

A Case Of Primary Angiitis Of The Central Nervous System Unmasked During Postpartum: Exploring The Pathogenesis.

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Abstract

Primary angiitis of the central nervous system (PACNS) is an extremely rare condition that is considered an immunologic emergency of the brain due to vasculitis. Although there are isolated cases of this rare entity occurring in the postpartum period, no literature has described the involved pathogenesis. We hereby present a case of PACNS manifesting in the postpartum period, and we have explored the causative mechanisms.

CASE REPORT

The patient was a 34-year-old Malay housewife with no known medical illness, who was a Para 4 lactating mother at 3 months postpartum. The preceding pregnancy period was uneventful. She presented with sudden onset of right-sided hemiparesis, which lasted for half an hour, followed by complete recovery. There were no other reported focal neurological deficits. This presentation of transient ischemic attack (TIA) was preceded by an intermittent, moderately severe headache of 2 weeks duration. There was no history of fever or symptoms of connective tissue disease. By the time she arrived at our hospital, she had regained full muscular power. Complete neurological examination and other systemic examination were normal. She was extensively investigated to identify the cause of TIA at such a young age.

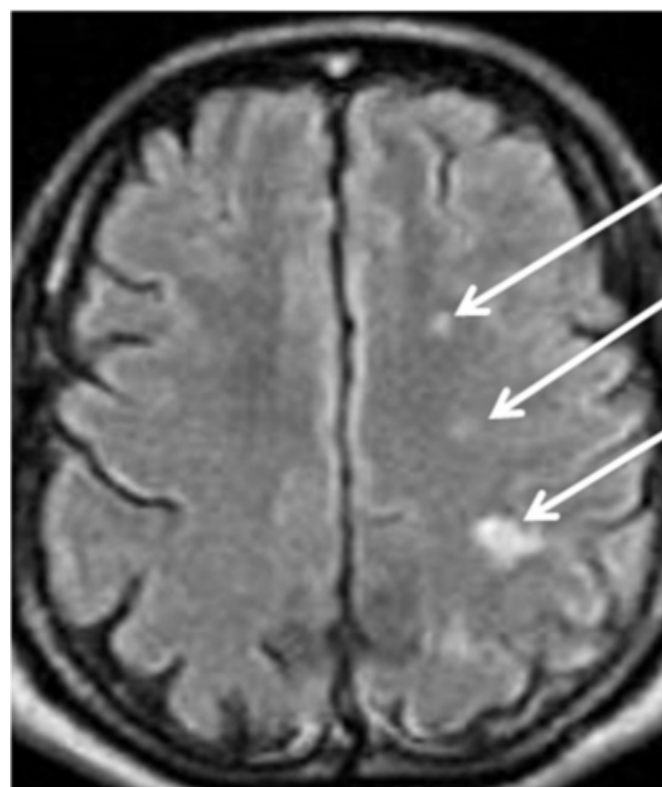
The following were her laboratory investigations: haemoglobin of 10.9 g/dL, white cell count of 8.5×10^9 cells per liter, platelet of 300×10^9 , albumin of 4 g/dL, erythrocyte sedimentation rate of 35 mm/hour, C reactive protein of 0.86 mmol/L, fasting blood sugar of 4.6 mmol/L. Lipid profile was normal. VDRL was non-reactive, while HIV screening was negative. Both connective tissue (rheumatoid factor, antinuclear antibody (ANA), antineutrophil cytoplasmic antibody (ANCA), lupus anticoagulant) and thrombophilia screening (protein C, protein S and antithrombin III) were normal. MRI brain scan showed multifocal infarctions (Figure 1). The lumbar

puncture performed had a normal opening pressure.

Cerebrospinal fluid (CSF) analysis revealed an elevated CSF protein of 72 mg/dL with normal cell counts.

Figure 1

Figure 1: MRI brain (T2 FLAIR) showing multifocal infarctions (arrows) in the left cerebral hemisphere.



We proceeded with a cerebral angiogram after carotid Doppler ultrasonography showed severe stenosis of the distal and mid portion of the left internal carotid artery. The Doppler ultrasonography of the renal and abdominal arteries was normal. Cerebral angiogram showed a beaded appearance of the right internal carotid artery with irregular outline and 60% short segment stenosis of the left internal carotid artery (Figure 2). The patient refused a brain biopsy out of concern about the potential complications. On clinical grounds, having fulfilled the 1988 diagnostic criteria by Calabrese and Mallek [2], a diagnosis of PACNS was made.

Figure 2

Figure 2: Cerebral angiogram showing right internal carotid artery with beaded appearance and irregular outline (arrow).



The differentials for the angiographic findings were reversible cerebral vasoconstriction syndrome (RCVS) and fibromuscular dysplasia. However, the subacute nature of the headache, abnormal CSF findings, and arterial abnormalities confined to the central nervous system were against RCVS and fibromuscular dysplasia [3,4].

She was pulsed with intravenous methylprednisolone 500 mg daily for 3 days, after which she was on tapering doses of oral prednisolone starting at 0.5 mg per kg. The patient was unable to wean off breastfeeding and requested to defer intravenous cyclophosphamide. During follow up 2 months later, the patient remained well with no neurological symptoms or signs.

DISCUSSION

PACNS is a rare form of vasculitis confined to the intracerebral blood vessels [1]. Even today there is no data on its incidence, as there is no univocal diagnostic criteria. For clinicians worldwide, this condition still poses a formidable diagnostic challenge. By and large, the 1988 diagnostic criteria by Calabrese and Mallek are the best-established and widely accepted criteria for PACNS. To diagnose PACNS, all of the following are required:

Although brain biopsy is the gold standard confirmatory test in PACNS, it is not a mandatory investigation to establish the diagnosis.

In a study involving 16 patients with PACNS, 3 out of 8 of the female patients developed symptoms within 3 weeks of childbirth [5]. Our literature search revealed 2 other similar case reports of isolated angiitis of the brains occurring during puerperium [6,7]. Hence, it is noteworthy that the occurrence of PACNS postpartum is not uncommon. Although there are several overlapping features, we believe that postpartum PACNS is a distinct entity from postpartum cerebral angiopathy, which is a subset of RCVS. In the postpartum period, RCVS appears to be more common than PACNS. To date, there are 24 reported cases of RCVS in pregnancy and puerperium. An important clinical feature that helps distinguish RCVS from PACNS is the acute “thunderclap” headache, which was absent in our patient. Besides, in RCVS the CSF protein is typically normal [3].

Although PACNS was first described in the 1950s, the pathogenesis involved remains obscure. The fundamental mechanism of PACNS is the immunological process with T cells as the key orchestrators directed against the cross-reacting epitopes of the CNS vasculature [8].

We believe that the triggers for the disease to project itself in the postpartum period are multifactorial. It is tempting to speculate that the resultant damage is due to the complex interplay of cellular immunity, haemodynamic and hormonal changes. The postpartum period is characterised by a surge in autoimmunity following an immune tolerance state induced by pregnancy, leading to flare ups of several autoimmune diseases such as autoimmune thyroiditis and rheumatoid arthritis. Studies have shown that the frequency of CD4+CD25+ T regulatory cells decreases significantly from pregnancy to postpartum. Lower levels of T regulatory cells which secrete interleukin-10 (IL-10) promote the production of proinflammatory cytokines [9]. To further

elucidate the mechanism of postpartum PACNS, an increase in peripheral large granular lymphocytes during this period, which have activities of natural killer and cytotoxic T cells, is proposed [10]. The decrease in the circulating levels of calcitriol (1,25-dihydroxyvitamin D3), a form of vitamin D, may also be involved. The calcitriol level drops rapidly after delivery. Calcitriol has immunomodulatory effects by selective suppression of T lymphocyte activation, cytokine production and antigen-induced lymphocyte proliferation [11].

In PACNS, transient ischemic attacks are fairly common with a reported incidence of between 30-50% [12]. Vasculitic thrombosis and tissue ischemia account for this clinical manifestation. In postpartum PACNS, all components of the Virchow's triad of thrombosis are affected. Inflamed vessels have more sluggish blood flow due to luminal irregularities and have associated endothelial injury [13]. From pregnancy to postpartum, there are dynamic changes in cerebral perfusion, cerebrovascular resistance and intrinsic myogenic tone of cerebral arteries and arterioles [14].

Moreover, after childbirth, women are in a hypercoagulable state due to the rise in plasma levels of fibrinogen, thrombin, factors VII, X, VIII, and von Willebrand factor. There is a concurrent fall in the levels of protein C, protein S and antithrombin III, which have antithrombotic activity. Lactating mothers like this patient are more prone to dehydration, which further promotes thrombosis [15].

In conclusion, the authors would like to highlight that PACNS has a tendency to manifest during postpartum. Theoretically, the vasculitic, haemostatic and thrombotic processes act hand-in-hand to cause the clinical presentation of postpartum PACNS. Further evidence is required to validate the proposed pathogenesis.

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