Brainstem cavernous malformation

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ABSTRACT

Cavernous malformation (CM) of the central nervous system (CNS) are acquired or developmental vascular malformations that represent the 5% to 15% of all vascular malformations of the CNS. Eighty to ninety percent of CM are supratentorial, 15% infratentorial, and 5% occur in the spinal cord. The subset of brainstem malformation presents as a very difficult paradigm for treating clinicians. The widespread use of magnetic resonance imaging (MRI) has increased the recognition of this disease. Clinical presentation, pathophysiology and treatment are discussed in this article.

KEYWORDS

Central nervous system neoplasms, central nervous system, magnetic resonance imaging, cavernous malformation, cavernoma.

RESUMO

Cavernomas de tronco cerebral

Os cavernomas do sistema nervoso central (SNC) são malformações vasculares do desenvolvimento ou adquiridas que representam 5% a 15% de todas as malformações vasculares do SNC. Dos cavernomas, 80% a 90% são supratentoriais, 15% são infratentoriais e 5% ocorrem na medula espinhal. As malformações do tronco encefálico se apresentam como um paradigma de decisão de tratamento muito difícil para os cirurgiões. O amplo uso das imagens por ressonância magnética aumentou o reconhecimento dessa patologia. A apresentação clínica, a fisiopatologia e o tratamento serão discutidos neste artigo.

PALAVRAS-CHAVE

Neoplasias do sistema nervoso central, sistema nervoso central, imagem de ressonância magnética, malformação cavernomatosa, cavernoma.

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Introduction

The recognition of abnormal arrangements of blood vessels within the central nervous system (CNS) dates back to Virchow in the early 19th century. Over the next decades, significant advances in the fields of pathology, genetics and neuroimaging, have improved our understanding of this heterogeneous and rather complex group of CNS vascular disorders.

Cavernous malformation (CM) of the CNS are acquired or developmental vascular malformations that represent the 5% to 15% of all vascular malformations of the CNS. CM can occur at any location in the central nervous system including the pineal, brainstem and thalamic regions and the chiasma or optic nerve. Eighty to ninety percent of CM are supratentorial, 15% infratentorial, and 5% occur in the spinal cord. Average lesion size of a CM is approximately 1.7 cm. Brainstem cavernomas (BC) account for 18%-35% of CNS cavernomas and can present with hemorrhage or progressive neurological deficit. Approximately 57% of the cavernomas occur in pons followed by midbrain (14%), pontomedullary junction (12%), and medulla (5%).[1]

The subgroup of brainstem malformation presents as a very difficult paradigm for treating clinicians. The widespread use of magnetic resonance imaging (MRI) has increased the recognition of this pathology. Clinical presentation, pathophysiology and treatment are discussed next.

Methods

The PubMed and Medline databases were searched for publications from 1990 through June 2012 using the MeSH terms "cavernoma", "cavernous malformation", "imaging", "brainstem cavernous malformation", "brainstem cavernomas", "gradient echo", "MR imaging", and "vascular malformation". The search was limited to articles in the English language and relating to human subjects. Reference sections of recent articles and reviews were reviewed and pertinent articles identified. Initially, relevant articles were retrieved in abstract format. Full-text manuscripts were subsequently obtained for all original articles applicable to the current review.

Etiology

The origin of cavernous malformation is still unclear. CM may develop as genetic mutation or after viral infections, trauma, and particularly following stereotactic or standard CNS radiation therapy. Local seeding along the tract may be responsible in a majority of cases. Hormonal influences have been implicated with an increase frequency of CM during pregnancies.

Genetics

The genetic analysis of families with multiple CM 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).[2]

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

Multilocus analysis of familial CM shows 40% of kindred linked to the CCM1 locus, 20% linked to CCM2, and 40% linked to CCM36. 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.

The familial form of cerebral CM usually presents with multiple CM, in contrast to sporadic cases, where lesions are usually solitary.[16] Importantly, there is no difference in the pathological features or clinical presentation of the sporadic and familial forms.[2,3]

Radiation

Radiotherapy plays an important role in the formation and posterior evolution of CM. It produces alterations on the walls of the capillaries and small veins (venules). The pathophysiology of radiation induces CM formation is not totally understood. It seems to be that immature brain of pediatric population may be more sensitive to radiation than an adult brain. That is why CM developed specially in boys with a mean age of 11 years old, and who had treatment of medulloblastomas, gliomas, or acute lymphocytic leukemia (in this descending order of frequency).[4]

Other

Viral infection also may play a role in producing or triggering the formation of cavernous malformations.

In immunodeficient rats the polyoma virus has been used to induce the formation of multiple intracranial cavernous malformations. There is also a report of the formation of a new lesion along the path used to obtain a biopsy specimen of a deep subcortical cavernous malformation.[5]

Pathological anatomy

Macroscopic view

In 10%-20% of the cases, CM are multiple, usually the familial form and medullary location. The size increase with age. In some cases could by cystic formation inside CM surrounded by a thin layer such as the one in chronic subdural hematomas. CM are lesions usually purple, like popcorn with surrounded tissue with hemosiderin or gliosis.

Histology

The pathologic characteristics of CM 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 capillary telangiectasia (CT). They could be surrounded by a thin layer of gliosis and are low-flow malformations.[6,7]

The immaturity of blood vessels also differentiates them from developmental venous anomalies (DVA). Evidence of previous hemorrhages may be found in the form of hemosiderin deposition.[8]

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

Epidemiology and natural history

Cavernous malformation occurs in sporadic or in Familial forms. They are the second most common vascular lesion behind developmental venous anomalies and account for 10%-15% of all vascular malformations. The ranges of incidence are from 0.4% to 0.8% with 25% of these occurring in children, this based on autopsy and MR imaging studies. The average age of adult presentation is in the 4th or 5th decade of life. Children present in a bimodal pattern with peaks at 0-2 years of age and 13-16 years of age.[1,9]

The familial form of CM comprises approximately 6%-50% of all cases, and a higher prevalence has been noted in people with Mexican-American ethnicity. Based on current imaging studies, more than 50% of patients with familial CM have multiple lesions compared with only 12%-20% in those with the sporadic form. In regard to sex, the prevalence of CM appears equal among men and women. However, some studies (see detailed discussion below) have raised the question of an increased incidence of symptomatic lesions in women.[10,11]

Clinical presentation

Bleeding

Patients most commonly present with bleeding, combined with an acute onset of neurological deficits. The majority (76.9%) of patients presented with hemorrhage and related sequelae.[12]

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[13] compared with the estimated annual bleeding rate between 0.25%-0.7%/year in those with no prior bleeding. Risk of hemorrhage also varies according to location. Among patients with deeply situated CM (brainstem, cerebellum, thalamus, or basal ganglia) the initial annual hemorrhage risk of 4.1%, compared with only 0.4% among those with superficial CM.

Some authors have suggested that intralesional bleeding, due to the rupture of caverns within the cavernoma, formation of new cysts, and possible reactive angiogenesis, may be responsible for the dynamic nature and growth of some lesions. Conversely, significant intracavernous hemorrhage may also destroy the lesion. It is unclear whether pregnancy increases the risk of hemorrhage in patients with cavernous malformations and some authors have suggested that female hormonal factors may play a role. Estrogen receptors have been reported in a few cavernous malformations from female patients by some authors.[14]

Seizures

Although not intrinsically epileptogenic, CM 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 micro hemorrhages. The estimated risk for seizures is estimated at 1.5%/patient/year, or 2.48% per lesion/year among patients harboring multiple CM.[15]

Mass effect and neurologic deficits

Symptoms may manifest as a new deficit or as an exacerbation or recurrence of an existing or previous neurological deficit. The onset of symptoms may occasionally be gradual and may mimic demyelination, infarction, neoplasm, or infection, in their clinical presentation. Despite the risk of significant neurological impairment related to the location of lesion within the brainstem, bleeding is usually limited because of the low flow characteristics of cavernomas.[16]

Presenting symptoms according to localization of the cavernoma

Overall, motor and sensory symptoms are present in 40% to 50% of, except for the medulla oblongata patients in which 100% of patients reported symptoms. Thalamic cavernomas presented as mass lesions in 60% of patients and cavernomas of the basal ganglia in 55%. Vertigo was mainly associated with pontine lesions (50%) and lesions of the cerebellar peduncle (100%). Abnormal eye movement and diplopia accompanied 80% of mesencephalic, 50% of pontine, and 33% of medulla oblongata lesions. Mesencephalic (60%) and thalamic (15%) lesions presented with symptomatic hydrocephalus. Ataxia was associated with 30% of mesencephalic, 40% of pontine, and 100% of medulla oblongata lesions. Thirty percent of pontine lesions presented with seventh cranial nerve palsy.[17]

Neuroimaging characteristics

Angiography

Is relatively insensitive and diagnosis reaches only 10% of cases. The capillary phase images may show avascular zone and during the venous phase displacement of adjacent venous structures. Other diagnostic features of cavernomas are a dense pattern of venous pooling and capillary ectasia localized area that persists even during the venous phase. Lesions located in the cavernous sinus and middle fossa can be highly vascular, showing well in the angiogram.[13]

Computed tomography

It is a method to detect lesions consistent with cavernomas but their findings are not specific for the diagnosis. Cavernomas are displayed as a hyperdense area, sometimes mixed (iso and hyperdense) inhomogeneous, spherical or nodular, with perilesional edema. Sometimes calcifications can be seen partially and enhance contrast. Typically the mass effect is minimal and no signs of perilesional edema (except in case of bleeding).[18]

Magnetic resonance imaging

The sensitivity of this method, especially with the images obtained at T2, increases the chances of detecting these malformations. Their frequent use has led to an increase in the incidental diagnosis of these lesions. This method also has a high specificity, especially T2.[19]

Images of CM are characterized by microhemorrhages surrounding the malformation. Hemoglobin degradation products of methemoglobin, hemosiderin, and ferritin allow for detection on MR imaging. Cavernous malformations are generally characterized on T2-weighted sequences as areas of mixed signal intensity in a central complicated core with decreased signal intensity along a peripheral rim. Gradient echo sequences have also been advocated as a more sensitive means of diagnosing CM because of the more recognizable lesion hypointensities on this sequence. Gradient echo sequencing comes with the caveat that it may portray a larger apparent size of the lesion because of the hemosiderin. This illusion of a larger size may complicate surgical planning if the true lesion size does not extend to the pial surface, as it can appear. Susceptibility-weighted imaging has also been advanced as a more sensitive MR sequence for multifocal familial lesions given its sensitivity to deoxyhemoglobin and iron content.

Cavernous malformations are generally classified into 4 main types based on MR imaging characteristics. Type I CM contain subacute hemorrhage characterized by a hemosiderin core, which is hyperintense on T1 and T2 sequences. Type II CM with loculated areas of hemorrhage are surrounded by gliotic tissue displaying a reticulated mixed signal on both T1 and T2 sequences with a classic "popcorn" appearance. Type III lesions, typically seen in familial CM, contain chronic resolved hemorrhage, with T1, T2, and gradient echo sequences displaying an isointense lesion. Familial lesions are also thought to more frequently lack a developmental venous anomaly, which becomes apparent on contrast enhanced MR imaging. Type IV lesions appear similar to telangiectasias and are only seen on gradient echo MR imaging as small punctate hypointense signals.[19,20]

Management

Decision for surgery

Defining criteria for selection of patients with brainstem cavernomas and surgery is challenging. The major considerations for surgical selection are: (i) the location of the lesion (superficial or deep-seated); and (ii) whether the lesion is incidental or symptomatic. Most authors agree that incidental lesions should not be operated, especially if deep-seated and small; others recommend surgery for patients with progressive symptoms and with superficially located cavernomas, where a surgical approach is possible. Samii *et al.* recommended intervention for superficial cavernomas if the patient is young, even for incidentally diagnosed lesions without hemorrhage. Additionally, they recommended surgery for patients with progressive deterioration, with further hemorrhage, even though the cavernoma may not be superficial.[21] Wang *et al.* included the following as indications of surgery: (i) progressive neurological deficits; (ii) clinical presentations such as coma or cardiac or respiratory instability; (iii) overt acute or subacute hemorrhage on MRI; or (iv) either cavernoma or hematoma reaching < 2 mm from the pial surface.[21] It is important emphasized the high risk of recurrences after a previous event and therefore, the need for surgery after the first event.

Surgery is ideally deferred in patients with intrinsic lesions within the paramedian floor of the fourth ventricle unless the patient is rapidly deteriorating. Indications for surgery for patients with clinically asymptomatic brainstem cavernomas who have MRI-documented bleeding will depend on the age of the patient and location of the lesion. Surgery is advised in young patients in whom there is radiological documentation of bleeding and the cavernoma is close to the floor of the fourth ventricle. However, if the lesion does not have pial contact, surgery is not usually recommended and these patients are managed conservatively. Patients over 65 years of age, who have had brainstem cavernomas detected incidentally with or without associated comorbidities, are normally treated conservatively with regular reviews.[22]

Radiosurgery

The use of radiosurgery for cavernomas has remained controversial, since the main goal of radiosurgery should be a significant reduction in bleeding risk. Some authors have insisted on the efficacy of radiosurgery for intracranial cavernomas, due to the reduced risk of hemorrhage after a latency period of 2 years. However, the annual risk of hemorrhage during the latency period after radiosurgery is greater than 10%. Edema and rebleeding in the first 6 months is present in 28% of the cases.[23]

Surgical management

A great variety of surgical approaches, such as the suboccipital midline, retrosigmoid or subtemporal approaches may be indicated. The choice of the proper approach depends on the relationship between the cavernoma and the pial or ependymal surface of the brainstem. The main goals of surgery for brainstem cavernomas are to achieve complete resection of the lesion and to avoid additional neurological damage to the patient.

Safe entry zones above and below the facial nucleus have been described and the importance of an awareness of the anatomy of the floor of the fourth ventricle cannot be overemphasized.[24] Intraoperative electrophysiological monitoring has been used by various authors to determine safe entry zones to approach brainstem lesions and thus avoid direct damage of cranial nerve nuclei. Unless the lesion is clearly exophytic, alternative entry points such as the anterolateral pons should be considered as complications are less likely when entering the brainstem via this zone. After the lesion is exposed, the surrounding hematoma is removed and the cavernous malformation exposed and dissected. Knowing the exact location of the cavernous malformation within the bleeding cavity is valuable for planning the surgical approach. In deeply located cavernomas the use of neuronavigation is highly recommended. It is important to use navigation in the early stage of exposure. Neuronavigation, when applied with minimal brain retraction and before large amounts of cerebrospinal fluid are drained, can precisely locate the cavernoma. Working around the borders of the lesion ensures that bleeding is minimized and facilitates dissection. After removal of the cavernous malformation meticulous hemostasis is essential. No effort is made to remove the hemosiderin-stained gliotic tissue that surrounds the cavity of the hematoma because it is unnecessary in the brainstem and may cause additional neurological damage.

Final remarks

The nervous system cavernomas are histologically benign lesions, but in certain circumstances due to its location behave aggressively. Surgical resection is indicated to treat this disease as they present a dissection plane which favors their removal even in the most delicate areas. Modern treatment options for brainstem

cavernomas include a variety of diagnostic and surgical tools, experience and dedication. Altogether, favorable outcomes can be achieved and surgically nontreatable lesions are extremely rare.

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