovenous malformations, and capillary telangiectasia. They also describe the potential significance of different associations of these vascular anomalies. (DOI: 10.3171/2009.8.FOCUS09161)

**Key Words** • vascular malformation • arteriovenous malformation • dural arteriovenous fistula • cavernous malformation • telangiectasia
trauma, surgical infections, and various thrombophilic conditions. Procoagulative states can be due to a genetic defect of a coagulative pathway or can be acquired, as in pregnancy or during oral contraceptive therapy. Heritable risk factors for sinus thrombosis include factor V Leiden mutation, prothrombin G20210A mutation, and protein C and protein S deficiencies. Since preexisting sinus thrombosis is related to the subsequent development of DAVFs, recent studies have suggested an association between such inherited prothrombotic states and DAVFs.

Gerlach et al. showed that genetic thrombophilic abnormalities occur in a higher percentage of patients with DAVFs than in the general population. Furthermore, they proposed that the differences in genetic abnormalities may be involved in different pathophysiological mechanisms resulting in cranial versus spinal DAVFs. Specifically, they found that the prevalence of the G20210A prothrombin mutation was almost 10-fold higher in patients with cranial DAVFs compared with the general population, whereas in patients with spinal DAVFs the prevalence of factor V Leiden mutation was increased about 3-fold. Other reports have implicated factor V Leiden mutation in the etiopathogenesis of DAVFs. Kraus and colleagues have observed increased prevalence of factor V Leiden mutation but not of other genetic thrombophilic anomalies with DAVFs. Severity of DAVF symptoms was higher in patients with activated protein C resistance as compared with patients without thrombophilia. Other thrombophilias, such as protein S deficiency and antithrombin III deficiency, have been found in patients with DAVFs, further strengthening a causal relationship between anomalies (prothrombotic states) involving the venous system and the genesis of DAVFs. Protein S deficiency has been shown in a child with a DAVF and venous sinus thrombosis, and development of multiple DAVFs has been found in a patient with antithrombin III deficiency. Importantly, prothrombotic states preferentially involving the arterial system have not been shown to be increased in patients with DAVFs. This observation, again, implicates the venous system and in particular intracranial venous sinus thrombosis in the formation of DAVFs.

The exact mechanisms triggering the formation and progression of arteriovenous dural shunts in patients with preexisting sinus thrombosis is unknown and likely multifactorial. Initial studies proposed that inflammation related to sinus thrombosis and the subsequent recanalization of the sinus may be responsible for DAVF formation. This inflammatory response was proposed to initiate angiogenic activity and lead to fistula formation between the arterial supply of the dura and the venous sinuses. This hypothesis, though, does not explain the formation of DAVFs distant to the venous sinus thrombosis. Animal models have confirmed that sinus thrombosis and the resulting elevation in sinus pressure may lead to the formation of DAVFs. In an elegant experiment, Lawton and coworkers demonstrated that in rats, increased venous pressure was related to increased angiogenic activity and both led to the formation of both dural AVFs and facial AVMs in rats. Other authors have confirmed a causal role of both sinus thrombosis and venous hypertension in the genesis of DAVFs. In one such study, Herman et al. showed that sinus thrombosis associated with sinus hypertension leads to the formation of DAVFs, while sinus occlusion without venous hypertension did not. This is clinically collaborated by the fact that very few patients with surgical occlusion of the sigmoid sinus develop DAVFs. Furthermore, through molecular studies it has been shown that venous hypertension induces angiogenic activity either directly or indirectly by decreasing cerebral perfusion and increasing ischemia and that aberrant angiogenesis is responsible for DAVF formation.

We can conclude that DAVFs are acquired vascular malformations that arise from impaired venous outflow most commonly due to sinus thrombosis. This in turn leads to venous hypertension and resulting tissue hypoxia and activation of angiogenesis, leading to eventual formation of DAVFs (Fig. 1). Hypercoagulable states predispose patients to venous sinus thrombosis and can occur after acquired conditions such as trauma or infection or in genetic conditions that result in thrombophilia.

Developmental Venous Anomalies

Developmental venous anomalies are also known in the literature as venous anomalies, venous angiomas, and venous caput medusae. These venous malformations drain normal parenchymal tissue with functionally normal arterial anatomy and lack of abnormal arteriovenous shunting. Developmental venous anomalies are common and constitute 60% of intracranial vascular malformations. On angiograms they appear as radially arranged medullary veins with a central draining trunk, an abnormality of cerebral surface veins, and a “star cluster” appearance of draining veins. Although, they have been reported to be associated with intracranial hemorrhage, seizures, and progressive neurological defects, the risk of significant hemorrhage is negligible (0.22–0.68%). With the widespread availability of MR imaging, DVAs are frequently encou-
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Figure 2. Mixed AVM-DVA in a 48-year-old woman who presented with hemorrhage. A and B: Midarterial phase (A) and late arterial phase (B) angiograms, right internal carotid artery injection, showing a diffuse AVM with a mixed DVA component.

Figure 3. Cavernous malformation of the cerebellar peduncle and an associated DVA. A: A T2-weighted MR image showing a CM. B and C: Gadolinium-enhanced T1-weighted MR images showing the CM and adjacent DVA in a “star cluster” appearance.

tered in association with other vascular malformations particularly CMs and less commonly parenchymal AVMs and capillary telangiectasia. When DVAs are associated with neurological symptoms, these are usually ascribed to the coexisting vascular malformations. The frequent coexistence of DVAs with other vascular malformations has led to speculations regarding their potential causal role in the genesis and progression of the associated vascular anomalies.

Venous Predominant Parenchymal AVMs

Venous predominant parenchymal AVMs are also known as atypical DVAs or arterIALIZED venous malformations. These malformations are characterized by the presence of a DVA (caput medusae with a large draining vein) associated with arteriovenous shunts, without a classic AVM nidus on angiography. Magnetic resonance imaging findings include contrast-enhancing dilated medullary veins in a spoke-wheel pattern and an enlarged central draining vein, which can easily be mistaken for developmental venous anomalies on MR imaging alone (Fig. 2). The clinical presentation associated with these lesions is nonspecific. In the largest study of these malformations, 6 of 13 patients had an incidental finding of the venous predominant parenchymal AVM, while 8 presented with intracranial hemorrhage, and 1 patient presented with seizures. Therefore, a high index of clinical suspicion needs to be present to proceed to angiography after MR imaging. Correct diagnosis of these lesions is important because incomplete removal of the arterialized feeding vessels or occlusion of only the main draining vein can lead to postoperative hemorrhage as in 2 of 15 patients in the case series reported by Im and coauthors.

The association of DVAs with arteriovenous shunts in “venous-predominant” AVMs suggests that these forms may be transitions in a spectrum evolving from the original DVA to the “mature” AVM. Mullan and coworkers have proposed that the DVA may serve as a skeleton for future AVM development and, in fact, the AVM may merely represent a fistulized DVA. In such a hypothetical model, the proposed formation of the AVM parallels DAVF development: thrombosis and subsequent partial recanalization of the DVA rootlets may induce arteriovenousizations of the DVA, creating the basis for a newly formed AVM. Indeed, in a very interesting case report, Nussbaum and coworkers documented development of multiple AVMs in the proximity of a DVA. These hypotheses and examples, while stressing the potential important role of the venous system in the genesis of AVMs, challenge the traditional concept of parenchymal AVMs as congenital lesions. However, several recent clinical and anecdotal observations support the view that even parenchymal AVMs may not be congenital. Increasing reports are clearly documenting de novo formation of parenchymal AVMs. Large AVMs—at times involving an entire hemisphere—are not that uncommon and yet, while vein of Galen AVMs are commonly detected in utero with modern ultrasound, there are only scant reports of parenchymal AVMs detected with this increasingly sophisticated prenatal diagnostic imaging method. Nevertheless, in the cases so far documented of de novo AVM formation (except for the one reported by Nussbaum et al.), no DVA was evident. We speculate that similar to preexisting dural sinus thrombosis, parenchymal vein thrombosis (which unlike dural sinus thrombosis may often go undiagnosed because of being asymptomatic or oligosymptomatic) could be the trigger for local venous hypertension and ischemia, which in turn leads to increased vascular endothelial growth factor (VEGF) production and aberrant angiogenesis resulting in the development of the parenchymal AVM. Indeed, patients with AVMs have been observed to have significantly increased levels of VEGF when compared with a control group.
Parenchymal DVAs Associated With CMs

Coexistence of a DVA with a CM is common, with the association reported in 24–86% of CMs (Table 1).1,51,55,76,77 A higher incidence of coinciding lesions (86%) was found when postoperative pathology reports were included in the analysis, or when CT angiograms (60%) were used as a diagnostic tool.27,55 as opposed to MR imaging alone.1 The radiological association between DVAs and CMs is much more commonly seen in infratentorial CMs (Fig. 3) than in their supratentorial counterparts (Fig. 4). Several reports have demonstrated de novo formation of a CM in the drainage territory of a DVA, thus suggesting that abnormal vascular anatomy of DVA may lead to the venous hypertension, which in turn leads to formation of the CM due to angiogenic proliferation.2,5,6,39,73 This is otherwise known as the hemorrhagic angiogenic proliferation hypothesis.78 Several reports also showed an increased incidence (12.5–28.3%) of white matter signal abnormalities proximal to a DVA on MR imaging, which leads to questioning whether these abnormalities are the early stages of CM development.58,60

Two different types of DVAs have been associated with CMs. The first type is characterized by classic venous drainage via a central vein, while the second type is characterized by atypical drainage that does not have any connection to the transcortical venous system.27,50 Whether there is a difference in symptoms or hemorrhage rates between the typical and atypical DVAs is unknown. Cavernous malformations associated with visible DVAs may have an increased incidence of hemorrhage and non-hemorrhagic neurological symptoms as compared with CMs without visible DVAs. The incidence rate of hemorrhage ranged from 62 to 93% in patients with CM with an associated DVA8,67,76 as compared with 38% in patients with CMs without visible DVAs8 or 0–68% in patients with DVA alone.18,20,45,50 Interestingly, no visible DVAs adjacent to CMs have been reported in patients with familial CMs, suggesting a different possible pathogenesis between the familial and the sporadic form. The potential role of DVAs in the genesis of CMs will be better clarified as we gain further understanding of the genetics and molecular biology of CMs.

Parenchymal DVAs Associated With Capillary Telangiectasia and CMs

Association of capillary telangiectasias with DVAs and/or CMs is rare.8,17,42,52 Telangiectasia typically occurs in the pons and consists of dilated capillary spaces within normal parenchyma. This triad was initially characterized in a single patient with a complex constellation of neurological symptoms; the lesions were identified by MR imaging of the brainstem.8 This patient was followed up conservatively and did not present with hemorrhage at any time during the period of evaluation.8 In a study of 6 cases of this triad in the brainstem, all of the patients presented with acute neurological symptoms and the lesions were identified using post-Gd MR imaging.51 Three of these 6 patients presented with hemorrhage requiring surgical treatment, and in 2 of these 3, histopathological confirmation was obtained.51 An example of a case involving a patient with a history of diplopia and MR imaging/histopathological confirmation of the triad of DVA, CM, and telangiectasia is presented in Fig. 4. These studies suggest that the mixed lesions comprising DVAs, capillary telangiectasia, and CMs have a more aggressive nature than the individual lesions alone as described above. Further characterization of this association will shed more light on the possible mutual interactions among the 3 different vascular anomalies.

Conclusions

In conclusion, growing evidence suggests an “active” role of the venous system in the genesis of various intracranial vascular malformations. In some lesions, such as DAVFs and CMs, this role is better defined and accepted, while in others, such as parenchymal AVMs, it is only putative and highly speculative. As more clinical and experimental evidence is collected, it is not difficult to anticipate further evolution of the causal role of the “venous side” in the genesis and evolution of these lesions. In the future, better understanding of this role may lead to a shift in the therapeutic targets and more precise prediction of clinical behavior in individual cases.

Disclaimer

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.
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Fig. 4. Representative case of a coinciding DVA, telangiectasia, and CM. This 35-year-old woman presented with onset of double vision and a history of a single episode of diplopia when she was a child. Hemorrhage was observed on CT, and MR imaging demonstrated a mixed-signal intensity lesion surrounded by a hypointense rim consistent with the characteristics of a CM. After Gd administration, a complex vascular malformation consisting of a DVA with multiple drainage channels through the pons and ventricular floor associated with a pontine telangiectasia became apparent. A and B: Sagittal (A) and coronal (B) fast spin echo T1-weighted MR images obtained after Gd administration revealing a CM surrounded by a capillary telangiectasia and a DVA, with multiple drainage channels through the pons. Reproduced with permission from Pozzati et al: J Neurosurg 107:1113–1119, 2007.


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