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FAMILIAL CAVERNOUS ANGIOMATOSIS: CASE REPORT OF A FAMILY WITH MULTIPLE INTRACRANIAL LESIONS

Familijarna kavernozna angiomatoza: prikaz obitelji s multiplim intrakranijalnim lezijama

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Abstract

Cavernous angiomas of the brain belong to a group of occult vascular malformations of the central nervous system, i. e. to changes not evident on conventional angiographic examinations. Intraoperatively or at autopsy, they represent raspberry-like clusters of veins. Magnetic resonance (MR) imaging of the brain is the diagnostic method of choice, where cavernomas typically appear as zones of mixed-signal intensity due to the presence of hemosiderin in the surrounding brain parenchyma. Familial form of cavernous angiomatosis is an autosomal dominant disorder which occurs as a result of the mutations in one of the three different genes, and is most often present in the Hyspanic-American population. Familial form of the disease is characterized by the presence of two or more lesions in the brain tissue, in two or more members of the same family. In 2008, three patients in close blood relation were hospitalized within a short period of time at the Neurosurgery Clinic Niš for multiple cavernous angiomas of the brain, as confirmed by MR imaging and a histopathologic finding in one surgically treated family member. Three other family members were subsequently examined and familial cavernous angiomatosis was confirmed in two additional members who were asymptomatic. MR imaging was performed using T1- and T2-weighted SE sequences and T2-weighted GRE sequence. The number of lesions seen in T2 SE (60) and T2 GRE (406) sequences was analyzed, and a discrepancy in the number of found cavernomas was displayed. The number of cavernomas by brain regions, the number of cavernomas in asymptomatic and symptomatic patients as well as their distribution, were also analyzed.

The obtained data show superiority of the T2 GRE sequence over T2 SE sequence in terms of sensitivity. Type IV cavernoma is detected only on T2 GRE images, according to Zabramski. Type IV cavernoma is one of the features of familial cavernous angiomatosis.

Key words

familial cavernous angiomatosis, cavernoma, cavernous angioma, gradient recalled echo

Sažetak

Kavernozni angiomi mozga pripadaju grupi okultnih vaskularnih malformacija središnjeg živčanog sustava, tj. promjenama koje se ne prikazuju na klasičnim angiografskim ispitivanjima. Intraoperativno ili na autopsiji predstavljaju vensko klupko slično malini. Dijagnostička metoda izbora je MR mozga na kojem se kavernomi prikazuju najčešće kao zone mješovitog signala uslijed prisustva hemosiderina u okolnom moždanom parenhimu. Familijarni oblik kavernozne angiomatoze je autosomno-dominantno nasljedni poremećaj, koji se javlja kao posljedica mutacija na jednom od tri različita gena i najčešće je prisutan u hispanoameričkoj populaciji. Karakteristika familijarnog oblika oboljenja je prisustvo dvije ili više lezija u moždanom tkivu, kod dvije ili više osoba iz iste obitelji. Tijekom 2008. na Klinici za neurokirurgiju Niš je u kratkom vremenskom razdoblju hospitalizirano troje pacijenata u bliskom srodstvu kod kojih je dokazano postojanje multiplih kavernoznih angioma mozga realizacijom MR mozga uz patohistološku potvrdu kavernoma kod jednog operiranog bolesnika iz obitelji. Naknadno su ispitane još tri osobe iz obitelji pri čemu je pozitivan nalaz familijarne kavernozne angiomatoze potvrđen kod još dva člana koji su bili asimptomatski.

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MR mozga je realiziran uz upotrebu T1 i T2 SE, kao i T2 GRE sekvence. Analiziran je broj lezija viđenih u T2 SE (60) i T2 GRE (406) sekvencama te je prikazana diskrepancija u nađenom broju kavernoma. Analiziran je broj kavernoma po regijama mozga, broj kavernoma kod asimptomatskih i simptomatskih pacijenata, kao i njihova distribucija.

Dobiveni podaci prikazuju superiornost T2 GRE sekvence u senzitivnosti u odnosu na T2 SE sekvencu. Tip IV kavernoma po Zabramskom detektira se samo na T2 GRE snimkama. Postojanje tipa IV kavernoma je jedna od karakteristika familijarne kavernozne angiomatoze.

Ključne riječi

familijarna kavernozna angiomatoza, kavernom, kavernozni angiom, gradient recalled echo

Introduction

Cavernous angiomas belong to the group of intracranial vascular malformations caused by a disorder in the development of the vascular bed. Macroscopically, they represent a collection of blood vessels resembling a raspberry [1]. They are mostly localized in the brain tissue, but can also be found in the spinal cord, retina or as skin changes [2, 3]. Pathohistologically, these are vascular channels made of walls that are lined with single endothelium, without smooth muscle tissue or elastic fibers, with the absence of brain tissue between the pathological blood vessels of the tangle. The number and size of these pathological channels inside the cavernoma grow throughout life.

Since cavernous angiomas are most often localized in the brain tissue, they can lead to epileptic seizures, focal neurological deficits or a fatal cerebral hemorrhage. Hemosiderin is present even in the absence of apparent hemorrhage in the surrounding parenchyma [4]. A quarter of patients are asymptomatic [5].

Considering that cavernous angiomas are not characterized by significant inflow of blood or significant venous drainage, they belong to occult vascular malformations that are not visible during conventional angiographic procedures. Owing to advances in MR imaging technology, cavernous angiomas are becoming one of the most commonly diagnosed vascular malformations with a prevalence of 0.4–0.9%. Prospective autopsy series have confirmed the incidence of cavernous angiomas from 0.49 to 0.53% [5]. Multiple lesions comprise 15–30% of all cases [6].

Familial cavernous angiomatosis represents an autosomal dominant disorder [7, 8] which is most common among Latino families. It comprises 10–15% of the total number of cavernoma cases [9]. In the familial form of cavernous angiomatosis, multiple lesions are present in 3/4 of patients.

Studies have shown changes on at least three different genes, affecting the occurrence of the familial form: CCM1 and CCM2 genes located on chromosome 7 and CCM3 gene located on chromosome 3, not yet completely analyzed [4, 10].

Objective

Literature review does not indicate that investigations of families with the familial cavernous angiomatosis have been carried out on the territory of Serbia. This is the first time that members of a family with multiple cavernous angiomatosis of the brain have been examined and the results analyzed and presented in a paper. MR imaging with T1 and T2 sequences and T2 GRE (Gradient Recalled Echo) sequences was performed on all of the studied patients. The MR findings in symptomatic and asymptomatic patients, as well as the type and number of lesions, were compared, according to the classification by Zabramski [11]. The number of cavernous changes in various brain regions was analyzed.

Materials and Methods

In 2008, three patients in close blood relation were treated for intracranial hemorrhage at the Department of Neurosurgery, Niš. MR exploration of the intracranium was subsequently conducted on three other members of this family and the MR images made prevously for epileptic equivalents were reviewed with regard to one more person. MR imaging of the brain using T1 and T2 SE sequences, as well as T2 GRE sequences, was performed on all the patients. The MRI equipment used was the Siemens Avanto 1.5T MRI Scanner.

All findings were independently reviewed by two specialists, radiologists and neurosurgeons. T1, T2 and T2 GRE sequences were compared and analysed with regard to the number and type of lesions found during the MR exploration.

Types and numbers of cavernous angioma were processed according to the classification by Zabrimski.

Statistical data were processed in the Statistica 8 soft (StatSoft, Tulsa) program, using the Mann-Whitney U test and Wilcoxon signed-Rank test.

Results

Type I lesions are characterized by subacute hemorrhage in the zone with the present change. On transverse sections, on T1 SE sequence, type I is characterized by the existence of a broad lesion involving a zone of high-signal intensity and a zone of low-signal intensity which indicates a more recent bleeding. T2 SE sequence shows the zone of bleeding more clearly. T2 GRE sequence clearly demarcates the change zone. These data are illustrated in Figures 1, 2 and 3.

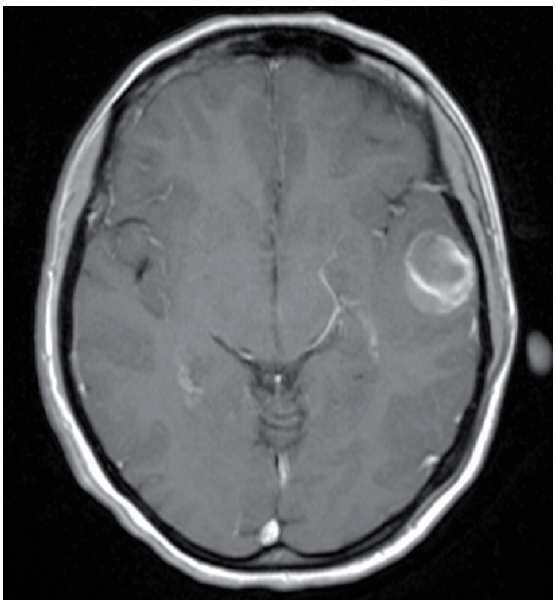


Figure 1. Type I cavernoma revealed in T1-weighted SE sequence.

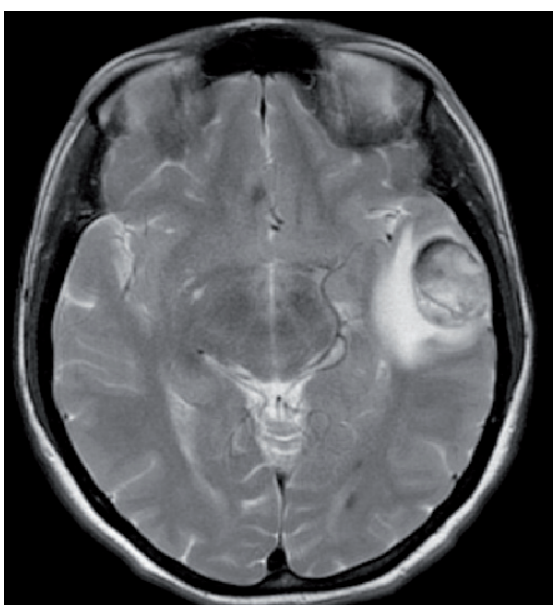


Figure 2. Type I cavernoma revealed in T2-weighted SE sequence.

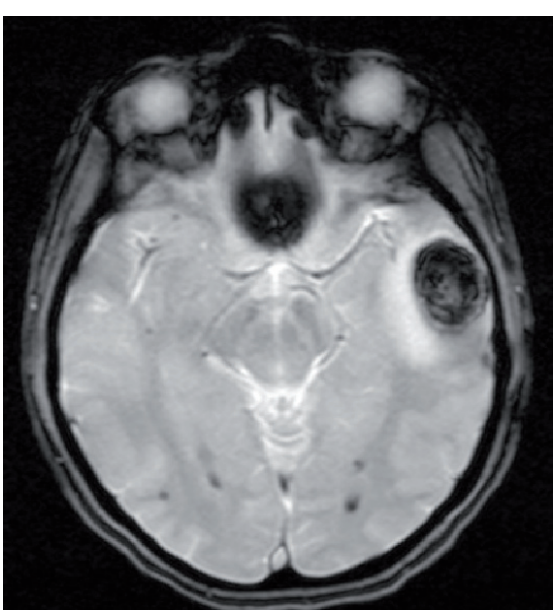
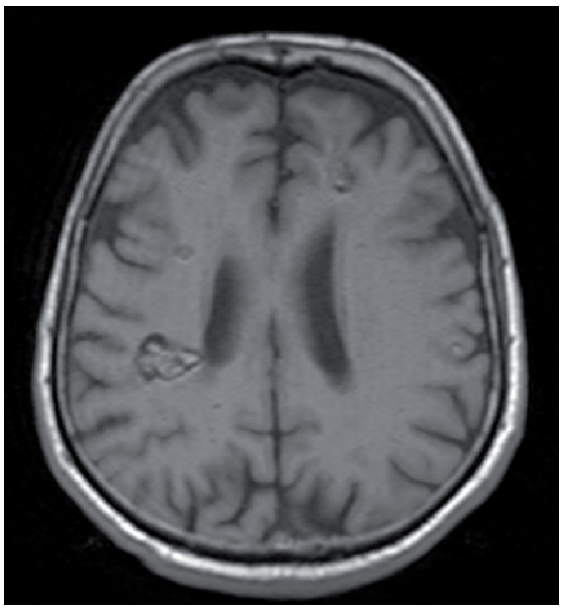


Figure 3. Type I cavernoma revealed in T2 GRE sequence.



Type II is a lesion with bleeding and thrombosis zones in multiple time intervals. It typically appears as most commonly verified, raspberry-like cavernoma of the brain. Type II lesion is shown in Figures 4, 5 and 6 with the central reticular nucleus and peripheral low-signal rim.

Figure 4. Type II cavernoma in T1-weighted sequence, with central reticular nucleus and a zone of peripheral low-signal intensity, resulting from the accummulated hemosiderin.

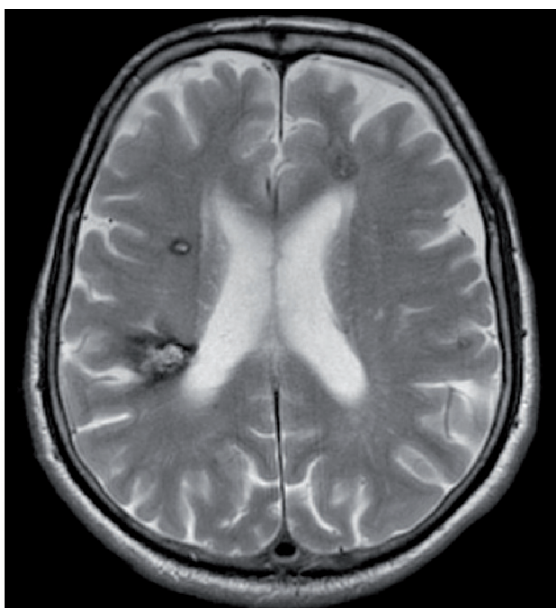


Figure 5. Type II cavernoma in T2-weighted sequence with a more clearly demarcated hemosiderin zone.

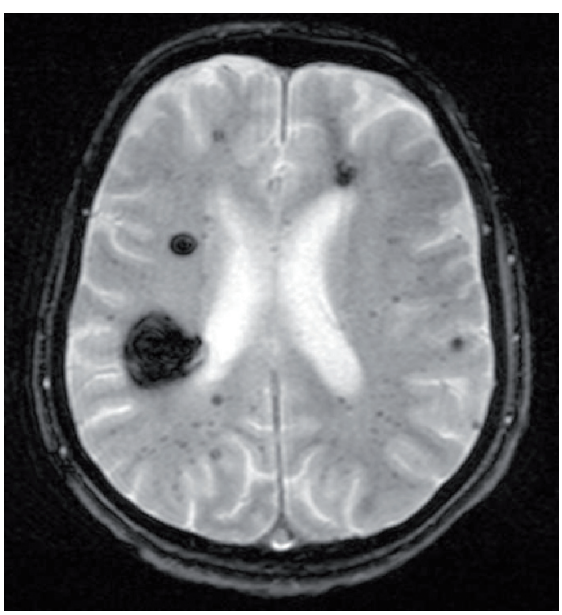
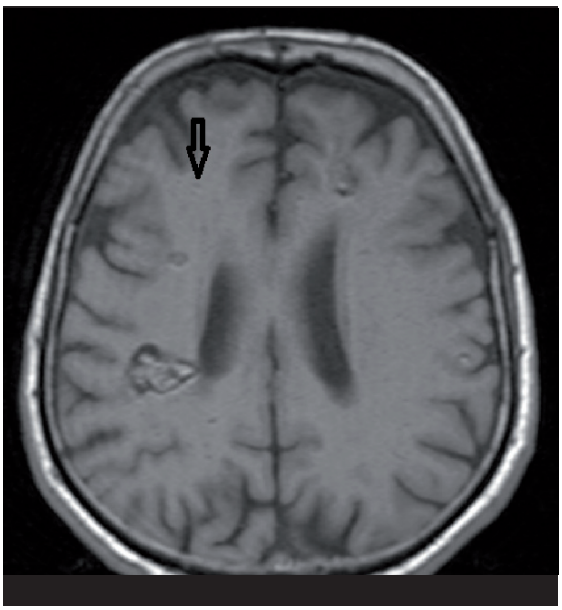


Figure 6. Type II cavernoma in T2 GRE sequence most clearly demarcating multiple Type II cavernomas as zones of low-signal intensity.



Type III lesion is characterized by chronic hemorrhage with hemosiderin within the lesion itself. With type III angiomas, the lesion is best displayed on the transverse T2 sequence as a zone of homogeneous low-signal intensity, as well as on GRE sequences, as shown in Figures 7, 8, 9.

Figure 7. T1-weighted sequence not clearly displaying Type III lesion.

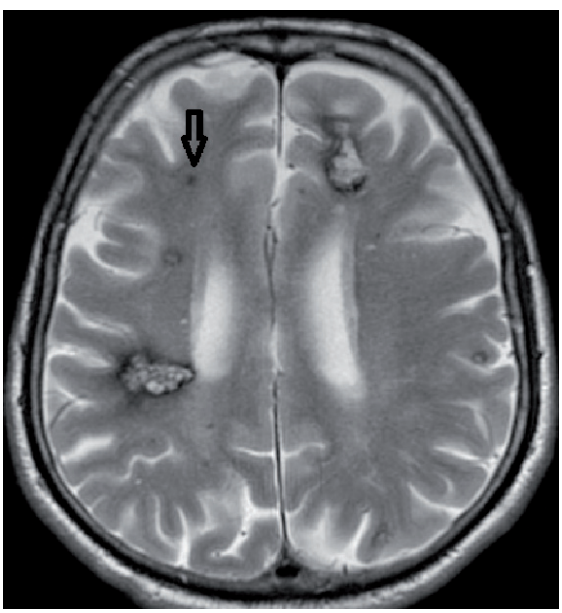


Figure 8. Clearly displayed uniform hyposignal Type III lesion on T2-weighted SE sequence.

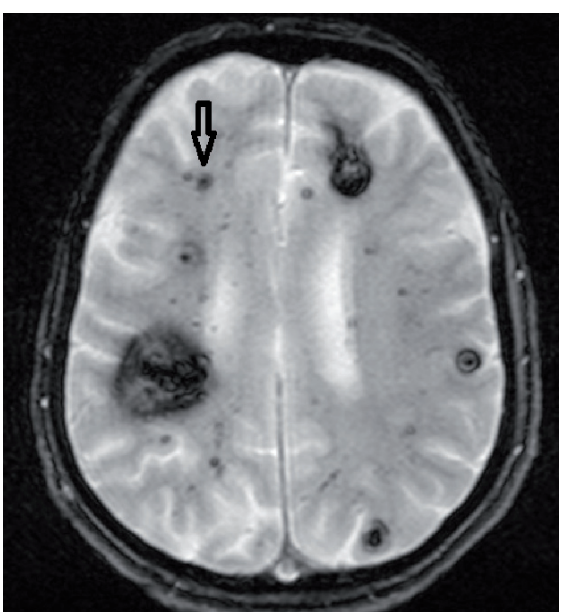
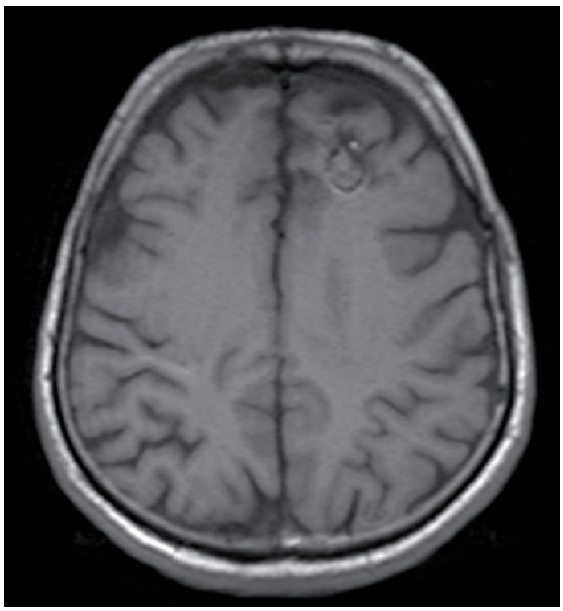


Figure 9. Type III lesion most clearly displayed on T2 GRE sequence.



Type IV is still an unclear type of lesion and may correspond to capillary telangiectasia or a cavernoma in an early stage of development. Type IV is characteristic of the familial form of cavernomatosis and is shown in Figures 10, 11 and 12.

The discrepancy between the SE and GRE findings of type IV cavernous angioma is a feature of the familial form of cavernous angiomatosis.

The obtained results in terms of the total number of cavernomas, number of lesions in asymptomatic and symptomatic patients, number of cavernomas found on T2 and GRE sequences and localization of cavernoma are presented in tables (Tables 1–5).

Figure 10. Type IV lesion not clearly displayed on T1-weighted sequence.

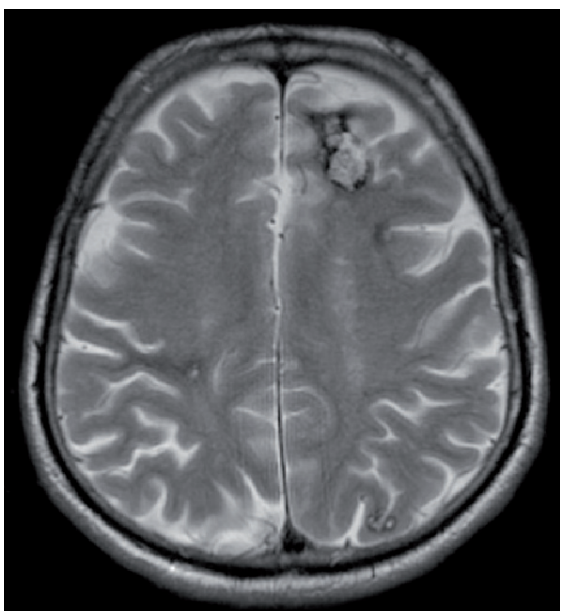


Figure 11. Type IV cavernoma not displayed on T2-weighted sequence.

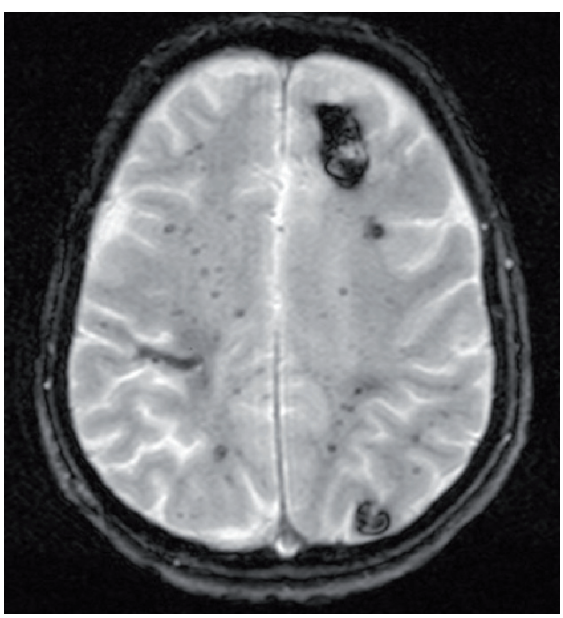


Figure 12. Hyposignal zones of multiple Type IV cavernomas in the white matter of the brain clearly displayed on T2 GRE sequence.

Table 1. Number of lesions in certain brain regions.

Region	Number of lesions
Brainstem	4 (0.98%)
Cerebellum	23 (5.70%)
Occipital lobe	97 (23.90%)
Parietal lobe	102 (25.12%)
Temporal lobe	116 (28.60%)
Frontal lobe	64 (15.80%)

Table 2. Total number of cavernomas seen on MR GRE and MR T2 sequences.

	GRE sequences	T2 sequences
Type I	4 (0.98%)	4 (6.66%)
Type II	46 (11.33%)	46 (76.68%)
Type III	10 (2.46%)	10 (16.66%)
Type IV	346 (85.23%)	*
*Type IV cavernomas may be detected on SE sequences		

Table 3. Number and location of lesions detected on MR T2-weighted sequences, in symptomatic and asymptomatic patients.

	Number of lesions		Location of lesion	
	Total number	Mean value*	Supratentorially	Infratentorially
Symptomatic patients	46	15.33	39 (84.8%)	7 (15.2%)
Asymptomatic patients	14	7	7 (50%)	7 (50%)
* Mean values represent calculated mean values of the number of lesions per patient				

Table 4. Number and location of lesions detected on MR GRE sequences.

	Number of lesions		Location of lesion	
	Total number	Mean value	Supratentorially	Infratentorially
Symptomatic patients	298	99.33	282 (94.6%)	16 (5.37%)
Asymptomatic patients	108	54	97 (89.8%)	11 (10.2%)
Numbers in brackets represent percentages				

Table 5. Distribution of the cavernoma types on MR GRE sequence, in symptomatic and asymptomatic patients.

	Type 1		Type 2		Type 3		Type 4	
	Number of lesions	Mean value*	Number of lesions	Mean value*	Number of lesions	Mean value*	Number of lesions	Mean value*
Symptomatic patients	4	1.33	35	11.66	7	2.33	252	84
Asymptomatic patients	0	0	11	5.5	3	1.5	94	47
* Mean values represent calculated mean values of the number of lesions per patient								

Discussion

Cavernous angioma belongs to a group of hamartomas of the blood vessels [12]. It is an occult malformation that is not displayed on the classic angiography. Multiple familial cavernous angiomatosis is defined by the existence of two or more brain lesions in two or more family members or by the presence of a gene mutation causing the disease [13, 14].

With the development of MR imaging, cavernomas are becoming the most commonly diagnosed vascular malformation of the brain, with a prevalence of 0.4–0.9%, as confirmed by autopsy findings. The familial form is present in 6–50% of all lesions, and is most often associated with the Latin American origin [15].

Clinical manifestation

Cavernous angiomas are most often clinically manifested as epileptic equivalents (38–55%), focal neurologic deficit (12–45%), non-specific headaches (5–55%) and intracranial hemorrhage (4–32%) [5]. Different studies speak about 10–90% of the symptomatic patients [16, 17]. Our findings suggest that 20% of the patients with the examined changes have epileptic seizures, 60% focal neurological deficits, 60% headache and 60% hemorrhage. Literature data [16] indicate that most patients become symptomatic between the third and fifth decade of life, while the results of our study show a slightly higher mean age of the patients, 51 years.

Asymptomatic patients

In our study, 40% of the patients are asymptomatic. The true incidence of familial form of the disease is probably concealed by a large number of asymptomatic patients.

Presence of multiple lesions in treated patients

Multiple lesions are found in 50–84% of the patients with the familial form of the disease [5]. Multiple changes are observed in all of the subjects from our study, more than 40 lesions per patient. According to most authors, there is no significant correlation between the number of changes in the brain and presentation of the disease, as our investigation also showed.

Number of lesions infratentorially and supratentorially

Literature data [5] indicate that the lesions are often positioned supratentorially (80–85%), whereas in our study the number of supratentorial lesions makes 76.66% of the total number seen on SE sequences, i. e. 93.34% of the total number of lesions seen on GRE sequences.

Number of lesions in certain brain regions

Of the total number of cavernomas, the largest number, i. e. 28.57%, is positioned in the temporal lobe and 25.12% in the parietal lobe, whereas the smallest number, i. e. 0.98%, is located in the brain stem (data from Table 1).

Number of lesions seen in T1, T2 and T2 GRE sequences

The total number of lesions seen on SE sequences in all treated patients is 60. The number of lesions seen on T2 GRE sequences in all the patients is 406. T2 GRE exploration is clearly more sensitive, compared to T1 and T2 sequences in presenting the cavernous angioma, which was statistically confirmed (data from Tables 2–5).

All our symptomatic patients have type I change, which is the cause of the neurological deficit or epileptic seizures. As there is no statistical significance in the total number of lesions in asymptomatic and symptomatic patients, the presence of type I lesions determines clinical presentation in our examined patients. According to the majority of available papers, the presence of type I and type II lesions determines the clinical picture (5.16).

The number of lesions increases with the patient's age. The oldest patient is 73 years old presenting with 187 changes, which proportionately increases by number, type and size of cavernoma.

The total number of changes regardless of the type of cavernoma in symptomatic patients is 298, in comparison to 108 in asymptomatic patients.

The total number of changes regardless of the type of cavernoma registered by exploration in T2 sequences is 60, and the number registered in GRE sequences is 406. After comparing the number of lesions found on T2 and T2 GRE sequences in all the patients, a significant difference was obtained by using the Wilcoxon signed-rank test ($Z = 2.023$, $p = 0.043$).

Type IV cavernoma was the most commonly found change, with a total number of 346.

By applying the Mann-Whitney U test, no significant difference was found in the medians of the number of lesions in SE sequences in asymptomatic and symptomatic patients ($U = 0.5$, $p = 0.139$, $r = 0.062$)

By applying the Mann-Whitney U test, no significant difference was found in the medians of the number of lesions in GRE sequences in symptomatic and asymptomatic patients ($U = 2$, $p = 0.564$, $r = 0.2576$). From the foregoing, it is concluded that the number of lesions does not have a major impact on the clinical presentation of the desease.

Changes relating to type I cavernoma were not found in asymptomatic patients. All three symptomatic patients had type I cavernoma which was the cause of the neurological deficits or epileptic seizures.

In the oldest of the symptomatic patients, 73 years of age, a total of 187 changes were registered. The youngest symptomatic patient had a total of 55 changes. Type IV cavernoma is the most frequently

encountered type of cavernomas. Literature data [5] confirm that the number of lesions and their size grow throughout life.

Conclusion

This paper deals with six family members from the first to third degree of consanguinity. In five patients, MRI revealed the existence of multiple cavernous angiomas. MR imaging of the brain is the method of choice in proving this type of vascular malformations. The superiority of MR GRE (Gradient Recalled Echo) sequences was shown to be superior in the diagnosis of lesions of the familial cavernous angiomatosis of the brain, making such images obligatory during the MR exploration of cavernomas due to their apparently greater sensitivity.

In the case of familial form of cavernous angiomatosis, the existence of Type IV cavernomas (classification according to Zabramski) is characteristic of the disease. Type IV cavernomas are detectable only when GRE sequences are used, as they cannot be detected by the classic SE exploration.

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