Cerebral Cavernous Malformation (CCM)

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Abstract: A cavernous malformation is relatively rare in the brain. The dilated capillaries conglomerate together to form a nidus and the cavernoma (CM) within the brain. Usually, a cavernoma is silent, but it can present with bleeding and a seizure. It can occur in any area of the brain, but it has a higher tendency in the brainstem, deep structure of the brain and temporal lobe. MRI GRE and SW images are diagnostic for a CM. A symptomatic or ruptured CM demands surgical removal. In this chapter, the pathology, distribution and management of cavernomas are mentioned.

Abbreviations

CCM	cerebral cavernous malformation	CM	cavernous malformation
CT	computed tomography	DT	diffusion tensor
DSA	digital subtraction angiogram	DVA	dural venous anomaly
fMRI	functional magnetic resonance imaging	GRE	gradient recall echo
MRI	magnetic resonance	MVM	mixed vascular malformation
SEZ	safe entry zone	SW	susceptibility-weighted

1. Introduction

A cerebral cavernous malformations is one variety of an arteriovenous malformation where the dilated capillaries conglomerate together to form a nidus and the cavernoma (CM) within the brain. Usually, a cavernoma is silent, but it can manifest when there is bleeding or when present with a seizure. It can occur in any area of the brain but has a higher tendency in the brainstem, deep structure of the brain and temporal lobe (Greenberg 2010).

2. Natural History of Cavernoma

The incidence of a CCM varies from 0.17 to 0.56 per 100,000 per population per year (Al-Shahi et al. 2003). A CCM frequently presents in the fourth and fifth decade, and there is small female preponderance (58%). Roughly 50% of CCM patients remain asymptomatic, whereas about 25% present with single or multiple attacks of seizure. Additionally, patients can present with either hemorrhage (Figure 1A) (~12%) or focal neurological deficits (~15%) (Salman et al. 2012). Overall, the annual risk of a first-time cavernoma-related hemorrhage is low (0.4–0.6% per year) and the risk of subsequent hemorrhage is much higher (3.8–23% per year). The risk gradually decreases over time. It can present as multiple cavernoma (cavernomatosis) (Figure 1B) and can be familial.

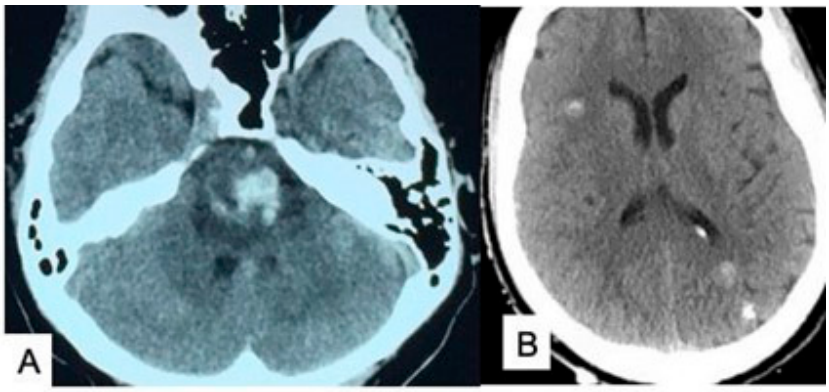

Figure 1. (**A**) CT scan showing bleeding in the pontine cavernoma. (**B**) CT scan showing multiple cavernoma. Source: Figure by authors.

3. Location

The distribution (locations) of CMs in a published series is shown in Table 1.

Table 1. Locations of cavernomas.

Location	Cavernoma	Percentage %
Cerebrum	84	69.4
Occipital	4	
Frontal	36	
Parietal	16	
Temporal	28	
Brainstem	17	14.0
Medulla	1	
Midbrain	2	
Pontomesencephalon	4	
Pons	8	
Pontomedullary	2	
Cerebellum	8	6.6
Cranial nerves	4	3.3
Spinal cord	8	6.6
Cervical	3	
Cervicomedullary	2	
Lumbar	1	
Thoracic	2	
Total CMs	121	99.9

Source: Authors' compilation based on data from Kirollos et al. (2019).

4. Developmental Venous Anomaly (DVA)

Developmental venous abnormalities (DVAs), also called venous malformations or venous angiomas, are frequently related to cavernomas. A DVA is a vascular abnormality that does not create any clinical signs on its own. In the proximity of a DVA, at least 40% of isolated cavernomas can occur.

The caput medusae indication of veins emptying into a solitary bigger collecting vein that then drains into either a dural venous sinus or a deep ependymal vein characterizes a DVA (Figure 2). The image has been compared to that of a palm tree. DVAs, on the other hand, can be found in any place, draining either superficially or deeply.

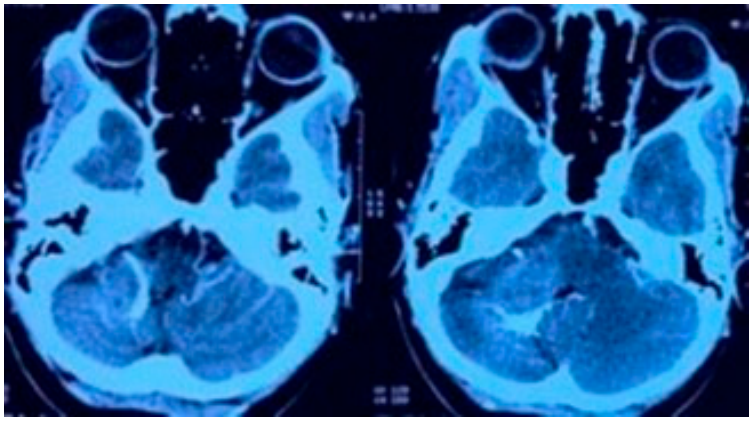

Figure 2. CT scan showing deep venous anomalies (DVAs), along with a cavernoma. Source: Figure by authors.

4.1. Associations

With the exception of the blue rubber bleb nevus syndrome, lesions are generally isolated (75%);

Mixed vascular malformations are found in 20% of cases (range: 8–33%) and are related to cavernous malformations (MVM)s;

Malformations of the venous system in the neck and head.

4.2. Classification Based on the Location

The most common locations (Figure 3) are as follows:

Fronto-parietal CM (36–64%), generally draining toward the lateral ventricle's frontal horn (Figure 3A,B);
Cerebellar hemispheric CM (14–27%), draining toward the 4th ventricle (Figure 3C);
Brainstem cavernoma (Figure 3D);
Spinal cavernoma (Figure 4).

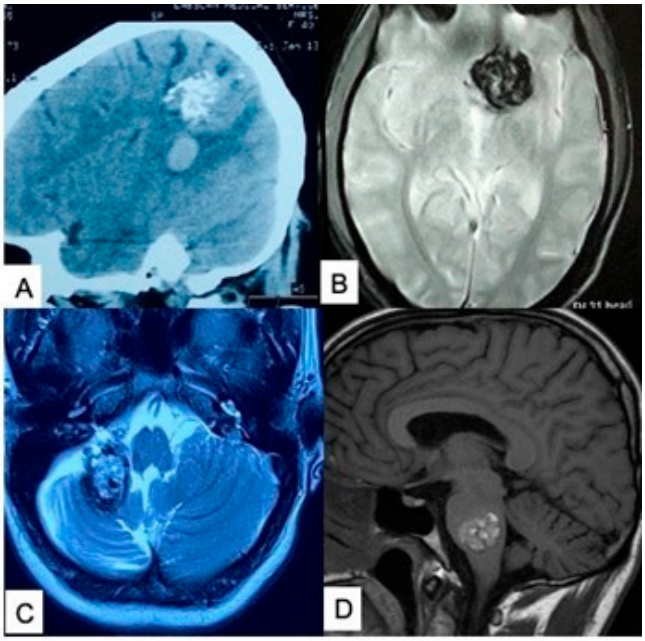

Figure 3. (**A**) CT scan showing a parietal cavernoma. (**B**) MRI showing a left basal frontal cavernoma. (**C**) MRI showing an rt cerebellar cavernoma. (**D**) MRI showing a pontine cavernoma. Source: Figure by authors.

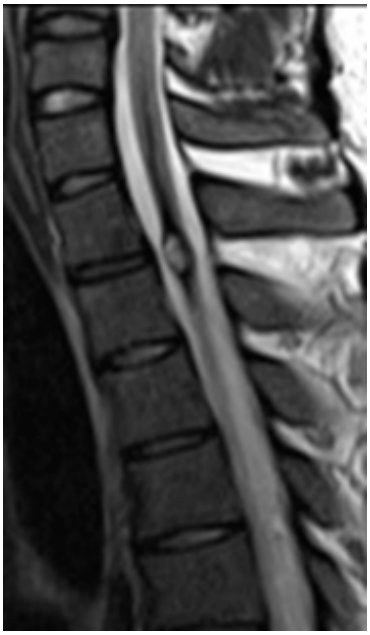

Figure 4. MRI showing a cervical spinal cord cavernoma. Source: Figure by authors.

5. Radiological Features of Cavernomas

State-of-the-art brain neuro-imaging techniques (called diffusion tensor tractography (DTI), gradient echo (GRE), as well as susceptibility-weighted (SW) sequences are used to permit for computational and noninvasive management planning (Table 2, Figure 5). Most cavernomas solely warrant observation with routine brain imaging to look for changes, recent bleeding ("hemorrhage") or new cavernoma/s.

Table 2. Imaging appearance of CMs.

CT	MRI	Angiography
Hyperdense	T2 bright areas with the susceptibility effect	Occult
	T1 can have bright areas, no appreciable enhancement, small adjacent DVA, if present strengthens the diagnosis	

Source: Table by authors.

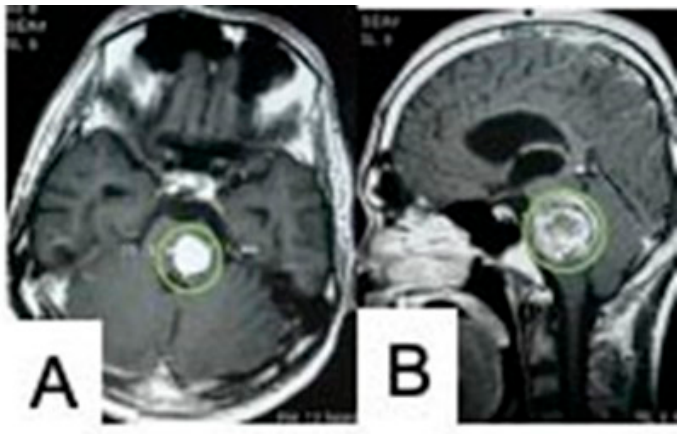

Figure 5. MRI of brain axial (**A**) and sagital (**B**) view showing a CM in the posterolateral pons with a halo sign. Source: Figure by authors.

A "popcorn" lesion is characterized by a center with a mixed signal in T1- and T2-weighted scans, that is bordered by a full hemosiderin ring with decreased signal intensity in T2W images. The severity of the hemorrhage affects the appearance of a CM. CMs have a tendency to expand with time. The common coexistence of a CM and DVA is thought to be the result of repetitive minor hemorrhages (D'Souza and Vadera 2022).

a. Zabramski classification of cerebral cavernous malformations (Zabramski et al. 1994):

Type I: Subacute hemorrhage. T1—hyperintense. T2—hyper- or hypointense.
Type II: The most common type—classic "popcorn" appearance. T1—heterogenous signal intensity at the center.
Type III: Chronic hemorrhage. T1—isointense to hypointense at the center.
Type IV: Numerous punctate micro-hemorrhages. T1—Hard to identify.

b. T 1 (Figure 6A): Variable signal based on the duration of the hemorrhage; Minimum fluid–fluid levels may be seen.

c. T 2 (Figure 6B):

- Rim is hypointense;
- Variable internal signal based on the duration of the blood products;
- In a recent hemorrhage, an adjacent edema may be observed.

d. Gradient Recalled Echo (GRE) MRI:
GRE T2/SWI (Figure 6C)

- Blooming is prominent;
- Helpful for finding tiny lesions that would otherwise go undetected by traditional spin echo sequences, particularly in individuals with familial or multiple cavernous malformations.

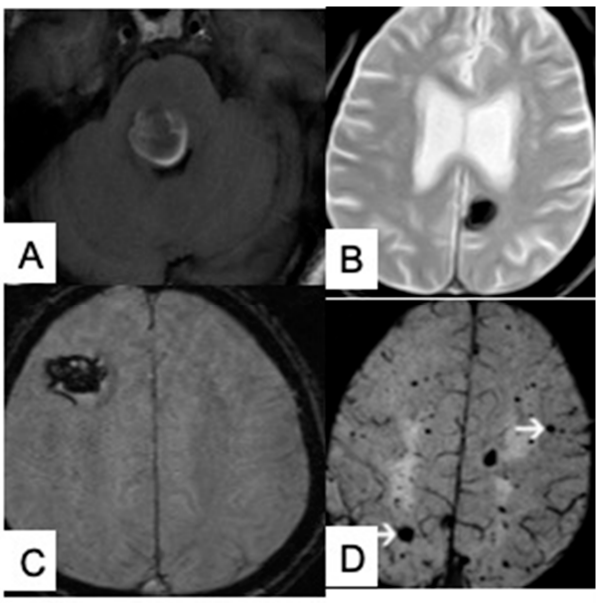

Figure 6. (**A**) MRI T1W image showing a high-signal hemosiderin ring. (**B**) MRI T2W image showing a hypointense lesion. (**C**) SW MRI showing an rt frontal cavernoma. (**D**) MRI showing multiple cavernomas. Source: Figure by authors.

With its capacity to show hemosiderin-filled cerebral parenchyma with a highly identifiable low intensity, a GRE MRI scan is a significant tool for diagnosing CMs. Traditional MRIs reveal an average of five lesions per patient in studies on familial CMs, whereas a T2W GRE MRI discovers a mean of sixteen pathologies per person. A GRE MRI is capable of not only identifying all existing lesions, but also delineating them more accurately. While a GRE MRI provides various advantages, it is vital to keep in mind that it increases the relative size of the CM. GRE MR imaging may also reveal multifocal CMs in older persons with hypertension, as well as a history of stroke, but these should not be confused with familial CMs; hypertensive angiopathy causes them.

e. Susceptibility-Weighted MR Imaging (Figure 6D): Since it reliably distinguishes deoxyhemoglobin and hemosiderin, susceptibility-weighted (SW) scanning is highly useful for identifying CMs. SW imaging is also the only approach for differentiating CMs and telangiectasias that do not bleed. It has been demonstrated to outline CMs more precisely, as well as discover additional CMs that are not seen with traditional imaging modalities.
f. Diffusion Tensor (DT) Imaging (Figure 7): Even though CMs are deeply placed in certain areas, DTI and fMRI are utilized preoperatively for better visualization of the lesions and nearby parenchyma in terms of improving the surgical success. The surgeon can see the white matter tracts that regularly pass over the hemosiderin rim of the CM using DT tractography. When removing CMs in the brain, an fMRI captures activity-dependent variations in cerebral blood flow, which is highly beneficial.

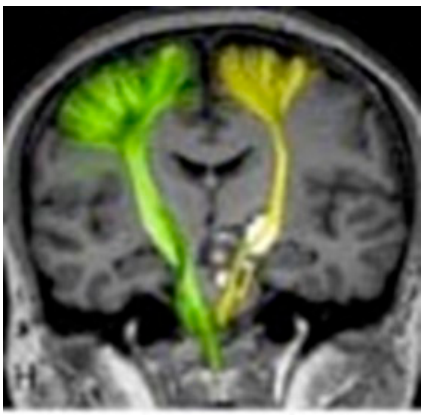

Figure 7. MR showing tractography in a cavernoma patient. Source: Figure by authors.

g. Angiography (DSA): CMs are angiographically occult and they do not have arteriovenous shunting.
h. CT scan of brain (Figure 8)

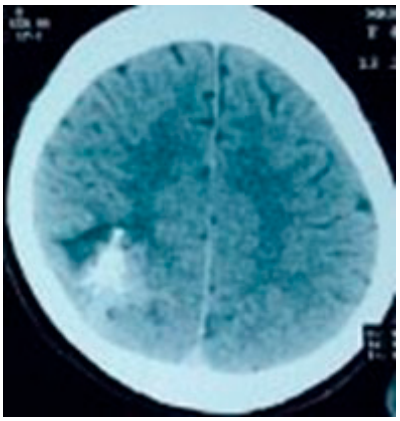

Figure 8. CT scan showing a calcified cavernoma. Source: Figure by authors.

6. Clinical Presentation

Seizures, headaches, neurologic deficits and asymptomatic presence are the four major kinds of clinical presentation. The most common presenting symptom is seizure, which affects 35–55% of patients. Several symptoms are found in many people. A bleed into the neighboring brain parenchyma occurs in some patients in each of the clinical groups. The hemorrhages are normally tiny, but they might be significant on rare occasions, causing the patient to rapidly deteriorate (Greenberg 2010).

7. Treatment

7.1. Microsurgery

Indications of surgery include a ruptured CM, CM with a mass affect, cranial nerve palsy and epilepsy. For a ruptured and symptomatic CM, it is the standard treatment (Greenberg 2010; D'Souza and Vadera 2022; Spetzler et al. 2020; Spetzler et al. 2017; Macdonald 2008; Mouchtouris et al. 2015).

7.1.1. Microsurgical Treatment of a Brainstem CM: Surgical Approaches

a. Brainstem anatomy: The diencephalon, midbrain, pons and medulla oblongata are the four components of the brainstem, which have an ectodermal origin. The brainstem links the cerebral hemispheres well with the spinal cord as well as the cerebellum. It is responsible for mandatory vital functions like respiration, cardiac pulsation, blood pressure, consciousness control and sleep. White and gray matter coexist in the brainstem.

Although complex, the internal anatomy of the brainstem is structured in three laminae (tectum, tegmentum and basis) that run the length of the brainstem (Spetzler et al. 2020).

b. Approaches to CMs in the brainstem

Microsurgical approaches to brain stem CMs are shown in Table 3.

c. Approaches to the midbrain
Supra cerebellar infratentorial approaches:

1. Midline;
2. Lateral;
3. Far lateral:

- Supracerebellar transtentorial approach;
- Occipital transtentorial approach.

The dorsal midbrain, pineal region and upper pons can also be approached by the occipital transtentorial approach:

d. Ventral midbrain approaches (shown Table 4);

e. For lateral midbrain and upper pons (shown Table 4).

Table 3. Surgical approaches to CMs in the brainstem.

Lesion location	Anterior	Lateral	Posterior
Midbrain	Pterional, orbitozygomatic (OZ) subtemporal	Lateral infratentorial supracerebellar (LIS)	LIS
Pons	Pterional, OZ subtemporal	Far lateral suboccipital retrosigmoid	Median suboccipital/4th ventricular
Medulla	Subtemporal, far lateral suboccipital transcondylar	Lateral suboccipital retrosigmoid	Median suboccipital/4th ventricular

Source: Authors' compilation based on data from Spetzler et al. (2017).

7.1.2. Safe Entry Zone (SEZ) to the Brainstem

A. Pons

Safe entry zones (SEZ) to the Brainstem are shown in Figure 9, and in pons are shown in Table 4.

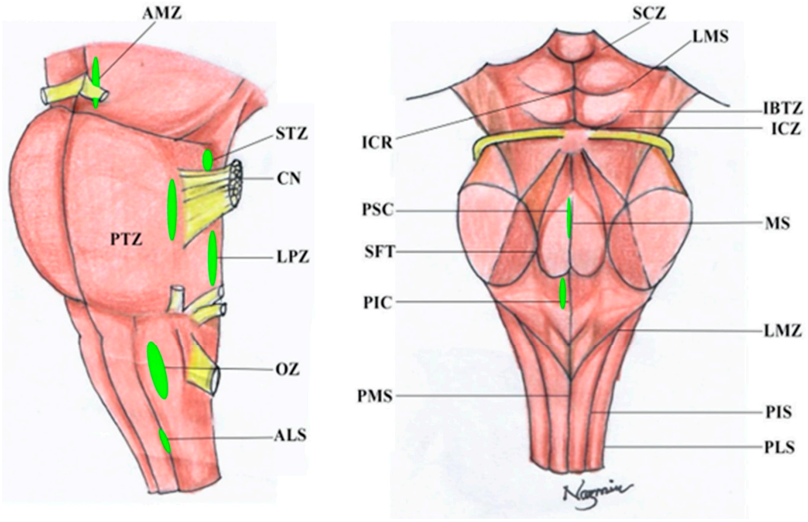

Figure 9. Principles of SEZs to the brainstem. The colored ellipses represent areas where petit neurotomies can be carried out to avoid minuscule perforators, prime nerve tracts and nuclei. (**Left**) Antero-lateral surface of the brainstem demonstrating some anterior and anterolateral SEZs. (**Right**) View of the dorsal surface of the brainstem demonstrating SEZs on the surface of the quadrigeminal plate, floor of the fourth ventricle. (ALS—anterolateral sulcus; AMZ—anterior mesencephalic zone; CN—cranial nerve; IBTZ—inferior brachium triangular zone; ICR—intercollicular region; ICZ—infracollicular zone; LMS—lateral mesencephalic sulcus; LMZ—lateral medullary zone; LPZ—lateral pontine zone; MS—median sulcus of fourth ventricle; OZ—olivary zone; PIC—paramedian infracollicular; PIS—posterior intermediatesulcus; PLS—posterior lateral sulcus; PMS—posterior median sulcus; PSC—paramedian supracollicular; PTZ—peritrieminal zone; SCZ—supracollicular zone; SFT—superior fovea triangle; STZ—supratigeminal zone). Source: Figure by authors.

Table 4. Pontine SEZ.

Approach	SEZ
Subtemporal transtentorial	Supratrigeminal
Anterior petrosectomy	Supratrigeminal, peritrigeminal
Suboccipital telovelar	Median sulcus of the 4th ventricle, paramedian infracollicular, superior fovea triangular
Retrosigmoid	Supratrigeminal, peritrigeminal lateral pontine
Retrolabrynthine	Supratrigeminal, peritrigeminal lateral pontine

Source: Authors' compilation based on data from Spetzler et al. (2017).

In the posterior pons/floor of the 4th ventricle, safe areas are the suprafacial triangle and infrafacial triangle (Spetzler et al. 2017). These areas are approached by a suboccipital teloveloar approach.

In the lateral pons, the safe areas are as follows:

- Supratrigeminal area;
- Peritrigeminal area;
- Infratrigeminal area (between 5th and 7th nerve);

The lateral pontine zone can be reached by a retrosigmoid approach.

To reach betel, more wide exposure is required and then we need to utilize a presigmoid approach.

B. Medulla Oblongata

Medullary safe entry zone: In the anterior medulla, the safe zone is the olivary area. The olive is a small elevation formed by the location of the inferior olivary nucleus.

Olivary zone: The olivary zone can be reached by the far lateral approach.

Dorsal medullary safe zone: The dorsal lateral medullary zone is a posterior midline sulcus and laterally medullary zone, respectively. This area is approached by midline suboccipital craniotomy.

7.2. Conservative Treatment

Conservative treatment is utilized for incidental CMs.

7.3. Stereotactic Radiosurgery

Stereotactic radiosurgery is usually not recommended.

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