Cerebral cavernous malformation prognosis

- Cavernoma of the left ventral striatum, anatomical and microsurgical implications of the ipsilateral transcallosal transrostral pathway
- The role of DTI in surgical management of brainstem cavernous malformations: A meta-analysis of 4159 cases
- Predictors of postoperative epileptic seizures after microsurgical treatment in supratentorial single cerebral cavernous malformations: a retrospective study
- Magnetic resonance-guided laser interstitial thermal therapy (MRgLITT) for paediatric intracranial cavernous malformations: case series and review of the literature
- Optimizing gamma knife radiosurgery for cerebral cavernous malformation: Analysis of 54 patients treated at our university center
- Management, and outcomes of pediatric cerebral cavernous malformations across age groups: A systematic review and meta-analysis of the literature
- Natural history, management, and outcomes of cerebellar cavernous malformations: A retrospective study of 130 patients
- A 15-year follow-up of permanent intraoperative internal carotid artery occlusion for hemostasis in a giant cavernous sinus hemangioma: a case report

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Cerebral cavernous malformation (CCM) prognosis varies widely depending on factors such as lesion size, location, prior hemorrhage, genetic predisposition, and associated symptoms.

General Prognosis

- Many CCMs remain asymptomatic and are discovered incidentally. In these cases, the long-term prognosis is generally favorable.

- Symptomatic CCMs (those presenting with seizures, focal neurological deficits, or hemorrhage) have a more variable prognosis depending on lesion behavior.

Risk of Hemorrhage

- The annual risk of hemorrhage for **sporadic CCMs** is around **0.5–1%** per lesion per year.

- If a CCM has **previously hemorrhaged**, the risk increases significantly to **4–5% per year** in the first few years post-hemorrhage.

- Familial CCMs (associated with mutations in genes like **CCM1, CCM2, and CCM3**) have a higher tendency for multiple lesions and recurrent hemorrhages.

Neurological Deficits

- CCMs located in **eloquent brain areas (brainstem, thalamus, spinal cord)** pose a greater risk for permanent neurological deficits, especially if hemorrhages recur. - Lesions in the **supratentorial region** (cortex, subcortical white matter) are more likely to cause seizures, which can often be controlled with medication.

Seizures - Seizures are a common symptom of CCMs, particularly in cortical locations. - About **30–40%** of patients with CCMs develop seizures, and surgical resection can significantly improve seizure control in drug-resistant cases.

Surgical Outcomes

- Surgical removal is often **curative** for accessible, symptomatic lesions, particularly if causing recurrent hemorrhage or medically refractory seizures.

- For deep-seated lesions (brainstem, thalamus), surgery carries a higher risk of morbidity, so observation or stereotactic radiosurgery may be preferred.

Long-Term Outlook

- **Asymptomatic patients** with stable lesions often have a normal life expectancy.

- **Patients with recurrent hemorrhage** or progressive neurological deficits may have a more guarded prognosis.

- **Familial CCM cases** tend to have multiple lesions and a higher risk of complications over time.

Ren et al. analyzed 290 surgical specimens from symptomatic CCM patients, utilizing whole-exome sequencing, droplet digital PCR, and targeted panel sequencing, alongside immunohistology to examine genotypic and phenotypic differences. Among 290 cases, 201 had somatic MAP3K3, PIK3CA, or germline CCM mutations, each associated with distinct clinical parameters: hemorrhage risk ($P < 0.001$), lesion size ($P = 0.019$), non-hemorrhagic epilepsy ($P < 0.001$), Zabramski classifications ($P < 0.001$), developmental venous anomaly presence ($P < 0.001$), and MRI-detected edema ($P < 0.001$). PIK3CA gene mutations showed a higher hemorrhage risk than MAP3K3 and combined MAP3K3 & PIK3CA mutations ($P < 0.001$). Within PIK3CA mutations, the p.H1047R variant correlated with higher bleeding risk than p.E545K ($P = 0.007$). For non-hemorrhagic epilepsy, patients with single MAP3K3 mutations or combined MAP3K3 & PIK3CA mutations were at greater risk than those with PIK3CA mutations alone. Histopathologically, lesions with PIK3CA mutations displayed cyst walls, pS6-positive dilated capillaries, and fresh blood cells, while MAP3K3 and double mutation lesions exhibited classic CCM pathology with SMA-positive and KLF4-positive vessels, collagen, and calcification. PIK3CA lesions had fewer KLF4-positive cells than double mutations lesions ($P < 0.001$), and EndMT (SMA-positive) cells compared to double mutation lesions ($P < 0.05$) and MAP3K3 mutations ($P < 0.001$), with more pS6 compared to MAP3K3 mutations ($P < 0.05$). This study underscores the diverse clinical, genomic, and histopathological characteristics in CCMs, suggesting potential predictive markers based on mutation subtypes and MRI features [1)].

Ren et al. present a compelling study linking genotypic variations in cerebral cavernous malformations to clinical, histopathological, and imaging features. The study provides valuable predictive markers for hemorrhage risk and epilepsy but would benefit from functional validation and broader cohort inclusion. Future studies should investigate the therapeutic potential of targeting the PI3K and MAP3K3 pathways in CCMs, integrating longitudinal patient data to refine risk assessment and treatment strategies.

1)

Ren J, Wang D, Wang L, Jiang C, Tian A, Cui Z, Ren Y, Bian L, Zeng G, Meng G, Shan Y, Liang J, Xiao X, Tang J, Wei Y, He C, Sun L, Ma Y, Yu J, Li G, Ye M, Hu P, Li J, Li Y, Niu L, Li Q, Ling F, Burkhardt JK, Zhang H, Hong T. Clinical, genomic, and histopathologic diversity in cerebral cavernous malformations. Acta Neuropathol Commun. 2025 Feb 5;13(1):23. doi: 10.1186/s40478-025-01940-1. PMID: 39910686.