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Multiple Cavernous Malformations: A Case Report

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Abstract

Cavernous malformations are alterations in the conformation of arteries and veins that can be found both intracranial and intraspinal; however, the variables are very important for the diagnosis and treatment of patients. The main clinical manifestation is epileptic seizures in cases of bleeding, but in many cases they are asymptomatic in the course of life and are found as findings related to neuroimaging studies for other reasons. It is more common to find unique lesions, but in cases of multiple lesions it is likely to find an autosomal dominant hereditary factor, which makes the person more likely to convulse due to sporadic bleeding. Medical management focuses on the clinical presentation and management of epileptic seizures, while surgical management takes into account the size, location and bleeding. Below is a clinical case that represents one of the different clinical manifestations and the approach that was given in said patient.

Keywords: ***Cavernous malformation; Arteriovenous malformation; Seizures***

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Introduction

Cavernous malformations are lesions of blood vessels in brain and spinal cord, made of slow flow abnormal capillaries. They are described as well-defined lesions of cavernous dilated capillaries with thin walls in sinusoidal areas that no not involve brain parenchyma, and are outlined by a single layer of endothelium, separated by a collagen matrix, smooth muscle and other vascular wall elements [1]. These malformations where described by Rudolf Virchow in 1863, and are part of the four vascular malformations of the central nervous system described by Russel and Rubinstein in 1998 [2,3].

From vascular malformations in the central nervous system, cavernous malformations account for 5-13% of the total. They affect approximately 0.02-0.5% of the population with a frequency of 0.5/100.000 [4], although the number is suspected to

be bigger as patients can go asymptomatic for a long period of time rarer frequently. 80% are supratentorial lesions, 15% are located in the posterior fossa and 5% in the spinal cord.

The medium age is currently 37, but cavernous malformations can occur at any age [5]. With age, increases the association of the malformation with developmental venous anomalies [6].

Etiology

For the most part, these lesions appear by one, and are not associated with developmental venous anomalies [5]. This kind of lesion is called sporadic. It is estimated that up to 25% of patients are asymptomatic [7]; percentage which could be underestimated due to the possibility of these asymptomatic patients of going undiagnosed their entire life.

Sometimes, less frequently, multiple cavernomatous malformations can develop, these, in some cases could correspond to a familiar or hereditary form of the disease, which possess an autosomal dominant inheritance, are mainly characterized by the presence of multiple lesions, and possess a major risk for complications [8,9]. Three protein codifying genes have been identified to be related with cerebral cavernous malformations (CCM): CCM1, CCM2, and CCM3 [10,11]. It is only needed that one of these genes is mutated for the phenotype to be manifested. These genes are part of a molecular pathway that regulates cellular growth and proliferation on the endothelial barrier. In familial cavernous malformations there are found in average 6.5 lesions per patient [12].

Pathogenesis and natural history of disease

The natural history of the disease goes with a wide history of seizures in 80% - 90% of the cases. Asymptomatic patients have a lesser risk of hemorrhage than the ones that have had a history of a previous symptomatic hemorrhage [13]. The risk for hemorrhages to be symptomatic becomes bigger when the hemorrhage surpasses the lesions capsule, and they are called open hemorrhages. Usually symptomatic hemorrhages are acute and have a greater recurrence.

The risk of hemorrhage also increases when an incomplete resection of the lesion has been made, which is associated with a high immediate postoperative morbidity rate [14].

The diagnose may be an incidental finding, as 20% of patients are submitted for exams requested for determining the possible causes of a headache. The clinical picture often presents with seizures, focal neurologic deficit, and occasionally with acute intraparenchymal or intraventricular hemorrhage. The symptoms are dependent on the localization and size of the malformation or the related hemorrhage. For example, seizures are more likely to occur on supratentorial lesions. The recurrence of further seizures is about 1.5% - 2.4% in asymptomatic patients per year. These seizures are associated with recurrent hemorrhages, and caused by the epileptogenic material of hemosiderin in the iron deposits left after the hemorrhage [7,8].

Diagnosis and Classification

The diagnosis cannot be based on clinic as the symptoms are nonspecific. The preferred diagnose is made with magnetic resonance (MRI). The findings in computed tomography (CT) show a hyperdense mass of defined borders with variable calcifications. The differential diagnosis includes hematoma, hemorrhagic of calcified neoplasm and other vascular malformations. It is recommended the use of angiography if vascular anomalies are suspected, even though cavernous malformations are usually avascular, without detectable contributing arteries o draining veins [15,16].

MRI findings are described as rare dilated sinusoids, without presence of associated arteries or veins, in various thrombosis and bleeding stages, sometimes associated to edema and acute hemorrhage. Differential diagnosis includes thrombotic arteriovenous malformations, thrombotic aneurysms, low grade calcified gliomas, hemorrhagic neoplasm, metastatic lesions (discarded for the lack of edema) [16].

These lesions were differentiated by Zambramksi [15] in 1994 in 4 subcategories according to their pathologic correlation and findings in CT/MRI

Type 1: They are described as homogenous and hyperintense on T1WI and T2WI. A subacute hemorrhage is predominant, which causes a hypointense rim that surrounds the lesion in T2WI that is caused by the deposition of macrophages charged with hemosiderin and other substances associated to the decomposition of hemoglobin.
Type 2: Multinodular and heterogeneous lesions described to have the form of a “berry” or “popcorn” for being reticulated, as seen in T1WIU and T2WI, which is caused by the presence of hemorrhage in various stages. A hypointense rim of hemosiderin can be seen in T2WI. When the lesions are large, areas of calcification may be seen.
Type 3: Masses of chronic hemorrhages, stained with hemosiderin in and around the lesion. They are seen as Iso- or hypointense lesion in T1WI and hypointense in W2TI, with a hypointense rim that make the lesion look larger. In gradient-echo (GE) sequence they are hypointense, with a larger hypointense rim that makes the lesion look even larger that in T2WI.
Type 4: Are poorly of not visualized at all in T1WI and T2WI, while in GE are seen as punctate hypointense lesions.

The use of GRE or SWI helps to identify the number of lesions that could have been by-passed in conventional MRI sequences.

Medical and surgical management

Medical management and monitoring depends on the presence of clinical manifestations, or in asymptomatic patients with an increased risk of complications. In these cases, a controlled monitoring is recommended each 1-2 years in MRI [17,18]. If neurological symptoms increase, the repetitions of the MRI should be considered.

Indication of surgical management should be an individualized decision based on the specific characteristic of the lesion and type of CM. Including localization, size, presence and frequency of hemorrhages, and the presence of other lesions.

Stereotactic radiosurgery remains controversial as treatment. For patients with intractable seizures, best treatment remains the surgical removal of the lesion, but for lesions present in high risk areas, radiosurgery tend to be considered [17]. However, for several years it has been shown that the management of this type of lesion with radiosurgery represents an equal or greater risk of bleeding when compared to expectant management, which is why it has fallen into disuse [19].

In order to improve vascular integrity, treatment with simvastatin or fasudil for inhibition of RhoA and cyclic adenosine monophosphate-elevating drugs are considered [20,21]. Further progression of CM could be reached by anti-angiogenic drugs targeting VEGF receptors, present in the endothelium of CM lesions. Antiplatelet and anticoagulation with Coumadin derivatives are not recommended [22,23].

Case

A 71-year-old female patient, with history of right equinovarus foot since childhood, difficulties for the mobilization and use of a walking stick, with a 3 year history of clinical symptoms, consisting of dysesthesia and progressive loss of the strength in the right side of the body, which has been exacerbated and is markedly worse one month before the admission to the hospital and also had asthenia and adynamia, associated with occasional tremor in the right side of the body, with difficulty in standing and walking, requiring the use of a walker.

Two days before admission, she had multiple episodes of loss of postural tone, altered consciousness and diaphoresis, which lasted approximately 30 seconds with full and spontaneous recovery. After that, she had two more episodes of loss of postural tone and consciousness but, these one lasted approximately 10 minutes, her son found her unconscious, and decided to consult the emergency department. The patient denies headache and abnormal movements. On admission reports, There was evidence of deviation of the labial commissure to the right, decrease in the right side force (4/5), right later opulsion, dysarthria, photophobia and loss of the sphincter control.

At the Physical exam she was stable, with a left external strabismus secondary to a trauma she had in childhood, without alterations in the respiratory, cardiovascular system, or in the abdomen. In the neurological exam, she was alert, oriented in person and place, mini mental score 17/27 points (corrected score of 22/35 points → mild cognitive impairment) equal round pupils (3mm), reactive to light and accommodation, upper left quadrantanopia to the campimetry by confrontation, to the fundus of the eye were shown bilateral cataracts with predominance on left eye, ocular movements were present but reduced at the left eye, the other cranial nerves do not have alterations. Decreased superficial sensitivity in all dermatomes, deep sensitivity without alterations, strength in right upper

limb 3/5, right lower limb 4/5, left body 5/5, musculotendinous reflexes ++/++++, proprioception without alterations, walking with right lateropulsion, no cerebellar or meningeal irritation signs.

Evolution

A cranial tomography (Figure 1) was made, showing intraparenchymal hyperdense lesions in the left frontal lobe, the limit between the parietal and the occipital lobes at the left side, right parietal lobe and in the brainstem at the level of the left cerebral peduncle.

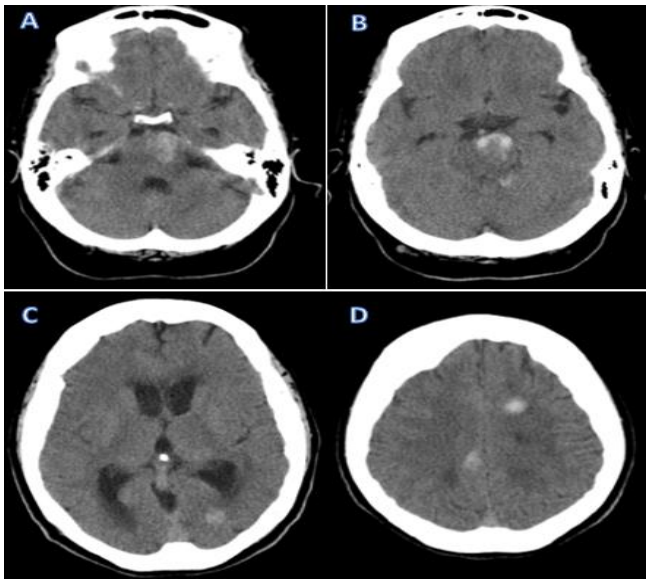

Figure 1: Simple cranial tomography: (a) Pontocerebellar cisterns and fourth ventricle enlarged. (b) Rounded lesion with irregular edges with different degrees of hyper density in the left and right cerebral peduncles, (c) Hyper dense lesion in the left parieto-occipital region, interstitial edema with transependymal migration. (d) Hyper dense lesions without perilesional edema in left frontal and right parietal lobe.

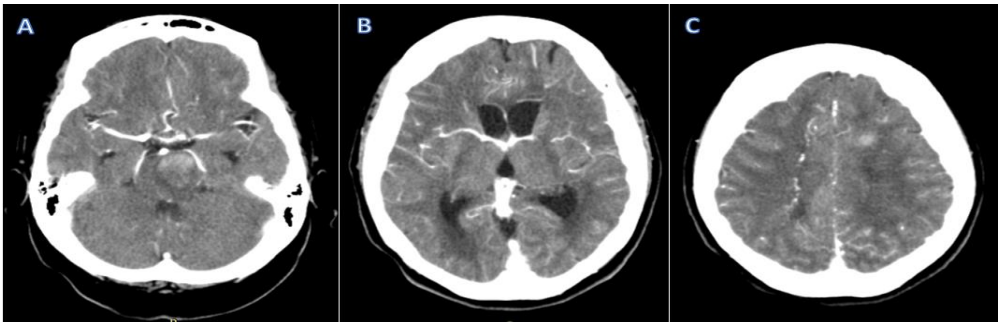

Figure 2: Contrasted tomography of the skull (a) Rounded lesion with different degrees of hyperdensity with defined edges with predominant in the left cerebral peduncle and mild inhomogeneous uptake of the contrast medium. (b) Hyperdense rounded lesion with poorly defined edges in left parieto-occipital region that does not capture the contrast. (c) Hyperdense lesion rounded frontal left with poorly defined edges and without contrast uptake.

Afterwards, a contrasted skull tomography was performed (Figure 2), in this image, was shown that the lesions do not homogeneously capture the contrast medium, after that result, the multiple lesions were considered to have a

neoplastic or an hemorrhagic origin, and different studies were made to eliminate the suspicion of metastatic disease: contrasted thoracoabdominal CT, thyroid ultrasound, colonoscopy and esophagogastroduodenoscopy, none of them showed lesions that explained secondary disease.

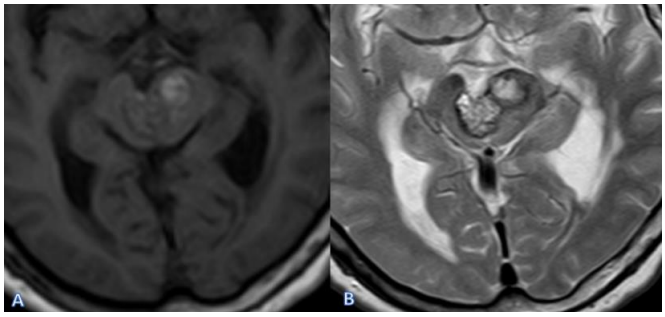

Figure 3: Simple brain magnetic resonance. Lesion in left cerebral peduncle, (a) T1 rounded lesion with poorly defined edges, isointense in central region with a hypointense ring on the edges, (b) T2 rounded lesion with different degrees of central hyperintensity and a hypointense ring at the edges.

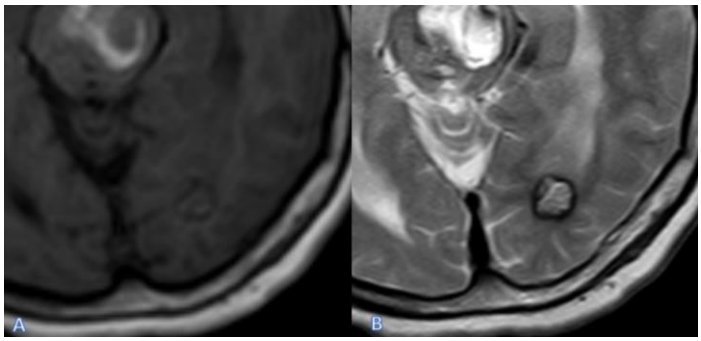

Figure 4: Simple brain magnetic resonance. Left parieto-occipital lesion (a) T1 rounded lesion with poorly defined edges, isointense in central region with a hypointense ring on the edges. (b) T2 rounded lesion with different degrees of central hyperintensity and a hypointense ring at the edges.

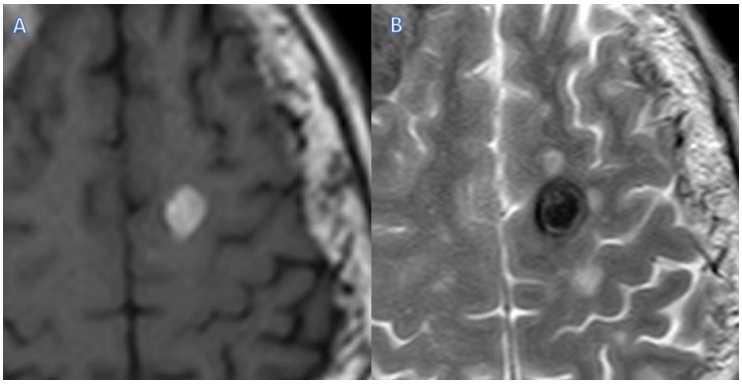

Figure 5: Simple brain magnetic resonance. Left parietal lesion (a) T1 Hyperintense rounded lesion with defined edges (b) T2 Lesion with different degrees of central hypointensity and hypointense ring on edges.

After those studies, a simple (Figure 3 - Figure 5) and contrasted (Figure 6 - Figure 7) cerebral magnetic resonance imaging was taken, showing lesions in different stages of bleeding suggestive of cavernomatous malformations in brainstem, frontal and parietal lobe, (Zabramski I and II). Because in the resonance images there is no evidence of

extracapsular bleeding, no uncontrollable epileptic seizures and given the location in the brain stem of the lesions, it is decided to give hospital discharge with outpatient control, due to high risk of morbidity in case of performing surgical management.

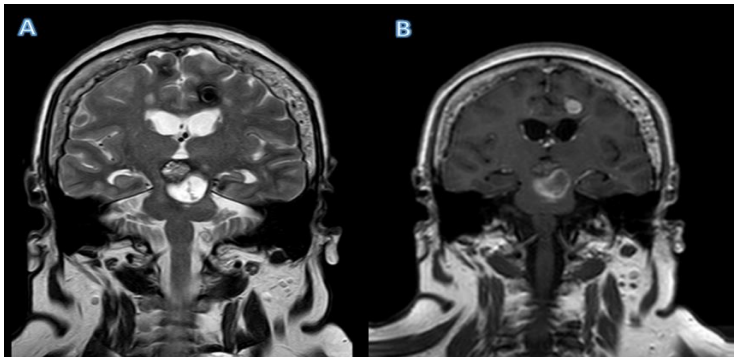

Figure 6: Coronal view (a) T2: 3 rounded lesions with different densities, (b) Contrast brain resonance.

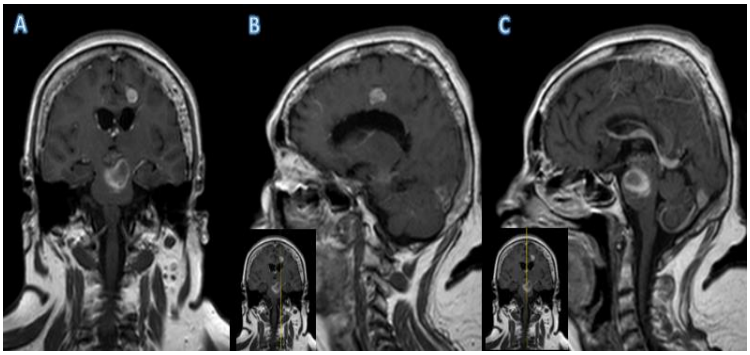

Figure 7: (a) Coronal view in T1, (b) Parasagittal view and (c) Sagittal view with contrast.

Discussion and Conclusion

Multiple cavernous malformations are part of one of the subtypes of arteriovenous malformations and a dominant inheritance pattern has been found in which it becomes more prone to bleeding and an epileptic seizure occurs as the first manifestation. The diagnostic and therapeutic approach to cavernous malformations is not always easier to take into account in some cases. In the case presented, it is shown how difficult it can be to obtain accurate diagnosis with basic images such as simple and contrasted tomography that can be thought of in other diagnoses such as hemorrhagic stroke or even bleeding metastatic lesions. Therefore, the study of these lesions with the simple and contrasting brain resonance study is required to better define the lesion and the behavior in the different weights for this way direct the definitive therapy.

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