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REVIEW

Developmental venous anomalies and brainstem cavernous malformations: a proposed physiological mechanism for haemorrhage

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Abstract

The incidental diagnosis of both developmental venous anomalies (DVAs) and cavernous malformations (CMs) in the central nervous system is increasing with improved imaging techniques. While classically silent diseases, these cerebrovascular pathologies can follow an aggressive course, particularly when present in the brainstem. In the last decade, substantial research has focussed on KRIT1-mediated tight junction gene expression and their role in CM development. However, our understanding of the physiologic conditions precipitating symptomatic CM development or CM haemorrhage with and without concomitant DVAs, remains lacking. The only established risk factor for CM haemorrhage is a previous history of haemorrhage, and literature currently reports trauma as the only precipitant for symptomatic events. While plausible, this occurs in a minority, with many patients experiencing occult events. This manuscript presents a hypothesis for symptomatic CM events by first discussing the anatomical pathways for intracranial venous outflow via the internal jugular veins (IJV) and vertebral venous plexus (VVP), then exploring the role of venous flow diversion away from the IJVs under physiologic stress during dynamic postural shift. The resultant increase in intracranial venous pressure can exacerbate normal and pre-existing structural DVA pathologies, with repeated exposure causing symptomatic or CM-inducing events. This pathophysiological model is considered in the context of the role of the autonomic nervous system (ANS) in postural intracranial venous outflow diversion, and how this may increase the risk of DVA or CM events. It is hoped that this hypothesis invokes further investigation into precipitants for DVA or CM events and their sequela and, also, furthers the current knowledge on pathophysiological development of DVAs and CMs.

Keywords Brainstem · Cavernous malformation · Developmental venous anomaly · Haemorrhage · Posterior fossa drainage

Introduction

Developmental venous anomalies (DVAs) and cavernous malformations (CMs) are cerebrovascular phenomena that can have significant impact on morbidity and mortality. Up to one in ten patients have a DVA identified over their life course, and a significant portion of these have an associated CM [1, 2]. Brainstem CMs account for 20% of central nervous system CMs [3]. While benign lesions, DVAs and CMs may follow symptomatic or uneventful clinical courses. Brainstem CMs are known to follow a more aggressive clinical course, though the reason for this remains unknown. It is worth noting that the word "event" is used throughout in this manuscript in the context of symptomatic presentation of a CM or DVA that may or may not be related to an overt haemorrhage, occult haemorrhage or microhaemorrhage.

This paper aims to explore the relationship between intracranial venous anatomy and factors affecting intracranial venous outflow. The current literature on DVA and CM development is reviewed before furthering the hypothesis on the physiologic mechanisms leading to symptomatic and asymptomatic events relating to DVAs and CMs. In an area lacking contemporary research, this paper serves to re-engage the neurosurgical community in a discussion that furthers our current understanding of this area.

Posterior cranial fossa venous drainage

The venous drainage of the posterior fossa follows one of two routes: through the internal jugular vein (IJV); or through the cerebrospinal outflow of the vertebral venous plexus (VVP)

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[4, 5]. Under normal physiologic conditions, the route of venous outflow is via the higher capacitance IJV (dominant in 72% of individuals), with the VVP of lower capacitance and smaller contribution to the cerebral venous outflow (dominant in only 6%) [4, 6]. It has been suggested that the VVP can withstand up to one third of cerebral venous outflow [6]. There are no direct anastomoses between the IJV and VVP, but the inferior petrosal sinus is a conduit between these two major venous outflow vessels that assists in drainage of the posterior fossa [5].

The major cerebral vessels that drain into the IJV include the sigmoid sinus and the inferior petrosal sinus. Brainstem tributaries to the inferior petrosal sinus are:

1) Anterior pontomesencephalic, transverse pontine, anterior medullary and parenchymal perforating veins, all of the anterior brainstem [7];
2) Brachial veins of the precentral cerebellar fissure [7];
3) Superior and inferior hemispheric veins above and below the cerebellar hemispheres [7];
4) Medial tonsillar and retro-olivary veins of the cerebellar-side of the brainstem [7]; and
5) Vein of the lateral recess of the fourth ventricle [7].

Postural changes to cerebral venous outflow

When sitting or standing, blood is redistributed unevenly in favour of the lower peripheries [8]. Similarly, postural changes in blood flow are seen in the vessels of intracranial venous outflow, such as the internal jugular vein [8]. Studies have shown that the luminal diameter of the IJV is reduced in sitting and standing positions, and during dynamic postural shift from supine to sitting, when compared to supine positions [4, 9, 10]. Postural changes result in changes to cerebral venous pressure, with extra-jugular pathways to the right atrium, such as the VVP, being utilised [4, 9–11]. Upright postural changes, thus, result in two changes to cerebral venous outflow:

1) IJV collapse (incomplete or complete) due to reduced cerebral venous outflow and tissue pressure exceeding IJV luminal pressure [4, 11];
2) Shunting of blood from the (now) high resistance-collapsed IJV to the (now) lower resistance VVP [4, 11].

With a reduced luminal diameter in sitting and standing positions, the IJV transforms into a higher resistance vessel unable to maintain a normal capacitance, with venous outflow diverted to the VVP [4]. Physiologic studies suggest that diversion of flow to the VVP results in suboptimal compensation [6, 12].

It is hypothesised that this redirection results in venous pooling in all tributaries of the IJV, most significant in the posterior fossa circulation, before achieving VVP-dominant outflow in non-supine positions. This venous pooling causes a transient, localised dilation in order to withstand this increase in blood [12]. As cerebral venous pressure rises above approximately 40 mmHg, the IJVs exceed tissue pressure and restore flow [12]. In normal vessels, this is an asymptomatic and manageable event, but can exacerbate existing structural venous pathology, which is discussed further below.

Cavernous malformations

Cerebral CMs are described histologically as dilated, thin-walled sinusoids with hyalinisation of capillary or venous origin [13–15]. They may be benign cerebrovascular lesions that follow an unremarkable clinical course [2, 3, 16, 17]. The diagnosis of benign CMs is usually incidental [17, 18]. Other CMs are more aggressive and present with symptoms such as seizures or focal neurologic deficits due to mass-effect or haemorrhage [3, 16, 17]. The symptomatic presentation of CMs depends on their location; with cerebral lesions most commonly manifesting with seizure; brainstem lesions with focal neurologic deficits; and cerebellar lesions with truncal or limb ataxias [19, 20].

The KRIT1 gene codes for proteins that strengthen tight junctions in endothelial cells [13]. Thirty-five defects in this gene are associated with CMs that have a familial association, and two mutations in sporadic CMs have been found [13, 21]. In addition to KRIT1, the genes RAP1A, PDCD10 and CCM2, which are involved in signalling for and synthesis of tight junction proteins, have lower expression in patients with CMs [21, 22]. It appears that the KRIT1 defect is most applicable to sporadic CM cases, whereas the other mutations occur almost exclusively in familial CM [13, 22].

The KRIT1 gene encodes for several tight junction proteins, including claudins, occludins, ZO-1, ZO-2 and ZO-3, which bind the basolateral surface of adjunctive endothelial cells [13, 21, 23]. Tight junctions are a functional barrier between endothelial cells that prevent blood and blood product from entering the parenchymal tissue; forming one of the major components of the blood-brain barrier (BBB) [16, 24]. The other major components of the BBB are perivascular astrocytic foot processes and the basement membrane [13, 25]. In all CM genotypes (KRIT1, RAP1A, PDCD10 and CCM2), an absence of astrocytes has been noted, with gaps up to 1 μm between endothelial cells [13, 22]. In place of these astrocytes is a thin and acellular collagenous membrane contributing to a compromised BBB [13].

Since 2014, research has established that CMs contain qualitative and quantitative defects in tight junction protein expression [16]. These CMs originate in seemingly normal

venous structures suggesting microscopic and genetic abnormalities, such as KRIT1 mutations, may precede the development of CMs [13, 21, 22]. Three groups of tight junction variants have been identified, and these remain heterogeneous across CMs, including [16]:

1) Focal qualitative defects in tight junction proteins;
2) Quantitative absence of tight junction expression; and
3) Normal tight junctions.

It is important to note that we are unsure if these phenotypes can occur independently of CMs, in a macroscopically normal vein. The heterogeneous collection of tight junctions within a CM may be temporally related to diseased venous segments and increased vascular permeability. Thus, blood extravasation related to a cause growth of a CM may have one of four spontaneous or precipitant-induced consequences [16, 20]:

1) Asymptomatic or symptomatic venous dilatation [16, 19];
2) Chronic asymptomatic blood extravasation (microhaemorrhage) [13, 20, 26];
3) Chornic or acute symptomatic blood extravasation (microhaemorrhage or macrohaemorrhage) [20, 26]; or
4) Blood extravasation with induction of local vascular growth factors (PDGF, TGF-beta, FGF, EGF and VEGF) to incite repair, leading to CM growth [27].

Symptomatic venous dilatation without haemorrhage has been characterised in the past, with the presence of symptoms attributed to increased venous flow through the venous segment due to an arteriovenous shunt; a decrease in outflow; or remote shunts with increased venous pressure [28]. A reduction in venous outflow is of significant importance in explaining a relationship with CMs and is discussed further later. While the discussion thus far has focused on normal venous segments, another consideration explored later is the role of dysfunctional venous segments and DVAs in the role of CM development.

Considering venous genetic mutations precedes sporadic CM development, vascular growth factors would promote proliferation of sinusoidal endothelial cells with these tight junction abnormalities, resulting in disorganised endothelial cell proliferation and CM development [13, 26].

Brainstem cavernous malformations — risk factors and interventions

Brainstem CMs are known to be more aggressive than those found in other regions of the CNS or body [29, 30]. They have an annually observed first-time haemorrhage rate up to 6.6% and a re-haemorrhage rate of up to 39.5%/year [31]. Thus, previous haemorrhage is a risk factor for CM re-haemorrhage [2, 32]. A more recent cohort study of 154 patients has suggested that young age, infratentorial location and presence of a DVA are significant risk factors for haemorrhagic events [30]. Other studied risk factors include sex and multiplicity of lesions, but their significance is less certain [3, 32–34]. The sporadic nature of haemorrhagic events creates difficulty in identifying any definite risk factors or precipitating events.

While identification of multiple risk factors for CM formation has been confirmed, there is also little information regarding precipitant events for haemorrhage. Current literature suggests the only proposed mechanism for overt haemorrhage is high-energy trauma [35, 36]. While plausible in some cases, other CM haemorrhagic events are occult.

With brainstem CMs having either benign or symptomatic presentations, it warrants the asking of whether the lesion itself or the haemorrhagic event is problematic and necessitates intervention. Indeed, haemorrhage of a CM is no small event, with vital structures located within the brainstem. It would make sense then, to intervene in a patient with recurrent haemorrhage from a brainstem CM, or if the first-time haemorrhage was large enough to cause a life-threatening presentation. However, the literature remains scant with research or case reports of patients with a long history of recurrent haemorrhage, any precipitating events, and the progression of their neurological deficits from these events or any interventions subsequently sought.

It would seem that the best treatment for brainstem CMs involves one of four management options: preventing the haemorrhage from occurring by identifying precipitating factors; targeting of the cellular signalling cascades associated with KRIT1 (and other gene products if identified); surgical removal of the CM; or radiation-induced fibrosis of the CM to reduce further haemorrhagic events. The latter two are well-established interventions for brainstem CMs. Genetic CM research has focused heavily on the importance of KRIT1 mutations and the implications of intracellular signalling in DVA and CM pathogenesis, with identification of important drug targets in rat models. Sulindac derivatives targeting beta-catenin signalling in the PDCD10 mutation of familial CMs have shown reduced aberrant vascular malformation development [22, 37]. This research is promising, but yet to be translated to humans, and the search for molecular targets for sporadic CM is ongoing [22].

Developmental venous anomalies — description and CM association

Developmental venous anomalies are well-described variants of normal cerebral veins, and among the most common of cerebrovascular malformations [14, 38]. Appearing as dilated

veins separated by nervous tissue, DVAs are sometimes characterised by thickening and hyalinisation of the venous wall with a lack of smooth muscle and elastin—features shared with CMs [39, 40]. They often intersperse normal cerebral venous architecture, and although their relationship with elevated venous blood pressure has been noted previously in the literature, it is not extensively studied [40]. Due to the rarity of their clinical significance, DVA imaging architecture is briefly discussed below.

Imaging modalities including computed tomography (CT) and, preferably, magnetic resonance imaging (MRI) can be used to visualise DVAs. Smaller DVAs may not be readily apparent, but larger DVAs are identifiable. DVAs appear on non-contrast CT imaging as small, dilated tributary veins feeding an engorged collecting vein [40]. Contrast CT imaging reveals multiple linear dots of enhancing foci that converge on a single dilated vein [40]. T1-weighted MRI sequences often do not show smaller vessels, and T2-weighted techniques will reveal a small, signal-void vessel [40]. Parenchymal abnormalities around a DVA have been described on MRI previously, although this is not necessary for diagnosis [40]

The prevalence of DVAs increases throughout the lifespan, with a linear increase seen from 1.5% in the first year of life, to 9.6% beyond the age of 18 [41]. Often benign and following an asymptomatic course, most DVAs are found incidentally or at autopsy [1]. A small portion of DVAs presents symptomatically with compression of local structures [1]. In the brainstem, this is typically as a focal cranial nerve deficit [1, 38]. These symptomatic presentations of brainstem DVAs can occasionally be attributed to the venous malformation itself, or if present, an associated CM [15].

It has been suggested that up to 23% of CM patients have a concurrent and adjacent DVA [20, 42]. Unpublished preliminary data from an analysis of 3110 patients with brainstem CM treated by gamma-knife radiation therapy or microsurgery suggests that up to 10.0% of brainstem CM patients have concurrent pathologies (W Maish et al., in press) [20, 42]. Interestingly, the prevalence of CMs with concurrent DVA increases from 0.9% in the first decade of life to 11.6% by the eighth decade of life [20]. It is unknown if the CM is a direct sequela of the DVA or an independent entity, with previous research suggesting that thrombosis or stenosis of a DVA or DVA tributary may cause CM development [14, 23]

A small single-centre study completed in 2005 suggested that DVAs and CMs are of distinct genetic cell lines, with DVAs being venous phenomena while CMs are capillary or arterial in nature [43]. Whilst the origin of DVAs is accepted to be venous, this literature search found no further data on the tissue origins of CMs to support their arterial origin. Multiple studies have sited the origin of CMs to be from capillary and venous structures, or a combination of both [14, 15, 44–47]. No gene product mutations were specified in these studies. Given suggestion of similar histological venous origins of CMs and DVAs, the relationship between these two entities regarding reduced structural venous integrity and haemorrhagic events requires ongoing investigation [15, 23, 30].

Current research of the genetics underlying developmental venous anomalies, particularly those associated with CMs, is equivocal. This is an area that warrants further investigation to establish the relationship of sporadic KRIT1-associated CMs with DVAs of similar cellular origin.

IJV autonomic regulation — a role in CM development?

We now diverge from CMs and DVAs to discuss the role of autonomic regulation of the IJV effecting cerebral venous outflow. Like other muscular vessels, the muscular layer of the IJV is under the influence of the autonomic nervous system, having adrenergic receptors present in its venous wall [12]. The presence of cholinergic receptors in the jugular veins of humans is debatable, and the influence of parasympathetic vasomotor tone in the IJV is subsequently unknown [12]. Sympathetic adrenergic activation can cause an increase in venous tone, leading to increased luminal pressure and maintenance of IJV [12, 48]. Inhibition or non-activation of these receptors would have the opposite effect, reducing venous tone and loss of IJV patency [48]. Daily activities, such as sitting and standing, can cause transient shifts in balance of the sympathetic and parasympathetic nervous systems—an "autonomic argument" [49, 50].

Both sitting and standing induce transient activation of the sympathetic nervous system, as evidenced by elevations in plasma catecholamine levels, heart rate and blood pressure [49–51]. With rapid switching between activation and non-activation of IJV adrenergic receptors, it may be that autonomic argument results in IJV venospasm, similar to the sympathoexcitatory vasospasm seen in subarachnoid haemorrhage patients with raised plasma catecholamine levels [52]. This venospasm creates a low-flow state, with subsequent diversion of cerebral venous outflow into the VVP. As the half-life of plasma catecholamines is reached, this venospasm becomes less apparent, with restoration of patency and normalisation of venous outflow [53]. In a normal venous system, this is an asymptomatic and transient event, but existing intracranial venous pathology may predispose venous endothelial segments to micro-tears, with multiple venospasm episodes required to elicit symptomatic trauma.

It should be noted that the phrase "venous hypertension" is avoided, as the classical definition of hypertension implies a sustained or chronic elevation in blood pressure [54]. Transient changes to venous blood pressure affected by

posture and the ANS do not produce a sustained change in venous pressure, and thus, this is not a true venous hypertension.

In exercise-trained individuals facing daily stress (such as postural changes), this response is dampened, and there is a more dominant role played by the parasympathetic nervous system [55]. That is, less 'autonomic argument' between the parasympathetic and sympathetic systems occurs on postural change in exercise-trained individuals when compared to non-exercise trained individuals. Exercise training is known to help reduce the autonomic argument that can alter the patency of the IJV. This topic requires further laboratory investigation in the setting of understanding adrenergic and cholinergic receptor presence in the IJV before determining their role, if any, in symptomatic and asymptomatic CM events.

A proposed mechanism for DVA and CM haemorrhage

There are known mutations that compromise the BBB in both familial and sporadic CMs, and known endothelial dysfunction in DVAs and venous segments associated with CMs. Postural compromise of IJV patency results in raised intracranial venous pressure, while the VVP incompletely compensates for venous outflow. IJV compromise may be further exaggerated by autonomic argument due to transient daily stressors. The engorgement of tributary veins is a pathologic state in a system compromised by KRIT-mutated tight junctions of venous segments precipitating CM development. Multiple episodes of elevated venous pressure may have significant sequela in these structures, including venous events, DVA haemorrhage, formation of a CM due to blood-product extravasation or CM haemorrhage [26].

While the extravasation of blood or blood products into the parenchyma through these dysfunctional tight junctions is a possible explanation for CM development, the BBB acts to prevent this occurrence [13, 25]. With dysfunctional venous segments in normal vasculature or DVA and tight junctions in CMs, the BBB loses structural integrity [13, 56]. The perivascular astrocytic foot processes and the basement membranes are the only remaining components attempting to maintain the BBB [13]. However, we know that astrocytes and normal basement membranes are absent in CMs, with a thin collagenous band replacing this tissue [13]. Under normal physiologic conditions, this dysfunctional BBB supported merely by collagen may be enough, yet transient elevations in venous pressure may exaggerate the abnormality, or exceed the capability for collagenous or endothelial repair.

The sporadic nature of haemorrhagic events are explained by three components. The first is the heterogeneous tight junction phenotype expressed by KRIT1 mutations present in CMs and their associated veno-capillary structures, and potentially macroscopically normal veins. Quantitative and qualitative defects are present in conjunction with normal tight junctions in all DVAs and CMs [16]. The second is the compromise of at least one, but likely all, layers of the BBB, leading to symptomatic or asymptomatic haemorrhagic events only when the capacity for normal physiologic range is exceeded. The final is transient postural changes in intracranial venous pressure. The combination of these three events provides a plausible mechanism for sporadic, and not constant, haemorrhage.

There is an argument for the role of venous stenosis in raising the pressure within a cerebral vein to cause symptomatic or asymptomatic events from DVAs and CMs. Radiologic studies have concluded that the presence of a venous stenosis is not correlated with significant clinical events, while confirming that DVAs or venous stenoses and CM presence do indeed have a relationship [57, 58]. With no significant correlate found, it can only be surmised that venous stenosis may be a contributing, and not precipitative, factor to DVA and CM events.

There remain certain triggers for a state where IJV patency is compromised, including sitting and standing positions, as well as autonomic argument. This has significant clinical implications for the treating clinician and patient, including operative, non-operative or conservative management and the potential to limit life-changing permanent neurological decline. Addressing the factors contributing to IJV compromise is difficult due to the practicality of sitting and standing in daily living, and an inadequate current understanding of influencing the autonomic nervous system by lifestyle, pharmacological, surgical interventions. Future research assessing the relationship of the ANS with the IJVs is needed, along with analysis of the standard of care—microsurgery—compared to both gamma-knife radiation therapy and conservative management.

Comments on interventions addressing IJV patency and venospasm

In exercise-trained individuals facing daily stress (such as postural changes), the rapid changes between autonomic system predominance is dampened, and a more dominant role played by the parasympathetic nervous system [55]. That is, there is less 'autonomic argument' between the ANS subdivisions during and after postural change in exercise-trained individuals when compared to non-exercise trained individuals.

It may be that consistent exercise improves the balance between, and control of, autonomic divisions, resulting in improved cerebral venous outflow in all postures. This would reduce the risk of IJV vasospasm secondary to autonomic argument, which has the potential implication of symptomatic DVA or CM haemorrhage. Exercise-induced autonomic

regulation and IJV spasm remains an area with scant research, perhaps because it is uncommonly clinically applicable. However, given the benefits of exercise on holistic health, it would be recommended that patients in a position to exercise do so at the discretion of their neurosurgeon and treating team.

Additional therapies for future consideration may address IJV patency in surgical and non-surgical settings. Current knowledge of the regulation of the IJV lies in our understanding that there are adrenergic receptors present in the vessel wall. However, current literature assessing class of these adrenergic receptors and establishing the presence or deficiency of cholinergic receptors is limiting further progress in this field. Laboratory studies in the future addressing this issue are needed before considering the highly experimental surgical approach briefly discussed below.

Positive pressure breathing in sitting or standing positions and a supine position are two non-surgical methods by which IJV patency can be maintained [4, 9, 10]. These are impractical techniques for the general population. IJV patency in all postures could theoretically be maintained through unilateral IJV stenting. Unilateral IJV stenting utilises the collateral VVP to create a parallel series of vessels, while maintaining some autonomic regulation in the contralateral IJV. This technique has been used controversially for cases of jugular stenosis in patients with multiple sclerosis [59].

A recent study highlighted that jugular percutaneous transluminal angioplasty (PTA) conferred no significant change to the number of new multiple sclerosis lesions at 12 months when compared to a sham group [60]. However, the authors did suggest that PTA may effect the dynamic of the BBB to account for the statistically insignificant reduction in the number of new lesions [60]. While controversial for multiple sclerosis, this remains an avenue for exploration in reducing long-term, transient elevations in venous pressure in patients with CMs.

The predominant side of the draining vein for the DVA or CM could be identified and stented to reduce the risk of venous congestion. A bilateral stenting procedure theoretically eliminates all autonomic jugular regulation, with significant implications for cerebral venous outflow and cerebral perfusion. A novel application of an external, unilateral peri-IJV stent applied with sutures approximating the mesh stent to the subendothelium of the IJV would reduce the risk of thrombus formation—a major complication of endovascular stenting. A perijugular stent may also reduce IJV autonomic control, and the luminal diameter of the stent would need to account for current venous flow in supine, sitting and standing positions to avoid undesirable cerebral outflow. The risk of adventitial dissection if the stent is too rigid is another consideration. This controversial approach would require an extensive study in animal models before consultation with vascular and haemodynamic experts was considered preceding human trials.

Conclusions

Haemorrhagic events from DVAs and CMs are likely multifactorial. Our understanding of the pathogenetic formation of DVAs and CMs is evolving, though the mechanism for haemorrhagic events remains elusive. We suggest that postural compromise of IJV patency and subsequent autonomic argument are two mechanisms that can explain intracranial venous pooling that may precipitate micro-trauma in cerebral veins with pre-existing tight junction defects. Multiple micro-tear events to this venous segment result in one of four sequalae in healthy venous segments or pre-existing DVAs: (1) symptomatic or asymptomatic dilatation; (2) blood asymptomatic extravasation; (3) symptomatic blood extravasation; or (4) CM development and haemorrhage. Consideration must be given to the DVA as the cause of haemorrhagic events and CM formation, and treatment of this. Further laboratory and in vivo research are of vital importance in understanding the relationship between CMs, DVAs and postural changes in cerebral venous outflow with autonomic regulation.

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