

Clinical Summary



Primary central nervous system angiitis

By

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Disclosures:

Dr. Khan has no relevant financial relationships to disclose.

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ICD codes

ICD-9:

Arteritis, unspecified: 447.6
 Polyarteritis nodosa: 446.0
 Hypersensitivity angiitis: 446.2
 Wegener granulomatosis: 446.4
 Giant cell arteritis/temporal arteritis: 446.5
 Takayasu disease: 446.7

ICD-10:

Arteritis, unspecified: I77.6
 Polyarteritis nodosa: M30.0
 Hypersensitivity angiitis: M31.0
 Wegener granulomatosis: M31.3
 Giant cell arteritis/temporal arteritis: M31.6
 Aortic arch syndrome [Takayasu]: M31.4

Synonyms

PACNS; BACNS; GACNS; IACNS

Historical note and nomenclature

Vasculitis or angiitis is defined as an inflammatory disease of arteries, veins, or both that results in histologically demonstrable structural injuries to the vessel wall, often accompanied by thrombosis and evidence of ischemic damage to the tissues served by the effected blood vessels. A vasculitis is considered primary when it occurs without an identifiable cause or when it is unassociated with an underlying disease and secondary when it occurs as a manifestation of a diverse group of underlying diseases.

The central nervous system vasculature can be affected secondarily by numerous forms of vasculitis such as generalized autoimmune diseases (systemic lupus erythematosus, Sjögren syndrome) or systemic vasculitis (Wegener granulomatosis, polyarteritis nodosa) as well as by drugs (amphetamines, cocaine), infections (bacterial, fungal, protozoal, mycoplasmal, rickettsial, viral), malignancy (Hodgkin lymphoma, non-Hodgkin lymphoma, leukemia, lung cancer), Behçet disease, Cogan syndrome, and sarcoidosis (Moore and Calabrese 1994).

Primary CNS vasculitis was first described by Harbitz in 1922, but it was not until 1959 that Cravioto and Feigin introduced the concept of vasculitis with a unique predilection for the CNS and coined the term

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"noninfectious granulomatous angiitis with a predilection for the nervous system" (Harbitz 1922; Cravioto and Feigin 1959). In their classical description, they explained 2 cases from their own series and also gave a literature review of suspected cases including 1 case from Harbitz (Harbitz 1922), 2 cases from Newman and Wolf (Newman and Wolf 1952), and 2 from McCormick and Neuburger (McCormick and Neuburger 1958). They questioned the diagnosis of Churg-Strauss syndrome in Newman and Wolf's cases and also temporal arteritis in McCormick and Neuburger's cases. They suggested that along with their own 2 cases, these 6 cases should be grouped together as delineating a distinct clinical and pathological entity. They also suggested the possible utility of biopsy in establishing the diagnosis and cortisone/ACTH in therapy. Another case was added in the literature in 1966 by Hughes and Brownell (Hughes and Brownell 1966).

By the 1970s, this disease was considered a severe, uniformly fatal disorder and unresponsive to therapy with few notable exceptions like the case reported by Snyder and McClelland in 1978 (Snyder and McClelland 1978). In all published case reports until that time, the entity had been recognized at postmortem examinations. Cupps and colleagues described the efficacy of cyclophosphamide and high-dose glucocorticoids, with the idea driven by the successful use of these agents in systemic angitic syndromes (Cupps et al 1983). Sigal in 1987 wrote an excellent review paper shedding light on the neurologic manifestations of vasculitic and rheumatological syndromes (Sigal 1987). Fauci and colleagues in 1979 and then Calabrese and Mallek in 1988 proposed the diagnostic criteria that relied equally on histopathology or, alternatively, cerebral angiography in the appropriate clinical setting (Fauci et al 1979; Calabrese and Mallek 1988). These criteria include:

- (1) An unexplained neurologic deficit despite aggressive diagnostic evaluation.
- (2) A high probability angiogram for arteritis or histopathological evidence of arteritis confined to the CNS.
- (3) Exclusion of all those disorders capable of mimicking the angiographic findings or associated with vascular inflammation of the CNS.

Over time it became increasingly common for patients to be diagnosed with primary angiitis of the CNS solely on angiographic grounds without supporting histopathology. As a result, patients, diagnosed solely on the basis of abnormal angiogram, were treated with prolonged and intensive immunosuppressive regimens based on the supposition that cases diagnosed by angiographic findings were clinically equivalent to biopsy-proven cases (Woolfenden 1998).

The achievements of 1980s proved to be lessons of the 1990s. First, enthusiasm for the empiric treatment of cerebral vasculitis waned because of recognition of the unreliability of cerebral angiography in its diagnosis. A second factor that lessened interest in empiric therapy with cyclophosphamide for CNS vasculitis was the recognition of permanent side effects in up to 40% of patients treated with oral cyclophosphamide for Wegener granulomatosis. Calabrese and colleagues described so-called benign angiopathy of the CNS among young women with the prior diagnosis of primary angiitis of the CNS (Calabrese et al 1993). They differed in the onset with a focal cerebral deficit, normal CSF, lack of progression, and spontaneous resolution. They proposed primary angiitis of the CNS as a heterogeneous disease

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with granulomatous angiitis of the CNS and benign angiopathy of the CNS, and with atypical forms as clinical subsets. Hajj-Ali and coworkers provided evidence that the pathologic process in benign angiopathy of the CNS is vasoconstriction rather than vasculitis, thus indicating that benign angiopathy of the CNS should not be included in the spectrum of primary angiitis of the CNS (Hajj-Ali et al 2002). Reversible cerebral vasoconstriction is the term now used to describe entities such as postpartum angiopathy, Call-Fleming syndrome (Call et al 1988), benign angiopathy of the CNS, and others. In 2005, MacLaren and colleagues explained that the clinical course of patients with primary angiitis of the CNS differed markedly depending on the size of the vessel involved (MacLaren et al 2005). They proposed 2 subsets of primary angiitis of the CNS: small-vessel disease and medium-vessel disease. But the debate still continues as these classifications continue to evolve. Calabrese rightly noted: "A penumbra is a space of partial illumination, such as in eclipse, between perfect shadow and full light. Despite significant progress, primary angiitis of the CNS remains foursquare in the penumbra awaiting full illumination" (Calabrese 2001). Our knowledge about this intriguing disease continues to expand, and excellent reviews were done in the last decade (Younger and Kass 1997; Younger et al 1997; Younger 2004; 2005).

Vasculitis predominantly affecting the CNS has been given several diagnostic labels in the past 90 years. Harbitz first described it as "unknown forms of arteritis" (Harbitz 1922). The same condition was later described as, "non infectious granulomatous angiitis involving the central nervous system" (Newman and Wolf 1952), as "giant cell arteritis involving small meningeal and intracerebral vessels" (McCormick and Neuburger 1958), as "noninfectious granulomatous angiitis with a predilection for the nervous system" (Cravioto and Feigin 1959), as "granulomatous angiitis of the nervous system" (Budzilovich et al in 1963) or simply "granulomatous angiitis" (Burger et al 1977), and as "isolated angiitis of CNS" (Cupps et al 1983; Moore 1989). The nomenclature of this unique disease entity continues to evolve, and terms such as granulomatous angiitis of the CNS and isolated angiitis of the CNS fall out of use as neither is appropriate because the histology can be granulomatous or lymphocytic and subclinical involvement of extracranial arteries (eg, pulmonary and abdominal visceral angiitis) have been reported. Granulomatous pathology in cerebral vessels is highly nonspecific as it had been shown to be associated with various disease entities like temporal giant-cell arteritis (Jellinger 1977), herpes zoster (Rosenblum and Hadfield 1972; Hilt et al 1983), lymphoproliferative tumors (Rajjoub et al 1977; Johnson et al 1989), sarcoidosis (Caplan et al 1983), amyloid angiopathy (Fountain and Eberhard 1996), and systemic lupus erythematosus (Scharre et al 1986). The final diagnostic label of "primary angiitis of the central nervous system" proposed by Calabrese and Mallek in 1988 and endorsed by Lie in 1991 and 1992 is the most appropriate and correct one according to our current understanding of this unique disease (Calabrese and Mallek 1988; Lie 1991; 1992).

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Clinical manifestations

Virtually every neurologic sign or symptom has been reported at least once in primary CNS angiitis (Calabrese 1997). Nonfatal symptoms such as headaches and confusion are the most common presentation,

with hemiparesis being the most common sign. Also common are ataxia, focal cortical dysfunction-like aphasia, and seizures. Movement disorders like chorea and myoclonus, radiculopathy, optic and cranial neuropathies, stroke-like episodes with hemispheric and brainstem deficits, and acute or subacute encephalopathy have been reported. Nonspecific visual complaints occur in approximately 15% of patients. Signs and symptoms of systemic vasculitis such as peripheral neuropathy, fever, weight loss, or rash are usually lacking. Scolding and colleagues defined 3 broad categories of clinical presentation (Scolding et al 1997):

(1) Acute or subacute encephalopathy, commonly presenting as confusional state, progressing to drowsiness and coma if left untreated.

(2) Atypical multiple sclerosis in phenotype, with a relapsing-remitting course and features such as optic neuropathy and brainstem episodes but also accompanied by other features less common in multiple sclerosis such as seizures, severe and persistent headaches, encephalopathic episodes, or hemispheric stroke-like episodes.

(3) Intracranial mass lesions with headaches, drowsiness, focal signs, and, often, raised intracranial pressure.

Twenty percent of patients will have signs or symptoms that fluctuate early in the course of disease. This can be explained by the size of the vessels involved and by the fact that the fundamental pathophysiological mechanism in all angiitides is tissue ischemia; it is not surprising that early manifestations of the disorder might fluctuate in intensity or even spontaneously improve. Although the classic picture is one of progressive, cumulative, and multifocal neurologic dysfunction, there are abundant exceptions, including patients whose presentations suggest cerebral tumor (Valavanis et al 1979), chronic meningitis (Reik et al 1983), demyelinating disease, acute encephalitis (Derry et al 2002), myelopathy (Caccamo et al 1992), subarachnoid hemorrhage (Kumar et al 1997), silent cortical hemorrhage (Ay et al 2002) dementia (Koo and Massey 1988), and degenerative disorders (Budzilovich et al 1963). When primary angiitis of the CNS presents as a stroke, it is usually because of intracerebral hemorrhage (Biller et al 1987), which occurs in approximately 15% of patients. It rarely causes cerebral infarct (Vollmer et al 1993) or transient ischemic attacks in the absence of clinical or laboratory evidence of a widespread CNS inflammatory disorder, such as CSF pleocytosis (Calabrese and Mallek 1988).

Isolated spinal cord vasculitis was initially reported by Feasby and colleagues in 1975 when they described a case presenting with subacute progressive cervical myelopathy with negative workup for secondary pathologies (Feasby et al 1975). Granulomatous angiitis involving the spinal cord is seen in about 14% of cases of primary angiitis of the CNS (Duna and Calabrese 1995). It may be the initial manifestation of primary angiitis of the CNS (Lie 1991) or systemic vasculitis (Moore and Fauci 1981). Initial case reports have demonstrated that all such patients may develop intracranial manifestations within a period of 3 months to 3 years. Patients usually present with back pain, progressive myelopathy, and an elevated CSF protein level with pleocytosis and normal erythrocyte sedimentation rate. MRI is sensitive enough to reveal diffuse enlargement of the cord, but this finding is highly nonspecific as such enlargement may be associated with diffusely infiltrating astrocytoma, lymphoma, leukemia, metastasis, sarcoidosis (neurovascular form) (Younger et al 1988), an

infectious process, and cord ischemia (Giovanini et al 1994). Therefore, the diagnosis should be confirmed by angiography or biopsy before starting immunosuppressive regimens.

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Clinical vignette

A case report from the landmark paper of Cravioto and Feign that formed the basis of this intriguing disease is summarized below (Cravioto and Feign 1959):

A 56-year-old female with no significant past medical history was admitted for an episode of aphasia followed by convulsive movements in the right side of the face and the right arm. She reported persistent vomiting with frontal headaches for the past 2 years. She signed off against medical advice.

A month later she had another episode of aphasia and a sudden episode of loss of consciousness that lasted for 30 minutes. She continued to have intermittent episodes of headache and vomiting. Later, she developed progressive weakness of both legs along with gradual mental deterioration and suffered from right-sided convulsive seizures. Physical examination revealed slight weakness and increased deep-tendon reflexes of the right extremities, right Babinski sign, and bilateral Hoffmann reflexes. All modalities of sensation appeared normal. Laboratory workup was largely unrevealing, with erythrocyte sedimentation rate noted to be slightly elevated at 35. Cerebrospinal fluid showed 62 RBC, 3 lymphocytes, 88 mg protein, negative Wassermann reaction, and a pressure of 220 mm of H₂O.

The patient's mental status deteriorated, and she developed right hemiparesis. She had severe convulsions involving the face and left leg and smacking movements of the lips. These were treated with intravenous amobarbital sodium. Repeat spinal tap showed slight xanthochromia with 363 RBC, 57 mg protein, and a pressure of 180 mm of H₂O. Later she again developed convulsive movements that were partially responsive to intravenous and intramuscular phenobarbital. She suddenly became apneic and expired.

At autopsy, the brain appeared externally normal apart from the thickened leptomeninges at the base. Microscopically, the severe granulomatous process diffusely involved arteries and veins. The process involved the entire thickness of the vessel walls, with arteries being more affected than veins. Leptomeninges and subependymal white matter were particularly affected. The vessel lumens were narrowed or completely occluded. No fungi, tubercle bacilli, or other bacteria were found. Study of other organs revealed no lesions resembling those in the brain.

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Etiology

Cause and pathogenesis are unknown. Younger and colleagues suggested that primary angiitis of the CNS is a nonspecific inflammatory reaction of diverse etiology (Younger et al 1988). Many systemic vasculitis syndromes are a result of deposition of immune complexes, but there is little support for this mechanism in primary CNS vasculitis. The infiltrating cells were CD4+ T lymphocytes in the few cases in which leukocyte typing was done. Reyes and colleagues reported a patient in whom they found intranuclear virus-like particles resembling herpes virus on electron microscopy of formalin-fixed brain

samples (Reyes et al 1976), but to date there is no convincing evidence of infection with any microorganism in isolated CNS vasculitis, although *Mycoplasma* does cause CNS vasculitis in animals. There is no animal model for pure primary angiitis of the CNS. The one most often cited is cerebral arteritis induced by intravenous injection of *Mycoplasma gallisepticum* (Thomas et al 1966), but the model has its own shortcomings.

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Pathogenesis and pathophysiology

The credit for the first pathological description of primary CNS angiitis goes to Harbitz (Harbitz 1922), but it was not until 1959 that Cravioto and Feigin elaborately discussed this entity (Cravioto and Feigin 1959). Further case reports were published by Budzilovich and colleagues between 1959 and the end of the following decade (Budzilovich et al 1963). By 1968, Kolodny and colleagues had accurately characterized the essential pathological features of the disorder (Kolodny et al 1968).

Gross examination of brain and spinal cord showed no changes specific to the disorder. The majority of cases have had infarcts or hemorrhages, but they are usually small. Light microscopic examination confirms the presence of infarcts, hemorrhages, and areas of ischemic cell changes. The vascular inflammation is usually of a chronic granulomatous nature, with monocytes and histocytes, lymphocytes, and plasma cells infiltrating the walls of small (200 µm) arteries and veins, particularly in the leptomeninges and the branches that arise from them to penetrate the cortex. Larger vessels may be involved but never to an extent exceeding that of smaller ones. Angiitic vessels up to 1 mm in diameter have been observed (Kolodny et al 1968; Koo and Massey 1988). Several case reports showed the involvement of the vessels of the circle of Willis or their larger branches but never without severe concomitant involvement of smaller vessels. Involvement of veins up to 2.5 mm has been seen, but that of larger veins or dural sinuses has not. Although present in most of the autopsy cases, giant cells of either Langerhans- or foreign body-type are not required to make the diagnosis. Skipped lesions are common as the disease is notoriously segmental in nature, resulting in only 50% of biopsy cases showing classic histopathology of primary angiitis of the CNS.

Granulomas that seem to separate from vessels are occasionally encountered. Serial sectioning reveals an involved vessel adjacent to most of these. Reticulin stains often will allow identification of a small residual lumen within a granulomatous mass (Burger et al 1977). Intimal fibrosis usually signifies healing or healed lesions. In most positive biopsies, acute healing and healed vasculitic lesions frequently coexist in different segments of the same artery or in adjacent arteries of the same biopsy. Kolodny and colleagues proposed the following sequence for the development of angiitic lesions (Kolodny et al 1968):

- (1) Intimal swelling and hyperplasia in arteries and adventitial lymphocyte infiltration in veins.
- (2) Subintimal fibrinoid change and adventitial accumulation of histocytes.
- (3) Necrosis and fibrinoid changes in the media, fragmentation of internal elastic lamina, and panmural infiltration of lymphocytes and histocytes.
- (4) In typical lesions, granulomatous mass replaces all or part of vessel wall-lymphocytes, large mononuclear cells, fibroblast,

multinucleated giant cells, and invariable number of plasma cells.

(5) Possibly a later stage, abundant fibrosis and relatively sparse lymphocytic infiltration, accompanied by large mononuclear and giant cells.

Small, clinically silent foci of vasculitis are occasionally present in 1 or more viscera; lungs (Kolodny et al 1968), heart (Nurick et al 1972), kidney (Kolodny et al 1968), prostate (Arthur and Margolis 1977), lymph nodes (Burger et al 1977), and aorta (Nurick et al 1972) but by definition produce neither laboratory nor symptomatic evidence of organ dysfunction.

Among the other syndromes that can cause CNS angiitis, polyarteritis nodosa only rarely displays a granulomatous inflammation and does not effect the veins. Fibrinoid necrosis and transmutable inflammation both are more prominent in polyarteritis nodosa than in isolated CNS angiitis, with a special predilection for bifurcation. Polyarteritis-type necrotizing vasculitis may be seen in up to 25% of positive biopsy results. Churg-Strauss syndromes (Churg and Strauss 1951) and Wegener granulomatosis have extravascular granuloma, and eosinophils are prominent in the former. The angiitis form of sarcoidosis is characterized by extravascular noncaseating granulomas and the absence of fibrinoid necrosis.

The etiopathogenesis of primary CNS angiitis is very limited due to the scant availability of necessary pathological tissues. The potentially invading organisms need to have culture, immunohistochemistry, and *in situ* identification studies done so the mechanisms can be understood. The pathogenesis can be reviewed in the following sequence:

- (1) Initiating factors (infection or immunocompromised state).
- (2) Mechanism of immunological damage (immune complex versus delayed hypersensitivity).
- (3) Pathogenesis of tissue damage (endothelium, platelets, cytokines).

The basic pathogenesis of all forms of angiitis almost certainly is immunologic; the inciting event may be nonspecific vascular damage, allowing deposition of immune complexes or exposing new antigens to the bloodstream. Crowe discusses 4 different mechanisms of immunologic tissue injury that might apply to the pathogenesis of angiitis (Crowe 1988):

- (1) Immune complexes
- (2) Antibody-directed damage
- (3) Delayed hypersensitivity
- (4) Catatonic T lymphocytes

The granulomatous nature of the inflammation suggests a primary role of cell-mediated immunity with persistent antigenic stimulus that attracts T lymphocytes specific to that antigen as opposed to an antibody-mediated process. Immune complexes do induce granulomatous formation in certain circumstances. Although circulating immune complexes, hypocomplementemia and vascular deposition of immunoglobulin or compliment have not been found in the cases of isolated CNS angiitis studied to date. The cellular infiltrate in primary angiitis of the CNS has not been immunophenotyped in large series of patients in order to make any concrete conclusion.

Once the immunological mechanisms have initiated an angiitis, proximal mechanisms of disease will lead to tissue damage, mainly by ischemia. This is simply the result of stenosis of vessels by the masses

of inflammatory cells in their walls. The endothelial surface normally is the site of a delicate balance between the prothrombotic and antithrombotic tendencies, with the later obviously dominant in the normal circulation. Angiitis can alter this balance to favor thrombosis. The cytokines TNF and IL-1 are products of stimulated macrophages; in cultured endothelial cells they cause a number of changes that would encourage thrombosis. There is convincing *in vitro* and emerging *in vivo* evidence of endothelial activation by TNF and IL-1 that increase the permeability of vessel walls and expose thrombogenic basal lamina to the bloodstream.

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Epidemiology

Cerebral vasculitis is a rare but potentially life-threatening condition with an annual incidence of 1 to 2 per million compared to 39 per million for systemic vasculitis (Watts and Scott 1997). There is no epidemiological study specifically for primary angiitis of the CNS as the literature only includes 140 well-described cases of granulomatous angiitis of the nervous system (Younger 2003). Of note, the disorder has been reported from many centers in Europe and North America, as well as from Australia and New Zealand. Whether the paucity of reports from Asia, Africa, and South America reflects a truly lower incidence in these regions is unknown. Primary angiitis of the CNS occurs predominantly in the fourth to sixth decades of life with a mean age of 45 years, although patients of ages from 3 to 71 years have been described. In earlier postmortem studies, males predominated 4:3 (Lie 1992a) but recent studies show an equal sex ratio. MacLaren and colleagues found an increased incidence for polyarteritis nodosa and primary angiitis of the CNS, but such observations do not necessarily correspond to an actual increase in incidence (MacLaren et al 2005); there may have been heightened diagnostic awareness as the American College of Rheumatology (Bloch et al 1990) and Chapel Hill Consensus Conference (Jennette et al 1994) criteria became established and broadly implemented.

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Prevention

Not applicable.

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Differential diagnosis

The differential diagnosis of this unique entity must be examined in various ways, such as clinically as well as with neuroimaging modalities (MRI) and angiography.

As mentioned above, primary angiitis of the CNS is a syndrome characterized by a range of pathology, at one extreme predominantly involving large intracranial vessels and at the other mainly involving cerebral microvasculature. It is useful to keep the pathological spectrum in mind when approaching the diagnosis. Thus, predominantly large-vessel disease is more likely to manifest at least in part with stroke-like features, whereas predominantly microvascular disease is more likely to manifest as a parenchymal mass, encephalopathy, or myelopathy. The differential diagnosis for these two extremes differ considerably (Nadeau 1997).

Table 1. Clinical Differential Diagnosis of Primary Angiitis of the Central Nervous System

Predominantly microvascular disease

- Glioma or glioblastoma multiforme
- Metastatic neoplasm
- Primary CNS lymphoma
- Lymphomatoid granulomatosis
- Cerebral abscess
- Tuberculoma
- Histoplasmosis
- Toxoplasmosis
- Syphilis (meningovascular form)
- Progressive multifocal leukoencephalopathy
- Herpes simplex encephalitis
- Other focal encephalitis (eg, cytomegalovirus, Rasmussen syndrome, arbovirus)
- Herpes zoster myelitis
- Idiopathic transverse myelitis
- Multiple sclerosis, especially fulminant forms
- Disseminated vasculomyelinopathy
- Behçet syndrome
- Venous sinus thrombosis
- Sarcoidosis

Predominantly macrovascular disease

- Thromboembolic stroke
- Intracranial atheromatous disease
- Systemic vasculitis
- Syphilis
- Reversible cerebral vasospasm
 - Idiopathic (eg, thunderclap headache)
 - Drug-induced (Levine et al 1990)
 - Postpartum
- Post-trigeminal zoster vasculopathy
- Sickle-cell disease
- Chronic progressive basal vasculopathy with moyamoya disease
- Migraine

Mixed

- Tuberculosis
- Syphilis
- Sarcoidosis
- Fungal meningitis (eg, cryptococcus, coccidiomycosis)
- Carcinomatous meningitis
- Intravascular lymphoma (eg, malignant angioendotheliomatosis) (Lie 1992b)
- Mitochondrial disorder (eg, MELAS)
- Thrombotic thrombocytopenic purpura
- Radiation vasculopathy

Table 2. MRI Mimickers

- Multiple infarcts (atherosclerotic versus embolic)

- Drug-induced vasculopathy (including methamphetamine, cocaine, ephedrine, phenylpropanolamine, and herbals)
- Cerebral autosomal dominant leukoencephalopathy (CADASIL) (Williamson et al 1999)
- Leukodystrophies (Finelli et al 1997)
- Gliomatosis cerebri
- Multiple sclerosis

Table 3. Angiographic Mimickers

Numerous entities, both inflammatory and noninflammatory, induce changes (sometimes transitory) resembling primary CNS vasculitis on cerebral angiography (Schmidley 2000).

- Neoplastic angioendotheliosis
- Spasm after subarachnoid hemorrhage
- Atherosclerosis
- Oral contraceptive use
- Migraine
- Postcoital headache
- Trauma
- Surgical manipulation of intracranial arteries
- Reversible cerebral segmental vasoconstriction
- Sumatriptan and isometheptene
- Hypertension
 - With pheochromocytoma
 - Postpartum
 - Eclampsia

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Diagnostic workup

The diagnosis of granulomatous angiitis begins with a high index of suspicion based on the clinical picture and the need to develop an organized approach. The clinical manifestations are diverse, with the typical patient presenting with headache of gradual onset, often accompanied by signs and symptoms of encephalopathy, and later developing focal symptomatology. Of particular note is the infrequency of marked systemic and constitutional symptoms. Absence of headache and mental status changes has good negative predictive values. A careful history and physical examination with attention to skin, eyes, testicles, paranasal sinuses, and lungs are likely to exclude systemic vasculitis. General medical laboratory investigations are frequently normal and unhelpful in confirming the diagnosis but extremely valuable in excluding other primary angiitis of the CNS mimickers. Erythrocyte sedimentation rate is usually modestly elevated but not to the degree seen in temporal arteritis. Screening blood studies, including white blood cell counts, hematocrit, rheumatoid factor, antinuclear antibody, cryoglobulin, total hemolytic complement, C1q binding for circulating immune complexes, SSA/SSB, p-ANCA, c-ANCA, and syphilis serology are all normal but clinically helpful to exclude other conditions (Calabrese and Mallek 1988).

Abnormalities of CSF observed in primary angiitis of the CNS generally reflect an inflammatory process within the CNS; elevated protein was observed in 70% of patients and lymphocytic pleocytosis in 68%. From a quantitative viewpoint, in 95% of the cases, the CSF protein level was

less than 500 mg/dl, and the cell count was less than 200 cells/mm, making the possibility of primary angiitis of the CNS in a patient with values exceeding these limits considerably less likely. The CSF analysis has a high negative predictive value, although a completely normal CSF cannot rule out primary angiitis of the CNS. Thus, the primary value of CSF examination in investigating suspected CNS vasculitis is to rule out infections including syphilis or neoplastic infiltration of meninges.

Electroencephalography is a highly sensitive test (81%) in the diagnostic evaluation of primary angiitis of the CNS. Unfortunately, the lack of specificity of results greatly compromises its usefulness in confirming the diagnosis. The most common abnormalities identified are the diffuse slow-wave pattern, but at times the pattern may be focal. Unfortunately, this pattern can be observed in a variety of infectious and metabolic disorders affecting the CNS. As with other diagnostic tests, the EEG may be useful in identifying other causes of unexplained neurologic symptoms, particularly when the clinical presentation is one of unexplained dementia (Calabrese and Mallek 1988). When this situation is secondary to prion disease, the EEG may reveal diagnostic changes and, thus, would eliminate primary angiitis of the CNS as a further consideration.

Magnetic resonance imaging with special sequences, including T2-weighted and FLAIR images, are found to have high sensitivity but lack specificity. Earlier case reports indicate low sensitivity for MRI, but unfortunately they did not include the FLAIR sequence (Imbesi 1999). Later, Wasserman and colleagues provided evidence that advanced neuroimaging sequences tailored to detect infarction (ie, diffusion-weighted, perfusion imaging and fluid-attenuated inversion recovery sequences) are needed to enhance the MRI sensitivity (Wasserman et al 2001). Alhalabi and Moore found abnormalities in 13 of 17 patients, with normal MRI in the other 4, yielding a sensitivity of 74% (Alhalabi and Moore 1994). Greenan and colleagues compared MRI and angiography in cerebral vasculitis of various etiologies and found MRI to be more sensitive (Greenan et al 1992); although MRI was abnormal in every case, cerebral angiography showed the disease to be more extensive. When combined with CSF, the sensitivity reaches 92% to 100% (Stone et al 1994). A combination of normal MRI and CSF test results has a strong negative predictive value and will exclude consideration of CNS vasculitis in most clinical situations, thus obviating the need for further invasive tests (Stone et al 1994; Calabrese and Duna 1995; Duna and Calabrese 1995). A negative MRI may exclude vasculitis more definitely than would a negative angiogram, and the likelihood of diagnosing CNS vasculitis with angiography is negligible in the setting of normal MRI (Harris et al 1994). The drawback is the lack of specificity. Characteristic focal findings include infarcts, often multiple and bilateral and in both grey and white matter (Alhalabi and Moore 1994; Kumar and Brown 1994). The abnormalities tend to be more prominent in white matter, especially on T2-weighted images, simulating demyelinating disease (Finelli et al 1997). Less commonly reported are hemorrhages, both parenchyma and subarachnoid, and rare instances of mass lesions (Valavanis et al 1979). Variable patterns of contrast enhancement are seen, including irregular subcortical streaks, leptomeningeal enhancement with comparatively little parenchymal involvement, focal cortical ribbing, or diffuse parenchymal vessel enhancement (Shoemaker et al 1994). Chances of positive biopsy are increased if the tissue is from the contrast-

enhancing areas. Ehsan and colleagues showed that serial imaging is useful in monitoring the clinical course of the disease (Ehsan et al 1995). An MRI scan should be performed to exclude other diagnoses, such as multiple cerebral metastasis, multicentric primary CNS tumors, and hydrocephalus or demyelinating diseases. The general consensus among clinicians is that MR angiography is not very useful due to its low spatial resolution. Yuh and colleagues pointed out the importance of perfusion imaging in assessing microcirculatory vasculopathy and diffusion imaging in detecting early changes of microcirculatory ischemia or infarctions that are characteristic findings of cerebral vasculitis and may not be appreciated by conventional MRI sequences (T2 or FLAIR) (Yuh et al 1999).

The enthusiasm for angiographic diagnosis of primary angiitis of the CNS has markedly fallen in the last decade since the realization of the fact that the findings are highly nonspecific and can be produced by a large number of inflammatory and noninflammatory conditions. The vascular changes revealed by angiography include beading, aneurysms, circumferential or eccentric vessel irregularities, multiple occlusions with sharp cutoffs, and an avascular mass effect. Among the pathologically documented cases, cerebral angiography may be normal in up to 40% of patients (sensitivity of 60%) (Calabrese and Mallek 1988; Hankey 1991). Hellmann and colleagues demonstrated that biopsy of angiographically abnormal vessels is safe and may better direct the surgeon to obtain tissue that will be most likely to show histopathological changes (Hellmann et al 1992). Alhalabi and Moore pointed out the fact that serial angiography can be used for monitoring the clinical course, but the procedure does carry the risk of transient (10%) or permanent (1%) neurologic deficits (Alhalabi and Moore 1994).

Brain and meningeal biopsy is the gold standard for the diagnosis of primary angiitis of the CNS because it is the only way to identify the characteristic pathology and to exclude other disorders like lymphoproliferative diseases, infections, sarcoidosis, and others (Parisi and Moore 1994). Brain biopsy is limited by poor sensitivity (Duna and Calabrese 1995). Premortem biopsies yield false-negative results in about 25% of autopsy proven cases (Calabrese et al 1992); sampling of the leptomeninges as well as the underlying cortex will likely increase the diagnostic yield because the vasculitis may be present in only 1 of the 2 sites. (Calabrese et al 1992; Parisi and Moore 1994; Chu et al 1998; Hunn et al 1998). Biopsy of radiographically abnormal areas, particularly in the presence of abnormal enhancement, improves the sensitivity of the procedure. In the absence of focal lesions, the temporal tip of the dominant hemisphere in an area with longitudinally oriented surface vessels is the preferred site (Calabrese and Duna 1995). An infratentorial approach should be considered in patients when there is suspicion of sarcoidosis or tuberculosis because the basilar meninges are preferentially involved (Ellner and Bennett 1976). Deep or stereotactic biopsy samples are not required unless approaching a mass lesion (Moore 1994; Lie 1997). Tissue samples should be stained and cultured for microorganisms. Although false-positive biopsies are rarely reported, areas of vascular inflammation may be encountered in lymphoproliferative disease and CNS infections (Duna and Calabrese 1995). Because the specificity of biopsy is not 100%, even a positive biopsy result should be interpreted in light of the entire clinical picture. Alrawi and colleagues proposed biopsy criteria for

definite and probable primary angiitis of the CNS (Alrawi et al 1999):

- (1) Minimum of 2 layers of lymphocytes within or around the walls of parenchymal or leptomeningeal and dural vessels ("lymphocytic inflammation").
- (2) Structural alterations of the vessel wall, such as prominence of the endothelial cells or indistinct appearance with or without necrosis.
- (3) Pink neuronal cytoplasm and pyknotic neuronal nuclei with or without pyknotic glial nuclei and astrocytic gliosis ("ischemic changes").
- (4) Neuronophagia.
- (5) Parenchymal (including perivascular) edema.
- (6) Exclusion of alternative diagnoses.

Probable primary angiitis of the CNS requires fulfillment of criteria 2 through 6.

There is insufficient experience with SPECT and PET scanning to know how, if at all, such modalities should be used in the evaluation of these patients. Meusser and colleagues have found that SPECT may hold promise in detecting early disease, with the diagnosis subsequently supported by the use of more established techniques (Meusser et al 1996).

Ophthalmoscopic examination. Dynamic recording of erythrocyte flow using video slit lamp microscopic recording and low dose fluorescein angiography to examine the vasculature of the anterior ocular chamber can be a useful additional investigation. Scolding and colleagues conducted a study in which 4 out of 5 patients had abnormal findings (Scolding et al 1997). Typical abnormalities are marked slowing of flow, multifocal attenuation of arterioles and erythrocyte aggregation. Fluorescein studies may confirm these changes and demonstrate areas of small vessel infarction along with post capillary leakage.

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Prognosis and complications

Primary angiitis of the CNS is a devastating disease. The consequence of missing the diagnosis is the death of the patient; the consequence of delay in diagnosis is likely to be severe disability. The prognosis is more favorable with early recognition and prompt treatment with an immunosuppressive regimen. But these therapies are not benign, with an estimated risk of 40% for severe, permanent side effects.

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Management

The current management scheme for primary angiitis of the CNS was first proposed by Cupps and colleagues and was based on reports of successful therapy in systemic vasculitides such as polyarteritis nodosa and Wegener granulomatosis with a combination immunosuppressive regimen (Fauci et al 1979; Moore et al 1981; Cupps et al 1983). High-dose prednisone plus cyclophosphamide is currently the treatment of choice (Calabrese 1997). Some patients recover or stabilize on corticosteroid therapy alone, but most progress and require addition of cyclophosphamide (Crane et al 1991). Prospectively randomized controlled trials are difficult because of the rarity of the condition and the lack of unifying diagnostic criteria. Retrospective analysis has revealed significant support for the use of steroids with cyclophosphamide therapy in confirmed cases (Joseph and Scolding 2002).

The management has been broadly divided into induction and

maintenance phases (Joseph and Scolding 2002). In the induction phase, the consensus opinion is to start with 1 mg/kg prednisone per day or its equivalent along with cyclophosphamide 1 to 2 mg/kg per day. There is a debate about using prednisone alone initially and only adding cyclophosphamide if the clinical condition deteriorates, as not all the cases of primary angiitis of the CNS require a combination regimen. Side effects of high-dose glucocorticoids should be anticipated, such as bone mineral loss, opportunistic infections, and neurologic side effects like delirium, mania, and schizophrenia-like states. The major toxicity of cyclophosphamide in the acute phase is myelosuppression, so its dose should be adjusted to keep the total WBC count above 3000 to 4000 and the absolute neutrophil count above 1000 to 1500. Other side effects include hemorrhagic cystitis, which can be minimized with hydration, frequent voids, and administration of mesna. The most serious long-term toxicity is an increased risk of malignancy, especially leukemias, lymphomas, and bladder cancer. Patients should be informed about the risks and benefits before starting this cytotoxic agent.

Once clinical remission has been achieved, treatment with cyclophosphamide should be continued for 6 months to 1 year and then later switched to azathioprine (2 mg/kg/day). Recommendations on when and how rapidly to taper off the prednisone varies widely. Monitoring of induced remission had been a matter of intense debate. There is no substitute for careful serial clinical evaluation. Although some symptoms may improve with treatment, neurologic deficits due to cerebral infarction or hemorrhage may be irreversible. Use of serial angiography was proposed initially (Stein 1987), but it exposes the patient to unnecessary risks of angiography. Later, serial MRI scans were also suggested to monitor the remission (Ehsan et al 1995). Calabrese and colleagues proposed that if CSF abnormalities are present before therapy begins, they are more likely to be sensitive indicators of disease activity (Calabrese et al 1992). Transcranial Doppler monitoring of blood flow has been applied to follow postpartum angiopathy, and this type of noninvasive monitoring may have some role but has not been studied (Bogousslavsky et al 1989).

Deterioration, failure to respond initially, or intolerance of the above regimen may require the use of alternative agents like methotrexate. Intravenous IgG has been administered with success a few times but its use has been poorly documented.

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Pregnancy

Peri-partum cerebral angiopathy is a clinical-angiographic syndrome that initially was confused with primary CNS angiitis because of the similar angiographic appearances, but now there is convincing evidence that it behaves differently with normal CSF analysis and recovers without the use of immunosuppressive agents. It is a clinical syndrome characterized by reversible multifocal brain ischemia due to multilobar segmental narrowing of large- and medium-sized cerebral arteries (Brick 1988). Patients usually present with severe generalized or occipital headaches with abrupt onset, similar to those seen in subarachnoid hemorrhage. Brain ischemia resulting from severe vasoconstriction typically leads to generalized motor seizure. Neurologic deficits such as cortical blindness, visual field deficits, confusion, aphasia, hemiparesis, and ataxia have been described. MRI usually

shows edema evident as T2 hyperintensities that is mostly reversible. Calabrese and colleagues, acknowledged that 2 of the patients whom they reported as examples of "primary CNS angiitis" should now be considered cases of postpartum angiopathy (Calabrese et al 1992).

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Anesthesia

Not applicable.

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Associated disorders

Call-Fleming syndrome
CNS vasculitis associated with connective tissue disorder
CNS vasculitis associated with drug abuse
CNS vasculitis associated with infectious diseases
CNS vasculitis associated with systemic necrotizing vasculitis
Cogan syndrome
Eale disease
Granulomatous angiitis associated with amyloidosis
Granulomatous angiitis associated with lymphoma
Neurobechet disease
Neurovascular sarcoidosis
Postpartum angiopathy
Susac syndrome

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Related summaries

Cerebral arteriopathies
Periarteritis nodosa
Stroke syndromes and their anatomic localization
Vasculitic neuropathies
Vasculitides presenting with dementia
Wegener granulomatosis

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Differential diagnosis

Glioma or glioblastoma multiforme
Metastatic neoplasm
Primary CNS lymphoma
Lymphomatoid granulomatosis
Cerebral abscess
Tuberculoma
Histoplasmosis
Toxoplasmosis
Syphilis (meningovascular form)
Progressive multifocal leukoencephalopathy
Herpes simplex encephalitis
Herpes zoster myelitis
Idiopathic transverse myelitis
Multiple sclerosis, especially fulminant forms
Disseminated vasculomyelinopathy
Behçet syndrome
Venous sinus thrombosis
Sarcoidosis

Thromboembolic stroke
Intracranial atheromatous disease
Systemic vasculitis
Reversible cerebral vasospasm
Post-trigeminal zoster vasculopathy
Sickle-cell disease
Chronic progressive basal vasculopathy with moyamoya disease
Migraine
Tuberculosis
Fungal meningitis (eg, cryptococcus, coccidiomycosis)
Carcinomatous meningitis
Intravascular lymphoma
Mitochondrial disorder
Thrombotic thrombocytopenic purpura
Radiation vasculopathy
Multiple infarcts (atherosclerotic versus embolic)
Drug-induced vasculopathy (including methamphetamine, cocaine, ephedrine, phenylpropanolamine, and herbals)
Cerebral autosomal dominant leukoencephalopathy (CADASIL)
Leukodystrophies
Gliomatosis cerebri
Neoplastic angioendotheliosis
Spasm after subarachnoid hemorrhage
Atherosclerosis
Oral contraceptive use
Postcoital headache
Trauma
Surgical manipulation of intracranial arteries
Reversible cerebral segmental vasoconstriction
Sumatriptan and isometheptene
Hypertension

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Demographics

For more specific demographic information, see the Epidemiology, Etiology, and Pathogenesis and pathophysiology sections of this clinical summary.

Age

3-71 years

Population

None selectively affected.

Occupation

None selectively affected.

Sex

male=female

Family history

None

Heredity

None

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**References especially recommended by the author or editor for general reading.

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