

Phenotypical variability of post-partum reversible cerebral vasoconstriction syndrome

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Abstract

Reversible cerebral vasoconstriction syndrome is recognized increasingly as a complication of the postpartum period. Our series of four cases illustrates its phenotypical variability, summarizes the diagnostic work-up, and outlines potential treatment strategies for this usually benign but sometimes disabling and life-threatening disease.

Introduction

Reversible cerebral vasoconstriction syndrome (RCVS) is an under-recognized condition of the puerperium.¹ Formerly known as benign angiopathy of the central nervous system, its clinical course has been described to be more malignant occasionally than this name suggests. We discuss four cases of postpartum RCVS and present one illustrative and severe case in detail. The other three cases are summarized in Table 1.

Case Report

In April 2006, five days after an uncomplicated pregnancy and childbirth, a healthy 40-year-old woman developed sudden, severe, and persisting headache. On day 1 postpartum she had been given a single dose of cabergoline (0.5 mg) for ab lactation. Cerebral computed tomography (CCT), magnetic resonance imaging (MRI), electroencephalography (EEG), and lumbar puncture at a primary hospital showed no abnormalities. On day 7 postpartum she suffered a generalized seizure with head trauma from a fall. The CCT demonstrated a cortical, frontoparietal, superficial subarachnoid hemorrhage (SAH), which was located beneath a skin bruise; hence the SAH was considered traumatic.

On admission to the stroke unit she complained of headache, responded slowly to ques-

tions, and had elevated blood pressure (200/100 mmHg), right peripheral visual deficits, and extensor pyramidal signs on the right side. The MRI revealed bilateral occipitoparietal vasogenic edema without evidence of sinus venous thrombosis (SVT) or arterial abnormalities (Figure 1). Transcranial Doppler ultrasound (TCD) showed normal flow velocities with no evidence of vasospasm. Antihypertensive therapy with intravenous (i.v.) urapidil was initiated. However, she complained further of double vision, developed severe right-sided hemiparesis, and became aphasic. Serial MRT scans showed segmental, rapidly progressive arterial narrowing of all cerebral vessels (Figure 1). Hence, nimodipin i.v. (1 mg/h) in combination with triple-H therapy (hypertension, hypervolemia, hemodilution) was started. However, multiple ischemic strokes and spreading of vasogenic edema emerged (Figure 1). Serum markers for connective tissue diseases, systemic vasculitis, urine catecholamines, and investigation of cerebrospinal fluid, biochemical testing for porphyrias, as well as transthoracic echocardiography were unremarkable. Because of progressive generalized vasospasm, i.v. methylprednisolon at a dosage of 1000 mg daily over five days was added, with dose tapering to 80 mg orally until discharge. Under this treat-

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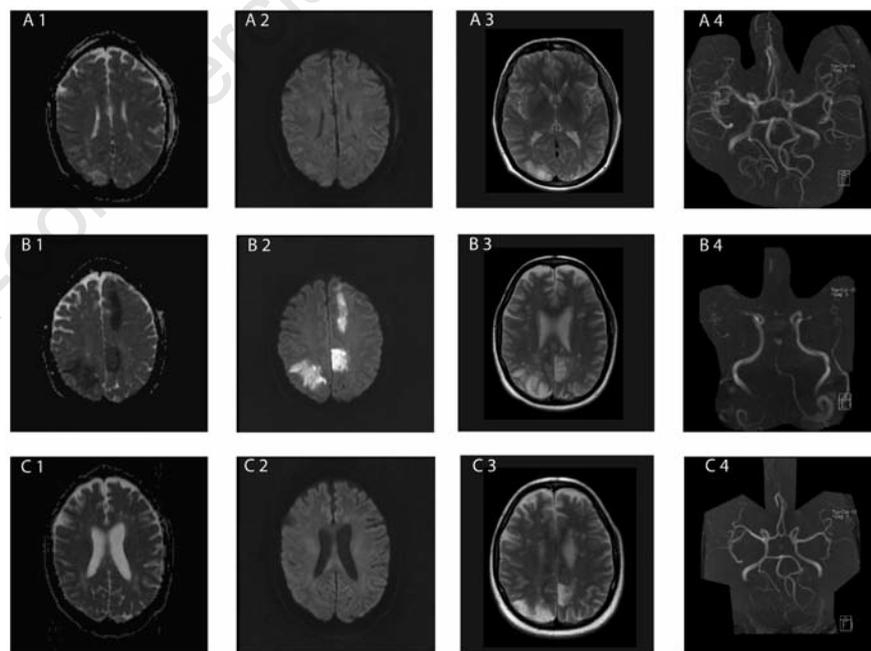


Figure 1. A1-A4: magnetic resonance (MR) images on admission of patient #1, showing hyperintensities (vasogenic edema) on ADC (apparent diffusion coefficient; A1), DWI (diffusion weighted imaging; A2) and T2-weighted (A3) images, accentuated in the right occipital pole. There were no vessel abnormalities on TOF-MRA (time of flight magnetic resonance angiography; A4). B1-B4: 10 days later, MR images show multiple ADC hypointensities (B1) and DWI hyperintensities (B2) on corresponding levels, typical for infarction. Vasogenic edema is still evident on T2-weighted images (B3). TOF-MRA (B4) reveals severe and multiple vasoconstriction. C1-C4: follow-up MR images after four months show no abnormalities in ADC (C1) and DWI (C2) maps. On T2-weighted images (C3), old cerebral infarctions are evident. TOF-MRA (C4) demonstrates complete resolution of cerebral vasoconstriction.

Table 1. Summary of all four cases.

Patient No.	Age (years)	Onset postpartum (days)	Medication prior to onset	Presenting features	Imaging findings (MR, CT, TCD, DSA)	Laboratory and CSF examinations	Initial clinical presentation	Clinical course	Treatment	Follow-up
1*	40	5	Cabergoline	Headache, generalized seizure, arterial hypertension (RR 200/100)	MR: vasoconstriction, DWI lesions, SAH, reversible posterior leukoencephalopathy TCD: elevated blood flow	Normal	Psychomotor slowing, dysarthria, partial hemianopsia	Right-sided hemiparesis, aphasia, blurred vision and double vision	i.v. nimodipin, corticoids, hydroxy-ethyl starch, urapidil	4 months: slight right-sided hemiparesis, complete resolution of vasoconstriction on MRA
2	33	4	Magnesium, dihydralazin	Generalized seizure, arterial hypertension (RR 170/100)	MR: reversible posterior leukoencephalopathy, vasoconstriction TCD: vasospasm	Platelets 69 G/L, GOT 56 U/L, GPT 91 U/L, gamma-GT 29 U/L, LDH 454 U/L, urine protein 5000 mg/dL	No focal deficits	Asymptomatic dissection of left ICA, complete resolution of vasospasm after 10 days	i.v. nimodipin magnesium dihydralazin	4 months: no further symptoms, normal vessel status on MRA
3	33	6	Bromocriptine	Headache, generalized seizure, arterial hypertension (RR 170/90)	MR: reversible posterior leukoencephalopathy, vasogenic edema, hemorrhagic changes DSA: vasoconstriction	Normal	No focal deficits	Benign clinical course, complete resolution 14 days after initial symptoms	Oral nimodipin, corticoids, urapidil, phenytoin	one year: no recurring events, normal vessel status on MRA
4	34	4	No vasoactive medication	Headache, generalized seizure	MR: reversible posterior leukoencephalopathy, vasoconstriction, SVT TCD: elevated blood flow	Normal	Headache, blurred vision, diplopia	Benign clinical course, normal vessels on MRA 11 days after onset	Oral anticoagulation for SVT, clobazam	One year: no further clinical symptoms, normal vessel status on MRA

*Illustrative case vignette; MR, magnetic resonance; CT, computed tomography; TCD, transcranial Doppler sonography; DSA, digital subtraction angiography; CSF, cerebrospinal fluid; RR, blood pressure in mmHg; DWI, diffusion-weighted imaging; SAH, subarachnoid hemorrhage; SVT, sinus venous thrombosis; ICA, internal carotid artery; MRA, magnetic resonance angiography; i.v., intravenous.

ment, the patient stabilized and improved substantially. In line with this, the MRI showed rapid regression of vasoconstriction and vasogenic edema, and shrinking of DWI (diffusion weighted imaging) lesions (Figure 2). She was transferred to a rehabilitation center for physical therapy and speech therapy. At a follow-up visit three months later, the aphasia had completely recovered and only a slight non-disabling paresis of the right leg persisted.

Discussion

Thunderclap headache, seizures, and occasionally visual or sensorimotor² deficits in combination with normal cerebrospinal fluid (CSF) and segmental arterial vasoconstriction are typical for RCVS.¹ Reversibility of vasoconstriction within two months and absence of vasculitis further support this diagnosis.^{3,4} Our illustrative postpartum case presented with all of these clinical features, whereas the other three patients suffered from headache, visual disturbances, and seizures (Table 1). In line

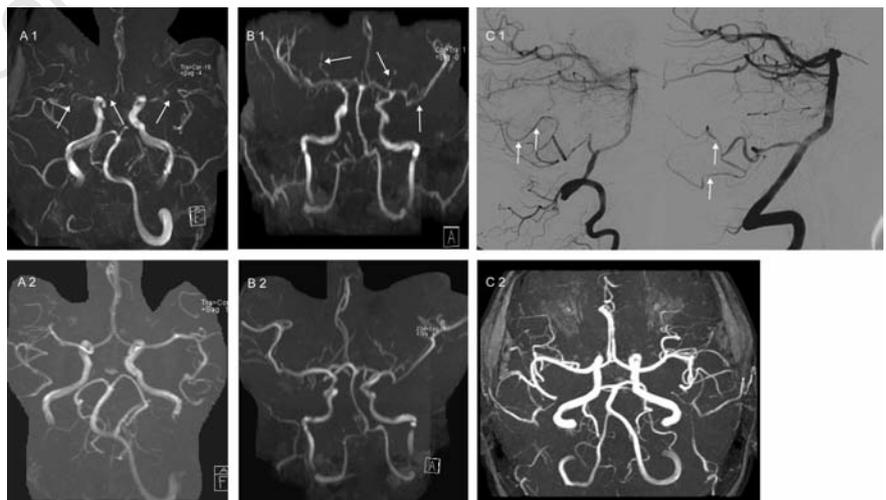


Figure 2. (A1 and A2) Cerebral magnetic resonance angiograms of patient #2 showing multisegmental vasoconstriction (white arrows, A1). Magnetic resonance angiography four months later (white arrows, A2) reveals normal vessel status. (B1 and B2) Magnetic resonance angiography of patient #4 reveals multisegmental vessel narrowing (white arrows, B1). One year later (white arrows, B2) no vessel abnormality is evident. (C1 and C2) Digital subtraction angiography demonstrates segmental narrowing of vessels, predominantly in both posterior inferior cerebellar arteries (white arrows, C1). Follow-up magnetic resonance angiography one year later shows normal vessel status (white arrows, C2).

with the literature, the outcome of our patients was excellent in three and good in one with mild residual deficits. However, severe disabling strokes, SAH, and even death have been reported.^{2,3,5,7} Because of a seizure-related fall, the superficial SAH in our leading case was considered as traumatic, but a vasospasm-mediated SAH is as likely. Lacking a CT scan immediately before the seizure, we are not able to discern if seizure induced the SAH or vice versa. An aneurysmal origin of the SAH can be excluded by its minor size and superficial localization.

The common feature of all four postpartum cases was seizures, occurring early in the disease, which is a well-known complication in RCVS.^{3,7} Interestingly, the phenomenology of symptoms apart from seizures was quite different. In two patients, there were no focal deficits. In these cases, the vascular pathology and parenchymal edema seen on central nervous system (CNS) imaging was less widespread than in the other two, probably indicating less exposure to a putative endothelial-noxious factor. However, we were not able to elicit predisposing factors from the history or from laboratory findings. Two cases exhibited unusual features; in one case, there was internal carotid artery (ICA) dissection, which may have been a result of mechanical strain from the initial generalized seizure. In another case, there was SVT remote from the area of vasoconstriction and vasogenic edema. Because SVT is a common complication of the peripartum period, this may have been a chance coincidence. However, it is tempting to speculate on a generalized vulnerability of the cerebral vasculature in both cases.

The pathophysiology of RCVS remains unclear. There are predisposing conditions like eclampsia or vasoactive drug intake;^{3,8} as in eclampsia, imbalances between the pro-angiogenic placental growth factor (PlGF) and the antiangiogenic soluble PlGF receptor (sFlt-1) are assumed to cause postpartum RCVS.⁷ In this setting, ergoline medication (e.g. for ab lactation) might facilitate vasoconstriction.^{2,5} In our cases, as in the literature, there is a broad overlap of eclampsia, hemolytic an-

emia/elevated liver enzymes/low platelets (HELLP)-syndrome, cerebral sinus thrombosis, and cervical artery dissection.⁹ Hypertension-induced endothelial dysfunction may be the common cause for vasogenic edema, thrombosis, or dissection through a cascade of vessel wall injury and endothelin-mediated vasoconstriction.

The most important differential diagnosis to RCVS is primary angiitis of the CNS (PACNS). However, PACNS is more prevalent in men than in women and has a median age range of 40 to 60 years. Moreover, the onset of symptoms is often insidious and CSF examination may demonstrate leukocytosis and elevated protein levels.¹⁰ As all this was absent in our patients, the diagnosis of PACNS was discarded. In addition, CNS imaging did not support a diagnosis of angiitis.

For treatment, most centers use oral, intravenous, or occasionally intra-arterial nimodipin.^{11,12} In our case vignette and in earlier reports, i.v. steroids were effective in patients nonresponsive to nimodipin, with a rapidly progressive, vasculitis-like course.^{13,14} In the absence of treatment guidelines for RCVS, therapeutic decisions have to be tailored for each patient and their efficacy needs to be constantly checked by clinical examination and imaging controls. Awareness of RCVS and its speedy recognition are crucial. Otherwise, gradual progression of vasoconstriction and serious complications, such as ischemic infarction, may ensue.

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