Cerebral Cavernous Malformations, Developmental Venous Anomaly, and Its Coexistence: A Review

Pretty Sara Idiculla\textsuperscript{a} Dhinshreddy Gurala\textsuperscript{b} Jobin Philipose\textsuperscript{b} Kartikeya Rajdev\textsuperscript{c} Prateek Patibandla\textsuperscript{d}

\textsuperscript{a}University of Missouri Health Care, Columbia, MO, USA; \textsuperscript{b}Staten Island University Hospital, Northwell Health, Staten Island, NY, USA; \textsuperscript{c}University of Nebraska Medical Center, Omaha, NE, USA; \textsuperscript{d}Tower Health Reading Hospital, West Reading, PA, USA

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Cerebral cavernous malformations · Developmental venous abnormality · Mixed cerebral vascular malformations

Abstract

Background: Cerebral cavernous malformations (CCMs) are intracranial vascular malformations that can exist as a single lesion or mixed vascular lesions. The most common mixed form is the coexistence of CCM with an associated developmental venous anomaly (DVA). In this paper, we aim to give a comprehensive review of CCM, DVA, and their coexistence as mixed lesions. A PubMed search using the keywords “Cerebral cavernous malformations, Developmental venous anomaly, Mixed Cerebral cavernous malformations with Developmental venous anomaly” was done. All studies in the English language in the past 10 years were analyzed descriptively for this review. Summary: The search yielded 1,249 results for “Cerebral cavernous malformations,” 271 results for “Developmental venous anomaly,” and 5 results for “Mixed Cerebral cavernous malformations with Developmental venous anomaly.” DVA is the most common intracranial vascular malformation, followed by CCM. CCM can have a wide array of clinical presentations like hemorrhage, seizures, or focal neurological deficits or can also be an incidental finding on brain imaging. DVAs are benign lesions by nature; however, venous infarction can occur in a few patients due to acute thrombosis. Mixed CCM with DVA has a higher risk of hemorrhage. CCMs are angiographically occult lesion, and cerebral digital subtraction angiography is the gold standard for the diagnosis of DVA. Mixed lesions, on the other hand, are best diagnosed with magnetic resonance imaging, which has also been effective in detecting specific abnormalities. Asymptomatic lesions are treated through a conservative approach, while clinically symptomatic lesions need surgical management. Conclusion: Individual CCM or DVA lesions have a benign course; however, when they coexist in the same individual, the hemorrhagic risk is increased, which prompts for rapid diagnosis and treatment.

Introduction

Cerebral cavernous malformations (CCM) are intracranial vascular malformations that can exist as a single or mixed vascular lesion. The most common mixed form is the coexistence of CCM with an associated develop
mental venous anomaly (DVA). These lesions follow a benign course as individual lesions but have a high risk of hemorrhage when they occur together. In this paper, we discuss in detail the topic of CCM, DVA, and their occurrence as a mixed vascular malformation.

Intracranial Vascular Malformations

Intracranial or cerebral vascular malformations are a group of vascular lesions with varying hemodynamic or structural properties (Fig. 1). Aneurysms – abnormal saccular outpouchings of the cerebral arteries [1]. Moyamoya disease – chronic occlusive cerebrovascular disease resulting in progressive stenosis of the internal carotid artery and its branches [2]. Capillary telangiectasia – dilated thin-walled capillaries due to the absence of smooth muscle or elastic fibers [3]. Arteriovenous malformations – clusters of abnormal arteries and veins with an increased risk of intracranial bleed, more common in young adults [4]. DVAs – most commonly encountered malformation involving the intracranial venous system, which are also known as venous angioma, cerebral venous medullary malformation, or cerebral venous malformation [5]. CCM – vascular spaces of varying sizes, lined by a single layer of endothelin with no distinct features of arteries or veins [6]. Mixed vascular malformation – coexistence of vascular malformations and the most commonly encountered form is a CCM that occurs in association with a DVA [7].

Cerebral Cavernous Malformations

CCMs are also called as cavernous angioma, cavernous hemangioma, or cavernoma.

Genetics

Hereditary or familial CCM – this constitute about 20% of all cavernomas in patients, has a positive family history, and it commonly occurs as multiple lesions. It occurs from autosomal dominant mutation of 3 genes CCM1, CCM2, and CCM3 [8] (Table 1). In most cases, it can be a nonsense, frameshift, or splice site mutation, resulting in a nonfunctional protein product. In some cases, there can be a deletion or duplication of multiple exons or the entire gene [9]. Sporadic CCM – sporadic cavernomas are less common and occur as single lesions. They are usually asymptomatic and may occur in association with a DVA [10].

Epidemiology

CCMs have an incidence of <1%, an annual hemorrhage risk of up to 3%, and a rebleed risk of 4.5–23% per year [12]. They are the second most common form of intravascular malformations, after DVA. The malformations can be present in any age group, though it is found to be more common during the third decade of life [10]. A prospective imaging study done in the Mayo Clinic involving 4,721 individuals of ages between 50 and 89 years found an overall prevalence of 0.46%, with a slightly high-
er prevalence among men than among women [13]. The overall prevalence of familial CCM is about 1:3,300–1:3,800, and the occurrence of symptomatic hereditary mutations is approximately 1:5,400–1:6,200 [14]. There are studies that suggest a higher occurrence of familial CCMs in patients with a Hispanic ancestry of Mexican or southwest US-American descent [15, 16].

Pathology
CCMs are single-layer endothelin-lined vascular spaces without intervening brain parenchymal tissue within them [17]. There is low pressure and slow flow of blood within the lesion, which results in thrombus formation, followed by its organization, and this occurs in a repetitive fashion. These features are grossly visualized as the characteristic “mulberry appearance” [18]. There is insufficiency of the tight and adherens junctions of the endothelial cells, resulting in leaking and a dysfunctional blood-brain barrier [14].

Clinical Presentation
CCMs can have varied presentations depending on the location of the lesion. They can be supratentorial, which affects the cerebral cortex, and infratentorial, affecting the brainstem or the cerebellum; however, most of them are supratentorial lesions [19]. When these lesions become symptomatic, it can have a wide array of clinical presentation that includes seizures, hemorrhage, headache, and focal neurological deficits [20]. Supratentorial lesions have been found to present more commonly with seizures, whereas infratentorial malformations present with focal neurological deficits [21]. There are studies that try to explain the natural course of hemorrhage occurring in patients with CCM [22, 23]. Gross and Du [24] summarized the risk factors for hemorrhage in these patients, which included prior hemorrhage from a cerebral cavernous angioma, female sex, and brainstem location of the lesion. Cavernous angiomas are a rare cause of an isolated non-aneurysmal SAH, and very few cases have been reported [25].

Diagnosis
Imaging Studies
CCM diagnosis is particularly challenging to the practicing physicians because they tend to be angiographically occult due to the slow blood flow through them. Due to their increased potential of recurrent bleeding, early detection and prompt management are demanded [9].

CT Scans
CT scans can detect lesions that are complicated by hemorrhage or calcification but lack the sensitivity and specificity to detect smaller lesions; hence, it is not the primary modality for diagnosis of these lesions [26].

Magnetic Resonance Imaging
MRI has been found to show a higher specificity to detect both symptomatic and asymptomatic lesions as well as cavernomas located in the posterior cranial fossa or the brainstem [27, 28]. Based on the MRI images, cavernous angiomas can be classified into 4 types (Table 2). The MRI findings of cavernomas can also be seen in other disease conditions like hemorrhagic neoplasms or metastasis, calcification of neoplasms, cryptic vascular malformations, oligodendrogliomas, and pleomorphic xanthoastrocytomas [29].

<p>| Table 1. Familial CCM genes [11] |
|-------------------------------|-----------------|----------|---------------------------------|</p>
<table>
<thead>
<tr>
<th>Gene</th>
<th>Gene locus</th>
<th>Chromosome</th>
<th>Function</th>
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<tbody>
<tr>
<td>KRT1</td>
<td>CCM1</td>
<td>7q</td>
<td>Regulate heart and vessel formation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Regulate angiogenesis</td>
</tr>
<tr>
<td>CCM2</td>
<td>CCM2</td>
<td>7p</td>
<td>Regulate heart and vessel formation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Maintain vessel integrity</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Stabilize endothelial cell junction</td>
</tr>
<tr>
<td>PDCD10</td>
<td>CCM3</td>
<td>3q</td>
<td>Stimulate cell proliferation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Regulate apoptosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Regulate heart development</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Regulate angiogenesis, vasculogenesis, and hematopoiesis</td>
</tr>
</tbody>
</table>

CCM, cerebral cavernous malformation.
Gradient Recall Echo MRI
Gradient recall echo (GRE) MRI is used for the accurate detection of CCM due to the characteristic hypointensity produced due to detection of hemosiderin-filled brain parenchyma [31]. Microhemorrhages seen on GRE MRI sequences are also a finding in elderly patients with hypertension and cerebral amyloid angiopathy [32].

Susceptibility Weighted MRI
Susceptibility-weighted (SW) MRI is more precise in detecting vascular malformations due to its high sensitivity to deoxyhemoglobin and iron content [33]. This is the only imaging method that can detect capillary telangiectasias and cavernomas that are nonhemorrhagic [34]. A study in 2008 has shown that the detection rate of familial CCMs by SW MRI was 1.7 times higher than that by T2/GRE MRI [35]. Though it can detect multifocal familial CCMs, it has not been proven superior to T2/GRE MRI. SW MRI is also not sensitive in detecting sporadic or solitary CCMs and CCM lesion associated with DVA and differentiating small venous structures from microhemorrhage and thrombosis [36].

Diffusion Tensor MRI and Functional MRI
Diffusion tensor MRI and functional MRI are used to visualize the lesions and surrounding brain tissue intraoperatively to improve the outcome of the surgery. Diffusion tensor MRI helps identify and avoid resection of areas like the white matter tracts, helping reduce the surgery-associated morbidity. Functional MRI helps assess cerebral blood flow to parts of the brain in association with activity, which helps assess the essential areas, thus aiding surgical resection of CCM [30].

Genetic Studies
Familial CCM patients should undergo a direct genetic sequencing of CCM1–3, followed by a deletion or duplication analysis. This has shown a detection rate of approximately 75% of all cases with multiple lesions [9].

Treatment
One study has described an algorithm summarizing the treatment options for cavernous angioma when it is diagnosed on a brain MRI: If the lesion was diagnosed incidentally and has no clinical manifestations, it only requires conservative management irrespective of the location and yearly MRIs to assess the growth of the lesions. If the lesion has a severe clinical presentation, surgical management with either microsurgical resection or stereotactic radiosurgery was suggested [31].

Conservative Management
Depending on the location of the CCM and the age of the patient, asymptomatic lesions can be treated by regu-
lar follow-up [37]. This is also preferred if the patient has increased risk associated with surgery. There are no set guidelines currently available for determining the frequency of imaging for follow-up [38].

Surgical Management
Surgical resection is the most preferred form of intervention for CCM. Selection of a procedure depends on the location and severity at the presentation, which includes intractable seizures, progressive neurological deterioration, one severe hemorrhage in a non-eloquent region of the brain, or at least 2 severe hemorrhages in eloquent regions of the brain [31]. A complete resection of the lesion is mandatory due to the increased risk of hemorrhage and seizures due to remnant tissue [38]. The procedure can also be complicated by occurrence of gliosis, calcification, and hyaline degeneration following resection of the lesion [39]. The removal of hemosiderin ring should be done in patients who undergo seizure surgery. Due to an increased risk of hemorrhage from remnants, an MRI is recommended within 72 h post-surgery [40]. Microsurgical resection that is done more using intraoperative imaging helps reduce the risk of surgical complications, making it a preferred modality for the treatment of cavernous angiomas [41].

Stereotactic Radiosurgery
When cavernous angioma is inoperable or carries with it a higher surgical risk, stereotactic radiosurgery may be used as an option for treating the lesion, though there is controversy about its effectiveness and concern about complications like radiation-induced genesis of new cavernomas [42]. Niranjan and Lunsford [43] proposed a guideline to select patients for stereotactic radiosurgery. It includes factors like age of the individual, location of the lesion, the risk of hemorrhage, the risk associated with surgery, and the history of previous hemorrhages.

Medical Therapy
There are no medications currently useful for treating CCM. The medications used are for treatment of clinical symptoms like seizures. Rosenow et al. [44] proposed a guideline for diagnostic evaluation and therapy for patients with seizures that occur in association with CCM (Table 3). Conservative management is preferred over surgery in these patients due to the low risk of seizure occurrence in patients with cavernomas. Headache is the most common symptom of CCMs. Standard migraine therapy is considered for those patients who meet the criteria for migraine [9]. Though some studies have shown a likely safety of antiplatelet and antithrombotic medications in lowering the bleeding risk in preexisting CCM, these studies have limitations [45, 46].

Developmental Venous Anomaly
DVAs are the most frequently encountered intracranial malformations on imaging.

Epidemiology
DVAs have an incidence rate of >2% based on both autopsy and imaging studies [47]. The hemorrhagic risk of DVA is considered <0.7% and has been seen more in patients having lesions in the posterior fossa or in pregnant patients [48].

<table>
<thead>
<tr>
<th>Situation</th>
<th>Guideline</th>
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<tr>
<td>Incidental CCM or CCM with intracranial hemorrhage or focal neurologic deficits</td>
<td>No prophylactic antiepileptic therapy</td>
</tr>
<tr>
<td>CCM with new-onset single or multiple seizures</td>
<td>Antiepileptic therapy is indicated</td>
</tr>
<tr>
<td>CRE patients who are symptom-free on antiepileptics</td>
<td>Regular follow-up with a seizure specialist</td>
</tr>
<tr>
<td>CRE patients with persistent seizures</td>
<td>Epilepsy surgery after complete preoperative evaluation</td>
</tr>
<tr>
<td>CRE patients with multiple cavernomas</td>
<td>Video electroencephalogram monitoring is mandatory</td>
</tr>
<tr>
<td>CRE patients with dual or triple pathology</td>
<td>Invasive evaluation to localize and identify the extent of epileptogenic zone may be considered</td>
</tr>
</tbody>
</table>

CRE, CCM-related epilepsy; CCM, cerebral cavernous malformation.
Etiology
The exact etiology of DVA is not known and is thought to develop as a compensation to the absence of normal vessels resulting from hypoplasia, aplasia, or an early occlusion of the developing veins [49].

Pathology
DVAs are radial clusters of dilated centripetally draining medullary veins, typically called the “caput medusa” that converge into a common collecting vein, which drains the normal brain parenchyma [50].

Clinical Presentation
DVAs were thought to be very rare lesions in the past, and with diagnostic MRI being used more, the number of cases that are diagnosed has also increased. DVAs are benign and asymptomatic in most scenarios. Acute thrombosis of the collecting vein may result in venous infarction of the surrounding brain parenchyma [51, 52]. The pathophysiological mechanisms underlying symptomatic DVA are explained in Table 4.

Diagnosis
DVAs can be diagnosed with a CT or an MRI and digital subtraction angiography, which is the gold standard for diagnosis as it helps study the flow of blood through the various channels of a DVA [50]. Regardless of the imaging modality that is used, DVA diagnosis depends on identifying the area of caput medusa that drains into a common collecting vein. In a CT without contrast, the collecting vein appears isodense and the acute thrombosis becomes hyperdense. It also helps in detecting calcifications, white matter lesions, atrophy, and hemorrhage associated with DVA [50]. Non-contrast MRI may show phase-shift artifact and flow voids caused by the larger radical venous branches and the collecting vein [54]. Contrast-enhanced CT or gadolinium administration with MRI has been found to demonstrate DVAs by showing marked enhancement of the radial veins and the main collecting vessel [55]. GRE or SW MRI helps in detecting any acute parenchymal bleed or intravascular thrombosis [51].

Treatment
DVAs that are asymptomatic or found incidentally are not treated. Though no large-scale controlled studies exist to support use of anticoagulants, it has been recommended in symptomatic, thrombosed venous angioma after extensive evaluation of affected patients for additional hemorrhagic risks [48]. Surgical excision of a DVA can result in venous congestion, leading to severe venous infarction thus favoring conservative man-

Table 4. Pathophysiology of symptomatic DVA [53]

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Explanation</th>
<th>Clinical presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanical</td>
<td>When a part of the DVA compressed on intracranial structures</td>
<td>Obstructive hydrocephalus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Neurovascular compression</td>
</tr>
<tr>
<td>Flow-related</td>
<td>When there is a loss of balance in the inflow (increased) and outflow (decreased) of blood in the DVA system, resulting in raised pressure</td>
<td>Inflow misbalance can result in hemorrhage and venous infarction resulting in headache, focal neurological deficits, seizures, coma</td>
</tr>
<tr>
<td></td>
<td>Increased inflow occurs as a result of microshunt into the DVA or due to an AVM utilizing the DVA as a drainage route</td>
<td>Outflow misbalance:</td>
</tr>
<tr>
<td></td>
<td>Decreased outflow can occur due to the following:</td>
<td>Anatomical causes – headache, seizure, altered mental status</td>
</tr>
<tr>
<td></td>
<td>Anatomical causes – thrombosis of the DVA, stenosis or occlusion of the collecting vein, or the draining sinus</td>
<td>Functional cause – venous hypertension</td>
</tr>
<tr>
<td></td>
<td>Functional cause – a distant shunt/AVM resulting in a remote arterial overload to the venous system</td>
<td></td>
</tr>
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</table>

DVA, developmental venous anomaly; AVM, arteriovenous malformations.
Management. Surgery is indicated in patients who present with a massive intracerebral hematoma and since they drain normal brain tissue radiosurgery is contraindicated [56].

Mixed CCMs with DVA

The coexistence of CCM and DVA is the most common form of mixed intracranial vascular malformation.

Epidemiology

A retrospective study of parenchymal abnormalities associated with DVA showed that approximately 13% of patients who had a cavernoma had an associated venous anomaly [57]. Hemorrhagic complications that occur in cases with a coexisting cavernoma with DVA is higher than an isolated cavernoma [58]. Mixed vascular malformations are currently being diagnosed at a higher rate, and there are reports on literature that suggest a causal relationship between a CCM and a DVA [59, 60].

Pathophysiology

DVAs are considered to play the evolutional role in the development and growth of CCM. The probable pathogenesis of this development is explained in Figure 2.

Diagnosis

The use of contrast-enhanced MRI has shown to increase the detection of cavernous angiomas with coexistent DVAs, and the use of T2-weighted gradient echo MRI or SW images may help to identify these combined lesions [63, 64].

Treatment

Surgical excision is a commonly accepted treatment option for patients with symptomatic cavernous angioma, and when associated with a DVA, the venous anomaly should be spared due to the potential danger of devastating venous infarction. Treatment of these lesions should be decided by gauging risks versus benefit of surgery over the natural course of these lesions [65].

Conclusions

CCMs and DVAs are intracranial vascular malformations whose natural history is still not well understood. Individually, these lesions have a benign natural course; however, when they coexist in the same individual, the hemorrhagic risk is increased, which prompts for rapid diagnosis and treatment. An MRI is helpful in the detection of individual and mixed vascular malformations. Conservative management for asymptomatic lesions and surgery for clinically symptomatic lesions appear to be a satisfying approach for the treatment of these CCM. Surgery is avoided in DVA patients due to the risk of thrombosis and infarction. In mixed lesions, if indicated, only the cavernoma is surgically resected and the DVA is left untouched.

Future Research

Further studies are also necessary to understand more about the following: The natural course of CCMs, DVAs, and mixed malformations. Assessment and screening of patients presenting with hemorrhage from single or multiple lesions. Guidelines to follow for the diagnosis of individual and mixed vascular malformations as well as the imaging modalities that can be used for rapid detection of such lesions. Comparison studies to assess the efficacy of the different imaging options that are available. Determine the efficacy of medical treatment options in place of surgery.
Conflict of Interest Statement

The authors declare that they have no conflicts of interests.

Author Contributions

All authors have been involved in the preparation of the manuscript. All authors have read and approved the manuscript. The corresponding author has full access to data and has the right to publish this paper.

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Cerebral Cavernous Malformations and Developmental Venous Anomaly


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