Variable Presentations of Postpartum Angiopathy

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Background and Purpose—Postpartum angiopathy (PPA), a rare cause of stroke in the puerperium, is heralded by severe headaches within 1–2 weeks after delivery. Angiography demonstrates segmental vasoconstriction that often resolves spontaneously. PPA is generally regarded as benign. We aimed to define clinical presentations, radiological findings, and outcomes of patients with PPA.

Methods—We retrospectively reviewed patients from 3 centers with acute neurological symptoms and angiography showing vasoconstriction in the postpartum period. Patients without neuroimaging and with diagnoses of cerebral venous sinus thrombosis and aneurysmal hemorrhage were excluded. Patient characteristics, clinical symptoms, neuroimaging findings, and clinical condition at hospital discharge were collected.

Results—Eighteen patients (mean age, 31 years; range, 15–41) were identified. Median gestation was 38 weeks. Twelve (67%) had a history of prior uneventful pregnancy. Neurological symptoms began on median day 5 postpartum and included headache (n=16, 89%), focal deficit (n=9, 50%), visual disturbance (n=8, 44%), encephalopathy (n=6, 33%), and seizure (n=5, 28%), often in combination. Brain imaging was abnormal in most (n=13, 72%). The most common abnormalities were intracranial hemorrhage (n=7, 39%), vasogenic edema (n=6, 35%), and infarction (n=6, 35%). Clinical outcomes were markedly variable with full recovery seen in 9 (50%), death after a fulminant course in 4 (22%), and residual deficits in 5 (28%).

Conclusions—In contrast to prior reports, this group of patients with PPA had a higher proportion of nonbenign outcomes. Most patients who undergo neuroimaging have parenchymal abnormalities, which are most often stroke (hemorrhagic or ischemic) or reversible vasogenic edema. (Stroke. 2012;43:00-00.)

Key Words: acute stroke ■ intracranial hemorrhage ■ women ■ eclampsia ■ PRES ■ postpartum angiopathy ■ reversible cerebral vasoconstriction syndrome

Acute neurological symptoms in the weeks after an uncomplicated pregnancy and delivery are unexpected and alarming. Postpartum angiopathy (PPA), characterized by multifocal narrowing of cerebral arteries in the absence of inflammation, is one potential cause. It is considered rare, but its exact incidence is unknown. A recent study using the Nationwide Inpatient Sample showed that the number of pregnancy-related stroke hospitalizations during the postpartum period increased by 83% from 1994–1995 to 2006–2007.1 Because cerebral angiography—a requisite for diagnosis—is not always performed in postpartum women with headache and/or transient neurological symptoms, the disorder probably is underrecognized and may be more common than appreciated. PPA is often grouped with other conditions within the category of reversible cerebral vasoconstriction syndromes (RCVS); yet, these conditions may or may not share the same underlying pathophysiology. Most of our understanding of PPA is derived from single case reports or small case series.2–37 The aim of this study was to characterize in greater detail the clinical and radiological characteristics of PPA in a larger series of patients.

Methods

We retrospectively identified consecutive patients with PPA at 3 institutions serving as referral centers for acute neurological diseases: Mayo Clinic (Rochester, MN), FLENI Institute (Buenos Aires, Argentina), and University of Miami (FL). Patients with acute neurological symptoms in the postpartum period with confirmation of arterial vasoconstriction on cerebral angiography were included. Cases of cerebral venous thrombosis, aneurysmal subarachnoid hemorrhage, ruptured arteriovenous malformation, and negative or unavailable neuroimaging were excluded.

At the Mayo Clinic, medical records were searched for the terms “cerebral angiopathy,” “CNS angiitis,” “CNS angiopathy,” “cerebral angiitis,” “cerebral vasoconstriction,” “Call-Fleming syndrome,” “eclampsia,” “HELLP syndrome,” “posterior reversible encephalopathy syndrome,” “reversible posterior leukoencephalopathy syndrome,” or “eclampsia” in women patients aged 15–55 years from January 1, 1999, to December 31, 2009.

At the University of Miami, a search of cases with diagnosis of “postpartum vasculopathy,” “eclampsia,” “posterior reversible encephalopathy syndrome,” “reversible posterior leukoencephalopathy syndrome,” and “eclampsia” in women patients aged 15–55 years was performed using the International Classification of Diseases, 10th Edition, codes 770.2 (eclampsia), 770.3 (oxytocin-induced hypertension), 770.4 (other multiple hypertension), 771.2 (postpartum conditions with multiple organ dysfunction), and 771.4 (other conditions with postpartum complications).

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syndrome," “cerebral vasoconstriction," and “cerebral angiopathy" in women aged 15–55 years, from January 1, 2008, to December 31, 2009, was performed.

At the FLENI Institute, an electronic discharge database was used to search for all female patients aged 15–55 years admitted to the cerebrovascular section from January 1, 2009, to December 31, 2010. We also reviewed female patients aged 15–55 years who attended the vascular neurology clinic during the same period of time. Among cases identified, we analyzed medical records for each case who met the inclusion criteria. In addition, we reviewed medical records from every patient with a reported delivery in the 30-day period before admission.

Data collected included age at delivery, duration of gestation, history of prior deliveries, miscarriages, history of hypertension, migraine headaches, autoimmune disorders, coagulopathy, smoking history, day of symptom onset, neurological symptoms, presence or absence of proteinuria peripartum, diagnosis of HELLP (hemolytic anemia, elevated liver enzymes, and low platelet count) syndrome, use of vasoactive medications before or just after delivery, brain imaging findings, noninvasive and conventional angiography imaging results, time to angiography, treatments, and clinical outcomes at hospital discharge. The study was approved by the institutional review boards of the 3 participating centers.

**Results**

**Clinical Characteristics**

Eighteen women met inclusion criteria (Table). Nine patients were from the Mayo Clinic, 5 from the FLENI Institute, and 4 from the University of Miami. Mean age was 31 years (range, 15–41 years). One-third (n=6, 33%) were nulliparous before the current pregnancy; 12 (67%) had a history of at least 1 previous uneventful delivery. Eight patients (44%) had a history of miscarriage. Coagulopathy was present in 6 (33%)—protein S deficiency in 2 patients, and 1 each of the following: antiphospholipid antibody syndrome, essential thrombocytosis, elevated international normalized ratio of thrombocytosis, and 1 patient with antiphospholipid antibody syndrome. Smoking history was available for 17 (94%). Of these, 4 (25%) were current tobacco smokers and 13 (76%) were nonsmokers (2 of these were known to be former smokers). One patient (6%)—also with a history of protein S deficiency—had prior venous thromboembolism.

Pregnancies were complicated by proteinuria in 7 cases (47% of 15 with this information available) and HELLP syndrome in 2 (11%). Preeclampsia or eclampsia was diagnosed in 7 (39%) patients. At the time of delivery, the gestational age was known in 14 patients, with median of 38 weeks (range, 28–40 weeks). Five women (28%) had preterm deliveries. The method of delivery was cesarean section in 12 (67%) and vaginal in 6 (33%). Medications with possible vasoconstrictive properties were given to 7 patients (39%). This included ergot alkaloid derivatives in 3, selective serotonin reuptake inhibitor in 3, and both in 1.

Neurological symptoms began on median day 5 postpartum (range, 0–30 days). Clinical symptoms—which frequently coexisted—included severe headache (n=16, 89%), focal neurological deficit (n=9, 50%), visual symp-

**Radiological Characteristics**

Two-thirds of patients (n=12, 67%) had a noncontrast head CT scan as the initial brain imaging study. The most frequent abnormal finding was acute intracranial hemorrhage (ICH) in 7 (39%). Four had intraparenchymal hemorrhages only; 1 had convexal subarachnoid hemorrhage and 2 had both. Bilateral areas of hypodensity suggestive of posterior reversible encephalopathy syndrome (PRES) were seen in 3 (17%). Global cerebral edema was seen in 1 (6%). There was no acute abnormality in 5 (28%). All patients except 1 had further imaging with brain MRI. Combined findings were common. For example, of 7 with acute ICH, 3 also had evidence of cortical infarction on diffusion-weighted imaging sequences. Acute cerebral infarction was present in 6 (35% of those with MRI). Symmetrical areas of predominantly posterior vasogenic edema consistent with PRES were seen in 6 (35%). Of these, 1 was vasogenic edema in isolation; 2 had associated hemorrhage, 2 had combined hemorrhage and ischemia, and 1 also had ischemia. Figures 1 through 4 show representative imaging findings.

Cerebral arterial vessel imaging was done in all patients. The initial brain angiogram (noninvasive in 17 and conventional digital subtraction angiogram in 1) was normal in 7 patients (39%). These included 1 digital subtraction angiogram at 2 days after symptom onset and 6 magnetic resonance angiograms (MRA) at median day 5 after symptom onset (range, 0–13 days). In all of the cases with initially normal vessel studies, subsequent angiography showed evidence of vasoconstriction (confirmed by digital subtraction angiogram in 5 and repeat MRA in 2). Median time to repeat vessel imaging was 1 day (range, 0–7 days). In the remaining 11 patients (61%), the initial noninvasive angiograms showed evidence of vasoconstriction at median day 7 after symptom onset (range, 0–16 days). Two patients also had evidence of arterial dissection.

**Treatments and Outcomes**

Treatments varied considerably, with the most common being oral calcium channel blockers, given in 12 cases (67%). Other therapies included short-term corticosteroids (n=9, 50%) and intravenous magnesium (n=8, 44%). Two patients with severe refractory cerebral vasoconstriction were treated by endovascular means with intra-arterial calcium channel blockers and balloon angioplasty. A full recovery was achieved in 9 (50%) patients. Two patients (11%) had mild hemiparesis, 1 had residual visual auras, and 1 had a homonymous hemianopia. One patient remained quadriparetic in a minimally conscious state, and 4 died. Deaths were a result of fulminant clinical courses despite aggressive interventions including induced hypertension, intra-arterial vasodilators, and balloon angioplasty.38

**Discussion**

This 3-center study, to our knowledge the largest detailed series of patients with PPA, provides important information about clinical and imaging characteristics in this population.
Prior series of RCVS have included up to 12 and 8 postpartum patients as part of a larger group, but without separate details. There are several notable findings in our study: (1) the majority of patients did not achieve complete recovery, (2) proteinuria complicating the pregnancy was common, and (3) arterial brain imaging was often normal early in the disease course.

Though typically considered a benign disorder with favorable prognosis, half of patients in this series were left with residual neurological symptoms or died.
prospective study of 89 patients with RCVS, which included 8 postpartum women, there were no deaths. Nevertheless, there have been a few other fatal cases reported, and it is recognized that patients can have residual deficits, particularly if hemorrhages have occurred. The frequency of more severe cases cannot be estimated from this study because of its retrospective nature and referral bias. Because of the potential for fulminant clinical courses, patients with neurological symptoms in the postpartum period deserve close neurological monitoring with prompt brain imaging and noninvasive angiography. Until there are prospective studies on PPA, the frequency of these fulminant cases remains unknown.

**Figure 1.** Axial Fluid-Attenuated Inversion Recovery (FLAIR) MRI on postpartum day 20 shows a subacute left basal ganglia hemorrhage (A, arrow) with posterior vasogenic edema (A, arrowhead). Repeat MRI 3 days later shows areas of T2 hyperintensity in both anterior cerebral artery distributions (B), which had associated restricted diffusion (not shown). Cerebral angiogram on day 21 shows diffuse multifocal arterial narrowings (C, arrows and D).

**Figure 2.** Noncontrast head CT in a 29-year-old patient with severe headache 1 day after delivery shows acute right ganglionic hemorrhage (A). Cerebral angiogram, right carotid injection, shows diffuse multifocal arterial narrowings (B, arrows). Axial Fluid-Attenuated Inversion Recovery (FLAIR) MRI in a 25-year-old patient with postpartum headache shows posterior vasogenic edema and convexal subarachnoid hemorrhage (C). Angiogram, right carotid injection, shows multifocal areas of arterial narrowing (D).
Almost half of the women in our series had pregnancies complicated by proteinuria. This is in contrast to the more traditional understanding that PPA tends to occur after an uncomplicated pregnancy. Our finding supports the more recent suggestion that there is an overlap between eclampsia and PPA because of frequent clinical and radiographic similarities. In a recent review using diagnostic codes from the National Inpatient Sample, postpartum patients with hypertensive disorders (including eclampsia/preeclampsia) were 3.5 times more likely to have a stroke compared with

**Figure 3.** Axial Fluid-Attenuated Inversion Recovery (FLAIR) MRI on postpartum day 10 in a 37-year-old patient with headache shows posterior vasogenic edema (A). Magnetic resonance angiogram (MRA) at that time was normal (B). Three days later, the patient developed visual changes. MRI with diffusion-weighted images showed acute left occipital lobe infarction (C). Repeat MRA showed multifocal arterial narrowings (D).

**Figure 4.** Axial Fluid-Attenuated Inversion Recovery (FLAIR) MRI 4 days after headache, seizures, and visual symptoms in a postpartum 32-year-old woman shows sulcal T2 hyperintensity over the left hemisphere consistent with convexal subarachnoid hemorrhage (A, arrow), which subsequently involved both hemispheres (B). In another patient with fulminant course, noncontrast head CT shows right frontal intraparenchymal hemorrhage (C). Left carotid angiogram in the same patient shows widespread vasculopathy (arrows, D).
those without hypertensive disorders. Whether this could be partially explained by the occurrence of PPA is speculative but possible. In addition to stroke, both conditions can be associated with vasogenic brain edema (PRES).31,42 PRES was present in about one-third of cases in our series, which is about the same rate as that in a large, retrospective RCVS study,39 but less than that in a prospective study (17%).40 The pathophysiologies underlying PRES and eclampsia are not known with certainty, but there is probably an overlap. In preeclampsia, antiangiogenic and placental proteins have been found increased in the circulation, which could provoke endothelial dysfunction.43–45 It is reasonable to speculate that a similar mechanism could play a role in the pathophysiology of PPA.

Our results confirm that the initial angiogram in symptomatic patients may be normal, especially if performed early in the clinical course of PPA. This is similar to what has been seen in large studies of patients with RCVS. In a prospective series of 67 patients, 21% had normal MRAs initially.41 In another series of 77 patients with RCVS and serial MRAs, the highest number of arterial segments affected by vasoconstriction was seen at 16 days after symptom onset.46 Radiographically, ICH was relatively common in our study. Our rate (39%) is comparable to the 35% seen in a recent large, prospectively collected series of patients with RCVS (8 with PPA) in which ICH was more frequent in women and was associated with more severe clinical presentation.40 It is unclear whether PPA is a distinct disorder, but these findings suggest that if it lies on the same spectrum of other causes of RCVS, it may be more often on the severe end of this spectrum. However, this has not been found consistently; in another large, retrospective series of patients with RCVS, which included 12 with PPA, postpartum women tended to have hemorrhage less frequently.39

Our study, conducted in 3 tertiary referral centers, has limitations. Documented vasculopathy by brain arterial imaging was required for inclusion. This strict definition may have created a selection bias for the more severe cases, thus potentially leading to an overestimation of the frequency of abnormal brain imaging results and poor clinical outcomes. Nevertheless, this criterion is necessary to ensure the validity of the diagnosis. In addition, the differentiation between reversible cerebral vasoconstriction and primary central nervous system vasculitis is difficult and may not be possible without biopsy. However, we think that vasculitis is an unlikely diagnosis in our series because patients with severe courses had pathology available that did not support vasculitis. Those with more favorable outcomes had outcomes similar to those traditionally reported in postpartum angiopathy, and over half of these patients were not treated with corticosteroids.

Our study does not allow determination of the incidence or prevalence of PPA because most of our patients were referred from other institutions, which created a bias. Thus, we acknowledge that our cohort may not entirely represent the spectrum of PPA. The treatments given to the patients markedly varied. Because PPA can spontaneously remit, it is unclear whether any treatments are effective in altering the natural course of the disease process. Furthermore, aggressive treatment interventions can be associated with potential complications, and the optimal timing of initiating treatment for an often-reversible disorder is uncertain. Further research with larger, prospective, multicenter studies is needed to overcome these limitations.

Our results indicate that PPA with angiographically confirmed vasoconstriction is sometimes associated with morbidity and mortality. Although most women with PPA have reasonably favorable outcomes and the frequency of more fulminant cases is unknown, women with acute neurological symptoms in the postpartum period require close neurological monitoring, brain imaging, and consideration of vessel imaging. If clinical suspicion remains high, repeat angiography may be needed for diagnosis because initial imaging is often normal.

Disclosures
None.

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出産後脳アンギオパチーの多様な病像
Variable Presentations of Postpartum Angiopathy

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背景および目的：出産後脳アンギオパチーは産褥期の脳卒中の中のまれな原因であり、分娩後1〜2週間以内に生じる重度の頭痛を前兆とする。血管造影では分節性の血管収縮が認められるが、多くの場合は自然に消失する。一般に、出産後脳アンギオパチーは良性とみなされている。本研究の目的は、出産後脳アンギオパチー患者の臨床像、X線検査所見、転帰を明らかにすることであった。

方法：3カ所の施設において、産後に急性神経症状を生じ、血管造影で血管収縮が認められた患者を後ろ向きに検討した。脳神経画像検査を行わなかった患者、脳静脈洞血栓症および動脈瘤出血と診断された患者は除外した。患者背景、臨床症状、脳神経画像所見、退院時の臨床状態についてデータを収集した。

結果：18例の患者を特定した（平均年齢31歳、範囲：15〜41歳）。妊娠期間の中央値は38週間であった。12例（67%）は過去に妊娠歴があり、その際に問題は認められなかった。神経症状は出産後5日に（中央値）からみられ、症状は頭痛（16例、89%）、局所神経脱落徴候（9例、50%）、視力障害（8例、44%）、脳症（6例、33%）、発作（5例、28%）などであり、複数症状の合併も多かった。画像所見ではほとんどの症例に異常が認められた（13例、72%）、特に発現頻度の高かった異常は、頭蓋内出血（7例、39%）、血管原性浮腫（6例、35%）、梗塞（6例、35%）であった。臨床転帰はそれぞれ大きく異なっており、9例（50%）は完全に回復したが、4例（22%）は病状の経過をとった後に死亡し、5例（28%）には障害が残った。

結論：過去の報告とは対照的に、本研究における出産後脳アンギオパチー患者では非良性の転帰の割合が高かった。脳神経画像検査を行った患者のほとんどの脳実質に異常があり、特に多かったのは、脳卒中（出血性もしくは虚血性）または可逆性の血管原性浮腫であった。

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