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CASE REPORT **OPEN ACCESS**

CEREBRAL PROLIFERATIVE ANGIOPATHY AS THE CAUSE OF SYMPTOMATIC EPILEPSY IN A YOUNG ADULT MALE: A FIRST CASE REPORT FROM INDONESIA

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ABSTRACT

Background: Cerebral proliferative angiopathy (CPA) is a rare and distinct vascular malformation that was once considered a subset of cerebral arteriovenous malformation (AVM). Due to its relatively benign course with no distinctive clinical feature, CPA may often be overlooked and misdiagnosed with other diseases. We would like to report a case of CPA as the underlying cause of symptomatic epilepsy.

Case: A 31-year-old male presented to the outpatient clinic with a history of focal to bilateral tonic-clonic seizure for 2 years. Following conservative management with an oral antiepileptic agent, the seizure frequency significantly decreased from once daily to once or twice monthly. The patient was lost to follow-up; however, he was incidentally referred back to our clinic two years later for further evaluation. A head Magnetic Resonance Imaging and Magnetic Resonance Angiography revealed a suspicion of giant AVM in the left hemisphere. Cerebral digital subtraction angiography (DSA) was performed and revealed a CPA in the left frontal area. The patient was managed conservatively, and during the 6-month follow-up period, the patient did not have any seizures.

Discussion: In young adults, seizures may be caused by an underlying vascular abnormality. Cerebral DSA remained the gold standard for distinguishing various etiologies of vascular malformation, including CPA.

Conclusion: Conservative treatment using oral antiepileptic agents was effective in controlling the seizure frequency in CPA. However, a complete diagnostic evaluation is still warranted to determine the most appropriate treatment while revealing some peculiar and unexpected etiologies in the process.

Keywords: cerebral angiography, cerebral proliferative angiopathy, conservative treatment, symptomatic epilepsy

Introduction

Cerebral proliferative angiopathy (CPA) is a distinct vascular malformation different from a "classical" cerebral arteriovenous malformation (AVM).[1] Previously, CPA was known as "holohemispheric giant (AVM)" or "giant nidus AVM", however the term was later discarded due to the peculiar angiogenetic features demonstrated by CPA.[2] Based on a prior study, CPA was identified in 2-4 % of patients initially diagnosed with cerebral AVM.[3,4] The relatively benign course of disease progression and the lack of distinctive clinical features may cause CPA to be overlooked and misdiagnosed.[5] Based on the literature search conducted, there were no case reports of CPAs from Indonesia. We would like to report a case of CPA as the cause of symptomatic epilepsy in a young adult male.

Case Report

A 31-year-old male presented to the outpatient clinic with a two-year history of focal-onset seizures that progressed to bilateral tonic-clonic seizures. The seizures typically began with discomfort around the back of his head, followed by lightheadedness and rhythmic jerking of the entire body that lasted for about two minutes. Afterward, the patient regained full consciousness within 5-10 minutes but had no recollection of the event. Seizures occurred approximately once daily and were often triggered by exhaustion. His medical history included hypertension, which was well-controlled with Amlodipine 10 mg. The patient denied any history of head trauma, stroke, or childhood seizures.

On physical examination, the patient was fully conscious with no neurological deficits, and his Mini-Mental State Examination score was 30, indicating normal cognitive function. The patient was prescribed Phenytoin 100 mg three times daily and further diagnostic evaluations were planned. However, he did not attend his next scheduled appointment and was subsequently lost to follow-up.

Two years later, the patient was incidentally referred back to the outpatient clinic for further diagnostic evaluation. His seizure frequency had significantly decreased with regular Phenytoin use, although he still experienced seizures once or twice a month, typically following high-intensity activities or stressful situations. The seizures were similar in nature to those he had previously experienced.

The patient underwent a comprehensive laboratory evaluation to rule out potential causes of acute symptomatic seizures. His serum electrolytes were normal (Sodium: 137 mmol/L; Potassium: 3.7 mmol/L; Chloride: 109 mmol/L). Complete blood count showed normal results (Hemoglobin: 15.9 g/dL; White Blood Cells: 11,000 cells/µL; Platelets: 314,000 cells/µL). Other metabolic panels were also within normal limits (ALT: 24.7 IU/L; AST: 22.8 IU/L; Creatinine: 0.81 mg/dL; Blood urea nitrogen: 8.3 mg/dL; Albumin: 4.47 g/dL). An electroencephalogram (EEG) showed a decreased background rhythm in the left hemisphere without epileptiform discharge.

Magnetic resonance imaging and angiography (MRI/MRA) revealed a large suspected arteriovenous malformation (AVM) (9.3 x 3.4 x 4.3 cm) in the left cerebral hemisphere, fed by arteries from both the left and right anterior cerebral arteries and the left middle cerebral artery. The lesion was classified as Spetzler-Martin Grade V (Figure 1).

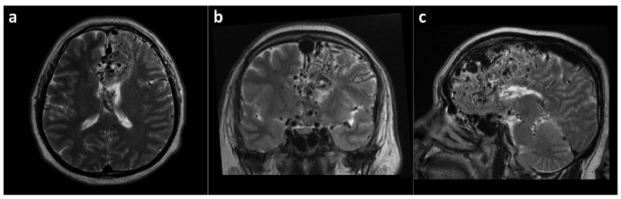

Figure 1. a-c T2-weighted MRI images showing an intraparenchymal flow void suggestive of a vascular malformation (CPA) in the left frontal lobe with an initial suspicion of a giant cerebral AVM

A cerebral digital subtraction angiography (DSA) was arranged one month after the MRI examination and revealed a diffuse CPA with arterial feeder from the contralateral anterior cerebral artery through anterior communicating artery, with draining vein to the cortical veins, internal cerebral veins, and continued to the superior sagittal sinus and straight sinus (Figure 2). Following this diagnosis, conservative medical management with antiepileptic and antihypertensive drugs was chosen over endovascular intervention. The patient was advised to monitor his blood pressure daily and avoid stress or exhaustion which may precipitate his seizure.

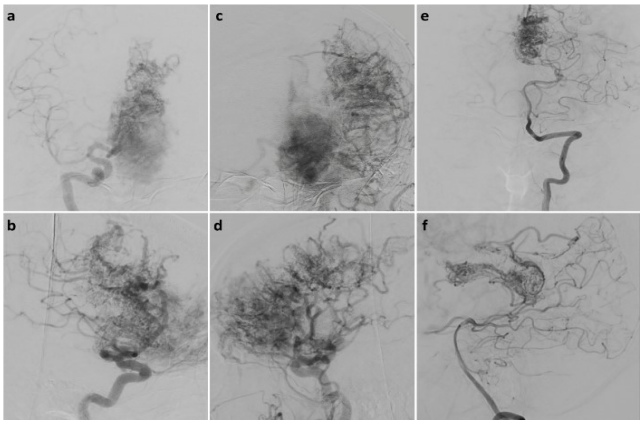

Figure 2. Cerebral DSA showed diffuse angiopathy with capillary ectasia in the left hemisphere, lacking a dominant arterial feeder and early venous phase, suggestive of CPA. Views include: right ICA injection (a, b); left ICA injection (c, d); left vertebral artery injection (e, f).

The patient regularly attends the outpatient clinic for a scheduled follow-up. After 6 months, the patient did not have any episodes of seizures. He still felt the usual seizure aura (dull headache and lightheadedness), but it did not progress into a seizure. The patient reported good compliance with his antiseizure medication and experienced no significant side effects. There were no neurological deficits found. A summary of the patient clinical condition before and after treatment is presented in Table 1.

Discussion

CPA is a rare phenomenon characterized by diffuse abnormal vessels within the brain parenchyma, supplied by several arteries and drained to several veins, without the presence of high-flow arteriovenous shunts.[4] This phenomenon was commonly observed among children and young adults with the mean age at presentation being 22-23 years and female predominance (60-67%).[1,2] Lasjaunias et al (2008) emphasized that the presence of non-focal angiogenetic activity was a major feature of CPA, distinguishing it from "classical" cerebral AVMs. Several additional angiographic features of CPA included: 1) Lack of dominant arterial feeders to a large nidus, 2) Discrepancy between the small draining veins relative to the large arteriovenous nidus, 3) Absence of flow-related aneurysms, 4) Presence of diffuse angiogenesis, 5) The small diameter of a multitude of feeding arteries and draining veins, and 6) Presence of brain parenchyma between the vascular spaces.[2,12]

The exact pathogenesis of CPA was not fully understood. A previous study using Positron Emitted Tomography scans of CPA revealed a decreased perfusion in the lesion area as well as the surrounding brain tissue.[6,13] It was presumed that the angiogenesis process was triggered in response to chronic cerebral hypoperfusion due to unknown signaling media. This resulted in an environment with locally increased blood volume but hypoperfusion in the perinidal areas.[14] In response, the brain will trigger yet another angiogenic response, leading to a vicious cycle of uncontrolled angiogenesis.[6,7] Another study also revealed ischemia in the area adjacent to the vascular lesion, which may be attributed to a vascular-steal phenomenon.[8,15]

Seizure was the sole clinical manifestation of CPA in our case, which was one of the most common features besides chronic headache and transient ischemic attacks.[1] Seizure caused by intracranial vascular malformation may manifest in various types.[16] According to a previous study in brain AVM, most of the seizure type was generalized onset tonic-clonic seizure (56.7%), followed by focal onset to bilateral tonic clonic seizure (20%), focal onset aware seizure (20%), and focal onset with impaired awareness seizure (3.3%).[9] However, there were still limited data regarding the seizure types in CPA. The EEG in our patient revealed an asymmetrical decrease in the background rhythm on the left hemisphere. This is possible because of the additional distance from the scalp to the brain due to the presence of CPA. Previous studies noted various EEG abnormalities of CPA, such as intermittent slow wave activity, diffuse slowing, or even periodic lateralizing epileptiform discharges.[5,10,11]

Table 1. Summary of the patient clinical condition and treatment response

Parametes	Pre-Treatment	Pre-Procedural (2y after treatment)	Post-Procedural Follow-up (2.5y after treatment)
Chief Complains	Seizure, Focal Onset to Bilateral Tonic Clonic	Seizure, Focal Onset to Bilateral Tonic Clonic	No Seizure, but Aura persisted
Aura	(+) Discomfort around the back of his head	(+) Discomfort around the back of his head	(+) Discomfort around the back of his head
Frequency	Once daily	1-2 times/ month	N/A
Triggers	Physical Exhaustion	Emotional Stress, High Intensity Activity	N/A
Duration	2 minutes	2 minutes	N/A
Supporting Examination	None	EEG, Laborator, Head MRI, Cerebral DSA	None
Treatment	Phenytoin 3x100 mg was initiated	Phenytoin 3x100 mg Amlodipine 1x10 mg Avoidance of Triggers; Drug Compliance	Phenytoin 3x100 mg Amlodipine 1x10 mg Avoidance of Triggers; Drug Compliance

The incidence of hemorrhage in CPA was estimated at 18%, which was significantly lower compared to cerebral AVM (50%).[2] This was consistent with our finding in which despite a large lesion size, the CPA did not lead to hemorrhage nor cause a focal neurological deficit.

The diagnosis of CPA was made based on angiographical findings. Previous studies have reported that head computed tomography angiography and MRA yielded good sensitivity to diagnose CPA and rule out other vascular abnormalities.[5] However,

our patient was initially misdiagnosed with a giant cerebral AVM based on the head MRI/MRA result. This signifies the role of cerebral DSA as a gold standard in diagnosing vascular abnormalities.[17]

CPA treatment options include conservative management, endovascular treatment, indirect revascularization, and radiosurgery.[18] The majority of CPA cases reported were treated conservatively due to frequent disparity in less severe symptoms and high risk for interventional treatment.[19,20] Also, most of the patients treated conservatively remained stable during a long-term follow-up period. Despite the limited evidence, indirect revascularization using an open surgery method and endovascular treatment using targeted embolization were correlated with positive neurological outcomes.[1,12]

Conclusion

Vascular malformations may be an underlying culprit of symptomatic epilepsy, especially in children and young adults. Despite the seizure being drug-responsive, further diagnostic evaluations should not be overlooked. This will guide clinicians in determining the most appropriate management while revealing some peculiar and unexpected etiologies in the process.

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