

# Postpartum Angiopathy With Reversible Posterior Leukoencephalopathy

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**Background:** Postpartum angiopathy (PPA) is a cerebral vasoconstriction syndrome of uncertain cause that affects large and medium-sized cerebral arteries. Postpartum angiopathy is frequently complicated by ischemic stroke. The reversible posterior leukoencephalopathy syndrome (RPLS) is a distinct clinical-radiological entity characterized by transient vasogenic edema on brain imaging. The pathophysiological features of RPLS are related to small-vessel dysfunction and breakdown of the blood-brain barrier.

**Objectives:** To report the coexistence of PPA and RPLS in 4 patients and to discuss possible interrelationships between these 2 entities.

**Design:** Four case reports and a review of the literature.

**Results:** Four women developed a clinical-radiological syndrome overlapping PPA and eclampsia shortly after an uncomplicated pregnancy. All had acute severe (“thunderclap”) headaches and hypertension. Three developed seizures. All patients had reversible angiographic narrowing of large and medium-sized cerebral arteries. Serial magnetic resonance imaging showed transient nonischemic brain lesions, resembling the lesions described in patients with RPLS. The results of extensive tests for cerebral vasculitis were negative.

**Conclusion:** These cases, and the literature, suggest an interrelationship between RPLS and cerebral vasoconstriction syndromes such as PPA.

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**T**HE REVERSIBLE CEREBRAL segmental vasoconstriction syndrome (RCV) is a clinical-angiographic syndrome characterized by the abrupt onset of severe headaches, seizures, focal neurological deficits, and segmental narrowing and dilatation of large and medium-sized cerebral arteries, typically in women aged 20 to 50 years. The vasoconstriction can be idiopathic or associated with conditions like migraine, vasoactive drug use, and pregnancy or puerperium (postpartum angiopathy [PPA]).<sup>1</sup>

The reversible posterior leukoencephalopathy syndrome (RPLS) is characterized by reversible posterior-predominant white and gray matter lesions (vasogenic edema) on brain magnetic resonance imaging (MRI), in patients with conditions like eclampsia, hypertensive encephalopathy, and uremia.<sup>2</sup> Acute headaches, seizures, and visual deficits are typical clinical features. The pathophysiological features of RPLS have been related to small-vessel

dysfunction and breakdown of the blood-brain barrier, usually in the face of severe hypertension.

Described herein are 4 patients with clinical and angiographic features of PPA, whose neuroimaging findings were consistent with RPLS (**Table**).

## REPORT OF CASES

### PATIENT 1

On days 4 and 13 after an elective cesarean section, a 37-year-old woman developed sudden-onset severe occipital headaches. She had no history of migraines. On hospital admission (day 13), her blood pressure was 150/78 mm Hg and she had no neurological deficits. Blood cell counts, electrolyte levels, and urinalysis results were normal. The results of extensive tests for vasculitis were negative, including tests for antinuclear and anti-double-stranded DNA antibodies, rheumatoid factor, anti-neutrophil cytoplasm antibodies, antibodies to proteinase 3 and myeloperoxidase, and anti-

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Patient Characteristics				
Characteristic	Patient No.			
	1	2	3	4
Age, y	37	21	23	31
History of migraine	-	+	+	-
Postpartum day of onset	4	7	12	4
Clinical features	Thunderclap headaches	Thunderclap headaches and seizures	Thunderclap headaches and seizures	Thunderclap headaches and seizures
Admission BP, mm Hg	150/78	180/108	200/100	200/100
Brain MRI findings	Reversible posterior bihemispheric lesions	Reversible bihemispheric and cerebellar lesions and SAH	Reversible bihemispheric and cerebellar lesions	Reversible posterior bihemispheric lesions
Arteries involved	ICA, MCA, and PCA	PCA, VA, and basilar artery	ACA and MCA	ICA, ACA, MCA, and PCA

Abbreviations: ACA, anterior cerebral artery; BP, blood pressure; ICA, internal carotid artery; MCA, middle cerebral artery; MRI, magnetic resonance imaging; PCA, posterior cerebral artery; SAH, subarachnoid hemorrhage; VA, vertebral artery; -, absent; +, present.

Ro, anti-La, anti-Scl-70, and anti-Jo-1 antibodies, and serological tests for syphilis and Lyme disease. A cerebrospinal fluid examination showed 0 red blood cells per microliter, 2 white blood cells per microliter, and protein level of 0.044 g/dL. Transcranial Doppler studies showed elevated blood flow velocities in all circle of Willis arteries. A brain MRI (on day 13) showed multiple lesions, hyperintense on T2-weighted and fluid-attenuated inversion recovery (FLAIR) sequences (**Figure 1A**), without restricted diffusion on apparent diffusion coefficient (ADC) maps. The results of MR venography were normal. Her hospital course was notable for frequent headache exacerbations with blood pressure elevations up to 190/100 mm Hg. Twenty-four-hour urine metanephrine and vanillylmandelic acid levels were normal. On day 17, a second brain MRI showed resolution of most previously noted parenchymal lesions, and the results of MR angiography (MRA) of the head and neck vessels were normal. She had an acute headache exacerbation on day 20. A repeat brain MRI was normal; however, MRA showed segmental vasoconstriction of the bilateral distal internal carotid arteries, middle cerebral arteries (MCAs), and posterior cerebral arteries (**Figure 2A**). She was treated with intravenous magnesium sulfate and antihypertensive agents. Head computed tomographic (CT) angiography on day 22 showed complete resolution of proximal MCA and posterior cerebral artery vasoconstriction (**Figure 2B**); however, segmental narrowing was still present in some MCA branches. Her headaches resolved over 10 days, and she was discharged from the hospital.

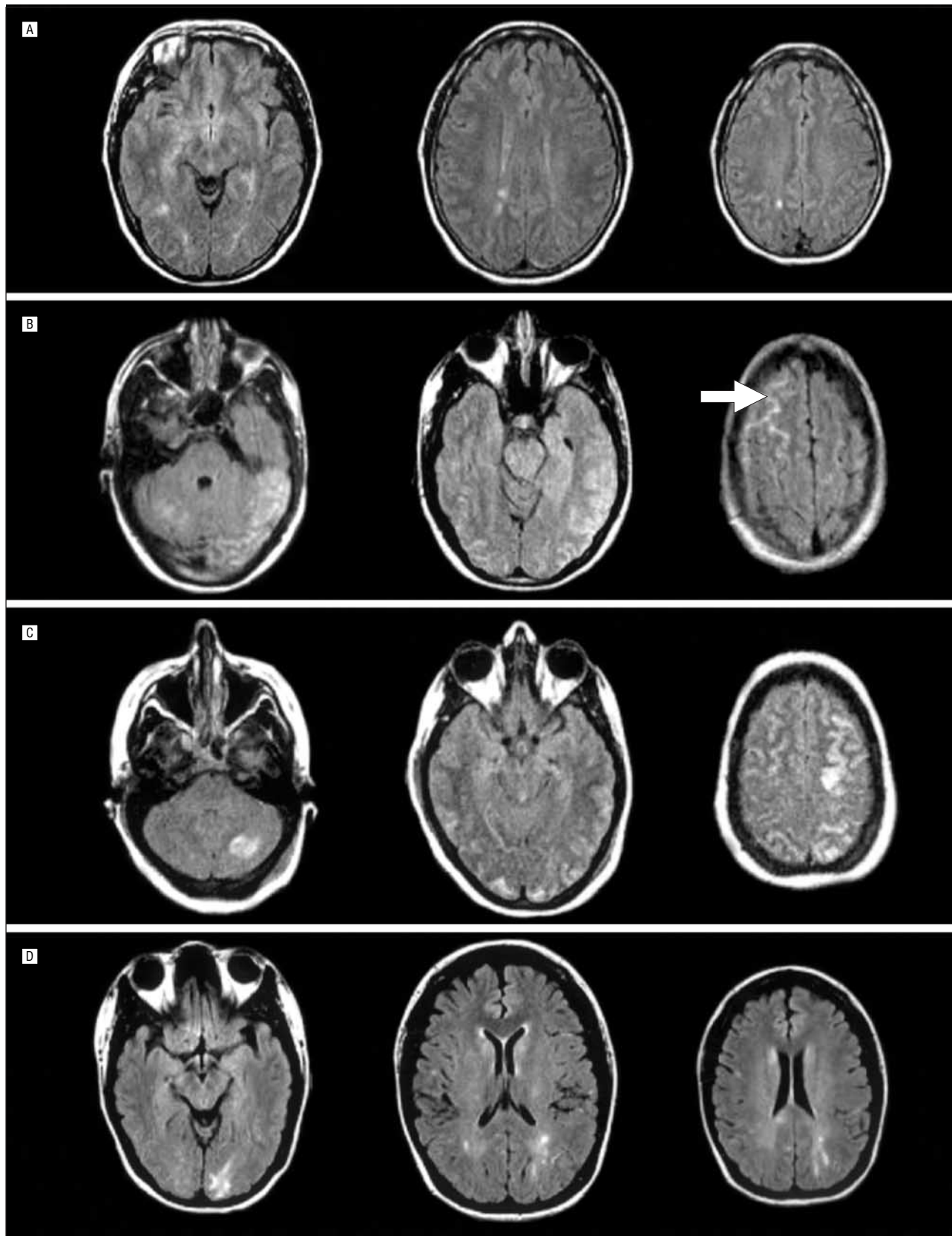
#### PATIENT 2

One week after an uncomplicated vaginal delivery, a 21-year-old woman developed a sudden severe headache followed by generalized seizures. She had a history of common migraine headaches and depression, treated with fluoxetine for 3 months. On hospital admission, her blood pressure was 180/108 mm Hg and she had hyperreflexia but no focal neurological deficits. A cerebrospinal fluid examination showed 1070 red blood cells per microliter, 0 white blood cells per microliter, and protein level of 0.051 g/dL. Brain MRI showed mul-

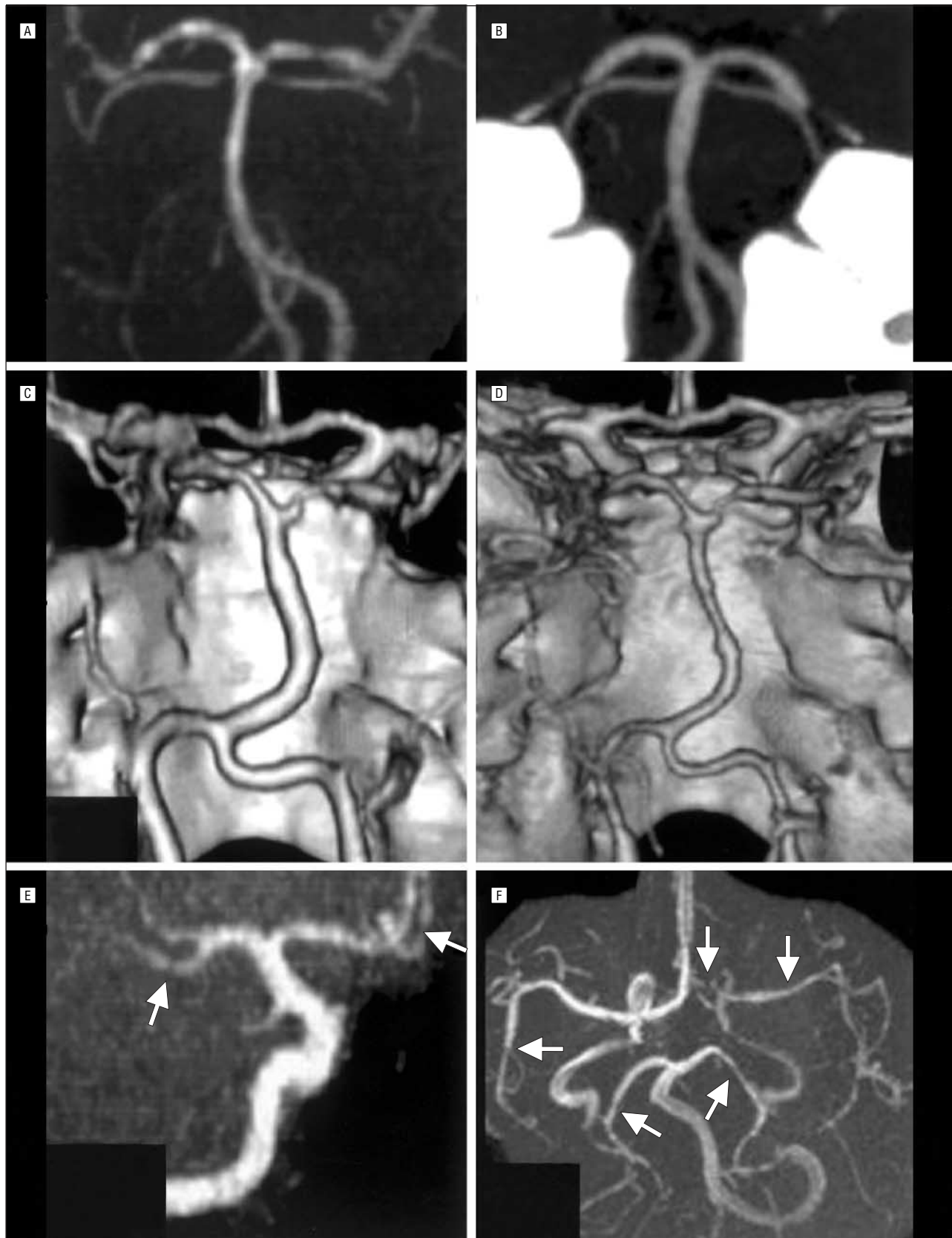
tle lesions, all hyperintense on T2-weighted and FLAIR sequences, without restricted diffusion on ADC maps. In addition, there was a minor subarachnoid hemorrhage overlying the right frontal cortex (**Figure 1B**). Transfemoral cerebral angiography and CT angiography (**Figure 2C**) showed narrowing of the left posterior cerebral artery, but no cerebral aneurysm. She was treated with intravenous magnesium, labetalol hydrochloride, and phenytoin. The following day, she developed another sudden severe headache. Repeat CT/CT angiography showed new vertebral and basilar artery narrowing (**Figure 2D**); however, the previously noted subarachnoid blood was no longer visualized. Severe headaches recurred, but with decreasing intensity and frequency. Brain MRIs on puerperal days 9 and 11 showed gradual resolution of the previously noted abnormalities. Transfemoral cerebral angiography, repeated after 1 month, showed complete resolution of vasoconstriction.

#### PATIENT 3

A 23-year-old woman with a history of common migraine developed mild headaches and dyspnea 12 days after an uncomplicated vaginal delivery. On day 15, she developed a sudden severe headache that was different from her prior migraine headaches, followed by generalized seizures and severe hypertension (blood pressure, 200/100 mm Hg). The result of head CT was normal, and there was no subarachnoid hemorrhage. Brain MRI showed multiple lesions (**Figure 1C**) that were hyperintense on T2-weighted and FLAIR sequences, without restricted diffusion on ADC maps. Head MRA showed vasoconstriction in the right anterior cerebral artery and MCA (**Figure 2E**). Transcranial Doppler studies showed diffusely elevated blood flow velocities with an abnormal spectral configuration, suggesting cerebral vasoconstriction. Blood cell counts, electrolyte levels, urinalysis results, serum and urine toxicology screen results, and 24-hour urine metanephrine and vanillylmandelic acid levels were normal. The workup for dyspnea included chest CT angiography (normal results) and cardiac ultrasonography, which showed diffuse hypokinesia and a low ejection fraction. She was diagnosed as having



**Figure 1.** Brain magnetic resonance imaging (MRI) fluid-attenuated inversion recovery sequences. A, Patient 1. The MRI findings on postpartum day 13 show subcortical white matter lesions in the right posterior temporal and parietal regions and the forceps major. B, Patient 2. The MRI findings on day 7 show multiple cortical and subcortical hyperintense lesions in bilateral temporal and parietal regions. In addition, a small amount of subarachnoid blood is present in the right frontal region (arrow). C, Patient 3. The MRI findings on day 15 show hyperintense lesions in the left cerebellar hemisphere and in the bilateral temporal, parietal cortical, and subcortical regions. D, Patient 4. The MRI findings on day 6 show subcortical hyperintense lesions in the posterior regions of both cerebral hemispheres.



**Figure 2.** Angiographic findings. A, Patient 1. Magnetic resonance angiographic (MRA) findings on postpartum day 20 show segmental vasoconstriction in the bilateral posterior cerebral arteries and basilar artery. B, Patient 1. Computed tomographic angiographic (CTA) findings on day 22 show complete resolution of the vasoconstriction. C, Patient 2. The CTA findings on day 7 show vasoconstriction of the proximal left posterior cerebral artery. D, Patient 2. The findings of a repeat CTA on day 8, performed to investigate severe headache exacerbation, show new vasoconstriction in the basilar and bilateral intracranial vertebral arteries. E, Patient 3. The MRA findings on day 15 show segmental vasoconstriction (arrows) of the right middle cerebral artery and left anterior cerebral artery branches. F, Patient 4. The MRA findings on day 17 show severe narrowing (arrows) of the left internal carotid and anterior, middle, and posterior cerebral arteries.



peripartum dilated cardiomyopathy, and treated with intravenous magnesium and captopril. After 1 week, a second brain MRI showed complete resolution of the previously noted abnormalities. The results of follow-up transcranial Doppler studies were normal. The cardiomyopathy resolved within 10 days. She had no further headaches or seizures, and was discharged from the hospital.

#### PATIENT 4

Four days after an uncomplicated vaginal delivery, a 31-year-old woman developed a sudden excruciating headache. On hospital admission, her blood pressure was 200/100 mm Hg and she had hyperreflexia but no focal neurological deficits. The result of head CT was normal. The headache and hypertension improved after intravenous magnesium and labetalol treatment. On day 6, the headache suddenly increased in intensity; her blood pressure measured 148/77 mm Hg. Brain MRI showed multiple lesions, all hyperintense on T2-weighted and FLAIR sequences (Figure 1D), without restricted diffusion on ADC maps. The result of MR venography was normal. Headaches recurred frequently, and on day 10, she developed generalized seizures. Serial brain MRIs on days 14, 17, and 19 showed initial progression and then resolution of the RPLS-like lesions. Magnetic resonance angiography on days 17 and 19 showed severe left internal carotid artery, anterior cerebral artery, MCA, and posterior cerebral artery narrowing (Figure 2F). In addition, there was incidental dissection of the extracranial left internal carotid artery. Carotid ultrasonography on day 22 showed normal blood flow velocities in both carotid arteries. Her clinical status improved gradually over 10 days, and she was discharged from the hospital. Repeat MRA at 6 months showed resolution of all arterial abnormalities.

#### COMMENT

All patients developed “thunderclap” headaches and hypertension in the postpartum period, 3 developed seizures, and all had angiographic segmental cerebral arterial vasoconstriction. Brain MRI showed posterior-predominant subcortical and cortical lesions that were hyperintense on FLAIR, T2-weighted, and ADC images, similar to the lesions described in patients with RPLS. Clinical features and imaging abnormalities resolved spontaneously within days to weeks. The results of extensive tests for cerebral vasculitis were negative. In patient 2, the sudden-onset basilar artery vasoconstriction was probably unrelated to the minor nonaneurysmal subarachnoid hemorrhage overlying the frontal cortex. Nonaneurysmal subarachnoid hemorrhages can occur in patients with pregnancy-induced hypertension and eclampsia, possibly due to the rupture of pial vessels in the face of sudden hypertension and impaired autoregulation.<sup>3</sup> This patient was exposed to fluoxetine, a serotonin-enhancing drug that might have contributed to the reversible cerebral vasoconstriction.<sup>4</sup>

Classification of these patients is a challenge. Features such as acute headaches, seizures, hypertension, and reversible vasoconstriction are consistent with the diag-

nosis of PPA. However, brain MRI showed lesions consistent with RPLS and not ischemic stroke, which is the usual lesion associated with PPA. Headaches, seizures, hypertension, and RPLS occurring more than 48 hours after delivery raise the possibility of postpartum eclampsia; however, none of the patients had proteinuria. Postpartum patients with segmental cerebral vasoconstriction who do not meet the criteria for eclampsia are usually classified as having PPA.<sup>5</sup> The constellation of clinical and imaging features in these patients is similar to those of previously published cases, and supports the view that PPA and eclampsia are interrelated conditions with similar pathophysiological features.<sup>5,6</sup>

The literature<sup>7-11</sup> suggests that a similar relationship exists between RPLS and RCV in patients with conditions other than pregnancy. Clinical features such as abrupt onset, severe (thunderclap) headaches, confusion, seizures, and visual deficits are common in patients with RPLS and RCV. While patients with RCV have large-artery (proximal) cerebral vasoconstriction and stroke, the pathophysiological features of RPLS have been related to endothelial dysfunction and failure of cerebral autoregulation involving distal arterioles and capillaries. The brain lesions of RPLS probably reflect fluid and protein extravasation (vasogenic edema) due to passive vasodilatation in the face of severe hypertension. Nevertheless, numerous reports<sup>7-12</sup> of decreased cerebral blood flow, cytotoxic edema, ischemic stroke, and angiographic vasoconstriction, in hypertensive and nonhypertensive patients with RPLS, suggest an important role for cerebral vasoconstriction in RPLS. In retrospect, one previously described patient with sumatriptan succinate-associated cerebral vasoconstriction probably had brain lesions consistent with RPLS.<sup>4</sup> Finally, the topographic features of ischemic strokes that occasionally complicate RPLS are similar to those of strokes associated with RCV—“watershed” distribution strokes that often spare the cortex while involving the subcortical regions.<sup>13</sup>

These data indicate that large and medium-sized cerebral vasoconstriction occurs in patients with RPLS, and that vasogenic edema can occur in patients with large-artery vasoconstriction syndromes such as PPA. Central to the pathophysiological features might be disturbances in the regulation of cerebral arterial tone (due to either intrinsic factors like endothelin or serotonin or extrinsic factors like vasoactive drugs), with regional variations determining whether the patient manifests with RCV, RPLS, or an overlapping syndrome, as in these 4 patients. For example, coexisting vascular changes in the distal arterial bed might lead to the development of vasogenic edema in patients with angiographic (proximal) arterial vasoconstriction.

Most patients with RPLS have normal cerebral angiogram results. Mild or medium-sized arterial narrowing might escape detection with newer imaging modalities, such as CT or MRA. Timing of the vascular imaging study might be another factor: vasoconstriction is not always present at the onset of symptoms, can begin abruptly, can fluctuate, and can resolve within days. In patients 1 and 2, the initial angiographic studies showed no significant vasoconstriction. However, repeat studies per-

formed soon after acute headache exacerbations showed severe reversible vasoconstriction (Figure 2B). Further study is needed to fully understand the pathophysiological features, causes, and interrelationships of these conditions.

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