Chapter 2
Definition and Structure of Cerebral Cavernous Malformations

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2.1 Definition and Terminology

Cavernomas have various different names. Cerebral cavernoma, cerebral cavernous malformation (CCM), cryptic angioma, cavernous hemangioma, and cavernous angioma are well used and sometimes confused in terms of nomenclature. As these lesions are not neoplastic, it has been argued that the terms 'hemangioma' and 'cavernoma' should be avoided. Additionally, it is important to note that according to newer nomenclature (ISSVA classification of vascular anomalies), these lesions are known as slow flow venous malformations [1]. It is probably helpful in reports to include the word 'cavernous' as this term is ubiquitous in the literature and most familiar to many clinicians. Therefore, the term 'cerebral cavernous malformations (CCMs)' are recommended and used in this chapter [1–6].

2.2 Structure

CCMs are abnormally formed blood vessels and consists of clusters of thin walled cavernous vessels without intervening stroma (Fig. 2.1).

They belong to the group of low-flow vascular malformations and occur in the venous-capillary vascular bed. CCMs consist of a mulberry- or raspberry-like cluster of enlarged endothelial channels (caverns) surrounded by a thick, segmental

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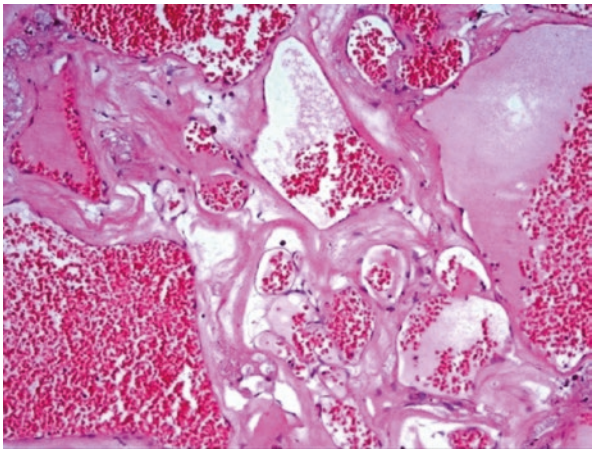

Fig. 2.1 Microscopic findings of CCM with 20 × magnification. This section shows a nidus of small caliber vascular channels which is sharply demarcated from surrounding white matter. Vessels have a back-to-back arrangement with no intervening brain parenchyma. The vessel walls are composed of collagen with no smooth muscle or elastic tissue identified

layered basal membrane. The vascular channels are generally arranged in a back-to-back pattern with little or no intervening brain parenchyma and are often surrounded by gliotic tissue. The cells that line these caverns sometimes ooze small amounts of blood into surrounding brain tissue and produce the hemosiderin in the parenchyma. This deposition of hemosiderin sometimes results in symptoms like seizure. CCMs can grow in size, but this growth is not cancerous, and they do not spread to other areas of the body [7–10].

2.3 CCMs Associated with Developmental Venous Anomalies (DVAs)

The association between developmental venous anomalies (DVAs) and CCMs has been well recognized. CCMs are known to occur in 8–33% of the DVAs [11–13]. The coexistence of a CCM and an associated DVA is the most common mixed vascular malformation. Patients with CCM associated with DVA are more likely to have lesions in the posterior fossa. The most prone site for the development of CCMs is the central portion of DVA where abnormal small branches of tributaries of medullary vein converged (Fig. 2.2).

The anatomical complexities of the DVAs may create certain anatomical angioarchitectural factors responsible for the occurrence of CCMs in its territory [11–15].

2.4 Demography and Genetic Factors

CCMs affect approximately 0.4%–0.6% of the population [16]. Approximately 20% of CCMs are familial, autosomal dominant, and the rest are sporadic. Familial CCMs tend to be multiple. Up to half of patients with CCMs, more in some studies,

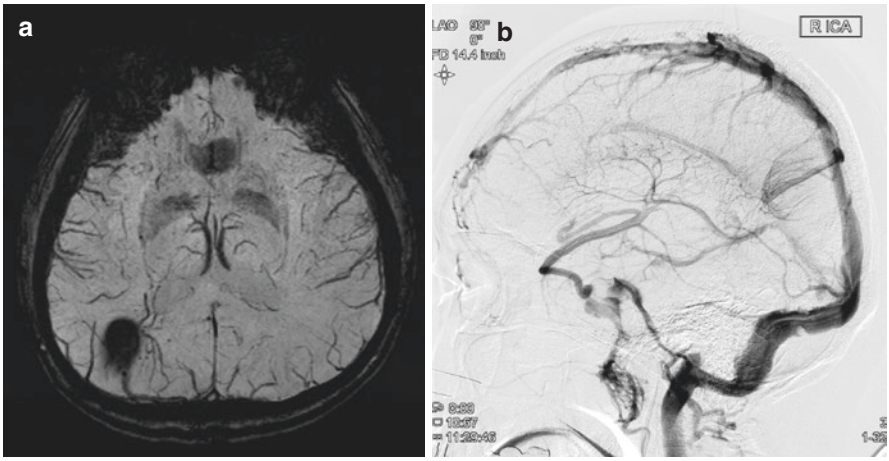

Fig. 2.2 (**a**) SWI showed the CCM associated with DVA. (**b**) Venous phase of angiography of the same patient demonstrates the typical appearance of DVA adjacent to the CCM. CCMs are always occult angiographically

remain asymptomatic through their lives. The rest have seizures, focal neurologic deficits, headaches, and cerebral bleeds. Symptoms usually develop between the second to fifth decade of life. Recent studies showed that CCMs are caused by mutations of three genes. The three genes associated with CCM disease encode the proteins KRIT1/CCM1 (Krev interaction trapped 1/cerebral cavernous malformations), CCM2/Malcavernin/OSM (cerebral cavernous malformations 2, osmosensing scaffold for MEKK3), and CCM3/PDCD10 (cerebral cavernous malformations 3/programmed cell death 10) [3, 4].

KRIT1 (CCM1) is a disease gene responsible for CCMs, a major cerebrovascular disease of proven genetic origin affecting 0.3–0.5% of the population. Mutations in the KRIT1 gene account for up to 50 percent of all familial CCM cases [3, 9]. One particular mutation is responsible for up to 70 percent of cases in people of Hispanic heritage. It is possible that CCMs are all caused by genetic defects in KRIT1 and related genes encoding proteins that lie in a single signal transduction pathway. This pathway may be important in the normal formation and function of microvasculature. Formation of competent cerebral microvasculature relies on appropriate signaling between adjacent endothelial cells and between endothelial cells, pericytes, astrocytes, and the extracellular matrix. These mutations place a premature stop signal in the instructions for making the KRIT1 protein, preventing adequate KRIT1 protein production [3, 8–10]. A shortage of this protein likely impairs the function of the complex. As a result, RhoA-GTPase signaling is turned on abnormally, weakening cellular junctions and increasing the permeability of blood vessel walls. The increased leakage into the brain can cause health problems such as headaches, seizures, and bleeding in the brain (cerebral hemorrhage) in some people with cerebral cavernous malformations [3, 4, 6, 8–10].

2.5 Neuroradiology of CCMs

CCMs tend to be supratentorial and more than 80% cases of CCMs are locating in the parenchyma of supratentorial telencephalon, but they can be found anywhere including the brainstem. They are usually solitary, although up to one-third of patients with sporadic lesions have more than one [17, 18].

CT Unless large, these lesions are difficult to see on CT. They do not enhance. If it would be large, then a region of hyperdensity can be seen. If there has been a recent bleeding, then it is more conspicuous and may be surrounded by a mantle of edema [19].

MRI MRI sequences sensitive to the magnetic susceptibility artefact of iron (such as gradient echo and susceptibility-weighting) have been found to be more sensitive for the detection of multiple CCM in comparison to conventional spin echo in studies undertaken in families with inherited CCM.

The CCMs can be defined by the MRIs' appearance, if they had more than two of the following findings:

1. a central core of reticulated mixed signal blood containing locules with "popcorn ball or raspberry like appearance"
2. a surrounding rim of low-signal intensity on T2-weighted image
3. minimal or no enhancement on SPGR (Spoiled Gradient-echo sequence) image

The developmental venous anomalies (DVAs) are defined on MRIs by typical stellate or tubular vascular lesions which converged on collecting vein and drained into dural or ependymal sinus and caput medusa appearance on SPGR image [12, 15, 20].

MRI is the best modality of choice, demonstrating a characteristic "popcorn" or "berry" appearance with a rim of signal loss due to hemosiderin, which demonstrates prominent blooming on susceptibility weighted sequences. T1 and T2 weighted images are varied internally depending on the age of the blood products and small fluid-fluid levels may be evident. Gradient echo or T2* sequences are able to delineate these lesions better than T1 or T2 weighted images. In patients with familial or multiple cavernous angiomas GRE T2* sequences are very important in identifying the number of lesions missed by conventional Spin echo sequences. Susceptibility weighted imaging (SWI) may have sensitivity equal to that of GRE in detecting these capillary telangiectasias in the brain. SWI is also highly sensitive in detecting calcification as compared to T1 and T2 images [17, 19].

If a recent bleed has occurred, the surrounding edema can usually be presented.

The lesions generally do not enhance, although enhancement is possible.

CCMs can be grouped into four types based on MRI appearances using the Zabramski classification [21] (Table 2.1).

This classification of cerebral cavernomas has been proposed as a way of classifying cerebral cavernous malformations, and although not used in clinical practice it is useful in scientific publications that seek to study cavernous malformations.

Table 2.1 Zabramski's classification based on the MRI findings (1994)

Type I: Subacute hemorrhage
T1: Hyperintense
T2: Hypo or hyperintense
Type II: Most common type - classic "popcorn" lesion
T1: Mixed signal intensity centrally
T2: Mixed signal intensity centrally
T2*: Low signal rim with blooming
Type III: Chronic hemorrhage
T1: Hypointense to isointense centrally
T2: Hypointense centrally
T2*: Low signal rim with blooming
Type IV: Multiple punctate microhemorrhages
T1: Difficult to identify
T2: Difficult to identify
T2* gradient Echo: "Black dots" with blooming
Difficult to distinguish from small capillary telangiectasias

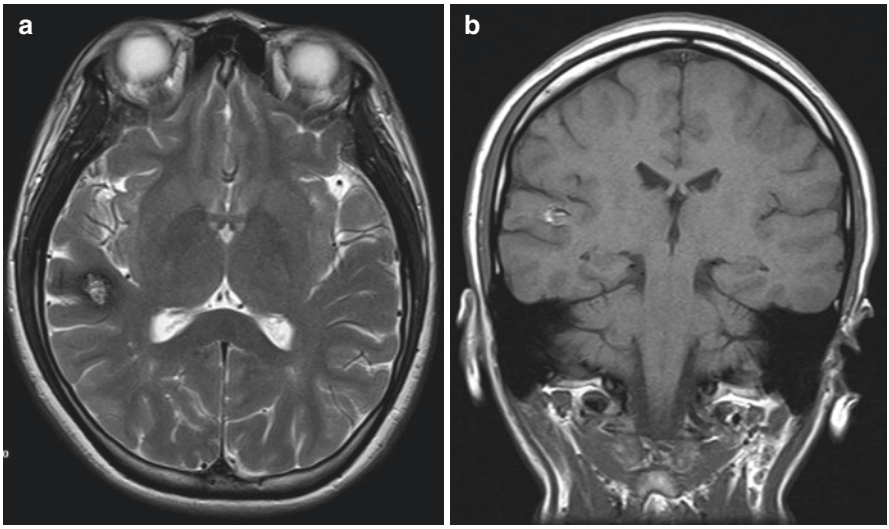

Fig. 2.3 (**a**) T2 weighted image: A mixed signal intensity lesion is seen centrally in the right superior temporal gyrus. (**b**) T1 weighted image: a classic "popcorn" lesion is seen

According to Zabramski classification, Type I lesions are characterized by hyperintensity on both T1- and T2-weighted images (depending on the state of methemoglobin) which is consistent with subacute hemorrhage. Type II malformations, loculated regions of hemorrhage are surrounded by gliosis and hemosiderin-stained brain parenchyma (Fig. 2.3).

Type III lesions demonstrate a core that is iso- or hypointense on T1-weighted sequences and hypointense on T2-weighted sequences as well as a rim that is hypointense on T2-weighted sequences, compatible with chronic resolved

hemorrhage or hemosiderin within and surrounding the lesion. Pathologically, Type 4 lesions may represent capillary telangiectasias or early stage CCMs seen frequently in the familial form.

Angiography The internal channel of CCM consists of numerous caverns. The mean transit time of the blood flow through the internal channels is so slow that the cerebral angiography does not show the opacification of the CCM itself even with the superselective angiography. Therefore, CCMs are angiographically occult and do not demonstrate any arteriovenous shunting. However, CCMs are often concurrent with DVAs, therefore the appearance of DVAs can be a clue to suggest the existing of CCM [11–13, 15, 22].

2.6 Differential Diagnosis

The differential, when cavernous venous malformations are numerous, is that of other causes of cerebral microhemorrhages, including Parry-Romberg syndrome [23–25]:

- Cerebral amyloid angiopathy: usually numerous small foci
- Chronic hypertensive encephalopathy: more common in the basal ganglia
- Diffuse axonal injury (DAI)
- Cerebral vasculitis
- Radiation-induced vasculopathy
- Hemorrhagic metastases
- Parry-Romberg syndrome

Larger lesions can mimic:

- Hemorrhagic cerebral metastases
- Hemorrhagic primary brain tumors (e.g. ependymoma, glioblastoma)

Calcified lesions, such as old neurocysticercosis, or other infections (e.g. tuberculoma) should also be considered [26].

2.7 Summary

The pathogenesis of CCMs remains to date unknown. Especially the familial form of CCMs is a dynamic disease. Therefore, patients with familial CCMs require careful follow-up monitoring with serial MRI. If DVAs would be observed on the MRI or the other modality of imaging, coexisting CCMs should be considered. Molecular targeted therapy or further specific pharmacological strategies are required for preventing the de novo formation of CCM lesions and counteracting disease progression and severity in susceptible individuals, including CCM gene

mutation carriers. If some established experimental model of the system would show the role of endothelial cells and associated molecular biology, the pathomechanism of CCMs will be clarified near future.

Conflict of interest Authors declare no conflict of interest.

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