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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. 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 feature may cause CPA to be overlooked and misdiagnosed.[5] Based on the literature search conducted, there were no case reports of CPA from Indonesia. We would like to report a case of CPA as the cause of symptomatic epilepsy in a young adult male.

Case Report

Male, 31-year-old, presented to the outpatient clinic with a history of focal onset to bilateral tonic-clonic seizures in the last two years. The seizure was initially preceded by a discomfort around the back of his head, followed by a lightheadedness, and a rhythmic whole-body jerk for around two minutes. The patient fully regained consciousness 5-10 minutes after the seizure and was unable to remember the

preceding event. The seizure frequency was around once daily and usually triggered when the patient was exhausted. His past history was significant for hypertension which was controlled with Amlodipine 10 mg. A previous history of head trauma, stroke, or childhood seizure was denied. On physical examination, the patient was fully conscious with no neurological deficit. His Mini-Mental State Examination score was 30. The patient was given Phenytoin 100 mg three times daily and was planned for further diagnostic evaluation. However, the patient did not return during the next scheduled appointment and was considered lost to follow-up.

The patient was incidentally referred to our outpatient clinic two years later for further diagnostic evaluation. His seizure frequency was significantly decreased following routine consumption of Phenytoin. However, the patient still experienced seizures once or twice a month usually after high-intensity activities and during stressful conditions. The seizure type was similar to the previous history. The patient underwent a complete laboratory evaluation to rule out a possible cause of an acute symptomatic seizure. Serum electrolyte was normal (Sodium: 137 mmol/L; Potassium: 3.7 mmol/L, Chloride: 109 mmol/L), complete blood count was normal (Hemoglobin: 15.9 g/dL; White Blood Cell: 11.000 cells/µL; Platelet: 314000 cells/µL), other metabolic panels were also within normal limit (ALT: 24.7 IU/L; AST: 22.8 IU/L; Creatinine: 0.81 mg/dL; Blood urea nitrogen: 8.3mg/dL; Albumin: 4.47 g/dL). An electroencephalography (EEG) examination revealed an asymmetrical decreased background rhythm in the left hemisphere with no epileptiform discharge. A head magnetic resonance imaging and angiography (MRI/MRA) examination revealed a suspicion of giant AVM (9.3 x 3.4 x 4.3 cm) in the left cerebral hemisphere with feeding artery from the left and right anterior cerebral artery and left middle cerebral artery, Spetzler-Martin Grade V (Figure 1).

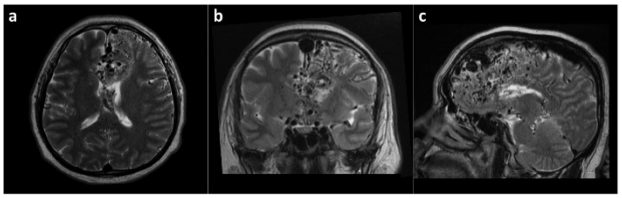

Figure 1. a-c T2-weighted MRI images showing an intraparenchymal flow void suggestive of a vascular malformation (CPA) in the left frontal lobe with an initial suspicion of a giant cerebral AVM.

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 continue 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.

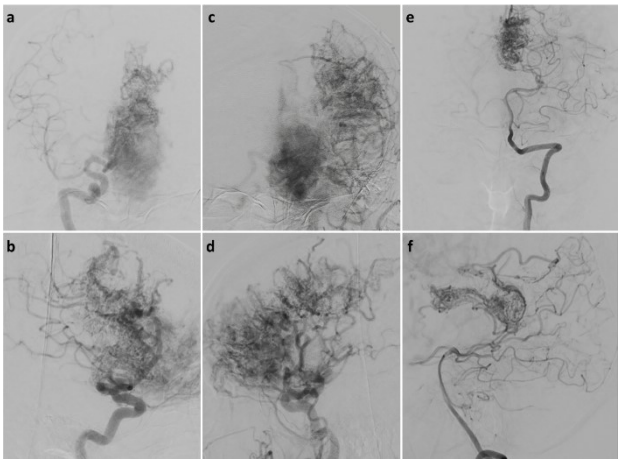

Figure 2. Cerebral DSA of the patient revealed a diffuse angiopathy with capillary ectasia in the left hemisphere with lack of dominant arterial feeder and no early venous phase, suggestive of a CPA. Anteroposterior **(a)** and lateral **(b)** view of the right ICA injection; anteroposterior **(c)** and lateral **(d)** view of the left ICA injection; anteroposterior **(e)** and lateral **(f)** view of the left vertebral artery injection.

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 was 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]

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] 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. 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]

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, Laboratory, 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

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. 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 of 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]

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 the diagnosis of vascular abnormalities.

Treatment options for CPA include conservative management, endovascular treatment, indirect revascularization, and radiosurgery. The majority of CPA cases reported were treated conservatively due to frequent disparity in less severe symptoms and high risk for interventional treatment. In addition, most of the patients who were 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 was drug-responsive, further diagnostic evaluations should not be overlooked. This will guide clinicians to determine the most appropriate management while revealing some peculiar and unexpected etiologies in the process.

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