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Multiple brain cavernomas and pregnancy: Risk of seizures during obstetrical management

Dania Al Mokhtar, Wafa Dauleh, Arshad Ali, Gamal Sayed

ABSTRACT

Introduction: Cerebral cavernous malformations (CCMs) are linked to seizures and severe complications, including intracranial hemorrhage. Research on CCMs during pregnancy is limited, with only a few case series and observational studies available. This report examines the management of CCMs during pregnancy, emphasizing the risks of seizures and their treatment in the peri-gestational period.

Case Report: A 25-year-old woman presented with vomiting, dizziness, diplopia, and difficulty walking. A magnetic resonance imaging (MRI) detected small brain lesions consistent with multiple cavernomas. Two years later, during her first pregnancy, she was closely monitored by an OBGYN team and underwent a cesarean section due to her pre-existing neurological condition. Afterward, she displayed mild symptoms but had stable neurological evaluations. Her second pregnancy was uneventful, yet she underwent another cesarean section. Following delivery, she had two seizure episodes and was prescribed levetiracetam. During her last follow-up, 18 months later, she remained stable and seizure-free.

Conclusion: The risk of developing epilepsy during pregnancy, labor, or postpartum in CCM patients is unknown. Vaginal delivery is safe for certain patients; however, hormonal changes may increase seizure risk in those with pre-existing CCMs. Further research is required to clarify the relationship between CCMs and pregnancy and to optimize management strategies.

Keywords: Brain cavernomas, Cerebral venous malformations, Intracranial hemorrhages, Pregnancy, Seizures

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INTRODUCTION

Cerebral cavernous malformations (CCMs), or cavernous angiomas or cavernomas, are vascular abnormalities in the brain characterized by dilated sinusoidal vessels made up of endothelial cells and lacking intervening connective tissue [1]. The natural history of CCMs carries a potential risk of hemorrhage and may present as seizures in untreated cases, thereby increasing the risks associated with pregnancy and labor. Despite ongoing controversies in the literature, most studies suggest that pregnancy does not significantly elevate the risk of hemorrhages resulting from pre-existing CCMs during gestational and obstetric management [2]. Observations indicate that pregnancy may heighten the threshold for seizure risk due to hormone-induced changes, with maternal seizures posing significant threats to fetal well-being [3]. This situation presents a substantial clinical challenge, especially considering the limited literature concerning the risks and management of epilepsy in patients with pre-existing CCMs during the peri-gestational period [3–5]. This report examines a case

involving multiple brain cavernomas in a patient who experienced epileptic seizures during delivery without any accompanying intracranial hemorrhage. This report aims to investigate the management of CCMs during the gestational period, particularly focusing on the risks of seizures during both pregnancy and the puerperium.

CASE REPORT

A 25-year-old female patient presented with vomiting, dizziness, diplopia, and difficulty ambulating persisting for a week. She had a significant medical history of surgical intervention (Rastelli repair) for truncus arteriosus during childhood. The physical examination revealed a right eye deviation accompanied by impaired adduction, as well as impairment in both adduction and abduction of the left eye, along with left facial palsy. Notably, the tandem gait test yielded a positive result, and an impaired nose-to-finger test on the right was observed. A differential diagnosis of posterior fossa mass lesion was suspected. Magnetic resonance imaging disclosed multiple small brain lesions located in the left paracentral pons, right central pons, right cerebellar lobe, and left parieto-occipital region. One lesion identified in the left pons exhibited a fluid level indicative of intra-lesional hemorrhage with perifocal edema, consistent with multiple brain cavernomas (Figures 1 and 2). The patient was managed conservatively, and her symptoms resolved within four months. Two years after the initial presentation, the patient became pregnant. Considering the high-risk nature of her condition, she was closely monitored by a multidisciplinary team (MDT) that included her neurosurgeon, obstetrician, and cardiologist. The MDT diligently observed both her health and that of the fetus throughout the pregnancy, during which she remained asymptomatic with no complications reported. She opted for a lower-segment cesarean section performed under regional anesthesia, and both her obstetric and puerperal periods were uneventful. Following the first pregnancy, the patient experienced mild symptoms such as headaches, dizziness, and blurred vision; these symptoms resolved spontaneously. Serial annual MRI assessments revealed stable supra- and infratentorial cavernomas, except for an increase in the size of the posterior pontine cavernoma from 10 × 6.7 mm to 14.5 × 10 mm. Two years later, during the second trimester of her second pregnancy, she manifested right eyelid drooping, facial numbness, headache, and vomiting. The physical examination was within normal limits, and a repeat MRI indicated stable cavernomas (Figure 3). The symptoms subsided spontaneously after a few days. The patient opted for a cesarean section. Postoperatively, she experienced two brief generalized tonic-clonic seizures. A computed tomography (CT) scan confirmed the presence of multiple brain cavernomas, with no change in size and no evidence of intracranial hemorrhage (Figure 4). Treatment with levetiracetam was initiated, resulting in no further seizures noted during her last follow-up, which occurred 18 months later post-pregnancy.

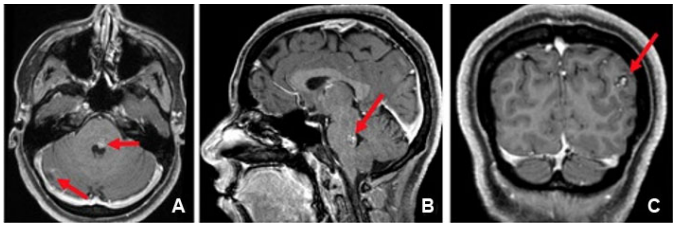

Figure 1: MRI post-gadolinium T1-weighted images in axial, sagittal, and coronal views showing the locations (pointed with red arrows) of multiple cavernomas in the posterior aspect of the left paramedian posterior pons, the right paramedian central aspect of the pons, in the right cerebellar lobe, and the left parieto-occipital cortical region.

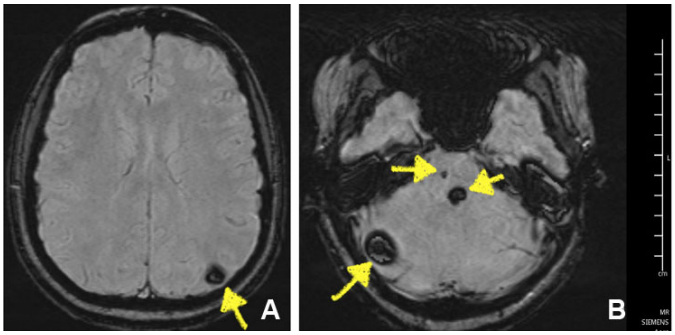

Figure 2: MRI susceptibility weighted images (SWI) showing the classical appearance of multiple cavernomas with hemorrhagic compositions (yellow arrows).

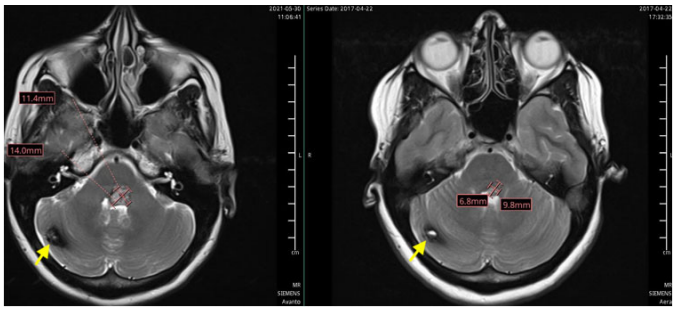

Figure 3: MRI T2-weighted axial sections comparing the increase in size of the cavernoma, located in the posterior aspect of the left paramedian posterior pons in 2017 and 2021 (yellow arrows).

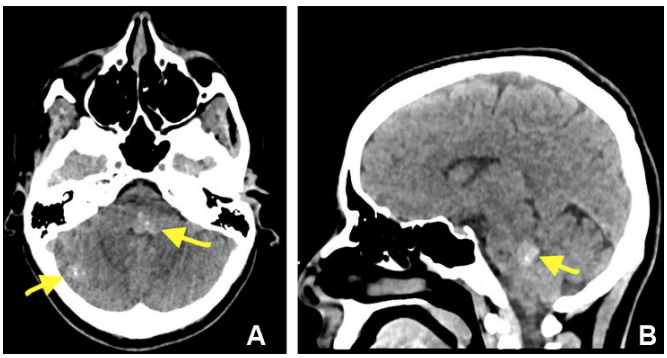

Figure 4: CT scan without contrast, axial, and sagittal images showing cavernoma in the left paramedian posterior pons (yellow arrows).

DISCUSSION

Cerebral cavernous malformations represent approximately 10–15% of all vascular malformations within the central nervous system [6, 7]. These malformations may manifest as singular or multiple lesions; multiple cavernous malformations may be of familial origin or arise sporadically [1, 6]. The most prevalent clinical presentations associated with CCM include seizures (4–6%) and intracranial hemorrhages (0–6%), which may or may not correlate with focal neurological deficits [1, 7].

In approximately 70–80% of cases, these malformations are identified supratentorially; however, a significant percentage of symptomatic patients present with seizures as the primary clinical manifestation [6].

Cerebral cavernous malformations can occur or be diagnosed at any age, with a higher prevalence in females due to hormonal factors. Both sporadic and familial forms have been reported, showing an incidence rate of 0.4–0.8% in the general population [1, 6, 7]. The literature documents a wide variety of clinical presentations, with common symptoms including headaches, seizures, focal neurological deficits, and intracranial hemorrhage [1, 6, 7]. In our case, the patient exhibited a fluctuating clinical course characterized by focal neurological deficits, worsened by seizures immediately following delivery. Cerebral cavernous malformations are generally considered benign, with 20% of patients remaining asymptomatic and 50% diagnosed incidentally. The natural history indicates a hemorrhage risk of 1.6% per patient-year and 0.9% per cavernoma year in asymptomatic patients [1, 6, 7, 8]. Cavernomas with dot-like patterns on imaging have an annual bleeding rate of 0.7% per lesion-year [7, 9]. Among symptomatic patients, seizures are the most common clinical manifestation [3, 10]. Some researchers have linked the occurrence of epileptic seizures during gestation to elevated serum estrogen concentrations in pregnant patients [11]. Studies show estrogen receptors are prominent in key brain regions associated with epileptogenesis, including the hypothalamus, hippocampus, and amygdala. Estrogens reduce the activity of gamma-aminobutyric acid (GABA) channel receptors in the pyramidal layers of cortical layers V and VI while enhancing the excitatory effects of glutamate on pyramidal neurons. Additionally, estrogens boost the rate of spontaneous neuronal secretion, especially in the medial amygdala, and stimulate excitatory responses to acetylcholine [3, 12]. Furthermore, the physiologically elevated levels of progestogens during pregnancy are known to decrease the seizure threshold [12].

Furthermore, angiogenic processes stimulated by growth factors, such as vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), or placental growth factor, play a critical role in the enlargement of cavernomas [3, 12]. Significant levels of angiogenic growth factors, including VEGF, bFGF, and transforming growth factors, are expressed in these conditions. Cerebral cavernous malformations promote angiogenesis and cellular proliferation in arteriovenous malformations [12]. Hyperdynamic circulation, coupled with increased extracellular fluid volume and cardiac output, intensifies turbulent blood flow within sinusoids characterized by thin walls, thus elevating the risk of cavernoma rupture [2, 3].

In a population-based study conducted in Scotland by Joseph et al. [10] found that the five-year risk of experiencing a first seizure among adults with CCMs was low, regardless of whether these individuals initially presented with intracerebral hemorrhage (ICH) or focal deficits (6%, 95% CI 0–14%) or if the CCMs were discovered incidentally (4%, 95% CI 0–10%). In contrast, for CCMs not associated with any intracranial hemorrhage or focal neurological deficits, the five-year risk of developing epilepsy after a first seizure was significantly heightened, estimated at 94%. The same study revealed that two-fifths of patients began treatment with antiepileptic medications following their first seizure, with a 47% chance of achieving seizure freedom for two years [10]. The patient in question was prescribed levetiracetam and experienced seizure freedom for 18 months until her most recent follow-up. An additional concern in managing these patients is the consideration of early lesionectomy, which involves the excision of the perifocal epileptogenic hemosiderin ring in pursuit of seizure remission. However, multiple brain cavernomas complicate the decision-making process regarding the surgical approach [13–15]. A surgical alternative was proposed in this case, but the patient opted to pursue medical management instead of treatment.

The ongoing debate about the delivery method for pregnant women diagnosed with CCMs remains contentious. Recent evidence suggests that the risk of hemorrhage associated with CCMs does not significantly vary throughout pregnancy, during delivery, or in the postpartum period [6, 9]. Regarding the development of seizures in neurosurgical conditions, prophylactic antiepileptic medications are not recommended for alert and conscious patients; instead, these medications are administered only after the onset of seizures in cases with a high propensity for epileptogenic activity [1, 3, 4, 6, 9–13]. Key factors linked to the onset of epileptic seizures in CCMs include lesion multiplicity and the cortical location of the CCMs [1, 2, 9]. In this specific scenario, after consulting an epileptologist, we decided not to initiate prophylactic antiepileptic treatment until the patient experienced a seizure.

CONCLUSION

The current evidence regarding the risks of intracranial hemorrhages and epilepsy during pregnancy, labor, or the postpartum period remains insufficient. Furthermore, the published data on other risks linked to the delivery

method is limited. Hormonal changes throughout pregnancy may lower the seizure threshold, thereby increasing the risk of seizures in individuals with pre-existing CCM. Therefore, it is essential to gather robust evidence from clinical trials to enhance the management of pregnancy-related cases of CCM in the future.

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Author Contributions

Dania Al Mokhtar – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Wafa Dauleh – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Arshad Ali – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Gamal Sayed – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Guarantor of Submission

The corresponding author is the guarantor of submission.

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Consent Statement

Written informed consent was obtained from the patient for publication of this article.

Conflict of Interest

Authors declare no conflict of interest.

Data Availability

All relevant data are within the paper and its Supporting Information files.