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An Update of the Mayo Clinic Cohort of Patients With Adult Primary Central Nervous System Vasculitis

Description of 163 Patients

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Abstract: Primary central nervous system vasculitis (PCNSV) is an uncommon condition in which lesions are limited to vessels of the brain and spinal cord. Because the clinical manifestations are not specific, the diagnosis is often difficult, and permanent disability and death are frequent outcomes. This study is based on a cohort of 163 consecutive patients with PCNSV who were examined at the Mayo Clinic over a 29-year period from 1983 to 2011. The aim of the study was to define the characteristics of these patients, which represents the largest series in adults reported to date. A total of 105 patients were diagnosed by angiographic findings and 58 by biopsy results. The patients diagnosed by biopsy more frequently had at presentation cognitive dysfunction, greater cerebrospinal fluid total protein concentrations, less frequent cerebral infarcts, and more frequent leptomeningeal gadolinium-enhanced lesions on magnetic resonance imaging (MRI), along with less mortality and disability at last follow-up. The patients diagnosed by angiograms more frequently had at presentation hemiparesis or a persistent neurologic deficit or stroke, more frequent infarcts on MRI and an increased mortality. These differences were mainly related to the different size of the vessels involved in the 2 groups. Although most patients responded to therapy with glucocorticoids alone or in conjunction with cyclophosphamide and tended to improve during the follow-up period, an overall increased mortality rate was observed. Relapses occurred in one-quarter of the patients and were less frequent in patients treated with prednisone and cyclophosphamide compared with those treated with prednisone alone. The mortality rate and degree of disability at last follow-up were greater in those with increasing age, cerebral infarctions on MRI, angiographic large vessel involvement, and diagnosis made by angiography alone, but were lower in those with gadolinium-enhanced lesions on MRI and in those with cerebral amyloid angiopathy. The annual incidence rate of PCNSV was estimated at 2.4 cases per 1,000,000 person-years. PCNSV appears to consist of several subsets defined by the size of the vessels involved, the clinical characteristics at presentation, MRI findings, and histopathological patterns on biopsy. Early recognition and treatment may reduce poor outcomes.

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Abbreviations: ABRA = Aβ-related angiitis, BACNS = benign angiopathy of the CNS, CAA = cerebral amyloid angiopathy, CAA-RI = cerebral amyloid angiopathy-related inflammation, CNS = central nervous system, CSF = cerebrospinal fluid, ESR = erythrocyte sedimentation rate, PCNSV = primary central nervous system vasculitis, RCVS = reversible cerebral vasoconstriction syndrome.

INTRODUCTION

Primary central nervous system vasculitis (PCNSV) is an uncommon and poorly understood disease that affects the brain and spinal cord. The earliest report of a case consistent with PCNSV was by Harbitz in 1922.[1] Later reports were published under a variety of names including ''noninfectious granulomatous angiitis of the nervous system'',[2] ''giant cell arteritis of the central nervous system'',[3] ''isolated angiitis of the central nervous system'',[4] and ''primary angiitis of the central nervous system''.[5] The outcome in early reports was usually fatal as the diagnosis was made at autopsy.[1–3,6–8] Later, biopsies and angiograms were also used to make the diagnosis.[4,5,9–11]

In 1988, Calabrese and Mallek suggested diagnostic criteria for PCNSV. These included the development of a neurologic deficit unexplained by other processes, plus the presence of either an angiogram with characteristic features of vasculitis, or a central nervous system (CNS) biopsy showing vasculitis.[5] Because of the more invasive nature of CNS biopsy, the majority of reported cases have been diagnosed by angiography. However, the accuracy of angiography remains uncertain because changes typical of vasculitis can also be seen in nonvasculitic disorders.[10–15] For example, patients with the reversible cerebral vasoconstriction syndrome, the most common mimicker of PCNSV, may have angiographic lesions similar to those observed in PCNSV.[11,16–18] Recent published series have improved the knowledge on this vasculitis[19–21]; however, there are still uncertainties regarding its clinical spectrum, the response to treatment, and its long-term outcome.

Several years ago we reported the results of a retrospective analysis of 101 patients with PCNSV examined at the Mayo Clinic over a 21-year period (1983–2003).[21] In the present study, we extended the previous cohort of PCNSV patients to include the period from 2004 to 2011. The aim of this study was to describe the characteristics of this enlarged cohort of patients

with PCNSV which represents the largest study of PCNSV reported in adults.

PATIENTS AND METHODS

Identification of the Patients

For this study, we extended our earlier PCNSV cohort of 101 consecutive patients examined at the Mayo Clinic (Rochester, MN) over the 21-year period from 1983 to 2003[21] to 29 years, from 1983 to 2011. The same predefined diagnostic and exclusion criteria that were used previously[21] were used to expand this retrospective cohort of PCNSV cases by including those examined at the Mayo Clinic from January 1, 2004 through December 31, 2011. During the recent review period, 62 additional patients fulfilled the diagnostic criteria for PCNSV. Therefore, 163 patients with PCNSV examined at the Mayo Clinic from 1983 to 2011 were included in this retrospective analysis. In this cohort study, we followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations for reporting descriptive observational studies.[22] The study was approved by the Mayo Clinic institutional review board.

Patients were considered to have definite PCNSV if a brain or spinal cord biopsy sample showed vasculitis (transmural destructive inflammatory infiltrate) or if angiograms showed changes that were highly suggestive of vasculitis (smooth-wall segmental narrowing, dilatation or occlusion affecting multiple cerebral arteries in the absence of proximal vessel changes consistent with atherosclerosis).[21] Angiograms were also divided into 2 groups: large/proximal artery (intracranial internal carotid and vertebral arteries, basilar artery, and proximal anterior, middle, and posterior cerebral arteries) and small/distal artery (intracranial artery and second division branches or smaller). We excluded patients with vasculitis in organs other than the CNS and those with evidence of other diseases such as systemic lupus erythematosus and infection. None of the patients had a history of exposure to vasoactive substances, were in the postpartum state, had migraine headaches, thunderclap headaches, or manifestations typical of reversible cerebral vasoconstriction syndrome (RCVS).[17] Because the majority of our cases were included on the basis of angiographic changes in multiple intracranial arteries without tissue confirmation, we were particularly careful to try to exclude cases with findings of RCVS.

Review of Biopsy Specimens and Angiograms

Biopsy specimens were reviewed by 2 pathologists (D.V.M. and C.G.), and angiograms were reviewed by a neuroradiologist. All biopsy specimens were reviewed in the same detailed manner. Conventional digital subtraction angiogram was the standard angiogram and was performed and interpreted by a defined clinical protocol used by the Division of Neuroradiology at the Mayo Clinic, which was not specifically designed for the study of these patients.

Clinical Data Collection

In cases with an uncertain initial diagnosis, the complete medical record was reviewed again by 2 rheumatologists (C.S. and G.G.H.) and 1 neurologist (R.D.B.) to reach a consensus. A standard data collection was completed for all cases. It included comprehensive information about clinical manifestations at presentation and during the follow-up, other medical conditions, laboratory investigations, radiological imaging, results of CNS biopsy or autopsy, type of, duration of, and response to treatment, number of relapses, functional status at follow-up, and cause of death. All patients had a complete neurologic examination performed by a neurologist at the time of diagnosis and on subsequent visits, including the last visit. Cognitive dysfunction was defined as the loss of intellectual functions such as thinking, remembering, and reasoning of sufficient severity to interfere with daily functioning.

Definitions

Relapse was defined as a recurrence of or worsening of symptoms of PCNSV, or evidence of worsening of existing lesions and/or new lesions on subsequent magnetic resonance imaging (MRI) examinations while the patient received no medication or received a stable dosage of medication. Patients with relapse required an increase in therapy.

To assess the effect of treatment, we used the treating physician's global opinion about the response to therapy that was obtained by a review of the detailed clinical, radiological, and laboratory data in the medical record.

The degree of disability at presentation and at the last visit was defined by a review of the detailed clinical data in the medical record and was categorized using the modified Rankin scale.[23] It is a standardized and commonly used scale which measures disability or dependence in activities of daily living in stroke patients. The scale consists of grades 0 to 6: 0 corresponds to no signs or symptoms; 1, no significant disability (able to carry out all usual activities, despite some symptoms); 2, slight disability (able to look after own affairs without assistance, but unable to carry out all previous activities); 3, moderate disability (requires some help, but able to walk unassisted); 4, moderately severe disability (unable to attend to own bodily needs without assistance, and unable to walk unassisted); 5, severe disability (requires constant nursing care and attention, bedridden, incontinent); and 6, death.

Subjects were followed until the death or their last follow-up visit (median follow-up duration: 12 mo; range: 0–13.7 y).

Statistical Analysis

Numeric parameters were compared by using a 2-sided 2-sample t test or a Wilcoxon rank-sum test when the distributions were skewed. Comparisons of categorical variables were performed using the χ^2 or Fischer's exact test when cell counts were small.

Survival was estimated with the Kaplan–Meier method, and 1-sample log-rank test was used to compare observed survival with survival of an age- and sex-matched reference population of whites in the United States.[24]

The Cox proportional hazards model was used to assess the relation between demographic, clinical, laboratory, radiological, pathological, and therapeutic parameters at diagnosis and survival. We reported "crude" and age-controlled univariate hazard ratios (HRs) and 95% confidence intervals (CIs). Logistic regression models were used to identify characteristics at diagnosis that increased the odds of a poor outcome. Overall univariate and age-controlled univariate odds ratios (ORs) and 95% CIs were reported.[25]

The estimated incidence rate of PCNSV in Olmsted County, Minnesota, was calculated using the estimates of country population. The rate reported herein was weighted by age and sex to reflect an underlying population that was demographically comparable with the US white population.

All P values were 2-sided; significance was defined at $P < 0.05$. The statistical analysis was performed using SAS, version 8 (SAS Institute INC., Cary, NC).

Rankin scores were dichotomized into 0 to 3 and 4 to 6 because it was medically relevant. Patients with Rankin score between 0 and 3 maintain some degree of independence in the activities of daily living, while patients with score >3 need complete assistance.

RESULTS

Patients and Diagnosis

From 1983 to 2011, a total of 163 patients examined at Mayo Clinic Rochester fulfilled the diagnostic criteria for PCNSV (Table 1). The first column of Table 1 includes the results for the entire cohort and the next 2 columns the results according to the diagnosis by tissue examination or angiogram. Several subsequent tables are arranged in the same manner.

There were 89 women and 74 men in the study. The mean overall age at the diagnosis was 48 years, with a wide range extending between 17 and 85 years. The median duration of time from onset of symptoms to diagnosis was 0.1 year (median: 0.08–5.2). At the time of diagnosis, 1 patient also was found to have chronic lymphocytic leukemia in addition to the PCNSV. The leukemia did not appear to influence the manifestations or course of the vasculitis.

In 105 patients, the diagnosis was established by cerebral arteriograms, including 82 who did not have biopsies taken and 23 whose biopsies were negative. In 58 others, the diagnosis was made by histologic examination of CNS tissue which showed vasculitis. In 24 of the 58 patients with a tissue diagnosis of vasculitis an angiogram was also done, but was positive only in 8 (Table 2).

Clinical Findings

Table 1 lists the clinical manifestations at diagnosis. A broad variety of neurologic symptoms and findings were present. Most patients had multiple manifestations. Headache and cognitive dysfunction were the most common symptoms at presentation, followed by hemiparesis, persistent neurologic deficit or stroke, and visual symptoms. Each of the above-mentioned symptoms was present in more than one-third of the 163 patients. Prominent constitutional symptoms which might reflect the localized intracranial inflammatory process, and fever, were present in <10%. Eight patients had neurological deficits with imaging related to spinal cord lesions.

Most manifestations listed in Table 1 occurred with similar frequency in both diagnostic groups. However, some were significantly more common in those diagnosed by biopsy or by angiogram (Table 1). Patients with positive CNS biopsy had higher frequencies of a cognitive dysfunction ($P = 0.014$), whereas those diagnosed by angiogram had higher frequencies of hemiparesis ($P = 0.0001$), a persistent neurologic deficit or stroke ($P = 0.0005$), transient ischemic attacks ($P = 0.039$), and visual field defect ($P = 0.02$). Other differences between the groups were not significant.

The main initial symptom of each patient was also evaluated (data not shown). Persistent neurologic deficit or stroke, headache, and altered cognition were the most common initial symptoms. These 3 symptoms together were the initial manifestations in 71% of patients. In the patients diagnosed by biopsy, altered cognition was more frequent than in those diagnosed by angiogram (21% vs 10.5%, $P = 0.09$), while persistent neurologic deficit or stroke was more common in the patients diagnosed by angiography (36% vs 14%, $P = 0.002$). The frequency of patients having headache as the main initial manifestation was similar in both groups (29% vs

TABLE 1. Clinical Manifestations at Presentation in 163 Consecutive Patients With PCNSV

Findings	All Patients (n = 163), n (%)	Biopsy Confirmed (n = 58), n (%)	Angiogram Confirmed (n = 105), n (%)
Headache	97 (59.5)	31 (53.4)	66 (62.9)
Cognitive dysfunction	88 (54)	39 (67.2)	49 (46.7)*
Hemiparesis	66 (40.5)	10 (17.2)	56 (53.3)*
Persistent neurologic deficit or stroke	66 (40.5)	13 (22.4)	53 (50.5)*
Aphasia	40 (24.5)	15 (25.9)	25 (23.8)
Transient ischemic attack	42 (25.8)	9 (15.5)	33 (31.4)*
Ataxia	31 (19)	6 (10.3)	25 (23.8)
Seizures	33 (20.2)	16 (27.6)	17 (16.2)
Visual symptoms (any kind)	61 (37.4)	14 (24.1)	47 (44.8)
Visual field defect	30 (18.4)	5 (8.6)	25 (23.8)*
Diplopia (persistent or transient)	23 (14)	7 (12.1)	16 (15.2)
Blurred vision or decreased visual acuity	18 (11)	3 (5.2)	15 (14.3)
Monocular visual symptoms or amaurosis fugax	2 (1.2)	1 (1.7)	1 (1)
Papilledema	7 (4.3)	4 (6.9)	3 (2.9)
Intracranial hemorrhage	16 (9.8)	5 (8.6)	11 (10.5)
Amnestic syndrome	10 (6.1)	5 (8.6)	5 (4.8)
Paraparesis or quadriparesis	8 (4.9)	5 (8.6)	3 (2.9)
Parkinsonism or extrapyramidal signs	1 (0.6)	0	1 (1)
Constitutional symptoms†	15 (9.2)	6 (10.3)	9 (8.6)
Fever	16 (9.8)	8 (13.8)	8 (7.6)

Excepted where indicated otherwise, values are the number (%) of patients. PCNSV = primary central nervous system vasculitis.
* Significant differences between biopsy-diagnosed patients and angiography-diagnosed patients.
† Defined as the presence of at least 1 of the following: fatigue, arthralgia, anorexia, and weight loss.

TABLE 2. Diagnostic Test Findings in 163 Consecutive Patients With PCNSV

Finding	Patients N = 163, n (%)
Angiogram positive, CNS biopsy not done	82 (50.3)
Angiogram positive, CNS biopsy negative	23 (14.1)
CNS biopsy positive, angiogram positive	8 (4.9)
CNS biopsy positive, angiogram negative	16 (9.8)
CNS biopsy positive*, angiogram not performed†	34 (20.9)

CNS = central nervous system, PCNSV = primary central nervous system vasculitis.
* For 2 patients, pathology confirmation was at the time of autopsy.
† Angiographic evaluation was not performed within 3 months of diagnosis by biopsy.

29%). None of these patients, in particular those with negative biopsy, described the headache as a thunderclap headache.

Laboratory Investigations

An erythrocyte sedimentation rate (ESR) was performed in 137 patients and was elevated above normal level (>30 mm/h) in 24 patients (17.5%), 6 (13%) in the group diagnosed by biopsy, and 18 (19.8%) in those diagnosed by angiograms. The median ESR value was 8 mm/h (range: 0–124 mm/h). C-reactive protein was performed in 58 patients and it was elevated in 19 (33%) patients. Rheumatoid factor (110/113) and antinuclear antibodies (121/131) were usually negative. Tests for antineutrophil cytoplasm antibodies (ANCA; 107 patients), extractable nuclear antigen antibodies (109 patients), lupus anticoagulant (99 patients), serum complement (95 patients), cryoglobulins (24 patients), and HIV (97) were all normal or negative.

Cerebrospinal fluid (CSF) specimens were obtained for analysis in 126 patients (Table 3). Spinal fluid showed 1 or more abnormal findings in 93% of patients. In the majority of patients, the changes included a mild elevation of the leukocyte count or total protein concentration, or both. In those whose diagnosis was made by biopsy compared with angiography, spinal fluid leukocyte counts were higher (median 16/mL vs 4/mL, $P < 0.001$), as was total protein concentrations (98 mg/dL vs 56 mg/dL, $P < 0.001$). Spinal fluid total protein was >70 mg/dL in 52% of the samples, 77% in cases diagnosed by biopsy, and 36.5% of those diagnosed by angiograms ($P = 0.0001$). Overall, the frequent spinal fluid alterations suggested the presence of a CNS process but there were no characteristic changes in patients with PCNSV to help with the specific diagnosis.

Radiologic Imaging

Cerebral Angiograms

Cerebral angiograms were performed in 129 of the 163 patients (Table 2) and 113 (88%) showed changes characteristic of vasculitis. Angiograms alone confirmed the diagnosis in 105 patients but were also positive in 8 additional patients who had brain biopsies showing vasculitis. Angiograms were normal in 16 other patients who had positive brain biopsies suggesting in those that the involved vessels were too small to be visualized. In all 113 patients with positive angiograms, abnormalities were present in multiple vessels which were bilateral in 108 (95.6%) (Table 4). In the majority of instances, both large and small vessel changes were found; however, small vessel changes were more common, occurring in 103 (91.2%), compared with 75 (66.4%) for large vessels. Small vessel changes were also more often bilateral (82.3%) than large vessel alterations (54.9%). Of the 75 with large vessel involvement, only 11 showed large vessel involvement alone, while of the 103 with small vessel involvement, 39 angiograms showed only small vessel involvement.

Magnetic Resonance Imaging

MRI was performed initially in 149 of the 163 patients (91%) and was abnormal in 143 (96%) (Table 5). Infarctions

TABLE 3. CSF Findings

	All Patients (n = 126), n (%)	Biopsy Confirmed (n = 47), n (%)	Angiogram Confirmed (n = 79), n (%)
Median leukocyte count (range), cell/mL	6 (0–615)	16 (0–535)	4 (1–615)†
Leukocyte count >5 cells/mL, number of patients/total	63/122 (51.6)	33/47 (70.2)	30/75 (40)
Median total protein concentration* (range), mg/dL	72 (15–1034)	98 (29–1034)	56 (15–242)†
Total protein concentration >45 mg/dL, number of patients/total	96/121 (79.3)	44/47 (93.6)	52/74 (70.3)
Median red blood cell count (range), cells/mL	7.5 (0–40,000)	10.5 (0–15,000)	7 (0–40,000)
Red blood cell count >0/mL, number of patients/total	96/116 (82.8)	36/44 (81.8)	60/72 (83.3)
Increased total protein concentration, leukocyte count, or red blood cell count, number of patient/total	114/123 (92.7)	45/47 (95.7)	69/76 (90.8)
Protein >45 mg/dL, or leukocyte >5 cells/mL, number of patients/total	100/123 (81.3)	44/47 (93.6)	56/76 (73.7)
Total protein concentration >70 mg/dL, number of patients/total	63/121 (52.1)	36/44 (76.6)	27/74 (36.5)†
Protein >70 mg/dL, or leukocyte >10 cells/mL, number of patients/total	77/121 (63.6)	38/47 (80.9)	39/74 (52.7)

CSF = cerebrospinal fluid. Except where indicated otherwise, values are the number (%) of patients.
* Normal range of protein is 14–45 mg/dL.
† Significant differences between biopsy-diagnosed patients and angiography-diagnosed patients.

TABLE 4. Characteristics of 113 Positive Cerebral Angiograms

	All Patients* (N = 113), n (%)	Biopsy Confirmed (N = 8), n (%)	Angiogram Confirmed (N = 105), n (%)
Bilateral vasculitis	108 (95.6)	7 (87.5)	101 (96.2)
Large-vessel changes consistent with vasculitis			
Total	75 (66.4)	5 (62.5)	70 (66.7)
Unilateral	13 (11.5)	0	13 (12.4)
Bilateral	62 (54.9)	5 (62.5)	57 (54.3)
Small vessel changes consistent with vasculitis			
Total	103 (91.2)	7 (87.5)	96 (91.4)
Unilateral	10 (8.8)	0 (0)	10 (9.5)
Bilateral	93 (82.3)	7 (87.5)	86 (81.9)

Angiographic test was performed within 3 months of diagnosis. All changes involved multiple vessels. Excepted where indicated otherwise, values are the number (%) of patients.

* Of the 129 patients who underwent cerebral angiography, 113 (88%) had findings consistent with vasculitis (8 of the 24 diagnosed by biopsy also had positive angiographic findings).

were the most common type of lesion and were seen in 81 (54%) of the 143 patients. Multiple infarctions were found in 72 of the 81 with infarctions (89%), whereas single infarctions were noted in only 9. In those with multiple infarctions, the lesions tended to be bilateral (60 of the 72, or 83%). Both the cortex and subcortex (40 of the 60, or 67%) were more frequently involved in patients with multiple, bilateral infarcts. Intracranial hemorrhage was uncommon, 12 patients (8%) had intracerebral hemorrhage at diagnosis, while only 4 (3%) had subarachnoid hemorrhage. Gadolinium-enhanced intracranial lesions occurred in 23% of the patients. In 29 (19.5%) patients, meningeal gadolinium-enhanced lesions were observed. Patients diagnosed by angiography compared with those diagnosed by biopsy had significantly more infarcts ($P = 0.0003$), while patients diagnosed by biopsy had significantly more frequent meningeal gadolinium-enhanced lesions ($P = 0.0001$).

Fifty-eight patients had both conventional angiography and a magnetic resonance angiography (MRA) performed. In 44 instances, both showed evidence of vasculitis, in 8 the angiogram was positive and MRA normal, and in 6 both were normal.

CNS Histopathology

Brain or spinal cord tissue (1 patient had spinal cord and 1 spinal nerve root biopsies) was obtained in 81 patients and showed vasculitis in 58 cases (72%). The 23 with no evidence of vasculitis on biopsy showed evidence of vasculitis on angiography. A granulomatous inflammatory histologic pattern was found in 34 patients (59%) (accompanied by vascular deposits of β-amyloid peptide in 20 [34%]) (Figure 1A), a granulomatous and necrotizing pattern in 1 (2%), an acute necrotizing pattern in 10 (17%) (Figure 1C), and a lymphocytic pattern in 13 (22%). A bad outcome (Rankin score 4 and 5, and death) at last follow-up was observed in 0/13 patients with lymphocytic vasculitis, 7/35 (20%) with granulomatous vasculitis, and 3/10 (30%) with necrotizing vasculitis. We registered a trend toward a reduction in the percentage of patients with bad outcome at last follow-up in the lymphocytic vasculitis group compared with granulomatous and necrotizing groups (0% vs 22.2%), but the difference did not reach statistical significance (=0.096). No patients died in the group with lymphocytic vasculitis at last follow-up compared with 5/45 (11.1%) in the other 2 groups; however, the difference was not statistically significant ($P = 0.577$). Pathologic findings and correlations are described in more detail elsewhere.[26–29]

Therapy

Of the 163 patients, 159 received treatment and 4 were given no specific therapy. The first patient was not treated for

TABLE 5. Neuroimaging Findings at Diagnosis

	All Patients (N = 149), n (%)	Biopsy Confirmed (N = 53), n (%)	Angiogram Confirmed (N = 96), n (%)
Presence of infarct	81 (54.4)	18 (34)	63 (65.6)*
Single infarct	9 (6)	4 (7.5)	5 (5.2)
Multiple infarcts in the same hemisphere	12 (8.1)	4 (7.5)	8 (8.3)
Multiple infarcts bilaterally	60 (40.3)	10 (18.9)	50 (52.1)
Gadolinium-enhanced lesions (intracerebral or meningeal)	60 (40.3)	39 (73.6)	21 (21.9)
Intracerebral gadolinium-enhanced lesions	34 (22.8)	18 (34)	16 (16.7)
Meningeal gadolinium-enhanced lesions	29 (19.5)	23 (43.4)	6 (6.3)*
Intracerebral hemorrhage	12 (8.1)	5 (9.4)	7 (7.3)
Subarachnoid hemorrhage	4 (2.7)	0	4 (4.2)

Excepted where indicated otherwise, values are the number (%) of patients.

* Significant differences between biopsy-diagnosed patients and angiography-diagnosed patients.

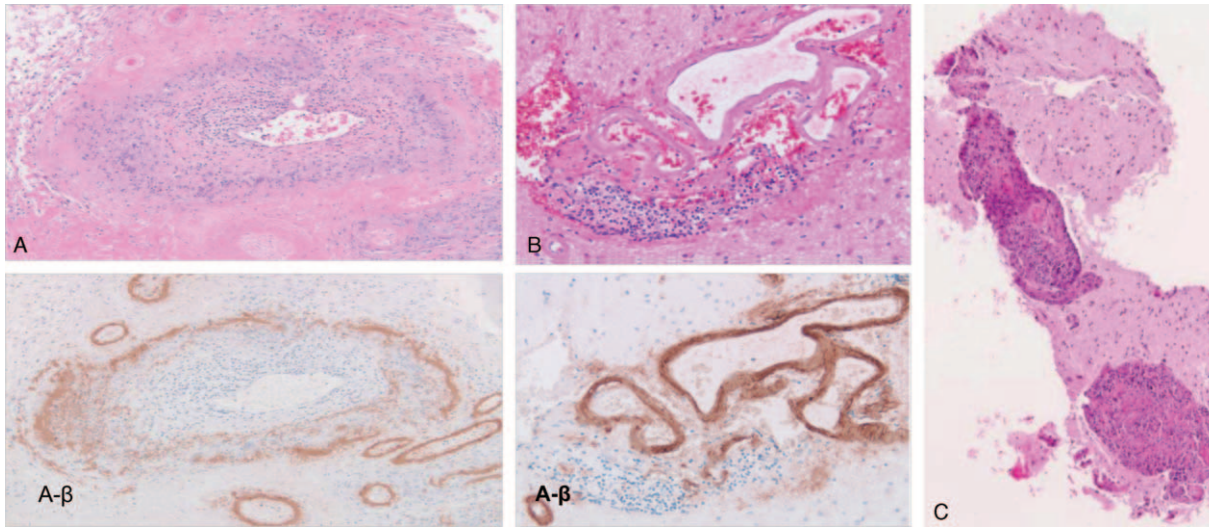

FIGURE 1. Pathological findings in primary central nervous system vasculitis and cerebral amyloid angiopathy-related inflammation (CAA-RI). (A) Granulomatous pattern with amyloid angiopathy (ABRA). Transmural inflammation, often granulomatous, associated with vascular wall disruption (upper; hematoxylin and eosin [H&E] stain) and amyloid-β deposition (lower; immunoperoxidase stain for βA4 amyloid) is typical of ABRA. (B) CAA-RI pattern. Mild perivascular inflammation often with giant cells surrounding leptomeningeal and cortical small vessels (upper; H&E stain) with vascular amyloid deposition (lower; immunoperoxidase stain for βA4 amyloid) is characteristic of CAA-RI. (C), Necrotizing pattern. A segment of intraparenchymal muscular artery shows extensive mural necrosis with karyorrhetic debris and acute neutrophilic inflammation (H&E).

concurrent *Candida glabrata* sepsis and enterocutaneous fistula secondary to a small bowel resection for repair of adhesions due to radiation therapy for endometrial cancer. PCNSV diagnosis was confirmed by 2 cerebral angiograms. The neurological condition apparently was stable, but the patient died 9 months later from unknown cause. The second patient had a mild clinical presentation (headache, numbness in upper and lower limbs, and fatigue) that spontaneously improved before the diagnosis. At last follow-up, 5 months later, the patient was in remission without treatment. The third patient was not treated because when the cerebral biopsy was performed (evidence of granulomatous vasculitis) the patient also had a ventriculoperitoneal shunt for raised intracranial pressure with marked improvement of neurological symptoms (papilledema and headache). Follow-up data on this patient were not available. The fourth patient was not treated because she had, initially, a diagnosis of biopsy proven cerebral amyloid angiopathy (CAA), the diagnosis of Aβ-related angiitis (ABRA) was made after the biopsy revision at Mayo Clinic 5 years later.

Glucocorticoid therapy was prescribed for 157 patients. In 66 of the 157 patients, intravenous pulse glucocorticoid doses were given before or at the time oral prednisone was started. Methylprednisolone, generally 3 to 5 pulses of 1 g/pulse was given most commonly. The median initial oral prednisone dose was 60 mg/d. The median length of oral prednisone therapy was 9 months. Three-quarters of patients were treated for 17 months or less. In 75 patients, glucocorticoids were the only therapeutic agent used initially. In 82 patients, another drug was given with prednisone. In 72 patients, the second drug was cyclophosphamide, given orally daily in 49 patients and by intermittent intravenous pulses in 23 patients. The median starting dose of oral cyclophosphamide was 150 mg/d and median length of treatment was 7 months. The median dose of intravenous pulse cyclophosphamide was 1000 mg/mo.

The patients initially treated with cyclophosphamide and prednisone compared with those treated with prednisone alone had a higher frequency at diagnosis of persistent neurologic deficit or stroke (52% vs 27%, $P = 0.005$) and infarcts at MRI (61% vs 43%, $P = 0.05$), while the frequency of seizures was lower (6% vs 33%, $P = 0.0001$). Furthermore, high disability scores (Rankin score 4 and 5) at presentation were more frequent in patients treated with cyclophosphamide and prednisone compared with those treated with prednisone alone (39% vs 20%, $P = 0.01$).

Six of the 82 patients were started on prednisone plus azathioprine at a median starting dose of 100 mg/d. Three patients received mycophenolate mofetil with prednisone and one patient rituximab. Two of the 163 patients received oral cyclophosphamide without glucocorticoids.

Of the 75 patients given prednisone alone initially, the records contained adequate information to judge the response at follow-up in 73, which was recorded as favorable in 62 (85%).

To assess the response to cyclophosphamide, patients started on oral and intravenous pulses were grouped together because of the small number of patients. In 69 of the 72 patients treated with cyclophosphamide and prednisone, the records provided adequate information to determine response. A favorable response to therapy was recorded in 55 (80%).

The response to treatment in those given prednisone alone was not different between the group with biopsy-diagnosed disease and the group with angiographically diagnosed disease or did not vary according to histopathologic pattern. The results were the same in patients given prednisone plus cyclophosphamide. It should be recognized that the numbers in the various groups analyzed were quite small. Further description of treatment is provided elsewhere.[30,31]

The experience in this cohort with azathioprine plus prednisone and mycophenolate and prednisone was limited; however, the available data suggested that both regimens were also effective.[30,31]

Forty-four of the 159 patients had relapses leading to an increase or change in therapy. Twenty-eight of the 44 had one

relapse, 10 had 2, and 6 had 3 or more relapses. No specific clinical symptoms, laboratory tests, or histopathologic findings were identified with those who had relapses. However, relapses were more common in patients treated initially with prednisone alone compared with those treated with cyclophosphamide and prednisone (39% vs 18%, $P = 0.006$). Patients with relapses were treated longer that those without relapses. The median length of treatment in those with relapses was 18 months, while in those without relapses the median length of therapy was 9 months ($P = 0.0001$).

No significant differences in the frequency of relapsing disease were observed between patients whose diagnosis was by biopsy or by angiography [18/54 (33%) versus 26/99 (26%), $P = 0.357$]. Relapses were observed in 22/71 (31%) patients with large-vessel involvement on angiography and in 12/51 (24%) patients with only small-vessel changes on angiography or angiography-negative and biopsy-positive cases ($P = 0.417$).

Outcome

The median duration of follow-up of the 163 patients was 12 months with a range from 0 to 13.7 years. At the end of the follow-up period, 138 patients were alive and 25 (15%) had died. The cause of death in the 25 patients was cerebral infarction in 10, stroke of undefined type in 1, myocardial infarction in 1, respiratory complication in 3, malignancy in 1, and unknown cause in 9.

Figure 2 shows an estimated age- and gender-matched survival curve of the PCNSV patients versus that expected of the age-matched US white population. Survival among the patient cohort is significantly reduced ($P < 0.001$).

Univariate logistic modeling was used to assess the association of clinical findings at diagnosis with the Rankin score outcomes at last follow-up (Table 6). High disability scores (Rankin score 4–6) at last follow-up were associated with increasing age (OR, 1.44) and cerebral infarction observed on MRI at presentation (OR, 3.74). Patients with gadolinium-enhanced meninges or lesions on MRI (OR, 0.35) and those with amyloid angiopathy (OR, 0.24) had lower disability at follow-up. High disability scores at last follow-up were more frequent in angiography-diagnosed patients than biopsy-diagnosed (27/105, 26% vs 10/58, 17%), but the difference was not significant. Those treated with prednisone versus prednisone plus cyclophosphamide had similar outcomes.

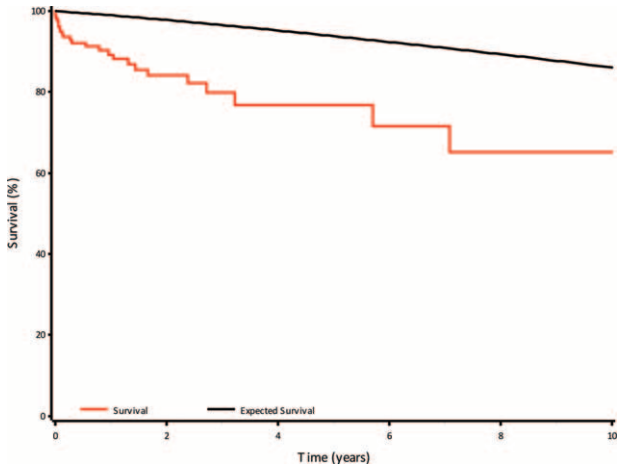

FIGURE 2. Estimated age- and gender-adjusted survival of primary central nervous system vasculitis (PCNSV) patients versus that expected of the US white population. Survival among PCNSV patients is significantly reduced ($P < 0.001$).

Univariate Cox proportional hazards modeling was used to assess the association of survival with clinical findings at the time of diagnosis. The clinical findings analyzed were the same as those evaluated for disability outcome (mentioned earlier). Four findings were associated with an increased mortality rate. These were increasing age (calculated per 10-y increments; HR, 1.39; 95% CI: 1.05–1.85; $P = 0.02$), diagnosis by angiography only compared with biopsy (HR, 3.28; 95% CI: 1.09–9.82; $P = 0.03$), cerebral infarction observed on MRI compared with those without an infarction (HR, 4.44; 95% CI: 1.61–12.2; $P = 0.004$), and the presence of large vessel involvement on angiograms (HR, 4.98; 95% CI: 1.47–16.9; $P = 0.01$). Patients with gadolinium-enhanced lesions or meninges on MRI had less risk of death during follow-up than patients who had no such lesions on MRI at presentation (HR, 0.20; 95% CI: 0.06–0.67; $P = 0.009$), as did patients with ABRA (HR, 0.17; 95% CI: 0.02–1.33); however, only a statistical trend was observed ($P = 0.09$).

There was no difference in survival between those treated with prednisone alone and those given prednisone plus cyclophosphamide, and different presenting manifestations.

Annual Incidence Rate of PCNSV

Eight of the 163 patients were residents of Olmsted County at the time PCNSV developed. The calculated annual incidence rate for these cases was 2.4 cases per 1,000,000 person-years (95% CI: 0.7–4.1) age- and sex-adjusted to 2000 US white population.

Comparison Between 1983–2003 and 2004–2011 Cohorts

We compared the 101 patients identified in the period 1983 to 2003 with the 62 identified in the period 2004 to 2011 to evaluate possible differences in demographic, clinical presentation, diagnostic modalities, types of treatment, and outcomes.

No differences in males/females ratio were observed (43/58 vs 29/33, $P = 0.600$). The median age at diagnosis was significantly higher in the new cohort of patients (51.5 y, range: 20–85 y, vs 47 y, range: 17–84 y, $P = 0.016$). Time from onset to diagnosis was similar in the 2 groups (0.1 y, range: 0.0–5.2 y, vs 0.1 y, range: 0.0–5.2 y, $P = 0.708$). No differences in clinical manifestations at diagnosis were observed in the 2 cohorts of patients: headache (53.2% vs 63.4%, $P = 0.200$) and cognitive dysfunction (61.3% vs 49.5%, $P = 0.143$) were the most common symptoms. The new cohort had a higher frequency of patients with meningeal gadolinium-enhanced lesions (30.5% vs 12,2%, $P = 0.006$), a reduced frequency of patients with large vessel changes at angiography (52.6% vs 72.4%, $P = 0.036$), and a higher percent of patients with MRA examinations (61.3% vs 31.7%, $P = 0.0001$), performed within 3 months of diagnosis. Also, the new cohort had a higher level of disability (Rankin score 4 and 5) at presentation (43.5% vs 21.8%, $P = 0.013$) and at last follow-up (14.5% vs 3%, $P = 0.022$), but mortality was not different at last follow-up (12.9% vs 16.8%), nor was frequency of bad outcome (Rankin score 4–6) at last follow-up (27.4% vs 19.8%, $P = 0.259$). No differences between the 2 groups were observed for laboratory investigations, including CSF analysis, histopathological patterns, and treatment. Treatment and disease course in the 2 groups are described in more detail elsewhere.[30]

TABLE 6. Characteristics Associated With High Disability Scores (Rankin score 4–6) at Last Follow-Up

Characteristics	OR	95% CI	*P*
Age (per 10-y difference)	1.44	1.11–1.86	0.005
Male vs. female	1.20	0.56–2.55	0.65
Main symptom at presentation			
Headache or constitutional symptom	1.00		
Focal manifestation vs. headache or constitutional symptom	2.57	0.90–7.35	0.079
Cognitive disorder vs. headache or constitutional symptom	3.31	0.86–12.8	0.082
Diagnosis by angiography only compared with biopsy	2.17	0.92–5.16	0.079
MRI findings			
Infarct vs no infarct	3.74	1.55–9.06	0.003
Gadolinium-enhanced lesions or meninges vs. normal or minimal changes	0.35	0.15–0.86	0.02
Large-vessel involvement vs. small vessel involvement*	2.12	0.86–5.18	0.10
Increased CSF protein level (>70 mg/dL)	1.28	0.52–3.19	0.59
Cerebral amyloid angiopathy, presence vs. absence	0.24	0.06–0.94	0.040
Prednisone alone vs. cyclophosphamide and prednisone	0.59	0.27–1.29	0.18
Rapid (<1 mo) vs. slow onset (>1 mo)	0.95	0.43–2.09	0.90

Univariate logistic model was used for age-adjusted analysis. CI = confidence interval, CSF = cerebrospinal fluid, MRI = magnetic resonance imaging, OR = odds ratio.
* For this measurement, n = 129.

Selected Index Cases Illustrative of the Different Presentation of PCNSV

In our cohort of patients with PCNSV, we identified specific subsets that appear to differ in terms of prognosis and optimum treatment. Several cases which illustrate features in some of the variants are described in the following sections.

Case 1. Rapidly Progressive PCNSV

A 47-year-old previously healthy man was admitted to the St Marys Hospital in February 2009 with bilateral strokes. His clinical status improved and he was dismissed. Ten days later he was readmitted with lethargy and a progressing right hemiparesis. Normal laboratory tests included ESR (3 mm/h; normal values: 0–22 mm/h), blood coagulation studies, antinuclear antibody panel, cryoglobulins, antiphospholipid antibodies (including lupus anticoagulant), and ANCA. Serology tests (for hepatitis B, hepatitis C, and human immunodeficiency virus [HIV]), and a fungal serology survey were negative. CSF protein concentration was 69 mg/dL (normal 14–45 mg/dL), erythrocyte count was 528/μL, and white blood cell count was 22/μL (1% neutrophils, 85% lymphocytes, and 14% monocytes). MRI showed the presence of multiple infarcts of various ages, including the lateral basal ganglia bilaterally and within the right parietal and occipital lobes bilaterally. MRA showed stenoses in multiple cerebral arteries. A conventional angiogram confirmed the presence of multiple bilateral narrowings in the left anterior cerebral artery, right and left middle cerebral arteries (MCA), and left posterior cerebral artery and their territories. Findings on chest radiographs, transesophageal echocardiogram, and duplex carotid ultrasonography were unremarkable. The patient had no history of exposure to vasoactive substances, thunderclap headaches, or other manifestations typical of RCVS. A diagnosis of PCNSV was made and the patient was treated with intravenous methylprednisolone (1 g/d for 5 d) followed by prednisone 60 mg/d, and IV cyclophosphamide (1 pulse of 1.5 g). However, despite the treatment, his neurological status continued to deteriorate, and he became unresponsive and was intubated. A second MRI, performed 7 days after the first, showed interval progression of the multiple areas of restricted water diffusion with several new areas of restriction involving a large wedge-shaped area of the right parieto-occipital region and several smaller focal areas involving the right basal ganglia, left paramedian cerebral hemisphere, posterior left centrum semiovale, posterior right frontal lobe, right parietal region, and right temporal lobe. One week later he died.

Comment: This case exemplifies the worst end of the clinical spectrum of PCNSV. Rapidly progressive PCNSV often has, as in our patient, a fatal outcome.[32,33] These patients are characterized by bilateral, multiple, large cerebral vessel lesions on angiograms and multiple bilateral cerebral infarctions frequently involving both the cortex and subcortex. The predominant vascular histopathological pattern is granulomatous and/or necrotizing.[32] PCNSV diagnosed in our patient was supported by angiographic changes highly suggestive of vasculitis, the clinical course and spinal fluid analysis. A careful clinical history that excluded the exposure to vasoactive substances and the absence of thunderclap headache made the diagnosis of RCVS improbable but a biopsy was not performed.[18] The diagnosis of rapidly progressive PCNSV requires a high degree of clinical awareness. In this condition, an aggressive therapy with intravenous pulse methylprednisolone and cyclophosphamide is recommended and should be started as soon as possible.

Case 2. Intracranial Hemorrhage and Spinal Cord Involvement

In March, 2001 a 37-year-old woman with well-controlled Crohn disease had a brief episode of nausea, vertigo, unsteadiness, transient headache, and generalized fatigue. Three months later she suddenly developed severe vertigo with nausea, vomiting, dysarthria, and severe headache. By next morning, she had difficulty getting up because of these symptoms. Brain computed tomography (CT) scan demonstrated acute hemorrhage within the medial left cerebellar hemisphere and right temporal operculum. She was hospitalized. Brain MRI without gadolinium confirmed the above-mentioned findings and also old

hemorrhages in the inferior right cerebellar hemisphere and left parietal area. Magnetic resonance venography (MRV) and MRA, and cerebral conventional angiography were negative. Coagulation studies and a workup for systemic vasculitis were negative. CSF analysis showed 320/μL erythrocytes, 50/μL white blood cells (90% lymphocytes and 10% monocytes), and protein concentration of 108 mg/dL. A repeat brain CT performed 4 days later demonstrated an increase in the hematoma involving the right parietal operculum. A brain biopsy was performed in the right temporal lobe with evidence of white matter focal macrophage accumulation most suggestive of microscopic subacute infarct, but no evidence of vasculitis or vascular β-A4 amyloid deposition. Despite the negative biopsy, PCNSV was suspected. The patient was treated with high-dose intravenous methylprednisolone (1 g/d) for 3 days, and then put on oral prednisone 60 mg/d. The neurological findings improved significantly. The prednisone was gradually tapered. A repeat MRI 3 months later showed a reduction in the size of right temporal hematoma, and no new hemorrhages. The prednisone treatment was stopped. After the discontinuation of the treatment she complained of daily headaches of short duration (several seconds to minutes) in right temporal or bifrontal regions. Four months later, pain and numbness in both legs and difficulty ambulating developed. She progressively lost sensation in her legs below the knees and had numbness in her posterior legs and buttocks. Other symptoms included difficulty with speech, and urination and stool incontinence. She was again hospitalized. Neurological examination showed an ataxic gait and sensory loss in the soles extending up in the posterior portion of the legs bilaterally and extending to the buttocks and perineal area bilaterally. Muscle strength was normal in the arms and mildly reduced in the legs. Mental status examination showed mild cognitive dysfunction. Brain MRI with and without contrast including diffusion-weighted images showed subtle abnormal intraparenchymal perivascular enhancement most prominent adjacent to the lateral ventricles and in the basal ganglia and subtle pial enhancement most prominent in the cerebellum and brainstem. No evidence of recent hemorrhage or infarction was present. MRA of the head was normal. The MRI of the spine without and with gadolinium demonstrated abnormal T2 signal, mass effect and enhancement within the conus medullaris. There was also enhancement of the roots of the cauda equine diffusely. Tests with normal or negative findings included ESR, serum liver enzymes, complete blood count, creatinine, urinalysis, serum antinuclear antibodies, antibodies against double-stranded DNA, ANCA, cryoglobulins, antiphospholipid antibodies including lupus anticoagulant, blood coagulation studies, angiotensin-converting enzyme, bacterial and fungal blood cultures, tuberculin skin test, serology tests (Lyme disease, HIV, hepatitis virus B and C, and syphilis) and fungal serology survey (*Aspergillus*, *Blastomyces*, *Coccidioides*, *Histoplasma*, *Cryptococcus* Ag, and *Sporothrix*). CSF protein was elevated (296 mg/dL), erythrocyte count was 48/μL, and white blood cell count was 59/μL (62% lymphocytes, 25% neutrophils, and 13% monocytes). Cytology was negative. CSF cytologic immunostaining did not show malignant cells or features consistent with leukemia or lymphoma. Additional CSF tests with negative results included the venereal disease research laboratory test (VDRL), *Cryptococcus* antigen test, and cultures for fungi and bacteria, and Gram stain. A nerve root biopsy (dorsal root and first sacral) showed necrotizing vasculitis involving small vessels associated with segmental root necrosis, and no evidence of lymphoma. Masson trichrome demonstrated the presence of fibrinoid necrosis in vascular walls. Immunohistochemical stains showed a population composed predominantly of $CD3^+$ reactive T lymphocytes and to a much lesser extent of $CD20^+$ B lymphocytes. Special stains for microorganisms (Grocott's methenamine silver and Gram stain) were negative. Cultures of spinal cord cauda equina for fungi, mycobacteria, bacteria, and anaerobes were negative, as negative were smear for fungi, acid fast smear, and Gram stain. A diagnosis of PCNSV with involvement of the cauda equine was made and the patient was treated with intravenous methylprednisolone (1 g/d) for 3 days, followed by oral prednisone (60 mg/d), and monthly pulse intravenous injections of cyclophosphamide (1 g/mo). One month later, she had an increase in lower extremity strength, was able to walk independently with a cane, her incontinence improved, and was beginning to regain the control of urination, and had less pain. Monthly cyclophosphamide was continued for 6 months. Prednisone was gradually tapered and suspended after 8 months. Eighteen months later she had no recurrence of symptoms attributable to vasculitis, she conducted almost normal activities, and a repeat brain MRI showed no new lesions.

Comment. This case exemplifies 2 possible presentations of PCNSV. Intracranial hemorrhage is a presenting feature in approximately 12% of patients.[28] Intracerebral hemorrhage is more common than subarachnoid hemorrhage which is a rare manifestation of PCNSV. Evidence of cerebral infarctions on MRI is uncommon in these patients. Necrotizing vasculitis, as shown in this patient, is the predominant histopathological pattern of biopsy specimens in patients with intracranial hemorrhage. Spinal cord involvement is observed in about 5% of patients with PCNSV, but rarely is the only manifestation.[34] Most patients with spinal presentation have previous (as this patient), concurrent, or subsequent brain involvement during the disease course. The thoracic cord is predominantly affected. Careful medical evaluation should be undertaken to exclude other disorders associated with acute or subacute transverse myelitis. Patients with intracranial hemorrhage or spinal cord involvement, as shown in our patient who associated both conditions, generally respond well to immunosuppressive treatment.

Case 3. Prominent Leptomeningeal Enhancement

A 45-year-old previously healthy truck driver was admitted with a 2-month history of progressive loss of memory, confusion, and headache. He also had 2 episodes lasting 10 hours characterized by sudden weakness and anesthesia of the entire left arm and leg. The 2 episodes were interpreted as partial seizures. The physical examination was negative, the neurological examination confirmed the cognitive dysfunction with poor attention, confusion, and difficulties in short-term memory. Blood tests with normal or negative findings included complete hematology counts, ESR, liver enzymes, blood chemistries, urinalysis, antinuclear antibody panel, cryoglobulins, anticardiolipin antibodies, blood coagulation studies (including lupus anticoagulant), angiotensin-converting enzyme, cultures, and numerous serology tests for viruses and fungi. CSF protein concentration was 125 mg/dL, and white blood cell count was 14 μL (76% lymphocytes, 19% neutrophils, and 5% monocytes). CSF cytology for malignant cells was negative as were studies and cultures for infectious diseases. Initial contrast enhanced MRI of the brain showed diffuse leptomeningeal enhancement involving both cerebral and cerebellar hemispheres (Figure 3A). Head MRA and conventional cerebral angiography were normal. An MRI-guided stereotactic brain biopsy revealed granulomatous vasculitis of the leptomeningeal

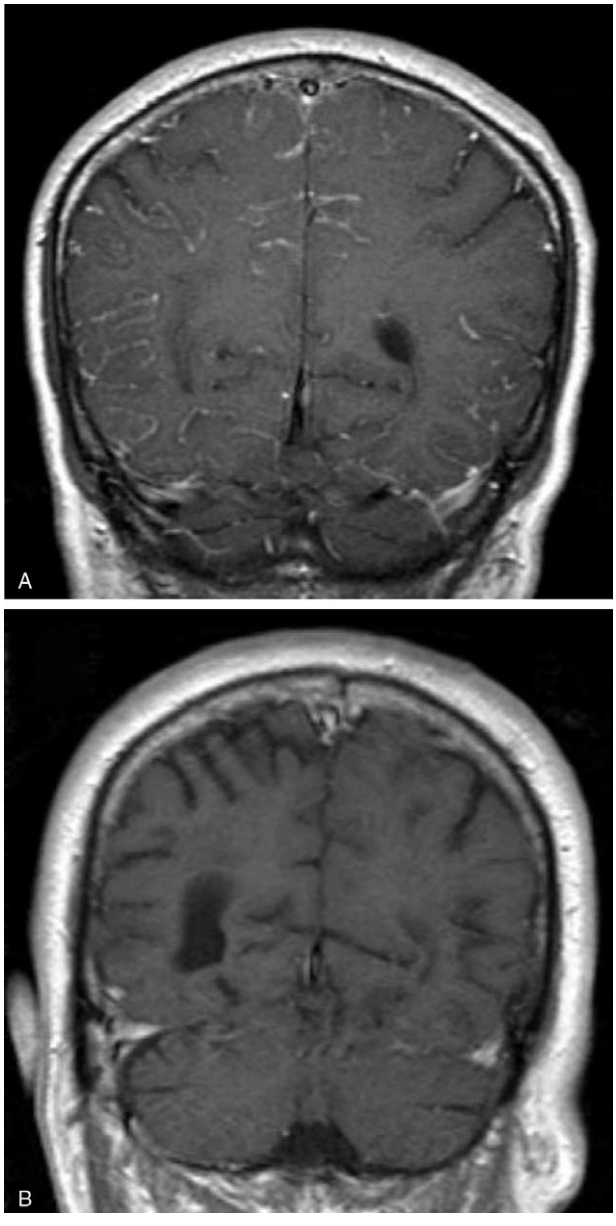

FIGURE 3. Magnetic resonance image (MRI) showing prominent leptomeningeal contrast enhancement. (A) MRI at symptom onset: diffuse, asymmetric, nodular, and linear leptomeningeal enhancement. (B) MRI after treatment: resolution of abnormal contrast enhancement and abnormal T2 signal within the sulci.

vessels. No abnormalities were observed in the dura. A β-amyloid stain was negative. PCNSV was diagnosed and the patient was started on oral prednisone (60 mg/d). Two weeks later he was much less confused, the headache was gone, the seizures subsided, and he was able to perform many of his previous activities. One month later repeat MRI showed a marked reduction of the leptomeningeal enhancement. The prednisone dosage was progressively reduced and stopped 5 months later. Follow-up MRI showed the complete resolution of the leptomeningeal enhancement (Figure 3B). Physical and neurological examinations were normal. Nine months later, at last follow-up, he was in complete remission without neurological symptoms, the neurological examination was negative and he restarted his work of truck driver.

Comment. Prominent gadolinium leptomeningeal enhancement on MRI points to a distinct subtype of PCNSV with small leptomeningeal artery vasculitis.[35,36] As in this case, the course tends to be more benign, characterized by rapid clinical onset, frequent presence of a cognitive dysfunction, negative angiography or MRA, and good clinical response to glucocorticoid therapy with an overall favorable course. Some may have β-amyloid peptide deposition in vessel walls.[29,35–37] Definite elevated concentration of protein in spinal fluid is another characteristic of this subgroup of patients.

Case 4. Granulomatous Vasculitis With Cerebral Amyloid Angiopathy (ABRA)

A 64-year-old previously health man was admitted with a 1.5-month history of severe headache, confusion, personality change, and progressive cognitive decline. On physical examination, he was ataxic. Laboratory test findings were unremarkable. The ESR was 2 mm/h. Tests with normal or negative results included serum antinuclear antibodies, ANCA, antibodies against double-stranded DNA, cryoglobulins, anticardiolipin antibodies, blood coagulation studies, tuberculin skin test, serology tests (for hepatitis B, hepatitis C, and HIV), and a fungal serology survey (*Coccidioides*, *Histoplasma*, and *Blastomyces*). CSF protein concentration was 97 mg/dL, erythrocyte cell count was 50/μL, and white blood cell count was 23/μL (90% lymphocytes and 10% monocytes). CSF cytologic immunostaining showed no malignant cells or features of leukemia or lymphoma. Additional CSF tests with negative results included the VDRL, *Cryptococcus* antigen test, fungal and bacterial cultures, and polymerase chain reaction assays for herpes simplex and zoster viruses, Epstein–Barr virus, cytomegalovirus, *Toxoplasma gondii*, and *Borrelia burgdorferi*. Chest radiographs, transesophageal echocardiogram, and duplex carotid ultrasonogram were unremarkable. Initial contrast-enhanced MRI of the brain showed diffuse bilateral leptomeningeal enhancement involving the cerebrum and the cerebellum, multiple infarcts, patchy T2-weighted white matter signal abnormality. Cerebral angiography was normal. An open brain biopsy showed granulomatous leptomeningeal and intraparenchymal vasculitis. Infarcts and vascular β-A4 amyloid deposition consistent with CAA were also present (Figure 1A). Stains of biopsy specimens were negative for fungal and mycobacterial organisms. PCNSV, or more specifically ABRA, was diagnosed and the patient was treated with oral prednisone (initial dosage, 40 mg/d) and monthly pulse intravenous injections of cyclophosphamide (1.7 g/mo) for 14 months. His neurologic state progressively improved in the first 3 months. He was much less confused, his headache resolved and he was able to perform many of his previous activities. At this time follow-up cranial MRI showed complete resolution of leptomeningeal enhancement and no new infarcts. At his final follow-up visit 12 months later, he was no longer taking prednisone or immunosuppressants and he had no recurrence of symptoms attributable to vasculitis. He had only a minimal disability and conducted normal activities.

Comment. About one-quarter of patients with biopsy-positive PCNSV have evidence of cerebral amyloid vascular deposition.[29,37] This condition is defined as ABRA.[38] As the history showed, these patients usually have cognitive dysfunction and/or seizures/spells at presentation, higher concentrations of CSF protein, and enhancing leptomeningeal lesions on MRI. They usually are angiography-negative because the vasculitis is

limited to small cortical and leptomeningeal vessels beyond the resolution of conventional angiography. Cerebral biopsy is required for the diagnosis. Brain biopsy samples show a granulomatous histopathological pattern plus vascular deposits of amyloid-β. As this case demonstrates, they usually respond favorably to treatment and have a good outcome. Early recognition and treatment of ABRA will help avoid serious outcomes.

Case 5. Amyloid Angiopathy With Perivascular Inflammation

A 69-year-old previously healthy woman was referred to Mayo in January 2011 with a 3-week history of three 5-minute episodes. The first occurred upon awaking from a nap. Her right index finger was weak and numb. There was also numbness in the right lip and tongue, drooping of the right side of her face with some slurring of speech. The next day she also noticed an episode of weakness in her right leg and limping. Three weeks later, she had the last episode characterized by sudden weakness of her right hand. On neurological examination, the patient was awake and alert, but had somewhat unusual affect; she had also an impaired short test of mental status (32/38). Neuropsychological assessment showed signs of anomia, difficulty with verbal response inhibition, and poor planning. Electroencephalogram showed a moderated degree of diffuse nonspecific slow wave abnormalities maximal temporally, but no epileptogenic activity. Laboratory test findings were unremarkable. The ESR was 7 mm/h. Tests with normal or negative findings included serum antinuclear antibodies, ANCA, antibodies against double-stranded DNA, cryoglobulins, antiphospholipid antibodies, blood coagulation studies, angiotensin-converting enzyme, tuberculin skin test, and syphilis serology tests (IgG and IgM syphilis Ab). CSF total protein concentration was 56 mg/dL, the erythrocyte cell count was 13/μL, and the white blood cell count 1/μL (59% lymphocytes, 40% monocytes, and 1% neutrophils). Cytologic findings were negative. Additional CSF tests with negative results included antineuronal nuclear antibody (ANNA)-1, ANNA-2, ANNA-3, antiglial nuclear antibody-1, Purkinje cell cytoplasmic antibody (PCA)-1, PCA-2, PCA-Tr, amphiphysin Ab, and collapsin response mediator protein 5 Ab. A chest radiograph was unremarkable. Contrast-enhanced MRI of the brain showed left greater than right cerebral hemispheric leptomeningeal enhancement, the findings were more evident in the left parieto-occipital area. MRV and cerebral digital subtraction angiography were negative. Left parietal stereotactic cerebral biopsy directed on the enhancing leptomeningeal lesion showed perivascular lymphocytic inflammation without giant cells surrounding intact leptomeningeal vessels (Figure 1B). A β-amyloid stain was strongly and diffusely positive in cortical and leptomeningeal vessels. A diagnosis of CAA-related inflammation (CAA-RI) was made and the patient was treated with high-dose intravenous methylprednisolone (1 g/d) for 5 days, followed by oral prednisone (60 mg/d). Three months later at last follow-up she was markedly improved, she stopped having spells, and brain MRI showed the complete disappearance of the leptomeningeal enhancement. She was on therapy with prednisone at a daily dose of 40 mg.

Comment. This patient was included here to demonstrate the close clinical relationship between CAA-RI and ABRA. CAA-RI cases are part of our report on amyloid angiopathy,[29] but were not included in the current cohort of 163 patients with PCNSV because the biopsy histopathologic appearance did not meet the criteria for definite vasculitis. The patient presented with findings similar to those seen in ABRA and had a favorable response to the prednisone treatment, but biopsies are separable. Two pathologic inflammatory reactions to the deposition of amyloid-β in the cerebral vessels have been described: first with a vasculitic transmural, often granulomatous, inflammation (ABRA), and the second with a perivascular non-destructive inflammatory infiltration, so called CAA-RI.[29,39,40] ABRA and CAA-RI more closely resemble PCNSV than CAA without vascular inflammation and likely are part of the same pathologic spectrum.[29]

DISCUSSION

Biopsy of CNS tissue showing vasculitis is the definitive diagnostic test for PCNSV. However, many physicians have preferred angiography in favor of biopsy because of the invasive nature of the former[41–46] even though angiograms have not been considered specific and their sensitivity is unknown. It has been noted on more than 1 occasion that angiographic alterations similar or identical to those present in vasculitis may be seen in association with a variety of other diseases.[12,14,47,48] Of the several reports in the literature that include 10 or more adult cases of PCNSV, most of the diagnoses were established by angiography.[41,49–52] In 3 recent series which included 12 patients, 101 patients, and 52 patients only 1 case, 31 cases, and 19 cases, respectively, were diagnosed using cerebral biopsy.[19,21,51] Thus, our understanding of PCNSV is based to a considerable extent on a small number of series of cases diagnosed predominantly by angiograms. Our present study represents the largest reported series of cases in adults, and largest number diagnosed by cerebral biopsy which permitted us to compare the clinical findings in those diagnosed by biopsy with those diagnosed by angiography. Furthermore, updating our previous cohort with a sizeable number of new cases strengthens the overall findings regarding the characteristics and outcomes of PCNSV. An annual incidence rate of PCNSV for Olmsted County could also be estimated.

To compare our cases with those previously reported, we used similar diagnostic criteria employed by others requiring either a biopsy with findings of vascular inflammation or an angiogram with characteristic alterations associated with vasculitis along with a compatible clinical examination.[5,11,13,16,21] However, to ensure including definite cases, we carefully reviewed all biopsy specimens and accepted only conventional angiograms clearly showing a multifocal vascular process. As a result, 95% of cases diagnosed by angiograms showed multiple bilateral vessel alterations suggesting vasculitis. MR angiography was not used for diagnosis as it did not appear as sensitive as conventional angiography. However, in the evaluation of patients, MR angiography may be helpful when suspecting a diagnosis of PCNSV. Using the comprehensive information contained in the Mayo Clinical medical records and the follow-up data available, we were able to exclude patients with vasculitis in organs other than the CNS and those with evidence of other diseases which can mimic PCNSV, in particular RCVS.

Clinical findings in this series, which were similar to our previous observations and to reports by others,[5,10,11,13,21] included the lack of a significant gender predisposition (56% women in our study), the median age of onset in early middle age (48 y), and a broad spectrum of clinical manifestations with headache, altered cognition, aphasia, focal neurologic deficits, and hemiparesis being most common. Also similar to earlier works, inflammatory markers were mostly normal, reflecting the localized intracranial nature of the inflammatory process. Although a minority of patients had elevated ESRs (17.5%), the

clinical findings and outcomes in these patients were not different from those with normal ESRs (data not shown). Spinal fluid analysis was abnormal in most (93%) of the patients. Changes consisted of a mildly increased leukocyte and erythrocyte counts and total protein concentration. Although CSF findings were generally mild and nonspecific, they were helpful in the patients without histological verification but with a high probability angiogram in differentiating PCNSV from RCVS, where CSF findings are usually normal.[17,18] CSF analysis also included in most patients appropriate stains, cultures, serological and molecular tests, and flow cytometry studies and they were useful to exclude infection or malignancy. MRI examinations were abnormal in nearly all cases tested (143 of 149 patients). But more suggestive findings such as infarctions occurred in a lower proportion (54%). Multiple infarctions were seen in most of these (89%). Gadolinium-enhanced lesions (intracerebral or meningeal) represented the second most frequent MRI finding observed. Sixteen patients (10.8%) had evidence of intracranial hemorrhage at presentation, mainly intracerebral hemorrhage as shown in Case 2, and also described in a previous manuscript.[28] The normal results of tests for serum antinuclear antibodies, anti-ENA, ANCA, lupus anticoagulant, HIV infection, and other related determinations help mainly to exclude other possible causes of the symptoms.

In this enlarged cohort, some clinical differences between the patients diagnosed by angiography and those diagnosed by biopsy that we found earlier now became significant (Table 1). The patients diagnosed by biopsy more frequently had a cognitive dysfunction at presentation, elevated CSF total protein concentrations, leptomeningeal gadolinium-enhanced lesions on MRI, and better outcomes with less mortality, but less frequent infarctions. The patients diagnosed by angiograms more frequently had hemiparesis or a persistent neurologic deficit or stroke at presentation, infarctions on MRI at diagnosis and an increased mortality. These differences were strictly related to the different size of cerebral vessels involved by the inflammatory process in the 2 groups. Sixteen patients had normal angiograms and positive biopsy findings, suggesting that vessels involved were small and beyond the resolution of conventional angiography, while 23 others had positive angiographic findings and negative biopsy suggesting that the affected vessels were of larger size while the small cortical and leptomeningeal vessels were apparently not or less involved. The different clinical course in PCNSV patients according to the size of the vessel involved was also shown by univariate analyses which demonstrated an increased mortality in patients with large/proximal vessel involvement compared with the patients with small/distal vessel involvement (patients with only small/distal vessel involvement at angiograms plus patients biopsy positive and angiogram negative). MacLaren et al[51] reported somewhat different results in a series of 12 patients diagnosed with PCNSV. Six patients grouped as having midsized vessel involvement (4 had angiograms showing characteristic vasculitis patterns, but no biopsies) responded to treatment, had an isolated episode and paucity of relapses, while 6 grouped as small vessel disease (1 case proven by biopsy) responded to treatment, but had a relapsing course causing more serious neurologic outcomes. We observed a correlation only between relapsing disease and the type of treatment (patients treated with glucocorticoids alone had more relapses/recurrences). There were no differences regarding relapses/recurrences between patients biopsy-proven and angiography-proven or between patients with distal/small vessel involvement and those with proximal/large vessel involvement. Furthermore, the patients with relapsing disease did not have a final outcome different from that of patients without relapses/recurrences. Differences in case documentation and selection may account for the differences between MacLaren and coworkers' results and ours.

The variations in findings and course observed in this cohort confirm our previous observations that PCNSV is a heterogeneous condition composed of >1 entity with differences in terms of clinical presentations, outcomes and response to treatment.[53] As noted, the size of the vessels involved in the inflammatory process seems to be responsible for many of these different clinical characteristics. Rapidly progressive PCNSV (exemplified by our Case 1) patients characterized by the angiographic presence of bilateral, multiple, large vessel lesions and MRI evidence of multiple cerebral infarctions often have fatal outcomes and represent the worst end of the clinical spectrum of PCNSV,[32,33] while angiography-negative patients with the involvement of small cortical and leptomeningeal vessels characterized by a cognitive disorder at presentation and MRI evidence of prominent leptomeningeal enhancement (Case 3) have a more benign disease that responds favorably to treatment.[35,36]

Calabrese et al initially suggested that most cases defined only by angiography may represent a more benign form of PCNSV (benign angiopathy of the CNS or BACNS).[16,49] Later, the same authors concluded that some of these patients did not have vasculitis and in 2007 they used the term RCVS to identify various disorders characterized by cerebrovascular spasm, including also the patients with BACNS.[17] In our study, we made special efforts to exclude patients with RCVS. The fact that our patients diagnosed by angiography, differently from Calabrese et al initial observations,[16,49] tended to have a progressive course with a higher mortality supports our view that they had characteristics of vasculitis rather than vasoconstriction.

Also the histopathological pattern may be a marker of a distinct condition. As observed in our Case 2, necrotizing vasculitis was significantly more frequent in patients with intracranial hemorrhage.[28] Overall, necrotizing vasculitis was a less frequently seen pattern, being present in only 17% of the patients with histological diagnosis. In these patients, the histologic appearance of the brain biopsy specimen resembles the pattern seen in polyarteritis nodosa. The destructive transmural vasculitic process with fibrinoid necrosis may cause severe vessel wall weakening, thus predisposing to blood vessel ruptures. Furthermore, a predominant granulomatous and/or necrotizing pattern characterizes patients with rapidly progressive course, little response to therapy, and frequent fatal outcome,[32,33] while lymphocytic vasculitis, the only histopathological pattern observed in children primary angiitis of the CNS,[13] seems to define in the adult a subset with a more benign vasculitis. None of our patients with lymphocytic vasculitis had at last follow-up a bad outcome or died. β-Amyloid peptide deposition in biopsies was found almost exclusively in those specimens with a granulomatous histologic pattern. Scolding et al[38] suggested that β-amyloid peptide related PCNSV is a recognizable clinicopathological entity which they refer to as ABRA. Our Case 4 represents an example of ABRA. As we and other authors demonstrated, ABRA represents a definable subset of PCNSV characterized by older age at diagnosis, high frequency of cognitive dysfunction and seizures/spells at presentation, increased spinal fluid protein levels, high frequency of enhancing leptomeningeal lesions, and favorable response to glucocorticoids alone or in combination with cyclophosphamide.[29,38] Cerebral angiography is often negative in patients

with ABRA (it was positive only in 2 of the 14 patients who had angiography) and cerebral biopsy is required for the diagnosis. In ABRA, the inflammation is mainly restricted to the small cortical and leptomeningeal vessels. Some patients have an inflammatory nonvasculitic condition related to vascular deposition of β-amyloid peptide with clinical characteristics similar to ABRA (as exemplified by Case 5) and good treatment response. These patients are pathologically characterized by a perivascular nondestructive inflammatory infiltration and this condition is defined CAA-RI.[29,39,40] It is possible that CAA-RI and ABRA are part of the same pathologic spectrum. Although CAA-RI patients were not included in our cohort of patients with PCNSV, this condition appears related to ABRA and the clinician must be aware of the whole spectrum of amyloid-β associated inflammation. Furthermore, in some cases the pathological distinction between ABRA and CAA-RI may be difficult.[26]

We compared the results from the old 1983 to 2003 cohort to those from the more recent 2004 to 2012 cohort to evaluate changes in demographic, clinical manifestations, diagnostic investigations, and outcomes. The age at diagnosis was higher in the new cohort of patients; however, the clinical manifestations at diagnosis in the 2 cohorts did not change. The higher frequency of patients with MRA examination at diagnosis in the more recent cohort reflected the increased use of this technique for PCNSV diagnosis. The new cohort of patients also had a more severe disease as pointed out by the higher level of disability at diagnosis and at last follow-up, notwithstanding the higher frequency of patients with meningeal enhancement and the reduced frequency of patients with large vessel disease, characteristics associated to a more benign disease. Differences in the treatment between the 2 groups are described in more detail elsewhere.[30]

The patients treated with cyclophosphamide and prednisone had a higher frequency of persistent neurologic deficit or stroke and MRI evidence of infarcts at diagnosis compared with those treated with prednisone alone. Therefore, the therapeutic choice of adding cyclophosphamide to prednisone at diagnosis reflected the presence of a more severe disease as also evidenced by the higher disability scores at presentation observed in the patients treated with cyclophosphamide and prednisone. However, a favorable response was observed in most of the patients to glucocorticoids alone and glucocorticoids in conjunction with cyclophosphamide. About 83% of the patients responded to the treatments, and the response rate was similar in the 2 treatment groups. This is encouraging for the management of these patients and emphasizes the need for early recognition in order to avoid irreversible CNS events. No differences in outcomes (disability and mortality) were observed in the 2 treatment groups, the only difference regarded the disease flares. Treatment with prednisone alone was associated with more frequent relapses. Treatment is described in more detail elsewhere.[30]

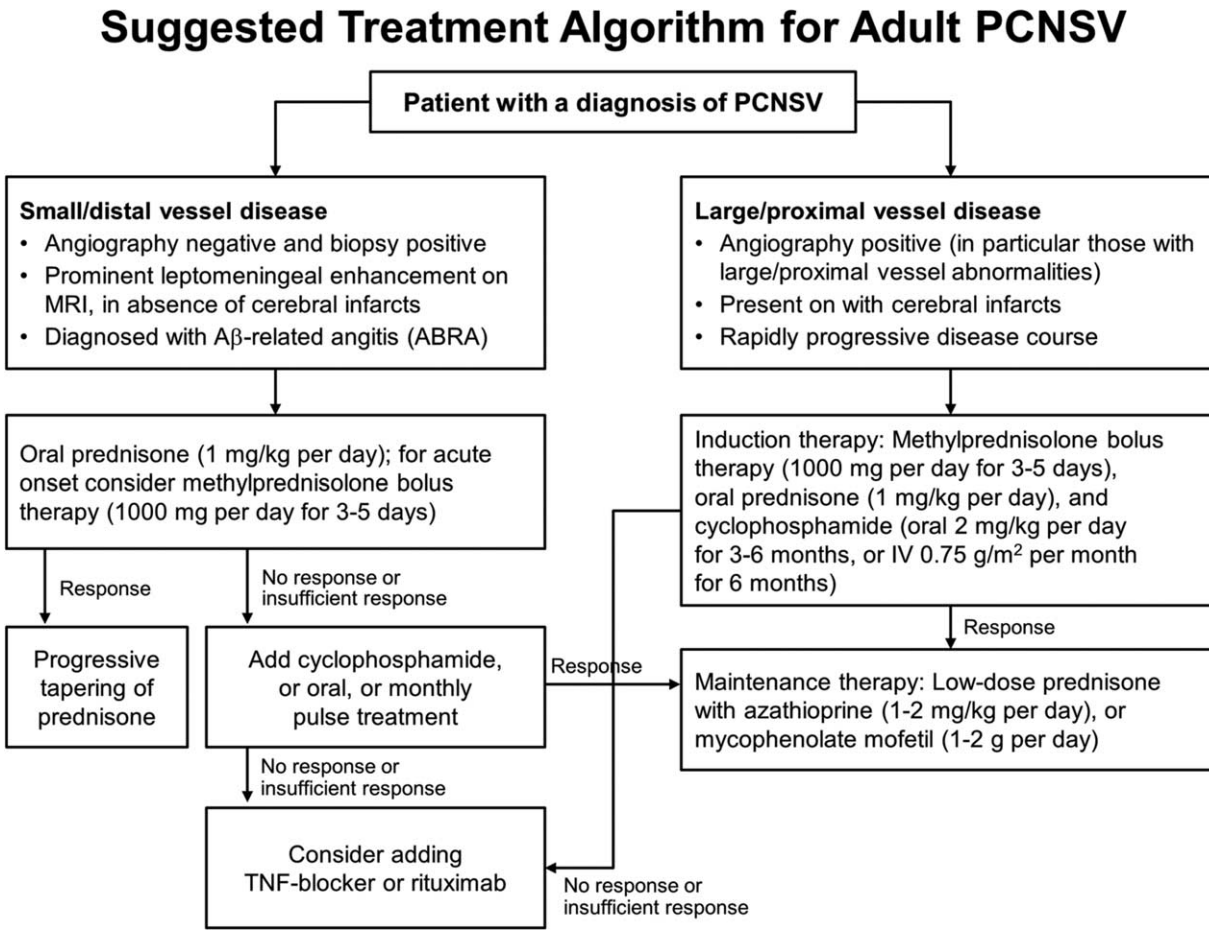

FIGURE 4. Suggested treatment algorithm for primary central nervous system vasculitis (PCNSV).

There are no standardized treatment protocols or randomized clinical trial evidence to guide therapy. A suggested treatment algorithm for PCNSV according to our experience and the data from the literature is shown in Figure 4. We recommend an initial dose of prednisone of 1 mg/kg/d (or equivalent) in patients with inflammation restricted to small cortical and leptomeningeal vessels who have a more benign disease and usually respond favorably to glucocorticoid treatment. If a patient does not respond promptly, cyclophosphamide should be started. Oral cyclophosphamide or intravenous pulses that have proved effective in other vasculitides can be used.[4,15,19] An option would be to replace cyclophosphamide with azathioprine or mycophenolate mofetil that are less toxic drugs. However, we have not considered this option in our algorithm because insufficient evidence exists for the effectiveness of these 2 drugs for the induction of remission. In patients with more severe large/proximal vessel disease and in those with rapidly progressive course, high-dose intravenous methylprednisolone (1000 mg daily for 3–5 d) and cyclophosphamide can be used to induce remission immediately after diagnosis. Subsequently, we suggest the use of a low-risk immunosuppressant such as azathioprine or mycophenolate mofetil for the maintenance of remission. Evaluating our cohort of patients with PCNSV, we observed a favorable response to these 2 drugs and a treatment course of 12 to 18 months was adequate in most patients.[30,31] Methotrexate was used in few of our patients and in literature; therefore this drug was not included in the algorithm. Tumor necrosis factor-α blockers or rituximab may be used in the patients who are intolerant or respond poorly to cyclophosphamide.[54–56]

We estimated the survival rate of our patients using the Kaplan–Meier method, comparing the outcome to the life expectancy of the US white population. As seen in Figure 2, the mortality rate was significantly increased in patients with PCNSV. The majority of the causes of death that were ascertained were related to neurovascular problems and presumably connected to the PCNSV. Increased mortality rates and high disability scores at last follow-up were specifically associated with characteristics associated to the size of the vessel involved. The presence of cerebral infarctions on MRI, large vessel involvement on angiograms, and diagnosis by angiography compared with diagnosis by biopsy reflect the development of more serious and widespread neurologic lesions correlated with the involvement of the larger cerebral vessels. Gadolinium-enhanced lesions and CAA characterize a vasculitic process that involves the smaller cortical and leptomeningeal vessels and a more benign course.

A strength of this study is the large number of unselected cases which should provide a more reliable perspective of the spectrum of clinical findings of PCNSV than the previous smaller series. The diagnostic exclusion of biopsies that lacked clear histologic features of vasculitis and angiograms with single or focal areas of vessel involvement likely eliminated at least some cases with non-vasculitis conditions. The longer period of follow-up helped confirm the diagnosis of included cases, provided time to assess response to treatment, and outcomes. We were particularly careful to try to exclude cases with findings of RCVS. The overall clinical characteristics and disease course of all patients diagnosed with only angiography were more consistent of an underlying vasculitic process, rather than the vasoconstriction syndrome.

The study has a number of limitations. Retrospective studies as this are associated with missing data which may influence the results. Other limitations include possible referral bias of cases and lack of tissue at diagnosis in the majority of patients.

In conclusion, our findings indicate that PCNSV is a heterogeneous condition. Presenting clinical manifestations, MRI findings, and histopathological patterns may identify separate disease subsets. However, in our enlarged cohort, distinct subtypes of PCNSV appeared primarily related to the size of the vessel involved. The involvement of small cortical/leptomeningeal vessel was associated with a more benign disease course, while the involvement of larger/proximal cerebral vessels characterized patients with a less favorable prognosis who should be treated more aggressively. We also confirmed that PCNSV is associated with an increased morbidity and mortality, but also with high rates of favorable response to glucocorticoids alone or with cyclophosphamide. An early recognition and treatment of this vasculitis will help avoid serious outcomes.

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