Granulomatous Angiitis
Twenty Years Later

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KEYWORDS

• Central nervous system • Stroke • Vasculitis • Granulomatous angiitis

KEY POINTS

- The vasculitides are diseases characterized by inflammation of blood vessels and inflammatory leukocytes in vessel walls.
- Granulomatous angiitis refers to distinctive clinicopathologic disorders with the essential features of granulomatous inflammation of cerebral and spinal arteries.
- No typically abnormal laboratory study excludes or makes the diagnosis except a positive brain and meningeal biopsy specimen.
- Therapy is aimed at preventing infarction or hemorrhage from inflamed or scarred vessels.

HISTORICAL CASES

Harbitz[1] first described primary central nervous system (CNS) vasculitis (PCNSV) due to granulomatous angiitis in 1922 in 2 patients, one with worsening headaches, mental change, and ataxia culminating in stupor, spastic paraparesis, coma, and death in 2 years. A second patient presented with hallucinations and confusion progressing to gait difficulty, stupor, coma, and death in 9 months. At postmortem examination, both had granulomatous vasculitis of the meninges comprising lymphocytes, multinucleated giant cells, and epithelioid cells with vessel necrosis and extension into the brain along involved veins and arteries of varying caliber.

Over the ensuing quarter century, additional patients with granulomatous angiitis of the brain (GAB) or the equivalent team, granulomatous angiitis, reported under the rubric of allergic angiitis and granulomatosis,[2] giant cell arteritis (GCA),[3] and sarcoidosis[4] were described. Cravioto and Fegin[5] delineated the clinicopathologic syndrome of noninfectious granulomatous angiitis; for 2 more decades, rare affected patients were identified in life, but there was no effective treatment. The identification of

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angiographic beading and a sausagelike appearance of cerebral vessels at sites of presumed arteritis was noted by Hinck and coworkers[6] in GCA, and later by Cupps and Fauci[7] in so-called isolated angiitis of the CNS (IACNS). The judged efficacy of a combination immunosuppressive regimen of oral cyclophosphamide and alternate day prednisone in 3 patients with IACNS defined angiographically, and in another with biopsy-proven granulomatous angiitis of the filum terminale, led to prospective diagnostic and therapeutic recommendations.[8] At that time, investigators regarded IACNS[7] and other cases typified by granulomatous angiitis as interchangeable terms with the former term emphasizing the restricted nature of the vasculitis, and the latter term emphasizing the granulomatous histology. The thinking was that giant cells and epithelioid cells, usually found at autopsy in cases of granulomatous angiitis, were an inconsistent finding in leptomeningeal and brain or spinal cord biopsy tissues and therefore considered unnecessary for antemortem diagnosis.

In 1988, Calabrese and Mallek[9] proposed criteria for the diagnosis of primary angiitis of the central nervous system vasculitis (PACNS) among 6 adults and 2 children aged 10 and 12 years. Seven patients, including both children, recovered either spontaneously (1 child) or with intensive immunosuppressant therapy (6 patients), empirically (4 patients) or based on a positive leptomeningeal and brain biopsy for vasculitis, although one died of autopsy-confirmed spinal cord vasculitis. Among 3 cases studied at postmortem (cases 4, 5, and 7), 2 had positive leptomeningeal biopsies, among them one with a normal cortex; a third had vasculitis of the spinal cord. The histopathology of case 5 was consistent with granulomatous small-vessel vasculitis affecting meningeal veins (**Fig. 1**) with proliferation of epithelioid cells along vascular walls, sparing the cortex. Cerebral angiography in that patient was negative, showing tortuosity and irregularity of the lumen of intracranial vessels without segmental or alternating stenosis and ectasia typical of arteritis.

Contemporaneously, Younger and colleagues[10] described the limits of GAB in 4 postmortem and 74 literature cases, all of which met the selection criteria of pathologic evidence of cerebral blood vessel inflammation by giant cells or epithelioid cells. Granulomatous giant cell or epithelioid cell infiltration was detected in the walls of larger named vessels in the first patient who had concomitant varicella herpes zoster virus ophthalmicus (HZO); in large and small leptomeningeal vessels together in the second patient with no other condition; in small leptomeningeal vessels in the third patient with Hodgkin lymphoma (**Fig. 2**); and leptomeningeal and cortical veins in the fourth patient with neurosarcoidosis, all with varying degrees of vessel wall destruction and necrosis. None had evidence of systemic vasculitis at autopsy. Brain infarcts were widespread, involving both brainstem and cerebral hemispheres. Spinal cord lesions were seen in other patients with clinical myelopathy. No typically abnormal laboratory study excluded, or made the diagnosis of GAB in a living patient except a "positive" CNS biopsy specimen.

Although some authorities[8] cite diagnostic changes on cerebral arteriography, this seems to be a dubious contention because vessel narrowing, beading, multiple dilatations, aneurysms, avascular mass lesions, and normal studies were all seen in granulomatous angiitis and in angiitis of other origins.[11] Polyarteritis nodosa, amphetamine abuse, and rheumatoid arthritis cause arteriographic changes that resemble granulomatous angiitis, but the lesions in these diseases characteristically do not include giant cells or epithelioid cells. Because the changes were associated with diverse and dissimilar diseases and pathologic alterations, no particular arteriographic finding could be considered diagnostic of granulomatous angiitis. Four patients with granulomatous angiitis had normal arteriograms a few weeks before death even though arteritis and stenosis of one or more large vessels were observed at postmortem examination. Of 8 patients with granulomatous angiitis proved by brain biopsy,

Fig. 1. Granulomatous angiitis located in small veins of the leptomeninges associated with a proliferation of epithelioid cells along the vascular walls in case 5. (*From* Calabrese HL, Mallek JA. Primary angiitis of the central nervous system: report of 8 new cases, review of the literature, and proposal for diagnostic criteria. Medicine 1988; 67:20–39; with permission.)

arteriographic findings were normal in 2, while 3 studies showed signs of an avascular mass suggesting brain tumor, with no 1 showing beading of vessels, and 2 nonspecific changes in vessels without frank beading. Beading of vessels considered diagnostic of granulomatous angiitis or IACNS was seen in only 3 patients and was not considered a reliable diagnostic sign.

To determine whether the "idiopathic" cases delineated a distinct disorder, Younger and colleagues[10] evaluated headache, hemiparesis, mental changes, abnormal cerebrospinal fluid (CSF) protein level, CSF pleocytosis, brain imaging, and cerebral

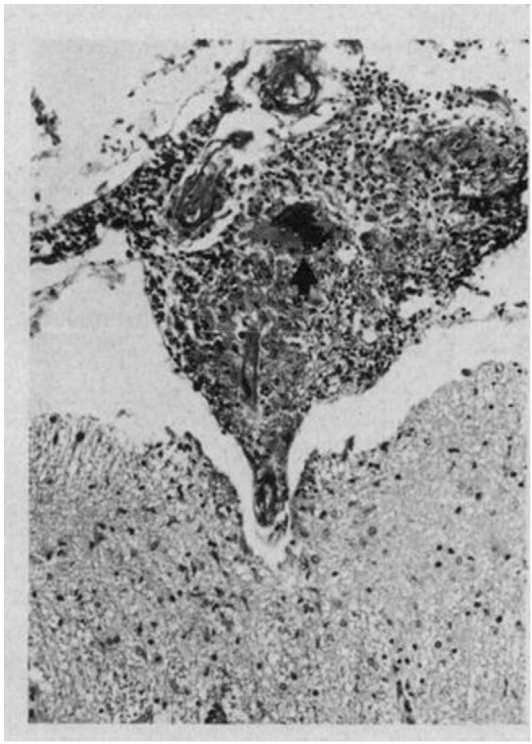

Fig. 2. Postmortem examination of a patient (case 3) with granulomatous angiitis of the brain in a patient with Hodgkin lymphoma. The photomicrograph on the left shows small leptomeningeal blood vessels of the left temporal lobe. A compact mass of epithelioid cells, multinucleated giant cell, and lymphocytes engulf several small blood vessels, one located in a depression of the cerebral cortical surface, in its path between leptomeninges and neural tissue. Mild astrocytosis is present in the molecular layer of cerebral cortex.

angiography. There was no difference in the frequency of these abnormalities in the idiopathic cases as compared with those with HZO, neurosarcoidosis, or lymphoma. There was no clear clinical syndrome that would mandate brain biopsy; nevertheless, biopsy of brain and overlying meninges would be warranted if there were no other cause to explain a clinical syndrome of encephalopathy (including confusion or alteration of consciousness), evolving over days or weeks and, especially, with focal "cerebral signs" or abnormal CSF with pleocytosis, high protein content (100 mg/dL), and normal glucose content. Signs of encephalopathy were dominant in 61 of 78 cases, including 10 of 12 patients who also had an acute stroke as well as all 7 with hemiparesis contralateral to skin lesions of HZO. In the absence of more diffuse encephalopathy, therefore, acute stroke with or without herpes zoster would not warrant biopsy.

Therapy for PCNSV is generally aimed at preventing infarction or hemorrhage from inflamed or scarred cerebral vessels. Seven of 10 patients with conditions diagnosed antemortem by CNS biopsy specimens were followed up prospectively for a mean of 7 months (range, 1 month to 1 year), including one each with HZO or lymphoma, and 5 with no associated disorder. All 7 improved taking corticosteroids alone (3 patients) or combined with cyclophosphamide or azathioprine (3 patients; or cyclophosphamide alone (1 patient).

In 1997, Younger and colleagues[12] conducted a historical review of pathologically confirmed cases of granulomatous angiitis, which still stands as the largest cohort of well-defined cases, presenting a balanced view of the merits of corticosteroids and other immunosuppressants, notwithstanding the selection bias due to the inclusion of cases of GAB.[10]

Altogether, 136 cases conformed to strict pathologic criteria. They included 78 patients described by Younger and colleagues[10] from 1922 to 1988; 57 additional literature patients, including 12 reported during the period surveyed by Younger and colleagues but not included in their analysis, and a new antemortem case. Overall, 35 of the 136 patients were diagnosed antemortem by brain and meningeal biopsy, and 100 were diagnosed postmortem. Fifty-one patients had granulomatous angiitis in association with other conditions, including 11 patients with temporal or systemic giant cell arteritis, 12 patients with herpes zoster virus (HZV) infection, 9 patients with lymphoma alone in 7 patients and together with HZV in 2 patients, 6 patients with sarcoidosis, 10 patients with amyloid angiopathy, 1 patient with systemic lupus, and 2 patients with human immunodeficiency virus (HIV) infection without AIDS.

Headaches, mental change, and gait disorder, that evolved over weeks to months or more followed by focal cerebral signs including seizure, aphasia, hemiparesis or tetraparesis, coma, and death, were noted in 77% (103/135) of patients overall. The neurologic disorder associated with temporal or systemic giant cell arteritis differed from other patients with granulomatous angiitis in the predilection for large intracranial vessels and the relentless progression despite corticosteroids. The neurologic disorder of granulomatous angiitis associated with HZV typically followed appearance of an ophthalmicus (V_1) rash by 2 to 3 weeks and was contralateral to the skin lesions and vasculitis involvement of the ipsilateral carotid, middle, or anterior cerebral artery, although several other patients had nonophthalmicus, spinal radicular dermatomal lesions, or disseminated HZV. Most patients with lymphoma-associated granulomatous angiitis had a subacute or chronic neurologic illness. One patient with a cavernous sinus syndrome had biopsy-proven granulomatous angiitis and occult primary lymphoma of the midbrain at autopsy. A second patient had a successfully treated malignant lymphoma of the parotid gland. At autopsy, there was evidence of granulomatous angiitis affecting spinal and cerebral leptomeningeal vessels, and a malignant lymphoma of the parotid gland. A third patient had headaches and progressive spastic paraparesis that prompted brain biopsy and discovery of granulomatous angiitis; reevaluation of a submandibular mass showed Hodgkin lymphoma. Treatment of the tumor with combination chemotherapy resulted in remission of the cancer and stabilization of the neurologic disorder. The neurologic disease in the 6 patients with sarcoidosis was essentially similar to other cases without sarcoid. Two patients had known systemic disease and were being treated with corticosteroids when neurologic symptoms developed. Asymptomatic systemic involvement was present in 3 of 4 others diagnosed at autopsy. The 10 patients with amyloid angiopathy were clinically and pathologically inseparable from other cases of granulomatous angiitis.

The pathologic heterogeneity of granulomatous angiitis was exemplified in the predilection of lesions for vessels of variable caliber, regardless of the presenting clinical syndrome or associated disorder. Of 50 cases studied postmortem, 6 had predominant involvement of small arteries and veins; 11 involved small and large vessels; 28 involved small and medium-sized arteries; and 5 had large cerebral vessel involvement alone. Isolated microscopic foci of vascular inflammation were seen in heart, lungs, and kidney specimens at general autopsy in 19 patients with otherwise typical granulomatous angiitis that were deemed to be of insufficient evidence for systemic vasculitis.

The diagnosis of granulomatous angiitis begins with a high index of suspicion based on the symptoms, signs, and laboratory studies at presentation and during the course of the illness. Screening blood studies, such as the white blood cells count, hematocrit, erythrocyte sedimentation rate, and serologic studies, are of little use in the diagnosis of granulomatous angiitis, but may be useful in suggesting the presence of an underlying systemic illness, serologically distinct connective tissue disorder, or systemic vasculitis. CSF should be analyzed in all suspected cases because pleocytosis of greater than 10 white blood cells/mm^3 and protein elevation of greater than 100 mg/dL lend strong support to the diagnosis of granulomatous angiitis. However, a normal profile does not exclude the diagnosis, because a quarter of proven cases had a normal cell count, and a third of proven cases showed a normal protein content. Oligoclonal bands were present in 3 of 6 patients with cerebral vasculitis so studied. It is important to culture CSF for obvious infectious organisms because mycobacteria, spirochetes, fungi, and herpes viruses can cause latent infection and cerebral vasculitis. Noninvasive imaging studies are of limited usefulness. MRI of the brain is generally more sensitive than computed tomography (CT), but both lack specificity. Brain CT was normal or showed nonspecific atrophy in 20 of 41 (49%) patients so studied; MRI was normal in none of 16 cases. The most common MRI findings were abnormal T_2 signal foci in the subcortical white matter, meningeal enhancement, and mass lesions, seen altogether in 75% of patients. Although these findings may be helpful in suggesting the need for further evaluation, magnetic resonance angiography (MRA), PET with ^{18}fluorodeoxyglucose, and single-photon emission CT (SPECT) provide useful complementary information to conventional MRI; however, the observed defects in cerebral blood flow do not always correlate with, or predict, neurologic symptoms and do not distinguish vasculitis from other forms of occlusive vascular disease. One patient with histologically proven granulomatous angiitis had abnormality of SPECT imaging. Fundic fluorescence angiography combined with slit-lamp microscopy has been advocated to estimate erythrocyte flow and cerebral perfusion in CNS vasculitis.

Cerebral angiography was normal in 23 of 49 (47%) patients. In 26% of patients, there were suggestive features of vasculitis, including segmental narrowing in 6 patients (12%), microaneurysms in 3 patients (6%), and beading in 4 patients (8%), but these too can be seen in nonvasculitic arteriopathy, intracranial atherosclerosis, vasospasm, mycotic aneurysm, infection, emboli, and tumor. Brain and meningeal biopsy is the gold standard for the diagnosis of cerebral vasculitis because it is the only way to identify the underlying histopathology and to exclude other causes. The preferred site for brain and meningeal biopsy is the temporal tip of the nondominant hemisphere in an area with a longitudinally oriented surface vessel. An infratentorial approach is considered in patients with sarcoidosis or tuberculosis because the basilar meninges are preferentially involved. A normal or nondiagnostic biopsy was noted in 9 of 43 (26%) histologically confirmed cases, reflecting the low sensitivity of the test. Six of 9 nondiagnostic biopsies contained brain tissue alone, compared with 2 of 35 diagnostic biopsies that combined brain and leptomeninges, indicating the importance of sampling the meninges to increase the likelihood of a diagnostic specimen. Tissue samples should be stained and cultured for bacterial, fungal, spirochetal, and viral organisms and preserved frozen for later investigations. It is difficult to know when to proceed with brain biopsy.

The outcome of treatment in 54 pathologically proven cases of granulomatous angiitis is summarized in **Table 1**. Among 30 patients diagnosed antemortem by meningeal and brain biopsy, 28 were treated with corticosteroids alone (in 11 patients) or with oral cyclophosphamide (in 16 patients), or azathioprine (in 1 patient), and followed for up to 1 year, of whom 18 (64%) improved, 7 (25%) remained unchanged, and 3 (11%) died

Table 1
Outcome of 54 patients with granulomatous angiitis of the nervous system

Outcome	CS	CS + CYC	CS + AZA	None	Total
Improved	8/0[a]	9/0	1/0	0	10/0
Same	3/0	4/0	0	1/0	8/0
Died	0/6	3/1	0	1/17	4/24

Abbreviations: AZA, azathioprine; CS, corticosteroids; CYC, cyclophosphamide.
[a] Patients diagnosed antemortem in the numerator, and patients diagnosed postmortem in the denominator.
From Younger DS, Calabrese LH, Hays AP. Granulomatous angiitis of the nervous system. Neurol Clin 1997;15:821–34; with permission.

with roughly equally satisfactory outcomes after treatment with corticosteroids with or without cyclophosphamide. Three patients diagnosed antemortem died while taking corticosteroids and cyclophosphamide; 2 patients suffered serious sequelae of the therapy, including fatal lymphoma, immunosuppression and opportunistic infection, or pneumonia and leukopenia. Of 24 patients diagnosed postmortem, 7 (29%) received treatment with corticosteroids alone (in 6 patients) or with cyclophosphamide (in 1 patient), and 17 (71%) were untreated. Thus, 17 of 18 (94%) untreated patients died, indicating that without therapy the disease was usually fatal. Treatment with corticosteroids, alone or in combination with cyclophosphamide, was associated with a considerable reduction in mortality; 24 of 34 (70%) so treated survived as either improved (50%) or clinically unchanged. Thus, there was no appreciable benefit in the addition of cyclophosphamide; however, the numbers were small, unmatched for age, disease activity, or other factors, and follow-up was not uniform. Cyclophosphamide should be reserved for histologically confirmed cases, especially those who continue to progress or fail to improve on corticosteroids alone, and those who can be monitored closely for serious medication side effects.

MODERN COHORTS

Commensurate with the refinement in clinical trials methods, adult patients with CNS vasculitis are reported in large retrospective cohorts at the Mayo Clinic[13] and in observational cohorts from the French Vasculitis Study Group, French NeuroVascular Society, and the French Internal Medicine Society consortia,[14] stratifying cases based on clinical, neuroradiographic, and histopathologic laboratory features, and offering additional insights into the management of CNS vasculitis. Patients included in each cohort based on tissue biopsy according to the original criteria of Calabrese and Mallek[9] continue to be a minority, attesting to the reliance of angiographic criteria for the diagnosis of cerebral vasculitis, a fact that adds selection bias to the frequency of granulomatous angiitis, and the assessment of the natural outcome or that of a given therapy.

In 2007, Salvarani and colleagues[15] diagnosed primary PCNSV from 1983 to 2003, 70 (69%) by angiography and 31 (31%) by histopathology, 18 of which were granulomatous, 8 of which were lymphocytic, and 5 of which were acute necrotizing among thirty–one patients diagnosed by histopathology, and 70 patients by angiography, of whom 18 had a granulomatous inflammatory pattern, 8 had a lymphocytic pattern, and 5 had an acute necrotizing pattern. Headache was the commonest symptoms so noted overall in 63% of patients, followed by abnormal cognition, hemiparesis, and persistent neurologic deficit. A granulomatous pattern of inflammation was seen most often in those with altered cognition and at an older age. There were no

significant differences in survival when patients were stratified by treatment (prednisone alone vs prednisone and cyclophosphamide) or method of diagnosis (angiography or biopsy). Four manifestations at presentation were associated with increased mortality, including focal neurologic deficit, cognitive impairment, cerebral infarction, and large cerebral vessel involvement.

Between 2004 and 2011, Salvarani and collaborators[13] enrolled 105 patients, of whom (64%) met inclusion criteria for the diagnosis of probable CNS vasculitis based on cerebral angiography manifesting areas of smooth-wall segmental narrowing or dilatation, and occlusions that affected multiple cerebral arteries without the proximal vessel changes of atherosclerosis or other causes; 58 patients (36%) who met the definite diagnosis based on a CNS tissue biopsy showed transmural vascular inflammation involving leptomeningeal or parenchymal vessels. The latter histopathology was granulomatous in 35 (60.3%), lymphocytic in 13 (22.4%), and necrotizing alone in 10 (17.2%) patients. These histologic patterns appeared to identify subsets of disease rather than different stages of the same process because no individual patient had histologic evidence of more than 1 pattern. A favorable response to therapy, including corticosteroids (prednisone) alone or in association with cyclophosphamide, was observed in 85% of patients. Three patients treated with biological agents, including rituximab (1 patient) and a tumor necrosis factor-α inhibitor (2 patients) for treatment of refractory disease, were also improved. Relapses were observed in 27% of patients, and 25% of patients had discontinued therapy by the time of the last follow-up visit. Although response to treatment was not associated with any histologic pattern of the biopsy specimen, treatment with corticosteroids alone was associated with more frequent relapses (odds ratio [OR], 2.90), whereas large named vessel involvement (OR, 6.14) and cerebral infarcts at the time of diagnosis (OR, 3.32) were associated with a poor response to treatment. Among the patients diagnosed exclusively by angiography alone, relapses were more frequent when there was large-vessel involvement (30%) than only small-vessel changes (9%), with an increased mortality due to fatal neurovascular problems caused by PCNSV. Subsets of patients with PCNSV showed equally interesting insights.

Salvarani and coworkers[16] noted granulomatous vasculitis in all 8 (100%) cerebral biopsies of patients with lymphoma and PCNSV, 2 of whom had concomitant cerebral amyloid angiopathy. Among 131 consecutive patients with PCNSV, 11 (8.4%) had a rapidly progressive course that was resistant to immunosuppressive therapy, resulting in severe disability or death. Such patients had bilateral cortical and subcortical infarction on initial brain MRI and large named cerebral vessel involvement on cerebral angiography with granulomatous and necrotizing vasculitis in brain tissue biopsies. All 11 patients failed to respond to aggressive immunosuppressive therapy, only one of whom survived with major fixed neurologic deficits.

In 2018, De Boysson and colleagues[14] described the treatment and long-term outcomes of an observational cohort of 112 patients with PCNSV derived from 3 main networks: the French Vasculitis Study Group, French Neurovascular Society, and the French Internal Medicine Society. The criteria inclusion were (1) involvement of CNS vessels evidenced by biopsy or based or imaging (on digital subtraction angiography or MRA), showing intracranial arterial stenoses, occlusions, or fusiform dilations; (2) a complete workup performed, including infectious and immunologic serologies (HIV, hepatitis B virus, hepatitis C virus, syphilis, tuberculosis, antinuclear and antineutrophil cytoplasmic antibodies, echocardiography, and whole body imaging), to exclude alternative conditions than PCNSV affecting CNS vessels; and (3) a 6-month or more follow-up (unless the patient died before 6 months of biopsy-proven PCNSV) to prevent the inclusion of other vasculopathies, such as reversible cerebral

vasoconstriction syndrome, where vascular lesions reverse within the first months.[17] The rate of prolonged remission was defined by the absence of relapse at ≥12 months after diagnosis; as was the functional status at last follow-up in accordance with 3 main groups of treatments administered: corticosteroids (group 1); induction treatment with corticosteroids and an immunosuppressant, but no maintenance (group 2); and combined treatment with corticosteroids and an immunosuppressant for induction followed by maintenance therapy (group 3). Good functional status was defined as a modified Rankin Scale score ≤2 at the last follow-up.

Among the 112 patients reported by De Boysson and colleagues,[14] 33 (29%) patients were included with a diagnostic CNS tissue biopsy, and 68 (61%) and 11 (10%), respectively, had digital subtraction angiography or MRA consistent with PCNSV. Remission was achieved with the initial induction treatment in 106 (95%) of the 112 patients. Prolonged remission without relapse was observed in 70 (66%) patients after a mean of 57 months (range 12–198) of follow-up. A good functional status at last follow-up (ie, modified Rankin Scale score ≤2) was observed in 63 (56%) patients. The overall mortality was 8%. More prolonged remissions ($P = .003$) and a better functional status at the last follow-up ($P = .0004$) were observed in group 3. In multivariate analysis, the use of maintenance therapy was associated with prolonged remission (OR, 4.32 [1.67–12.19]; $P = .002$) and better functional status (OR, 8.09 [3.24–22.38]; $P < .0001$). These findings suggest that maintenance therapy with an immunosuppressant combined with corticosteroids leads to the best long-term clinical and functional outcomes in patients with PCNSV after having achieved remission with either corticosteroids alone or in combination with another immunosuppressant. In that regards, cyclophosphamide in combination with corticosteroids for induction and azathioprine for maintenance were the 2 main immunosuppressants used in this registry. Whether other combinations or sequences can achieve better results remained to be ascertained.

The PedVas Initiative, a Canadian and United Kingdom collaborative study (ARChiVe Investigators Network within the PedVas Initiative [ARChiVe registry], BrainWorks, and Diagnostic and Classification Criteria in Vasculitis Study [DCCVS]) of pediatric and adult cases of antineutrophil cytoplasmic antibody-associated vasculitis (AAV) and PACNS (NIH identifier, NCT02006134), has been prospectively collecting clinical and biobank data since January 2013 of registered cases, within 12 months of study entry, with an expected completion in December 2019. The approach to the diagnosis and classification of childhood PACNS (cPACNS) is to start with inflammatory brain disease as the common denominator and to exclude mimics of angiography-positive cPACNS, and angiography-negative, brain biopsy-positive small vessel (SV)-cPACNS before initiating cytotoxic therapy for presumed cPACNS.[18] Children with angiographically negative SV-cPACNS[19] have persistent headache, cognitive decline, mood disorder, focal seizures, and abnormal brain neuroimaging. Among 13 such children in whom detailed brain biopsy findings were available,[20] the inflammatory cell infiltrate was located in intramural arterioles, capillaries, or venules in 11 patients so studied, consisting predominantly of a mixture of lymphocytes and macrophages, with occasional plasma cells, polymorphonuclear cells, and eosinophils. Granulomatous inflammation and multinucleated giant cells were characteristically absent. Affected blood vessels were found in leptomeninges, cortex, and subcortical white matter in 7 of 9 specimens. The remaining 2 patients without definable vasculitis exhibited nonspecific perivascular lymphocytic inflammation. A similar pathologic condition was noted in the distribution of large named cerebral vessels and single stenosis on cerebral angiography in a child with focal seizures and large arterial ischemic lesions.[21] It has been difficult to reconcile the early outcome of empiric

cytotoxic therapy for any subtype cPACNS especially when the PedVas Initiative using corticosteroids, cyclophosphamide, methotrexate, or rituximab for remission-induction of childhood granulomatosis with polyangitiis[22] for AAV found a disappointing rate of remission status (42%) and visceral organ damage (63%) in its study cohort.

The aim of treatment in cPACNS is to rapidly control the underlying inflammatory response and stabilize the blood-brain barrier while protecting the brain from further insults. Methylprednisolone has been the first-line agent administered intravenously at a dose of 30 mg/kg/d to a maximum of 1 g per day for 3 to 5 days[23] followed by 1 to 2 mg/kg/d of oral CS to a maximum of 60 mg/d of prednisone.[24,25] After stabilization, immunosuppressive treatment is directed at the likeliest inflammatory pathways involved in the primary vasculitic process. Induction therapy with corticosteroids and pulse cyclophosphamide followed by maintenance therapy with azathioprine or mycophenolate mofetil has been recommended in cPACNS.[26] Children with SV-cPACNS treated in an open-label study[26] with cyclophosphamide in doses of 500 to 750 mg/m^2 monthly infusions for 6 months, and followed with maintenance treatment of azathioprine of 1 mg/kg/d and a target dose of 2 to 3 mg/kg/d, and mycophenolate mofetil at titrated doses of 800 to 1200 mg/m^2/d were followed for up to 24 months using pediatric stroke outcome measures (PSOM). Among 19 such patients, 13 completed 24 months of follow-up, of whom 9 had a good neurologic outcome by Pediatric Stroke Outcome Measure (PSOM) scoring, 8 experienced disease flares, and 4 achieved remission of disease; mycophenolate mofetil was more effective than azathioprine. Rituximab, which may be appropriate therapy at doses of 375 mg/m^2 for 4 consecutive weeks or 500 mg/m^2 weekly for 2 weeks in cPACNS, was recently reported in SV-cPACNS.[27]

SUMMARY

It has been 2 decades since the seminal publication of Younger and colleagues[12] on granulomatous angiitis in the *Neurologic Clinics*. There has been a wealth of insight into the management of affected children and adults and overwhelming progress in observational and prospective cohorts. The future brings uncertainty in the current lack of postmortem-proven cases and diminished rates of CNS tissue biopsies in forming observational and prospective case cohorts, when it is still thought that the disease is imminently fatal if not promptly recognized and aggressively treated.

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