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Unusual presentation of cerebral proliferative angiopathy: extensive lesions with minimal clinical expression

Presentación inusual de la angiopatía proliferativa cerebral: lesiones extensas con mínima expresión clínica

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Abstract

Cerebral proliferative angiopathy is an extremely rare intracranial vascular disorder that, despite certain similarities with arteriovenous malformations, it is considered as a distinct clinical entity. We report a 25-year-old woman with no known cognitive impairment, who presented epileptic seizures. Digital subtraction angiography revealed a multilobar vascular lesion with diffuse involvement, supplied by multiple afferent vessels, delayed venous drainage, and lacking a well-defined vascular nidus. A conservative management approach was adopted. This case highlights the presence of minimal symptoms despite the extensive involvement, characteristic angiographic imaging, and the diagnostic workup of patients with this disease. Further studies are needed to clarify the underlying mechanisms, diagnostic criteria, and treatment strategies for this condition.

Keywords: *Cerebral proliferative angiopathy. Arteriovenous malformation. Cerebrovascular disease. Indirect revascularization. Case report.*

Resumen

La angiopatía proliferativa cerebral (APC) es un trastorno vascular intracraneal extremadamente raro que, a pesar de ciertas similitudes con las malformaciones arteriovenosas, debe considerarse como una entidad clínica distinta. Presentamos el caso de una mujer de 25 años sin antecedentes de deterioro cognitivo, que presentó crisis epilépticas. La angiografía por sustracción digital reveló una lesión vascular multilobar con compromiso difuso, irrigada por múltiples vasos aferentes, drenaje venoso tardío y ausencia de un nido vascular bien definido. Se optó por un manejo conservador. Se requieren estudios adicionales para esclarecer los mecanismos subyacentes, los criterios diagnósticos y las estrategias terapéuticas para esta condición.

Palabras clave: *Angiopatía proliferativa cerebral. Malformación arteriovenosa. Enfermedad vascular cerebral. Revascularización indirecta. Reporte de caso.*

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Introduction

Cerebral proliferative angiopathy (CPA) is an intracranial vascular malformation characterized by multiple feeding arteries, and the absence of early venous drainage. Unlike arteriovenous malformations (AVMs) no vascular nidus is found; instead, CPA is associated with development of new vessels and progressive vascular dilation, with normal brain parenchyma surrounding and interspersed within the lesion[1-3]. This entity is extremely rare, with approximately 115 cases reported in global medical literature to date[2-4]. A possible predisposition has been noted in young adult women[2], and its clinical presentation is highly heterogeneous, encompassing behavioral changes, cognitive dysfunction, seizures, and both ischemic and hemorrhagic events[2,5].

Case presentation

A 25-year-old woman arrived for outpatient care at our Institution. She had no history of perinatal complications. At the age of three, she was diagnosed with a patent ductus arteriosus, successfully treated with an Amplatzer™ Septal Occluder (Abbott, St. Paul, MN, USA)[6]. Her development and academic performance were within normal limits. She completed technical studies and worked as an elementary school teacher.

Two years before diagnosis, the patient presented with focal epileptic seizures with bilateral progression, with a total of 6 episodes in this period. These were characterized by rightward gaze deviation, tonic posture, and clonic movements. Her relative reported no sphincter incontinence, tongue biting, or preceding aura. The postictal phase was marked by right hemiparesis, generalized fatigue, somnolence, and intermittent impaired speech. She was treated with Levetiracetam 500 mg BID, with partial response due to seizure persistence. Due to socioeconomic constraints, the patient delayed specialized medical attention.

On evaluation, she was alert, focused, calm, and cooperative, with no limitations in activities of daily living. Cognitive functions were apparently normal, although subsequent neuropsychological evaluation demonstrated impaired attention and altered executive functions such as planning, problem-solving, mental flexibility, inhibition, and working-memory. No deficits were noted in motor strength, sensory system, or gait. Meningeal signs and abnormal movements were negative. Due to her epilepsy, she was no longer able to perform her professional activities.

Computed tomography (CT) revealed a hypodensity area in the left precentral region, not confined to a specific vascular territory. In addition, contrast-enhanced vascular reconstruction with maximum intensity projection images demonstrated numerous tortuous vessels with abnormally increased diameters, without evidence of a well-defined vascular nidus. Notably, there was dilation of both the superficial and deep venous drainage systems (Fig. 1).

We performed a digital subtraction angiography (DSA) with angiographic acquisitions from the carotid (Fig. 2) and vertebral arteries (Fig. 3). The patient presented dilated and tortuous vessels in the arterial and venous segments. We found no defined vascular nidus relative to AVM, arterial stenosis, or intracranial aneurysms. Venous systems exhibited delayed drainage, with a normal anatomical trajectory. The external carotid artery demonstrated multiple dilated branches with anastomoses to the right internal carotid artery (ICA), as well as evidence of transdural arterial supply (Fig. 2). This patient also presented signs of diffuse angiogenesis, such as transdural supply and small diameter of multiple feeding arteries and draining veins.

Once the CPA diagnosis was confirmed, we held an interdisciplinary committee meeting with neurosurgery, neurological endovascular therapy, and neuroradiology, in which we decided to pursue conservative management, emphasizing lifestyle measures and facilitating reintegration into her daily activities. Antiepileptic medication was adjusted to suppress ictal activity. The patient remains under regular follow-up, with no additional clinical changes to date.

Discussion

CPA remains a rare vascular entity that has previously been described heterogeneously as “diffuse nidus type AVM” or “holohemispheric giant cerebral AVM.” However, some of the features that distinguish it from AVM are the absence of a defined malformation nidus, the lack of predominant afferent arteries, and delayed venous drainage. These characteristics support the consideration of CPA as a separate pathological entity[7]. CPA is also characterized by lesions typically exceeding 6 cm, with a predilection for the supratentorial compartment and the right cerebral hemisphere and rarely exhibiting bilateral extension[8].

CPA exhibits a broad spectrum of clinical and radiological features. A recent systematic review reported its most frequent clinical manifestations as recurrent bleeding (67%), headache (41-45%), epileptic seizures

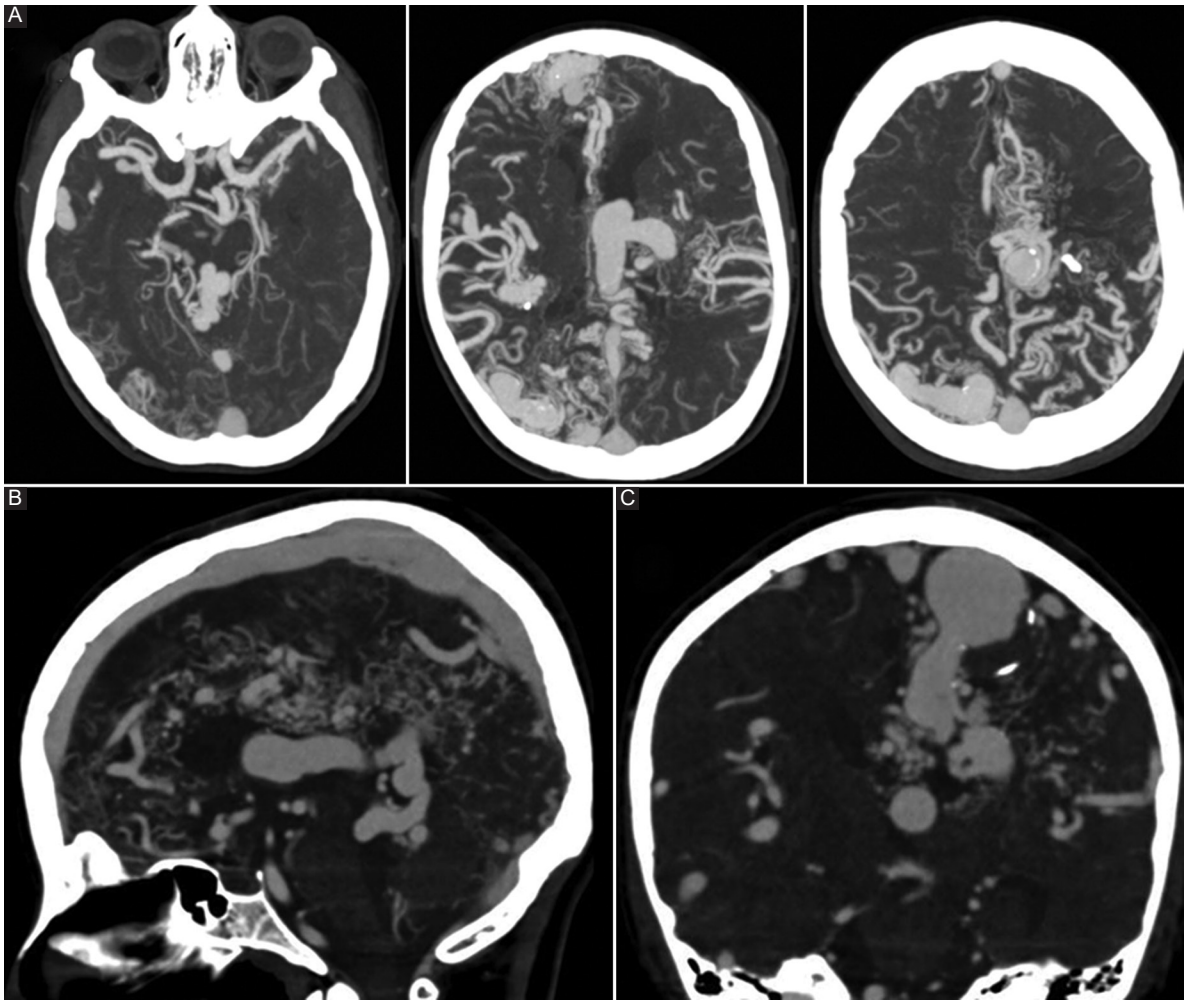


Figure 1. CT of the skull with MIP images in **A:** axial, **B:** sagittal, and **C:** coronal sections revealed multiple meandering vessels without a clearly defined vascular nidus, and dilation of the venous drainage system. CT: computed tomography; MIP: maximum intensity projection.

(37-45%), focal neurological deficits or transient ischemic attacks, (16-34%), and intracranial hemorrhage (12-18%)[2,9]. These symptoms may worsen over time due to the progressive nature of the disease, which is often associated with expansion of the malformation and, consequently, increased symptom burden[10]. In our case, despite the extensive and diffuse nature of the lesion, the patient presented only with epileptic seizures, without motor deficits or previous hemorrhagic events, although CT suggested a prior ischemic insult. Nevertheless, she achieved normal academic development, although her seizures have intermittently affected her employment status.

The etiology of CPA remains unknown. Several pathophysiological mechanisms have been proposed, based on analogies with other well-characterized conditions. One hypothesis suggests that chronic oligemia and impaired perfusion may trigger angiogenesis, promoting the formation of new perforating and transdural vessels as a compensatory response to ischemia-mechanisms reminiscent of those observed in Moyamoya disease[7,9,11]. This angiogenic response is uncontrolled, resulting in abnormal blood flow dynamics that can compromise the structurally weak walls of anomalous vessels. Such alterations may lead to the formation of vascular dilations, increasing the risk of intracranial hemorrhage due to wall fragility[3]. Elevated levels of vascular endothelial growth factor and basic fibroblast growth factor have also been demonstrated in the cerebrospinal fluid; these proteins promote endothelial cell proliferation, migration, differentiation, and maturation[5,11].

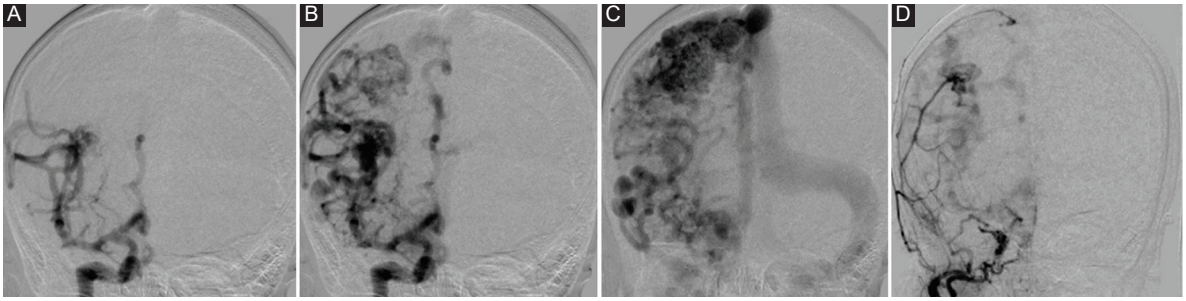


Figure 2. Digital subtraction angiography. Right internal carotid artery, posteroanterior view in **A:** early arterial, **B:** late arterial, and **C:** venous phases. External carotid artery , posteroanterior view acquisition (**D**) demonstrated transdural arterial supply.

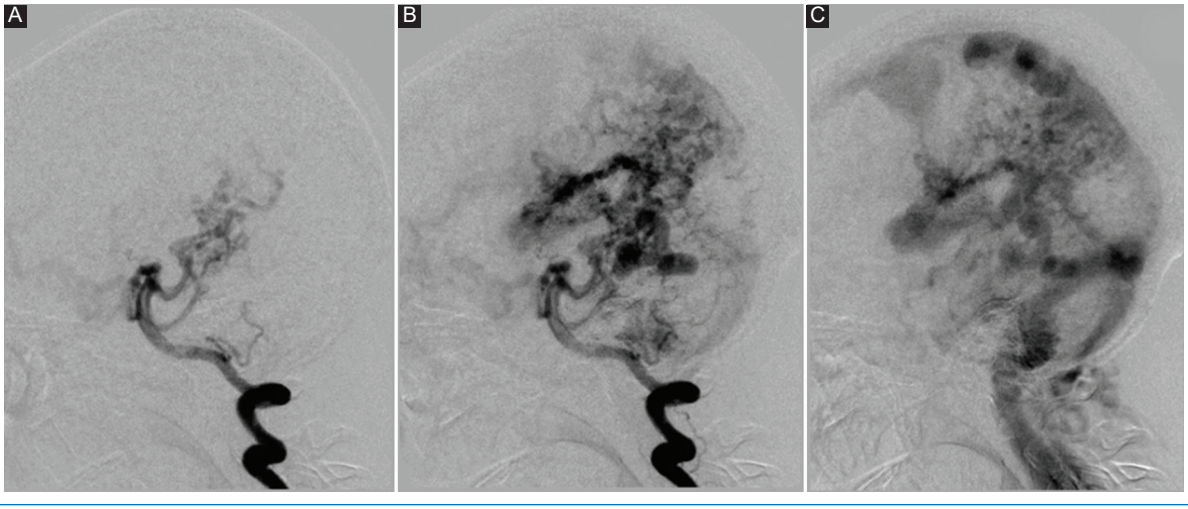


Figure 3. Digital subtraction angiography. Right vertebral artery, lateral view in **A:** early arterial, **B:** late arterial, and **C**: venous phases demonstrated multiple dilated vascular lesions.

DSA remains the gold standard for diagnosis, enabling the differentiation of CPA from classical AVMs. According to Lasjaunias et al.,[9] the diagnosis of CPA is established by: a diffuse network of densely enhancing vascular spaces with intermingled normal brain parenchyma, and absence of dominant feeders to a large nidus[8]. Due to the high flow demand in CPA, an increased volume of contrast medium is often required to achieve adequate angiographic definition. Transdural arterial supply is seen in approximately 34% of cases and may contribute to both the malformation and adjacent normal tissue, with unilateral or bilateral involvement. Multiple feeding arteries are reported in 80% of patients, while associated aneurysms and deep venous drainage are each seen in only 6% of cases. Feeding arteries tend to be of uniform diameter, and proximal stenosis of these vessels (particularly the internal carotid artery [ICA], first segment of the medial cerebral artery [M1] and the first segment of the anterior cerebral artery [A1]) is observed in up to 39% of cases[2,3,5,9,10]. Pivotal signs for the attending physician are the presence of normal, functioning neural tissue interspersed between the abnormal vessels, and the typically progressive nature of neurological deficits, both features assist in differentiating CPA from other vascular malformations.

CT angiography (CTA) with high-intensity projections, or magnetic resonance imaging (MRI), with vascular reconstruction, may also reveal a dense vascular network intermingled with preserved parenchyma. On

T1- and T2-weighted MRI, small flow voids are typically seen. Most lesions occur in the border zones between vascular territories, known as watershed areas. MRI perfusion-weighted imaging shows perfusion abnormalities extending beyond the morphological boundaries visible on conventional MRI[12], where increased blood volume within the nidus, prolonged mean transit time suggestive of capillary and venous ectasia, and hypoperfusion within the affected hemisphere can be found[9].

These distinct angioarchitectural and clinical features guide toward therapeutic decision-making. At present, the primary objectives are to improve perfusion and to prevent future ischemic injury. Treatment options may include partial endovascular embolization of non-eloquent areas, radiosurgery, or surgical revascularization techniques such as encephalo-duro-arterio-synangiosis (EDAS), or trepanation when transdural supply is limited[3,4,9,10]. Nonetheless, conservative management is generally preferred due to the high rate of complications associated with interventional procedures, reported in up to 66% for surgery and 73% for endovascular therapy-particularly pondering the presence of viable, functional brain tissue within the malformation[7,13]. In our case, the patient was managed conservatively with symptom control and clinical surveillance.

Conclusion

This patient with CPA exhibited extensive and diffuse cerebral involvement with minimal clinical manifestations. Given the rarity of this entity, a comprehensive diagnostic workup using advanced neuroimaging techniques is warranted to ensure accurate characterization and appropriate longitudinal assessment. Although therapeutic options remain limited, an individualized and cautious management strategy is essential to optimize patient outcomes. Future research is expected to shed light on the etiology, pathophysiology, diagnostic criteria, and therapeutic approaches for patients with this condition.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of human subjects and animals. The authors declare that no experiments on humans or animals were performed for this research.

Confidentiality, informed consent, and ethical approval. The authors have obtained approval from the Ethics Committee for the analysis of routinely collected and anonymized clinical data; therefore, individual informed consent was not required. Relevant ethical recommendations have been followed.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing or creation of the content of this manuscript.

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