REVIEW ARTICLE

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Primary Central Nervous System Vasculitis

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CME

Primary central nervous system (CNS) vasculitis, also known as primary angiitis of the CNS, is a rare form of vasculitis that is limited to the brain and spinal cord and causes a variety of neurologic syndromes.[1,2] Because of its rarity and the similarity of some of these syndromes to more common disorders, primary CNS vasculitis is often misidentified. Descriptions of this condition date back only to the mid-1950s.[3] Primary CNS vasculitis may occur in children, although this is uncommon. In this review, we focus on the disorder in adults.

EPIDEMIOLOGY

Primary CNS vasculitis has had an estimated annual incidence of 2.4 cases per 1 million person-years in Olmsted County, Minnesota. The disorder affects persons of all ages, and its prevalence is similar among male and female patients.[1] Mortality has been reported to range from 8 to 23%, with approximately a quarter of patients having severe disability despite treatment.[4-8] Factors associated with higher mortality include advanced age, cognitive impairment at the initial presentation, and cerebral infarctions on imaging.[6] An estimated 40% of patients have unfavorable outcomes, and 5% do not survive long enough to be discharged from the hospital.[9]

CLINICAL MANIFESTATIONS

Clinical manifestations at the time of diagnosis vary and may suggest other, more common neurologic disorders. Table 1 summarizes the clinical manifestations observed in two clinical series.[1,10] The most common manifestation at the initial presentation has been a sudden onset of focal neurologic deficits, which is suggestive of an ischemic event such as a stroke or transient ischemic attack that includes aphasia, ataxia, and visual-field defects. Other common features are headaches, progressive cognitive decline, and acute or subacute encephalopathy, which is often characterized by an acute confusional state that may progress to drowsiness and coma.

Headaches are usually severe and persistent and may be generalized or localized; they are rarely a thunderclap headache, which is a sudden, severe headache that peaks in less than a minute and is more typical of reversible cerebral vasoconstriction syndrome. Seizures, intracerebral hemorrhage, and, less commonly, subarachnoid hemorrhage may occur. Spinal cord involvement with myelopathy, including transverse myelopathy, and systemic manifestations such as fever and weight loss have been reported but are infrequent. Clinical manifestations that simulate other neurologic syndromes, such as a brain tumor, or have distinctive characteristics and occur in approximately 10% of patients or less are described in Table 2.[7,9,11-20]

KEY POINTS

PRIMARY CENTRAL NERVOUS SYSTEM VASCULITIS

- Primary central nervous system (CNS) vasculitis is a rare, frequently misdiagnosed condition that affects the brain and spinal cord and is characterized by a variety of neurologic symptoms at presentation, such as focal neurologic deficits, headache, and cognitive decline.
- Cerebral angiography is often used for diagnosis; however, the specificity is low, and the results must be interpreted with consideration of the patient's medical history, as well as clinical and laboratory findings and the results of magnetic resonance imaging and magnetic resonance angiography. A CNS-tissue biopsy showing vasculitis can provide a definitive diagnosis.
- Small-vessel and medium-to-large-vessel inflammatory involvement characterize two subsets of primary CNS vasculitis with different diagnostic methods (biopsy vs. angiography) and distinct clinical characteristics and outcomes.
- The differential diagnosis includes reversible cerebral vasoconstriction syndrome, intracranial atherosclerosis, intravascular lymphoma, moyamoya disease and syndrome, secondary cerebral vasculitis (which can occur in connective-tissue diseases), systemic vasculitis, and infections.
- Early recognition is important because treatment with glucocorticoids with or without cytotoxic drugs, particularly cyclophosphamide, is effective in many patients and may prevent serious outcomes.

We and others have proposed two subsets of primary CNS vasculitis that are distinguished by the size of the affected vessel (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).[4,6,21,22] In the first subset, small cerebral vessels are primarily affected, and consequently, findings on angiography are typically normal, thereby necessitating biopsy for diagnosis.

In some patients with a small-vessel vasculitis, there is amyloid-beta (Aβ) vascular deposition in the small cortical and leptomeningeal cerebral vessels, as well as a transmural inflammatory infiltrate (known as Aβ-related angiitis).[23,24] On magnetic resonance imaging (MRI), Aβ-related angiitis is characterized by a combination of focal, multifocal, or diffuse subcortical areas of white-matter hyperintensities consistent with vasogenic edema on T2-weighted fluid-attenuated inversion recovery sequences, leptomeningeal enhancement, and cortical–subcortical microbleeds. The clinical manifestations of this disorder at presentation can resemble those of primary CNS vasculitis; however, whether Aβ-related angiitis represents a separate disorder or a subtype of primary small-vessel CNS vasculitis remains unclear.

The second subset predominantly affects medium-to-large cerebral vessels.[4,6,21,22] Patients typically present with acute focal neurologic deficits, multiple cerebral infarctions, and segmental concentric enhancement of the vessel wall on high-resolution MRI.

PATHOLOGICAL FINDINGS

The diagnosis of CNS vasculitis is based largely on histologic evidence of vascular-centered, transmural inflammation with vessel-wall damage. There are three main histopathological patterns, which typically remain stable over time in an individual patient but occasionally overlap (Fig. 1). Of the three patterns, the most common are granulomatous vasculitis (occurring in 32 to 61% of patients) and lymphocytic vasculitis (occurring in 24 to 79% of patients).[6,10,25] Granulomatous vasculitis is characterized by mononuclear inflammation and well-formed granulomas with multinucleated giant cells in vessel walls; lymphocytic vasculitis shows lymphocyte infiltration without granulomas. The third pattern, necrotizing vasculitis, is less common (occurring in 14 to 42% of patients), shares histologic similarities with polyarteritis nodosa, and is characterized by transmural fibrinoid necrosis. Granulomatous vasculitis can be associated with amyloid-beta vascular deposition in Aβ-related angiitis.[25] Necrotizing vasculitis is associated with intracranial hemorrhage,[14] whereas lymphocytic vasculitis may have a more benign course that is characterized by less disability and lower mortality.[6]

Table 1. Main Clinical Manifestations of Primary CNS Vasculitis at Presentation in Two Cohorts.*

Manifestation	Mayo Clinic Cohort (N=101)	French Cohort (N=52)
	number (percent)	
Focal neurologic deficits	68 (67)	43 (83)
Headaches	64 (63)	28 (54)
Cognitive impairment	50 (50)	18 (35)
Speech disorders (aphasia or dysarthria)	43 (43)	18 (35)
Visual symptoms†	32 (32)	8 (15)
Ataxia	19 (19)	6 (12)
Seizure	16 (16)	17 (33)
Vertigo or dizziness	9 (9)	15 (29)
Fever	9 (9)	7 (13)
Intracranial hemorrhage	8 (8)	10 (19)‡
Psychiatric disorders	NR	13 (25)
Amnestic syndrome	9 (9)	NR

* This table was adapted from Salvarani and colleagues (Mayo Clinic cohort)[1] and de Boysson and colleagues (French cohort).[10] CNS denotes central nervous system, and NR not reported.
† Visual symptoms include visual-field defect, blurred vision, and decreased visual acuity.
‡ Of the 14 patients reported, only the 10 with intracerebral hemorrhage were included, and the 4 with diffuse microbleeds alone were excluded.

PATHOPHYSIOLOGY

The pathophysiology of primary CNS vasculitis is incompletely understood, with research focusing primarily on cerebrospinal fluid (CSF) markers that provide evidence of inflammatory processes within the brain. Elevated levels of the proinflammatory cytokine interleukin-17, which is primarily produced by CD4+ T cells, along with natural-killer cells and B cells, are found in the CSF.[26,27] This feature suggests that interleukin-17 could serve as a promising target for therapy. Investigation into the complement system have yielded diverse results.[28,29]

Gene-expression profiling of cerebral-biopsy specimens has shown differing transcription profiles in the two main histologic types and Aβ-related angiitis.[30] Granulomatous vasculitis and Aβ-related angiitis share gene signatures that are associated with CD4+ naive T cells and monocytes, whereas lymphocytic vasculitis gene signatures have been linked to plasma cells, immunoglobulin production, and $\gamma\delta$ T cells.

DIAGNOSIS

Diagnostic criteria for primary CNS vasculitis were proposed in 1988 on the basis of intracranial angiographic or histopathological features, with the exclusion of other causes (Table S2).[2] The criteria have not been validated in prospective studies. Additional criteria have considered the diagnosis to be dependent on biopsy-proven vasculitis in cranial or spinal cord tissue.[31,32] A biopsy specimen should encompass sufficient parenchymal and leptomeningeal tissue to allow examination of small vessels including arterioles, capillaries, and venules.[25] Obtaining tissue from an area that is abnormal on imaging is preferred over random sampling. When random sampling is necessary, performing the biopsy on the nondominant frontal lobe provides a tissue sample while minimizing the risk of causing a clinically significant neurologic deficit. However, the diagnostic sensitivity of brain biopsy has been relatively low, with 30 to 50% of positive cases having nondiagnostic or normal findings in some series because of the irregular distribution of vascular lesions or because affected vessels may have a large diameter and, owing to the risk of bleeding, cannot be safely included in a biopsy.[25,32] Nevertheless, the risk of severe complications from biopsy is low.[33] In some series, cerebral biopsy identified an alternative diagnosis to primary CNS vasculitis in 30% of cases.[25,34]

Cerebral angiography is often used in clinical practice for diagnosis instead of brain biopsy owing to the invasive nature of biopsy. However, digital subtraction angiography, as compared with biopsy, shows low sensitivity (approximately 15 to 43%).[1,34,35] European Stroke Organization guidelines for the diagnosis and treatment of primary CNS vasculitis recommend performing brain biopsy in patients with a normal angiogram when there is diagnostic suspicion of small-vessel vasculitis.[36] However, if angiography indicates a high probability of vasculitis involving medium-to-large vessels, the guidelines suggest performing a biopsy only to rule out other diagnoses.

Angiographic findings that are compatible with vasculitis include smooth-wall segmental stenosis of multiple cerebral arteries.[1,2] Stenoses are occasionally accompanied by poststenotic dilatation or beading (Fig. 2). Arterial occlusions are uncommon, and aneurysmal dilatation of

Table 2. Special Clinical Manifestations of Primary CNS Vasculitis.*

Manifestation	Prevalence	Characteristics	Treatment	Outcome
	%			
Tumorlike mass lesion[11,12]	4–12	Proved by biopsy Often normal findings on DSA and MRA Seizures, headache, and focal neurologic deficit at presentation Lesions with gadolinium enhancement on MRI Association with CAA	Glucocorticoids alone or in most cases combined with cyclophosphamide	Favorable response to treatment Good outcomes Poorer outcomes in the patients with CAA Better outcomes with glucocorticoids and cyclophosphamide than with glucocorticoids alone
Prominent leptomeningeal enhancement[13]	8	Prominent gadolinium leptomeningeal enhancement on MRI Sudden clinical onset Cognitive dysfunction at presentation Normal findings on DSA and MRA Proved by biopsy Association with CAA	Glucocorticoids alone or combined with cyclophosphamide	Rapid and favorable response to treatment Good outcomes
Intracranial hemorrhage[7,9,14]	9–13	Intracerebral more common than subarachnoid hemorrhage Infrequent cerebral infarcts Association with necrotizing vasculitis	Glucocorticoids alone or combined with cyclophosphamide	Favorable response to treatment and outcomes
Spinal cord involvement[15,16]	5	Rarely the only manifestation; usually, there is subsequent brain involvement Association with lymphoma (Hodgkin's disease) Multisegmental longitudinal lesions Cervical and thoracic spinal cord involvement	Glucocorticoids and cyclophosphamide	Therapeutic response Mortality of 20–25% among treated patients and 75% among untreated patients
Rapidly progressive and catastrophic course[17,18]	8–11	Granulomatous or necrotizing vasculitis (or both) Frequent paraparesis or quadriparesis at presentation Bilateral, progressive, large-vessel vasculitis with newly developing lesions Multiple and bilateral acute cerebral infarctions High CSF protein level	Glucocorticoids and cyclophosphamide	High mortality (27–73%), particularly in the first 2–3 weeks Poor therapeutic response
Lymphoma association[19]	6	Vasculitis and lymphoma diagnosed simultaneously in most cases (70%) More often Hodgkin's lymphoma Spinal cord involvement Gadolinium leptomeningeal enhancement on MRI Granulomatous vasculitis	Glucocorticoids alone or glucocorticoids and cyclophosphamide	Therapeutic response in two thirds of patients Poor response in one third of patients Mortality of 30% High incidence of neurologic disability
Unihemispheric relapsing vasculitis[20]	1.4	Negative on angiography and positive on biopsy Different neuropathologic patterns Multiple flares Seizures at diagnosis and during flares Unilateral lesions with gadolinium enhancement on MRI Normal CSF in most patients	Glucocorticoids, cyclophosphamide, azathioprine, mycophenolate mofetil, methotrexate, rituximab	Response to glucocorticoids Long-term therapy with glucocorticoids at high doses for maintenance of remission Resistance to traditional immunosuppressants Usually slight disability with mild cognitive impairment

* CAA denotes cerebral amyloid angiopathy, CSF cerebrospinal fluid, DSA digital subtraction angiography, MRA magnetic resonance angiography, and MRI magnetic resonance imaging.

affected vessels is rare. Angiographic changes characteristic of vasculitis can also be observed in nonvasculitic conditions, such as intracranial atherosclerosis, infection, vasospasm, and cerebral arterial emboli. Moreover, the absence of abnormalities at angiography does not rule out a

diagnosis of primary CNS vasculitis, since vasculitic involvement in small parenchymal and leptomeningeal vessels may not be visualized.[22]

A systematic review and meta-analysis showed a low level of agreement between histologic and angiographic findings.[35] When both cerebral angiography and histopathological examination (biopsy and postmortem analyses) were performed, disagreement between these two diagnostic tests was more likely than agreement, with only 11.9% of patients having a classic angiographic appearance combined with pathologically confirmed vasculitis.[37]

Magnetic resonance angiography (MRA) or CT angiography (CTA) are alternatives to digital subtraction angiography for preliminary evaluation, but these have a lower sensitivity for changes in the contour of lumen of medium-sized and posterior circulation vessels. European guidelines recommend considering digital subtraction angiography in patients with clinical features that are strongly suggestive of primary CNS vasculitis when findings from MRA or CTA are normal.[36] Repeat vascular imaging may be needed to clarify the diagnosis. Arterial stenoses may be reversible in patients with primary CNS vasculitis, but the condition typically progresses in untreated CNS vasculitis.

High-resolution MRI of the vessel wall reveals segmental, concentric, and homogeneous enhancement (Fig. 2), findings that aid in the diagnosis of primary CNS vasculitis by distinguishing it from atherosclerotic plaques and reversible cerebral vasoconstriction syndrome.[38] The specificity of this enhancement for the identification of vasculitis lesions has not been established.[36] Some studies have indicated a correlation between a decrease in vessel-wall enhancement on follow-up imaging and a favorable treatment response.[39] However, the usefulness of high-resolution MRI of the vessel wall for monitoring disease activity remains incompletely studied, particularly regard-

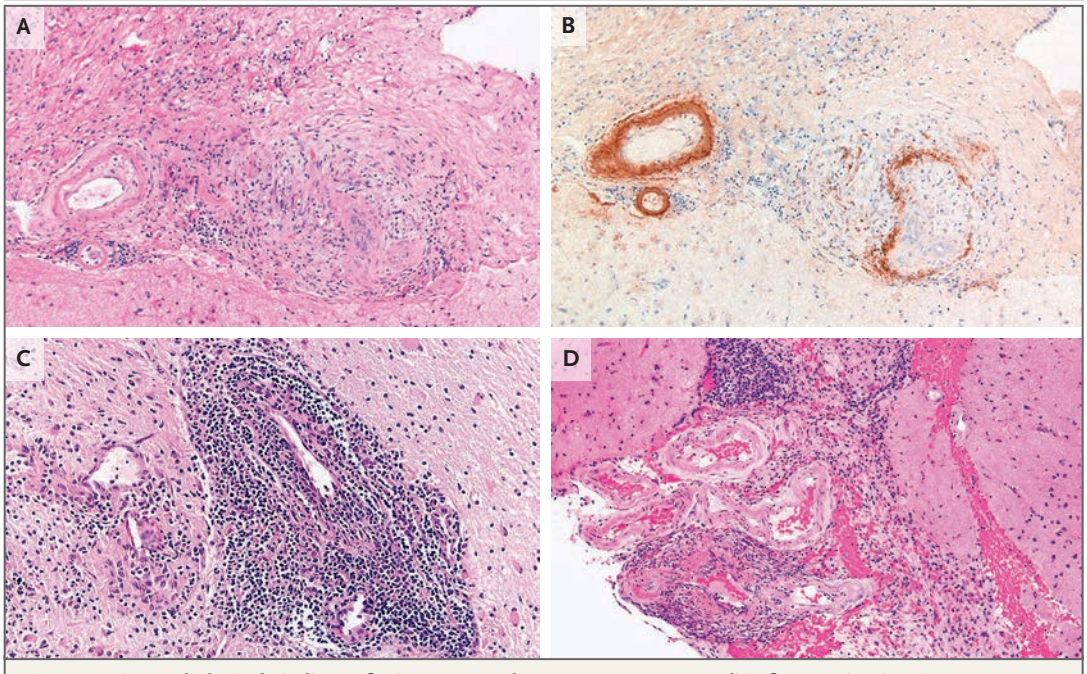

Figure 1. Histopathological Findings of Primary Central Nervous System Vasculitis from Brain Biopsies.

Panel A shows granulomatous vasculitis with extensive amyloid deposits in the leptomeningeal vessels, where the vessel wall is thickened by an amorphous eosinophilic material indicative of amyloid, with Panel B showing confirmation by amyloid-beta immunostaining. Granulomatous inflammatory infiltrate is present in the vessel on the right, causing obliteration of the lumen and destruction of the vascular wall. Panel C shows dense perivascular and transmural lymphocytic infiltrate typical of the lymphocytic pattern of vasculitis. Panel D shows necrotizing vasculitis with transmural acute inflammation and segmental transmural fibrinoid necrosis involving a leptomeningeal small artery, without giant cells or granulomas. The image in Panel C is shown at twice the magnification of the images in Panels A, B, and D.

ing whether persistent enhancement signifies ongoing inflammation or vessel-wall remodeling.

The most frequently observed findings on imaging are multiple cerebral infarctions (Fig. 2), lesions with parenchymal or leptomeningeal enhancement, and intracranial hemorrhage.[1,4,7,10] As a general summary statement regarding MRI of the brain, normal findings make CNS vasculitis very unlikely.[1,37]

Inflammatory CSF, which is characterized by a mildly increased leukocyte count (>5 cells per milliliter), an increased protein concentration (>45 mg per deciliter), or both, occurs in approximately three quarters of patients, particularly in those with small-vessel vasculitis.[1,21,22] Gram staining, culture, serologic and molecular tests, cytologic analysis, flow cytometry, or detection of clonal rearrangements with a standard polymerase-chain reaction assay are generally performed to rule out malignant or infectious conditions mimicking primary CNS vasculitis. Mild pleocytosis, an elevation in CSF protein concentration, or both can also occur in patients with ischemic stroke unrelated to vasculitis or in healthy persons[40]; therefore, abnormalities in CSF should primarily be used to rule out other conditions. The level of C-reactive protein and the erythrocyte sedimentation rate are normal in most patients.[1,10]

DIFFERENTIAL DIAGNOSIS

The nonspecific nature of clinical features of primary CNS vasculitis makes it difficult to differentiate from conditions with overlapping features. The categories below present the greatest challenges.

NONVASCULITIC DISORDERS

Nonvasculitic disorders are alternative diagnostic considerations, particularly when there are multiple strokes that occur over time. A history of thunderclap headaches and typical precipitating factors for reversible cerebral vasoconstriction syndrome, along with normal findings on MRI of the brain or the presence of convexity subarachnoid hemorrhage and minimal or no enhancement on high-resolution MRI of the vessel wall, aid in the differentiation of reversible cerebral vasoconstriction syndrome from primary CNS vasculitis (Table S3).[41] A scoring system comprising clinical and imaging findings can be used to diagnose and differentiate reversible cerebral vasoconstriction syndrome from its mimics.[42]

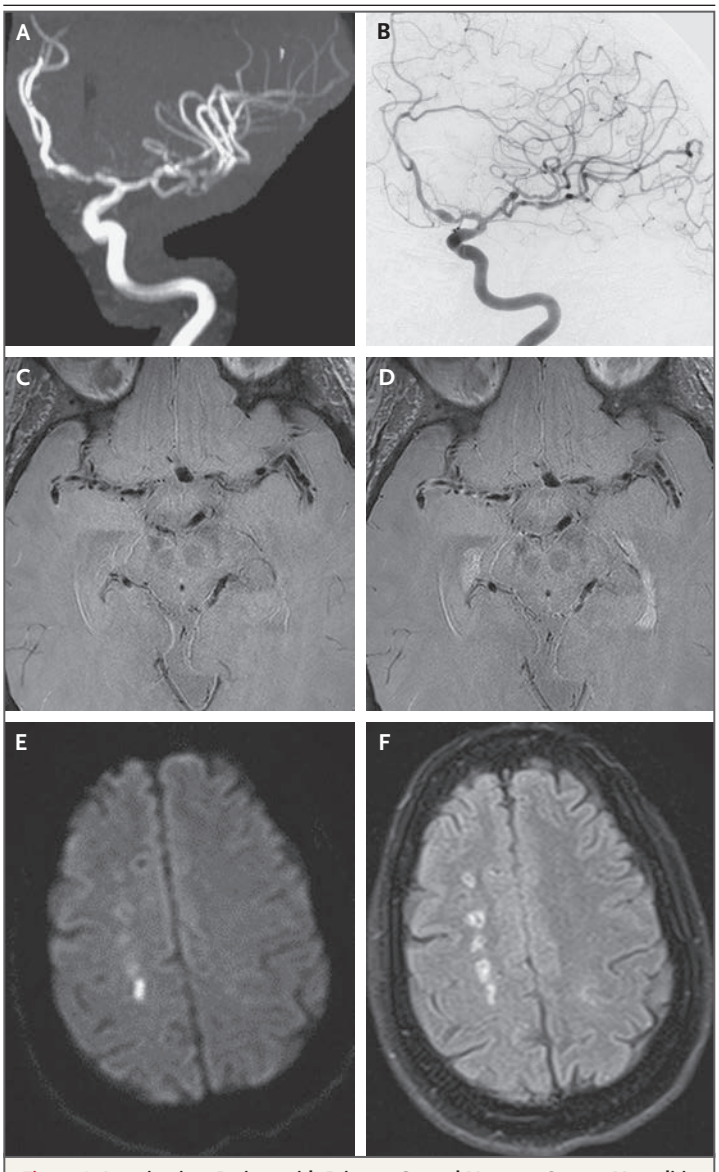

Figure 2. Imaging in a Patient with Primary Central Nervous System Vasculitis.
Magnetic resonance angiography (Panel A) and digital subtraction angiography (Panel B) show alternating stenosis and dilatation of the left anterior cerebral artery and left middle cerebral artery. Vessel-wall imaging before (Panel C) and after (Panel D) gadolinium administration shows enhancement in the wall that is consistent with inflammation in the right middle cerebral artery. Diffusion-weighted magnetic resonance imaging (MRI) shows a recent infarction (Panel E), and T2-weighted fluid-attenuated inversion recovery MRI shows chronic infarctions in the right middle cerebral artery distribution (Panel F).

Intracranial atherosclerosis in medium-to-large vessels can be misdiagnosed as primary CNS vasculitis in young adults with multiple progressive

cerebral infarctions. High-resolution MRI of the vessel wall may help in differentiating atherosclerotic lesions from vasculitic ones.[38] Other mimicking conditions include fibromuscular dysplasia, moyamoya disease and syndrome, recanalized cerebral embolism, intravascular lymphoma, primary CNS lymphoma, post–subarachnoid hemorrhage vasospasm, radiation vasculopathy, antiphospholipid antibody syndrome, and other prothrombotic states.[43-45]

Mimics of small-vessel primary CNS vasculitis include myelin oligodendrocyte glycoprotein encephalomyelitis and genetic disorders, such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy, and retinal vasculopathy with cerebral leukoencephalopathy.[46] Most cases of drug-induced cerebral vasculitis that are identified through cerebral angiography are attributed to vasospasm; histologically confirmed cases of vasculitis are rare.[47]

SYSTEMIC DISORDERS THAT MAY CAUSE CNS VASCULITIS

Secondary CNS vasculitic involvement, although uncommon, can occur in the context of systemic disorders. In these cases, there is typically evidence of active disease outside the nervous system, and an evaluation, especially for manifestations of organ involvement beyond the CNS, should generally be conducted to rule out these conditions before a diagnosis of primary CNS vasculitis is made. Cerebral infarctions, white-matter lesions, and a variety of clinical manifestations, including progressive cognitive decline, may be present in such cases.

Secondary cerebral vasculitis in postmortem studies of rheumatologic disorders has reportedly occurred in 7 to 10% of patients with systemic lupus erythematosus and is seen less frequently in patients with rheumatoid arthritis, Sjögren's syndrome, dermatomyositis, and mixed connective-tissue disease.[48] Cerebral vasculitis in rheumatoid arthritis is associated with seropositive, long-standing, erosive, nodular disease. Secondary CNS vasculitis has occasionally been described in patients with neurosarcoidosis, inflammatory bowel disease, and graft-versus-host disease.

Angiography- or biopsy-verified CNS vasculitis is also uncommon among patients with systemic vasculitis, a group of disorders characterized by inflammation of blood vessels in multiple organs. The condition has occurred in less than 2% of patients with granulomatosis with polyangiitis and in 4% of patients with eosinophilic granulomatosis with polyangiitis. Angiography- or biopsy-verified CNS vasculitis is also rare in patients with hepatitis C virus–related cryoglobulinemic vasculitis, giant-cell arteritis, and Takayasu arteritis.[49] CNS manifestations have been reported in 5 to 25% of cases of polyarteritis nodosa, but there are limited data on the frequency of angiography- or biopsy-proven vasculitis.[50]

Neurologic symptoms occur in 5.3 to 14.3% of patients with Behçet's syndrome.[51] In cases of Behçet's syndrome that have parenchymal brain involvement, there is predominantly brain-stem meningoencephalitis, whereas in cases with nonparenchymal neurologic involvement, Behçet's syndrome can manifest with thrombosis in the cerebral venous sinuses due to inflammation-induced thrombosis resulting from an impaired immune-inflammatory response.

In infectious vasculitis, cerebral lesions may be caused directly by the infectious agent through endothelial invasion and vessel-wall damage, or it may result from the immune response triggered by the pathogen. Cerebral vasculitis caused by the varicella–zoster virus (VZV), particularly in the trigeminal dermatomes, affects cerebral arteries after VZV reactivation (shingles) or primary infection (chickenpox).[52] The vasculitis can cause stroke, aneurysm, and hemorrhage. Simultaneous involvement of both large and small cerebral arteries occurs, with angiographic changes such as segmental stenoses and poststenotic dilatation. High-resolution MRI of the vessel wall shows concentric vessel-wall enhancement. Diagnosis relies on a recent VZV infection followed by strokelike neurologic symptoms; anti-VZV IgG antibodies may be found in the CSF and are more common than the finding of VZV DNA.

Infectious cerebral vasculitis has also been reported in patients with human immunodeficiency virus, neurosyphilis (in which it was once common and associated with menigovascular inflammation), hepatitis C virus, parvovirus B19,

Borrelia burgdorferi, and *Mycobacterium tuberculosis* infections.[53] In addition, fungal infections, such as aspergillosis and candidiasis, have been associated with cerebral vasculitis. In bacterial endocarditis, multiple intracranial arterial stenoses are the result of septic emboli, but a vasculitic pattern on cerebral angiography has been reported.

TREATMENT AND OUTCOMES

Evidence-based recommendations for the treatment of primary CNS vasculitis from randomized, controlled clinical trials are lacking. Current treatment protocols have been based primarily on retrospective cohort studies, in which a limited number of patients is often enrolled, and on therapeutic approaches that are used in other forms of vasculitis. For decades, glucocorticoids, often in combination with a traditional immunosuppressant such as cyclophosphamide, have been used to treat primary CNS vasculitis.[54] This has remained the most common approach to inducing remission and reducing reliance on long-term glucocorticoids.[4-6,8,55]

Oral prednisone at a dose of 1 mg per kilogram of body weight per day, often preceded by intravenous methylprednisolone pulse therapy (1000 mg daily for 3 to 5 days), has been a typical initial treatment for inducing remission, a strategy that is based on anecdotal evidence. Remission is characterized by the absence of recurrence or worsening of neurologic symptoms attributable to active primary CNS vasculitis, with stability of existing lesions and no new lesions on MRI. Immunosuppressive agents are often used in addition to glucocorticoids, particularly in patients with relapsing or severe cases with a rapidly progressive neurologic course, in which case cyclophosphamide is usually administered as monthly intravenous pulses (0.5 to 1.0 g per square meter of body-surface area) for 6 months; this intravenous treatment is less toxic than treatment with the oral formulation because of reduced total drug exposure. A favorable response to glucocorticoids, administered alone or in combination with cyclophosphamide, has been reported in three quarters of patients with primary CNS vasculitis.[5,6] We typically initiate cyclophosphamide treatment in addition to glucocorticoids in patients presenting with multiple infarcts, necrotizing or granulomatous vasculitis, and involvement of medium-to-large vessels and use glucocorticoids alone in patients with small-vessel vasculitis, particularly those with lymphocytic vasculitis and no infarctions, who generally have a milder disease course.

There is evidence from two observational uncontrolled studies that mycophenolate mofetil (2 to 3 g daily) is as effective as cyclophosphamide in inducing remission in patients with severe primary CNS vasculitis, and it may represent a less toxic alternative to cyclophosphamide. Mycophenolate mofetil was also effective as maintenance therapy.[56,57]

European guidelines suggest the use of glucocorticoids alone in mild cases and recommend that cyclophosphamide or mycophenolate mofetil is added in all other cases.[36] Although experience is limited to few cases, rituximab and tocilizumab may represent therapeutic options for patients with disease relapse and in patients with refractory disease or who are unable to receive traditional immunosuppressants.[58,59]

These therapeutic regimens are associated with the risk of infection and potential long-term complications related to glucocorticoid use. Therefore, adequate prophylactic treatment to prevent osteoporosis and opportunistic infections is advisable. Specifically, prophylaxis for pneumocystis pneumonia with trimethoprim–sulfamethoxazole is recommended when a patient is receiving high-dose glucocorticoids, cyclophosphamide, or rituximab. Aspirin appeared to be beneficial in one study that showed an association with long-term remission.[6] The European guidelines suggest adjunctive aspirin therapy for patients with medium-to-large-vessel involvement.[36]

The results of two large cohort studies support the use of maintenance therapy with mycophenolate mofetil or azathioprine, after successful induction therapy with cyclophosphamide and glucocorticoids.[5,6] An association between maintenance therapy and a lower incidence of relapse, as well as less disability and fewer deaths, was observed in these studies. Although the ideal duration of maintenance therapy remains uncertain, European guidelines advocate for its continuation for a minimum of 2 years before cessation in patients with remission.[36]

COURSE OF THE DISORDER

The course of primary CNS vasculitis and prognosis of patients with the disorder have varied across studies. In the largest reported cohorts, induction therapy resulted in remission in 68 to 95% of patients. Depending on the criteria used, the percentage of patients with long-term remission has ranged from 21.5 to 66%.[5,6] Flares have occurred in 12 to 59% of patients.[5-8,55] Good neurologic functional status with a low level of disability (modified Rankin scale score of ≤2; range, 0 to 6, with lower scores indicating less disability) has been observed in 46 to 73% of patients. Factors associated with poor therapeutic response and long-term disability and death are older age at diagnosis, delay in diagnosis, cognitive dysfunction at presentation, spinal cord involvement, and medium-to-large–vessel vasculitis and cerebral infarctions on imaging, and male sex and lesions with gadolinium enhancement have been associated with a relapsing course.[5-8,55]

Refractory disease is defined by nonresponse to induction therapy or a lack of complete remission. In such instances, it is important to revisit other potential diagnoses and to consider either a first biopsy in cases diagnosed solely by angiography or a repeat cerebral biopsy to confirm vasculitis and rule out other conditions.

Serial MRI and MRA 3 to 4 months after the diagnosis, then every 4 to 6 months or when a new neurologic symptom arises, along with regular neurologic examinations, have been valuable in our experience for monitoring disease activity and adjusting treatment. In our opinion, without other signs of active vasculitis, persistent vessel-wall enhancement or MRA findings showing a lack of improvement do not clearly warrant intensification of immunosuppressive therapy.

CONCLUSIONS

Primary CNS vasculitis is a rare disease that affects the brain and spinal cord with a range of nonspecific neurologic symptoms. Diagnosis relies on findings from brain MRI, intracranial CTA or MRA, digital subtraction cerebral angiography, and cerebral biopsy and on the ruling out of alternative causes. The size of the predominantly affected arteries allows categorization of primary CNS vasculitis into small-vessel and medium-to-large vessel types that have distinct clinical characteristics and outcomes. The management of this condition involves balancing immunosuppressive therapies against their potential risks. Future research could define the underlying pathophysiology, discover biomarkers, and refine diagnostic criteria and treatment for this disorder.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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