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## **Cerebral cavernous malformations: congruency of histopathological features with the current clinical definition**

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## Abstract

**Aim:** Cerebral cavernous malformations (CCMs) are defined as a mulberry like assembly of thin-walled vascular sinusoids lined by a thin endothelium lacking smooth muscle and elastin, displaying no intervening brain parenchyma. In this study we analyse the congruency of histopathological features with the current clinical definition on a large series of neuroradiologically verified CCMs.

**Methods:** 87 patients without primary treatment prior to surgery were included. Preoperative MRIs of all patients were reviewed. Twelve histopathological parameters were assessed systematically, using HE, Prussian blue, elastica van Gieson and congo red for amyloid detection.

**Results:** 71/87 (81.6%) of the cases fulfilled the basic histological criteria of CCMs. Still, the thickness of vessel walls and the calibre of malformed vessels were highly variable. 16/87 cases (18.4%) were histologically non diagnostic. Non diagnostic specimens significantly associated with radiological signs of hemorrhages ( $p=0.001$ ). A few cases (4.6%) regionally contained capillary-like malformed vessels. Intervening brain parenchyma between malformed vessels throughout the lesion was seen in 50/71 (70.4%) diagnosable lesions. Hemosiderin deposits, gliosis, thrombosis, fibrotic changes, hyalinized vessel walls, calcification and cholesterol crystals were present in a considerable range. In addition, we show amyloid deposits in 14/87 (16.1%) specimens.

**Conclusion:** In dis-congruency with the current clinical definition the absence of intervening brain parenchyma does not represent an essential histopathological criterion of CCMs in our series. Further, the diameter of the vessel lumina and the thickness of vessel walls vary considerably. Based on these findings, adaptation of the current definition on basis of interdisciplinary interaction needs to be considered.

## Introduction

The histopathological classification of cerebral vascular malformations was elaborated by Russel and Rubinstein and McCormick and colleagues in the period 1959 to 1968. [1-4] This classification is still widely accepted and used in clinical diagnostics.

According to this classification, the spectrum of cerebral vascular malformations comprises four groups: arteriovenous malformations (AVMs), cavernous malformations (CCMs), capillary telangiectases and venous malformations (VMs). [1-6] In more recent publications, intermediate and combined forms of vascular malformations were additionally recognised. [7,8] In a recent paper Raychaudhuri, Batjer and Awad summarise the literature on CCMs and define them as a mulberry like assembly of thin-walled vascular sinusoids lined by a thin endothelium lacking smooth muscle, elastin, and intervening parenchyma, surrounded by hemosiderin deposits and gliosis, which may or may not be thrombosed. [9] In contrast to this definition, previous studies reported intervening CNS tissue in a fraction of CCMs. [10-12]

In order to clarify systematically the histopathological spectrum of CCM appearance and to test the congruency of histopathological features with the current clinical definition we analysed a large consecutive series of neuroradiologically verified CCMs.

## Patients and Methods

In the period January 1980 until December 2004, 152 patients underwent surgery at the Department of Neurosurgery, Medical University Vienna due to the clinical diagnosis of a cavernous malformation (CCM). We used the following patient inclusion criteria: 1. no primary treatment of the lesions prior to surgery (e.g. radiosurgery), 2. availability of MR scans with T1 and T2 weighted imaging, and 3. availability of archived tissue specimens for histopathological analysis. 87/152 patients (51 females, 36 males) fulfilled these inclusion criteria. Median patient age at the time of the operation was 37 years (1.6 – 74.8 years). In 65/87 (74.7%) cases, the lesions were located supratentorially, and in 22/87 (25.3%) cases, the lesions were infratentorial. For more details on localisation see table 1.

Localisation	n	%
frontal	21	24.1
parietal	12	13.8
temporal	20	23.0
occipital	9	10.3
basal ganglia /thalamus	1	1.1
corpus callosum	1	1.1
brainstem	15	17.2
cerebellum	8	9.2

*Table 1: Detailed localisation of operated cerebral cavernous malformations (CCMs)*

Table 1 shows the detailed localisation of the 87 operated CCMs in number (n) and percentage (%). The distribution pattern is similar to previously published large series of CCMs. [20, 21]

**Radiological examination:** MRIs of all patients were reviewed by a senior radiologist (ST) using the radiological classification system for CCMs by Schefer, Valavanis and Wichmann. [13] This radiological classification system comprises four types of lesions: type I shows the classic morphology of a CCM without hemorrhage; type II shows intralesional hemorrhage; type III shows extralesional hemorrhage compressing or displacing the CCM itself; type IV represents the totally calcified CCM. [13]

**Histological examination:** The study was performed on archived tissue specimens of the Institute of Neurology, Medical University Vienna.

Surgical specimens were fixed in a phosphate-buffered 4.5% solution of formaldehyde, embedded in paraffin and cut at a thickness of 3–5µm and routinely processed for plain histology and immunohistochemistry. All sections were stained with hematoxylin&eosin (HE), Prussian blue, and elastica van Gieson.

All cases were reviewed by a junior neuropathologist (JMF) and a senior neuropathologist (JAH) on a multiheaded microscope. A general summary of macroscopic, histopathological and hemodynamic characteristics of the 4 types of cerebral vascular malformations is provided in table 2.

<b>Cerebral cavernous malformations</b>	<b>Arteriovenous malformations</b>	<b>Venous malformations</b>	<b>Capillary telangiectases</b>
Mulberry like assembly of thin walled vascular sinusoids	Tangled, serpiginous mass of abnormally dilated vessels corresponding to arteries and veins	Single dilated or conglomerates of varicose veins drained by a single large vein	Dilated capillaries of differing calibre Occasionally petechial hemorrhage appearance
Low flow dynamics	High flow dynamics		
Single layer of endothelium, collagenous adventitia	Arteries with muscular and elastic laminae Veins "arterialised", thickened collagenous walls with increased cellularity due to proliferation of fibroblasts	Venous walls mostly normal or thickened by muscular hyperplasia and hyalinization	Walls consist of basement membrane and endothelium
No smooth muscle, no elastic fibres			No smooth muscle, no elastic fibres
No intervening brain parenchyma	Intervening gliomatous brain parenchyma within the interstices of the nidus	Normal intervening brain parenchyma	Normal intervening brain parenchyma
Peripheral rim of hemosiderin deposits	Hemosiderin pigmentation often present	No hemosiderin pigmentation	No hemosiderin pigmentation
Gliomatous reaction in surrounding parenchyma	Gliomatous reaction	No gliomatous reaction	Rarely gliomatous reaction
Hyalinization, thrombosis, calcification, cholesterol crystals possible within lesion	Foci of calcification possible	Thrombosis possible	

*Table 2: Distinct features of cerebral vascular malformations*

This table shows macroscopic, histopathological and hemodynamic features of cavernous malformations, arterio-venous malformations, venous malformations and telangiectases. [8, 14-18] Based on these features we defined 12 parameters for uniform histopathological assessment of our CCM series (see materials and methods and Table 3).

In order to achieve a uniform histopathological assessment we defined 12 parameters (P1-P12) (Table 3). These parameters were extracted from the pertinent literature (see legend to Table 2). Parameter 1 (P1) asked for the presence of a vascular lesion characterised by a mulberry like assembly of malformed sinusoid vessels with a single layer endothelium, collagenous adventitia, no smooth muscle cells and no elastic fibres (CCM characteristics). [4,8,9,14-18]

The parameters P2 to P4 asked for the presence of other types of vascular malformations. P2: arteriovenous malformation (AVM): assembly of dilated, malformed vessels showing features of arteries or veins (presence of smooth muscle elements, lamina elastica). [8,15] P3: venous malformations (VM): presence of single or multiple dilated venous vessels. P4: capillary telangiectases: dilated capillary-like vessels with walls consisting of basement membrane and endothelium. [8,15] Further parameters (P5 to P7) questioned for the

presence of intervening brain parenchyma (P5) between the cavernous vessels, the presence of hemosiderin deposits (P6) in vessels walls and intra-and perilesional brain parenchyma, and for gliomatous reaction of the brain parenchyma (P7).

Further, the presence of thrombosis (P8) of CCM vessels or fibrosis (P9) was noted. Other parameters (P10 to P12) asked for presence of hyalinisation of vessels walls (P10), calcification (P11) or cholesterol crystals (P12).

Assessment of all parameters was performed as follows: positive (+), negative (-), questionable (?) and not available (n.a.). In case of P5 the presence of intervening brain was also evaluated semi-quantitatively. We distinguished between minor (+), moderate (++) and extensive (+++) intervening brain parenchyma.

In cases in which hyalinisation of vessel walls was seen, we additionally performed congo red staining for amyloid detection.

Statistical analysis: Descriptive analysis included total number and percent or median values and ranges. The correlation between histological and radiological findings was assessed by chi-square test. SPSS 14.0 statistical software system (SPSS Inc., Chicago, IL) was used for calculations. A p-value smaller or equal to 0.05 is considered statistically significant.

## Results

The review of MR images revealed 31/87 (35.6%) classical cavernous malformations (CCM) type I, 37 (42%) CCMs type II with intralesional hemorrhages, 18 (21%) CCMs type III with extralesional hemorrhages; 1/87 (1.2%) CCM was totally calcified, corresponding to type IV.

The histopathological findings are summarised in table 3. 71/87 (81.6%) of our neuroradiologically verified cases fulfilled the basic histological criteria of CCM (P1).

Some histological features of CCMs were highly variable (Figure 1). The calibres of malformed vessels ranged from 0.025mm to 4.25mm in diameter. The thickness of vessel walls ranged from 0,001mm to 0,4mm. In some cases, the circumference of cross-cut vessels was irregular, with focal vessel wall thickenings protruding and occluding the vessel lumina. These thickenings contained collagenous, partly hyalinized material, and thrombotic blood aggregates at the luminal surface.

A group of 16/87 (18.4%) cases did not fulfill histological CCM criteria: 6/87 (6.9%) did not show vascular structures but only blood. 1/87 (1.2%) case contained only CNS tissue but no malformed vessels or blood. 9/87 (10.3%) cases were defined as questionable CCMs because the available material only showed fragments of malformed vessel walls or one single, large sized and thin-walled malformed vessel. In these cases a definite classification of the type of vascular malformation was not possible. None of these 16 cases was neuroradiologically classified as classical CCM type I. 15/16 (93.8%) cases displayed intra- or extralesional bleeding (type II or III) on MRI. The remaining case showed features of a totally calcified CCM (type IV) on MRI. Therefore, a significant association ( $p=0.001$ ) between CCMs displaying radiological signs of hemorrhages and histologically non diagnostic biopsies could be shown in our series.

In none of the cases, the malformed vascular structures showed histological characteristics of AVM (P2) or VM (P3). 4/87 (4.6%) cases regionally contained capillary-like distended vessels resembling telangiectatic vessels. Intervening brain parenchyma (P5) between lumina of malformed vessels was seen in 50/87 (57.5%) of all cases. 21/87 (24.1%) cases displayed no intervening brain parenchyma. In the remaining 16/87 (18.4%) cases this parameter could not be evaluated (designated as "n.a." in Table 3). As described above, these 16/87 cases were histopathologically not diagnostic for a CCM (P1). Therefore, it is appropriate to calculate the percentage of intervening brain parenchyma only in the cohort of 71 lesions which fulfilled the basic histological criteria of CCM (P1): 50/71 (70.4%) cases showed variable extent of intervening brain parenchyma. In 45/71 (63.4%) cases intervening brain was minor to moderate, whereas 5/71 (7%) showed extensive intervening brain parenchyma (Figure 1).

	<b>P1 (CCM)</b>	<b>P2 (AVM)</b>	<b>P3 (Venous M.)</b>	<b>P4 (Telangiect.)</b>	<b>P5</b>	<b>P6</b>	<b>P7</b>	<b>P8</b>	<b>P9</b>	<b>P10</b>	<b>P11</b>	<b>P12</b>
	Single layer endothelium Collagenous adventitia No smooth muscle No elastic fibres	Arteries with muscular and elastic laminae Arterialised veins	Venous walls mostly normal	Walls consisting of basement membrane & endothelium	Presence of intervening brain parenchyma	Hemosiderin deposits	Gliomatous reaction	Thrombosis	Fibrosis	Hyalinisation	Calcification	Cholesterol crystals
<b>+</b>	71 (81.6%)			4 (4.6%)	50 (57.5%)	86 (98.8%)	74 (85.1%)	37 (42.5%)	44 (50.6%)	48 (55.2%)	28 (32.2%)	10 (11.5%)
<b>-</b>	7 (8.1%)	87 (100%)	87 (100%)	83 (95.4%)	21 (24.1%)	1 (1.2%)		50 (57.5%)	43 (49.4%)	39 (44.8%)	59 (67.8%)	77 (88.5%)
<b>?</b>	9 (10.3%)											
<b>n.a.</b>					16 (18.4%)		13 (14.9%)					

*Table 3: Histopathological findings*

For analysis of our CCM series we defined 12 parameters (P1-P12 – see materials and methods). Parameters were categorised as positive (+), negative (-), questionable (?) and not available (n.a.). The findings are summarised as total numbers and percentages. Percentages are calculated from the total of 87 cases included in our study.

CCM (cerebral cavernous malformation); AVM (arterio-venous malformation) ; Venous M. (venous malformation) ; Telangiect. (telangiectases)

Hemosiderin deposits were detectable in- and around malformed vessel walls, and in intervening and perilesional brain parenchyma. The amount of hemosiderin deposits was highly variable. However, only 1/87 (1.2%) biopsy was devoid of any hemosiderin deposits (P6). This was the case containing only CNS tissue but no malformed vessels or blood. 74/87 (85.1%) specimens contained intervening or perilesional brain parenchyma which presented with a gliomatous reaction in each case (P7). Thrombosis (P8) was detectable in 37/87 (42.5%) and fibrotic changes (P9) in 44/87 (50.6%) cases. Extent of fibrosis showed a considerable range among the cases. Hyalinized vessel walls (P10) were seen in 48/87 (55.2%) specimens. Calcification (P11) was present in 28/87 (32.2%) and 10/87 (11.5%) cases showed cholesterol crystals (P12). Some of the cases also displayed metaplastic bone material.

48/87 cases displaying hyalinized vessel walls were stained with congo red for amyloid detection. 14/48 (29.2%) cases showed small globular or patchy amyloid deposits (Figure 1). In relation to the total number of cases 14/87 (16.1%) displayed amyloid deposits. In one case, multinucleated giant cells engulfed amyloid deposits.

## Discussion

CCMs are currently defined as a mulberry like assembly of thin-walled vascular sinusoids lined by a thin endothelium lacking smooth muscle and elastin, displaying no intervening brain parenchyma, surrounded by hemosiderin deposits and gliosis, which may or may not be thrombosed. [9] In this study we systematically evaluate features of CCM histopathology in a large series of neuroradiologically verified CCMs and analyse their congruency with this clinical definition. We included patients without any treatment of the lesion prior to surgery, whose preoperative MRIs were available and whose lesion fulfilled criteria of CCM according to the radiological classification of Schefer et al. [13] Analysing our patient cohort, we find similar sex distribution, age range and lesion localisation as reported in previous publications. [14,18-22] We therefore conclude that our patient series is unbiased and representative for CCMs.

For detection of CCMs the MRI has emerged as highly sensitive and specific tool. [9,14] Nevertheless, the neuropathological analysis of resected specimens remains the gold standard for a definite diagnosis and identification of diseases clinically and neuroradiologically mimicking CCMs. [14,23] Still, the neuropathological verification of CCMs turns out to be difficult if specimens are very small, destroyed due to hemorrhage, or artificially damaged in the course of the neurosurgical procedure. Therefore, a detailed knowledge of the histopathological spectrum of CCMs is important.

### CCMs and intervening brain parenchyma

The current, broadly accepted definition of CCMs states that this type of vascular lesion does not contain brain parenchyma between malformed vessels. [9] However, some authors point out that those vessels at the edges of the malformation may be separated by intervening brain parenchyma, but not the nidus. [17] Contrary to the current definition of CCMs, Rigamonti et al. as well as Tomlinson et al. reported intervening brain parenchyma in major areas of CCMs in a significant fraction of cases. In some cases even the nidus of the lesion showed separated vessels. [11,12] Though variable in extent, the vast majority of cases in our large series of CCMs showed intervening brain parenchyma between the malformed vessels. We even identified cases in which all areas of the lesion showed separation of vessels by intervening brain parenchyma. Thus, the absence of intervening brain parenchyma does not seem to represent an essential histopathological feature of CCMs, as suggested previously in smaller series. [11,12]

What might restrict our results is that CCMs are a heterogeneous group of three-dimensional lesions and that the structure of the histopathological specimen might also depend on the surgical dissection technique. The surgical dissection technique again is determined by the localisation of the lesion and the patient's clinical state. For a part of the lesions the observation of intervening brain parenchyma between the vessels might as well

be caused by only cutting the surface of the three-dimensional lesion. However, in our series the majority of all lesions presented with intervening brain parenchyma, which was present in serial sections throughout the lesions. Different surgical resection techniques apply especially among patients presenting with seizures. Recent studies suggest that CCMs associated with epilepsy should be removed including the adjacent hemosiderin stained tissue. [24-26] Resection of this adjacent hemosiderin stained parenchyma may influence the observation of intervening brain parenchyma. In our present series 33/71 (46.5%) patients, with diagnosable lesions, clinically presented with seizures. In 9/33 (27.3%) patients with seizures the CCM was removed together with the adjacent hemosiderin rim. In order to evaluate if removal or no removal of the adjacent hemosiderin stained parenchyma influences the observation of intervening brain parenchyma we compared these two groups. There is no significant difference in the distribution of lesions with intervening brain parenchyma between these groups.

In contrast, a brainstem CCM is always resected without surrounding brain tissue due to the eloquent area. [14,27] Nevertheless, we found intervening brain parenchyma in 5/9 (55.6%) brainstem CCMs.

#### Vessel structure and other CCM features

In the recent literature, CCMs are also defined as vascular lesions composed of thin-walled vessels. [9] In our series, thickness of vessel walls ranged between 0,001mm and 0,4mm. Luminal diameters ranged between 0.025mm and 4.25mm. Thus, dimensions of vessel walls and luminae in CCMs are highly variable, as reported in the original neuropathological descriptions of CCMs in the pre-imaging era. [15] We further observed a considerable range of fibrosis, thrombosis, hemosiderin deposits, and calcifications. Synoptically, these features indicate dynamic changes in CCMs which is in accordance with the dynamic nature and growth potential of this type of cerebrovascular malformations. [28-32] A fraction of cases additionally contained small granular or patchy amyloid deposits in and around the walls of the malformed vessels. So far, amyloid deposits have been described in AVMs but not in CCMs. [15] To our experience this observation may be of diagnostic relevance: in a case of multiple heavily fibrosed intracerebral CCMs (referral case not included in this cohort), a tiny biopsy containing amyloid deposits lead to the consideration of multiple amyloidomas. [33]

#### Mixed malformations

In addition to pure CCMs, mixed malformations are described in the literature. [7,8,14,17] An association of CCMs and telangiectases has been reported in several publications, either as regionally separated lesions or as true combined lesions. [7,8,14,17] In our series, a few cases regionally contained capillary-like malformed vessels, which were separated by intervening brain and thus would be compatible with telangiectases in these foci. However, these telangiectases-like areas showed continuous transition into areas with clear-cut CCM features. Therefore, we feel that in our series the observation of telangiectases-like areas does not justify the designation of true mixed type of vascular malformation. Our opinion on this issue is shared by another independent group. [12] Due to the co-occurrence of CCMs and capillary telangiectases (including transitional forms) it has been suggested previously that these types of vascular lesions may represent a spectrum within a single pathological entity and that telangiectases may represent potential precursors of CCMs. [11,15] However, arguments against such a synthetic concept are that if the CCMs represent a later stage of development of telangiectases, then telangiectases should be observed in greater numbers and in earlier life than CCMs. [15] An association of CCMs with VM has been reported with a range of 6% to 100%. [14,27,34] We did not find such an association in any case in our histopathological series. Indeed, the observation of combined CCM / VM in previous studies is predominantly based on intraoperative or radiological findings. [27,34,35] Only few studies report an association of CCM and AVM. [7,36] None of our cases contained malformed artery-like vessels with muscular and elastic laminae or arterialisated veins, thus excluding combined CCM / AVM. In several cases, surrounding CNS tissue contained small sized normal arteries and veins. The lack of any combined type of vascular malformation in our series may further be explained by our stringent selection criteria: we only included cases in

which CCM was neuroradiologically diagnosed on preoperative MRI, whereas previous studies included angiographically occult vascular malformations or autopsies. [11,12,17,37]

#### Non diagnosable lesions

Preoperative MRIs of all patients were reviewed by a senior neuroradiologist. Only patients whose lesions were radiologically verified as CCMs in this review were included in this study. Still, in a fraction of our cases a definite histopathological diagnosis was not feasible. These biopsies contained blood only or blood with non-diagnostic membranous fragments of malformed vessels. CCMs are lesions rich of blood. Bleeding into CCMs with thin walled vessels may destroy the lesion. It is also possible that during the surgical procedure the major part of the lesion was sucked undeliberately by the surgeon or that simply not enough material was sent in for neuropathological diagnosis. We included these 16 non diagnosable lesions in order to disclose the whole spectrum that is seen in daily clinical routine. Further, our finding of a significant association of CCMs displaying radiological signs of hemorrhages and histologically non diagnostic biopsies indicates that bleeding of CCMs is a major cause for non-diagnostic histology.

#### **Conclusion**

In dis-congruency to the current clinical definition the absence of intervening brain parenchyma does not seem to represent an essential histopathological criterion of CCMs. Further, the diameter of the vessel lumina and the thickness of vessel walls vary considerably. In addition to previously published features, we demonstrate for the first time small amyloid deposits in a fraction of cases. Based on these findings, adaptation of the current definition of CCMs needs to be considered and should be worked out on basis of a multidisciplinary collaboration including neuropathology, neuroradiology and neurosurgery.

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#### **Competing interests**

None of the authors has any competing interests regarding the presented work.

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## Figure legend

### *Figure 1: Histopathological features of cerebral cavernous malformations (CCMs)*

(A-C) Typical CCMs with closely packed malformed vessels without intervening brain parenchyma. The surrounding brain parenchyma (black asterisks) is loaded with hemosiderin deposits (brown dots). (A, B) Focal calcification (black arrow). (A) hematoxylin & eosin staining; (B) elastica van Gieson staining of the same case shown in Fig. 1A. (C) elastica van Gieson staining of another CCM.

(D, E) Elastica van Gieson staining of a CCM displaying highly variable vessel walls and vessel calibres. (E) Higher magnification of the CCM shown in Fig.1D.

(F) Combined elastica van Gieson staining and GFAP (glial fibrillary acidic protein) immunostaining of a CCM with extensive intervening brain parenchyma. Vessel walls are stained in red (Gieson). Intervening brain parenchyma is stained with anti - GFAP in brown color (white asterisks). (G) Elastica van Gieson staining of the same CCM in higher magnification than shown in Fig.1F. The extensive intervening brain parenchyma (black asterisks) is loaded with hemosiderin.

(H, I) Hematoxylin & eosin (H) and elastica van Gieson (I) staining of CCMs containing capillary-like malformed, telangiectatic vessels separated by intervening brain parenchyma. (I) These telangiectatic vessels are part of a CCM in which all vessels throughout the lesion were separated by brain parenchyma.

(J-L) CCM section stained with congo red for amyloid detection. (J) Light microscopy showing amyloid depositions between malformed cavernous vessels in brick red. A multinucleated giant cell engulfs a small amyloid deposit (black arrow). The black rectangle outlines the corresponding area shown in Fig. 1K. (K, L) Apple-green birefringence of amyloid under polarized light. (K) The multinucleated giant cell engulfing the amyloid deposit (white arrow) is seen in higher magnification than in Fig. 1J. (L) Amyloid deposits around another cavernous vessel in the same section.

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