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Developmental Venous Anomaly: Benign or Not Benign

Rie Aoki,[1] and Kittipong Srivatanakul[1]

[1]*Department of Neurosurgery, Tokai University, Kanagawa, Japan*

Abstract

Developmental venous anomalies (DVAs), previously called venous angiomas, are the most frequently encountered cerebral vascular malformations. However, DVA is considered to be rather an extreme developmental anatomical variation of medullary veins than true malformation. DVAs are composed of dilated medullary veins converging centripetally into a large collecting venous system that drains into the superficial or deep venous system. Their etiology and mechanism are generally accepted that DVAs result from the focal arrest of the normal parenchymal vein development or occlusion of the medullary veins as a compensatory venous system. DVAs per se are benign and asymptomatic except for under certain unusual conditions. The pathomechanisms of symptomatic DVAs are divided into mechanical, flow-related causes, and idiopathic. However, in cases of DVAs associated with hemorrhage, cavernous malformations (CMs) are most often the cause rather than DVAs themselves. The coexistence of CM and DVA is common. There are some possibilities that DVA affects the formation and clinical course of CM because CM related to DVA is generally located within the drainage territory of DVA and is more aggressive than isolated CM in the literature. Brain parenchymal abnormalities surrounding DVA and cerebral varix have also been reported. These phenomena are considered to be the result of venous hypertension associated with DVAs. With the advance of diagnostic imagings, perfusion study supports this hypothesis demonstrating that some DVAs have venous congestion pattern. Although DVAs should be considered benign and clinically silent, they can have potential venous hypertension and can be vulnerable to hemodynamic changes.

Key words: developmental venous anomaly, symptomatic, venous congestion, hemorrhage, treatment

Introduction

Developmental venous anomalies (DVAs) are the most frequently encountered common form of vascular malformations with a reported incidence of up to 2.6% in a series of 4069 brain autopsies.[1)] Since the advent of magnetic resonance imaging (MRI), the detection rate was 0.48–0.7%.[2)] In 1967, Wolf et al. reported regarding the first patient who died of intracranial hemorrhage because of a lesion that was diagnosed as a venous angioma.[3)] Since then, various terminologies have been used, such as venous malformation, venous angioma, and medullary venous malformation, implying that they were considered to be rare lesions, conferring a high hemorrhage risk. In 1986, Lasjaunias et al. suggested that they should be considered as normal anatomic variants and should be differentiated from venous angiomas and vascular malformations. They named this variation as DVA.[4)] DVAs are composed of dilated centripetally draining medullary veins and merge into a collecting transcerebral vein that opens into either superficial subcortical veins or subependymal veins, thus forming the so-called caput medusae. Although the etiology is still under debate, they are generally accepted to result from the focal arrest of medullary vein development or occlusion of the medullary veins between Padget's fourth and seventh stages.[5)] DVAs are usually benign and incidentally discovered. Although symptomatic DVAs are rare, several abnormalities on images of DVAs have been demonstrated.[6–12)] Here, we reviewed the current concepts of DVAs and suggest that although DVAs serve as normal venous drainage, they are associated with potential weaknesses on the basis of the angioarchitectural characteristics.

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Structure of Medullary Veins

To understand DVAs, it is important to know the structure of medullary veins. Parenchymal veins are divided into superficial and deep draining veins. Superficial draining veins include pial veins, intracortical veins, subcortical veins, and superficial medullary veins. Deep draining veins run deep and form the four zones of venous convergence on their

Fig. 1 A schema showing a developmental venous anomaly (DVA) that is consisted of dilated deep medullary veins in the candelabra zone. Because the caput medusa resembles the deep medullary veins in the candelabra zone, we presume that DVAs may be formed based on the structure of medullary veins that Okudera et al. has described. (1. superior sagittal sinus, 2. developmental venous anomaly, 3. intracortical vein, 4. superficial medullary vein, 5. zone 1 (bamboo–branch union) of deep medullary vein (DM), 6. zone 2 (candelabra zone) of DM, 7. zone 3 (palmate zone) of DM, 8. zone 4 (subependymal zone) of DM, 9. transcerebral vein, 10. longitudinal caudate vein).

way to reaching the subependymal veins. The first zone, the so-called bamboo branch union, is the most superficial zone and is located in the white matter. The second zone is named the candelabra zone and is the most conspicuous of the four. Deep medullary veins are transversely connected to the main venous stem in the candelabra zone. These venous stems run deep and converge in the palmate zone (the third zone). In the fourth zone, which is named the subependymal zone, the veins coming from the third zone converge to form subependymal veins. Anastomoses between pial veins and subependymal veins which are recognized as transcerebral veins also exist (Fig. 1).[13,14]

Two theories regarding the development and growth of medullary veins exist. In the first theory, the surface origin theory, some of the superficial parenchymal veins are assumed to grow more deeply with further growth and increasing thickness of the telencephalon. They may form a venous plexus in the subependymal area and may divide into the superficial and deep parts later on. In the deep origin theory, the rapid development of the germinal matrix is considered to form venous plexus within the outer portion of the germinal matrix that is related to cortex development. The development of the venules from this venous plexus is induced by the migration of neuroblasts. Thus, the deep medullary veins are formed centrifugally from the subependymal veins.[13]

Etiology and the Structure of DVAs

The etiology of DVAs is not well understood. They are generally accepted to result from aplasia, hypoplasia, or early occlusion of normally developing veins during Padget's fourth and seventh stages.[5,13] They are considered as compensatory venous systems developing because of the absence of normal veins.[15] Lasjaunias et al. mentioned that the DVA venous pattern may be induced by the requirement for an anatomic adaptation at the venular level that was influenced by one or more specific triggers.[16] Moreover, they suggested that if DVAs result from venous thrombosis, this should lead to neural tissue damage or dysfunction, which is usually not the case in DVAs. Furthermore, they suggested that DVAs may be associated with cortical cell migration and should not exist in the diencephalon, brainstem, or spinal cord[16] as deep medullary veins attributing to DVAs are formed along with the migration of neuroblasts.[4] However, there have been reports of DVAs in the brain stem and the spinal cord that make this theory questionable.[17–22] In the former, the enlarged vein inside the brain stem may represent a collecting vein of a DVA in adjacent area or the drainer of other abnormalities such as capillary telangiectasia in the brain stem interpreted as DVA inside the brain stem itself. In the latter, such DVA appearance may represent the exaggerated magnification of the normal intrinsic collecting system by the flat panel detector catheter angiotomography, a technique that has never been used for the study in this area. Another explanation is that these could be enlarged veins, not specifically DVA, that have been reported in cases of brain and brain stem cavernous malformations (CMs). In these reports, all CMs initially diagnosed as isolated CMs were found to be associated with venous abnormalities either intraoperatively[23] or by using 7 Tesla MRI.[24] These reports suggest that DVAs associated with CMs in the brain stem and spine may represent dilated venous structures related to CMs and not the true DVAs as they lack the typical caput medusae appearance.

However, further architectural investigations with modern imaging would be of great interest in exploring the true etiology of DVAs in these areas.

A postmortem specimen study demonstrated that there are no pial veins in the territory of DVAs in compensation for the markedly dilated deep medullary veins.[13] These structural characteristics imply a functional adaptation of DVAs to the absence of normal cortical or deep venous drainage pathways. In our opinion, the occlusion of the medullary veins in the third zone may lead to dilated veins in the candelabra zone, potentially leading to the formation of the so-called caput medusae or umbrella shape with the structure of caput medusae being similar to medullary veins in the candelabra zone (Fig. 1).

Clinical Presentation

Prior to the advent of computed tomography (CT) and MRI, DVAs were considered to be rare causes of intracranial hemorrhage and seizures. With the extended use of MRI, DVAs are now more frequently discovered[2] and are benign and asymptomatic thus playing a role in the normal cerebral venous drainage.

Garner et al. reported that the risk of hemorrhage truly associated with DVAs is 0.22% per year,[25] DVAs are associated with CMs in 13–40% of cases;[7,26] these CMs are considered to be responsible for the vast majority of hemorrhagic cases (Fig. 2).[27]

Mechanisms underlying symptomatic DVA are divided into mechanical, flow-related, and idiopathic

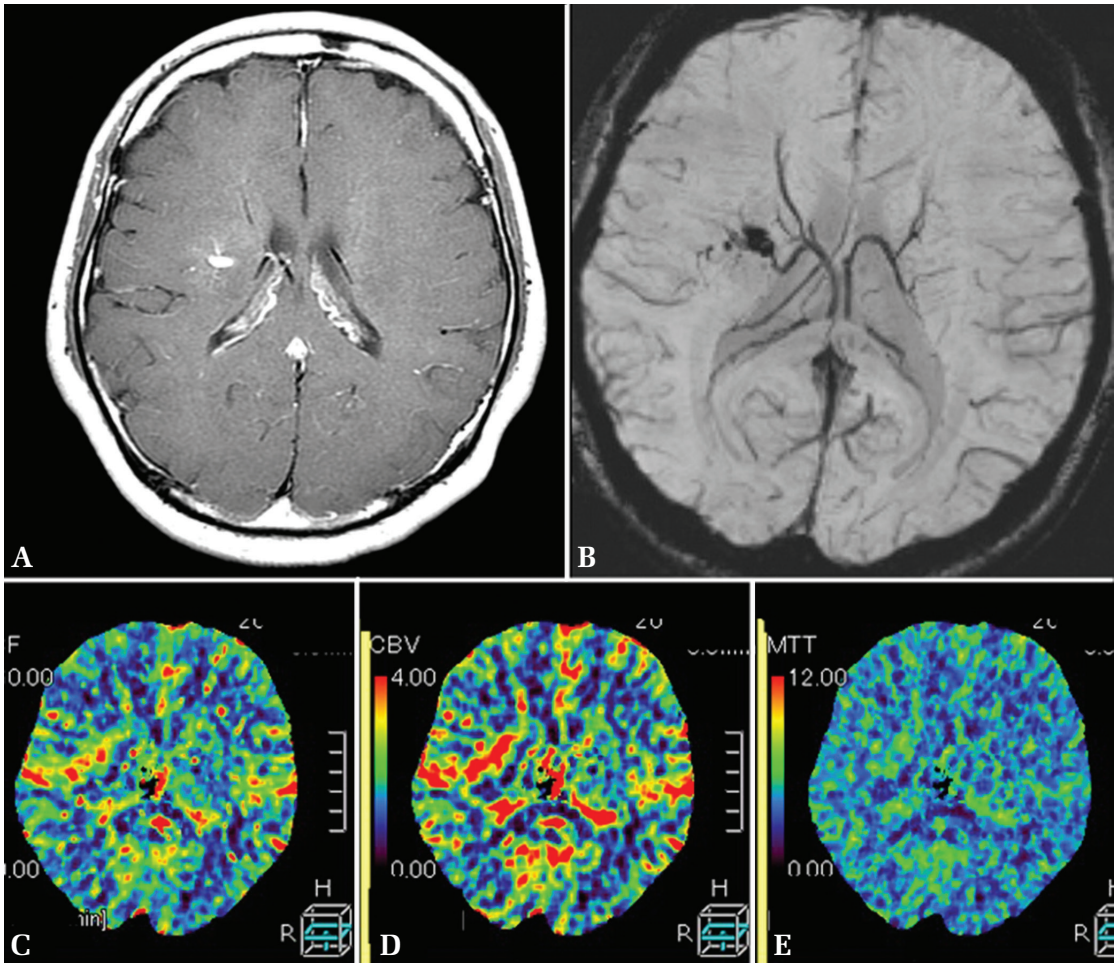

Fig. 2 A representative case showing the potential relationship between venous congestion around developmental venous anomaly (DVA) as a trigger of cavernous malformation (CM) formation and bleeding. A 33-year-old man complaining of sudden onset of severe headache presented with a slight left hemiparesis. In this case, CM that was associated with DVA was considered to be the cause of hemorrhage. A perfusion study reveals venous congestion around CM in the territory of DVA. (A) Gadolinium-enhanced gradient-echo T_1-weighted MRI showing DVA in the right corona radiata. (B) Susceptibility-weighted imaging showing CM in the right corona radiata, located within the territory of DVA. CT-perfusion image showing an increase of cerebral blood flow (C) and cerebral blood volume (D), and prolongation of mean transit time (E), which is compatible with venous congestion.

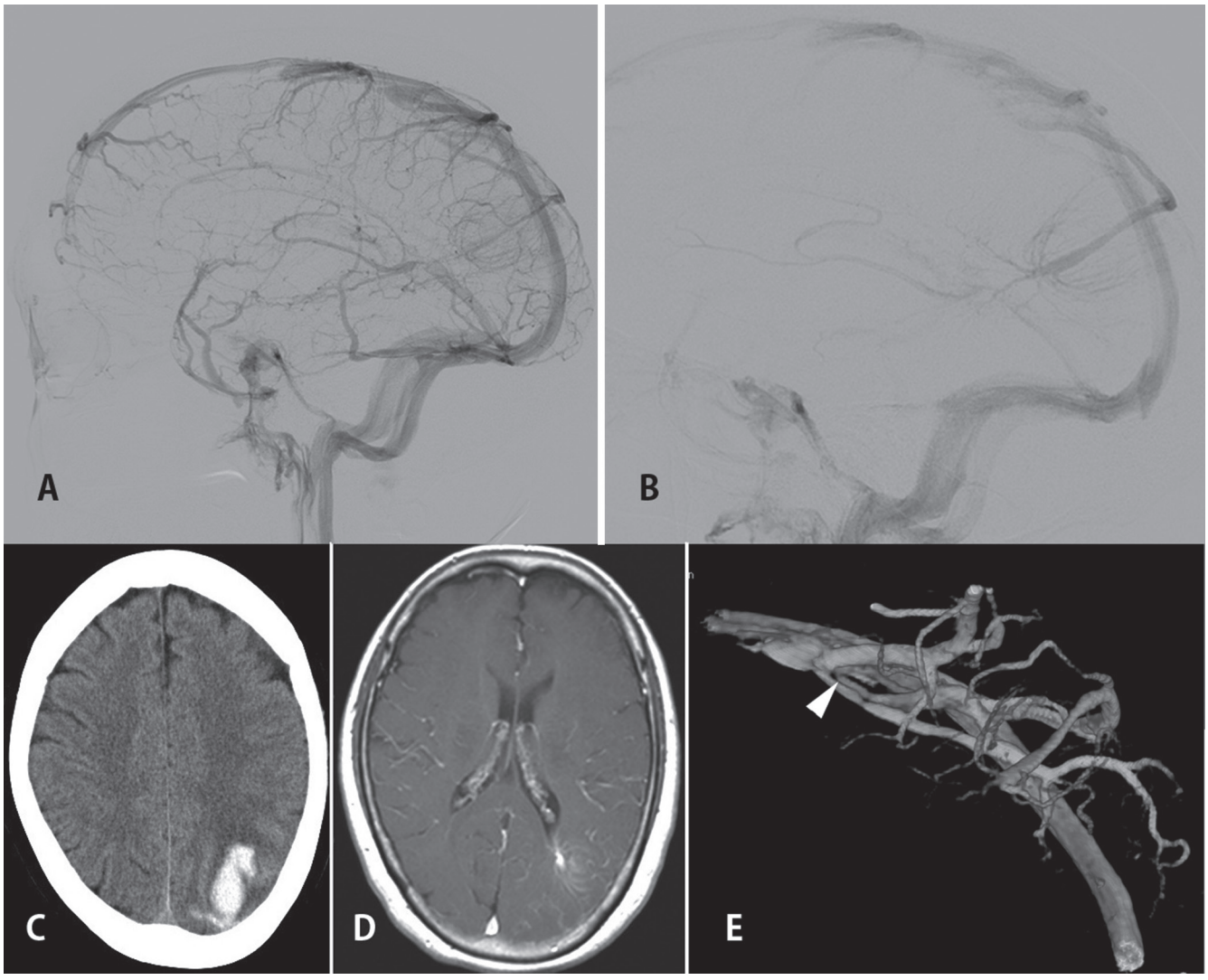

Fig. 3 An illustrative case of developmental venous anomaly (DVA) causing symptoms due to decreased outflow. A 55-year-old woman complained of sudden severe headache and vomiting. Angiogram shows the left internal carotid injection (lateral view) in early arterial phase (A) and late arterial phase (B). In the late phase, venous stagnation was observed in the DVA. (C) CT revealing an intracerebral hemorrhage in the left parietal lobe. (D) Gadolinium-enhanced gradient-echo T_1-weighted MRI showing DVA in the hemorrhage area. (E) A 3D rotational angiography showing stenosis of a collecting vein at the entrance to SSS. It is considered that the hemorrhage was induced by venous congestion due to DVA with stenosis of the collecting vein (*arrow head*).

causes. Pereira et al. reported that mechanical causes, including hydrocephalus or nerve compression syndrome, accounted for 14/69 cases; flow-related causes, including DVA with arteriovenous shunt, or decrease in out flow, or remote shunt with increased venous pressure, accounted for 49/69 cases; and idiopathic causes were identified in 6/69 cases.[28] Mechanical compression was reported to be the cause of obstructive hydrocephalus (50%) and neurovascular nerve compression syndrome (42.8%). Flow-related complications are divided into an increase in inflow and a decrease in outflow. In cases of increases in inflow that include DVAs with arteriovenous shunts (AVS) or arteriovenous malformations (AVM), patients may initially present with headache (61%), neurological deficit (38%), seizures (22.2%), and coma (22.2%). The morphological presentation includes hemorrhage (66%) and venous infarction (33%). Patients with a decrease in outflow are influenced by mechanical or functional causes. The mechanical causes include thrombosis of collecting veins (51.7%), stenosis of the DVA drainage pathway (24.1%), or complete thrombosis of DVA (24.2%) (Fig. 3). The clinical presentation

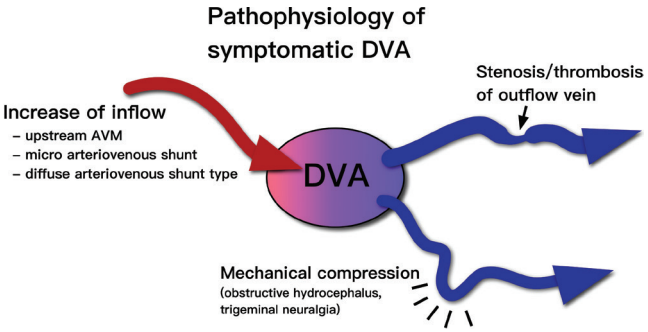

Fig. 4 A diagram of symptomatic developmental venous anomalies (DVAs). The pathophysiology of symptomatic DVAs consist of increasing of inflow, decreasing outflow, and mechanical compression. The increase of inflow can result from upstream arteriovenous malformations (AVM), DVA with micro arteriovenous shunt, or DVA with diffuse arteriovenous shunt. The decrease of outflow includes stenosis or thrombosis of outflow vein. The mechanical compression of the outflow vein can result in obstructive hydrocephalus or neurovascular nerve compression syndrome.

includes headache (58.6%), seizure (41.3%), and altered consciousness (20.7%). The functional cause includes venous hypertension that is induced by a remote AVS (Fig. 4).[28]

Whenever a surgical procedure is required for hemorrhage or swelling, DVA resection must be avoided so as to not cause a catastrophic venous infarction.[29] In cases of thrombosed DVAs, anticoagulation therapy may be effective as in the case of sinus thrombosis, although no studies are available to support the relevant treatment of thrombosed DVAs.[30]

Relationship between DVAs and CMs

The coexistence of CM and DVA represents the most common mixed vascular malformations, occurring at a rate of 13–40%.[7,26,31] Since Roberson et al. published the first case of CM and DVA in 1974, several authors reported the association between CM and DVA.[32] De novo formation of CM around DVA has been reported.[33,34] Repeated microhemorrhage around DVA possibly resulting from blood leaking through the walls of the venous radicles of caput medusae are considered to induce CM formation by activating angiogenic growth factors, such as the vascular endothelial growth factor.[35,36] Hong et al. suggested that CM results from hemodynamic changes that were attributed to DVA.[37] They reported that CMs associated with DVAs are always located in the territory of DVA; more precisely, in the area subject to hemodynamic changes.[37] Sharma et al. demonstrated that the mean transit time (MTT) for DVA with CM was longer than the MTT for DVA without CM.[38] Furthermore, several studies have suggested that the CMs that are associated with DVAs are more aggressive.[39] The hemorrhagic incidence of CMs that were associated with DVAs may be higher than the 2.6 and 3.1% per patient-year that was reported for isolated CMs.[24,40–42] The etiology of CM that is associated with DVA and its clinical course are presumed to be based on venous congestion caused by DVA (Fig. 2).

Associations with Other Vascular Malformations

DVAs may drain into a sinus pericranii, which reflects anomalous extracranial drainage of the intracranial circulation.[43] Associations between DVAs and head and neck venous malformations have been reported. Up to 20% of patients with a large cervicofacial venous malformations have DVAs.[44]

Brain Abnormalities Observed on MRI Associated with DVAs

Although the parenchyma drained by DVAs is generally considered to be normal, brain abnormalities found on MRI within the DVA territory are quite frequently observed. Santucci et al. reported that 28/175 cases had associated signal-intensity abnormalities in the drainage territory.[6] Ruiz et al. reported that brain abnormalities within the territory of a DVA include atrophy in 29.7%, white matter lesions in 28.3%, and dystrophic calcification in 9.6% of cases. It is hypothesized that chronic local venous congestion leads to these phenomena.[7] Noran reported that demyelination, degenerative alterations of nerves cells, gliosis, and leukomalacia are observed around DVAs as evidenced by histopathology (Fig. 5).[45]

Varices that are associated with DVA are very rare. Uchino et al. reviewed eight cases with varices that are associated with DVA in draining veins and found that 1/8 varices presented with hemorrhage. The natural history and etiology of DVAs-associated varices are unknown. Uchino et al. suggested that the increased flow in these veins might have increased the venous blood pressure causing venous dilation (Fig. 6).[12]

Perfusion Study

Some DVAs have been observed to exhibit abnormal perfusion parameters on MR perfusion-weighted imaging, CT perfusion, and single photon emission CT.[8,9,11] Perfusion studies enable the division of DVAs into two hemodynamic patterns. One is the normal perfusion type and the other is the venous congestion

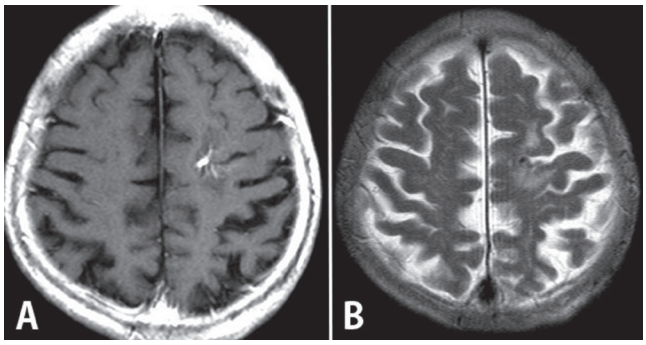

Fig. 5 A case of asymptomatic developmental venous anomaly (DVA) with white matter abnormality observed on MRI. A 72-year-old woman underwent brain dock and a DVA was discovered incidentally. (A) Gadolinium-enhanced gradient-echo T_1-weighted image showing DVA in the left frontal lobe. (B) T_2-weighted image demonstrating high intensity area representing gliosis due to venous congestion within the territory of DVA.

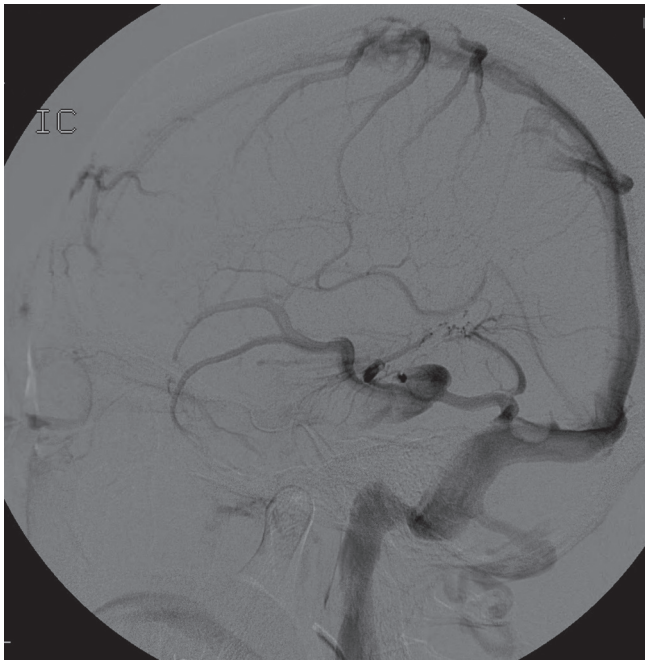

Fig. 6 A case of developmental venous anomaly (DVA) with varix. A 49-year-old woman complaining of intermittent headaches underwent cerebral angiography to evaluate a vascular lesion discovered on MRI (not shown). Angiogram of the left internal carotid injection (lateral view) in the venous phase showing varix formation at the venous outlet of DVA at the vein of Labbé.

type which is characterized by increased cerebral blood flow (CBF), increased cerebral blood volume (CBV), and prolonged MTT. Asymptomatic DVAs with the normal perfusion type, asymptomatic DVAs with the venous congestion type, and symptomatic DVAs with the venous congestion type were demonstrated.[8–11] The relationship between venous hypertension and symptomatic DVAs is not yet clear because these reports include small numbers of DVAs. These perfusion studies suggested that DVAs with venous congestion patterns may develop into symptomatic DVAs, forming CMs or parenchymal abnormalities later on. It is assumed that perfusion studies may predict the risk of developing symptomatic DVAs.[11]

Venous Hypertension

Histological studies of surgical resection of DVAs revealed characteristics dilated thin-walled vessels within the normal white matter and a large caliber vein composed of a thick fibrous, collagen wall with no elastic lamina, and loosely arranged smooth muscle layers.[29]

These histological findings are assumed to result from long-lasting regional venous hypertension.[29] Consequently, the formation of thick fibrous walls because of chronic venous hypertension leads to stenosis or occlusion of collecting veins resulting in venous infarction or hemorrhage.[7,46]

Although, DVAs are considered to be an extreme variant of medullary veins, and DVAs specifically associated with symptom are very rare. DVAs have to bear the burden of larger venous drainage than normal medullary veins because of the particular angioarchitecture. It is hypothesized that DVAs have the potential to cause focal venous hypertension and to be vulnerable to hemodynamic change.

DVAs with an Early Venous Filling

Previous reports have described DVAs with early venous filling.[47] They have been referred to using various terminology, such as "arterialized DVA," "DVA with arterial component," "atypical AVM with venous predominance," "AVM associated with venous angioma," "DVA or venous angioma (VM) with AVM," or "DVA of VM with AVS."[48–52] It appears that there are three types of DVAs with early venous filling. The first one is DVA with diffuse AVS (DVAdAVS), which is characterized by capillary brush-like shunts that are micro and diffuse shunts in the territory of DVA (Fig. 7). The second type is DVA with micro AVS (DVAmAVS) which has a very small-localized shunt point. The third type is DVA with AVM (DVAwAVM), which is a combination of DVA and AVM. DVA is located on the drainer of AVM. The etiology of DVA with early venous filling is unknown. The hypothesis is that DVAdAVS and DVAmAVS may result from opening the potentially pre-existing arteriovenous

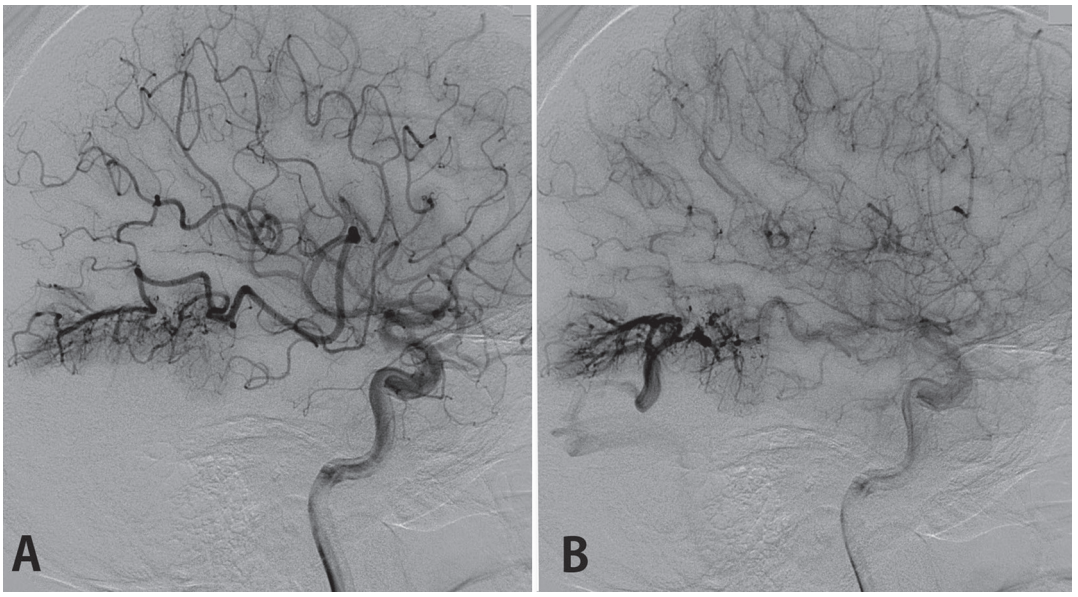

Fig. 7 A case of developmental venous anomaly (DVA) with diffuse arteriovenous shunts. A 49-year-old man underwent MR scan for unspecified reason and was suspected of have an arteriovenous malformation. Angiogram was performed to make the final diagnosis. Angiogram of the right internal carotid injection (lateral view) in the arterial phase (A) showing early filling of DVA from the temporo-occipital branch of middle cerebral artery in the late arterial phase (B) with diffuse shunts draining into the vein of Labbé.

anastomosis in the parenchyma because of venous congestion of DVAs.[53] The etiology of DVAwAVM presumably involves an arterialized DVA that is induced by partially thrombosed involved DVAs leading to AVM development similar to the process of dAVF formation.[54]

Concerning treatment of DVAs with early venous filling, for those presented with hemorrhage, the hematoma may be evacuated when necessary. DVAs per se, should not be surgical targets because of the risk of inducing catastrophic venous infarction.[55] Six cases of DVAwAVM that underwent treatment have been reported. One was treated by proton beam radiosurgery,[56] one by surgery,[57] two by embolization,[53,58] and two cases by gamma knife.[49,59] In five cases, AVMs were successfully obliterated and DVAs were preserved.[49,53,56–59] In one case that presented with intracerebral hemorrhage, the AVM was removed but the DVA was disrupted unintentionally. As a result, the patient deteriorated due to massive venous infarction.[57] The treatment of DVAwAVM may be challenging and need to leave the DVA component completely intact to prevent such venous infarction.

Oran et al. reported two cases of DVAwAVM and one case of DVAdAVS treated by gamma knife. In the former group, the case that radiation was given only to the AVM but not to the DVA had good outcome. The latter case developed radiation necrosis and died.[49] In the report on radiosurgery for 13 cases of venous angioma by Lindquist et al., three cases were DVAwAVM which in one case the DVA was also obliterated resulting in radiation necrosis while the other two with having only the AVM as the radiation target had good outcome.[60] The necrotic radiation and surrounding edema might imply a venous congestion. They indicated that radiosurgery has a limited role in the treatment of DVAdAVS.[49,60] Thus, indication for the treatment of asymptomatic DVA with all types of AVS should be considered on a case by case basis because natural history these DVAs with AVS is not well understood. DVAdAVS should be observed conservatively because it is impossible to treat them without injuring the DVA itself. DVAmAVS and DVAwAVM may be treated according to the presentation focusing on the shunt itself, while DVA must be preserved as it serves the normal venous drainage.

Conclusion

DVAs are considered to be an extreme anatomical variant of medullary veins. They drain the normal brain as a compensatory venous drainage system. Usually DVAs are found by coincidence. Hemorrhagic cases are most often attributed to DVA-associated CM. In rare circumstances, DVAs with AV shunts are associated with hemorrhage. Symptomatic DVAs are rare and surgical treatment targeting the DVAs

should not be performed. Removal of DVAs potentially confers a risk of developing regional venous congestion because of the extraordinary angioarchitecture. It is hypothesized that venous congestion may induce CM formation, histological change in the walls of DVAs, abnormal parenchymal findings, varix formation, and stenosis or occlusion of collecting veins. Consequently, perfusion studies assessing venous congestion may be a key to predicting the risk of symptomatic DVAs in the future.

One must recall that DVAs are generally benign and nothing else but anomalies different from abnormalities and true disease. However, they can be vulnerable to hemodynamic stress.[4,30]

Conflicts of Interest Disclosure

The authors have no disclosure to report.

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Address reprint requests to: Rie Aoki, MD, Department of Neurosurgery, Tokai University, 143 Shimokasuya Isehara-shi, Kanagawa, 259-1193, Japan.
e-mail: s9021@nms.ac.jp