

A case of postpartum cerebral angiopathy with subarachnoid hemorrhage

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Background. A 33-year-old woman experienced a thunderclap headache immediately postpartum. The headache recurred over the next 10 days, and the patient also developed generalized tonic-clonic seizures. A subarachnoid hemorrhage was demonstrated on a head CT scan.

Investigations. Physical examination, laboratory tests, brain CT scan, brain MRI scan, brain magnetic resonance angiogram, brain magnetic resonance venogram, cerebral angiography, transcranial Doppler ultrasound, EEG.

Diagnosis. Postpartum cerebral angiopathy.

Management. NSAIDs and opioid analgesics administered on postpartum day 3 provided partial headache relief. The next day, a blood patch was performed and intravenous caffeine, fluid and opioid analgesia were given to treat a suspected dural puncture headache. Following diagnosis of postpartum cerebral angiopathy on postpartum day 10, nimodipine was initiated to treat the vasospasm, and the headache was treated with opioid analgesics and toradol, followed by naproxen. The patient also received a 3-day course of intravenous magnesium sulfate.

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The case

After a normal, 38-week pregnancy, a 33-year-old Filipino woman gave birth to her second child, a healthy boy (2,940 g), by cesarean section. For the delivery, she underwent spinal anesthesia with a 24-gauge needle, and, shortly after the procedure, experienced the “worst headache of her life”. The headache started with a painful sensation ascending from the middle of her back to the occipital region of the skull. The pain spread to involve her entire head within seconds. She described the pain as 10/10 in severity and explosive in nature. An eclampsia work-up revealed no peripheral edema, proteinuria, abnormal laboratory tests or arterial hypertension. After delivery and discontinuation of the spinal catheter, and during the early postpartum period, her headache persisted with fluctuating severity, but her neurological examination remained normal. The patient had no other complications associated with her delivery. On postpartum day 3, she experienced a severe exacerbation of her headache, which was only partially relieved with NSAIDs and opioid analgesics.

The next day, several hours after she was discharged home, the patient returned to the emergency room complaining of a severe, unremitting headache that was worse in the upright position. On the basis of this history, she was presumed to have a dural puncture headache, and a blood patch was performed, which produced immediate, moderate relief. The patient was

also given intravenous caffeine (one intravenous 500 mg dose) and fluids, as well as opioid analgesia, which are the standard medical therapies to treat dural puncture headache in our institutions. Approximately 90 minutes later, she experienced two generalized tonic-clonic seizures (GTCSs), each lasting approximately 1 minute and preceded by blurry vision. She did not experience diplopia, dysarthria, dysphagia, vertigo, nausea, vomiting, visual field obscuration, fortification spectra, scotomata, or focal weakness in association with her headaches. Because of the seizures, she underwent head CT, brain MRI, magnetic resonance (MR) angiography, MR venography and EEG, all of which were normal. She was discharged on postpartum day 7 with a persistent headache, which she rated 4/10 in severity. No antiepileptic drugs were prescribed.

On postpartum day 10, the patient again developed a severe, progressive headache without obvious positional exacerbation, and she was readmitted to the hospital. Head CT on admission revealed a subtle hyperdense signal over the right cortical convexity within the right Sylvian fissure, and over the tentorium cerebelli. Approximately 12 hours after the initial CT scan, the patient experienced another GTCS, again preceded by a vague visual prodrome. She did not experience any associated diplopia, dysarthria, dysphagia, vertigo, nausea, vomiting, visual field obscuration, or focal weakness. A repeat CT scan revealed a substantial accumulation of subarachnoid blood over the right cortical convexity, the right Sylvian fissure, the interhemispheric fissure, and

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Competing interests

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the basal cisterns, with thick clot in the right ambient cistern (Figure 1). Owing to suspicion of aneurysmal rupture, she was then transferred to our Neuroscience Critical Care Unit (NCCU). On admission, she complained of a nonpositional headache, which she rated 3/10 in severity. Neurological and general medical examinations were both normal.

The patient's past medical history was notable for migraines and recurrent positional vertigo. She had no history of hypertension, stroke or seizures. She was taking no medications, other than over-the-counter analgesics, and received no sympathomimetics at any time, including around delivery. She did not use ethanol, tobacco, or illicit drugs such as cocaine, and she had no family history of subarachnoid hemorrhage (SAH). 8 years before her current presentation, she had an entirely uncomplicated pregnancy and delivery of a healthy child, the only notable occurrence being a 1-day headache following epidural anesthesia for that delivery.

During the time that the patient spent on the NCCU, the following serologies and laboratory values were all normal: antinuclear antibody, antidouble stranded DNA antibody, rapid plasma reagin, antineutrophil cytoplasmic antibody, Sjögren antibodies (SS-Ro and SS-La), lupus anticoagulant and antiphospholipid antibody panel, renal and hepatic function panels, complete blood count, basic metabolic panel, urine analysis, blood cultures, and serum and urine toxicologies. Her C-reactive protein was elevated at 27 mg/l (normal upper limit 5 mg/l), raising suspicion of vasculitis or an inflammatory disease.

A transfemoral cerebral angiogram was performed and revealed no aneurysm, cerebral sinus thrombosis, vascular malformation, or dissection to account for the SAH. The angiogram was remarkable, however, for a diffuse pattern of sausage-like dilatation with proximal and distal stenoses (the pearl and string sign; Figure 2a). MRI of the brain revealed high fluid-attenuated inversion recovery signal consistent with SAH with no restricted diffusion, and hemosiderin deposition on the cortical convexity and right ambient cistern on gradient echo sequences (Figure 3). Transcranial Doppler ultrasound (TCD) demonstrated high blood-flow velocities consistent with vasospasm, most notably within the right M1 segment of the middle cerebral artery (MCA; velocity 206 cm/s; normal range 50–60 cm/s) and the C1 segment of the right internal carotid artery (ICA; velocity 165 cm/s; normal range 30–40 cm/s). The left vertebral artery also showed elevated velocity (80 cm/s; normal value 30–40 cm/s).

The patient was closely monitored in the NCCU for 2 days and was subsequently sent to the neurology floor. Nimodipine (30 mg by mouth every 2 hours) was initiated at this time to treat the vasospasm, and the patient's headache was treated with opioid analgesics and toradol (30 mg administered intravenously every 6 hours for 5 days) followed by naproxen (500 mg by mouth every 12 hours). No lumbar puncture was performed. The

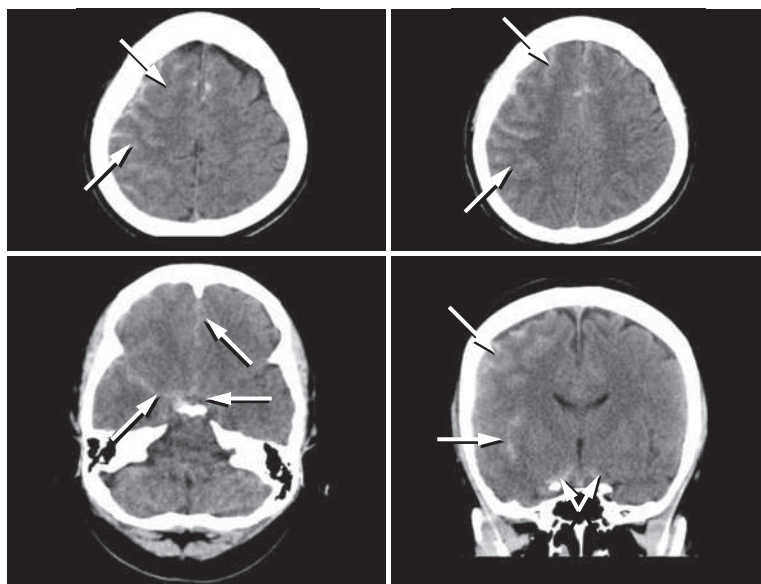


Figure 1 | Brain CT scan. Arrows indicate areas of increased density consistent with subarachnoid hemorrhage. Hemorrhage is visible in the convexity on the right Sylvian fissure and along the tentorium—a typical pattern seen in subarachnoid hemorrhage.

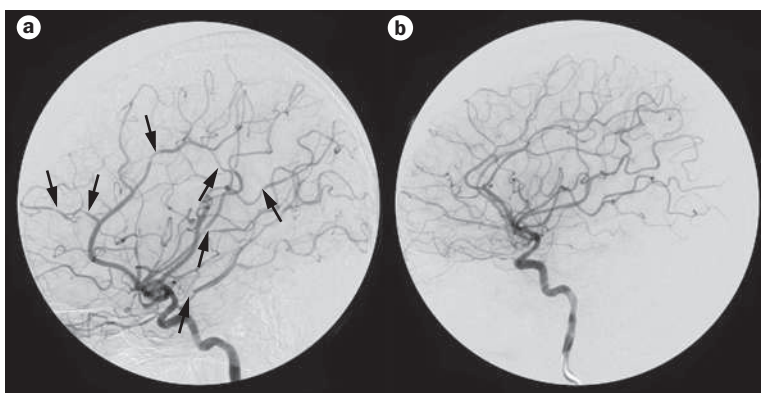


Figure 2 | Cerebral angiography. **a** | Initial angiogram performed on postpartum day 6. Arrows indicate areas of vasoconstriction. **b** | Follow-up angiogram performed 2 weeks later, showing resolution of angiographic abnormalities.

patient was also treated with a 3-day course of intravenous magnesium sulfate (2 g every 6 hours) with her serum magnesium level peaking at 2.9 mg/dl (1.19 mmol/l). The patient's neurological examination remained normal and her headache improved. Follow-up TCD studies during her stay on the neurology floor showed resolving vasoconstriction, with blood-flow velocity falling to ~180 cm/s in the M1 segment of the right MCA. A second cerebral angiogram was performed on postpartum day 20 and the vasospasm was unchanged. A CT angiogram on postpartum day 14 also confirmed proximal and distal cerebral vasospasm. 10 days after discharge, the patient was evaluated in the outpatient clinic, and her headache had continued to improve. Her neck stiffness and pain had completely resolved and her neurological examination continued to be normal.

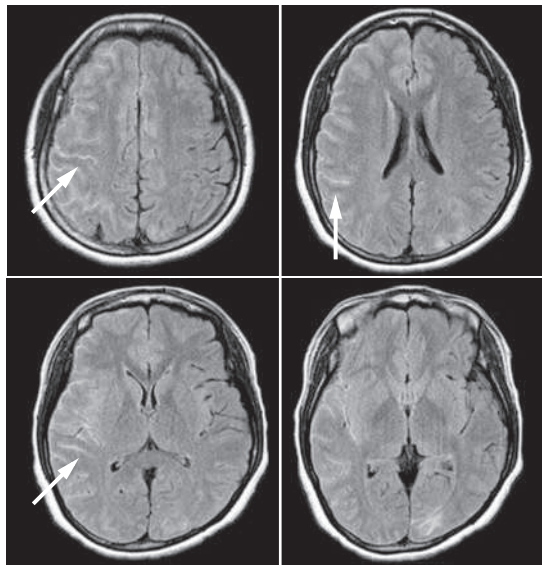


Figure 3 | MRI FLAIR sequences of the patient's brain. The FLAIR abnormalities are typical of those seen in subarachnoid hemorrhage, namely, bright signal in the sulci of the cortical convexities consistent with the bright signal of the CT scan, and edema of the cerebral cortex where the blood collects. Of note, no hypertension-related abnormalities are evident in the occipital lobes. Arrows indicate areas of increased FLAIR signal consistent with acute or subacute subarachnoid hemorrhage. Abbreviation: FLAIR, fluid-attenuated inversion recovery.

TCD performed during this clinic visit demonstrated decreased velocities in the M1 segment of the right MCA (140 cm/s) and the C1 segment of the right ICA (140 cm/s), consistent with significantly improved vasospasm. A follow-up brain MRI scan demonstrated no ongoing injury.

Discussion of diagnosis

Postpartum cerebral angiopathy (PCA) is characterized by a reversible, multifocal, diffuse segmental narrowing of the cerebral arteries that presents with neurological deficits. Sequelae of PCA commonly include both ischemic strokes and intracerebral hemorrhages. SAH, as described in this case, is a less common sequela of PCA, which is itself a rare disorder.

The differential diagnoses in this case initially included pre-eclampsia–eclampsia, aneurysmal SAH, venous sinus occlusion, persistent low pressure postdural puncture headache, and migraine.¹ Eclampsia can, in rare cases, produce a reversible vasoconstriction syndrome with a similar appearance on conventional angiogram to the vasoconstriction seen in our patient.^{2,3} Indeed, PCA and eclampsia could be considered together on the same spectrum of peripartum cerebrovascular illness. In this case, however, a negative eclampsia panel ruled out eclampsia according to the traditional definition: during hospitalization, the patient's systolic blood pressure stayed in the low 100s, which was near her baseline; urinalysis was negative for proteinuria; her liver enzymes were normal; and she

had no peripheral edema on examination. Eclampsia without hypertension but with cerebral edema was also considered, but was deemed unlikely because of an absence of any other defining features of eclampsia and a lack of relevant findings on MRI.

Two conventional angiograms separated by approximately 13 days showed no aneurysm, and also showed resolution of vasoconstriction (Figure 2b), which argues strongly against aneurysmal rupture. Occlusion of the venous sinuses and cerebral veins was also considered, but was ruled out on the basis of normal MR venography and patent venous sinuses on cerebral angiography. Arteriovenous malformation and arterial dissection related to childbirth were also ruled out by cerebral angiography and MR angiography. Pituitary apoplexy or infarction (Sheehan syndrome) was considered, but was excluded by brain MRI. In light of the cerebral angiogram, which revealed a diffuse pattern of focal arterial stenosis, clinical suspicion was narrowed to PCA and CNS vasculitis. On the basis of angiography alone, PCA can be difficult to distinguish from CNS vasculitis. The possibility of the SAH occurring secondary to spinal anesthesia or blood patch was also raised. Spinal MRI imaging was normal, however, and asymmetric layering of blood over the brain convexity would be an unusual occurrence in the latter etiology. The rapid clinical and angiographic improvement, as well as the close temporal relationship with her pregnancy, led to the final diagnosis of PCA in this patient.^{4,5}

Reversible cerebral vasoconstriction syndrome (RCVS), of which PCA is a subset, is rare, and its pathogenesis is poorly understood.⁶ RCVS is defined by a reversible, segmental, multifocal vasoconstriction of the cerebral arteries, and severe headaches (usually characterized as 'thunderclap' with an acute and excruciating onset), with or without focal neurological deficits or seizures.⁷ The typical findings on imaging consist of diffuse segments of narrowing involving large and medium-sized arteries in the anterior and posterior circulations, with occasional dilated segments. This pathology gives rise to the radiological pearl and string sign.⁶ In the present case, the diffuse findings on angiography did not match up perfectly with the TCD findings. It is possible, however, that the vasoconstriction was patchy, causing focal areas of elevated velocities to be missed on TCD.

PCA is typically self-limited and occurs within the first postpartum week in women after an uneventful pregnancy and delivery.⁸ In some instances, it can be associated with either ischemic strokes or intracerebral hemorrhage.⁵ Of note, in one case series, a cortical hematoma occurred in eight out of nine patients, which suggests that either cortical or leptomeningeal vessels are primarily involved in the process.⁴ The occurrence of SAH is rare in the context of PCA, with a review of the literature revealing only six such cases (Table 1).^{4,9–11}

The pathophysiology of PCA remains uncertain, although several mechanisms have been proposed. Pathological or toxic processes that affect cerebrovascular

Table 1 | Published cases of SAH associated with postpartum cerebral angiopathy

Study	Patient characteristics and history	Neurological features	Imaging results	Treatment	Outcome
Present case	33-year-old woman; 0 days postpartum; blood pressure 136/82 on presentation	Persistent headache following cesarean section, generalized tonic-clonic seizures	Diffuse SAH on CT and MRI scans; diffuse segmental narrowing on transfemoral cerebral angiogram; increased velocities in MCA and posterior cerebral artery on TCD	Nimodipine, opioid analgesics, toradol, naproxen, intravenous magnesium sulfate	Headache resolved, normal examination and imaging
Edlow <i>et al.</i> (2007) ⁹	37-year-old woman; 8 days postpartum; uncomplicated pregnancy; history of childhood meningitis; blood pressure 174/90 on presentation	Generalized tonic-clonic seizures	Frontal SAH on CT and MRI scans; diffuse segmental narrowing on angiogram	Intravenous magnesium sulfate; diltiazem, amlodipine	Normal examination, persistent focal narrowing at 3 weeks
Edlow <i>et al.</i> (2007) ⁹	25-year-old woman; 0 days postpartum; uncomplicated pregnancy; history of migraines; blood pressure 170/100 on presentation	None	Frontal SAH on CT and MRI scans; mild narrowing of supraclinoid ICA, MCA and basilar artery on angiogram	Calcium channel blocker	Persistent headache and chronic SAH on MRI scan
Singhal <i>et al.</i> (2004) ¹⁰	21-year-old woman; 7 days postpartum; history of common migraine; blood pressure 180/108 on presentation	Headache, generalized tonic-clonic seizures	RPLS and cortical SAH on MRI scan; narrowing of left posterior cerebral artery and vertebral and basilar arteries on angiogram	Intravenous magnesium sulfate, labetalol, phenytoin	Normal
Ursell <i>et al.</i> (1998) ⁵	39-year-old woman; 5 days postpartum (fourth child); history of ICH following delivery of third child; blood pressure normal on presentation	Aphasia, right hemiparesis	Frontal SAH on CT scan; diffuse segmental narrowing on angiogram	Methylprednisolone	Normal examination
Sengoku <i>et al.</i> (2005) ¹¹	32-year-old woman; 0 days postpartum; uncomplicated pregnancy; blood pressure normal on presentation	Altered mental status, left hemiparesis	SAH and right putaminal ICH on CT scan; diffuse narrowing on angiogram	None	Clinically improved, imaging resolved

Abbreviations: ICA, internal carotid artery; ICH, intracranial hemorrhage; MCA, middle cerebral artery; RPLS, reversible posterior leukoencephalopathy syndrome; SAH, subarachnoid hemorrhage; TCD, transcranial Doppler ultrasound.

tone must be considered. For example, the postpartum state itself could explain the rapid clinical and radiographical improvements observed in PCA: changes in vascular tone during pregnancy, which can predispose to stroke, normalize as the woman transitions from pregnancy to postpartum. Pregnancy-related hormonal factors could also have a role;⁴ for example, hormonal changes seem to induce remodeling of arterial walls during pregnancy. Transformations in the connective tissue of the arterial wall that occur during pregnancy consist of a reduction in collagen and elastin content, leading to a transient loss of distensibility that begins to normalize near term.¹² Increased contractility, decreased stiffness, and an increased relaxant response in the MCA have all been observed in animal models.¹³ Such changes, in light of the altered hemodynamics of pregnancy and the puerperium (for example, increased blood volume, heart rate, cardiac output and stroke volume), could lead to raised endovascular pressure against a weakened arterial wall, leading to an increased risk of vessel wall rupture and hemorrhage.¹ In some cases of PCA, the angiopathy occurred in the setting of vasospastic drug use (for example, bromocriptine, dihydroergotamine, heroin, isometheptene or ergonovine).^{4,8}

Treatment and management

Table 1 summarizes the treatment and management of previously published cases of SAH in association with PCA. According to the literature, PCA is a self-resolving disorder, and we chose to treat the symptoms and the vasoconstriction with pharmacological interventions in the present case. The headache was initially treated with NSAIDs and opioid analgesics. Subsequently, nimodipine was used to treat vasoconstriction secondary to SAH. We also addressed the possibility of subclinical pre-eclampsia–eclampsia by treating the patient with intravenous magnesium sulfate, which has also been shown to reduce vasoconstriction in SAH. We withheld methylprednisolone treatment, as no evidence of inflammation or vasculitis was present and anti-vasoconstriction therapies were working, making a fixed vasculopathy unlikely.

Conclusions

SAH in the context of PCA is rare, and only five other cases have been reported previously (Table 1). The rapidly reversible diffuse segmental vasoconstriction and resolution of symptoms are crucial in differentiating PCA from other, more-common vasculopathies.

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