Cerebral cavernous malformations: epidemiological, clinical and diagnostic imaging aspects

Czekalska I.[1A,B,C,D,E], Tyrakowska–Dadełło Z.[1B,C,D,E], Werel P.[1B,C,D,E], Tarasów E.[1,2 C,D,F], Grodzka E.[3 D,E*]

1. Department of Radiology, Medical University of Bialystok, Bialystok, Poland
2. TMS Diagnostyka, Bialystok, Poland
3. Student of the Electroradiology, Faculty of Health Sciences, Medical University of Bialystok, Poland

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ABSTRACT

Introduction: Cerebral cavernous malformations (CCMs) are one of the most common vascular malformations of the central nervous system. Symptoms of CCMs are not typical; the disease can be asymptomatic or be manifested by a wide range of neurological symptoms.

Purpose: To evaluate chosen epidemiologic and clinical issues as well as advanced imaging diagnostics of CCMs in computed tomography and magnetic resonance imaging.

Materials and methods: The study was based on retrospective analysis of CT and MRI examinations from the 5 years period. The analysis covered 61 persons, 29 males, and 32 females. The CCMs were diagnosed based on MRI examination in 43 patients and CT in 13 patients.

Results: The rate of CCMs occurrence in own material was 0.2%. Single lesions were present in 90.2%, while multiple in 9.8% of cases. Supratentorial CCMs were observed in 77% of cases whereas subtentorial in 23%. Mean size of CCMs in the supra- and subtentorial area equaled 10.6±6.3 and 15.1±5.8 mm, respectively ($p<0.05$). Clinical symptoms occurred in 65.8% of patients, most frequently in patients with CCMs above 5 mm or with subtentorial lesions. All CCMs were hyperdense in CT images, with calcifications in 13.1%. In MRI, malformations showed diverse intensity of the central part with peripheral low-intensity rim of hemosiderine deposits in T2-weighted images.

Conclusions: The clinical symptoms occur in most cases of CCMs. These patients require periodic follow-up MRI examinations, specifically those with haemorrhagic incidents or epileptic seizures, with large size or subtentorial CCMs.

Keywords: CNS vascular malformations; cerebral cavernous malformation; computed tomography; magnetic resonance imaging

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***Corresponding author**
Ewelina Grodzka
Department of Radiology, Medical University of Bialystok
Sklodowskiej 24a St, 15-276 Bialystok, Poland
Tel.: +48-85-8318901; fax: +48-85-8318926; e-mail: ewelina.grodzka1@gmail.com

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INTRODUCTION

Cerebral cavernous malformations (CCMs) are the second frequent type of vascular malformation of the central nervous system [1]. The occurrence of CCMs may be familial or sporadic. It is assumed that CCMs are had an autosomal dominant pattern of inheritance with incomplete penetrance [2]. Neurological symptoms of cavernous malformations are not typical; the malformations may be manifested clinically or have an asymptomatic course [3]. Epileptic seizures or haemorrhage occur relatively often in patients with malformations; therefore some patients require neurosurgical treatment [4,5]. The effectiveness of surgical treatment is high, however only 75% of cases showed total withdrawal of epileptic seizure [4,6]. Moreover, procedures in the cases of malformations of the brainstem were of high risk and post-operative morbidity reached approximately 1.5% [5]. Thus, the proper qualification for the surgery is crucial. As for operating procedures, neuronavigation, sometimes connected with intraoperative MRI or gamma-knife radiosurgery, is specifically useful in the treatment of brainstem cavernous malformations [7,8]. Diagnostic imaging of CCMs is mainly based on computed tomography (CT) and magnetic resonance imaging (MRI); angiographic methods are of less importance [9]. CT images of malformations are not characteristic, doubts in their diagnostics can also be observed in MRI [10]. The aim of the study was the evaluation of chosen epidemiological and clinical issues as well as images diagnostics of CCMs, based on CT and MRI data in the material of the Medical Center "Diagnostics" in Białystok.

MATERIALS AND METHODS

The examination was conducted based on retrospective data, including CT and MRI exams from the Medical Center „Diagnostics" in Białystok from the years 2007-2012. After initial searching, the database, verification and including the images to further analysis was performed. A group of patients selected for further study included 61 persons, 29 males (47.5%, mean age 52±16.5 years) and 32 females (52.5%, mean age 58±16.3 years; $p>0.05$).

MRI examination was carried out using two systems: Toshiba Vantage Atlas 1.5T scanner (Toshiba Medical System Corporation, Japan) with the use of 4-elements superficial coil and Picker Eclipse 1.5T scanner (Picker Eclipse, Picker International Inc., Highland Heights, USA) with the use of polarized head coil. MRI examination was conducted in 43 patients (70.5%). Routine image sequences were performed – T1- and T2-weighted and FLAIR (Fluid Attenuation Inversion Recovery) in transverse plane, T1-weighted in the sagittal and coronal planes. Angio-MRI with the use of TOF sequence (Time of Flight) was performed in 4 persons (6.5%). In cases justified by clinical diagnosis, i.e. in 32 (74.5%) patients, the examination was performed after intravenous administration of contrast medium (CM) (Gadovist, Bayer Schering Pharma AG, Berlin, Germany) in the dose of 0.1 ml/kg of body mass.

The diagnosis was determined in 13 patients (21.3%) by CT imaging. The examinations were performed with 2 Toshiba systems (Toshiba Medical System Corporation, Japan): Toshiba Aquilion – 16-row and Toshiba CRX 64-row scanners. Basic parameters of acquisition for both types of CT scanners were the same. CT examination, after intravenous administration of CM, was performed in 3 patients (4.9%), and in 1 patient (1.7%) angio-CT examination was conducted. Iomeron 400 (Bracco Imaging Germany), a non-ionic CM was used in all patients.

The clinical symptoms were evaluated in 41 examined patients (67.2%) based on referral to CT and MRI examinations. In 23 patients (37.7%) follow-up examinations were also available; in 4 persons – CT and in 19 – MRI. Mean time between follow-up examinations was 23±19.8 months.

The number, localization, shape and size of the changes were evaluated in the study (Table I). We determined density in CT exams (in Hounsfield units, HU) or characteristics of the signal in MRI exams (the dominant signal of the central part of the lesion in T1- and T2- weighted images were taken into consideration - Table II); the presence of calcifications (in CT images); marginal gliosis in MRI (in FLAIR sequence) and hemosiderin deposits (in T2-weighted images); as well as enhancement after CM administration.

Statistical analysis

The results were analyzed statistically, and the arithmetic mean, and standard deviation was calculated for measurable features. Due to the number of patients, non-parametrical Mann-Whitney's test was used for group comparison. In calculations, $p<0.05$ was considered statistically significant, and the statistical analysis was performed using statistical package SPSS.

RESULTS

The exams of 61 patients with diagnosed CCMs were selected for the analysis. The analysis was based on MRI – in 43 patients (70.5%) and CT – in 13 patients (21.3%). Additionally, angio-MRI was performed in 4 patients (6.5%) and angio-CT

in 1 patient (1.7%). There were approximately 30.000 head CT and MRI examinations conducted by the Medical Center „Diagnostyka" in the years 2007-2012. Therefore, the rate of cavernous malformations in own material was 0.2%. In 55 cases (90.2%), single cavernous malformations were diagnosed, while in 6 patients (9.8%) there were multiple malformations detected; 4 persons (6.5%) showed 2 lesions and 2 persons (3.3%) - 3 or more lesions.

Table 1 presents the arrangement of localization, size and shape of malformations. The most frequent occurrence was in the parietal lobe, less frequent in the frontal or temporal lobes. On the whole, CCMs were observed in 77% in the supratentorial area and in 23% were subtentorial lesions. As far as the brain hemispheres are concerned, CCMs were situated mainly in the subcortical area, rarely in the periventricular area and most rarely in the deep white matter and in the basal ganglia (Fig. 1, 2). Malformations were usually round or oval, rarely elongated or elliptical.

Table 1. Localization, size and shape of malformations in examined patients

	Number of patients N (%)	**Mean size of lesions ±SD (mm)**	**Shape* N**	**Localization ** N**
Frontal lobe	15 (24.6%)	10.6±6.4	6/6/3/0	9/2/0/4
Temporal lobe	14 (23%)	11.8±5.5	3/6/4/1	11/1/1/1
Parietal lobe	16 (26.2%)	9.6±6.8	10/2/4/0	11/1/1/3
Occipital lobe	1 (1.6%)	8.0	1/0/0/0	0/0/0/1
Thalamus	1 (1.6%)	10.0	0/1/0/0	-
Brainstem	11 (18%)	16.0±5.5	2/6/3/0	-
Cerebellum	2 (3.3%)	15.0±4.2	1/1/0/0	-
Medulla oblongata	1 (1.6%)	10.0	0/1/0/0	-

* Shapes in order of consideration: round/oval/irregular/elliptical

** Localization in order of consideration: subcortical/white matter/basal ganglia/periventricular

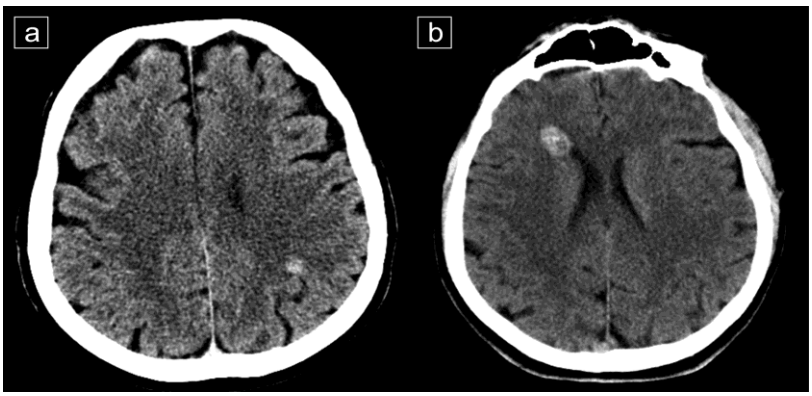

Figure 1 a, b. CT examination, small subcortical CCM in left periatal lobe (a), periventricular CCM in the area of the frontal horn of lateral right ventricle, hyperdense lesion with small calcification (b)

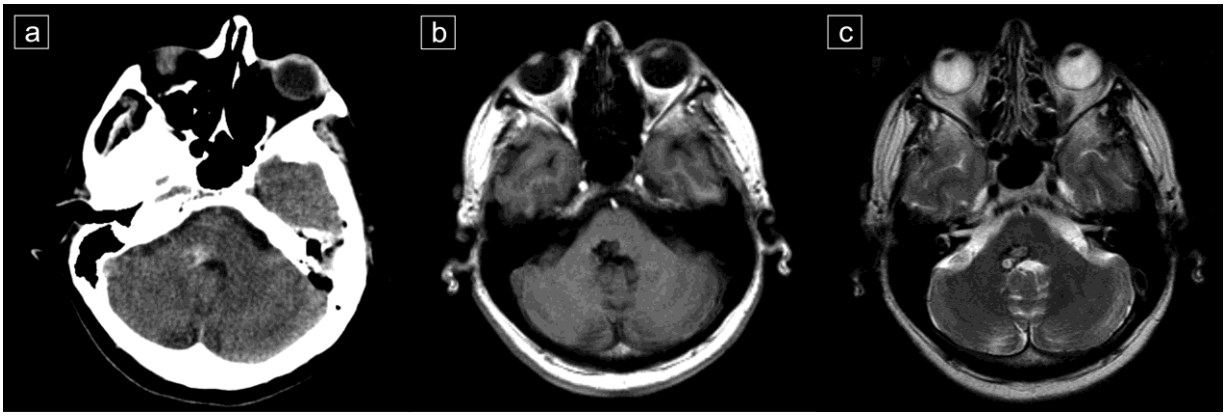

Figure 2 a-c. Cavernous malformation in the IV ventricle area; hyperdense lesion in CT (a), hypointense in T1-weighted image in MRI (b), hyperintense in T2-weighted image (c)

The size of cavernous malformations varied from 3 mm to 27 mm. The biggest ones were situated in the brainstem or cerebellum (16.0±5.5 mm and 15.0±4.2 mm, respectively) (Fig. 3).

Hemisphere CCMs had comparable size regardless the localization – from 8 mm to 11.8 mm. Mean size of malformations in the supratentorial area was 10.6±6.3 mm while in the subtentorial area it was 15.1±5.8 mm ($p<0.05$).

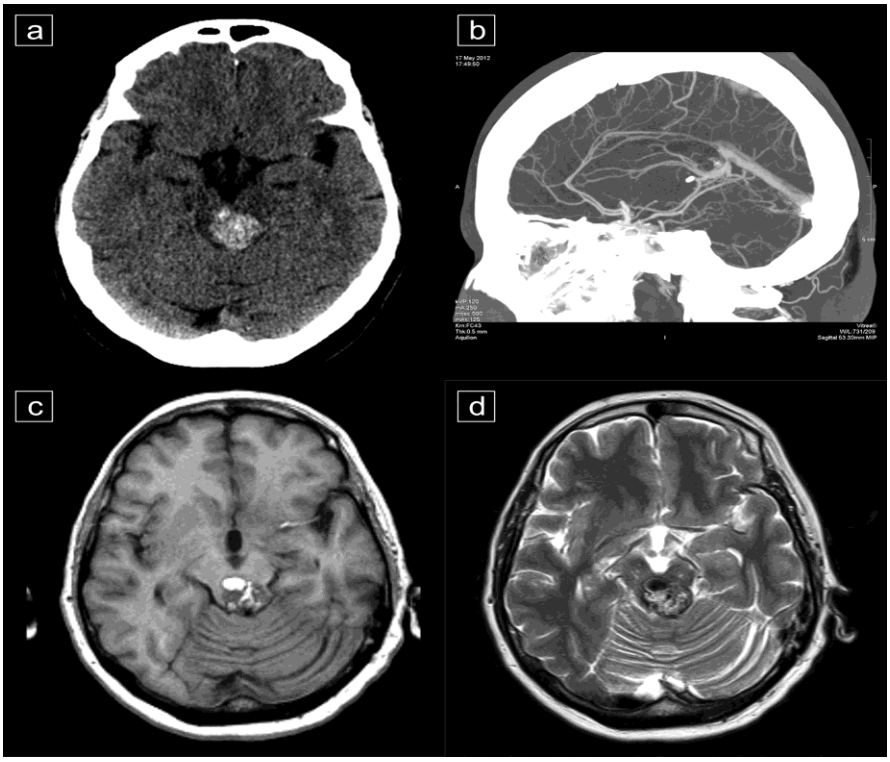

Figure 3 a-d. Large cavernous malformation in mesencephalon. Hyperdense lesion with slight calcification in CT (a); malformation invisible in angio-CT, in sagittal MIP reconstruction (b). MRI examination – hyperintense cavernous malformation in T1-weighted image (c), hyperintense in T2-weighted images (d)

Clinical symptoms were present in 27 patients (65.8%), 14 patients (34.2%) did not report complaints. The most common complaints were headaches – in 23 out of 41 patients (56.1%) and focal neurological symptoms – also in 23 patients (56.1%). Dizziness and past intracranial bleeding (in the interview) were stated in 17 patients (34%). Epileptic seizures were very rare – only four patients (10%) showed them.

Clinical symptoms occurred with similar frequency, regardless the localization. They were stated in most patients with cavernous malformations in the subtentorial area. We did not observe such symptoms in 2 persons with malformations localized in the cerebellum. All clinical symptoms, except epileptic seizures, occurred most frequently in patients with cavernous malformations of more than 5 mm in size (Fig. 4).

In CT images all the malformations were hyperdense, 8 patients (13.1%) showed small, punctate calcifications within the malformations (Fig. 1, 2). Density of CCMs in CT examinations was from 40 to 60 HU (mean 56±7,5 HU). After contrast administration, CCMs were not enhanced significantly (59±14 HU; $p>0,05$).

In MRI, malformations showed differentiated intensity of the signal of the central part (Table II). In T1-weighted images they were mostly hypointense (the dominant signal) and relatively often they were hyperintense. In T2-weighted images, cavernous malformations were most frequently hyperintense and rarely hypointense (Fig. 5, 6). CCMs usually did not show significant contrast enhancement, only in 3 patients weak enhancement was observed. Developmental venous anomaly (DVA) accompanied cavernous malformations were found in 2 patients (6.25%) (Fig. 7).

In most cases there was no hyperintense gliosis area around cavernous malformations in FLAIR images; narrow marginal gliosis was observed only in 16.3% of patients. Peripheral low-intense rim of hemosiderine deposits in T2-weighted images was visible in almost all cases (Fig. 5, 6) except 2 patients.

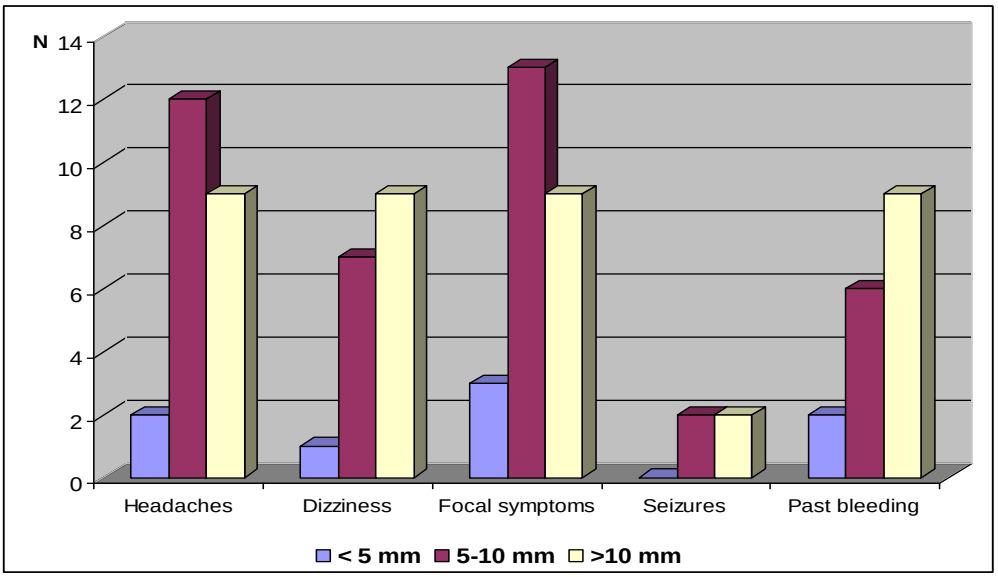

Figure 4. Clinical symptoms depending on malformation size

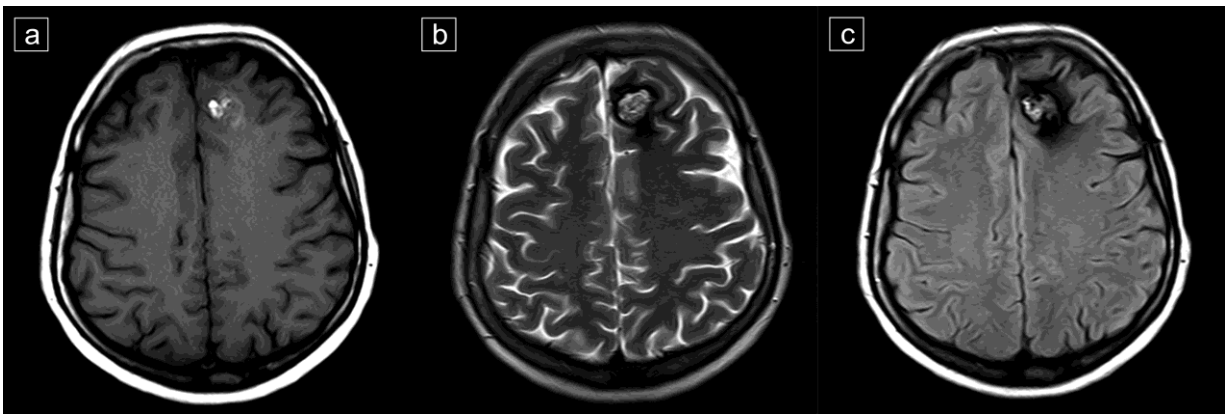

Figure 5 a-c. MRI examination – large subcortical CCM in the left frontal lobe. Hyperintense lesion in T1-weighted image (a), T2-weighted (b), and in FLAIR sequence (c). In T2-weighted and FLAIR - visible wide hypointense hemosiderine rim after bleeding.

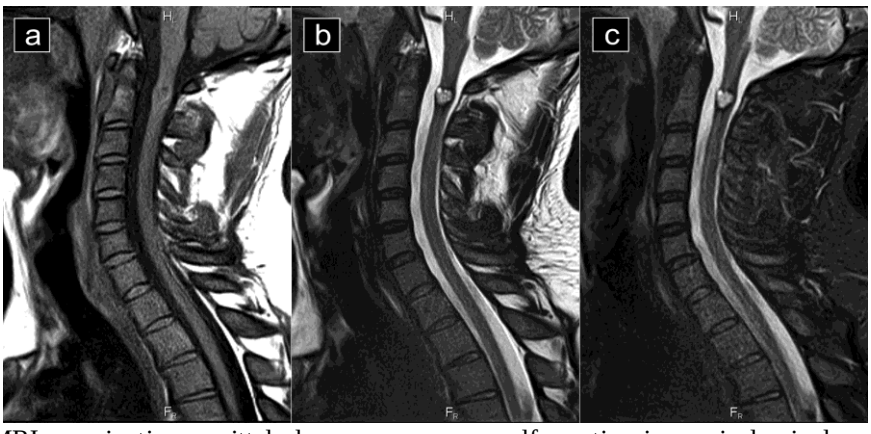

Figure 6 a-c. MRI examination, sagittal plane – cavernous malformation in cervical spinal cord; isointense in T1-weighted image (a), hyperintense in T2-weighted image (b), and in STIR sequence (c). In T2-weighted images and STIR – visible hemosiderine rim

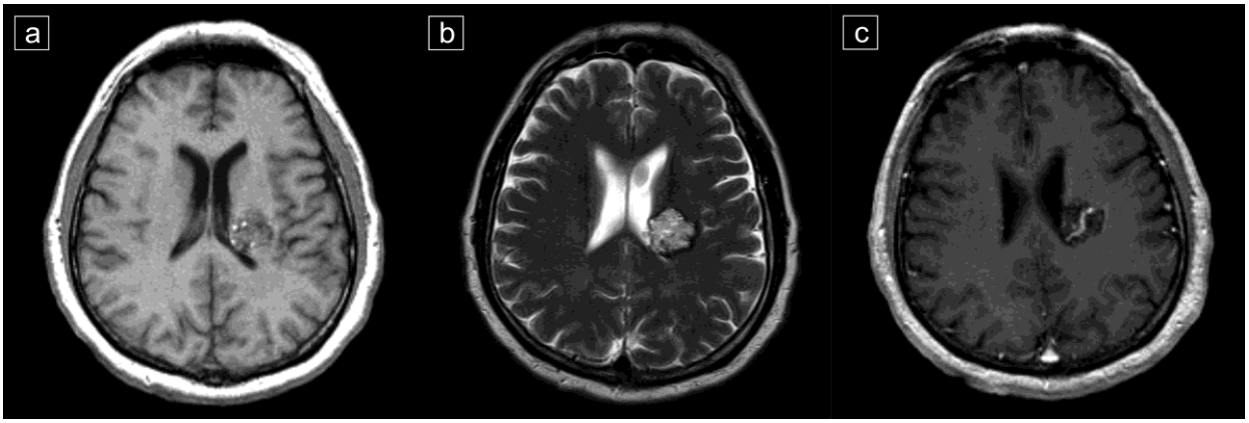

Figure 7 a-c. MRI examination; large periventricular CCM. In T1-weigthed image – lesion of heterogeneous intensity (a), hyperintense in T2-weighted image (b), after contrast medium - visible developmental venous anomaly (c)

DISCUSSION

Epidemiological and clinical aspects

Cerebral cavernous malformations are the second frequent vascular CNS malformations after developmental venous malformations (DVA), most frequent in the pediatric population [11,12]. They are estimated to be 10-15% of all vascular malformations of the central nervous system [13]. Gamrot et al. [14] determined the rate of CCMs occurrence to be 0.5-0.7% of general population. In autopsy examinations, the rate was 0.3% while in large prospective cohort studies it was 0.4-0.6% [15]. Above results are in accordance with our studies, where the rate was about 0.2%.

Cavernous malformations may occur as single or multiple lesions. Isolated, single changes occur more frequently while multiple ones are observed in approximately 50% of inherited cases and only in 12-20% of sporadic cases [13]. Our study showed single malformations in predominant number of patients (90.2%) while multiple lesions were observed only in 9.8% of patients. Multiple CCMs did not show familial origin of malformation.

CCMs can occur in all age groups. Previous studies showed the connection between malformations and sex, mainly female in the 3rd-4th decades of life, which however was not confirmed in our studies [16]. Malformations were observed in males (47.5%) as frequently as in females (52.5%). Mean age in sex groups was also similar and was not statistically significant. It is in accordance with latest studies which point to lack of connection between age and CCMs [13].

Clinical symptoms of CCMs are not typical; they can be manifested by various neurological symptoms or have an asymptomatic course. Symptoms depend mainly on lesion localization [13]. In the analyzed material, clinical symptoms occurred in 65.8% of patients; 34.2% were asymptomatic. The symptoms occurred with similar rate, regardless localization, however they were predominant in patients with subtentorial localization. All symptoms, except epileptic seizures, occurred more frequently in patients with malformations of the size bigger than 5 mm. It is in accordance with observations of Al-Houlou et al. [11] who described symptomatic course in patients with large size CCMs.

Epileptic seizures, intracranial bleeding and neurological deficits are most common as far as clinical signs of cavernous malformations are concerned [13]. The rate of epileptic seizures reaches 79%, according to some studies, with 43% of partial seizures (focal epilepsy), secondarily generalized [17]. Unlike the literature, our studies showed epileptic seizures to be the most rare as far as clinical symptoms were concerned – only in 10% of patients, which is close to the results obtained by Gamrot et al. [14], who observed epileptic seizures only in 16% of patients. Moreover, low rate of epileptic seizures was stressed by Mottolese et al. [18] who claimed them to be secondary to chronic or recurrent microhaemorrhage.

General rate of bleeding in patients with CCMs was estimated to be 4.46%/lesion/year [19]. Many authors stressed the fact that the risk of rebleeding increases significantly in the group of patients after the first incidence of bleeding. In the group of patients without bleeding, the episodes occurred in 0.6% of patients whereas in those who suffered from bleeding, recurring episodes were observed in 4.5% of patients [20]. Most probably, microstructural integrity of malformations is damaged during the first bleeding [21]. The risk factors of recurrent bleeding are: age $\geq$ 50 years, size $\geq$ 2cm, the oedema around the lesion or accompanying venous malformation [22,23]. According to some authors, localization in the subtentorial area can be connected with the

possibility of symptomatic bleeding. Wang et al. [24] stated that the rate of multiple bleeding of the brainstem malformations equaled 67.2% and was connected with severe neurological deficits. According to meta-analysis of Taslimi et al., [25] the time between bleeding of brainstem malformations was 10 months, mortality – 2.2%, and the risk of repeated bleeding decreased only after 2 years.

In the analyzed group, past bleeding, stated in the interview, was observed in 34% of patients. More frequent bleeding was observed in lesions of the supratentorial area than in the subtentorial malformations and the bleeding was confirmed in the referral only in 1 patient with malformation of the brainstem. However, as data concerning haemorrhage were obtained from interview they may be inaccurate; as the latest literature claims that the rate and risk of bleeding should be based on imaging examinations because clinical evaluation is not fully reliable – it depends on both the presence of bleeding and localization [9]. Thus, bleeding from malformations of the brainstem is more frequently clinically symptomatic than cavernous malformations in other localizations. Therefore, Nikoubashman et al. [9] suggested to divide CCMs into 3 groups with various stages of risk of bleeding: with high, medium and low risk of haemorrhage. According to these studies, time intervals between haemorrhagic episodes are: 22, 28 and 38 months, respectively. It is in accordance with Jeon et al. [19] studies who showed that type I and II malformations (according to the Zabramski's classification) have the highest risk of bleeding (9.47% and 4.74% annually, respectively) while the type III malformations had the lowest risk; only 1.43% annually.

In our studies, focal neurological symptoms were present in 56.1% of patients, which is slightly higher than it was suggested in the literature [13,14.. According to Gamrot et al. [14], neurological deficits in patients with CCMs occurred in 45% of cases; according to others – in 20-40% of patients. In our studies, the symptoms were present in all patients with subtentorial lesions, which suggests the necessity of frequent imaging examinations in this group of patients.

Headaches are non-specific symptoms of CCMs, however some authors claim they are the first symptoms of cavernous malformations occurrence [14]. Our studies showed headaches to be the most frequent – they occurred in 65.8% of examined patients. Other symptoms are: cerebellar symptoms, brainstem disorders, internal hydrocephalus, vision disturbances. Manifestations of the these symptoms is strictly dependent on the change localization [14]. The analyzed group did not present such symptoms but frequently dizziness was observed – in 34% of patients.

Imaging of cavernous malformations

Cerebral cavernous malformations are localized mainly in the brain hemispheres, rarely in the cerebellum, pons or spinal cord [20]. It is assumed that they are usually localized supratentorially, in the frontal and temporal lobes [13]. High rate of CCMs occurrence in the supratentorial area was confirmed in our studies (supratentorial cavernous malformations – 77%, subtentorial – 23%). Malformations occurred most frequently in the parietal lobe, not so frequently in the frontal and temporal lobes. Such a localization is explained by the hypothesis that cavernous malformations occurrence is proportional to the volume of affected structures [13]. In our group CCMs were observed in the brainstem in 18% of patients while only in 3.3% in the cerebellar hemispheres.

The size of CCMs is estimated differently by different authors, the diameters range from several millimeters to a few centimeters. According to Clatterbuck et al. [26], 107 cavernous malformations gave the mean volume of lesion of 2,779 mm^3. These lesions had the size of 0.5 to 46,533 mm^3 (46.5 cm^3). In own material, the size of CCMs ranged from 3 to 27 mm. Malformations in the brainstem and cerebellum were statistically bigger than hemispheric changes and had mean size of 15.1±5.8 mm. A similar range of size of brainstem malformations was given by Fritschi et al. [27].

According to the literature, CCMs have strong tendency to change shape, size and structure; they can increase quickly or markedly diminish their volumes and rarely are without change. It is assumed that repeated micro-bleeding to the malformation and the surrounding nervous tissue as well as recanalization after thrombus formation have the influence on the lesion growth. Thus, malformations of such type are characterized with variability in imaging examinations [16]. In Clatterbuck et al. [26] study, in the period of 26 months an average decrease in malformations volume by approximately 1 cm^3 was observed, with further decrease of 0.65 cm^3 during the following 18 months. The authors noted both a marked increase in the size of the lesion and significant decrease. The observation was not confirmed in our study. In 23 patients, whose follow-up studies were available, mean size of CCMs only changed slightly, without statistical significance, despite 2-year-observation period. It was probably due to the fact that in case of lack of repeated haemorrhagic incidents, the size of cavernous malformations may remain unchanged even in long-term observation.

CT and MRI are main methods of CCMs imaging unlike less important angiographic methods [9,11]. However, cavernous malformations images in CT are not characteristic [10]. Malformations may occur as acute, subacute, or chronic intacerebral haematomas. In these cases, the malformation core is frequently invisible, particularly when accompanied

by fresh bleeding or the lesion with the diameter of less than 1 cm[10]. A weakly hyperdense focus without the mass effect and without oedema is the characteristic image of CCMs in CT exam. Malformations may enhance slightly and are better visible after contrast medium administration, however the examination after CM does not contribute much to the diagnosis [28]. The observations were confirmed by own studies; all CCMs were weakly hyperdense in CT, small punctate calcifications were present in 13.1%. The density of malformations in CT was 56±7.5 HU and did not change statistically after administration of contrast medium ($p>0.05$), which is in accordance with other authors' results mentioned above [28].

The images of CCMs in MRI examinations are rather typical and reflect their macroscopic structure [29]. Malformations are built out of cavities forming canals with the walls lined with endothelium; they do not have the muscular membrane and tunica adventitia. The interior is filled with liquid blood, thromboses, and calcification. Hemosiderine deposits and gliosis area are detected in the malformations surroundings. The supplying and outlet vessels are tiny; thus cavernous malformations are lesions with the low flow [29].

In MRI, malformations have the shape of spongy-like structure whose cavernous space is hyperintense in T2-weighted images, their peripheral zone have usually low intensity of the signal [10,26] In T1-weighted sequences, malformations are most frequently visible as hypointense lesion with hyperintense rim that correspond to calcification and fibrosis. Due to the content of haemoglobin in various blood-degradation products, CCMs may have heterogeneous, mixed signal in T1- and T2-weighted images [9,30]. In long-term observation, cavernous malformations had the tendency to change the signal, from typical for subacute bleeding, through mixed changes, to signal characteristic for chronic bleeding [26]. The observation was confirmed in own studies. CCMs in the examined group showed differentiated intensity of signal in MRI, both in T1- and T2-weighted images. There is a classification of cavernous malformations prepared by Zabramski et al. [30], based on the differentiation of cavernous malformations images. However, the classification is relatively rarely used due to poor connections with the clinical risk.

After the administration of contrast medium, a part of cavernous malformations is enhanced however intensity is usually weak without typical pattern [26]. In our studies CCMs did not show significant contrast intensity; only in 9.6% of patients a weak enhancement was observed. Developmental venous anomaly (DVA) accompanies cavernous malformations quite often, approximately in 20% of cases [23]. In our examined group DVA was observed only in 2 patients (6.25%).

According to the literature, the peripheral low-intense rim of hemosiderine deposits in T2-weighted images was visible in almost all cases – in 95.3% of patients [30]. However, there was no marginal gliosis zone around most malformations in FLAIR images; a narrow hyperintense zone of gliosis was observed only in 16.3% of patients. T2*-weighted gradient-echo images and SWI, that show sensitivity higher than routine MRI sequences are especially useful in diagnosis and evaluation of CCMs [31]. These sequences were not used in our patients because in the analyzed period they did not belong to the routine protocol of the study, which limited the analysis.

CONCLUSIONS

Cerebral cavernous malformations are frequently occurring vascular lesions; the rate of their occurrence in our studies was 0.2%. CCMs occur most frequently in the supratentorial and rarely in the subtentorial area. In the group of patients with cavernous malformations, clinical symptoms occur in most cases, although they are non-specific. Clinical symptoms are observed more often in patients with subtentorial lesions with the size of more than 5 mm. Patients with CCMs require periodic follow-up MRI studies. The supervision of patients with cavernous malformations after bleeding incidents or with epileptic seizures, with large cavernous malformations in the subtentorial area is, of great importance.

Conflicts of interest

All contributing authors declare no conflicts of interest.

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