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Review Article

Vascular Malformations of the Brain and Its Coverings

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Vascular malformations of the brain and its coverings encompass several different vascular pathologies of the brain and its coverings, which substantially differ in morphology, clinical presentation, and prognosis, reaching from incidental, asymptomatic vascular abnormalities to life-threatening diseases with high risks of morbidity, most frequently caused by intracranial hemorrhage. In this article, the most common vascular malformations of the brain with and without arteriovenous shunting of blood (e.g., arteriovenous malformations [AVMs], dural arteriovenous fistulas [DAVFs], and cavernous malformations) are explained with a focus on definition, diagnosis, classification, and management.

Keywords ▶ vascular malformations, hemorrhagic stroke, intracranial hemorrhage, arteriovenous malformation, dural arteriovenous fistula

Introduction

Vascular malformations of the brain and the brain's coverings encompass several different vascular pathologies of the brain and its coverings, which substantially differ in morphology, clinical presentation, and prognosis. The spectrum of vascular malformations of the brain reaches from incidental, asymptomatic pathologies without any risk of complications (e.g., developmental venous anomalies (DVAs) or capillary telangiectasias) to potentially life-threatening pathologies with highly elevated risks of bleeding (e.g., arteriovenous malformations [AVMs] or dural arteriovenous fistulas [DAVFs]).

Vascular malformations of the brain and its coverings are generally rare; however, cerebral vascular malformations are the main cause for non-traumatic intracerebral hemorrhages in young adults. The prevalence of the vascular malformations, which are further described in this article, varies from 0.1% (DAVFs) to 25% (DVAs in autopsy studies). The focus of this study lies on the definition, clinical presentation, and diagnosis and therapy of AVMs and DAVFs. Furthermore, the most important characteristics of cavernous malformations, DVAs, and capillary telangiectasias will be described.

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Classification of Cerebral Vascular Malformations

In the literature, many different classifications can be found for vascular malformations of the brain and its coverings. Most classifications are based on the hemodynamics (presence or absence of arteriovenous shunts/high-flow or low-flow malformations) or on the section of the pathologically altered blood vessels (arterial, capillary, or venous). The algorithm illustrated in **Fig. 1** can help to make the diagnosis of a cerebral vascular malformation, based on morphologic, imaging-based factors (adapted from Geibprasert et al.[1]). The important characteristics encompassed in this algorithm are the presence of pathological blood vessels within the cerebral parenchyma, the morphology of a network of small pathologic blood vessel (the so-called nidus), the presence of early venous drainage (generally associated with an arteriovenous shunt), and the origin of the involved vessels.

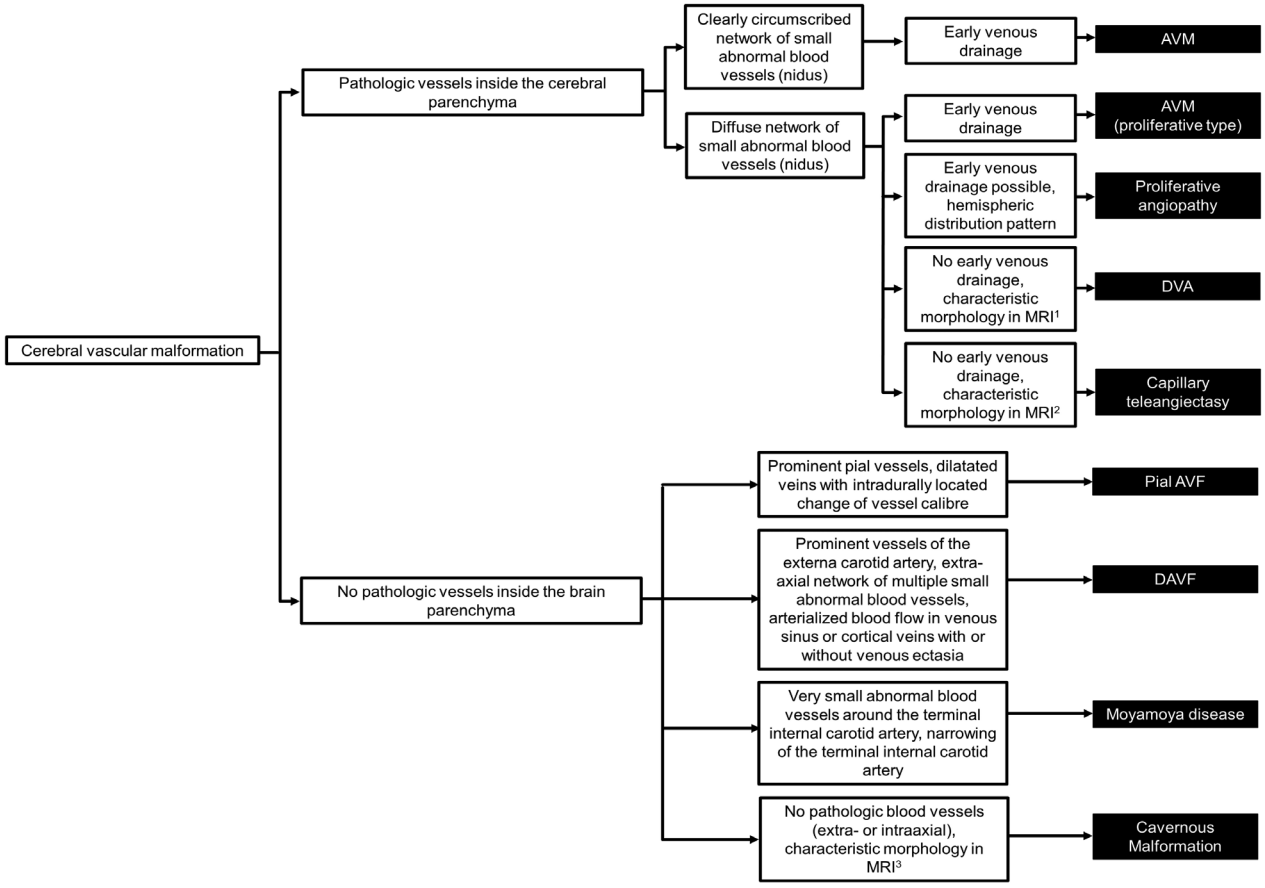

Fig. 1 Algorithm for morphology-based diagnosis of cerebral vascular malformations. AVF: arteriovenous fistula; AVM: arteriovenous malformation; DAVF: dural arteriovenous fistula; DVA: developmental venous anomaly; MRI: magnetic resonance tomography. [1]"Caput medusa" or "palm tree" appearance, corresponding to several prominent vessels converging to a collecting vein; [2]Contrast-enhancing patchy, brush-like lesion with blurry margins, hypointense in susceptibility-weighted imaging, typically located within the pons; [3]"Popcorn" appearance with mixed signal in T2-weighted imaging and peripheral hypointensities in susceptibility-weighted imaging

Imaging of Cerebral Vascular Malformations

In case of a suspected cerebral vascular malformation, the first step on the way to the diagnosis is often CT including CT angiography or MRI including MR angiography of the brain. To identify the major characteristics of vascular malformations, the following imaging techniques can be useful:

- Pathologic blood vessels
  - CT angiography
  - Time-of-flight (TOF) MR angiography
  - Contrast-enhanced MR angiography (TOF or conventional)
  - Contrast-enhanced T1-weighted imaging
  - T2-weighted imaging (blood vessels visible as hypointense "flow voids")
- Acute, subacute, or old hemorrhage(s)
  - Native CT
  - T1-weighted imaging
  - Susceptibility-weighted imaging
  - Fluid-attenuated-inversion-recovery (FLAIR) imaging
- Hemodynamics including arterialized blood flow within dural sinuses and/or cerebral veins
  - TOF-MR angiography
- Brain edema
  - Native CT
  - T2-weighted imaging
  - FLAIR imaging

If non-invasive imaging using CT and MRI confirms the suspicion of a vascular malformation which potentially has to be treated because of intolerable symptoms, danger of progression, or risk of hemorrhage, invasive catheter angiography (digital subtraction angiography [DSA]) is indicated for further and more detailed assessment of the malformation. Based on the findings of DSA, the prognosis of the underlying disease can be estimated

Table 1 The Spetzler-Martin classification for AVMs

Diameter of the nidus	Small (<3 cm)	1 point
	Medium (3–6 cm)	2 points
	Large (>6 cm)	3 points
Eloquence of adjacent brain	Non-eloquent	0 point
	Eloquent[a]	1 point
Venous drainage	Superficial cerebral venous system only	0 point
	Involvement of deep cerebral venous system	1 point

According to these criteria, an AVM is classified on a scale, ranging from 1 to 5 points. [a]Eloquent: Sensorimotor, language and visual cortex, hypothalamus, thalamus, brain stem, cerebellar nuclei, or regions immediately adjacent to these structures. AVM: arteriovenous malformation

more accurately and the need and the modality of treatment can be planned.

Arteriovenous Malformations

Definition

Cerebral AVMs are complex vascular malformations, composed of feeding arteries, an intervening network of small pathologic blood vessels (the so-called nidus), located within the brain parenchyma, and draining veins. The absence of an intervening capillary bed allows for high-flow arteriovenous shunting of blood. While they can occur throughout the entire body, AVMs of the brain are of particular relevance due to their ability to cause severe neurological symptoms and their significant risk of hemorrhage.[2] For decades, the main belief was that AVMs are congenital. Due to the increasing understanding of their morphology, the extreme rarity of fetal AVMs and reports of de novo AVMs, nowadays AVMs are believed to develop after birth.[3]

Clinical presentation

Most commonly, the reason for symptoms caused by AVMs is rupture of the AVM with resulting intracerebral hemorrhage (41%–79%). The most frequent symptoms are headaches (9%–70%), seizures (11%–33%), and other focal neurologic deficits (20%).[4–7] These symptoms can be caused by a hemorrhage, the space-occupying effect of the AVM and by the so-called steal effect, which is a hypoperfusion of the brain parenchyma adjacent to the AVM. Cerebral AVMs with high shunt volumes can also cause chronic congestive heart failure, caused by the constantly increased volume load.[8] Approximately 15% of AVMs are asymptomatic.

The risk of hemorrhage averages 3% per year and is strongly dependent on several risk factors.[9] The most important risk factors are previous hemorrhage, deep location of the AVM within the brain, venous drainage into the cerebral deep venous system, and the presence of associated aneurysms.[9] Accordingly, the risk of hemorrhage is variable, ranging from below 1% (non-ruptured, superficial AVMs with superficial venous drainage) to over 30% per year (previously ruptured, deeply located AVM with deep venous drainage and associated aneurysms).

Classification

The most common classification is the Spetzler-Martin classification.[10] Originally, this classification is based on the presence of risk factors for neurological complications after open surgery of an AVM. However, nowadays, it is also used for general classification of AVMs. An estimation of the risk of hemorrhage of an AVM using the Spetzler-Martin classification is not possible. According to the factors listed in **Table 1**, AVMs are classified on a scale ranging from 1 to 5.

Imaging

The example of an AVM is shown in **Fig. 2**. Imaging typically shows enlarged pial arteries supplying the nidus, a contrast-enhancing tangle of small abnormal blood vessel. The draining vessels are often dilatated but can also sometimes be stenotic. Arterial flow signal in TOF angiography can be observed within the feeding arteries, the nidus, and the draining veins. Aneurysms associated with the AVM can occur in all of these segments (feeding arteries, nidus, and veins) and are a common cause of hemorrhage. Most AVMs are located supratentorially.

Treatment

In general, cerebral AVMs can be treated conservatively or interventionally. The indication for conservative or interventional treatment and the choice of the respective modality should always be performed in an interdisciplinary team, consisting of neurologists, neurosurgeons, interventional neurosurgeons or interventional neuroradiologists, and radiation therapists. Conservative treatment includes pharmacological therapy (e.g. analgetic and antiepileptic drugs) as well as pharmacological and non-pharmacological

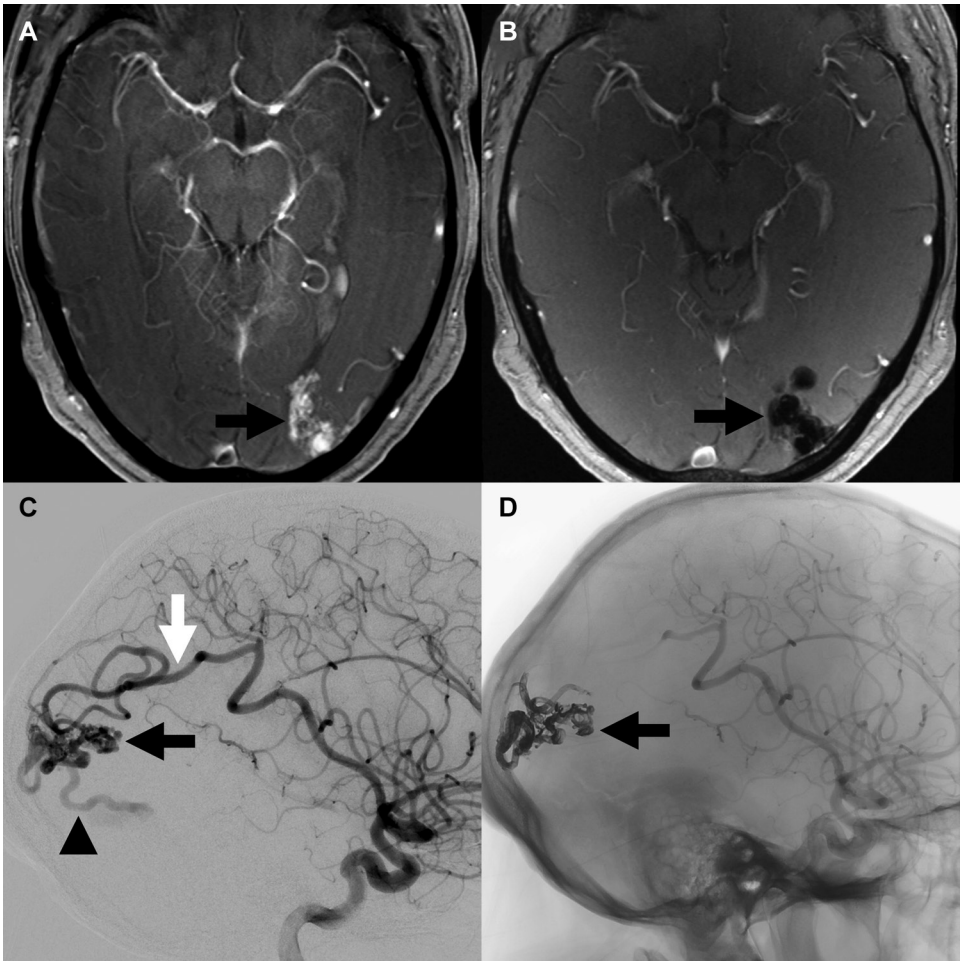

Fig. 2 Example of an arteriovenous malformation. Pre- (**A**, **C**) and post-interventional (**B**, **D**) images of a patient with a symptomatic, unruptured AVM. In the contrast-enhanced TOF angiography before treatment, the nidus of the AVM is visible as multiple contrast-enhancing small tubular structures, the so-called nidus (arrow in **A**). Pre-interventional DSA shows feeding arteries from a branch of the middle cerebral artery (white arrow in **C**) supplying the nidus (black arrow in **C**) and venous drainage into the superficial venous system (black arrowhead in **C**). After embolization with a liquid embolic agent, which is visible as hypointense material in MRI (arrow in **B**), the AVM is completely occluded (radiopaque cast of liquid embolic agent in **D**). AVM: arteriovenous malformation; DSA: digital subtraction angiography; MRI: magnetic resonance imaging; TOF: time-of-flight

reduction or minimization of risk factors, such as hypertension. Interventional treatment options are microsurgial exstirpation, endovascular embolization, and radiotherapy (also called radiosurgery). The aim of microsurgery is complete resection of the AVM. The principle of endovascular embolization is catheter-based occlusion of the malformation with embolic agents. Radiotherapy leads to the occlusion of the AVM as well; however, this effect occurs after a delay of several months up to 3 years. During this latency period, radiotherapy may confer some protective effects on the rupture risk.[11] In case of favorable location or angioarchitecture, both microsurgery and embolization can achieve high cure rates of over 90%.[12,13] For AVMs, which are primarily unresectable, endovascular therapy and radiation therapy can be effective treatment options. For large and/or complex AVMs, a combination of these different treatment modalities is often necessary.

The aim of every interventional treatment should be the complete elimination of the AVM. After partial resection, embolization, or radiation, the risk of hemorrhage mostly stays unchanged. In selected cases, for AVMs with components which are prone to hemorrhage, this risk of hemorrhage can be reduced by selective treatment of these factors. AVMs with associated aneurysms which have bled or have a high risk for hemorrhage, for instance, can be selectively treated by liquid

Table 2 The Cognard and Borden classifications for DAVFs

DAVF type		Cognard classification	Borden classification
Type I		Drainage in venous sinus, antegrade blood flow within the sinus	Drainage in duralen Sinus
Type II	IIa	Drainage in venous sinus, retrograde blood flow within the sinus	Drainage in venous sinus, antegrade or retrograde blood flow within the sinus, reflux in cortical veins
	IIb	Drainage in venous sinus, antegrade blood flow within the sinus, reflux in cortical veins	
	IIa+b	Drainage in venous sinus, retrograde blood flow within the sinus, reflux in cortical veins	
Type III		Direct drainage into cortical veins, no venous ectasia	Direct drainage into cortical veins with or without venous ectasia
Type IV		Direct drainage into cortical veins, presence of venous ectasia	-
Type V		Drainage in perimedullary spinal veins	-

or coil embolization of the aneurysms without occlusion of the whole malformation.

For unruptured AVMs, different opinions regarding the indication for an interventional therapy and the selection of the best treatment modality exist. In 2014, a randomised trial of unruptured brain arteriovenous malformations (ARUBA), in which patients with unruptured AVMs were randomized between conservative and interventional management, was stopped prematurely after including 223 patients.[14] The primary endpoint, which was defined as symptomatic stroke or death, was observed in 10% of the patients in the conservative treatment arm and in 31% of the patients in the interventional treatment arm. The results of this study are discussed controversially. One major criticism is that the observation period of 3 years is very short and allows only limited predication on the long-term course of treated and non-treated AVMs, whose risk of hemorrhage persists for the whole patient's life. Another point of criticism is that subgroup analyses regarding the different interventional treatment modalities will not be possible due to the low number of patients. However, according to the current literature, the decision on the treatment of unruptured AVMs should only be performed after a thorough consideration of risks and benefits. A treatment recommendation can be made in selected patients with AVMs with a high cumulative risk of hemorrhage and with a favorable location, size, or angioarchitecture for the respective treatment modality.

AVMs which have already bled should generally be treated interventionally because of the increased risk of re-rupture, which varies depending on the presence of risk factors between 5% (no risk factors) and 34% (two risk factors).[15] In this context, clinically silent hemorrhages, which can be diagnosed using susceptibility-weighted MRI, have a high predictive value for a new, clinically apparent hemorrhage.[16,17]

Dural Arteriovenous Fistulas

Definition

DAVFs are pathological connections between arteries which normally supply the dura and the dural and/or cerebral venous system. Arterial blood directly shunts into a dural sinus or into cortical veins without an intervening nidus. However, in some cases, multiple feeding arteries and multiple dilated cortical veins can be present which should not be misdiagnosed as a nidus of an AVM. DAVFs are usually acquired and can occur after craniocerebral trauma, operations of the head or brain and after thrombosis of the cerebral venous system. In most cases, however, no cause can be found.

Classification

The two most common classifications are the Cognard and Borden classifications which are summarized in **Table 2**.[18,19] These classifications are based on the way of venous drainage (dural sinus or cortical vein), the direction of blood flow in the affected venous sinus (antegrade or retrograde) and the presence of venous ectasia. They can be used for the estimation of the risk of hemorrhage of a DAVF.

Clinical presentation

The symptoms of a DAVF are dependent on several factors: Location, arterial supply, extent of the arteriovenous shunt, and type of venous drainage. The most common

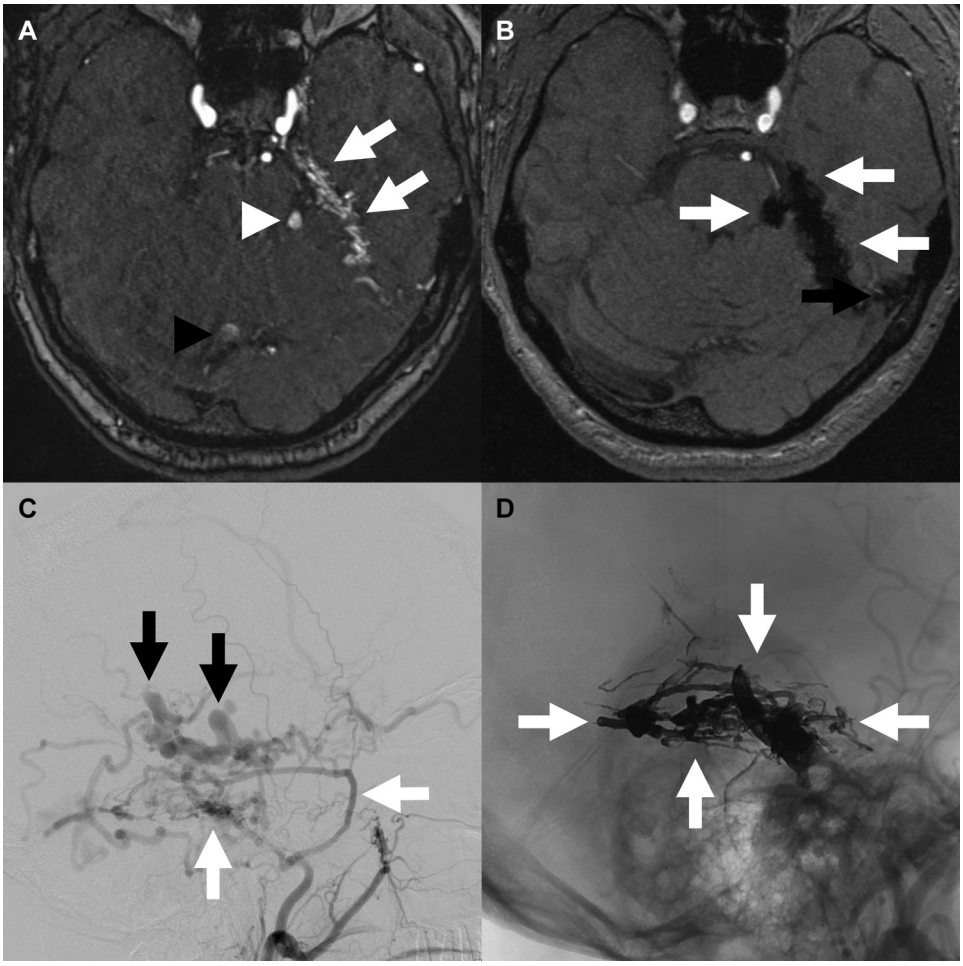

Fig. 3 Example of a DAVF. Pre- (**A**, **C**) and post-interventional (**B**, **D**) images of a patient with a symptomatic (pulsatile tinnitus) DAVF of the tentorium. MRI TOF angiography shows multiple hyperintense tubular structures around the left-sided tentorium, (arrows in **A**) and arterialized blood flow within adjacent dilated cortical veins (white arrowhead in **A**) and within the straight sinus (black arrowhead in **A**). In the pre-interventional DSA, multiple feeding arteries from the middle meningeal artery (white arrows in **C**) shunt into dilated cortical veins (black arrows in **C**), corresponding to a Cognard IV/Borden type III DAVF. After endovascular liquid embolization (radiopaque embolic agent: white arrows in **D**), the DAVF is completely occluded and the pulsatile tinnitus is no longer present. In post-interventional MRI (**B**), the embolic agent is visible as hypointense material (arrows in **B**). Pathological arterialized blood flow is now longer visible. DAVF: dural arteriovenous fistula; MRI: magnetic resonance imaging; TOF: time-of-flight

symptoms are pulsatile tinnitus, which can be frequently observed in patients with DAVFs of the transverse and sigmoid sinus, and headaches.[20] Especially large DAVFs with venous congestion can cause seizures and acute or chronic encephalopathy syndromes. The higher the type according to the Cognard and Borden classifications, the higher the bleeding risk of a DAVF. Cognard type V are a rare exception to this rule. Because of the drainage into perimedullary veins, these fistulas are associated with a risk of spinal venous congestion, potentially resulting in progressive myelopathy and imminent paraplegia, whereas intracranial hemorrhages are untypical for Cognard type V DAVFs. For low-grade DAVFs (Cognard I and IIa), the risk of hemorrhage is not increased, while for high-grade DAVFs (Cognard IIb to IV) it can be up to 20% per year.[20] For DAVFs of the transverse and sigmoid sinus, besides cortical venous reflux, which is a major risk factor for hemorrhage, sinovenous outflow obstruction is another important risk factor for intracranial hemorrhages.[21]

Imaging

The example of a DAVF is shown in **Fig. 3**. The feeding arteries, most frequently arteries of the territory of the external carotid artery (typically the middle meningeal

artery or the occipital artery), are often enlarged and near to the fistula point (the shunt between arterial and venous side) multiple small feeders can regularly be observed. The angioarchitecture of DAVFs ranges from singular feeding arteries and draining veins to complex fistula networks. A distinctive feature of DAVF in contrast to AVMs is the absence of an intra-axially located nidus. An important diagnostic criterion for DAVFs is the presence of arterialized blood flow within the venous system (venous sinus or cortical veins) in TOF angiography.

Therapy

The indication for therapy depends on the patient's symptoms and the risk of hemorrhage. For asymptomatic low-grade DAVFs (Cognard I and IIa), no treatment is necessary. Low-grade DAVFs with intolerable symptoms, mostly pulsatile tinnitus, and high-grade DAVFs (Cognard IIb and higher) should be treated for symptom reduction and to prevent hemorrhage. Nowadays, most DAVFs are treated safely and effectively by endovascular embolization.[22,23] One of the most frequent endovascular treatment techniques is transarterial embolization using liquid embolic agents, sometimes transvenous coil embolization is performed. In selected cases, special balloon catheters can be used to increase the effectivity and safety of the endovascular treatment.[24,25] Surgical treatment of a DAVF can be an option, especially in cases of subtotal or partial embolization, in which complete embolization cannot be achieved by endovascular means.[22] Radiation therapy is only rarely performed since the occlusion rate is comparatively low because of the shunt volume, which is typically high for DAVFs.[26]

Subtype: carotid-cavernous fistulas

Carotid-cavernous fistulas (CCFs) are a subtype of DAVFs. They consist of abnormal shunts between the between branches of the internal and/or externa carotid artery and the cavernous sinus. Generally, CCFs are idiopathic, but rarely they may be caused by rupture of an aneurysm of the cavernous segment of the internal carotid artery or by trauma. CCFs can be classified into direct and indirect fistulas and according to the involved vessel (internal or external carotid artery).[27] In this context, it is important to mention that direct CCFs, caused by aneurysm rupture or trauma, are strictly speaking no real "dural" arteriovenous fistulas. Common symptoms of CCFs of any kind are dilatation of scleral blood vessels (98%), pulsatile exophthalmus (88%), chemosis and subconjunctival bleedings (59%), as well as progredient loss of vision (50%).[28] Intracranial hemorrhages, caused by CCFs, are extremely rare.[29] Imaging often shows asymmetric dilatation of the cavernous sinus and of the superior ophthalmic veins, exophthalmos, and distension of the external eye muscles. Most CCFs can be treated safely and effectively by endovascular embolization, which frequently consists of transvenous coil occlusion of the affected cavernous sinus.[30] Both for indirect and direct CCFs, due to the deep location of this subtype of DAVF, surgical therapy often confers a high risk of postoperative morbidity.[31,32]

Cavernous Malformations

Cavernous malformation (also called cavernomas) are vascular malformations of the brain without an arteriovenous shunt. In contrast to AVMs and DAVFs, cerebral vascular malformations without arteriovenous shunting of blood, such as cavernous malformations, DVAs, and capillary telangiectasias, are generally accompanied by a comparetively low risk of hemorrhage. These malformations are often incidental findings in cerebral imaging and are most frequently asymptomatic.

Cavernous malformations are benign vascular pathologies which consist of multiple small blood-filled cavities which are lined with endothelium. They do not contain brain parenchyma. In 20% of the cases, more than one cavernous malformation is present, and in 75%, a familial form is the underlying cause of multifocal cavernous malformations.[33] Approximately 40% of all cavernous malformations are incidental findings.[34] Besides headaches, seizures are the most common symptom of cavernous malformations with a frequency of 25%.[35] The risk of hemorrhage of a cavernous malformation averages 1% per year.[36] The most important risk factor for hemorrhage is a previous hemorrhage: For asymptomatic patients without a previous hemorrhage, the risk of bleeding is 0.6%, while for patients who had a previous symptomatic hemorrhage, the risk is 4.5% per year.[33] In MRI, cavernous malformations show a typical morphology: popcorn-like configuration and mixed signal in T2-weighted images, as well as peripheral rim-like hypointensities which represent hemosiderin depositions (**Fig. 4**). The therapy of cavernous malformations depends on the patient's symptoms, the risk of hemorrhage, and the surgical accessibility. For incidental, asymptomatic cavernous malformations, conservative management is justified, while cavernous malformations which have bled or which are the underlying cause of epilepsy, microsurgical resection should be considered if the malformation is

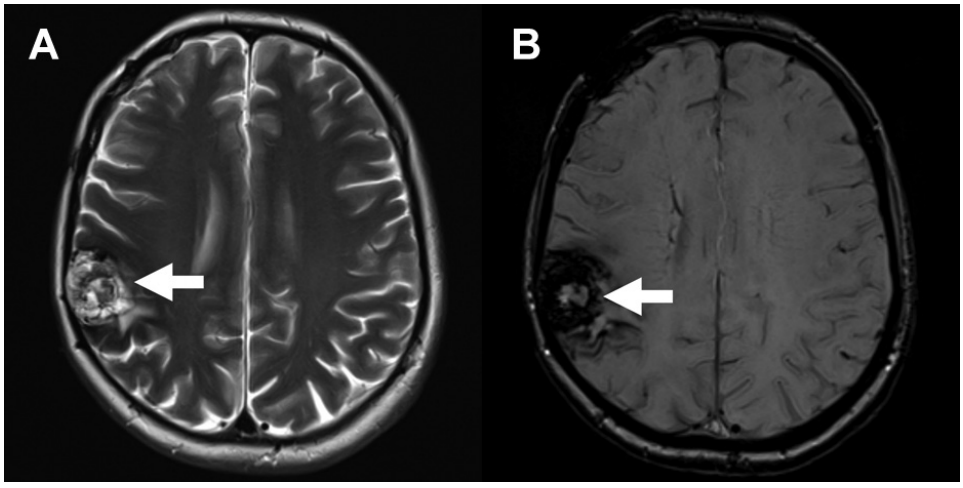

Fig. 4 Example of a cavernous malformation MRI of a patient with a symptomatic (headache) cavernous malformation in the right parietal lobe. The cavernous malformation shows heterogeneous signal in T2-weighted images (**A**) with a popcorn-like appearance. Susceptibility-weighted imaging (**B**) shows the hypointense rim at the periphery of the malformation, which is typical for this disease. MRI: magnetic resonance imaging

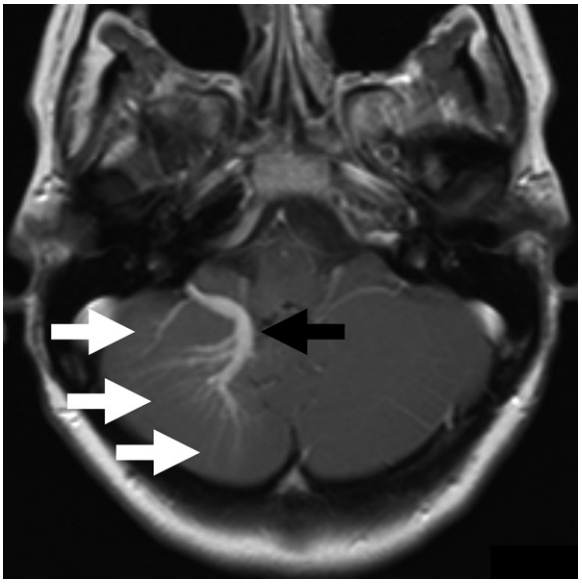

Fig. 5 Example of a developmental venous anomaly MRI of an asymptomatic patient. Contrast-enhanced T1-weighted image shows abnormal blood vessels passing through the right cerebellar hemisphere. Various blood vessels (white arrows) unite to a larger collecting vein (black arrow), resembling the head of the goddess medusa or a palm tree. MRI: magnetic resonance imaging

surgically accessible.[35] In cavernoma-associated epilepsy, microsurgical resection leads to complete cure of the epilepsy in 75% of the cases.[35] Cavernous malformations and DVAs can occur in the same location, which is referred to as mixed malformations.

Developmental Venous Anomalies

DVAs (also called venous angiomas) are a residuum of an embryological variant of the normal venous drainage of the cerebral parenchyma and accordingly congenital. DVAs are asymptomatic in the vast majority of cases. Only very rarely, headaches, hemorrhages, seizures, or focal neurologic deficits are observed. However, these symptoms are often not caused by the DVAs themselves but by associated cavernous malformations.[37] In MRI, DVAs are best identified in contrast-enhanced T1-weighted images and in susceptibility-weighted imaging and show a typical "palm tree" or "caput medusae" configuration (**Fig. 5**). Resection of DVAs is contraindicated since the collecting vein (the trunk of the palm tree or the base of medusa's head) participates in the physiological drainage of the brain, consequently obliteration of this vein can lead to venous congestion and infarctions.[37]

Capillary Telangiectasias

Capillary telangiectasias are a cluster of dilated capillaries with normal brain parenchyma between these vessels. The etiology of these malformations is unclear, normally they are congenital. Capillary telangiectasias are asymptomatic and are not accompanied by an increased risk of hemorrhage. Therefore, they do not have to be treated.[38] In MRI, they are visible as patchy, brush-like contrast-enhancing

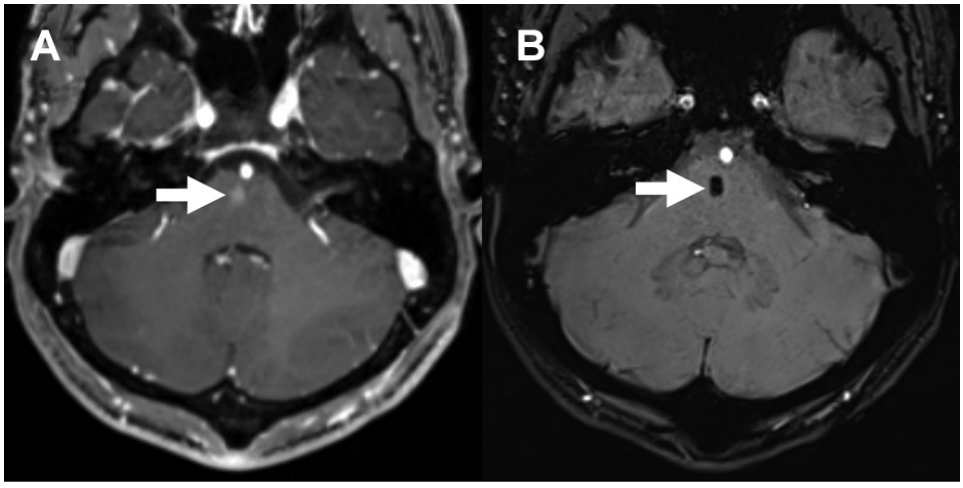

Fig. 6 Example of a capillary telangiectasia MRI of an asymptomatic patient. In contrast-enhanced T1-weighted imaging (**A**) shows an area of brush-like hyperintensities in the right-sided pons, corresponding to a capillary telangiectasia. In susceptibility-weighted imaging (**B**) capillary telangiectasias are typically hypointense. In T2-weighted imaging (not shown), they are often invisible. MRI: magnetic resonance imaging

areas with correlating hypointensities in susceptibility-weighted images (**Fig. 6**).

Disclosure Statement

The following conflicts of interest are present: DFV has received travel support outside this work from MicroVention and Stryker GmbH & Co. KG; MB reports board membership: DSMB Vascular Dynamics; consultancy: Roche, Guerbet, Codman; grants/grants pending: DFG, Hopp Foundation, Novartis, Siemens, Guerbet, Stryker, Covidien; payment for lectures (including service on speakers bureaus): Novartis, Roche, Guerbet, Teva, Bayer, Codman; MAM has received consulting honoraria, speaker honoraria, and travel support outside this work from Codman, Covidien/Medtronic, MicroVention, Phenox, and Stryker. All other authors have nothing to disclosure.

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