

Primary Angiitis of the Central Nervous System

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Primarily angiitis of the central nervous system (PACNS) is a rare form of vasculitis of unknown cause. The mean age of onset is 50 years, and men are affected twice as often as women. Headache and encephalopathy are the most frequent initial symptoms. Stroke or focal symptoms develop in less than 20% of patients at the onset of disease and are uncommon in the absence of headache or encephalopathy. Symptoms or signs of vasculitis outside of the central nervous system are rare; serologic markers of inflammation are typically normal. Magnetic resonance imaging of the brain is abnormal in more than 90% of patients, but the pattern of abnormal findings is not specific. Cerebrospinal fluid analysis is also usually abnormal because of modest, nonspecific elevations in total protein level or white blood cell count. Angiography has a low sensitivity and low specificity. Most patients suspected of having PACNS have another disease. The diagnosis of PACNS is established by brain biopsy. The differential diagnosis of PACNS is broad and includes reversal cerebral vasoconstriction. In contrast to patients with PACNS, patients with reversal cerebral vasoconstriction are more often young women who experience a thunderclap headache and have a normal cerebrospinal fluid analysis. Patients with biopsy-proven PACNS are treated with cyclophosphamide and prednisone.

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Primary angiitis of the central nervous system (PACNS) causes focal and diffuse neurologic symptoms due to vasculitis of the intracerebral blood vessels. The broad swathe of symptoms that can mimic PACNS includes angiocentric infections and malignant neoplasms. However, whereas immunosuppressant therapy can be harmful in patients with infections, such cytotoxic-based regimens are necessary for treating PACNS, which is otherwise relentlessly progressive and fatal. Therefore, knowledge of the spectrum of demographic, clinical, angiographic, and radiographic features seen in PACNS is necessary for diagnostic accuracy as well as for safely instituting immunosuppressant treatment.

At the outset, it is important to emphasize the rarity of PACNS, which accounts

for just 1% of the systemic vasculitides. Most patients suspected of having PACNS actually will have a different disorder. In addition to nonspecificity of clinical symptoms, most abnormal findings on angiograms interpreted as being highly suggestive of PACNS will instead be attributed to vasospasm. However, despite the nonspecificity of *individual* clinical signs and symptoms, this review article emphasizes that the *constellation* of certain demographic, symptom, cerebrospinal fluid (CSF), and radiographic features may indicate a diagnosis of PACNS. Familiarity with these prototypical features suggestive of PACNS sharpens diagnostic contrast with other syndromes that are initially difficult to distinguish from PACNS.

We also restrict the discussion of PACNS to inflammation and damage of central nervous system (CNS) vessels, without any evidence of vasculitis out-

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side the CNS. Although rare, CNS vasculitis can occur as a systemic manifestation of other primary vasculitides, including small-vessel vasculitis (eg, Wegener granulomatosis, Churg-Strauss syndrome), medium-vessel vasculitis (eg, polyarteritis nodosa), and large-vessel vasculitis (eg, giant-cell arteritis, Takayasu arteritis).

CLINICAL FEATURES

Most often, PACNS affects middle-aged men. Studies of more than 8 patients have reported a median age at onset of approximately 50 years,¹⁻³ and men are affected twice as often as women. Symptoms suggestive of PACNS in patients younger than 30 years or older than 70 years should lead to consideration of other possible diagnoses. The most common symptoms of PACNS, headaches and encephalopathy, are due to diffuse cortical dysfunction. Headaches occur in as many as 63% of patients with PACNS,¹⁻⁵ are indolently progressive, and usually are not severe enough to warrant emergency evaluation for subarachnoid hemorrhage. Similarly, cognitive impairment in patients with PACNS is insidious, and more acute alterations in consciousness, or coma, are very unusual.¹ The nonspecificity of these symptoms of headache and cognitive impairment, along with their insidious progression, accounts for a protracted duration between symptom onset and diagnosis of up to 6 months.

Strokes or persistent neurologic deficits occur in 40% of patients with PACNS,¹ and transient ischemic attacks have been reported in 30% to 50% of patients.^{1,6} However, strokes or focal symptoms occur in less than 20% of patients at the onset of disease and are uncommon in the absence of headaches or encephalopathy. Although PACNS is classically considered a small-vessel vasculitis, the frequency of symptoms related to large-vessel disease, including aphasia (28%) and visual field deficits (21%), may be more common than initially appreciated.¹ Seizures have been reported in less than 25% of patients,^{1,2,5,6} and, in contrast to other primary systemic vasculitides, symptoms or serologic markers related to systemic inflammation are uncommon. Fevers, weight loss, and night sweats have been reported in less than 20% of patients.^{1,5} Similarly, the erythrocyte sedimentation rate is elevated in less than 25% of patients.¹

DISTINGUISHING BETWEEN PACNS AND REVERSIBLE VASOCONSTRICTION SYNDROME

Thus far, our discussion has highlighted common demographic and clinical features of patients with PACNS, characterized by inflammation and destruction of vessels. However, a substantial number of patients suspected of having PACNS will have signs and symptoms caused by vasospasm rather than true vasculitis of intracerebral vessels. This diagnostic distinction is crucial because cytotoxic therapy is not warranted for syndromes caused by vasoconstriction. Hajj-Ali et al⁷ initially proposed the diagnostic term *benign angiopathy of the CNS* to encapsulate syndromes potentially mediated by vasoconstriction. Other authors noted that benign angiopathy of the CNS did not necessarily have a more favorable course,⁸ and the term *reversible vasoconstriction syndrome* (RVCS) is now preferred.

Table 1. Discriminating Features of PACNS and RVCS

Characteristic	PACNS	RVCS
Demographics		
Sex	Men more than women	Women more than men
Median age range, y	40-60	20-40
Clinical symptoms		
Headache	Chronically progressive	Acuity and severity warranting evaluation for subarachnoid hemorrhage
Focal symptoms (eg, strokes, TIAs)	Yes, but rare at onset of symptoms of headache	Yes, may occur with onset of headache
History of provocative vasospastic syndromes (eg, migraine, peripuerum) or medication use	No	Yes
Dynamic improvement of angiographic abnormalities after 3 mo	Variable, depending on chronicity of symptoms as well as affected vessel size	Yes
CSF sample findings	Leukocytosis and elevated total protein level, mild to moderate	Normal
Drug treatment	Prednisone with cytotoxic agent	Prednisone with calcium channel blockers

Abbreviations: CSF, cerebrospinal fluid; PACNS, primary angiitis of the central nervous system; RVCS, reversible vasoconstriction syndrome; TIAs, transient ischemic attacks.

Table 1 highlights demographic and clinical symptoms that distinguish PACNS from RVCS.⁹ Whereas PACNS typically affects middle-aged men, RVCS is primarily seen in women aged 20 to 40 years. A history of syndromes or provocative agents associated with vasospasm, including the peripuerum period, migraines, illicit drug use, and use of over-the-counter cold medicines, is frequently elicited. The most common presenting syndrome is of a thunderclap headache of sudden onset and sufficient severity to warrant diagnostic evaluation for subarachnoid hemorrhage. Focal symptoms can predominate, with strokes or transient ischemic attack as a presenting feature. Compared with patients with PACNS, patients seeking treatment for severe headaches and focal symptoms initially undergo more intense diagnostic evaluation, with a shorter time between onset of symptoms and ultimate diagnosis.

The entity of RVCS subsumes a range of different syndromes, likely sharing the mechanism of vasoconstriction but with different nomenclatures described in the rheumatologic, neurologic, and obstetric literature. For example, postpartum angiopathy¹⁰ and migrainous vasospasm¹¹ likely refer to an angiopathy with symptoms caused by vasoconstriction rather than true inflammation of blood vessels.

MAGNETIC RESONANCE IMAGING

Magnetic resonance imaging (MRI) should be the neuroimaging modality of choice for patients with suspected PACNS, and findings from MRI are abnormal in 90% to 100% of patients.^{1,8} The most common abnormalities are seen in the subcortical white matter, followed by the deep gray matter, the deep white matter, and the cerebral cortex.¹² Infarcts may be seen in approximately 50% of cases; when present, infarcts are usually seen bilaterally in multiple-vessel tributaries, affecting the cortex as well as the subcortex.¹ Infarcts may also appear in patients of different ages. Mass lesions, which are sometimes mistaken for malignant neoplasms, can be seen in as many as 15% of cases. Other common patterns include diffuse small-vessel changes of ischemic demyelination. Less common patterns include confluent white-matter lesions, which can be mistaken for multiple sclerosis, or cortical laminar necrosis. MacLaren et al¹³ showed that findings from MRIs may be abnormal even in the context of normal findings from angiograms and hypothesized that multifocal regions of cortical and subcortical ischemia may be angiographically occult if the affected vessels are below the resolution of angiography.

Gadolinium enhancement may occur in as many as one-third of cases; leptomeningeal enhancement may occur in 10% to 15% of cases, and when present in the non-dominant lobe, may represent an ideal site for biopsy.¹ Both subarachnoid and intraparenchymal hemorrhages occur in approximately 10% of cases. In contrast to subarachnoid hemorrhages, which occur along the cortical surface in patients with RVCS, the location of the subarachnoid and intraparenchymal hemorrhages in patients with PACNS does not suggest petechial transformation caused by reperfusion injuries.⁹ The rarity of microaneurysms in angiographic studies accounts for the lower rate of subarachnoid hemorrhage seen on MRIs.

CSF STUDIES

The CSF analysis is abnormal in 80% to 90% of patients with true PACNS.^{1,2,5,14} Similar to the discrepant sensitivities reported for MRI, studies that propose lower sensitivities of CSF testing are contaminated by patients with a clinical spectrum more suggestive of RVCS.^{6,8}

The CSF samples of patients with PACNS may show only modest elevations in white blood cell count and total protein level. For example, in their cohort of 101 patients with CNS vasculitis, Salvarani et al¹ reported a median white blood cell count of only 5 cells/ μ L (range, 0-535 cells/ μ L) (to convert to 10^9 per liter, multiply by 10^{-3}) and a median total protein level of only 0.7 g/dL (range, 0.15-1.03 g/dL [to convert to grams per liter, multiply by 10.0]).

The possibility of infection must be scrupulously considered, especially given the similar CSF profiles of PACNS and viral and/or fungal infections. In general, the differential diagnosis for CSF abnormalities includes all entities that can cause chronic meningitis. Appropriate fungal stains, viral polymerase chain reaction titers, and flow cytometry studies should be performed, especially given that most of these infectious and malignant entities can cause focal and diffuse syndromes that can clinically resemble CNS vas-

culitis. In patients with PACNS, the CSF pleocytosis rarely exceeds 250 cells/ μ L; the presence of CSF leukocytosis greater than 250 cells/ μ L, along with a white blood cell differential showing polymorphonuclear rather than lymphocytic proliferation, should be a red flag necessitating an aggressive search for infection.

Although isolated CSF evaluations and MRI studies may have limited sensitivity and specificity, the constellation of results from these studies do allow for diagnostic clarity. In general, the combination of normal findings on MRI and a CSF sample negative for a normal CSF analysis has a high negative predictive value for the diagnosis of CNS vasculitis.¹⁴ Such patients will likely have a noninflammatory vasculopathy or, less likely, RVCS in the appropriate clinical context. These patients do not generally need to undergo a brain biopsy, and the benefits of immunosuppressant treatment do not warrant the associated toxicities.

ANGIOGRAPHY

Findings from a CNS angiogram may support the diagnosis of PACNS. However, there are limitations to angiography, both in the technique and the diagnostic context of PACNS, that should temper enthusiasm for its use as a diagnostic gold standard.

First, angiograms provide information about regional changes in vessel contours without providing further information about the pathologic processes and mechanisms that cause abnormal findings. A range of non-inflammatory vasculopathies—including atherosclerosis, vasospasm, radiation vasculopathy, infections, neoplasia, atrial myxomas, neurofibromatosis, and fibromuscular dysplasia—can cause angiographic findings similar to those seen with PACNS.¹⁵ Therefore, angiograms have limited specificity.

In addition, a CNS angiogram also has limited sensitivity for detecting vasculitis, even when compared with the criterion standard technique, biopsy. Overall, the sensitivity of angiography in detecting PACNS has been estimated at between 50% and 90%^{1,2,5,16,17}; angiographic findings suggestive of vasculitis include “beading,” or multiple regions of narrowing in a given vessel, with interposed regions of ectasia or normal luminal architecture. The beading may be smooth or irregular and typically occurs bilaterally.¹⁵ Although PACNS is classically considered a small-vessel vasculitis, several studies have also emphasized that angiographic changes may be seen in larger vessels as well.^{1,15} Other angiographic findings include single regions of vessel narrowing in multiple-vessel tributaries, collateral flow, and regionally prolonged circulation time. Unlike systemic vasculitides affecting organs other than the CNS, there is no predilection for angiographic abnormalities at sites of vessel bifurcation. In addition, microaneurysm, which is an important angiographic feature of polyarteritis nodosa, is seldom seen in patients with PACNS.¹⁵

ROLE OF BIOPSY

All patients with a suspected diagnosis of PACNS should undergo biopsy to confirm a tissue diagnosis of PACNS.

There are several reasons why biopsy should be encouraged, especially when there are plans for prolonged immunosuppressant treatment.

First, findings from a biopsy may disclose other syndromes, which at best may not be helped by immunosuppressant treatment and at worst might jeopardize a patient's life. For example, Alrawi et al¹⁸ reported that, of 61 patients referred for biopsy to test for suspected PACNS, alternative diagnoses were established in 24 cases (39%); 12 patients had infections, including 3 patients with brain abscesses, and 8 patients had malignant neoplasms, including 6 with primary CNS lymphoma. Angiocentric inflammation caused by malignant neoplasms, including primary CNS lymphomas and lymphomatoid granulomatosis, can cause patterns of beading in a multivessel distribution that are indistinguishable from vasculitis.² Similarly, infections—including herpes simplex virus (often seen with inflammation affecting the middle cerebral artery vessel and tributaries), human immunodeficiency virus, opportunistic infections, and fungal infections—can also cause similar angiographic findings. Therefore, the spectrum of syndromes that can clinically and angiographically mimic PACNS should discourage the most emphatic clinical diagnosis of PACNS. The ongoing risk of infection and malignant neoplasms associated with prolonged immunosuppressant treatment, continued during the 2 to 3 years of maintenance therapy, justifies attempts to secure a tissue diagnosis.

Vasculitis affects vessels in a skipped and segmental pattern. Therefore, the inherent patchiness of vasculitic inflammation accounts for negative findings in biopsy specimens because of sampling error. Salvarani et al¹ reported that 18 of 47 patients (38%) who were thought to have a high probability of PACNS had biopsy specimens that were negative for vasculitis. Lie³ reported that 7 of 15 patients (47%) had biopsy specimens negative for PACNS, with tissue diagnoses only secured during postmortem examination. Therefore, the sensitivity of brain biopsy may be less than 50%. There is conflicting data as to whether sampling regions of leptomeningeal enhancement increases sensitivity. Stereotactic biopsy is generally only recommended for mass lesions

For reasons of safety and optimal yield, a biopsy should be performed at the nondominant temporal tip. Owing to frequent involvement of the leptomeningeal vessels, the leptomeninges should be included to enhance diagnostic yield.

HISTOPATHOLOGIC ANALYSIS

The most common histologic pattern is of granulomatous vasculitis.³ Both foreign body and Langerhan-type giant cells may be seen, with associated lymphocytes, plasma cells, and histiocytes constituting a reactive pleomorphic infiltrate. The other types of vasculitic patterns include a lymphocytic pattern as well as a pattern of fibrinoid necrosis, as is commonly seen in polyarteritis nodosa.

Scolding et al¹⁹ have suggested that there is a distinct clinicopathologic vasculitic pattern associated with cerebral amyloid angiopathy. If such an association does have a distinguishing clinical profile, then it is intriguing to consider that the pattern of granulomatous in-

flammation associated with amyloid angiopathy may represent a more specific foreign body reaction.¹

Other histopathologic findings seen in patients with biopsy-proven vasculitis are thromboses in vessels without evidence of vasculitis; a bland pattern of neointimal proliferation, which may be caused by chronic disease; and a healing pattern of resolving vasculitic inflammation.³ In the context of other compelling clinical, CSF, radiographic, and angiographic findings, such nondiagnostic studies still may further support the diagnosis of CNS vasculitis.

DIAGNOSTIC CRITERIA

In 1988, Calabrese and Mallek² proposed diagnostic criteria for PACNS:

1. a history of an unexplained neurologic deficit that remains after a vigorous diagnostic workup, including lumbar puncture and neuroimaging studies;
2. either classic angiographic evidence of vasculitis or histopathologic evidence of vasculitis within the CNS; and
3. no evidence of systemic vasculitis or any other condition to which the angiographic or pathologic evidence can be attributed.

As we have discussed, the nonspecificity of CNS angiograms results in patients with syndromes more consistent with RVCS who are being diagnosed and treated for PACNS. To prevent patients with RVCS from being treated with cytotoxic therapy, we propose the following changes in the previous criteria, stratified by levels of certainty about the diagnosis:

1. patients receive a *definite* diagnosis of PACNS if there is confirmation of vasculitis on analysis of a tissue biopsy specimen; and
2. patients have a *probable* diagnosis of PACNS, in the absence of tissue confirmation, if there are high-probability findings on an angiogram with abnormal findings on MRI and a CSF profile consistent with PACNS.

Patients with high-probability findings on an angiogram but a normal CSF analysis may have either RVCS or PACNS. In these cases, consideration of the demographic and clinical features of the patient's neurologic symptoms (Table 1) assumes increasing importance in discriminating between RVCS and PACNS.

DIFFERENTIAL DIAGNOSIS

Inflammatory and noninflammatory vasculopathies that should be considered in the differential diagnosis of PACNS are listed in **Table 2**. Based on salient demographic and clinical features, the following distinctions are particularly important.

1. In patients younger than 40 years, consider the diagnosis of RVCS, especially when associated with acute onset, thunderclap headache, and focal presentation. In patients older than 75 years, consider the diagnosis of amyloid angiopathy, especially when associated with lobar hemorrhages or a history of dementia.

Table 2. Differential Diagnosis of PACNS

Noninflammatory vasculopathies
RVCS
Atherosclerosis
Neurofibromatosis
Fibromuscular dysplasia
CADASIL
MELAS
Susac syndrome
Hypercoagulable state
Infections
Emboli from subacute bacterial endocarditis
Basilar meningitis caused by TB or fungal infection
Bacterial infections
Parainfection syndromes (eg, ADEM)
Demyelinating syndromes
Multiple sclerosis
ADEM
Sarcoidosis
CNS vasculitis, secondarily affected as part of a primary vasculitis
Large-vessel vasculitis (eg, giant-cell arteritis, Takayasu arteritis)
Medium-vessel vasculitis (eg, polyarteritis nodosa, Kawasaki disease)
Small-vessel vasculitis
ANCA-associated vasculitis (eg, Wegener granulomatosis, Churg-Strauss syndrome, microscopic polyangiitis)
Immune-complex deposition (eg, Henoch-Schönlein purpura, cryoglobulinemia)
Rheumatic syndromes (eg, lupus, Sjögren syndrome, scleroderma)
Malignant diseases
Primary CNS lymphoma
Lymphomatoid granulomatosis
Carcinomatous meningitis
Gliomatosis cerebri

Abbreviations: ADEM, acute disseminated encephalomyelitis; ANCA, antineutrophil cytoplasmic antibody; CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CNS, central nervous system; MELAS, mitochondrial encephalopathy with lactic acidosis and stroke-like syndromes; PACNS, primary angiitis of the central nervous system; RVCS, reversible vasoconstriction syndrome; TB, tuberculosis.

2. In patients with clinical or radiographic signs of basilar inflammation, consider sarcoidosis, fungal infections, or tuberculosis.

3. In patients with symptoms or serologic markers of systemic inflammation (eg, elevated erythrocyte sedimentation rate, night sweats), consider infection, malignant neoplasm, or secondary involvement of the CNS as part of a systemic vasculitis.

4. In the context of immunosuppression—including not only patients with human immunodeficiency virus but also patients with diabetes mellitus, significant alcohol consumption, and a history of immunosuppression—strongly consider infection, including subacute bacterial endocarditis.

TREATMENT

We treat patients with definite PACNS initially with oral cyclophosphamide (2 mg/kg/d) and corticosteroids (usually in the form of prednisone, 1 mg/kg/d). If the patient has immediate life-threatening disease, we begin corticosteroid therapy with methylprednisolone (1 g intravenously daily for 3 d). Thereafter, the patient is given

oral prednisone (1 mg/kg/d) for 1 month, and the dosage then is tapered slowly over 12 months. When taking such high doses of prednisone, all patients also should be given bisphosphonate prophylaxis in addition to receiving adequate calcium and vitamin D. Appropriate adjustments for cyclophosphamide therapy, considering the patient's age, renal status, and other comorbidities, have been described elsewhere.²⁰ In addition, all patients should be given *Pneumocystis* infection prophylaxis; we use a combination of trimethoprim and sulfamethoxazole (80 mg/400 mg), 1 tablet daily. Surveillance and treatment of the adverse effects of cyclophosphamide, such as infections, hemorrhagic cystitis, myelosuppression, and malignant neoplasms, have been described elsewhere. It is a common yet dangerous misconception that the efficacy of cyclophosphamide requires achieving leukopenia. Indeed, leukopenia is to be avoided or minimized. Because the myelosuppressive effects of cyclophosphamide are unpredictable, we recommend complete blood cell counts at least every 15 days.

A National Institutes of Health study of Wegener granulomatosis demonstrated that as many as 42% of patients sustained irreversible damage as a consequence of prolonged cyclophosphamide treatment.²¹ Accordingly, we now treat patients with both Wegener granulomatosis and PACNS with cyclophosphamide for 3 to 6 months until there has been induction of remission. We then stop cyclophosphamide therapy and start azathioprine for maintenance of remission, although other immunosuppressants, such as methotrexate and mycophenolate, can be used. These agents are then continued for 2 to 3 years after induction of remission.

SUMMARY

Given the morbidity associated with cytotoxic therapy, a chief diagnostic goal for most systemic vasculitides is confirmation in tissue specimens. Especially given the non-specificity of angiographic studies, all patients with suspected PACNS should undergo biopsy. The most common symptoms of PACNS are indolent progression of headache and cognitive changes. Features that are more suggestive of RVCS are acute thunderclap headache, normal CSF analysis, and comorbid conditions (eg, pregnancy, migraines, and drug use) that may be associated with vasospasm. Fever and elevated inflammatory markers occur in a few patients with true PACNS. We have proposed changes in current diagnostic criteria that account for a level of certainty based on tissue diagnosis as well as neuroimaging and CSF studies. The goal of these proposed diagnostic criteria is to discriminate between PACNS, which requires cytotoxic treatment, and RVCS, which can be treated with prednisone monotherapy and possibly calcium channel blockers. Additional multicenter prospective studies will be needed to validate these criteria and elucidate the heterogeneous mechanisms leading to PACNS.

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