REVIEW ARTICLE - VASCULAR NEUROSURGERY - OTHER

Symptomatic developmental venous anomalies

Lorenzo Rinaldo [1] · Giuseppe Lanzino [1,2] · Kelly D. Flemming [3] · Timo Krings [4] · Waleed Brinjikji [1,2]

Abstract
Cerebral developmental venous anomalies (DVAs) are variations of venous vascular anatomy related to an underdevelopment of either the superficial or deep venous emissary system, resulting in a dilated transmedullary vein fed by multiple smaller venous radicles responsible for drainage of normal brain parenchyma. While typically benign and found incidentally on imaging studies, DVAs can rarely be symptomatic. The radiographic appearance of DVAs, as well as their symptomatic manifestations, is diverse. Herein, we will discuss the pathophysiology of symptomatic DVAs while providing illustrative case examples depicting each of their pathogenic mechanisms.

Keywords Developmental venous anomaly · Pathologic processes · Vascular malformation · Venous thromboembolism

Introduction

Developmental venous anomalies (DVAs) are relatively common vascular malformations found ubiquitously throughout the cerebrum, cerebellum, and brainstem. Their characteristic appearance is that of multiple parenchymal veins that coalesce into a larger collector vein, which subsequently drains into normal superficial or deep venous systems [44]. Typically an incidental finding on brain magnetic resonance imaging, estimates of DVA prevalence range from roughly 5 to 10% [23, 27, 34]. While the vast majority of DVAs are asymptomatic and follow a benign clinical course, there have been numerous reports of DVAs causing clinical symptoms, notably through multiple different pathophysiologic mechanisms [44] (Table 1). These lesions can represent challenging clinical

scenarios, as any treatment strategy must necessarily preserve the DVA, which by definition provides venous drainage to surrounding brain parenchyma [49]. In this review, we will summarize current understanding of the pathogenesis of DVA formation and discuss mechanisms by which DVAs can become symptomatic.

Pathogenesis

The cerebral venous network is composed of both superficial and deep venous systems. The former is primarily responsible for drainage of the cortex and underlying white matter via subcortical and superficial medullary veins, respectively, which drain outwardly in the coronal plane into pial veins. These surface veins then travel on the cortical surface and eventually empty into one of the large dural sinuses [43]. In contrast, the latter, which serves subcortical nuclei and deeper white matter, is composed of deep medullary veins draining inwardly towards the subependymal and Galenic venous systems [43]. Anastomotic connections between superficial and deep systems exist in the form of transmedullary veins, the direction of flow through which depends on pressure gradients between surrounding superficial and deep venous systems [43].

Cerebral veins demonstrate a high capacity for structural plasticity, evidenced by the reorganization of venous drainage patterns in response to occlusion of major outflow pathways. The restructuring of venous networks is believed to underlie

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✉ Lorenzo Rinaldo
Rinaldo.lorenzo@mayo.edu

1 Department of Neurosurgery, Mayo Clinic, 200 1st Street SW, Rochester, MN 55902, USA

2 Department of Radiology, Mayo Clinic, Rochester, MN, USA

3 Department of Neurology, Mayo Clinic, Rochester, MN, USA

4 Division of Neuroradiology, Department of Medical Imaging, Toronto Western Hospital, Toronto, Canada

DVA formation, with improper embryologic development or thrombosis of superficial or deep venous systems inciting the recruitment and dilatation of transmedullary veins to facilitate venous drainage [31, 41, 50]. This hypothesis underscores the importance of DVA preservation during any surgical approach, as within this conceptual framework the DVA exists to provide drainage to brain areas whose typical venous drainage patterns have been disrupted. DVAs have historically been considered congenital lesions, with their formation thought to be triggered by venous vascular accidents occurring during early embryonic development [41]. Supporting this view are reports describing the detection of DVAs on fetal MRI [22]. On the other hand, the prevalence of DVAs detected on intracranial imaging has been noted to increase with age, suggesting that DVAs may develop during later periods of venous development [8]; de novo formation of DVAs during childhood has also been reported [33]. One possible explanation for these observations is that DVAs develop secondary to venous occlusion occurring in the post-natal phase. An additional possibility is that while the venous insult and associated adaptations in venous architecture may transpire in utero, flow through and subsequent hypertrophy of the DVA happens in response to hemodynamic changes induced by normal events in post-natal venous development, for example, capture of the Sylvian vein territory by the cavernous sinus [8]. Supporting this hypothesis, serial imaging of DVAs through infancy has demonstrated the dynamic nature of DVA morphology during this period [25]. Ultimately, given the available evidence, it is our opinion that DVAs, at least in their characteristic form, are likely not congenital lesions, and the term "developmental" may not be strictly accurate.

Pathophysiology of symptomatic DVAs

Subsets of DVAs can become symptomatic through a variety of different mechanisms, which can be categorized as mechanical compression, decreased outflow or thrombosis, or increased inflow.

Mechanical compression

The most conceptually straightforward mechanism by which DVAs can result in clinical symptoms is mass effect, typically resulting in a compressive neuropathy or obstructive hydrocephalus. The most common type of DVA-associated compressive neuropathy is trigeminal neuralgia, 18 cases of which have been reported to date [51]. The symptomatology in this clinical context is similar to that of classical trigeminal neuralgia, characterized by stabbing pain in a trigeminal branch distribution in response to mild stimulation, though trigeminal neuralgia in this context tends to manifest in younger populations [51]. While large series investigating efficacy are unavailable due to rarity, surgical microvascular decompression or percutaneous ablative procedures have anecdotally been successful at ameliorating patient symptoms (Fig. 1). Similarly, hemifacial spasm secondary to compression from a DVA has also been reported [5, 14].

Blockage of ventricular outflow pathways by an adjacent DVA can result in obstructive hydrocephalus, with the site of compression occurring most commonly at the foramen of Monro or cerebral aqueduct [12]. Similar to trigeminal neuralgia, DVA-associated hydrocephalus again tends to manifest clinically in younger populations, though the age range among reported cases is fairly broad [12]. Traditional methods of cerebrospinal fluid diversion, specifically endoscopic third ventriculostomy or ventricular shunting, are effective treatment modalities.

Decreased outflow or thrombosis

The underlying pathophysiology of most symptomatic DVAs is venous hypertension, typically secondary either to decreased outflow, stenosis, or outright thrombosis. Several studies have documented perfusion abnormalities, specifically increased cerebral blood flow and volume, mean transit time, and maximum time to peak, in brain areas dependent on a DVA for drainage, though notably such abnormalities are also seen in asymptomatic patients (Fig. 2) [11, 26]. However, clinically relevant venous hypertension associated with a

Table 1 Overview of symptomatic DVAs

Mechanism	Symptomatic manifestations	Treatment options
Mechanical compression	Cranial nerve compression syndromes	Microvascular decompression; percutaneous rhizotomy
	Obstructive hydrocephalus	ETV, ventricular shunting
Decreased DVA outflow or thrombosis	Focal neurologic deficits, seizures, venous infarction	Symptomatic management, anti-epileptics, anticoagulation
Increased inflow/arteriovenous shunting	Focal neurologic deficits, seizures, venous infarction, intracranial hemorrhage (AVMs)	Observation, microsurgical resection, stereotactic radiosurgery

Abbreviations: *AVMs*, arteriovenous malformations; *DVA*, developmental venous anomaly
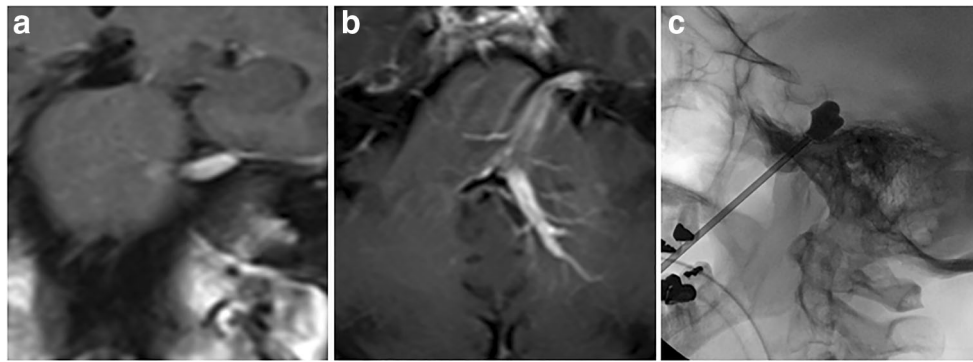
Fig. 1 DVA causing trigeminal neuralgia. A middle-aged female presented with paroxysmal facial pain consistent with trigeminal neuralgia. **a** Coronal and **b** axial gadolinium-enhanced T1-weight images demonstrated a large DVA fed by radicles originating in the deep cerebellar structures that traveled through the cerebellopontine angle and drained into the superior petrosal sinus. **c** The patient underwent percutaneous balloon compression with subsequent amelioration of her symptoms. Abbreviation: DVA developmental venous anomaly

DVA can occur. In such cases, patients typically present with focal neurologic deficit, headache, or seizure, with the nature of patient presentation depending on the acuity of the perfusion deficit secondary to the hypertension. In more severe cases, the impaired outflow can result in ischemia or hemorrhage. In Fig. 3, we present a case example of a middle-aged female presenting with acute onset of aphasia and right hemiparesis. Imaging studies demonstrated a large DVA in the left basal ganglia and an area of infarction in the caudate nucleus and corona radiata. Susceptibility-weighted images demonstrated evidence of medullary venous congestion and dilatation in that area. Sequelae of chronic venous hypertension can include cerebral edema, gliosis, demyelination, and siderosis or calcification, the symptomatology of which depends on the affected brain area. In spite of relative DVA stability, in such cases neurologic symptoms attributable to the DVA often worsen over time, likely stemming from progressive brain atrophy secondary to chronic venous congestion. In Fig. 4, we present images from a patient with a deep DVA providing venous outflow to right basal ganglia who experienced worsening left-sided hemiparesis over the span of two decades (Fig. 4). Comparison of CT scans obtained at initial presentation and later in his disease course demonstrated worsening mineralization of the right basal ganglia and progressive hydrocephalus ex vacuo (Fig. 4). Extreme examples of venous hypertension can be seen in the setting of DVAs associated with dural arteriovenous fistulas. Six of such cases have been reported, and in all instances the DVA drained into a dural sinus affected by the fistula [18, 30, 38, 40, 53, 58]. In these circumstances, the downstream shunt prevents normal arteriovenous transit time and produces a functional outflow obstruction, resulting in retrograde venous outflow and associated neurologic dysfunction and venous infarction in severe cases.

DVA thrombosis can precipitate venous hemorrhagic infarction in a manner similar to dural venous sinus thrombosis (Fig. 5). Even in patients with symptomatic anomalies, however, the risk of hemorrhage associated with a DVA is nevertheless small, estimated to be less than 1% per year [19, 34]. In such cases, treatment consists primarily of symptomatic management, for example initiation of anti-epileptic medications and decompressive surgery in instances of significant mass effect and cerebral herniation syndromes, though infarcts large enough to warrant the latter are likely to be exceedingly uncommon. In addition, there have been a numerous report detailing symptomatic improvement after initiation of anticoagulation in patients

Fig. 2 DVA associated with local perfusion abnormalities. **a** Coronal and **b** axial gadolinium-enhanced T1-weight images demonstrate a DVA draining the right posterior frontal cortex. **c** Axial images from arterial spin labeling sequences demonstrated increased cerebral blood volume in the region served by the DVA. Abbreviation: DVA developmental venous anomaly
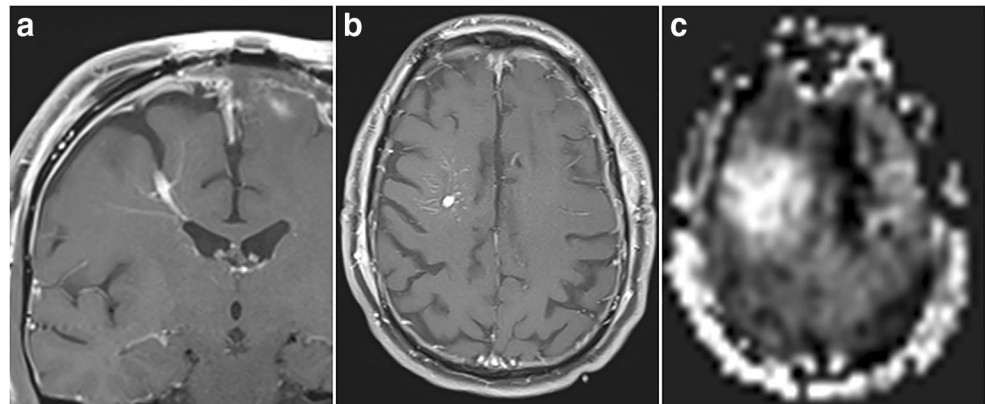
with a thrombosed DVA [4]. Whether anticoagulation in such cases provides a significant improvement over the natural history of small venous infarctions and should be considered, standard therapy requires further investigation.

Interestingly, DVA thrombosis and resultant hemorrhage may be related to the pathophysiology of cavernous malformations (CMs), though it should be emphasized that DVA thrombosis is not strictly necessary for CM formation. The association between DVAs and sporadic CMs is well-known [1, 45], and it has been theorized that the latter may form in response to neoangiogenic signaling cascades triggered by venous insufficiency [55, 56]. While not all sporadic CMs occur in tandem with a DVA on standard imaging, a recent study utilizing 7-Tesla MRI demonstrated that locoregional derangements in venous outflow were present in all patients with sporadic CMs, regardless of the presence or absence of a classical DVA on standard imaging, suggesting a pathologic link between impaired venous outflow and CM formation [15]. In support of this hypothesis is the observation that DVA-associated CMs are uncommon in pediatric populations and that their prevalence significantly increases with age, consistent with an acquired lesion [7]. Risk factors for the development of DVA-associated sporadic CMs have been identified and include infratentorial location (of the DVA), tortuosity, multiplicity, kinking, outflow obstruction, and the presence of comorbid inflammatory disorders (Fig. 6) [29, 60].

In the absence of thrombosis with or without associated hemorrhage, whether or not seemingly uncomplicated DVAs can cause clinical symptoms, presumably secondary to mild venous hypertension but potentially through other mechanisms, is not entirely clear. A common but sometimes challenging clinical scenario is that of a patient found to have a DVA on an MRI obtained for evaluation of headaches. Indeed, in multiple case series detailing the clinical history of patients harboring a DVA, headache was most often the symptom prompting the imaging study leading to the diagnosis [21, 42, 57]. Based on these reports, however, in most cases headaches are rarely attributable to a DVA, which is most likely incidental. Headache characteristics that may indicate venous hypertension related to a DVA include acute to subacute onset and focal distribution, suggesting possible DVA thrombosis. In the setting of a suspicious headache, MRI with susceptibility-weighted images should be undertaken to evaluate for venous thrombosis and small CMs that may be occult on less sensitive imaging modalities [48]. For most patients, however, the natural history headaches occurring in the setting of a DVA is likely self-limited and benign [37]. In a prospective series in which patients found to have a DVA underwent long-term follow-up, the prevalence of headaches decreased over time despite management of the DVA with simple observation, suggesting that the DVA was most likely unrelated to the initial presentation [42]. A similar clinical scenario is that of patient

Fig. 3 Cerebral infarction secondary to impaired venous outflow through DVA. A middle-aged woman presented with right-sided hemiparesis. a and b Non-contrast head CT demonstrated a hypodensity in the left caudate nucleus and corona radiata suggestive of infarction. Also noted were dense calcifications in the left basal ganglia (arrow). c An area of ischemic infarction was confirmed on diffusion weighted images. d Coronal images from magnetic resonance angiography demonstrated a large DVA draining the caudate nucleus and other subcortical structures. Axial images from gradient echo sequences demonstrate e the chronic mineralization of the basal ganglia and f T2-star signal in the medullary veins of the left cerebral hemisphere indicative of venous congestion. Abbreviation: DVA developmental venous anomaly
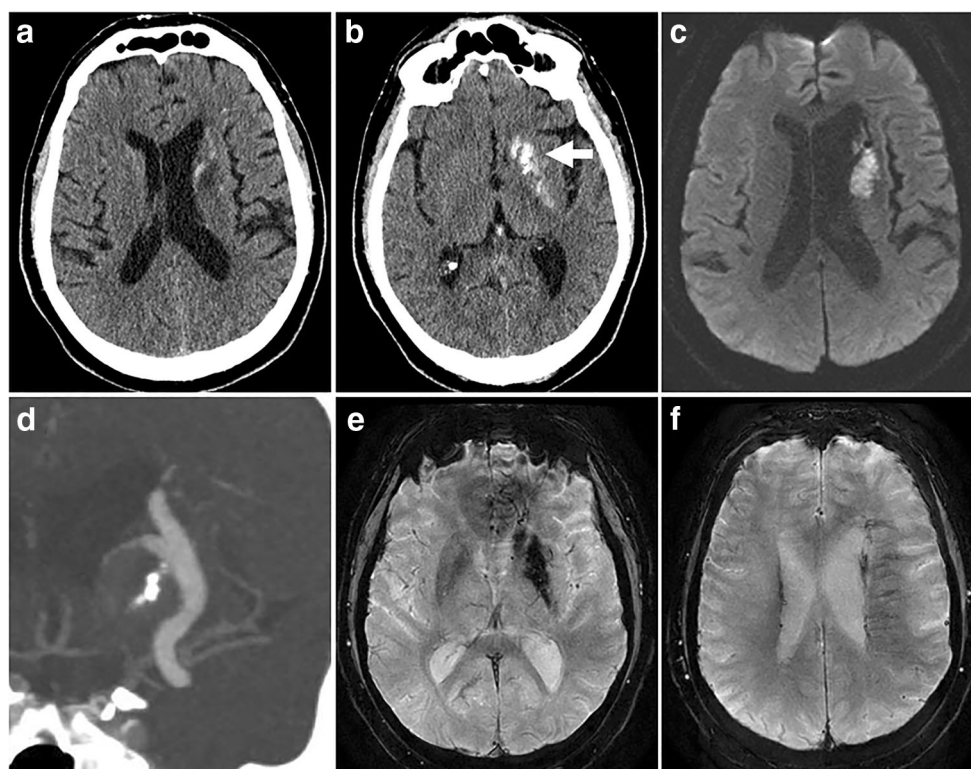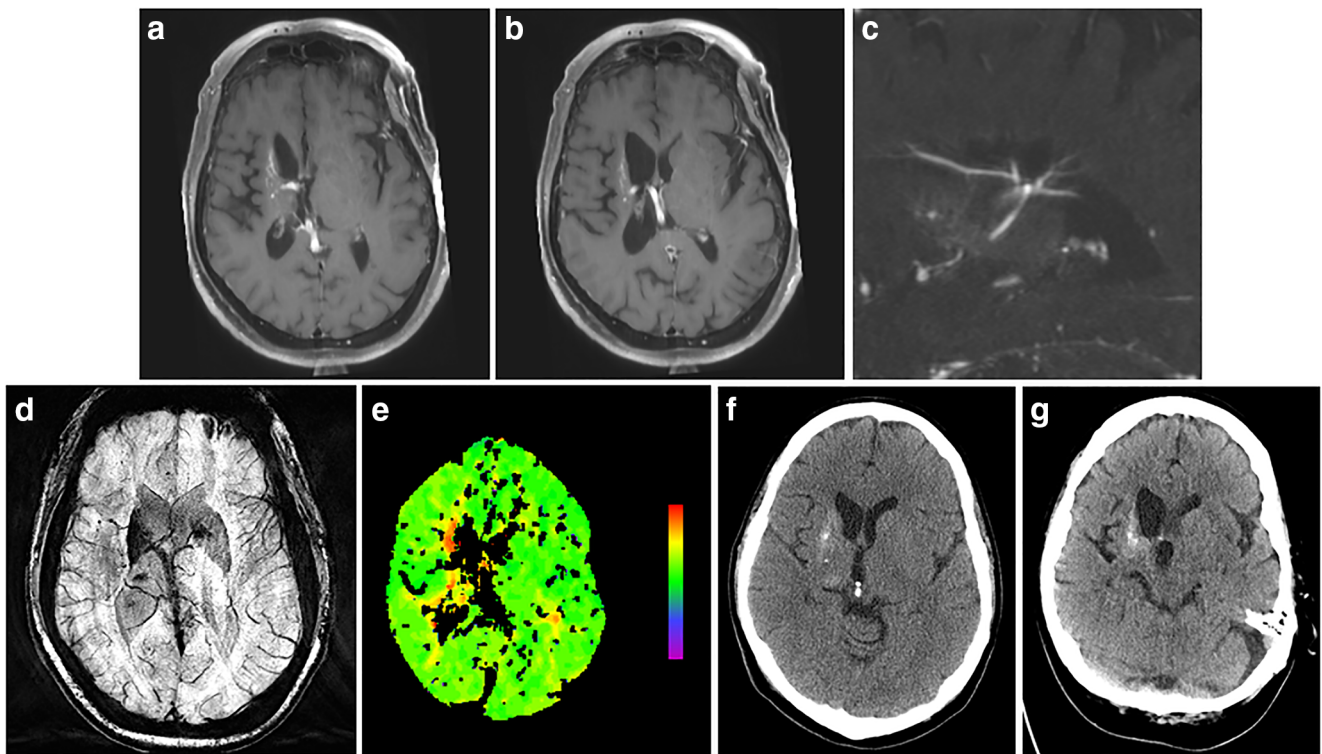
Fig. 4 Progressive hemisyndrome in setting of DVA. Axial **a–b** and sagittal T1-weighted gadolinium enhanced images demonstrating a DVA with radicles originating in the right corona radiata and basal ganglia. **d** Increased T2-star signal in the right basal ganglia suggestive of venous congestion. **e** CT perfusion study demonstrating subtle increased time to peak in the area drained by the DVA. **f–g** Non-contrast head CT imaging at initial presentation (**f**) and at a follow-up visit approximately 10 years later demonstrating increased mineralization within the right basal ganglia and ex vacuo dilatation of the right lateral ventricle

with a DVA presenting with seizures. While the epileptogenicity of CMs is well-established, available literature suggests that isolated DVAs rarely cause seizures in the absence of associated thrombosis or hemorrhage [39, 54, 57, 59]. These findings reinforce the dictum that conservative management of a newly discovered DVA, even in the presence of neurologic symptoms potentially attributable to the lesion, is the most appropriate initial management strategy.

Increased inflow

After thrombosis of a DVA and associated reactive neoangiogenesis, subsequent recanalization of the DVA may lead to arteriovenous shunting, again producing venous hypertension in adjacent brain parenchyma due to competition for drainage with arteriovenous shunts. There have been reports of DVA-associated CMs that subsequently transformed
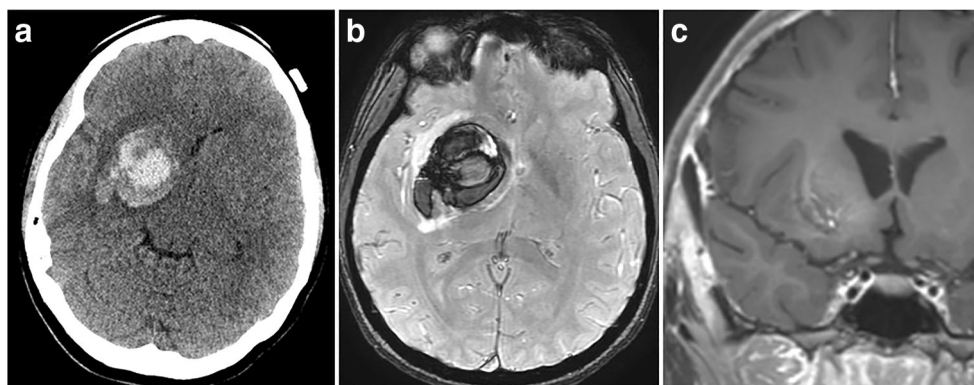

Fig. 5 DVA associated with large basal ganglia hemorrhage. **a** Non-contrast head CT demonstrated a large basal ganglia hemorrhage. **b** T2-weigted FLAIR images from an MRI performed shortly after the hemorrhage did not show evidence of an underlying mass or other etiology for the hemorrhage. **c** Coronal T1-weighted gadolinium enhanced images from an MRI obtained several months after the initial hemorrhage demonstrated a DVA in the area of the previously seen hematoma, suggesting DVA thrombosis as the underlying cause of hemorrhage. Abbreviation: DVA developmental venous anomaly

into arteriovenous malformations (AVMs) [3], and 22 cases of AVMs with venous drainage through a DVA have been reported [16]. The location of shunting is within a characteristic nidus, which then empties into a DVA. Arteriovenous shunting directly through a DVA in the absence of a classical compact nidus is referred to as a transitional venous anomaly (TVAs). Differentiating these entities from AVMs associated with DVAs can be challenging due to similarities in their radiographic appearance; however, for TVAs, shunting occurs exclusively within radicles of a DVA, giving their nidus a more diffuse appearance (Fig. 7), whereas for DVA-associated AVMs shunting occurs outside of DVA radicles. In addition, TVAs do not exhibit signs of high-flow arteriopathy, for example, feeding artery aneurysms and arterial dilation, and venous opacification is not seen until the capillary phase due to the lower flow through these lesions relative to AVMs [16]. TVAs are rare, with only 30 prior cases reported in the literature [16], and the pathologic processes leading to their formation are not known. It is possible that venous hypertension due to impaired outflow through a DVA fosters development of arteriovenous shunting in a manner akin to the proposed pathophysiology of dural arteriovenous fistulae [13]. In particular, venous hypertension likely triggers

release of vascular endothelial growth factor and subsequent neoangiogenesis [24, 28], leading to arteriovenous connections within DVA radicles. Regardless of their etiology, these anomalies remain as the venous outflow pathway for normal brain parenchyma despite the shunting, and thus are associated with a high incidence of hemorrhage and neurologic dysfunction related to venous hypertension. A review of reported cases found respective incidences of hemorrhage of 61.1 and 55.2% in patients with TVAs and AVMs with venous drainage through a DVA. In patients presenting without hemorrhage, a significant proportion was nevertheless symptomatic, with the most common symptoms including headache, seizures, and focal neurologic deficits. Treatment of symptomatic TVAs, either via micro- or radiosurgery, has been associated with a high rate of venous infarction [16], and thus we strongly favor observation as an initial management strategy. In the setting of progressive and worsening symptoms, determining the safest option between micro- and radiosurgery is difficult, and hinges on the ability of either modality to specifically target the arteriovenous connections while preserving normal venous outflow pathways. In the setting of numerous and diffusely interspersed DVA radicles (Fig. 7b), radiosurgery may be a safer option;

Fig. 6 Cavernous malformations associated with DVAs. **a** and **b** Left posterior frontal cavernous malformation associated with an underlying somewhat tortuous DVA. **c** and **d** Axial images from 7-Tesla susceptibility-weighted imaging sequences demonstrate a large, highly tortuous DVA draining the deep cerebellar nuclei associated with multiple small brainstem cavernous malformations (*arrows*). Abbreviation: DVA developmental venous anomaly
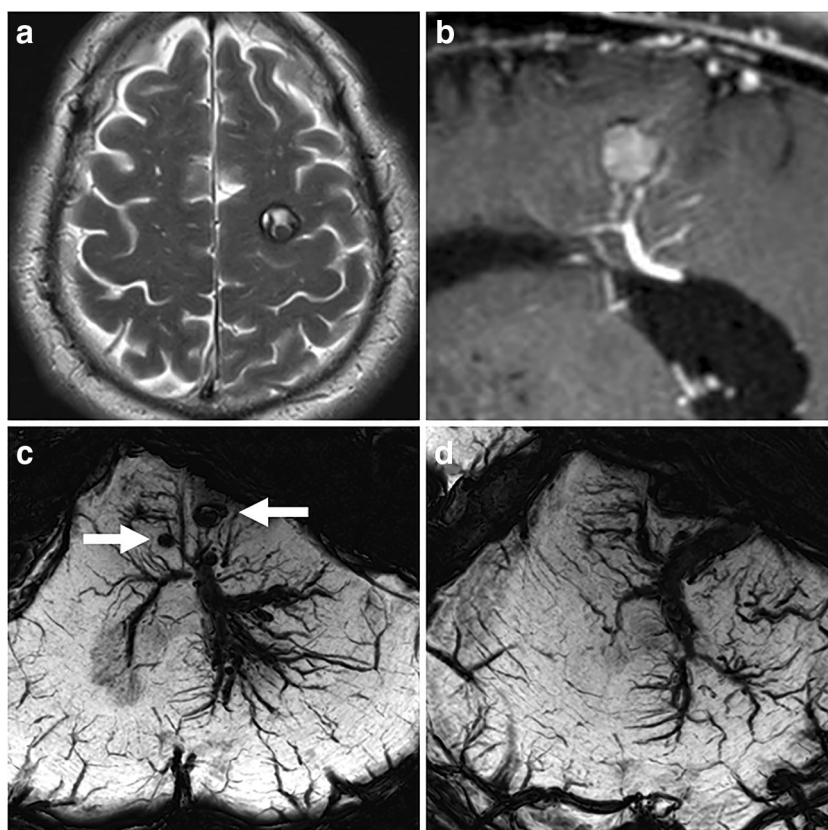
however, this is unproven and requires further investigation. Regarding AVMs associated with DVAs, traditional treatment paradigms employed for standard AVMs are associated with favorable rates of complete obliteration and low rates of morbidity and mortality [16], though during treatment every attempt should be made to spare the DVA if possible [61].

Other venous anomalies and their potential correlation with DVAs

Venous abnormalities that are congenital in nature but different from the abovementioned classical DVAs include sinus pericranii and dural sinus malformations. Sinus pericranii are rare lesions consisting of an intradiploic emissary vein egressing from the superior sagittal sinus and draining into the subgaleal space, usually within a large venous varix [36]. Patients typically present with a non-pulsatile midline mass that becomes more prominent under Valsalva conditions (Fig. 8). These lesions represent a connection between the intra- and extra-cranial venous system, and up to 50% of these lesions have been associated with cerebral DVAs, often serving as the drainage pathway for the DVA when present (Fig. 8) [20]. Patients with a suspected sinus pericranii (SP) should undergo Doppler ultrasonography as an initial diagnostic study to determine whether the mass is vascular. Subsequent magnetic resonance or computed tomographic venography is generally sufficiently diagnostic. SP are potentially disfiguring lesions, but can also be the cause of neurologic symptoms, again through venous hypertension. If treatment of a SP is considered, the importance of the lesion to cerebral venous outflow must be clearly defined, necessitating formal cerebral angiography. If angiography demonstrates the flow of contrast to be predominant through the SP and not the dural venous sinuses, then the SP is considered dominant and should be preserved. If only a small proportion of venous egress occurs through the SP, then it is considered accessory and can be treated [20].

Non-shunting dural sinus malformations are also rare lesions characterized by enlargement of the torcula herophili and adjacent transverse sinuses [9]. This ballooning is believed to occur at some point between the 4th and 7th month of fetal development and persists into child- and adulthood for unknown

Fig. 7 Transitional venous anomaly. **a** Non-contrast head CT demonstrating an area of focal calcification and punctate hemorrhages in the right frontal cortex. **b** Cerebral angiography demonstrated a transitional venous anomaly, with arteriovenous shunting occurring in the radicles of the collector vein. **c** The patient underwent craniotomy and resection of the lesion. **d** An area of venous infarction is seen on post-operative non-contrast head CT
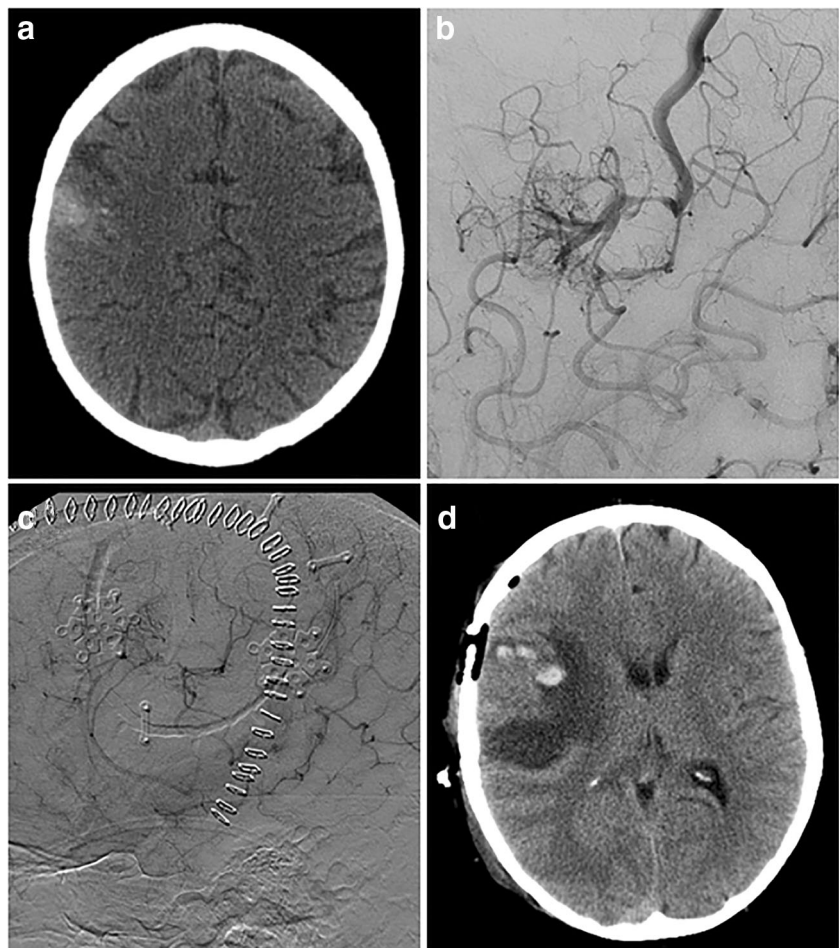
Fig. 8 Sinus pericranii associated with paramidline foramen. **a** Three-dimensional reconstructions from a CT venogram performed in a patient with a midline scalp mass demonstrated a subgaleal venous varix in connection with the cerebral venous system, consistent with a sinus pericranii. The lesion did not appear to constitute a dominant pathway for cerebral venous drainage. **b** The paramidline foramen was seen on three-dimensional reconstructions of bony windows
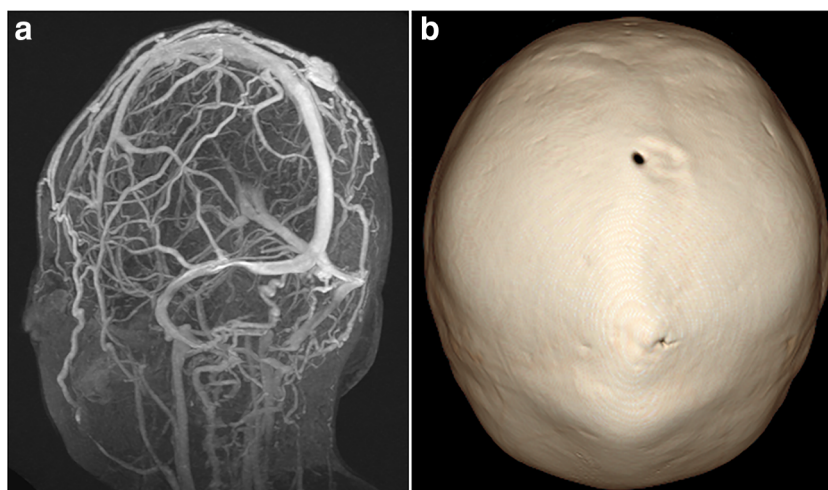
reasons [36]. While these malformations have been associated with a number of additional vascular abnormalities, including cerebral DVAs, cavernous malformations, facial venous malformations, SP, and others, isolated dural sinus malformations have not been found to cause symptoms and should be managed with observation. There is also a subset of
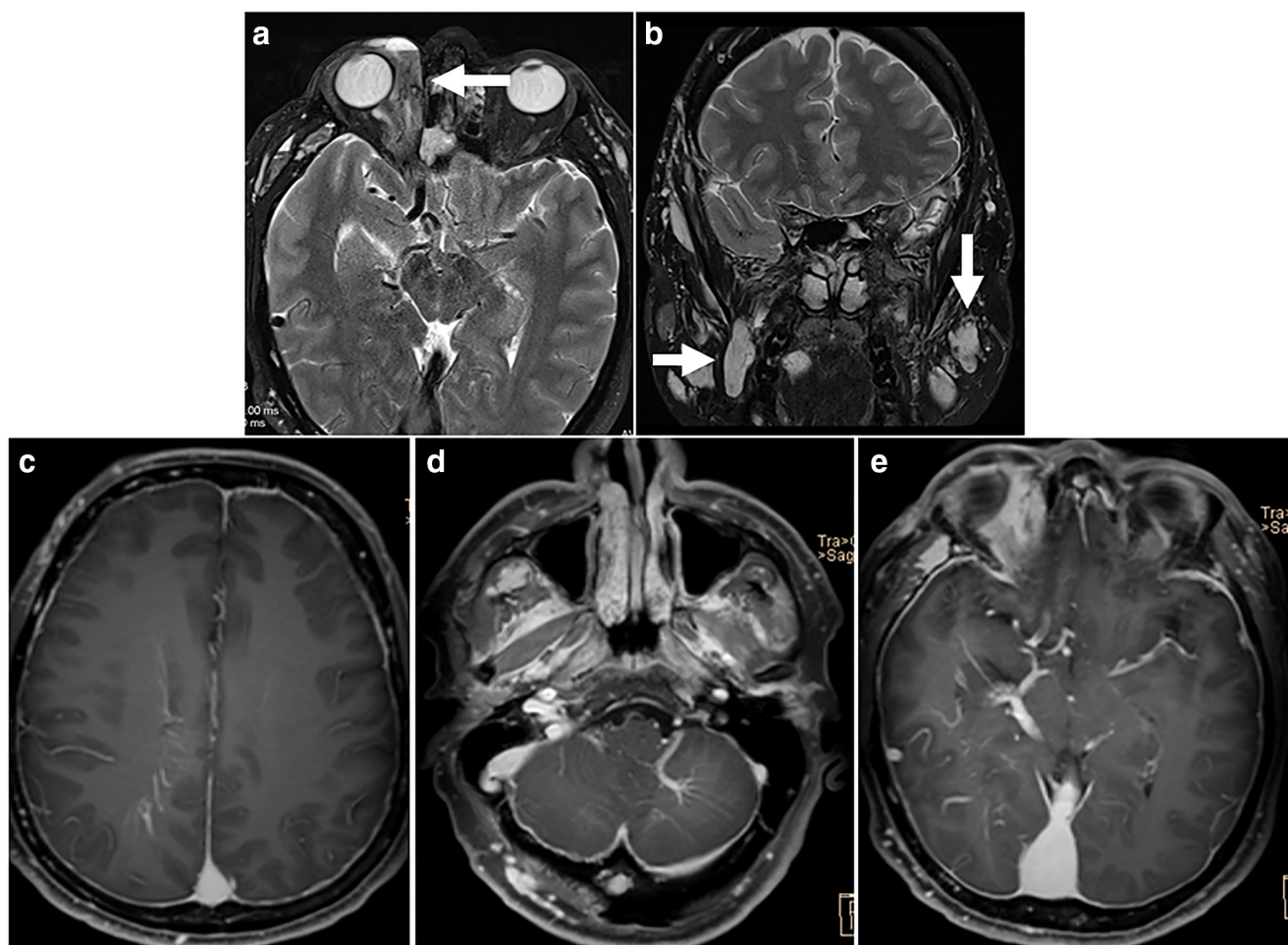
Fig. 9 Cerebral venous metameric syndrome (CVMS) types 2 and 3. A patient with multiple orbito-facial venous vascular anomalies in a pattern consistent with CVMS types 2 and 3. T2-weighted images demonstrating multiple **a** orbital (*arrow*) and **b** facial venous malformations (*arrows*). **c** and **d** Axial gadolinium-enhanced T1-weight images demonstrating multiple DVAs. **e** Slight engorgement of the torcula herophili was also noted. Abbreviations: CVMS cerebral venous metameric syndrome, DVA developmental venous anomaly

dural sinus malformations in which the dural sinus ectasia is associated with the presence of multiple arteriovenous shunts. These lesions are typically managed with staged embolization and do not have as strong an association with multiple venous vascular anomalies as non-shunting dural sinus malformations.

DVAs and cerebrofacial venous metameric syndrome

A fairly strong association between the presence of facial venous malformations (FVMs) and cerebral DVAs has also been observed [6, 10], a discussion of which is worthwhile as it yields potential insight into the underlying pathogenesis of DVAs. Facial venous malformations (FVMs) are uncommon lesions consisting of enlarged venous channels found in the head and neck regions typically manifesting as soft-tissue swelling underlying a bluish discoloration of the skin. Though they exhibit a benign and indolent natural history, FVMs can be quite disfiguring and even cause symptoms due to local mass effect, for example, airway compromise [2]. In a majority of patients with both FVMs and DVAs, the DVA has been observed to be ipsilateral to the FVM and located in the same metamere [10], suggesting the possibility of a common underlying etiology. The presence of both a maxillofacial and cerebral venous malformation meets criteria for cerebral venous metameric syndrome (CVMS), of which there are multiple types (1–3) depending on the respective locations of the FVM and DVA [32]. An example of CVMS type 2 and 3 is presented in Fig. 9. The underlying pathophysiology of CVMS is incompletely understood, but may be related to a prothrombotic state, potentially secondary to molecular defects of vascular endothelium, leading to vaso-occlusive events early during development and subsequent proliferation of facial and venous vascular malformations in a metameric distribution [10]. Efforts to understand the pathologic processes underlying CVMS are ongoing and may illuminate the molecular processes underlying DVA formation.

Other associated syndromes

A number of pathologic conditions have been associated with the presence of cerebral DVAs, including constitutional mismatch repair deficiency syndrome (CMMRD) [52], Cowden syndrome (CS) [17], and diffuse adult [47] and diffuse intrinsic pontine gliomas [46]. Both CMMRD and CS are cancer-predisposition syndromes, the former of which occurs due to bi-allelic mutations in any number of genes involved in correction of DNA replication errors [52], while the former is secondary to mutations in the phosphatase and tensin homolog (PTEN) gene, which plays a role in arresting cell growth and division [19]. These conditions are associated with a variety of different malignancies, including primary central nervous system neoplasms. While the molecular biology of adult gliomas is diverse and involves myriad signaling pathways, diffuse intrinsic pontine gliomas are frequently observed in the setting of histone H3 mutations, leading to aberrant DNA methylation patterns and subsequent unrestrained cell growth [35]. What all these conditions and their underlying molecular pathophysiology have in common with DVAs are unclear. In addition, whether or not the presence of DVAs is related to cancer development or contributes to disease severity is an intriguing, though speculative, possibility. To date, what can be gleamed from these various associations is that the processes underlying DVA formation are likely heterogeneous. Further investigation into the mechanisms underlying these associations will hopefully lead to a better understanding of DVA pathophysiology.

Conclusion

In this review, we have discussed the pathophysiology of symptomatic DVAs and provided a radiographic overview of their symptomatic manifestations. DVAs are fascinating lesions, the underlying pathophysiology of which is incompletely understood. Critical to the management of DVAs is the recognition that they drain normal brain, and thus in most, if not all, circumstances must be preserved.

Compliance with ethical standards

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