

## CASE REPORT

# Postpartum cerebral angiopathy treated with intra-arterial nicardipine and intravenous immunoglobulin

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Received 29 November 2011

Revised 16 January 2012

Accepted 31 January 2012

Published Online First

19 February 2012

## ABSTRACT

Postpartum cerebral angiopathy (PCA) is a rare vasoconstriction syndrome that can lead to severe disability and death. The pathophysiology of PCA is unknown. A case of a 39-year-old woman who developed PCA 3 days after twin delivery is reported. She presented with right hemiparesis, aphasia and lethargy. Imaging studies demonstrated severe segmental narrowing of multiple cerebral arteries comprising the anterior and posterior circulations. She continued to deteriorate despite induced hypertension, immunosuppression, intravenous magnesium and oral nimodipine. Intra-arterial administration of nicardipine on three consecutive occasions reversed the angiographic vasospasm and led to symptom resolution. Definite improvement occurred after a 5 day course of intravenous immunoglobulin (IVIg). The patient described in this report developed recalcitrant PCA-induced vasospasm which resolved with endovascular administration of nicardipine and immunotherapy with IVIg.

## INTRODUCTION

Postpartum cerebral angiopathy (PCA) is a rare cerebrovascular disorder that typically occurs after an uncomplicated pregnancy and delivery. This entity is part of the reversible vasoconstriction syndromes (RVS) and is characterized by segmental narrowing of large and medium sized cerebral arteries. In some cases, multiple strokes can cause severe disability and even death in this otherwise healthy population.<sup>1</sup>

Few reports have described the use of endovascular interventions in the treatment of these patients.<sup>1–4</sup> We describe a patient with PCA who was treated with intra-arterial (IA) administration of nicardipine on three occasions due to severe symptomatic vasospasm. Moreover, despite maximized conventional medical treatment and IA infusion of nicardipine, the patient continued to be symptomatic. Intravenous immunoglobulin (IVIg) was administered in the hope of stopping the vasculopathy triggering the recurrent vasospasm.

## CASE REPORT

A 39-year-old woman with a normal pregnancy developed a steady holocephalic headache 3 days after delivering full term twins via cesarean section. The headaches increased in intensity and after 7 days she decided to seek medical attention. She

did not have a prior history of headaches, hypertension, smoking, alcohol or illegal substance use. Her only medications included ibuprofen for pain and daily vitamins.

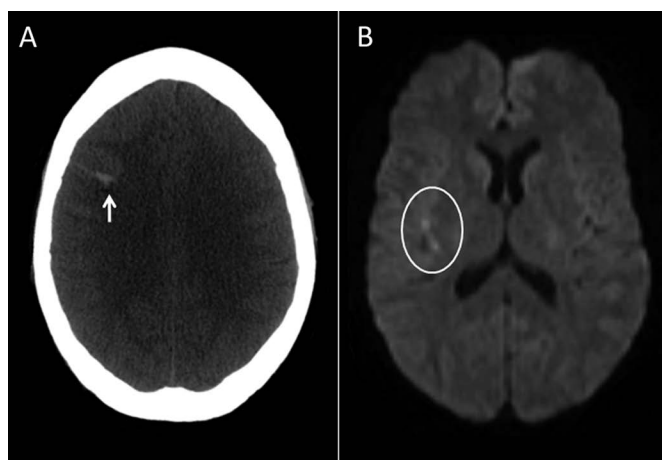
Fluid attenuated inversion recovery MRI sequence revealed a hyperintensity along the right frontal cortical sulci, suggestive of a subarachnoid hemorrhage (SAH). On transfer to our facility, she was in mild distress from a severe and continuous headache. She was awake, alert and oriented, with normal and fluent speech and intact higher cortical functioning. Her vital signs, physical and neurological examinations were normal. She was admitted for observation and treated with acetaminophen.

A head CT 48 h after admission (postpartum day 12) demonstrated a new right frontal SAH (figure 1A). Her transcranial Doppler (TCD) velocities were within normal limits. A catheter diagnostic cerebral angiogram showed evidence of multifocal, mild segmental stenosis of the distal branches of the posterior cerebral arteries and posterior inferior cerebellar arteries. Evaluation for systemic vasculitis or rheumatological diseases was negative and included: erythrocyte sedimentation rate, C reactive protein, rheumatoid factor, cryoglobulin, antinuclear antibodies, HIV, hepatitis panel, complement, anticardiolipin antibody, anti-neutrophil antibodies and lupus anticoagulant.

On postpartum day 15 she developed right hemiparesis, right face, arm and leg numbness, mild expressive aphasia and marked drowsiness. A brain MRI demonstrated new scattered foci of SAH along the right frontal sulci as well as new small infarcts along the right insula and right posterior periventricular white matter (figure 1B). MR angiography demonstrated multiple areas of intracranial stenosis affecting both the anterior and posterior circulations, suggestive of evolving vasculopathy (figure 2A).

She continued to deteriorate and became less arousable despite induced hypertension, volume expansion and oral nimodipine. A diagnostic cerebral angiogram performed the next day demonstrated generalized vasospasm, especially in the anterior circulation. After a total infusion of 15 mg of nicardipine in both internal carotid arteries, the angiographic vasospasm improved and her neurological deficits resolved almost immediately (figure 3).

In the following days, she was treated with intravenous magnesium and steroids (methylprednisolone 40 mg every 6 h) as a diagnosis of PCA was



**Figure 1** (A) CT on postpartum day 12 demonstrating a right frontal subarachnoid hemorrhage (arrow). (B) Diffusion weighted imaging sequence on postpartum day 17 with small infarcts in the right insula (circle). These findings did not account for the patient's right hemiparesis and aphasia but were considered to be a consequence of the generalized vasospasm affecting the anterior and posterior circulations.

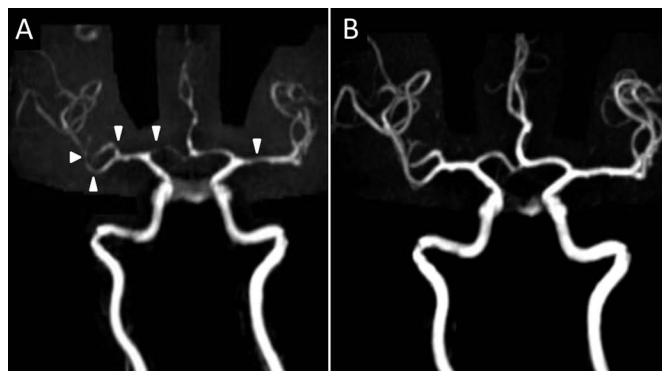
entertained. In spite of these therapies she continued experiencing episodes of right hemiparesis, expressive aphasia and lethargy. Worsening of her neurological status was associated with increased TCD velocities, which suggested vasospasm induced hypoperfusion. She was treated on two more occasions with IA nicardipine with subsequent immediate resolution of her neurological deficits each time. Several areas of vasospasm affecting mainly the anterior circulation were visualized in each angiogram. A 24 h video EEG did not demonstrate seizure activity.

The case was reviewed in various multidisciplinary conferences and on postpartum day 20 it was decided to start a 5 day course of IVIg (400 mg/kg) in the hope of attenuating the immune process that may be triggering the evolving vasculopathy. Forty-eight hours after initiation of IVIg, TCD velocities improved and the patient remained clinically stable. One week later she was discharge with mild headache and a normal neurological examination. Repeat MR angiography 3 months later demonstrated resolution of the vasospasm (figure 2B).

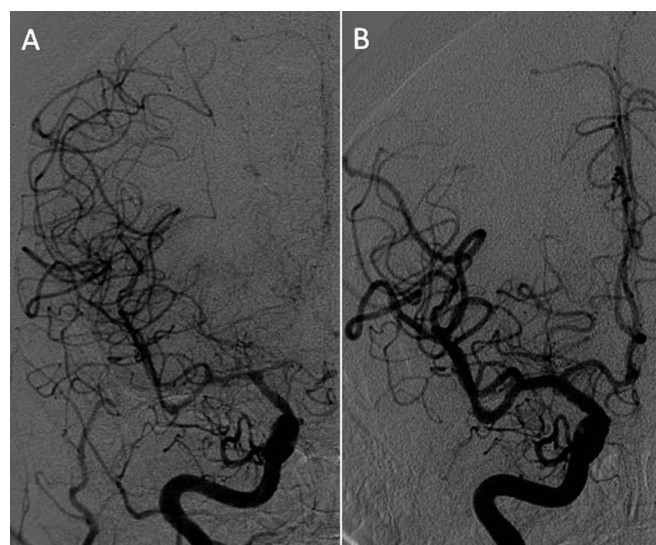
## DISCUSSION

### Definition

RVS may occur during eclampsia and hypertensive encephalopathy.<sup>5</sup> PCA is considered a subset of RVS. Postpartum women



**Figure 2** (A) MR angiography (MRA) on postpartum day 17 with multiples areas of vasospasm (arrowheads) in the bilateral internal carotid artery territories. (B) MRA 3 months later demonstrates resolution of vasospasm with excellent distal flow.



**Figure 3** (A) Postpartum day 18 cerebral angiography demonstrates extensive vasospasm in the terminal right internal carotid artery, M1 and M2 segments of the middle cerebral artery and anterior cerebral artery. (B) Angiogram after infusion of nicardipine with resolution of the vasospasm and visualization of the anterior cerebral artery.

who present within the first 2 weeks of delivery with cerebral vasoconstriction and without clinical or laboratory data to suggest eclampsia may have PCA. Systemic vasculitis or primary CNS vasculitis should be ruled out as part of the diagnosis of PCA.

Discrimination between PCA and postpartum pre-eclampsia or eclampsia is based on the absence of systemic vascular disease in PCA.<sup>6</sup> However, some authors postulate that postpartum pre-eclampsia, eclampsia and PCA are within the same spectrum of peripartum cerebrovascular illness and share a common pathophysiological process.<sup>7</sup>

PCA is typically self-limiting and occurs within the first 2 weeks postpartum in women with an uneventful pregnancy and delivery.<sup>8</sup> Additionally, PCA has been associated with reversible posterior leukoencephalopathy syndrome (RPLS).<sup>9</sup>

### Pathophysiology

A disturbance in the regulation of cerebral arterial tone due to intrinsic (endothelin or serotonin) or extrinsic (vasoactive drugs and blood pressure) factors may be the main pathophysiological process. Regional vascular variations may determine whether a patient manifests with PCA, RPLS or an overlapping syndrome. Common vasoactive substances related to the development of PCA include pseudoephedrine, bromocriptine, sumatriptan, cocaine and amphetamine derivatives.<sup>10 11</sup> The patient described in this report did not develop RPLS and was not exposed to vasoactive substances.

Strokes may result from vasoconstriction which can involve proximal large vessels or small distal branches. It is unclear what causes SAH. In a large series of 30 patients with RVS (five postpartum) described by Ducros *et al*, 17% of patients with hemorrhagic RVS initially presented with isolated headaches and normal brain imaging. Cortical SAH or other type of cerebral hemorrhage developed a few days after recurrent severe headaches.<sup>12</sup> This suggests that an abnormal vascular process starts before hemorrhage. Moreover, small vessel dysfunction may disrupt the blood-brain barrier and manifest with cortical SAH.<sup>9 12</sup>

**Table 1** Postpartum cerebral angiopathy patients treated with endovascular approaches

	Age (years)	Onset* (days)	Clinical presentation/imaging	Medical management	Endovascular treatment	Outcome
Fletcher <sup>1</sup>	28	4	Headaches Cortical SAH	Steroids, magnesium, nimodipine and induced hypertension	IA verapamil	Permanent disability
Song <sup>2</sup>	42	8	Seizures and left hemiparesis Ischemic infarct	Steroids, magnesium, nimodipine and induced hypertension	Angioplasty of the MCA and supraclinoid ICAs	Moderate disability
Ringer <sup>3</sup>	27	5	Seizures and headaches Ischemic infarct and RPLS	Steroids, antihypertensives and magnesium.	Angioplasty of the PCA, BA, VA, MCAs and ICAs.	Mild cognitive impairment
Singhal <sup>4</sup>	36	10	Seizures and headaches Ischemic infarct	Magnesium, intrathecal nicardipine and induced hypertension	IA nicardipine left VA and ICAs	Death
BCVI (this study)	39	3	Headaches Cortical SAH	Steroids, magnesium, nimodipine, IVIg and induced hypertension	IA nicardipine	Normal

\*Days after delivery.

BA, basilar artery; BCVI, Baptist Cardiac and Vascular Institute; IA, intra-arterial; ICA, internal carotid artery; IVIg, intravenous immunoglobulin; MCA, middle cerebral artery; PCA, posterior cerebral artery; RPLS, reversible posterior leukoencephalopathy syndrome; SAH, subarachnoid hemorrhage; VA, vertebral artery.

It has been hypothesized that the intima of the cerebral vasculature is hormonally altered during PCA due to acute elevations in blood pressure.<sup>13 14</sup> This theory is supported by autopsy findings of intimal hyperplasia.<sup>13</sup> Moreover, pregnancy related hormonal changes seem to induce arterial wall remodeling during pregnancy. Histopathological studies in animal models have shown that during pregnancy there is a reduction in collagen and elastin content, leading to a transient loss of distensibility that normalizes near term.<sup>15</sup>

The vasoconstriction seen in PCA has been related to transient inflammation.<sup>11</sup> Brain autopsy specimens of women with PCA have shown marked inflammatory cell infiltration of intraparenchymal arterioles and capillaries near zones of infarction.<sup>16</sup> Brain biopsies have also demonstrated perivascular chronic inflammation.<sup>2</sup>

In summary, the variety of theories around the pathophysiology of PCA suggests that we lack a clear understanding of the disease process and its etiology.

## Treatment

Most patients with PCA have excellent functional recovery and only manifest with headache.<sup>17</sup> However, aggressive treatment should be pursued if patients experience neurological deficits. Multiple hemorrhagic and ischemic strokes due to severe vasoconstriction may lead to disability and death.<sup>1 2 4 13 16 18 19</sup> PCA treatment modalities reported in the literature include intravenous magnesium,<sup>7 20 21</sup> oral calcium channel blockers,<sup>11 21 22</sup> induced hypertension,<sup>2 4</sup> antiplatelets,<sup>23</sup> intrathecal nicardipine,<sup>4</sup> hypervolemia<sup>24</sup> and immunosuppression with corticosteroids and cytotoxic drugs.<sup>16 17</sup> In most cases no treatment is necessary and symptoms resolve spontaneously.<sup>3</sup>

Blood pressure management in PCA can be challenging. Acute hypertension is believed to be a precipitant factor, especially when linked to pre-eclampsia or eclampsia.<sup>11</sup> Conversely, hypotension can theoretically reduce cerebral perfusion in patients with severe vasoconstriction. We favor induced hypertension in patients with deteriorating neurological symptoms and severe vasoconstriction, such as the case described in this report.

The experience with endovascular therapies in the treatment of PCA is very limited. Endovascular treatment has usually been reserved for severe cases that do not respond to medical management. Four cases of PCA that were treated with endovascular approaches have been reported in the literature (table 1).<sup>1 3 4 16</sup> Three of these cases presented with seizures and hypertension, suggesting delayed postpartum eclampsia.<sup>2-4</sup> Angioplasty was not chosen as the primary treatment modality

in the case reported in this manuscript because the vasospasm affected several vascular territories and long arterial segments (figure 2A, B).

The patient described in this report continued to deteriorate despite aggressive medical management that included induced hypertension, nimodipine, intravenous magnesium and steroids. IA nicardipine was administered in light of evolving neurological deterioration and angiographic evidence of severe vasospasm. IA nicardipine appeared to be effective in resolving the vasospasm and temporarily improving the patient symptoms. However, it did not provide definite symptom resolution. This suggested an evolving vasculopathy recalcitrant to calcium channel blockers, magnesium and induced hypertension. IVIg was administered in the hope of stopping the presumed immune process triggering these vascular changes.

It is unclear if IVIg exerted an immunomodulatory effect on the patient described in this report. Certainly, after 2 days of IVIg infusion, TCD velocities improved and she did not experience more episodes of neurological deterioration. However, we cannot rule out the possibility that these findings are due to a self-limiting disease process that was coincidental with the administration of IVIg.

**Contributors** Study concept and design: EAS. Acquisition of the data: GMG and FT-C. Analysis and interpretation of the data: EAS, IL and GD. Drafting of the manuscript: EAS, GMG and FT-C. Critical revision of the manuscript for important intellectual content: IL and GD. Administrative, technical and material support: GMG and KF.

**Competing interests** None.

**Patient consent** Obtained.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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*J NeuroIntervent Surg* 2013 5: e12 originally published online February 19, 2012

doi: 10.1136/neurintsurg-2011-010220

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