Original Article

Primary central nervous system vasculitis: analysis of 101 patients

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Abstract

Objective

To analyze the clinical findings, response to therapy, outcome, and incidence of primary central nervous system vasculitis (PCNSV) in a large cohort from a single center

Methods

We retrospectively studied 101 patients with PCNSV, selected by predetermined diagnostic criteria, who were seen during a 21-year period. This was a collaborative study by five departments at a large multispecialty clinic. Clinical findings and outcomes were compared among patients categorized by method of diagnosis, response to therapy, survival, and degree of disability. An annual incidence rate was calculated

Results

Seventy patients were diagnosed by angiography and 31 by central nervous system biopsy. Three histological patterns were observed during biopsy. Although most patients responded to therapy, an increased mortality rate was observed. Relapses occurred in one fourth of patients. Mortality rate and disability at last follow-up were greater in those who presented with a focal neurological deficit, cognitive impairment, cerebral infarctions, and angiographic large-vessel involvement but were lower in those with prominent gadolinium-enhanced lesions when evaluated by magnetic resonance imaging. The annual incidence rate of PCNSV was 2.4 cases per 1,000,000 person-years

Interpretation

PCNSV is a rare disease that may result in serious neurological outcomes or death. Angiography and brain biopsy may complement each other when determining the diagnosis. Early recognition and treatment may reduce poor outcomes. PCNSV is a variable syndrome that appears to consist of several subsets of heterogeneous diseases. Ann Neurol 2007

Article Text

Primary central nervous system vasculitis (PCNSV) is an uncommon and serious form of vasculitis that is limited to the brain and spinal cord.[1-9] In 1988, Calabrese and Mallek[5] suggested diagnostic criteria for PCNSV that included development of a neurological deficit unexplained by other processes, an angiogram with characteristic features of vasculitis, or a central nervous system (CNS) biopsy specimen showing vasculitis. Because of the more invasive nature of CNS biopsy, angiography has become preferred for evaluating patients with suggestive symptoms. However, optimal angiographic criteria for the diagnosis of PCNSV have not been delineated, and the relative accuracy of angiography when compared with biopsy remains uncertain. Angiographic changes typical of vasculitis may be seen in patients with normal brain biopsy findings or with other diseases.[9][10] Some investigators have found that cases diagnosed by angiography alone have a more benign form of the disease; such cases may also have findings that are difficult to distinguish from those of reversible cerebral vasoconstriction syndrome.[11-13] Because of the lack of uniform diagnostic criteria and the relatively small numbers of patients in previous series, the clinical spectrum of PCNSV, its response to treatment, and its long-term outcome are still uncertain. In this study, we reviewed all cases of PCNSV seen at Mayo Clinic (Rochester, MN) from 1983 through 2003.

Patients and Methods
Identification of Patients
We used our institution's medical record diagnostic linkage system to identify all patients treated at Mayo Clinic (Rochester, MN) from January 1, 1983, through December 31, 2003, who had a diagnosis of vasculitis involving the CNS. We reviewed records of all patients with findings of vasculitis involving the CNS and excluded patients with findings consistent with other diagnoses (eg, polyarteritis nodosa, lupus erythematosus, and infections). For cases with an uncertain initial diagnosis, two rheumatologists (C.S. and G.G.H.) and one neurologist (R.D.B.) reviewed the complete medical record again and reached a consensus. This study was approved by the Mayo Clinic Institutional Review Board.

Diagnostic Criteria
Diagnostic criteria of PCNSV were similar to those suggested earlier[5]: (1) recent history or presence of an acquired neurological deficit unexplained by other causes, (2) evidence of vasculitis in a CNS biopsy specimen, or (3) a cerebral angiogram with changes characteristic of vasculitis. We were careful to exclude diseases that might mimic PCNSV, including hypercoagulability, varicella zoster, other infectious vasculitides, and other processes.

Diagnostic histopathological features included transmural vascular inflammation involving leptomeningeal or parenchymal vessels. The types of infiltrating inflammatory cells, presence of vascular wall fibrinoid necrosis, and patterns of inflammation were recorded. Vascular amyloid deposition was assessed by immunoperoxidase staining of β-amyloid proteins. Parenchymal findings of ischemia were recorded.

Angiographic changes indicating a high probability of vasculitis included areas of smooth-wall segmental narrowing or dilation and occlusions that affected multiple cerebral arteries without the proximal vessel changes of atherosclerosis or other causes. Angiograms were also divided into two groups: large artery (intracranial internal carotid artery and proximal anterior, middle, and posterior cerebral arteries) and small artery (intracranial artery, second division branches or smaller). Cases with angiograms showing a single abnormality in multiple arteries or multiple abnormalities in a single artery were reviewed (by R.D.B., C.S., and G.G.H.) again but generally were excluded.

Clinical Data Collection
A standard data collection form for all findings was completed for the confirmed cases. All patients had a detailed neurological examination. Relapse was defined as a recurrence of or increase in symptoms of PCNSV (eg, headache or cognitive impairment), progression of disease activity (eg, new focal events), or evidence of new infarction 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. 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 by using the Rankin Disability Scale.[14] This scale consists of seven grades (grades 0-6): 0 indicates no neurological signs or symptoms, 1 indicates no significant disability (despite symptoms), 2 indicates slight disability, 3 indicates moderate disability, 4 indicates moderately severe disability, 5 indicates severe disability, and 6 indicates death.

Statistical Analysis
Patient characteristics were summarized overall and by group (eg, by diagnostic modality). Numeric characteristics were compared by using a two-sided two-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 a one-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.[15] The Cox proportional hazards model was used to assess the relation between clinical characteristics and survival. We reported "crude" and age-controlled univariate hazard ratios (HRs) and 95% confidence intervals. Logistic regression models were used to identify characteristics that increased the odds of a poor outcome. Overall univariate and age-controlled univariate odds ratios (ORs) and 95%

confidence intervals were reported.[16] Because of the low number of deaths and relatively few poor outcomes, multivariate analysis was not feasible. The estimated incidence rate of PCNSV in Olmsted County, Minnesota, was calculated using estimates of county 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 two-sided; $p < 0.05$ indicated statistical significance.

Results

Patients and Diagnosis

Between 1983 and 2003, 101 patients (58 female and 43 male patients) treated at Mayo Clinic (Rochester, MN) fulfilled the diagnostic criteria for PCNSV. The median age at diagnosis was 47 years (range, 17-84 years), and 50% of patients were between age 37 and 59 years at diagnosis. The median time between symptom onset and diagnosis was 0.1 year; diagnoses were determined in 75% of patients within half a year after onset of symptoms. More male patients had the diagnosis determined by biopsy (17 male vs 14 female patients), but the reverse was true for diagnosis by angiography (26 male vs 44 female patients). At diagnosis, one patient had chronic lymphocytic leukemia in addition to PCNSV. The leukemia did not influence the manifestations or course of vasculitis.

Table 1 shows the tests used to establish the diagnosis of PCNSV. For 70 patients, the diagnosis was established by cerebral angiography and included 52 who did not undergo biopsy and 18 with negative biopsy findings. For 31 patients, the diagnosis was established after histological examination of CNS tissue showed vasculitis. In 29 of these 31 patients, positive CNS biopsy findings were obtained during the diagnostic evaluation, and vasculitis was confirmed in 2 at autopsy. Fourteen of the 31 patients with a tissue diagnosis of vasculitis also had an angiographic evaluation, but the study showed abnormal findings in only 6. In eight patients, the angiogram results were normal, but biopsy results showed PCNSV (see Table 1).

Table 1. Diagnostic Test Findings (N = 101)

Finding	Patients, n
Angiogram, positive; CNS biopsy, positive	6
Angiogram, positive; CNS biopsy, negative	18
Angiogram, positive; CNS biopsy, not performed	52
Angiogram, negative; CNS biopsy, positive	8
Angiogram, not performed[a]; CNS biopsy, positive[b]	17

[a]Angiographic evaluation was not performed within 3 months of diagnosis by biopsy.
[b]For one patient, pathology confirmation was at the time of autopsy.
CNS = central nervous system.

Clinical Findings

Table 2 lists the various symptoms and findings at diagnosis. Most patients had multiple manifestations, most frequently headache, altered cognition, focal neurological manifestations, persistent neurological deficit or stroke, and visual symptoms. Intracranial hemorrhage was infrequent.

Table 2. Clinical Manifestations at Presentation

Characteristics	All Patients (N = 101), n (%)	Patients Diagnosed by Biopsy (n = 31), n (%)	Patients Diagnosed by Angiography (n = 70), n (%)
Headache	64 (63)	16 (52)	48 (69)
Altered cognition	50 (50)	22 (71)	28 (40)
Hemiparesis	44 (44)	6 (19)	38 (54)
Persistent neurological deficit or stroke	40 (40)	8 (26)	32 (46)
Aphasia	28 (28)	11 (36)	17 (24)
Transient ischemic attack	28 (28)	5 (16)	23 (33)
Ataxia	19 (19)	5 (16)	14 (20)
Seizure	16 (16)	2 (7)	14 (20)
Visual symptom (any kind)	42 (42)	9 (29)	33 (47)
Visual field defect	21 (21)	5 (16)	16 (23)
Diplopia (persistent or transient)	16 (16)	5 (16)	11 (16)
Blurred vision or decreased visual acuity	11 (11)	0 (0)	11 (16)
Monocular visual symptoms or amaurosis fugax	1 (1)	0 (0)	1 (1)
Papilledema	5 (5)	2 (7)	3 (4)
Intracranial hemorrhage	8 (8)	2 (7)	6 (9)
Amnestic syndrome	9 (9)	4 (13)	5 (7)
Paraparesis or quadriparesis	7 (7)	4 (13)	3 (4)
Parkinsonism or extrapyramidal sign	1 (1)	0 (0)	1 (1)
Prominent constitutional symptom	9 (9)	4 (13)	5 (7)
Fever	9 (9)	4 (13)	5 (7)
Nausea or vomiting	25 (25)	6 (19)	19 (27)
Vertigo or dizziness	9 (9)	3 (10)	6 (9)
Dysarthria	15 (15)	2 (7)	13 (19)
Unilateral numbness	13 (13)	0 (0)	13 (19)

When patients were grouped by diagnostic modality, most manifestations occurred with similar frequency in both groups (see Table 2). However, incidence of hemiparesis, blurred vision or decreased acuity, and unilateral numbness was significantly greater in patients diagnosed by angiography ($p < 0.02$ for all). The main initial symptom of each patient also was recorded. Persistent neurological deficit or stroke and headache were the most common initial symptoms (affecting 68% of patients overall). No significant differences in the frequencies of initial symptoms were noted between the two diagnostic subgroups (data not shown). Of the 18 patients with the diagnosis established by abnormal angiography findings only (normal biopsy findings), 9 were female patients (see Table 1). Seven of the 18 had headache as the initial main manifestation, but none described it as a "thunderclap" headache.[12]

Laboratory and Imaging Findings
HEMATOLOGICAL STUDIES.
Median hemoglobin levels, leukocyte counts, platelet counts, and erythrocyte sedimentation rates were typically within reference levels and did not differ according to the method of diagnosis (data not shown). Erythrocyte sedimentation rates were measured for 85 patients; the rate was increased (>30mm/hr) for 6 in the group diagnosed by biopsy and for 13 diagnosed by angiography. Serum test results were usually negative for rheumatoid factor (62/64 patients), antinuclear antibodies (71/79 patients), and anticardiolipin antibodies (57/58 patients). Results were negative or normal in all sera tested for antineutrophil cytoplasm antibodies (59 patients), complement levels (58 patients), human immunodeficiency virus (61 patients), and lupus anticoagulant (58 patients).

CEREBROSPINAL FLUID ANALYSIS.
Cerebrospinal fluid (CSF) specimens were obtained from 75 patients (Table 3). Samples were obtained from 27 of 31 with biopsy-based diagnoses (87%) and 48 of 70 with angiography-based diagnoses (69%). CSF tests showed 1 or more abnormal findings for 66 patients (88%). In most patients, changes included a mildly increased leukocyte count or total protein concentration, or both. Patients with a diagnosis made by biopsy had greater leukocyte counts (median, 17 vs 4 cells/ml; $p = 0.005$) and greater total protein concentrations (median, 98 vs 54mg/dl; $p < 0.001$) in the CSF. These findings were somewhat similar to those of Hajj-Ali and colleagues.[17] Of the 18 patients with abnormal angiographic findings but normal biopsy

findings, the CSF leukocyte count (median, 4/ml) and total protein concentration (median, 53mg/dl) were essentially the same as that of the overall group of 70 patients diagnosed by angiography.

Table 3. Cerebrospinal Fluid Findings

Findings	All Patients[a] (N = 75)	Patients Diagnosed by Biopsy (n = 27)	Patients Diagnosed by Angiography (n = 48)
Median leukocyte count (range), cell/ml	5 (0–535)	17 (0–535)	4 (1–373)
Leukocyte count > 5 cells/ml, number of patients/total	36/73 (49.3%)	19/27 (70.4%)	17/46 (37.0%)
Median total protein concentration (range), mg/dl	72 (15–1,034)	98 (44–1,034)	54 (15–166)
Total protein concentration > 45 mg/dl, number of patients/total	53/73 (72.6%)	26/27 (96.3%)	27/46 (58.7%)
Median red blood cell count (range), cells/ml	6 (0–10,000)	12 (0–2,277)	4.5 (0–10,000)
Red blood cell count > 0/ml, number of patients/total	55/70 (78.6%)	20/26 (76.9%)	35/44 (79.5%)
Increased total protein concentration, leukocyte count, or red blood cell count, number of patients/total	66/74 (89.2%)	26/27 (96.3%)	40/47 (85.1%)

[a] Analysis was not performed for 26 of the 101 patients in the cohort. Data were missing for some variables.

CEREBRAL ANGIOGRAPHY.

Cerebral angiography was performed in 84 of the 101 patients, and 76 (90%) showed changes characteristic of vasculitis (Table 4). Of the 76 patients with angiograms showing vasculitic changes, multiple-vessel abnormalities were bilateral in 71 (93%). Small-vessel changes were more common (small-vessel changes, 70 patients [92%]; large-vessel changes, 54 patients [71%]). Bilateral changes occurred more often with small vessels (82%) than with large vessels (62%). Of the 54 patients with large-vessel involvement, only 6 showed large-vessel involvement alone, whereas 48 angiograms showed that large and small vessels were affected. Of the 70 angiograms showing small-vessel involvement, 22 showed only small-vessel involvement.

Table 4. Characteristics of 76 Positive Cerebral Angiograms

Findings	All Patients[a] (N = 76), n (%)	Patients Diagnosed by Biopsy (n = 6), n (%)	Patients Diagnosed by Angiography (n = 70), n (%)
Bilateral vasculitis	71 (93)	5 (83)	66 (94)
Large-vessel changes consistent with vasculitis			
Total	54 (71)	4 (67)	50 (71)
Unilateral	7 (9)	0 (0)	7 (10)
Bilateral	47 (62)	4 (67)	43 (61)
Small-vessel changes consistent with vasculitis			
Total	70 (92)	6 (100)	64 (91)
Unilateral	8 (11)	0 (0)	8 (11)
Bilateral	62 (82)	6 (100)	56 (80)

Angiographic test was performed within 3 months of diagnosis. All changes involved multiple vessels.
[a] Of the 84 patients who underwent cerebral angiography, 76 (90.5%) had findings consistent with vasculitis (6 of the 14 diagnosed by biopsy also had positive angiographic findings).

Of the 52 patients whose diagnoses were made by angiography alone (see Table 1), both large and small vessels were involved in 36, 12 had only small-vessel involvement, and 4 had only large-vessel changes. Of the 18 patients whose diagnoses were made by angiography and whose brain biopsy findings were negative (see Table 1), 8 had both small and large vessels affected, 8 had only small-vessel abnormalities, and 2 had only large-vessel changes. Of the six with positive biopsy and angiography findings, four had large and small vessels affected and two had only small vessels affected.

MAGNETIC RESONANCE ANGIOGRAPHY.

Magnetic resonance angiography (MRA) was performed in 32 of the 101 patients (data not shown). MRA was performed in all but one of these patients before the diagnosis or within 23 days after the diagnosis. Results were suggestive of vasculitis in 19 patients (59%). Both large- and small-vessel involvement was seen in 14; 3 patients had only large-vessel involvement, and 2 had only small-vessel changes. Of the 14 with large- and small-vessel involvement, 11 showed bilateral involvement for both, and 3 showed various combinations of large- and small-vessel and unilateral and bilateral involvement.

Conventional cerebral angiography also was performed for 27 of the 32 patients. In 19 patients with MRA findings suggesting vasculitis, conventional angiograms also suggested vasculitis. For six other patients, MRA showed normal findings, but conventional angiograms suggested vasculitis. Four of the six had only small-vessel vasculitis, and two had small- and large-

vessel changes. For 2 of the 27 patients, both studies had normal findings. Thus, conventional angiography and MRA yielded the same results for 21 of 27 patients (78%), and conventional angiography was somewhat more sensitive than MRA for detecting vasculitis of intracranial vessels.

MAGNETIC RESONANCE IMAGING.
MRI was performed initially for 90 of the 101 patients (89%) and showed abnormal findings for 87 (97%). Infarctions were the most common type of lesion and were seen in 48 of 90 patients (53%). Multiple infarctions were found for 41 of the 48 (85%) patients. Of those with multiple infarctions, lesions frequently were bilateral (34/41; 83%) and also involved both the cortex and subcortex (26/41; 63%). The appearance of the infarcts varied: some suggested a large-artery distribution, others showed a branch-artery distribution, and others had multiple subcortical infarctions in a small-artery pattern. Intracranial hemorrhage occurred in 7 of 90 patients (8%).

Gadolinium-enhanced intracranial lesions were observed for about one third of patients (33/90). Eight had prominent gadolinium-enhanced meninges.

COMPUTED TOMOGRAPHY.
Diagnostic computed tomography scans were performed for 56 patients and showed abnormal findings in 43 (77%). Changes suggesting infarctions were observed in 28 patients (50%).

ELECTROENCEPHALOGRAPHY.
Electroencephalograms were obtained for 38 patients and showed abnormal findings in 28 (74%). Dysrhythmias were observed in 24 patients, epileptogenic changes in 4, and delta waves in 13. No specific combinations of these abnormal findings were seen, and there were no electroencephalographic changes associated with specific clinical findings.

CENTRAL NERVOUS SYSTEM HISTOPATHOLOGY.
CNS biopsy specimens were examined histologically in 49 of the 101 cases. Biopsy findings were positive in 29 of the 47 patients (62%) and in the 2 postmortem cases. Twenty-seven of the 29 positive biopsy specimens were from the brain, and 2 were from the spinal cord.[18] Histological patterns of positive specimens varied. Eighteen patients had a granulomatous inflammatory pattern, eight had a lymphocytic pattern, and five had an acute necrotizing pattern. No specimen showed more than one pattern. β-Amyloid peptide deposition was identified in eight specimens (all showed a histological granulomatous vasculitis pattern). β-Amyloid peptide vascular deposition (amyloid angiopathy) was also identified for a patient whose biopsy findings for vasculitis were negative (diagnosis was made by angiography). Two biopsy specimens were obtained from each of seven patients. In four patients, both specimens had positive vasculitis findings and identical histological patterns of inflammation.

No clear clinical relation was identified among the three histological patterns. However, biopsy specimens with a granulomatous pattern were identified more frequently in older-onset patients (54 vs 42 years) and for patients who presented initially with altered cognition (33 vs 8%). Patients with a lymphocytic pattern were more often men (6/8). The likelihood of positive biopsy findings was greater if a biopsy specimen was obtained when the MRI showed an abnormality.[18]

Therapy
Glucocorticoid therapy was prescribed for 97 of the 101 patients. In 43 patients, glucocorticoids initially were the only therapeutic agents used. For 25 of the 97 patients, intravenous pulse glucocorticoid doses (typically, 1 to 6 pulses of methylprednisolone [1gm/pulse]) were administered before or at the time oral prednisone therapy was initiated. The median initial oral prednisone dose was 60mg/day. The median length of oral prednisone therapy was 10 months, and three fourths of the patients were treated for 19 months or less.

Fifty-four patients received medication in addition to prednisone. The second medication was cyclophosphamide in 46 patients (35 had daily oral doses, 11 had intermittent intravenous pulses). The median initial dose of oral cyclophosphamide was 150mg/day, and the median length of treatment was 10 months. The median dose of intravenous pulse cyclophosphamide was 1,000mg/month. Three of the 54 patients were administered prednisone and azathioprine at an initial dose of 100 or 150mg/day. Five of the 54 patients also initially received a nonsteroidal antiinflammatory drug. Two of the 101 patients received oral cyclophosphamide without glucocorticoids, and 2 had no specific therapy. Of the 43 patients treated with prednisone alone for the first course of therapy, medical records showed a favorable response for 34 of 42 (81%) patients.

To assess response, we grouped together patients receiving oral and intravenous pulse cyclophosphamide. We had sufficient data to evaluate the results in 47 patients. A favorable response to therapy was observed for 38 (81%). Response to treatment was not associated with any histological pattern of the biopsy specimen.

Relapses
Twenty-six of the 101 patients had relapses that led to a change in therapy. Fifteen of the 26 had 1 relapse, 8 had 2 relapses, and 3 had 3 or more. No specific clinical symptoms, laboratory test results, or histopathological findings were associated with relapse. However, relapse was somewhat less common for patients with angiograms that showed only small-vessel involvement. Fifty-four patients had large-vessel involvement or large- and small-vessel involvement (measured by angiography) (see Table 4); relapses occurred for 16 of these patients (30%). Of the 70 patients with small-vessel involvement, 22 had only

small-vessel changes, and of those, relapses occurred for 2 (9%) (*p* = 0.06). Patients with relapse were treated longer (median, 14 months) than those without relapse (median, 7 months).

Outcome

The median duration of follow-up for the 101 patients was 13 months (range, 0-13.7 years). Seventeen patients died during follow-up. The cause of death included cerebral infarction (six patients), stroke of undefined type (one patient), myocardial infarction (one patient), and respiratory complication (two patients). Cause of death was unknown for seven cases. Four patients with cerebral infarction, one with stroke, and two with unknown causes of death died within the first year of follow-up. The other two cases with cerebral infarction died within 5 years of diagnosis. The Figure shows an estimated age- and sex-matched survival curve of patients with PCNSV and the expected survival curve of an age-matched US white population. Survival of the patient cohort was significantly reduced (*p* < 0.001).
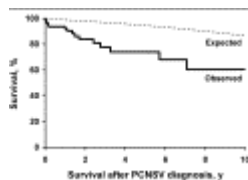
Figure 1. Age- and sex-adjusted survival of patients with primary central nervous system vasculitis (PCNSV) versus estimated survival of the US white population (*p* < 0.001).
[Normal View 24K | Magnified View 41K]

The univariate Cox proportional hazards model was used to assess the association between survival and clinical and laboratory findings at the time of diagnosis (Table 5). Four manifestations at presentation were associated with an increased mortality rate. These included focal neurological deficit versus headache or constitutional symptoms (HR, 3.60), cognitive impairment versus headache or constitutional symptoms (HR, 4.00), cerebral infarction versus no infarction (HR, 4.39), and large-vessel involvement versus small-vessel involvement (HR, 7.93). In the group of 84 patients evaluated by angiography, 14 deaths occurred during follow-up (13 had large-vessel involvement). Patients with prominent gadolinium-enhanced lesions or meninges (assessed by MRI) had a lower risk for death during follow-up than patients with no such lesions at presentation (HR, 0.11).

Table 5. Clinical Characteristics Associated with Survival

Characteristics	HR	95% CI	*p*
Age (per 10-year difference)	1.14	0.80–1.63	0.47
Male vs female	0.74	0.26–2.16	0.59
Main symptom at presentation			0.23
Headache or constitutional symptom	1.00		
Focal manifestation vs headache or constitutional symptom	3.60	0.78–16.6	
Cognitive disorder vs headache or constitutional symptom	4.00	0.65–24.8	
Diagnosis by angiography only compared with biopsy	1.57	0.50–4.94	0.44
MRI findings			0.22
Infarct vs no infarct	4.39	1.37–14.0	0.01
Gadolinium-enhanced lesions or meninges vs normal or minimal changes	0.11	0.01–0.83	0.03
Large-vessel involvement vs small-vessel involvement[a]	7.93	1.03–61.1	0.05
Increased cerebrospinal fluid protein level (>70 mg/dl) or white blood cell count (>10 cells/ml)	0.84	0.29–2.44	0.75
Prednisone vs cyclophosphamide (Cytoxan) only or Cytoxan and prednisone	1.37	0.49–3.82	0.55
Rapid (≤1 mo) vs slow onset (>1 mo)	0.67	0.23–1.97	0.47

Univariate Cox proportional hazards model was used for age-adjusted analysis.
[a]For this measurement, n = 84.
HR = hazard ratio; CI = confidence interval; MRI = magnetic resonance imaging.

No differences in survival were observed when patients were stratified by treatment (prednisone alone vs prednisone and cyclophosphamide), method of diagnosis (angiography vs biopsy), or by other manifestations (see Table 5). Survival was not associated with increased erythrocyte sedimentation rate at the time of diagnosis.

Modified Rankin disability scores[14] were recorded at presentation and at last follow-up. The patients were grouped into two populations, those with Rankin scores of 0 through 3 (good outcome with no residual disability, slight disability, or moderate disability) and those with scores of 4 through 6 (poor outcome with moderately severe disability, severe disability, or death by cerebral infarction or stroke). Univariate logistic modeling was used to assess association of clinical findings at diagnosis with Rankin score outcomes. Findings were expressed as ORs with 95% confidence intervals (data not shown). The clinical findings analyzed were the same as those studied for mortality (see Table 5), and the results were also similar. High disability scores (Rankin scores, 4-6) at last follow-up were associated with presenting manifestations of focal neurological deficit or stroke (OR, 4.09), cognitive impairment (OR, 7.36), cerebral infarction at diagnosis (assessed by MRI; OR, 4.46), and large-vessel involvement (OR, 3.23). Other clinical factors (see Table 5) were not associated with a high Rankin score, including diagnosis by biopsy or angiography (OR, 1.19). Similar to survival findings, patients with prominent gadolinium-enhanced meninges or lesio Table 6 compares Rankin disability scores at diagnosis with scores at last follow-up. The scores at diagnosis were grouped into three categories (0-2, no or slight disability; 3, moderate disability; 4-5, moderately severe and severe disability). Follow-up periods were grouped into three categories (<1, 1-4.9, and 5-15 years). Although the overall mortality rate of the cohort with PCNSV was increased (see Fig), most patients with relatively low disability scores at diagnosis (Rankin score, 0-2; 57 patients) continued to have low scores at last follow-up (Rankin score, 0-3). Most of the 22 patients with severe disability at diagnosis (Rankin score, 4-5) had less disability at follow-up (Rankin score, 0-3). Thus, a high Rankin score at diagnosis did not necessarily predict a poor outcome, and most patients had improved status at last follow-up.

ns had lower disability at follow-up (OR, 0.12).

Table 6. Rankin Disability Score at Last Follow-up Visit (N = 101)

Rankin Score at Diagnosis	Patients, n	Rankin Score at Last Follow-up Visit								
		<1 yr			1–4.9 yr			5–15 yr		
		0–3	4–5	Deceased	0–3	4–5	Deceased	0–3	4–5	Deceased
0–2	57	25	0	1	20	0	4	6	0	1
3	22	11	0	2	3	0	1	3	0	2
4–5	22	5	0	4	7	2	2	1	1	0

Of the 18 patients with abnormal angiographic findings but with normal biopsy findings, the initial median Rankin score was 3, and the score at last follow-up was 2. Thus, the outcome of this group of patients was similar to that of the other patients in this study (see Table 6).

Annual Incidence Rate of Primary Central Nervous System Vasculitis

Five of the 101 patients were residents of Olmsted County, Minnesota, when PCNSV developed. The average annual incidence rate was 2.4 cases per 1,000,000 person-years (95% confidence interval, 0.3-4.4), adjusted to the US white population (in 2000).

Discussion

Progress in understanding PCNSV has been slow because its occurrence is infrequent and its identification is difficult. The diagnosis is made definitively by brain biopsy, but many clinicians have preferred angiography because of concern about the invasiveness of biopsies and the possibility of not sampling affected tissue.[19-24] However, diagnoses based on angiograms are not as definitive as those made by biopsy, and the sensitivity is unknown.[10][25]

In previous reports that included 10 or more adult cases of PCNSV (121 patients total), diagnosis was established by clinical or angiographic studies in 81 and by biopsy in 40.[8][17][21][26-30] Lie's[8] and Alrawi and colleagues'[30] studies included only pathologically verified cases and accounted for all but 3 of the 40 tissue-diagnosed cases. Lie[8] also noted the rarity of PCNSV in a tissue diagnosis; his 15 histologically proven cases were from a cohort of 1,337 patients with vasculitides of all types. Thus, our current knowledge of PCNSV is influenced heavily by a number of smaller series of cases with diagnoses confirmed predominantly by angiograms. Furthermore, in the largest study of PCNSV in children, diagnoses for all were established by conventional angiography or MRA with frequent focal or unilateral changes.[31]

Our diagnostic criteria were more conservative than some earlier investigations. As a result, more than 90% of our conventional angiograms with positive findings showed multiple bilateral vessel alterations of vasculitis. In contrast with our histological criteria, criteria used in some previous studies did not require transmural inflammation; other studies included varicella zoster infection and abnormal findings from conventional angiography and MRA that were frequently unilateral or limited to a single

vessel.[28][31][32] Clinical findings in our series that were similar to those of previous reports included the sex distribution, median age of onset in early middle age, and the broad spectrum of clinical manifestations. Most laboratory test results were also similar to those of earlier studies.[5][8][9][17][26-29][31] Normal median values of hematological tests did not reflect the intracranial inflammatory processes. Although CSF and electroencephalographic findings were abnormal in most, they generally were minor and nonspecific. However, CSF fluid findings may help exclude infections or subarachnoid hemorrhage, and serum immunological studies may exclude autoimmune diseases.

MRI findings were abnormal for nearly all patients tested (87/90 patients), but findings more indicative of PCNSV (eg, multiple infarctions) occurred in a lower proportion. Prominent gadolinium-enhanced meninges were observed in eight patients and appeared to be part of a subset of PCNSV manifestations that were associated with milder clinical findings

Because we included only patients with a diagnosis of PCNSV, the relative usefulness of angiography and biopsy for establishing the diagnosis could not be assessed directly. The similarity of clinical characteristics and outcomes suggests that both tests provided equivalent results. Although we found some clinical differences, we had no clear indication that a patient with a diagnosis established by angiography had a more benign course when compared with others.[11-13] It is apparent, however, that the two tests did not provide the same information for all patients. For example, we had eight patients with normal angiograms and positive biopsy findings, which suggested that vessel involvement was small and beyond the resolution of conventional angiographys.

Eighteen patients had positive angiogram findings and negative biopsy findings, which suggested that affected vessels may be larger and did not extend to the parenchymal surface or to leptomeningeal tissues. Sampling error is another explanation. It is possible that the pathogenic substrate is truly patchy in nature. We also cannot completely exclude the syndrome of reversible cerebral vasoconstriction as the cause of the findings in some of the 18 patients. In this syndrome, patients are predominantly female and typically have abrupt and severe (thunderclap) headache and neurological findings. An angiogram shows cerebral vasoconstriction resembling vasculitis, especially of the arteries around the circle of Willis. CSF examination shows minimal changes. The clinical manifestations improve over weeks, and vasoconstriction resolves in 3 to 4 months. None of our patients had disease onset with an acute, severe headache or had a history of other findings sometimes noted in this syndrome such as migraine headaches, use of vasoactive amines or other medications associated with vasospasm, or were in a postpartum period. Nevertheless, this syndrome may closely resemble vasculitis, and we cannot be certain that none of our patients diagnosed by angiograms alone had vasoconstriction rather than vasculitis. For patients with symptoms that are clinically suspicious of PCNSV, both cerebral angiography and brain biopsy may be necessary, especially if angiographic changes are absent or not widespread.

It is not completely clear whether the three histopathological patterns represented different stages of a single pathological process or were reactions to different causative agents and indicated different diseases. Supporting the latter hypothesis was the finding that histological patterns of specimens from individual patients were similar throughout the sample, and in the four patients who each had two positive biopsy specimens, patterns were the same in both. β-Amyloid peptide deposition was identified during biopsy only in specimens with a granulomatous histological pattern. Scolding and coworkers[33] suggested that β-amyloid peptide-related PCNSV is a recognizable clinicopathological entity. The different histological patterns did not appear to result from different treatments.

Most patients showed a favorable response to glucocorticoids alone or in combination with cyclophosphamide. The early response rates of 81% of patients were the same for both treatment groups. This encouraging finding emphasizes the need for early diagnosis and initiation of therapy that may help avoid irreversible CNS events. Because the study was retrospective, the contribution of pulse glucocorticoids (at the beginning of therapy) and cyclophosphamide was difficult to assess. Nevertheless, it may be reasonable at this time to consider starting more aggressive treatment with prednisone and cyclophosphamide in patients who present with symptoms associated with severe outcomes. Prednisone alone could be prescribed for those with stable manifestations or less emergent symptoms. The results of our study suggest that a treatment course of 12 to 18 months with careful follow-up is adequate for many patients with PCNSV.

Patients with relapse required longer therapy but otherwise had similar outcomes to those without relapse. However, in the group of 70 patients with diagnoses established by angiography, relapses were more frequent for those with large-vessel involvement (30%) than those with only small-vessel changes (9%). These findings differed from MacLaren and colleagues'[28] findings, which noted more frequent relapses for patients with small-vessel involvement. Differences in the definition of "large artery" may explain this disparity.

The increased mortality rate was related to neurovascular problems presumably caused by PCNSV. Increased mortality rates and Rankin disability at last follow-up were associated with several clinical findings (see Table 5). These manifestations probably reflected the development of more serious and widespread neurological lesions and the potential influence of large-artery involvement on outcome. A rapid onset did not portend a favorable outcome (see Table 5), as noted previously.[17] Improvement of Rankin scores at follow-up likely resulted from treatment and resolution of active disease.

A strength of this study was the large number of unselected, consecutive cases. Compared with individual cases or smaller previous series, our cohort likely provided a more complete spectrum of clinical findings. The longer period of follow-up helped confirm diagnoses and provided time to assess response to treatment and determine outcomes. Internal consistencies included the frequent favorable response to treatment and the improvement of Rankin scores over time. Also, similar risk factors influenced survival and Rankin disability scores during follow-up. In addition, we provided the first estimate of the annual incidence rate of PCNSV.

The investigation had a number of limitations. As in all retrospective studies, incomplete datasets may have influenced findings. It is possible that the nonsignificant differences in clinical findings noted in some groups of patients would be meaningful when larger populations are studied. Our results may not pertain to other patient populations (eg, children), and our investigation did not explain why vasculitis was limited to vessels of the brain and spinal cord.

In conclusion, our findings confirm that PCNSV is a rare disease associated with increased morbidity and mortality. Careful delineation of findings on angiography and biopsy will ensure an accurate diagnosis of PCNSV, as shown by the similar clinical findings and outcomes of patients assessed by either method in our study. Because of the varied vessel involvement, diagnostic information from angiograms and CNS biopsies appear complementary. Brain biopsies are more likely to yield positive results when MRI or computed tomography findings are abnormal. Recognition of clinical findings associated with poor outcomes may aid decisions regarding therapy. The high rate of favorable response to glucocorticoids alone or in combination with cyclophosphamide suggests that early recognition and treatment will help avoid serious outcomes. Although our findings were not definitive, these data suggest that the PCNSV syndrome is composed of more than one entity.

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