

# BRAINSTEM CAVERNOUS MALFORMATIONS

## A review with two case reports

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**Abstract** – Central nervous system (CNS) cavernous malformations (CMs) are developmental malformations of the vascular bed with a highly variable clinical course due to their dynamic nature. We present one case of “de novo” brainstem cavernous malformation after radiation therapy adding to the increasing number of reported cases in the medical literature, and the case of a pregnant patient with symptomatic intracranial hemorrhage related to brainstem CMs to illustrate the complex nature in management of these patients, followed by a review of clinical and radiographic characteristics. CMs account for 8–15% of all intracranial and intraspinal vascular malformations. Although traditionally thought to be congenital in origin, CMs may present as acquired lesions particularly after intracranial radiation therapy. Clinical manifestations are protean and surgical treatment should be considered for patients with progressive neurologic deficits.

KEY WORDS: cavernous malformations, epilepsy, “de novo”.

### Malformações cavernosas do tronco cerebral: uma revisão com relato de dois casos

**Resumo** – Malformações cavernosas (MFC) do sistema nervoso central são malformações do desenvolvimento do leito vascular com múltiplas apresentações clínicas devido a sua natureza dinâmica. Apresentamos dois casos de malformações cavernosas do tronco cerebral: o primeiro após radioterapia e o segundo em paciente grávida com hemorragia intracraniana sintomática. MFC são responsáveis por cerca de 8-15% de todas as malformações vasculares. Embora tradicionalmente sejam genéticas, as MFC podem também ser adquiridas, particularmente após radioterapia. As manifestações clínicas são variáveis e o tratamento cirúrgico deve ser considerado para pacientes com quadros neurológicos progressivos.

PALAVRAS-CHAVE: malformações cavernosas, epilepsia, “de novo”.

Central nervous system (CNS) cavernous malformations (CMs) are developmental or acquired vascular malformations of the intracranial vessels increasingly recognized with the widespread use of magnetic resonance imaging (MRI). Clinical presentation is heterogeneous, depending on anatomical location and whether there is an associated hemorrhage.

Brainstem CMs may present as a difficult paradigm for treating clinicians. Recent discoveries in molecular genetics continue to provide new insights regarding the etiology of CNS CMs. Traditionally, CMs have been considered congenital malformations but it is now clear that they may also be acquired lesions particularly among patients who have received cranial radiation therapy.

We present one case with a “de-novo” brainstem CM

following radiation therapy of a cerebellar astrocytoma, and another patient who became symptomatic during her pregnancy to highlight the challenging aspects regarding treatment of these CNS vascular malformations.

### CASES

#### Case 1

A 61-year-old right-handed woman had surgery at the age of 38, for a left cerebellar astrocytoma, followed by radiation and ventriculo-peritoneal shunt, which required multiple revisions. Seven years later, she developed progressive loss of equilibrium, double vision and progressive bilateral hearing loss. She was found to have a midbrain hemorrhage. A catheter cerebral angiogram showed no abnormalities. She then had recurrent mid-brain hemorrhages with permanent focal deficits including bi-

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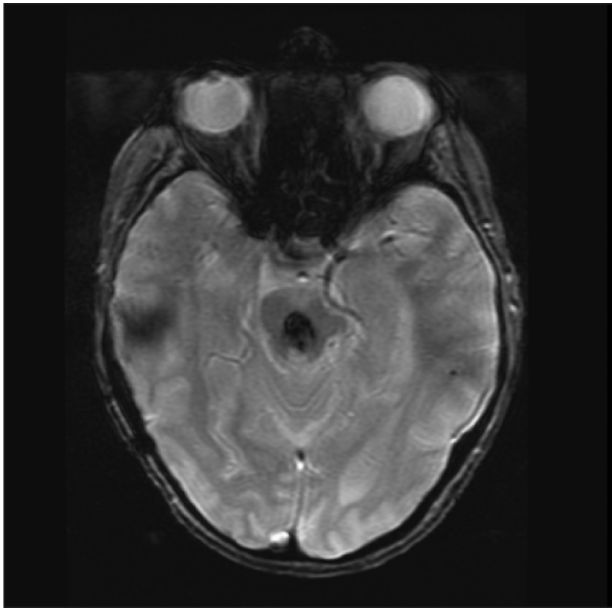


Fig 1. T2-weighted gradient-echo, magnetic resonance imaging (MRI) shows a midbrain cavernous malformation.

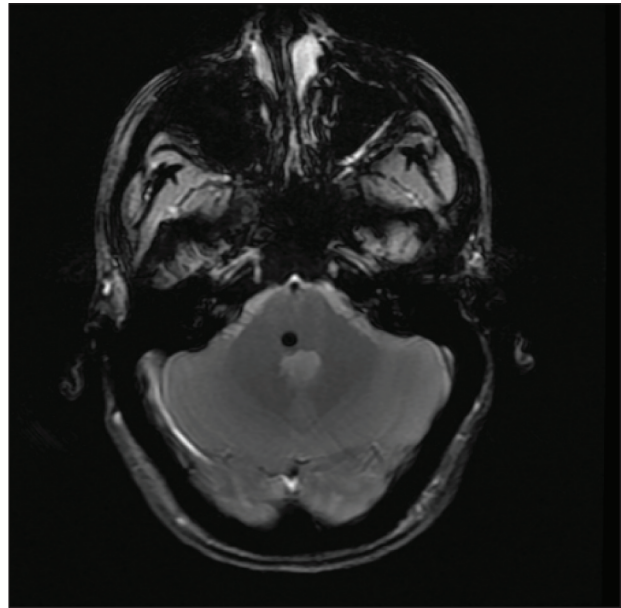


Fig 2. T2-weighted gradient-echo, magnetic resonance imaging (MRI) shows a right dorsal pontine cavernous malformation.

lateral internuclear ophthalmoplegia (INO), disequilibrium, and bilateral hearing loss (Fig 1).

#### Case 2

A 38-year-old right-handed woman, during her second pregnancy developed binocular horizontal diplopia secondary to a right abducens palsy. MRI showed a dorsal pontine right CM. Her diplopia resolved, and she had an uneventful vaginal delivery. A midbrain developmental venous anomaly was also noticed. Neurologic examination was normal. Patient developed a transient episode of fever associated with some coldness and numbness of the 2<sup>nd</sup>, 3<sup>rd</sup>, and 4<sup>th</sup> digits of the left hand lasting approximately 4 hrs.

MRI showed some interval evolution of the CM in the posterior aspect of the right side of the pons, with some apparent increase at the level of the brachium pontis, raising the possibility of an interval episode of hemorrhage. Conservative treatment was recommended (Fig 2).

#### CNS CAVERNOUS MALFORMATIONS

The recognition of abnormal arrangements of blood vessels within the CNS dates back to Virchow in the early 19<sup>th</sup> century<sup>1</sup>. In more recent years, Voigt et al.<sup>2</sup> published the first overview of the entity of “intracranial cavernous haemangiomas” with emphasis in the incidence, localization, diagnosis and clinical findings. Over the next decades, remarkable advances in the fields of pathology, genetics and neuromaging, have improved our understanding of this heterogeneous and rather complex group of CNS vascular disorders.

CNS vascular malformations encompass four dis-

crete pathologic entities; (1) arteriovenous malformations, (AVMs) (2) capillary telangiectasias (CTs) (3) developmental venous anomalies (DVAs) and (4) cavernous malformations.

Cavernous malformations are developmental malformations of the vascular bed, presenting as discrete, multilobulated lesions containing hemorrhages in various stages of evolution (Fig 1). CMs appear as well-circumscribed, lobulated, darkened mulberry-like lesions. Pathologic characteristics include thin walls, simple endothelial layer, thin collagen ring and lack of an internal elastic layer, and no intervening neural tissue, thus differentiating them from CTs (Fig 3).

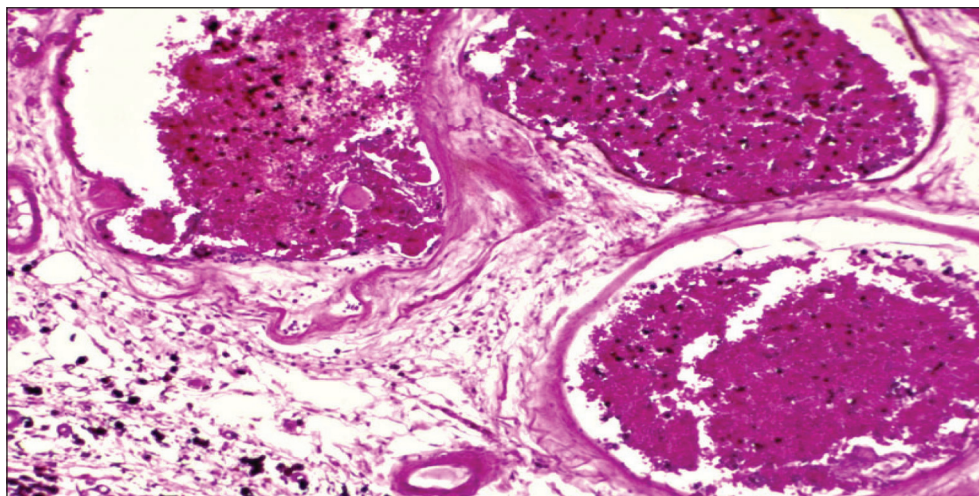
The immaturity of blood vessels also differentiates them from DVAs<sup>3-5</sup>. Evidence of previous hemorrhages may be found in the form of hemosiderin deposition.

An association between CMs and DVAs has been increasingly recognized. Approximately 10–30% of patients with DVAs have an associated CM.

#### Etiology and natural history

The etiology of CMs remains incompletely understood. Genetic analysis of families with multiple CMs has shown the presence of at least three genetic defects: (1) CCM1 gene, affecting chromosome 7 at band 7q11.2–q21 (protein product-KRIT1 protein), (2) CCM2 gene, involving chromosome 7 at band p15–p13, (protein product- malcavernin) and (3) CCM3 gene on chromosome 3 at band 3q 25.2-27 (PCD10 gene coding for a 212 amino acid protein lacking any known domains<sup>3-7</sup>).

The CCM1 locus appears to affect endothelial tube de-



*Fig 3. Histology of a typical cavernous malformation with endothelium-lined, sinusoidal cavities without other features of normal blood vessels, such as muscular or adventitial layer. Note the hemosiderin deposition in lower left side.*

velopment, having also a role in regulating  $\beta 1$  integrin-mediated angiogenesis through KRIT-1<sup>7</sup>.

The CCM2 locus (MGC4607 or malcaverin gene) encodes a protein containing a putative phosphotyrosine-binding domain<sup>8</sup>. The CCM3 encodes for a 212 amino acid protein lacking any known domains but linked to apoptosis, which is an essential process in arterial morphogenesis<sup>9</sup>.

These proteins appear to interact with the endothelial cytoskeleton during angiogenesis, potentially explaining the occurrence of these lesions in the CNS<sup>10,11</sup>. There is also evidence suggesting a convergence of disruptive pathophysiologic mechanisms involving the three CCM genes through a similar (currently incompletely understood) molecular pathway<sup>7,12</sup>.

Multilocus analysis of familial CMs shows 40% of kindred linked to the CCM1 locus, 20% linked to CCM2, and 40% linked to CCM3<sup>6</sup>. All of these mutations follow an autosomal dominant pattern of inheritance. There also appears to be an ethnic predisposition, with approximately 50% of Hispanic patients having a familial form, compared with only 10 to 20% of Caucasians<sup>13-15</sup>.

The familial form of cerebral CMs usually presents with multiple CMs, in contrast to sporadic cases, where lesions are usually solitary<sup>16</sup>. Importantly, there is no difference in the pathological features or clinical presentation of the sporadic and familial forms<sup>3,5,7</sup>.

CMs may also develop after viral infections, trauma, and particularly following stereotactic or standard CNS radiation therapy<sup>4</sup>. Local seeding along the tract may be responsible in a majority of cases. Hormonal influences have been implicated with an increase frequency of CMs during pregnancies. Shahid et al. reported 76 patients with "de-novo" CMs following radiation treatment<sup>17</sup>.

CMs developed particularly among boys (mean age 11 years) who had radiation therapy for treatment of

medulloblastomas, gliomas, or acute lymphocytic leukemia (ALL) in this decreasing order of frequency. The pathophysiology of radiation-induced CMs formation is not clearly understood, although the immature brain among pediatric patients may be more sensitive to radiation than the adult brain<sup>18</sup>.

CMs represent 8–15% of all CNS vascular malformations, with a prevalence of 0.1 to 0.5% based on large autopsy studies<sup>19</sup>, similar to data from MRI studies showing a prevalence rate of 0.39% to 0.9%. In approximately 40% to 60% of cases of CM, lesions are solitary<sup>10</sup>. Multiple CMs are observed in 15–33% of cases.

### Clinical presentation

A highly variable clinical course is due to the dynamic nature of these CNS vascular malformations<sup>15</sup>. CMs may be asymptomatic and discovered by routine neuroimaging studies. Most common manifestations at presentation include seizures in approximately 40–50% of cases, followed by headaches in 30% and intracranial hemorrhage in 10–25%. The most common anatomic location of these malformations is the frontal or temporal lobe. Eighty to ninety percent of CMs are supratentorial, 15 % infratentorial, and 5% occur in the spinal cord. Average lesion size of a CM is approximately 1.7 cm<sup>15,20</sup>.

Although not intrinsically epileptogenic, CMs can induce seizures through their effect on surrounding brain tissues, either through ischemia, venous hypertension, gliosis, inflammatory responses or hemorrhage from deposition of ferric ions after erythrocytic breakdown caused by repeated microhemorrhages. The estimated risk for seizures is estimated at 1.5% / patient / year, or 2.48% per lesion / year among patients harboring multiple CMs<sup>21</sup>.

CMs may also present as intraparenchymal hemorrhages. Recurrent hemorrhages may be associated with



clinical exacerbations. Spinal cord lesions, may present with an acute or subacute myelopathy. Risk of clinically relevant hemorrhage is 0.4% to 2% per year among those presenting with seizures or asymptomatic patients, while the annual rate of recurrent bleed is 4–5% per year among patients presenting with symptomatic hemorrhages<sup>20,22,23</sup> compared with the estimated annual bleeding rate between 0.25%–0.7% / year in those with no prior bleeding<sup>20,24</sup>. Risk of hemorrhage also varies according to location. Among patients with deeply situated CMS (brainstem, cerebellum, thalamus, or basal ganglia) the initial annual hemorrhage risk of 4.1%, compared with only 0.4% among those with superficial CMS<sup>24</sup>.

Progressive neurologic deficits has been particularly noticed among patients with symptomatic brainstem CMS<sup>25,26</sup>. Patients usually present with unilateral or bilateral headaches, diplopia, face or body sensory disturbances, ataxia, arm or leg paresis, vertigo, dizziness, or dysarthria<sup>26,27</sup>.

Challenging issues exist among pregnant women harboring CMS. Pregnant women may be at higher risk of complications of CMS. Size of CMS may increase during pregnancy. Exacerbation of symptoms such as seizures and headaches, symptomatic hemorrhages, and “de novo” appearance of CMS are common during pregnancy<sup>28–30</sup>. There has also been reported an increased risk of hemorrhage after delivery<sup>28</sup>.

Expression of growing factors during pregnancy may promote angiogenic processes and proliferation of new vessels in CMS, which are normally dormant in adult brain tissue<sup>28</sup>. The management of CMS during pregnancy and the peripartum period is based on when the symptoms developed during the course of pregnancy. Other factors to be consider include localization of CMS, presence of neurologic deficits, and history of prior hemorrhages<sup>28</sup>.

### Neuroimaging characteristics

CMS may be undetectable by cranial computed tomography (CT) in up to 30 to 50% of cases. When visualized, they appear as oval or nodular-appearing lesions with mild-to-moderate increased attenuation on non-enhanced CT scans<sup>19</sup> with or without associated calcifications. Older lesions may contain hypo-attenuating and non-enhancing areas, corresponding to cystic cavities from resolved hematomas. Approximately 70–94% of CMS demonstrate mild-to-moderate enhancement after contrast administration.

With the advent of MRI, CMS have been increasingly recognized, suggesting a higher prevalence than previously reported. MRI is the most sensitive diagnostic tool to visualize CMS. Typically they exhibit a “popcorn-like”, smoothly circumscribed, well-delineated appearance. A low signal rim due to hemosiderin deposition may be seen surrounding the lesions. Gradient echo (GE) sequenc-

es may improve the sensitivity to detect small lesions and previous areas of hemorrhage and it is particularly useful in familial cases with asymptomatic lesions. Susceptibility-weighted imaging (SWI) is a new MRI sequence that allows higher sensibility to detect CMS compared with T2-weighted fast spin echo and T2\*GRE sequences.

CMS are low flow lesions, hence, angiographically occult. If lesions are large enough or associated with hematomas, mass effect can be appreciated on imaging studies.

### MANAGEMENT

Management is usually considered for patients with multiple episodes of clinically or radiographically apparent hemorrhage or seizures. Optimal management of patients presenting with epileptic seizures is still a matter of debate.

Baumann et al.<sup>31</sup> recently published a large non-randomized study on seizure outcome after resection of single supratentorial CMS. Predictors for favorable seizure outcome after removal of CM include age >30 years, lesion size <1.5 cm, no additional seizure focus on EEG, and presence of simple partial or complex seizures.

However, caution is needed when considering surgery for treatment of epilepsy with cerebral CMS, because these lesions may be frequently multifocal<sup>10</sup>. Larger lesions and those associated with bleeding are more likely to be the source of epileptic seizures. However, smaller lesions should not be taken for granted<sup>10</sup>. “Lesionectomy” is often associated with excellent postoperative seizure control in many patients, but complete lesion excision is often necessary for adequate seizure control<sup>10,32</sup>. Whenever feasible, resection of the gliotic hemosiderin-stained brain parenchyma around the lesion should be attempted<sup>10</sup>. This is also true for cases of extratemporal lesional epilepsy, where lesion resection alone has provided seizure control rates varying from 65 to 95%<sup>33</sup>.

Most patients harboring a single CM, undergoing “lesionectomy” for treatment of recent-onset, localization-related epileptic seizures, are seizure free postoperatively and up to half, may successfully taper -off all antiepileptic drugs<sup>28,34,35</sup>.

One must always consider the possibility that the CM identified on neuroimaging studies may represent an incidental finding and play no role in seizure onset. This may be the situation in up to 6% of cases of patients with CMS and epileptic seizures<sup>36</sup>.

Similarly, patients presenting with focal neurologic deficits due to hemorrhages may benefit from surgical resection. However, focal neurologic deficits due ruptured CMS may often improve spontaneously.

Furthermore not every bleeding episode results in significant neurologic impairment. Therefore, preventing hemorrhage is not always an absolute indication for sur-

gery<sup>24</sup>. This may not apply to CMs located in eloquent brain areas, particularly those located in the brainstem. Repeated hemorrhages from brainstem CMs are much more common, and usually cause new neurologic deficits<sup>37</sup>. With advancement of microneurosurgical techniques surgical indications for brainstem CMs are evolving in parallel with our better understanding of the natural history, thus resulting in better perioperative outcomes. Stereotactic-assisted surgical resection is considered the optimal treatment for supratentorial lesions. Surgery is often indicated for patients with progressive neurologic deficits, overt acute or subacute hemorrhages on MRI either within or outside CMs with mass effect; and exophytic CMs reaching the brainstem surface<sup>20,37</sup>.

The use of radiosurgery to treat CMs remains controversial. New radiation protocols have shown good outcomes for unresectable lesions, with a decreased risk of bleeding, usually after a 1- to 3-year latent period<sup>38-40</sup>. However, other reports have shown higher risk of morbidity among patients treated with radiosurgery<sup>20</sup>.

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