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Familial cerebral cavernous malformation syndrome in Serbian family

Aleksić Vuk[1], Mandarić Aleksandar[2], Mihajlović Miljan[1], Aleksić Nemanja[3], Rapaić Marko[4], Jovančević Miroljub[5], Stanić Milenko[1], Samardžić Marko[1], Popović Igor[1], Miladinović Vladimir[1], Spaić Milan[1]

[1]Department of Neurosurgery, Clinical Hospital Center Zemun, Belgrade, SERBIA
[2]Department of Radiology, Clinical Hospital Center Zemun, Belgrade, SERBIA
[3]Clinic for Cardiac Surgery, Clinical Center of Serbia, Belgrade, SERBIA
[4]Faculty for Special Education and Rehabilitation, University of Belgrade, SERBIA
[5]Department of Radiology, "Euromedik" Hospital, Belgrade, SERBIA

Abstract: Cavernomas are benign vascular malformations, and about 50% of all cases are multiple. The hereditary form of brain cavernomas is uncommon, and it is certainly under diagnosed. Another entity is familial cerebral cavernous malformation syndrome. It is defined as the occurrence of multiple cavernomas or the occurrence of cavernomas in at least two members of a family or the presence of a mutation in one of the three genes causing familial cerebral cavernous malformation syndrome. We present a Serbian family in which three consecutive members of family had brain cavernoma. According to our knowledge, this is second case of hereditary cavernoma described in Serbian population.

Key words: Cavernoma; Familial cerebral cavernous malformation syndrome; multiple cavernomas

Introduction

Cavernomas are a benign vascular malformations (e.g. hamartomas), and about 50% of all cases are multiple (1). They are located in the brain or rarely in the spinal cord. The size of cavernomas ranges from a few millimeters to several centimeters. Cavernomas increase or decrease in diameter and increase in number over time. The majority of cavernomas become apparent between the second and fifth decades with presentation such as focal neurological defcit, headache, seizure, or cerebral hemorrhage (2). The hereditary form of cavernomas is relatively rare, and this, usually autosomal dominant pathology generally presents with focal neurological symptoms and seizures, however, many patients remain

asymptomatic, although, acute hemorrhages sometimes appear over time (3).

We present a Serbian family in which three consecutive members of family had brain cavernoma. According to our knowledge, this is second case of hereditary cavernoma described in Serbian population.

Case presentation

The first patient is a 35 years old female who presented to our emergency department with headache, right sided paresthesis, and persistent singultus (hiccup). She rated the pain as 8 out of 10. A head CT was performed and brain stem bleeding was suspected. The cranial MRI revealed a cavernoma with signs of hemorrhage in the region of medulla oblongata and medulla spinalis junction (Figure 1).

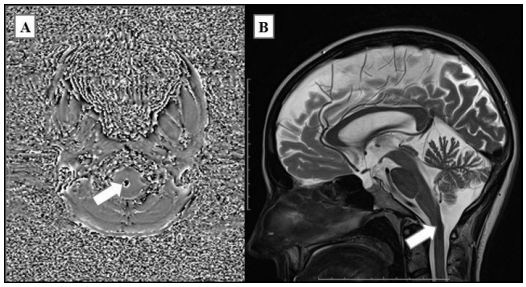

Figure 1. Cranial MRI showing a cavernoma with signs of hemorrhage in the region of medulla oblongata and medulla spinalis junction. (A) SWI sequence. (B) T2 sequence

Corticosteroid therapy was started, and symptoms disappeared. However, she had occasional attacks of right sided body numbness. One year after first onset of symptoms, control MRI showed enlargement of cavernoma with signs of hemosiderin deposits, after which she was accepted for stereotactic radio-surgery treatment in another hospital, which was performed about 2 years after the first onset of symptoms. Also, she was treated with a total of 1200cGy to 85% isodense line to the cavernoma lesion, using 6D skull IGRT system. She didn't suffer from any side effects, and control MRI showed signs of cavernoma regression, without signs of de novo hemorrhage (Figure 2).

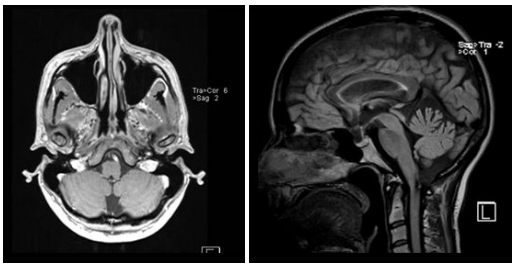

Figure 2. Control MRI with signs of cavernoma regression

Her neurological finding was normal, and she was without complaints. Control MRI after two years showed state after radiation therapy, and cavernoma dimensions were unchanged. However, SWI MRI sequence was performed and multiple brain cavernomas without signs of hemorrhage were found, and further neuro-radiological follow ups were advised. Control MRI was performed in another hospital, and we couldnt obtainen the images, but only radiological description. Also, since multiple cavernomas were found on the last MRI, familial form of cerebral cavernous malformation was suspected. MRI was performed in patient's father at the age of 73, and multiple brain cavernomas, without sigs of hemorrhage were found (Figure 3).

Patient had normal neurological finding, and also only follow ups were recommended. In further investigation, we performed brain MRI in patient's 15-year old son, and single caveroma located in pons was found (Figure 4).

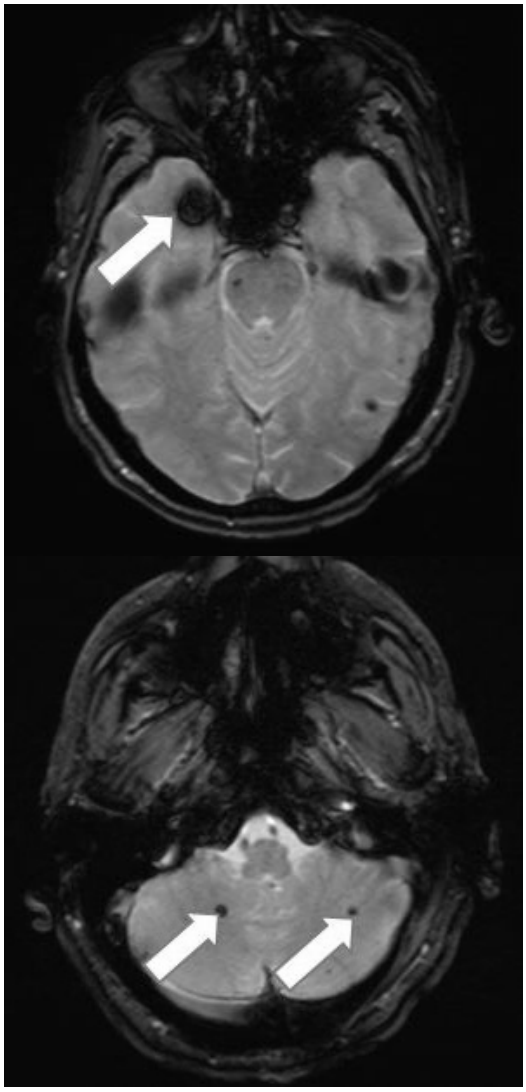

Figure 3. Brain MRI showing multiple cavernomas

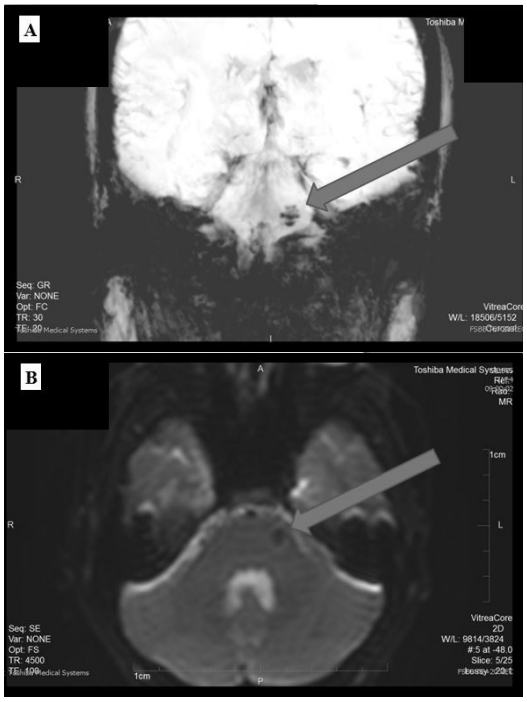

Figure 4. Brain MRI showing caveroma located in pons. (A) SWI sequence. (B) DWI sequence

This young patient had normal neurological status, and since he is symptom free, only regular brain MRI controls are recommended. No other members of family undergo radiological investigations.

Discussion

Brain cavernous malformations or cavernous angiomas are vascular malformations in the brain or sometimes in spinal cord. In one third of patients, these cavernous malformations are multiple. The hereditary form of brain cavernomas is uncommon, and it is certainly under diagnosed (3). We present a Serbian family in which three consecutive members of family had brain cavernoma, of which in 2 members,

cavernomas were multiple, and one member had solitary lesion.

Another entity is familial cerebral cavernous malformation syndrome. It is defined as the occurrence of multiple cavernomas (usually 5 or more) or the occurrence of cavernomas in at least two members of a family or the presence of a mutation in one of the three genes causing familial cerebral cavernous malformation syndrome. Three genes are known to cause muta¬tions in familial cerebral cavernous malformation syndrome: KRIT-1 (CCM-1), CCM-2, and PDCD-10 (CCM-3) (Table 1) (3-6).

TABLE I

Diagnostic criteria's for familial cerebral cavernous malformation syndrome (at least 1 of the following criteria)

The presence of multiple brain or spinal cord cavernomas (typically 5 or more)
The occurrence of brain or spinal cord cavernomas in at least 2 members of a family
The presence of a mutation in one of the three genes causing familial cerebral cavernous malformation syndrome

According to presented criteria's, this is almost typical familial cerebral cavernous malformation syndrome, and to our knowledge, this is second case of hereditary cavernoma described in Serbian population, first being described by Mitić et al. (7).

The disease frequently presents with focal neurological deficit (35-50%), and epileptic seizures (38-55%) (8). A headache, spontaneous paraplegia, or signs of cerebral hemorrhage are less frequently encountered symptoms and signs. Also, one quarter to one half of patients with cavernomas remain symptom free during life (9). In presented family, one patient had two frequent symptoms: headache, and focal neurological deficit-parestheis. However, this patient also had prolonged hiccups (singultus), which is defined as singultus lasting more than 2 days. Eisenacher and Spiske presented a similar case in which patient had persistent hiccups as the presenting symptom of medullary cavernoma. Conducting literature review we found two more similar cases of persistent cavernoma due to presence of medullary cavernoma (10). According to described cases, as well as study of Musumeci et al, conducted on animals, the region of the medulla oblongata lateral of the obex is probably responsible for the singultus reflex (11). Overall, singultus is rarely described in the context of a tumor or vascular malformation (e.g. cavernoma) in the region of the medulla oblongata, but persistent singultus, lasting more than 48 hours should arouse suspicion on this rare cause or some other rare neurological disorder.

Genetic testing may confirm suspicion on familial cerebral cavernous malformation syndrome. Three genes muta¬tions are found in this hereditary syndrome: KRIT-1 (CCM-1), CCM-2, and PDCD-10 (CCM-3) (6). Also, this is an autosomal dominant disease, and

each child of a person with familial cerebral cavernous malformation syndrome has a 50% chance of inheriting the mutation. A higher incidence of this disease is found in Hispano-American individuals of Mexican descent, probably due to a common ancestor with a mutation in the KRIT-1 gene (12). In presented family, we didn't perform genetic testing, since family wasn't motivated.

In majority of cases, MRI shows multiple focal regions of susceptibility induced signal loss of different size, well seen on gradient-echo sequences, or better on susceptibility-weighted imaging (SWI sequence). Lesion can be multiple (about 30% of patients), and in familiar form, the number of cavernomas is higher, in majority of cases more than 5. Number of lesions is increasing with age. However, young patients may already have numerous cavernomas (13). In our case, MRI features of all patients were typical, with SWI sequence being most valuable. In two out of 3 patients from presented family, cavernomas were multiple, while the youngest patient had only one cavernoma. One patient received stereotactic radio-surgery treatment, after which neuroradiological follow ups were advised. For other two patients only regular follow ups were indicated.

Microsurgical removal of cavernoma is may be reasonable if patient has epileptic seizures, or focal deficit due to mass effect or recurrent bleeding. Stereotactic radiosurgery is a safe therapy for cavernomas located in deep or eloquent sites (3, 14). It is important to find structural and the functional abnormalities with data from EEG, MRI, and SPECT so the spatial relationships may be demonstrated, which can help in the decision making for right therapy approach. In presented family, one patient had to be subjected to stereotactic radiosurgery, since she had cavernoma presented with focal neurological deficit, and radiological signs of repeated bleeding, while other two patients were asymptomatic, and only neuro-radiological follow ups were advised.

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