



CASE REPORT

Primary Angiitis of CNS: A Diagnostic Dilemma

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Introduction

Primary angiitis of the central nervous system (PACNS) is a rare disease of unknown etiology.¹ It is a serious type of vasculitis that not only affects CNS vessels in the absence of systemic inflammatory diseases,² but potentially causes neurological deficits in less than 40% of patients.³ Persistent unexplained headaches and altered mental status are the most common presenting symptoms with PACNS. It is more common in males than females with the presenting age in the 5th decade of life. Magnetic resonance imaging (MRI), cerebrospinal fluid, and cerebral angiograms are found to be abnormal, but non-specific. Brain biopsy is performed, not only to establish diagnosis, but for planning the management.

Case Report

A 42-year-old female, known to have migraine headaches, presented with a history of occipital headaches and neck stiffness of a few hours duration. She took acetaminophen and oxycodone for pain without relief. While driving, she felt dizzy and nauseated. She later had six episodes of vomiting. She developed generalized weakness to the point that she could not stand. She has no history of falls.

The physical examination, including the neurological examination, was normal. It was unclear if any neurological deficits, that

might prevent her from standing, resolved or if the complaints of generalized weakness were subjective. Initial evaluation including lumbar puncture and MRI revealed moderate cervical stenosis without any acute pathology and some occipital edema, thought to be attributed to migraine. The patient was given analgesics and her symptoms improved. She was discharged on day four of hospitalization with a diagnosis of complicated migraine.

Eight days later, the patient again presented with intractable headache, weakness of lower extremities, and photophobia. Her neurological examination revealed diminished motor strength 4/5 in all four extremities. An MRI on admission revealed leptomeningeal enhancement over the cerebral hemispheres. A lumbar puncture showed no evidence of any infectious process. Cerebrospinal fluid (CSF) analysis revealed protein at 51 mg/dL, glucose at 55 mg/dL, white blood cells at 9 cells/ μ L, lymphocytes at 42%, and neutrophils at 47%. HIV, Lyme's disease, tularemia, syphilis, *Bartonella hensellae*, mycoplasma, *Coxiella burnetti*, and West Nile virus serologies were normal. ANA, C-ANCA, and P-ANCA were negative.

The patient was given analgesics with minimal relief. On day 4 of this hospital admission, the nature of her headache changed from occipital to spinal. On day 5, she developed left upper extremity weakness.

MRI was repeated and showed ischemia in the right paracentral lobule. A magnetic resonance angiogram (MRA) revealed multiple short segment areas of stenosis with normal intervening segments throughout the bilateral middle, anterior, and posterior cerebral arteries, suggestive of vasculopathy. These findings were verified by arteriogram. Later, her weakness evolved from left to right upper extremity and she developed slurred speech.

The patient was started on IV methylprednisolone. After a few days of steroid therapy, her speech improved with residual weakness in her right upper extremity. A brain biopsy was performed from the occipital region and samples were taken from dura, cortex and white matter. After stabilizing her condition, she was sent home with tapering steroids. Biopsy results later showed mild gliosis.

Discussion

Diagnostic criteria of primary angitis of CNS were proposed in 1988 by Calabrese and Mallek.⁴ Those criteria included: (a) an unexplained neurologic deficit despite aggressive diagnostic workup, (b) a high-suspicion angiogram for arteritis and/or histopathological evidence of arteritis limited to the CNS, and (c) no evidence of systemic vasculitis or exclusion of all those disorders capable of mimicking with vascular inflammation of the CNS.

Reversible cerebral vasospastic syndrome (RVCS) is the most important and most common clinical mimic of PACNS.⁵ Early differentiation between the two is critical since the management for PACNS may require cytotoxic agents.⁶ Headache, encephalopathy, and focal neurological deficit are found commonly in PACNS. Non-specificity of symptoms and their subtle progression result in extended duration between symptom onset and diagnosis. In contrast, patients with RVCS present with

severe headaches of sudden onset and focal neurological symptoms. Typically, RVCS patients initially undergo a more intense diagnostic evaluation with a shorter time between onset of symptoms and ultimate diagnosis.⁷

CSF analysis is abnormal in 80% to 90% of patients with true PACNS, though it is usually normal in RVCS. CSF samples of patients with PACNS may show only modest elevations in white blood cell count and total protein level.³

MRI is abnormal in 90% to 100% of patients.⁸ Infarcts may be seen in approximately 50% of cases. When present, infarcts are usually seen bilaterally in multiple-vessel tributaries, as mass lesion, ischemic demyelination, or cortical necrosis.³ In contrast to this, MRI is normal in the vast majority of patients with RCVS.⁹

CNS angiogram has limited sensitivity for detecting vasculitis.¹⁰ A range of noninflammatory vasculopathies can cause angiographic findings similar to those seen with PACNS. Therefore high pretest probability plays a major role in supporting the angiographic findings, which range from normal to areas of regular or irregular vascular luminal abnormalities. Although the initial findings may be similar as of PACNS, the most specific finding of RCVS on angiogram is the reversibility of vascular abnormalities over the period of time.

Cerebral biopsy is required for accurate diagnosis of PACNS and starting prolonged immuno-suppressive treatment.¹¹ Vasculitis affects vessels in a skipped and segmental pattern. The sensitivity of brain biopsy may be less than 50%.⁷ PACNS usually runs a progressive and fatal course if left untreated. High doses of corticosteroids and cyclophosphamide are the mainstay of treatment. RVCS, on the other hand, is treated with a short course of glucocorticoids and nifedipine, which typically results in complete radiological recovery.¹²

Differentiation of PACNS from RCVS is a diagnostic dilemma due to lack of any specific criteria to differentiate between the two (see Table 1). Since PACNS follows a more severe course, early administration of immuno-suppressive agents is required to reduce mortality and morbidity. On the other hand, RCVS cases simply can be observed or treated with corticosteroids and calcium channel blockers. Therefore, physicians should avoid treating patients with RCVS unnecessarily with immunosuppressive agents. Misdiagnosing PACNS patients with RCVS can prove fatal. Further research is needed to clarify grey areas.

Table 1. Characteristics of PACNS and RCVS.*

	PACNS	RCVS
Gender Predominance	Men > Women	Women > Men
Median Age at Presentation	40-60 years	20-40 years
Presentation	Chronically progressive headaches	Acute and severe headaches
Focal Symptoms Neurological Symptoms	Yes, but rare at onset of headache	Yes, may occur with onset
CSF Findings	Leukocytosis and elevated total protein level, mild to moderate	Normal
Treatment	Prednisone with cytotoxic agent	Prednisone with calcium channel blocker

*Table adapted from Birnbaum and Hellmann.⁷

Conclusion

The most important clinical mimic of PACNS is RCVS. Both diseases follow different courses with PACNS being fatal as compared to the more benign and reversible course of RCVS. Early administration of immunosuppressive agents has significant impact on the prognosis of PACNS. Early differentiation is important to avoid adverse outcomes.

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