Cerebral cavernous malformations (CCM) - The „cavernoma"

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Introduction

Cerebral cavernous malformations (CCM), also known as "cavernomas" or "cavernous haemangiomas", are commonly diagnosed, relatively "benign" vascular anomalies that are pathophysiologically caused by a capillary endothelial dysfunction. What does that mean? Circumscribed small areas of the capillary vessel system do not work properly. This leads to several pathological processes: mainly recurrent (micro-) bleeding and thrombosis in combination with reactive local tissue reconstruction.

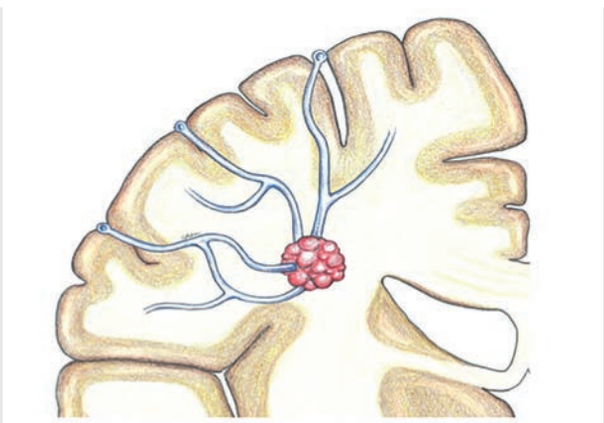


Fig. 1:
Schematic drawing of an intracerebral CCM. The lesion is embedded in the capillary vessel system.

Altogether, this process results in the rapid formation of a multi-compartment ("cavernous") "ball" of pathological vessels, ranging from few millimetres to sometimes several centimetres in size (Fig. 1). The lesions can occur anywhere in the body; however, problematic are mainly lesions occurring in the brain (referred to as cerebral CCM) or in the spinal cord. The frequency of cerebral CCM is roughly 0.5%, making it the second most common cerebral vascular malformation. At present, we distinguish between a more common sporadic disease (mainly singular lesions, no familial history, aetiology unclear) and a less common (15-20%) familial disease (often multiple lesions, autosomal dominant form of inheritance, lifetime development of de-novo lesions, mutations on 3 gene loci discovered (CCM1-3)). The form of the disease has a huge impact on potential treatment.

Interestingly, sporadic CCM show a frequent co-existence with other vascular lesions, mainly developmental venous anomalies (DVA). However, the relevance of this co-existence has not yet been clarified.

As mentioned earlier, normally, CCM are "benign" lesions. When discovered, 50% of them are asymptomatic and may not produce any symptoms in the future. Therefore, in most cases, a treatment of incidentally discovered CCM is not indicated. However, in some cases, they may cause symptoms. Depending on the specific anatomical location (superficial, deep, cerebrum, cerebellum, brainstem) of the CCM, they can cause neurological deficits (paralysis, sensation disorder, speech disorder, etc.), seizures (cavernoma related epilepsy (CRE)) or, in rare cases, symptoms of increased intracranial pressure (headache, vomiting, loss of consciousness).

The reason for the occurrence of these symptoms is most frequently symptomatic haemorrhage of the CCM. This means a larger bleeding of the lesion irritates or even damages adjacent brain tissue. The risk of such an event is relatively low (0.5% - 1.5% / year). However, in some cases (5-year risk roughly 30%), a first bleeding introduces further subsequent bleeding(s).

> *The typical method for discovering or further analysing a CCM is magnetic resonance imaging (MRI). No clear evidence for any factor provoking a bleeding of a CCM has yet been determined.*

Indications for (surgical) treatment?

In view of the relatively benign natural course of CCM, most of them can simply be observed and may never cause any "severe" problems for the patient. Currently, no medical treatment exists for CCM. However, we expect some pharmaceutical studies in the next years. The current treatment normally consists of a microsurgical resection of the lesion (standard treatment). A radiosurgical treatment is an alternative treatment option, which is, however, still being discussed.

> *Each treatment indication is a balance act between the risks of the natural course of the lesions and the risks of treatment*

What are typical situations in which treatment should be considered?

Large, acute symptomatic haemorrhages with mass-effect to the brain and severe neurological impairment of the patient are absolute indicators for surgery. Fortunately, such massive haemorrhages are extremely rare.
In most cases, symptomatic haemorrhages cause more

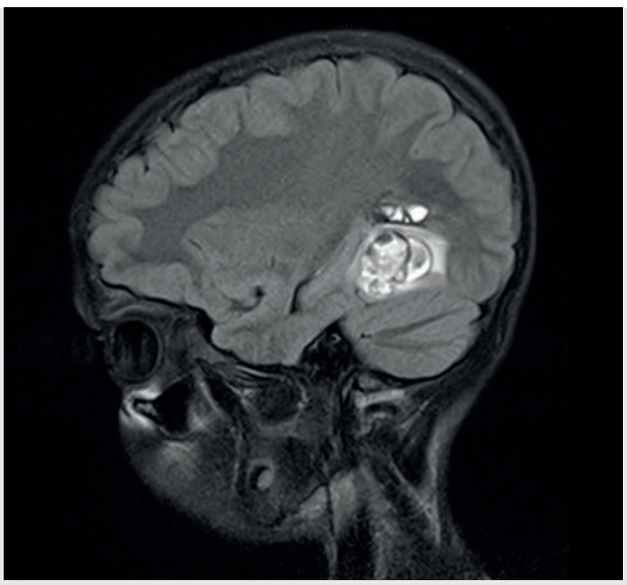


Fig. 2: 12-year-old patient with acute symptomatic bleeding (bright areas in this MR image) presenting with various neurological deficits)

mild symptoms, which are of temporary nature. However, if these haemorrhages re-occur in a short interval of time ("active lesion"), a surgical resection should also be considered (Fig. 2).

A typical indication for a surgical treatment is cavernoma-related epilepsy (CRE). This is a situation in which a CCM has been confirmed to cause epilepsy. This may be the case even without symptomatic haemorrhage. Epilepsy experts recommend the resection of the CCM if patients do not respond well to a medical treatment of the epilepsy. However, even after a first seizure, some arguments favour a direct resection of the epilepsy-causing CCM: good "accessibility" of the lesion, avoidance of long-term medical treatment side-effects, prevention of further haemorrhage in an active lesion, sporadic lesion, young patient age. The treatment of a CRE should always be a cooperation between an epileptologist and a neurosurgeon.

Sometimes, a CCM may be located in a very "vulnerable" region of the brain, for example the brainstem or the deep brain nuclei or the spinal cord. This occurs in approximately 30% of the cases and may cause a complex situation, which can pose quite a dilemma. On the one hand, a larger bleeding in this area may produce severe symptoms, on the other hand, a resection of the lesions in these delicate areas may be associated with a significant chance of operative morbidity.

> The resection of lesions in these areas can be considered as one of the most difficult procedures to indicate and perform in the field of neurosurgery.

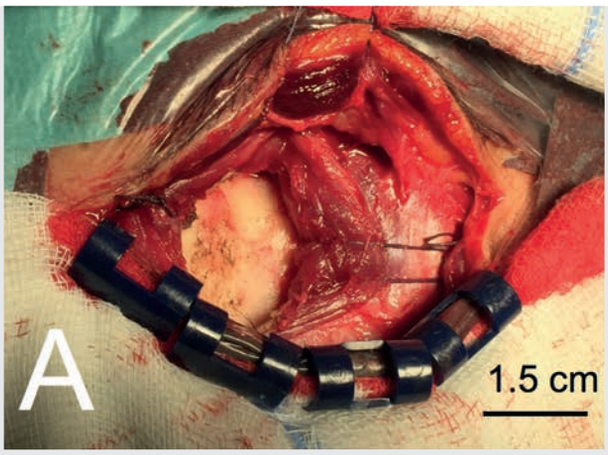
If symptomatic haemorrhage occurs in such a region, it is advisable to consult a neurosurgical centre which has lots of prior experience with such complex cases and operations.
Further rare indications for a surgical resection are very large (several centimetres) space-occupying cavernomas which irritate the surrounding brain or disturb the circulation of the cerebrospinal fluid, causing a hydrocephalus.

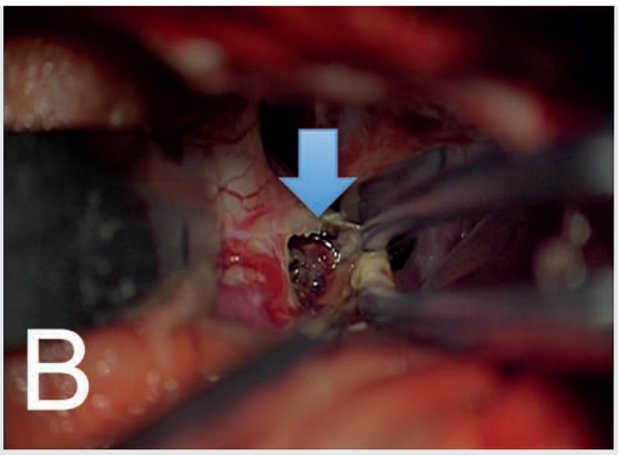
Operative risks and morbidity

Every type of brain surgery carries certain general risks, mainly infection of the surgical site, secondary intracranial bleeding and stroke. These risks are of fundamental nature and of course also account for the surgical treatment of CCM. They can be generally classified as relatively low.

The specific risks of a CCM resection mainly depend on the location of the lesion (see above). The more important the region (brainstem, speech areas, etc.), the more severe the consequences in case of potential complications. The more vulnerable the region (many important structures located in a small area, e.g. brain stem), the more likely are potential complications. Furthermore, some areas of the brain are part of larger networks which can better compensate potential damages, while in others, damages are likely to result in a permanent neurological dysfunction.

> *In general, the risk of a CCM resection is quite individual and should therefore be elucidated individually by the surgeon planning to perform the surgery.*





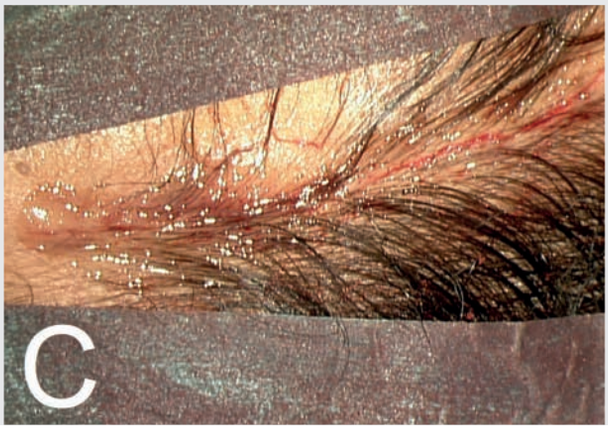


Fig. 3:

Example of a resection of a CCM located in the temporal lobe using a small „mini pterional" approach. In this case, the CCM had caused an epileptic attack..

(A) shows the dissection of the muscle and the surface of the temporal bone below.

(B) shows the microscopic view of the mulberry-like lesion (arrow) that is carefully dissected from the surrounding brain tissue.

(C) shows the closure of the wound, in this case with a tissue glue.

Larger studies showed a general risk of 5%-15% of a permanent deficit, depending on the location. When performing surgery in vulnerable areas (e.g. brainstem), the patient should also be prepared for potential temporary neurological deficits. These occur more frequently (30%) but are normally resolved within 3-6 months after surgery.
Resections of CCM in less vulnerable regions present much lower risks of permanent or temporary neurological deficits. In many cases, patients "only" suffer from the consequences of the microsurgical approach (local pain, healing process of soft tissue, cosmetic impairment). Nowadays, many approaches are small and show optimal cosmetic results.

Summary

In summary, CCM present a common finding. With the increasing utilization of MRI for "screening" purposes, incidental discoveries of CCM are likely to increase even further. Most patients harbouring a CCM will never face any or any severe symptoms. In these patients, the lesion can be monitored or even neglected. In some patients however, recurrent bleedings of the lesion or epilepsy may make a treatment necessary, normally consisting of a surgical resection. Any evidence for a familial disease (multiple lesions, familial history of seizures) should be monitored by a human genetics counsellor (see article by Prof. Felbor).