

Cavernous malformations of the central nervous system — a review

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Introduction

Cavernous malformations (CMs) of the brain and spinal cord (also known as cavernous angiomas, cavernous haemangiomas, cavernomas, angiographically occult vascular malformations, occult vascular malformations and cryptic vascular malformations) are low-flow, low-pressure vascular malformations of the central nervous system (CNS). Although traditionally regarded as a separate pathological entity compared with other CNS vascular malformations, current research suggests that there may be pathogenetic links to the other types of malformation.

Classification of vascular malformations

To date the most commonly used classification scheme of CNS vascular malformations is that of McCormick *et al.* published in the mid-to-late 1960s^{1,2} and later by Russel and Rubenstein.³ This categorises CNS vascular malformations into one of four types (Table I).

Table I. Categorisation of CNS vascular malformations

1. Arteriovenous malformation (AVM)
2. Capillary telangiectasia
3. Cavernous malformation
4. Venous malformation

These were based mainly upon microscopic and gross histopathologic criteria. More recently the presence of mixed/combined or intermediate forms of malformation have been described, blurring the classical classification scheme.⁴ Further improvements in the understanding of the natural history, pathogenesis and cellular biology of CNS vascular malformations will probably eventually result in further revision of this classical pathoanatomical classification to be replaced by a more biologically based one.

Pathology

CNS vascular malformations are considered to be vascular hamartomas.^{5,6} Grossly cavernous malformations appear as well circumscribed multilobulated masses filled with blood with a red to purple colour resembling mulberries. They can range in size from millimetres to several centimetres. They are surrounded by a transi-

tion zone or 'capsule' of haemosiderin-stained gliotic brain tissue. Histologically they are composed of multiple thin-walled sinusoidal vascular channels or caverns. The walls of these channels are lined by a single layer of endothelium surrounded by a thin layer of dense fibrous tissue with complete absence of elastic fibres or smooth muscle, similar in appearance to dilated capillaries. This has led some authors to suggest that both CMs and capillary telangiectasias may represent different variants of the same pathological entity.⁷ There is little or no intervening normal brain tissue between the sinusoids of a CM, whereas this is present in the capillary telangiectasias. Many of the dilated channels contain stagnant blood or thrombus, and focal areas of calcification may be seen.

CMs increase in size as the result of recurrent episodes of local intralesional haemorrhage and thrombosis. They are low-flow and low-pressure lesions with the result that the haemorrhages tend to be limited and generally contained within the lesion. These repeated episodes of haemorrhage and thrombosis lead to a gradual progressive deposition of haemosiderin and other blood breakdown products in the normal brain parenchyma around the CM. Occasionally a haemorrhage within a lesion can extend beyond the capsule resulting in a parenchymal or less commonly a subarachnoid haemorrhage.

CMs can be classified as either sporadic or familial. They may also be single or multiple. In sporadic cases up to 33% have multiple lesions⁸ whereas in familial cases

multiple lesions may be seen in over 70%.^{8,9} Some 20 - 30% of patients with CMs in North America may have the familial form. An autosomal-dominant pattern of inheritance is seen in the familial form. There is a particularly high incidence of familial CMs in the American Hispanic population¹⁰ where the abnormal gene responsible for the development of these CMs has been identified on the long arm of the 7q chromosome.¹¹ Further point mutations have been identified in other ethnic groups including two on the short arm of chromosome 7(7p15-13) and the long arm of chromosome 3(3q 25.2.27)(CCM52 +3).^{12,13}

The first of these genes, CCM1, has been identified more recently as encoding the KRIT1 protein which probably plays a role in intracellular signalling, particularly to endothelial cells.¹⁴ The importance of this is that a genetic component has now actually been identified as playing a role in the development of CNS vascular malformations, and that many of these abnormalities still remain to be defined at a molecular level.¹⁵

CMs have long been presumed to be congenital lesions present at birth.¹⁶ A number of cases have been reported in neonates supporting a congenital origin for some lesions.¹⁷⁻¹⁹ More recently cases of spontaneous *de novo* CM formation in adults have been described in both the familial and sporadic forms of this condition.^{9,20,21} *De novo* development may occur seemingly spontaneously or may be associated with a number of associated events or abnormalities. CM development has been documented

after brain biopsy¹⁹ and both stereotactic and conventional radiation therapy.^{22,23} Other factors that may be involved include head trauma,¹⁹ brain surgery²⁰ and viral infections including cytomegalovirus.²⁴ Infection of nude mice with the polyoma virus in laboratory experiments has been shown to induce the development of multiple CMs in the brains of these mice.^{25,26} Finally there is the association of CMs with other CNS vascular malformation types including telangiectasias and developmental venous anomalies (DVAs).^{4,27,28} Further theories suggest that CMs may develop from pre-existing telangiectasias or may develop in response to micro haemorrhages or pressure changes in telangiectasias and venous malformations.²⁹ Thus even if the CMs themselves are not congenital there must be some predisposing factor or defect that is, which in turn is exposed to a trigger factor at some later stage in life thereby leading to the formation of the CM by interference with normal angiogenesis or vascular modelling or remodelling mechanisms.

Immunohistochemical studies are revealing new information concerning the biomolecular structure of the constituent elements of the walls of CMs as well as angiogenic factors related to their development.^{30,31} For instance, fibronectin and laminin are proteins responsible for maintaining the structural integrity of a vessel wall by anchoring endothelial cells to the underlying internal elastic membrane and smooth muscle layers. Fibronectin is found predominantly in the initial stages of angiogenesis whereas

laminin is found in the maturation stages. In one study, AVM subendothelia were found to contain more laminin whereas CM subendothelia contained more fibronectin.³¹ Thus, compared with AVMs, CMs have a more angiogenically immature and fragile wall which is more prone to bleed at non-arterial pressures. Angiogenic factors such as VEGF, TGF α and bFGF have been identified in CMs as well as in normal brain tissue adjacent to the CMs. The expression of these growth factors suggests that angiogenic processes which are normally dormant in the adult brain may become triggered, leading to the development of these malformations as a final common pathway regardless of whether the underlying defect is genetic or acquired.

Mixed malformations

The presence of multiple malformation types in the same patient has been well documented generally involving some combination of CMs, capillary telangiectasias, venous malformations and arteriovenous malformations.^{4,6,32} One report even describes the juxtaposition of a capillary telangiectasia, CM and DVA in the brainstem of the same patient.³³ The presence of mixed malformations suggests a possible common pathogenesis resulting in transitional forms of vascular malformation in the same anatomical location. One theory suggests that elevation of venous pressure in a DVA leads to ectasia in an acquired capillary telangiectasia then leading to the development of a CM.^{29,34} Histologically the archi-

texture of the vascular channels in a CM resembles that of the capillary telangiectasia consisting of a single endothelial cell layer and sub-endothelial fibrous layer with absence of smooth muscle and elastic fibres. Rigamonti *et al.*⁷ having observed capillary telangiectasias and transitional capillary-venous malformations at the periphery of CMs in autopsy series, suggested that these two lesions represent a phenotypic spectrum of the same pathological entity. The commonest vascular malformation associated with CM is the DVA.^{32,35} Abe *et al.*³² reported a 23% rate of coexistence of occult vascular malformations and DVA, with most (83%) occurring infratentorially. Other reported frequencies of this coexistence vary from 2% to 29%.

Incidence

CMs have an estimated prevalence of between 0.45% and 0.9% of the population based on MR studies,⁸ and 0.5% - 0.7% based on autopsy studies.³⁶ Most CMs (75%) are supratentorial.³⁷⁻³⁹ Within the posterior fossa the commonest location is the pons.⁴⁰ Spinal lesions are rare (< 5%). Size can range from 3 mm to 80 mm.³⁹

Natural history

The natural history of CMs remains a controversial issue, and a review of the literature serves to confirm this confusion. Del Curling *et al.*³⁷ calculated a bleeding rate of 0.25% per person per year. Robinson *et al.*³⁹ calculated a bleeding rate of 0.7% per person per year. Zabramski *et al.*⁹ found a 6.5% bleeding rate per person per year and 1.1% rate per lesion per year.

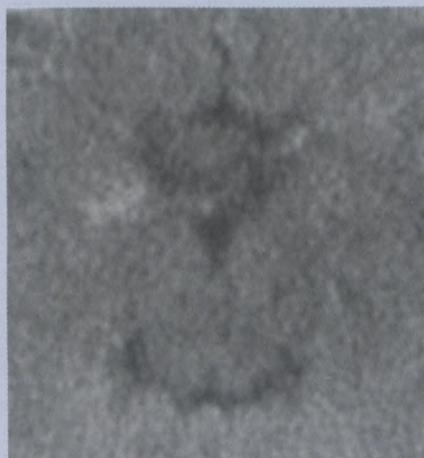


Fig. 1a. Right-sided medial temporal cavernoma, axial unenhanced CT image.

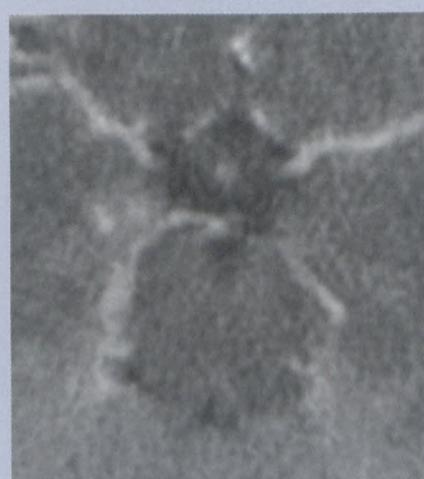


Fig. 1b. Same lesion, axial contrast-enhanced CT image.



Fig. 1c. Same lesion, axial T1-weighted MR image.

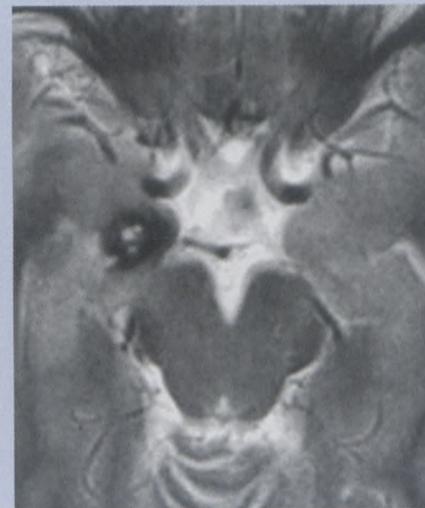


Fig. 1d. Same lesion, axial T2-weighted MR image.

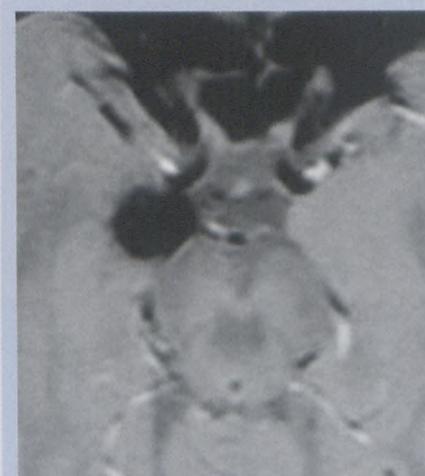


Fig. 1e. Same lesion, axial T2-FFE image.



Fig. 1f. Same lesion, axial FLAIR image.

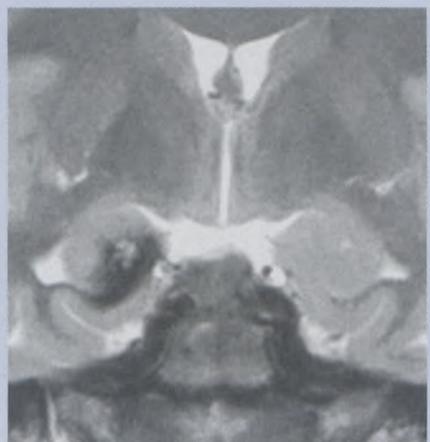


Fig. 1g. Same lesion, coronal T2-weighted MR image.

Aiba *et al.*⁴¹ described a 0.4% bleeding rate per person per year for patients who presented with a non-haemorrhagic event versus 22.9% for those who had a haemorrhagic presentation.⁴¹ Willinsky *et al.*⁴² found a 6.1% bleeding rate per patient per year, with a 10.9% rate for posterior fossa lesions and 1.7% for supratentorial ones. Kondziolka *et al.*¹⁶ calculated the overall annual bleeding rate of 1.3%, with a rate of 0.6% for patients without a prior bleed and 4.5% in patients with a prior haemorrhage. One of the major criticisms about the reporting of 'haemorrhage' in many studies is that CMs grow and increase in size as a result of recurrent focal haemorrhage and thrombosis thus blurring the definition of what exactly constitutes a significant haemorrhage. Porter *et al.*⁴³ referred instead to an annual clinical neurological event rate, including seizures (36%), haemorrhage (25%), and focal neurological deficit without documented haemorrhage (20%). They calculated an overall annual event rate of 4.2% versus an annual haemorrhage rate of 1.6%. Deeply located lesions

(brainstem, cerebellar nuclei, thalamus or basal ganglia) predisposed significantly to a much higher annual event rate of 10.6% per year compared with superficially located ones (0% per year). They also assessed that only one-third of patients recovered fully from their neurological deficits on long-term follow-up. Kondziolka *et al.*¹⁶ found no difference in the bleeding rate between different brain locations in their series. A number of studies report a higher bleeding rate in females especially during pregnancy,^{39,41,44,45} not confirmed in the studies by Kondziolka *et al.*¹⁶ and Porter *et al.*⁴³ Kupersmith *et al.*⁴⁶ in their review of 37 patients with brainstem CMs described a bleeding rate of 2.46% per year, a rebleeding rate of 5.1% per year and an overall clinical event rate of 3.4% per year. They found a higher risk of bleeding with brainstem cavernomas of at least 10 mm in diameter. These reported figures are considerably lower than those quoted by Porter *et al.*⁴⁷ with a 5% annual risk of bleeding and 30% risk of rebleeding, and Fritschi *et al.*⁴⁸ with an annual bleeding rate of 21%. Extralesional bleeding episodes were noted in 8.1% of the total number of cases, with an extralesional haemorrhage rate of 0.44% but an extralesional rebleed rate of 14.2% per year. Their conclusion that rebleeding is not more common among patients who first present with bleeding and often has little effect on the neurological status of patients with significant morbidity occurring in only 8% of patients during the mean follow-up period of 4.9 years drew sharp criticism from several sources who

preferably advocate a less conservative approach to patients with brainstem cavernomas.^{49,50}

The natural history of familial CMs differs somewhat from the sporadic form primarily by virtue of the high incidence of multiplicity of lesions. Zabramski *et al.*⁹ reported an overall annual rate of symptomatic haemorrhage of 6.5% per person or 1.1% per lesion per year and an overall haemorrhage rate of 13% per patient per year or 2% per lesion per year. An average of 6.5 ± 3.8 lesions were seen per patient. During the mean follow-up period of 2.2 years, 'de novo' lesions were found in 29% of cases or 0.4 new lesions per patient per year. Labauge *et al.*⁵¹ in a series of 173 patients from 57 unrelated French families found an average of 5.9 lesions per patient with an annual haemorrhagic risk of 2.5% per lesion per year and an overall haemorrhage rate of 11% per patient per year. 27.5% developed new lesions during the mean follow-up period of 3.2 years. Their calculated risk of haemorrhage was 1.9% per lesion per year for supratentorial lesions and 5% per lesion per year for infratentorial ones. Also of importance in these two studies was the reported rates of change in the size and signal characteristics of individual lesions (14% and 10% of lesions respectively) indicating the dynamic nature of this disease process.

Imaging characteristics

Due to the low-flow nature of CMs they are usually not visualised at angiography, hence the previous

term 'angiographically-occult vascular malformation'. Angiography may be completely negative or may show an avascular mass or region or a faint blush in the capillary phase or contrast pooling in the venous phase in larger lesions.^{52,53} With unenhanced computed tomography (CT) a rounded isodense to moderately hyperdense focal lesion may be seen (Figs 1a, 1b, 4a, 4b).⁵⁴ Calcification is common and is usually seen peripherally. Ossification is occasionally seen.⁵⁵ MR imaging is the most sensitive and specific imaging modality. The characteristic MR appearance is described as a rounded lesion with a central heterogeneous core consisting of T1 and T2 hyperintense areas in a pattern often described as 'popcorn-like' (Figs 1c-g, 3a-c). The different signal intensities are due to the presence of blood products at different stages of alteration in different areas of the lesion (Figs 5a,b). A rim of low signal surrounds the



Fig. 2. Zabramski type I cavernoma. Also previously referred to as a 'chronic intracerebral haemorrhage'.

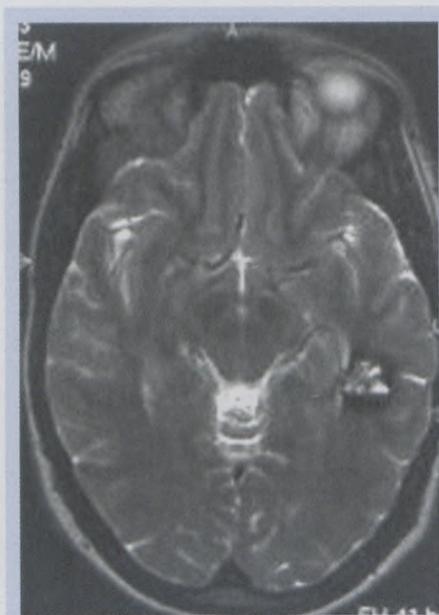


Fig. 3a. Axial T2-weighted image of a left temporal cavernoma showing the typical reticulated appearance (Zabramski type II).

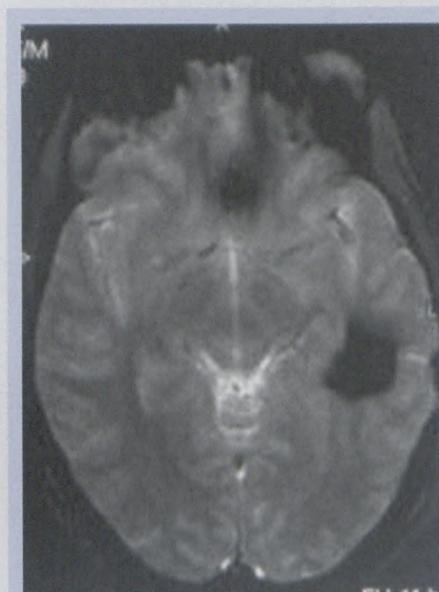


Fig. 3b. Axial T2 gradient echo image of the same lesion shows the intense paramagnetic 'bloom' of the haemosiderin in and around the cavernoma.

entire lesion which is of variable thickness and appears most hypointense on T2 images, particularly gradient echo T2 sequences (Figs 1e, 3b). This peripheral low signal represents haemosiderin and ferritin deposited at the interface with the adjacent brain parenchy-

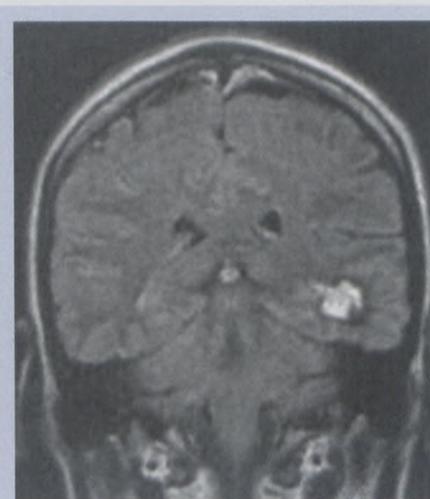


Fig. 3c. Same lesion, coronal FLAIR image.

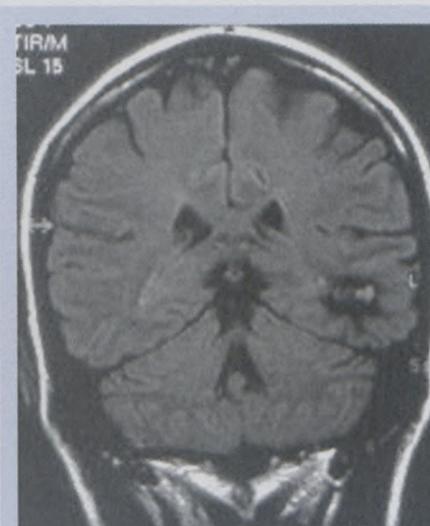


Fig. 3d. Same lesion, coronal FLAIR image, 21 months later. Note the change in appearance with thickening of the hypointense periphery due to further haemosiderin deposition. The appearance now corresponds to a Zabramski type III cavernoma.

ma.^{52,56} No enlarged feeding arteries or draining veins are seen except in cases where there is an associated DVA (Figs 3e, 3f). No oedema or mass effect are seen unless there has been a recent haemorrhage⁴⁰ (Fig. 2). Zabramski *et al.*⁹ in their paper on familial CMs proposed a classification of CMs on the basis of MR signal characteristics. Type 1 lesions showed evidence of subacute haemorrhage with a hyperintense

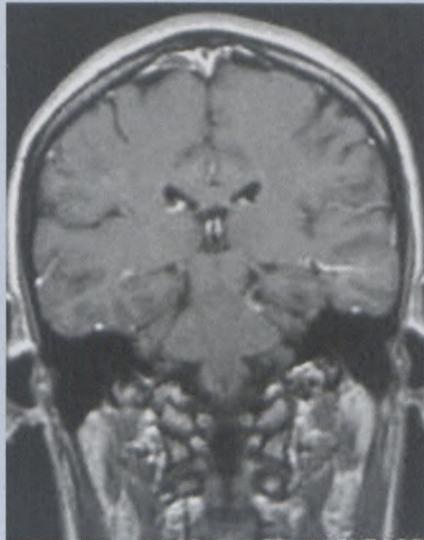


Fig. 3e. Same lesion, coronal T1 gadolinium enhanced image showing a small associated developmental venous anomaly (DVA).

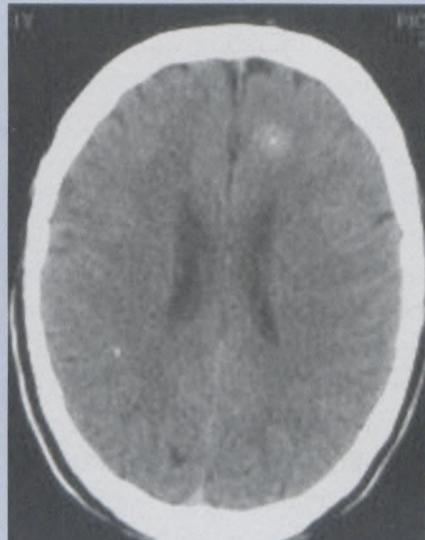


Fig. 4a. Unenhanced axial CT image showing a moderately hyperintense lesion containing calcification in the left frontal lobe.

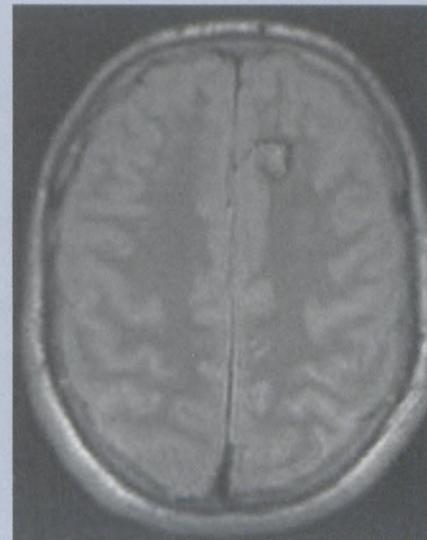


Fig. 4c. Axial FLAIR MR image showing the typical MR appearance of the same cavernoma.



Fig. 3f. The venous return phase of a selective left internal carotid arteriogram showing the associated DVA.

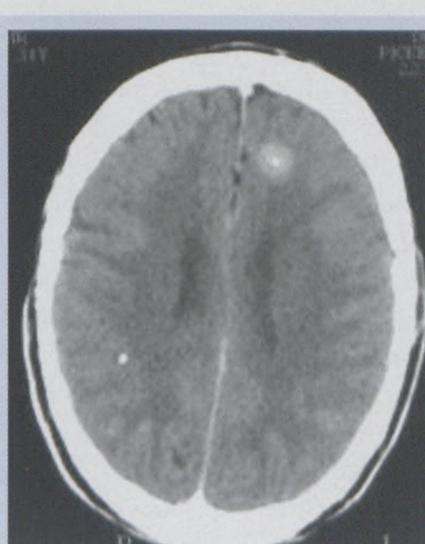


Fig. 4b. Following contrast administration the lesion shows slight enhancement.

core on T1-weighted images and either a hyperintense or hypointense appearance to the core with a hypointense rim on T2-weighted images (Fig. 2). Lesions were considered subacute (or type I) until the T1 hyperintensity became iso- or hypointense with the surrounding brain.

Type II lesions have a reticulated, mixed signal core due to loculated areas of thrombosis and haemorrhage of varying age (the

'popcorn-like' core) surrounded by the haemosiderin ring (Figs 3a, 4c). CT of these lesions may show areas of stippled calcification. This appearance corresponds to the 'classic' description of CMs in the general neuroradiological literature. Type III lesions showed chronic areas of haemorrhage with an iso- or hyperintense core on T1-weighted images and diffuse

hypointensity on T2-weighted images (Fig 3d). The marked T2 hypointensity is due to a large quantity of haemosiderin in and around the CM. Type IV lesions are poorly visualised on both T1 and T2-weighted sequences being very small (Fig. 7). They are really only visualised as tiny punctate hypointensities on gradient echo sequences. There is a debate as to whether these lesions represent minute CMs or a transitional type of lesion. Two such lesions have in fact been verified pathologically as capillary telangiectasias.⁷ Zambraski *et al.*⁹ found that most clinically symptomatic lesions were type I or type II (93%). Labauge *et al.*⁵¹ found in their series that the haemorrhagic risk was greater in type I lesions. Willinsky *et al.*⁴² found, however, that this classification system was not useful in predicting future bleeds in their study. They did note that mass effect and oedema were found most often with type I lesions. Follow-up of individual lesions often shows increase

in size due to intralesional haemorrhage and decrease in size with increased T2 hypointensity during periods of quiescence or resolution of haemorrhage. However, not all type I or type II lesions were seen to progress to a type III appearance over time in the above studies and as type III lesions can also bleed it is possible that the different types represent either a spectrum or continuum of histological types rather than a temporal progression of lesions.^{7,51}

Extra-axial and spinal cavernomas

Extra-axial CMs are uncommon lesions found most frequently related to the cavernous sinus and middle cranial fossa.^{57-61,62,63} Others have been reported in the torcula and petrosal sinus and involving the optic chiasm, sella turcica and chiasmatic cistern.⁶⁴⁻⁶⁶ Cranial nerve lesions have also been described⁶⁷⁻⁷⁰ affecting the II nd, III rd, VII th and VIII th nerves. Most extra-axial lesions affect the cavernous sinus and expand the sinus. Histologically they are identical to intra-axial CMs but have very different clinical presentations, natural history and imaging features. Ninety-four per cent of cases are women, with a large number of Japanese origin.⁵⁹ These lesions are also termed cavernous haemangiomas, which is a misnomer as they are not tumours although they are locally aggressive due to mass effect. Early symptoms of cavernous sinus CMs include retro-orbital pain, headaches and symptoms related to the cranial nerves supplying the extra-ocular muscles.

Other signs and symptoms include visual deterioration, exophthalmos, endocrine disturbances and trigeminal neuralgia.

Haemorrhage is much less common. Although histologically identical to parenchymal CMs, the extra-axial ones tend to show more homogeneous density or signal intensity and contrast enhancement on CT and MR imaging respectively. They closely resemble meningiomas or schwannomas on sectional imaging but are angiographically occult. The lesions are difficult to treat surgically because of excessive bleeding, with a significantly high morbidity and mortality.^{59,61} Spinal cord lesions are rare. Patients range in age from 12 to 87 years, with a 2:1 female preponderance.⁷¹ Ojemann *et al.*⁷² and Ogilvy *et al.*⁷³ reviewed 36 patients with 37 lesions in 1991 and found that 69% of cases were female, 8% occurred at the cervicomedullary junction, 32% in the cervical cord, 54% in the thoracic region, 3% in the lumbar cord and 3% in the conus. They described four clinical categories of symptoms.

1. Recurrent episodes of clinical deterioration followed by remission. The episodes would last hours to days and the interval between events from months to years.

2. Slowly progressive neurological deterioration over several years.

3. Acute onset of symptoms followed by rapid progressive worsening over days.

4. Acute onset of symptoms followed by a slow progressive neurological decline over weeks to months.

Intramedullary CMs vary in size

from a few millimetres to several centimetres (Figs 5, 6). Surgery is advocated for symptomatic lesions with reported outcome showing improvement in most patients.^{71,72,75,76}

Co-existing brain and spinal



Fig. 5a. Sagittal T2-weighted MR image of the cervical cord showing a large intramedullary cavernoma. Note the darker areas of hemosiderin deposition.



Fig. 5b. Corresponding sagittal T1-weighted image. Note the areas of bright signal indicating blood products at different stages of breakdown.

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References: 1. Gadovist® Package Insert, Schering. 2. Benner T, Tombach BT, Synnott JP, Schuierer GT, Reimer P†, Greens V**, Østergaard L, Sørensen AG. Human Cerebral Blood Flow Maps Improve with Higher Concentration of Contrast Agent. MGH-NMR Center, Charlestown, MA, USA; †Dept. of Clinical Radiology, Westfalian Wilhelms-University, Münster, Germany; **Schering AG, Berlin, Germany.

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Fig. 6a. Sagittal T1-weighted MR image showing a cavernoma within the upper cervical cord.



Fig. 6b. Same lesion, sagittal T2-weighted MR image.



Fig. 6c. Same lesion, coronal T2-weighted MR image.

cord CMs are described but rare.^{72,74} Extra-axial spinal lesions can occasionally be found in the intradural extramedullary space, the spinal epidural space and even in the vertebral bodies.⁷⁵ They are also extremely difficult to resect due to excessive bleeding.

Clinical features

CMs occur with an approximately equal incidence in males

and females and in all ages from neonate to 84 years.^{36,38,77,78} Most patients with CMs present in their second to fourth decades. There is a very strong female preponderance in extra-axial CMs⁵⁹ and a 2:1 female preponderance in spinal cord CMs.

The commonest presenting feature in brain CMs is seizure, occurring in 23 - 52% of patients.^{9,37,39,41-43,79} Headache occurs in between 6% and 30% of cases.^{9,16,37,39,43,79} Focal neurological deficits occur in between 21% and 45% of cases.^{9,37,39,42,43,79} Often combinations of symptoms are found in the same patient. Presentation as a result of documented haemorrhage was seen in between 9% and 56% of cases.^{16,37,39,41-43} The issue of haemorrhage, as mentioned, is somewhat controversial as CMs grow because of small intralesional bleeds and thus not all bleeds would be documented by imaging. Only large intralesional or extralesional ones would become clinically apparent so as to warrant imaging. Symptoms may also be caused by the occurrence of spontaneous

thrombosis within the lesion. Seizures are thought to be due to perilesional parenchymal irritation by the peripheral haemosiderin accumulation and perilesional gliosis. Progressive neurological deficits are due to slow growth within a lesion, probably due to small repeat haemorrhages and thrombosis. A rare presenting feature of a CM is that of subarachnoid haemorrhage.⁸⁰ Brainstem CMs can present with facial pain/hypermesthesia, hemiparesis, ophthalmoplegia, severe headaches, hemisensory deficit, VII, VIII, IV, X, XI, XII nerve deficits, ataxia, dysmetria or Parinaud's syndrome.⁸¹

Differential diagnosis

Any rounded lesion exhibiting T1 shortening can mimic a CM. This T1 shortening can be due to subacute haemorrhage (methaemoglobin), high protein content or fat.⁴⁰ The differential diagnoses of CMs are listed in Table II.

Management

There are three possible methods of treating CMs of the CNS, namely surgery, radiation therapy (radiosurgery) and conservative treatment. As with any medical therapy the risk of complications associated with the treatment must not be greater than those associated with the natural history of the disease. It is therefore vital to understand the natural history of any disease as fully as possible before contemplating the need for and possible method of any therapeutic measure. With CMs other factors to be considered include the age of the patient, number and location of

Table II. Differential diagnosis of CMs

Solitary haemorrhagic lesions

Isolated spontaneous haematoma (subacute to chronic)

Neoplasm

- Primary (glioblastoma, oligodendroglioma, ependymoma)
- Solitary metastasis, especially haemorrhagic

Multiple haemorrhagic lesions

Metastases — especially haemorrhagic metastases (bronchogenic CA, choriocarcinoma, renal cell CA, thyroid CA)

Melanotic melanoma

Amyloid angiopathy

Sequelae of diffuse axonal injury

Treated at prior infection

- Toxoplasmosis
- Cysticercosis

Multiple haemorrhages associated with blood dyscrasia

- Disseminated intravascular coagulopathy (DIC)
- Leukaemia

Fatty mass

Lipoma

- Dermoid
- Lipomatous meningioma

(From: Hallam DK, Russel EJ. Imaging of angiographically occult cerebral vascular malformations. *Neuroimag Clin North Am* 1998; 8: 323-347.)³⁹

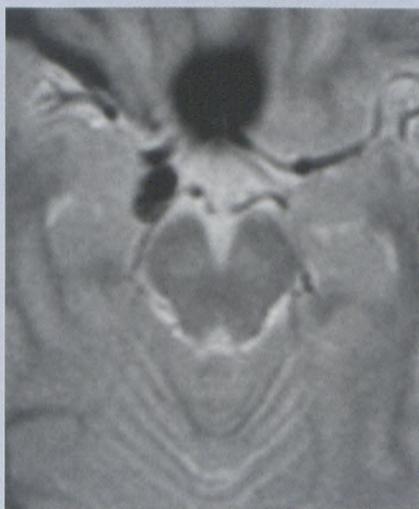


Fig. 7a. Axial T2 gradient echo MR sequence in a young woman presenting with epilepsy. A small hypointense focus is seen in the right uncus.

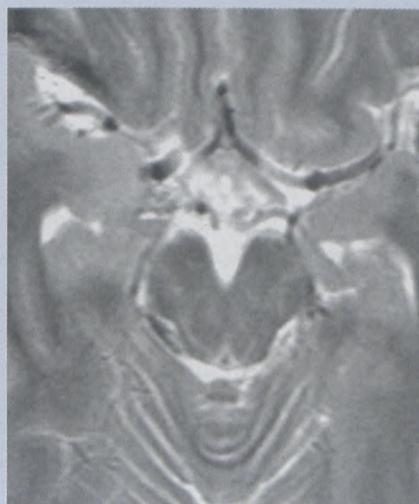


Fig. 7b. Axial T2 fast spin echo sequence. The same lesion is barely seen as a small hyperintensity with a relatively hypointense margin.

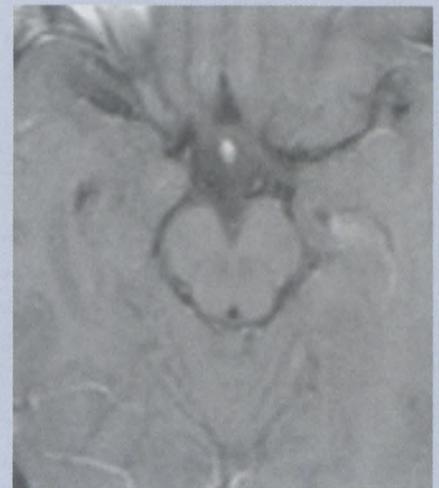


Fig. 7c. The lesion is also hardly visible on the gadolinium-enhanced T1 image. This cavernoma is bordering on a Zabramski type IV.



Fig. 7d. Unenhanced axial CT at the same level done after the MR scan shows the lesion as mildly hyperintense, possibly in part due to retained gadolinium enhancement.

the lesions, familial history and overall risk of operative treatment.⁸²

Well-established indications for surgery include medically intractable seizures, recurrent overt

haemorrhage and severe focal or progressive neurological deficits unless the location is associated with an unacceptably high surgical risk.^{37,38,72,83} Further potential but also relatively controversial indica-

tions for surgical resection include patients with a single haemorrhage from a CM, onset of seizures or infrequent seizures or patient insistence.⁷² Robinson *et al.*⁴⁵ recommended surgery for any CM that manifests with overt haemorrhage. Scott *et al.*⁸⁴ and Fortuna *et al.*⁸⁵ recommended surgery for children with CMs who have bled in the past. Robinson *et al.*³⁸ and Huhn *et al.*⁸⁶ recommended surgical excision of any accessible CM in a young

woman contemplating pregnancy. For women diagnosed with a CM during pregnancy, normal vaginal delivery can probably be recommended based on the low-flow characteristics of the CM.⁸²

Surgical excision of superficial CMs generally carries good operative outcomes with low mortality and morbidity rates of 0 - 6% (mean 3%) and 0 - 12% (mean 3.6%) respectively.⁸² Review of the seizure-related outcomes suggest that 75 - 100% of patients with 5 seizures or less or less than a 12-month history of seizures were found to be seizure-free after removal of a CM compared with 50 - 62.5% of patients with more than 5 seizures or a seizure history of more than 1 year pre-operatively.⁸³ The suggestion made is that early surgery rather than medical treatment with anticonvulsants may be preferable for patients presenting with seizures. Lesionectomy is suggested as the early surgical technique, with more extensive excision reserved for patients with a longer history or greater number of seizures associated with CMs.

The surgical management of deep-seated CMs (basal ganglia, thalami, IIIrd ventricle) is associated with a significantly higher mortality and morbidity of 0 - 12.5% (mean 5%) and 6 - 67% (mean 22%) respectively.⁸² Surgery for those lesions is recommended when there are recurrent episodes of haemorrhage or progressive neurological deficits. Brainstem CMs carry a greater risk still for surgical intervention based on the extreme eloquence of the brainstem itself, with mortality rates of 0 - 6%, transient complication rates

of 25 - 70% and permanent complication rates of up to 25%.⁸³ Surgical management of brainstem CMs is recommended for symptomatic lesions abutting the pial surface.^{47,87} Any DVAs associated with CMs must always be preserved during surgical resection. Surgical resection of CMs done solely to prevent significant haemorrhage represents a highly controversial indication. Here the known natural history must be carefully weighed against the patient's neurological status and age, location of the lesion and risk of operative approach.⁸²

Spinal cord CMs are rare and the number of reported series is small. Ogilvy *et al.* reported 36 cases of resected intramedullary CMs.⁸⁸ Following surgery 70% showed improvement, 11% showed no change, 17% showed worsening and there was 1 death (2.8%). Spetzger *et al.*⁸⁹ found 88% of their patients were normal or had improved neurological status following spinal CM resection. Although some authors have reported transient or permanent exacerbation of pre-existing neurological deficits after surgery, operative intervention does seem to have resulted in long-term improvement or stabilisation of function in the majority of cases.⁸³

Stereotactic radiosurgery is another treatment modality to be considered for CMs. It has been used to treat high-risk lesions, particularly deep-seated and brainstem lesions. Kondziolka *et al.*⁹⁰ in a study of the effects of radiation treatment on haemorrhagic risk concluded that stereotactic radiosurgery is an effective treatment for

deeply located CMs with a history of two or more prior haemorrhages (high-risk, authors' definition) or where the haemorrhagic risk reduction more than justifies the side-effects (26% neurological worsening of which three-quarters were transient) and costs of the radiosurgery in patients who had suffered from two or more haemorrhages. The morbidity at radiosurgery is considered too high to justify its use in CMs that have never bled.⁹¹ In a more recent report by the same group⁹² the authors concluded that in patients with symptomatic imaging-confirmed haemorrhages from CMs at high risk for surgical resection, gamma knife radiosurgery conferred a reduction in the risk of haemorrhage which was only significant after 2 years post treatment (12.3% annual haemorrhage rate for the first 2 years post treatment followed by a risk of 0.76% per year thereafter). They also recommended that treatment after one major haemorrhage be considered in selected younger patients. Stereotactically-guided radiofrequency ablation is yet another modality currently under investigation for the treatment of selected cerebral CMs.

In familial/multiple CMs the recommendation is that surgery be considered only for lesions that produce repetitive or progressive symptoms and that prophylactic resection of asymptomatic lesions is not recommended.⁹

Almost all asymptomatic lesions can be observed indefinitely for haemorrhage or development of symptoms. Another group that can simply be followed up are those with symptomatic lesions in deep

or eloquent areas where the risks of surgery are high and where there is no recurrent haemorrhage or increasing neurological deficits.⁷² There are still no clear guidelines about MRI follow-up intervals for patients who are to be observed. Ojemann *et al.* have recommended 6-month interval studies for up to 2 years and longer thereafter, Huhn *et al.*⁸⁶ recommended 6 - 12-monthly repeat scans.

Conclusion

It is obvious that our understanding of the pathogenesis and natural history of CNS CMs is far from complete. In conclusion let us summarise all the pertinent points concerning CMs discussed above. The classical four category patho-anatomical classification of cerebral vascular malformations has recently become complicated by the recognition of mixed and transitional malformation types. CMs are low-flow lesions which 'grow' by recurrent episodes of intralesional haemorrhage and thrombosis. They may be found in close anatomical association with DVAs and may share a common pathogenesis with capillary telangiectasias. CMs can be sporadic or familial. Familial ones tend to be multiple. A genetic defect has been identified in the familial form. CMs are dynamic lesions and some have been identified as arising *de novo* in children and adults. Clinically significant events are due to haemorrhage or thrombosis within the lesions, mass effect or parenchymal irritation by the surrounding hemosiderin ring. Not all intralesional haemorrhages produce clinical effects, leading to con-

fusion about the significance of reported haemorrhagic rates in the literature. The rate of rebleeding appears greater in patients who have already had one or more previous documented bleeds. The haemorrhagic and event rates are higher in deep-seated (diencephalic, basal ganglia, cerebellar nuclei) and brainstem lesions than in superficial ones. Some studies suggest a higher risk of bleeding during pregnancy. The risk of haemorrhage is higher in familial (multiple) lesions. CMs are low-flow lesions and thus angiographically occult. MRI is the preferred imaging modality for diagnosis and follow-up. The MR characteristics are fairly typical and have been characterised into four morphological types although there is some debate as to whether these represent different stages of development or different pathological entities. The radiological differential diagnosis includes any lesion that can haemorrhage or contain melanin, calcium or fat.

Extra-axial CMs are rare and can mimic skull base tumours such as meningiomas and schwannomas in both clinical presentation and imaging features. Spinal lesions are also rare and can exhibit various modes of presentation from acute to slowly progressive. Brain CMs can present clinically with seizures, headaches and acute or slowly progressive neurological deficits. Treatment options are primarily surgical, with good clinical outcomes and low rates of mortality and morbidity reported for symptomatic superficial lesions but poorer results for deep-seated and brainstem ones. Stereotactic radio-

surgery appears to offer protection against haemorrhage for high-risk lesions but only beyond 2 years after treatment. Evidence suggests that early surgery for CMs presenting with seizures may lead to a better long-term seizure-related outcome. There is no justification for prophylactic surgery in asymptomatic lesions. Regular radiographic and clinical follow-up is required in asymptomatic lesions regardless of location, and in deep-seated symptomatic ones in high-risk or eloquent areas of the brain.

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