

Angiography-Negative Primary Central Nervous System Vasculitis

A Syndrome Involving Small Cerebral Vessels

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Abstract: Primary central nervous system vasculitis (PCNSV) is a rare and poorly understood syndrome. We describe the clinical findings in 8 patients who appear to have a distinct subset of PCNSV. We identified 101 consecutive patients with PCNSV who were seen between January 1, 1983, and December 31, 2003. The diagnosis was based on conventional angiography in 70 patients and on central nervous system biopsy in 31 patients. Six of the 31 patients also had angiograms showing changes of vasculitis. Thus, 76 patients of the cohort had abnormal angiograms. Eight of the 101 patients had normal angiograms ("angiography-negative") but had brain biopsies that showed vasculitis. We compared the clinical and laboratory findings and outcomes of the 8 patients with angiography-negative PCNSV with those of the 76 patients with PCNSV whose angiograms showed evidence of vasculitis ("angiography-positive"). In comparison with the 76 patients with angiography-positive PCNSV, the 8 patients with angiography-negative PCNSV more commonly had 1) a cognitive disorder (87.5% vs. 43.4%; $p = .024$); 2) cerebrospinal fluid abnormalities (a protein level ≥ 700 mg/L or a white blood cell count $\geq 10 \times 10^6$ /L) (100% vs. 35.5%; $p = .034$); and 3) meningeal or parenchymal enhancing lesions on magnetic resonance imaging (75.0% vs. 23.9%; $p = .007$). Other differences between the 2 groups were observed but were not significantly different. All patients with angiography-negative PCNSV responded to treatment and none died. Angiography-negative PCNSV appears to be a distinct subtype of cerebral vasculitis with small vessel involvement beyond the resolution of conventional angiography and is associated with a favorable outcome.

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Abbreviations: CNS = central nervous system, CSF = cerebrospinal fluid, MRI = magnetic resonance imaging, PCNSV = primary central nervous system vasculitis.

INTRODUCTION

Primary central nervous system vasculitis (PCNSV) is an uncommon condition in which vascular inflammatory lesions are limited to the brain and spinal cord^{2,4,13,17}. Brain biopsy provides a definitive diagnosis when results are positive, but obtaining the sample is an invasive process. Therefore, the diagnosis of PCNSV is often based on a cerebral angiogram that shows findings typical of vasculitis, even though angiography is a less specific diagnostic test than biopsy¹¹.

Some investigators have noted that PCNSV is heterogeneous in severity and therapeutic requirements^{3,7,12}. However, because of the lack of uniform diagnostic criteria in various studies and the relatively small number of cases reported, uncertainties exist about the clinical spectrum of PCNSV, the factors that influence its response to treatment, and its long-term outcome.

We recently identified 101 patients with PCNSV seen at Mayo Clinic Rochester over a 21-year period¹⁷. Eight of the 101 patients had a normal conventional angiogram but had a brain biopsy result that was positive for vasculitis. We describe the clinical characteristics of this subset of 8 patients and compare them with the characteristics of 76 other patients with PCNSV who had positive angiograms.

METHODS

Using the Mayo Clinic medical records linkage system and chart reviews, we identified 101 patients with PCNSV who were seen between January 1, 1983, and December 31, 2003. Patients were considered to have definite PCNSV if a recent neurologic deficit occurred that was not explained by other causes and if biopsy of brain or spinal cord showed vasculitis, or if an angiogram showed changes highly suggestive of vasculitis (that is, segmental narrowing, dilatation, or occlusion affecting multiple cerebral arteries in the absence of proximal vessel changes of atherosclerosis)¹⁷. We excluded patients who had vasculitis outside the central nervous system (CNS) and those with evidence of another

disease that might explain the findings, such as systemic lupus erythematosus or an underlying infection.

A standard data collection form was completed for all 101 cases. It included comprehensive information about clinical findings at presentation and during follow-up, laboratory investigations, results of CNS biopsy or autopsy, response to treatment, follow-up functional status, and cause of death. To assess treatment, we used the treating physician's global opinion about the patient's response to therapy.

The modified Rankin Scale was used to evaluate functional status at presentation and at the latest visit¹⁹. A standardized and commonly used scale, it measures disability or dependence in activities of daily living in stroke victims. The scale consists of 7 scores: 0 corresponds to no signs or symptoms; 1, no significant disability, despite symptoms; 2, slight disability; 3, moderate disability; 4, moderately severe disability; 5, severe disability; and 6, stroke death.

Vasculitis was found in 31 (63%) of 49 CNS tissue specimens taken for diagnosis. A granulomatous inflammatory histologic pattern was found in 18 patients (accompanied by vascular deposits of amyloid β peptide in 8), a lymphocytic pattern in 8, and an acute necrotizing pattern in 5.

Changes of vasculitis were found in 76 (90%) of 84 angiograms. Angiograms alone were used to confirm the diagnosis in 70 patients but were also positive in 6 additional patients whose brain biopsy showed vasculitis. Eight patients were observed whose angiograms were negative but who had positive findings on brain biopsy, suggesting involvement of small cerebral vessels that were below the resolution

of conventional angiography. We compared clinical and laboratory findings in these 8 patients with those of the 76 patients who had angiography results that were positive for vasculitis ("angiography-positive").

Statistical Analysis

Differences between the patients with small vessel disease and those with angiography-positive PCNSV were tested with 2-sided Wilcoxon rank sum tests for numeric characteristics and Fisher exact tests for categorical characteristics.

RESULTS

Demographic and Clinical Features

The demographic characteristics and clinical symptoms of the 8 patients who had PCNSV with negative angiography results ("angiography-negative") are compared in Table 1 with those of the other 76 patients in the cohort who had angiography-positive PCNSV and are summarized individually in Table 2. Of the 8 patients, 4 were men. The median age at diagnosis was 55.5 years (range, 26–75 yr). The time from onset of symptoms to diagnosis was less than 1 month in only 1 of the 8 patients (median, 76 d; range, 17–342 d). Focal neurologic manifestations, headache, and presence of a cognitive disorder were the most common symptoms at presentation. One patient had mild left hemiparesis and 2 transient ischemic attacks. No focal cerebral manifestations occurred later in the disease course of this patient. Four patients had a rapid and dramatic cognitive decline: 1 patient had a sudden change in level of consciousness; in the other

TABLE 1. Clinical Features of 8 Patients With Angiography-Negative PCNSV and 76 Patients With Angiography-Positive PCNSV

Feature	Angiography-Negative PCNSV* (n = 8)	Angiography-Positive PCNSV* (n = 76)	p Value
Male:female ratio	4:4 (50:50)	29:47 (38.2:61.8)	.706
Age at diagnosis, yr	55.5 (26.0–75.0)	46.0 (17.0–81.0)	.697
Period from symptom onset to diagnosis, d	76.0 (17.0–342.0)	39.0 (2.0–1913.0)	.184
Headache	5 (62.5)	52 (68.4)	.708
Cognitive disorder	7 (87.5)	33 (43.4)	.024
Focal manifestations	8 (100)	75 (98.7)	1.000
Intracerebral hemorrhage	0 (0)	6 (7.9)	1.000
Systemic manifestations [†]	3 (37.5)	9 (11.8)	.083
CSF abnormality			
Protein ≥ 450 mg/L or WBC $\geq 5 \times 10^6$ /L	7 (100) [‡]	35 (46)	.096
Protein ≥ 700 mg/L or WBC $\geq 10 \times 10^6$ /L	7 (100) [‡]	27 (36)	.034
ESR, mm/h	5.0 (1.0–110.0)	10.0 (1.0–107.0)	.481
Modified Rankin Scale score at latest follow-up			
0–3	8 (100)	60 (78.9)	.343
4–6	0 (0)	16 (21.1)	
Patients who were free of relapse or recurrence	4 (50.0)	58 (76.3)	.197

Abbreviations: ESR = erythrocyte sedimentation rate, WBC = white blood cell.

*Categorical data are expressed as number and percentage of patients; continuous data are expressed as median and range.

[†]Presence of at least 1 of the following systemic manifestations: fatigue, anorexia, weight loss, fever.

[‡]CSF findings recorded in 7 of the 8 patients.

TABLE 2. Clinical Characteristics and MRI Findings at Presentation of 8 Patients With Angiography-Negative PCNSV

Patient	Age/ Sex (yr)	Clinical Characteristic	Brain MRI Finding	Time From Onset of Symptoms to Diagnosis
1	51/F	Confusion, rapid cognitive decline, personality change, mild left hemiparesis, aphasia	Multiple infarcts in central gray matter of both cerebral hemispheres, involving predominantly the heads of the caudate, as well as portions of the lentiform, nucleus on the left; extensive punctate and confluent areas of increased T2 signal intensity in the periventricular and subcortical white matter tracts of both cerebral hemispheres; no white matter lesion enhancement noted	2 mo
2	75/M	Subacute dementia, personality change, focal TIAs, aphasia	Small subcortical infarcts; several foci of nodular enhancement in the sulci or adjacent cortex; sulcal effacement most prominent in the left frontal lobe associated with T2 hyperintensity in the sulci of the left frontal, bilateral posterior temporal, bilateral parietal, and bilateral occipital regions on FLAIR images; subtle T1 hyperintensity in left frontal lobe in the sulci or adjacent cortex on T1-weighted sagittal images; generalized prominence of vessels within these abnormal sulci in both hemispheres on T1-weighted images after contrast medium	2 mo
3	30/M	Headache, confusion	Gadolinium-enhancing mass in the deep white matter of the right posterior frontoparietal region	2 mo
4	31/F	Sudden drowsiness at onset, confusion, cognitive decline, personality change (behavior like a baby), fatigue, headache, aphasia	Diffuse decreased attenuation and increased T2 signal in the white matter of both cerebral hemispheres and confluent T2 signal abnormality extending from subcortical to subependymal white matter; diffuse small nodular foci of contrast enhancement arranged in beadlike radial strands from subependymal to subcortical regions; changes more marked in frontal and parietal lobes	5 mo
5	63/F	Confusion, cognitive decline, headache, aphasia, visual field defect	Diffuse leptomeningeal enhancement over left cerebral hemisphere and right frontal and temporal regions	17 d
6	26/M	Ataxia, diplopia, nystagmus, fever (37.7 °C), vertigo, dizziness, nausea, vomiting	Increased T2 signal in left midline cerebellar area and brainstem; no abnormal meningeal or parenchymal enhancement	11.5 mo
7	62/F	Confusion, focal TIAs, headache, fatigue, anorexia, weight loss	Area of abnormal T2 signal in anterior right centrum semiovale and extending inferiorly to involve the right basal ganglia; linear areas of enhancement that converge adjacent to body of right lateral ventricle in T2 abnormality	8 mo
8	64/M	Confusion, rapid cognitive decline, personality change, headache, ataxia	Diffuse leptomeningeal enhancement involving both cerebral hemispheres and cerebellum; multiple infarcts, patchy T2 abnormality of white matter	1.5 mo

Abbreviations: FLAIR = fluid-attenuated inversion recovery, TIA = transient ischemic attack.

3 patients, the cognitive impairment was indolently progressive. Constitutional symptoms of anorexia with weight loss, fatigue, or fever, or a combination, were present in 3

patients. Symptoms related to spinal cord involvement occurred in 1 patient (Patient 3) at 19 months after symptomatic brain involvement.

Other medical disorders were noted in 3 patients, including hypothyroidism (2 patients) and Graves ophthalmopathy (1 patient).

Laboratory Investigations

Laboratory and pathology results at diagnosis are shown in Tables 1 and 3. The erythrocyte sedimentation rate was normal in 7 of the 8 patients (median, 5 mm/h; range, 1–110 mm/h), and cerebrospinal fluid (CSF) examination findings were abnormal in all 7 patients who had a spinal tap. All 7 had a CSF protein level that was elevated above 700 mg/L (median, 1180 mg/L; range, 720–5730 mg/L). Of these 7 patients, 6 had an elevated CSF white blood cell count of $10 \times 10^6/L$ or more (median, $20 \times 10^6/L$; range, $2\text{--}405 \times 10^6/L$). Lymphocytes were prevalent.

Radiology Results

As noted, results of conventional cerebral angiography were negative in all 8 patients. Brain magnetic resonance angiography was performed in 4 patients and showed no evidence of vasculitis.

Brain magnetic resonance imaging (MRI) at presentation with and without contrast medium was abnormal in all 8 patients (Tables 2 and 4). Patchy or confluent T2 abnormalities were present in the T2-weighted images of 6 patients. Enhancing lesions were observed in 6 patients: 2 patients had prominent and diffuse leptomeningeal enhancement, 3 patients had multiple punctate or linear parenchymal enhancing lesions, or both, and 1 patient had evidence of

an enhancing mass in the deep white matter. Evidence of multiple infarcts was observed in 3 patients. No patients had intracerebral hemorrhage.

Biopsy Results

Five open and 3 stereotactic brain biopsies were performed (see Table 3), and all showed evidence of vasculitis. In 5 patients, inflammatory infiltration showed a granulomatous pattern (Figure 1); in 2 patients, a lymphocytic pattern; and in 1 patient, a necrotizing pattern.

The inflammation was mainly angiocentric in 7 patients and was also perivascular and parenchymal in 1 patient. In 3 patients, leptomeningeal and parenchymal vessel involvement was observed; in 2, only leptomeningeal vessels were involved; and in 3, only parenchymal vessels were involved. In 3 patients, vascular deposits of amyloid, with deposition of amyloid β peptide, were present. Evidence of ischemic changes or infarcts was present in 3 patients.

Treatment and Outcome

The details of treatment, follow-up MRI, and the status of patients at their last visit are shown in Table 5. The median duration of follow-up was 19.5 months (range, 7–105 mo). All patients were treated with prednisone. The median starting dosage of oral prednisone therapy was 60 mg/d (range, 30–80 mg/d). In 2 patients (Patients 2, 4), oral prednisone treatment was preceded by methylprednisolone pulse therapy (1 g/d intravenously for 3 d in Patient 2

TABLE 3. Laboratory and Pathology Results in 8 Patients With Small Vessel PCNSV

Patient	CSF			Pathology
	WBC (cells $\times 10^6/L$)	Protein (mg/L)	ESR (mm/h)	
1	12 (92% lymphocytes, 8% monocytes)	720	110	Stereotactic brain biopsy: granulomatous leptomeningeal, angiocentric inflammation
2	20 (95% lymphocytes, 5% monocytes)	1180	17	Open brain biopsy: granulomatous leptomeningeal, marked angiocentric inflammation; β amyloid deposits
3	NA	NA	2	Stereotactic brain biopsy: necrotizing intraparenchymal, marked angiocentric inflammation associated with multiple acute/subacute infarcts
4	14 (73% lymphocytes, 15% neutrophils, 12% monocytes)	1290	5	Open brain biopsy: granulomatous intraparenchymal, marked angiocentric inflammation
5	68 (78% lymphocytes, 17% monocytes, 5% neutrophils)	5730	25	Open brain biopsy: granulomatous leptomeningeal and intraparenchymal, marked angiocentric inflammation; β amyloid deposits
6	2 (65% lymphocytes, 19% monocytes, 16% neutrophils)	830	1	Stereotactic brain biopsy: lymphocytic intraparenchymal, marked angiocentric inflammation; presence of infarcts
7	405 (95% lymphocytes, 5% monocytes)	1990	9	Open brain biopsy: lymphocytic leptomeningeal and intraparenchymal, perivascular and parenchymal inflammation
8	23 (90% lymphocytes, 10% monocytes)	970	2	Open brain biopsy: granulomatous leptomeningeal and intraparenchymal, marked angiocentric inflammation; β amyloid deposits; presence of infarct

Abbreviation: NA = not available.

TABLE 4. Treatment and Diagnostic Findings in 8 Patients With Angiography-Negative PCNSV and 76 Patients With Angiography-Positive PCNSV

Treatment, Finding*	Angiography-Negative PCNSV (n = 8)	Angiography-Positive PCNSV (n = 76)	p Value
Initial treatment			
Prednisone alone	6 (75)	33 (44)	.143 [†]
Prednisone and cyclophosphamide (oral/pulse)	2 (25)	37 (49)	
Prednisone and azathioprine	0 (0)	3 (4)	
Cyclophosphamide oral alone	0 (0)	2 (3)	
None	0 (0)	1 (1)	
Duration of therapy, mo			
Prednisone	12.5 (2.0–100)	10.0 (1.0–44.0)	.558
Cyclophosphamide	6.0 (3.0–91.0)	10.0 (1.0–25.0)	.623
Patients not taking therapy at latest follow-up	0 (0)	23 (31) [‡]	.099
Brain biopsy pattern			
Lymphocytic	2 (25)	1 (20)	1.000
Granulomatous	5 (63)	4 (80)	
Necrotizing only	1 (13)	0 (0)	
CNS specimens with amyloid angiopathy	3 (38)	3 (13) [§]	.161
MRI findings			
Minimal/age-consistent white matter changes	0 (0)	2 (3) [¶]	1.000
Presence of infarct	3 (38)	42 (63) [¶]	.254
Intracerebral hemorrhage	0 (0)	5 (8) [¶]	1.000
Gadolinium-enhancing lesions (intracerebral or meningeal)	6 (75)	16 (24) [¶]	.007
Gadolinium-enhancing lesions (intracerebral)	4 (50)	14 (21) [¶]	.088
Gadolinium-enhancing lesions (meningeal)	2 (25)	3 (5) [¶]	.085

*Categorical data are expressed as number and percentage of patients; continuous data are expressed as median and range.

[†]Comparison of patients receiving therapy with any immunosuppressive agent and patients receiving therapy with prednisone alone.

[‡]A total of 75 patients were considered because 1 patient had no therapy.

[§]CNS specimens were available for 23 patients.

[¶]A subset of 67 patients underwent MRI.

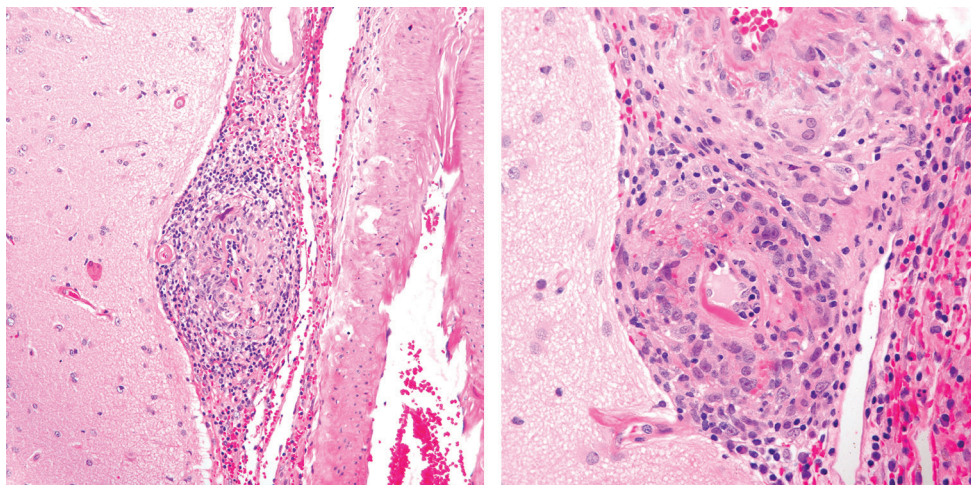


FIGURE 1. Photomicrograph of brain specimen including cortex and leptomeninges. *Left*, Small vessel with granulomatous vasculitis (hematoxylin-eosin; original magnification $\times 100$). Normal small muscular artery is to right of involved vessel. *Right*, Granulomatous character of inflamed vessel, with vessel wall destruction (hematoxylin-eosin; original magnification $\times 400$).

TABLE 5. Treatment, Outcome, and Follow-Up Duration in 8 Patients With Angiography-Negative PCNSV

Patient	Treatment	Follow-Up MRI	At Latest Follow-Up		Follow-Up Period [†] (mo)
			Status	MRS*	
1	Prednisone (initial dosage, 50 mg/d) × 6 mo and oral cyclophosphamide (100 mg/d) × 6 mo	Cystic degeneration of some older infarcts; extensive increased T2 signal was unchanged in the region of the centrum semiovale and subcortical white matter throughout entire cerebrum	Improved	1	8
2	Methylprednisolone (1 g/d IV) × 3 d, then oral prednisone (initial dosage, 60 mg/d) × 4 mo	NA	Stable	3	7
3	Dexamethasone (24 mg/d IV) × 7 d, then oral prednisone (60 mg/d, reduced to 5 mg/d) × 16 mo and cyclophosphamide (1 g/mo IV) × 5 mo Treatment of relapse: Methylprednisolone (1 g/d IV) × 4 d, then oral prednisone (60 mg/d) and oral cyclophosphamide (125 mg/d) × 1 mo	NA	Improved	1	19
4	Methylprednisolone (1 g/d IV) × 5 d, then oral prednisone (initial dosage, 60 mg/d) × 100 mo and cyclophosphamide (initial dosage, 150 mg/d) × 91 mo	Resolution of extensive punctuate foci of contrast enhancement, no significant changes in the confluent area of increased T2 signal in the white matter of both hemispheres	Improved	2	105
5	Prednisone (initial dosage, 80 mg/d) × 13 mo	Resolution of leptomeningeal enhancement	Improved	1	87
6	Prednisone (initial dosage, 40 mg/d) × 15 mo, cyclophosphamide (500 mg/mo IV) × 3 mo, and methylprednisolone (1 g/d IV) × 4 d	NA	Stable	2	26
7	Prednisone (initial dosage, 60 mg/d) × 12 mo	Resolution of enhancing lesions	Improved	0	20
8	Prednisone (initial dosage, 30 mg/d) × 2 mo, cyclophosphamide (1.7 g/mo IV) × 14 mo	Resolution of leptomeningeal enhancement; absence of new, recent infarcts	Improved	1	15

Abbreviations: IV = intravenous, MRS = modified Rankin Scale score.

*0, no symptoms; 1, no significant disability, despite symptoms; 2, slight disability; 3, moderate disability; 4, moderately severe disability; 5, severe disability; 6, stroke death.

[†]From the onset of symptoms.

and for 5 d in Patient 4); in 1 patient (Patient 3), it was preceded by dexamethasone pulse therapy (24 mg/d intravenously for 7 d). Additionally, 2 other patients (Patients 3, 6) received methylprednisolone pulse therapy (1 g/d intravenously for 4 d) for a relapse. The median duration of oral prednisone therapy was 12.5 months (range, 2–100 mo).

Initial treatment in 6 patients (Patients 2, 3, 4, 5, 6, 7) was corticosteroid therapy alone. In 2 patients (Patients 1, 8), initial treatment was prednisone plus cyclophosphamide therapy. Three patients (Patients 3, 4, 6) were treated with prednisone and cyclophosphamide for a relapse. In the overall disease course, 2 patients (Patients 6, 8) received monthly pulse intravenous injections of cyclophosphamide, 2 patients (Patients 1, 4) received daily oral cyclophosphamide, and 1 patient (Patient 3) received both monthly intravenous cyclophosphamide pulse therapy and daily oral cyclophosphamide at different times during the disease

course. The median duration of cyclophosphamide treatment was 6 months (range, 3–91 mo).

Of the 8 patients, 4 (Patients 3, 4, 5, 6) had a relapse. Patient 3 was initially treated with dexamethasone pulse therapy, oral prednisone, and monthly pulse intravenous cyclophosphamide injections for neurologic symptoms related to vasculitic involvement of the brain. His condition dramatically improved, and 3 months later, his neurologic examination was normal. However, 13 months later—while he was taking prednisone (5 mg/d)—he had a relapse involving the spinal cord. The patient was treated with methylprednisolone pulse therapy, oral prednisone, and oral cyclophosphamide and had partial improvement in his neurologic status during the 1-month follow-up period.

Patient 4 had a relapse as her oral prednisone dosage was being reduced after 4 months of treatment. Oral cyclophosphamide was added to the prednisone. However,

she was unable to decrease her prednisone dosage to less than 20 mg/d because of a relapsing course of the disease (4 other relapses) during the 9-year follow-up period. In all the relapses, an increased dosage of oral prednisone resulted in rapid improvement of neurologic status.

Patient 5, initially treated with prednisone, had a recurrence characterized by headache, confusion, and expressive aphasia 6 years after suspension of therapy. At the recurrence, results of brain MRI showed the reappearance of meningeal enhancement. She was treated again with prednisone alone and had complete remission on the basis of neurologic and MRI findings.

Patient 6 initially received prednisone and monthly pulse intravenous injections of cyclophosphamide. The cyclophosphamide therapy was stopped after the third injection because of improvement in his neurologic status. Nine months later, however, he had a relapse characterized by the reappearance of diplopia, dizziness, nausea, and vomiting. Pulse glucocorticoid therapy (1 g/d of methylprednisolone) was given for 4 days, after which the oral prednisone dosage was increased to 60 mg/d. His neurologic status improved dramatically within days.

In summary, all 8 patients responded well to therapy. Response was rapid and generally noted in the first 2–3 weeks of treatment. A rapid response was also noted in the 4 patients who had relapses. Follow-up MRI studies were available in 5 patients, and gadolinium enhancement was no longer detectable after therapy. In 2 patients, the extensive areas detected on T2-weighted imaging did not change. Outcome was favorable in all patients. No patients had permanent major neurologic dysfunction. Five patients had total or nearly total recovery, and 3 patients had recovery with residual disability that was slight or moderate. The median modified Rankin Scale score at the latest visit was 1 (range, 0–3), compared with the median value of 2 (range, 1–4) at presentation. No deaths occurred.

Comparison of Angiography-Negative and Angiography-Positive PCNSV

The 8 cases of angiography-negative PCNSV are compared with the 76 cases of angiography-positive PCNSV in Tables 1 and 4. The comparison showed that the presence of a cognitive disorder (87.5% vs. 43.4%; $p = .024$), CSF abnormalities (a protein level ≥ 700 mg/L or a white blood cell count $\geq 10 \times 10^6/L$) (100% vs. 35.5%; $p = .034$), and gadolinium-enhancing lesions (75.0% vs. 23.9%; $p = .007$) were significantly more frequent in patients with angiography-negative PCNSV than in the others. Parenchymal and meningeal gadolinium-enhancing lesions were also more frequently seen in the patients with angiography-negative PCNSV. Prominent leptomeningeal enhancement and parenchymal multiple punctate areas of gadolinium enhancement were observed only in patients with small vessel PCNSV.

Patients with angiography-negative PCNSV had a greater median age at diagnosis. They had a less acute clinical onset and a higher median period from onset of symptoms to diagnosis, and they more frequently had constitutional symptoms at diagnosis. However, these differences were not significant. In addition, they were more often

treated initially with glucocorticoid therapy alone and less often in combination with cyclophosphamide.

Although none of the 8 with angiography-negative PCNSV had severe disability or died during follow-up, relapses were common, and all of them were receiving therapy at latest follow-up.

DISCUSSION

In our analysis of 101 patients with PCNSV who were seen at our institution over 21 years¹⁷, we noted that 8 patients whose brain biopsy findings showed vasculitis had normal angiograms. We assume that these 8 had involvement only of small cerebral vessels that were below the resolution of conventional angiography. To determine whether the 8 patients had clinical characteristics different from those of other patients with PCNSV, we compared them with 76 patients who had angiography-positive PCNSV—that is, the patients with inflammation in vessels that were large enough to be visualized on angiography. Although the findings in the 8 patients were not identical, there were sufficient similarities among these 8 cases to suggest that they represent a recognizable subgroup in the spectrum of PCNSV.

The prominent clinical feature of the 8 cases with small vessel PCNSV was the presence of cognitive dysfunction that was significantly more frequent in these patients than in the 76 patients with angiography-positive PCNSV. In most of the 8 cases, the cognitive impairment was rapid and dramatic.

Although the 8 patients with angiography-negative PCNSV had a higher frequency of systemic manifestations, erythrocyte sedimentation rates were normal in 7 patients and were not useful in differentiating them from the other 76 patients. CSF abnormalities were significantly more marked in patients with angiography-negative PCNSV. In particular, they presented a striking elevation in median total protein level (median, 1180 mg/dL; range, 720–5730 mg/dL), which was also higher than the median value reported in our total cohort of 101 patients (median, 72 mg/dL; range, 15–1034 mg/dL)¹⁷. This marked elevation in total protein level may reflect a more diffuse nature in the intracranial inflammatory processes and provides evidence that these patients may represent a relatively homogeneous disease subset.

MRI results were abnormal in all patients with angiography-negative PCNSV^{5,10}. Meningeal and parenchymal enhancement was observed significantly more often in the 8 patients with angiography-negative disease than in those with angiography-positive PCNSV. Leptomeningeal enhancement was present in 2 of the 8 and has been previously described in several reports^{8,9,14,16}.

Gadolinium enhancement of parenchymal multiple punctate areas or linear areas, or both, represents a different pattern of enhancement that was observed in 3 of our patients (Patients 2, 4, 7). To our knowledge, this pattern has been previously reported in only 1 patient with histologic evidence of PCNSV in whom, as in our cases, angiography results were negative for vasculitis¹⁸. This pattern of enhancement is probably due to a combination of vascular

and perivascular inflammatory changes that include the meninges and surrounding gray and white matter. Some investigators have suggested that this “perivascular” type of enhancement, although unusual, could be specific to PCNSV⁵. In the current study, Patient 3 had evidence of a gadolinium-enhancing mass in the deep white matter. The brain biopsy performed to evaluate for a neoplastic condition unexpectedly revealed PCNSV. Duna et al⁶, in their review of published analyses, observed that in 15% of the reported PCNSV cases, patients had a mass lesion at presentation. Such gadolinium-enhancing lesions on MRI are not specific for vasculitis.

Although the clinical findings in the 8 patients with angiography-negative PCNSV were similar, the histologic pattern found on brain biopsy was not uniform. Granulomatous inflammatory pattern was prevalent and seen in 5 of the 8 patients; however, lymphocytic and acute necrotizing patterns were also observed. In 5 patients, biopsy samples showed evidence of vasculitis in leptomeningeal vessels (in 2 patients, only leptomeningeal vessels were involved). An optimal biopsy should include adequate samples of dura, leptomeninges, cortex, and white matter¹⁵.

The published findings on the therapy response and outcome of PCNSV are varied. Earlier reports considered PCNSV a progressive CNS disorder that had a fatal course unless it was treated vigorously with glucocorticoids and immunosuppressive agents^{2,4,13}. More recent case reports have indicated subsets of patients with different prognoses and treatment requirements^{3,7,12}. In our cohort of 101 patients with PCNSV, we found a favorable response to glucocorticoids both alone and in conjunction with cyclophosphamide in most patients¹⁷.

Patients with angiography-negative PCNSV appeared to have a more relapsing, benign disease than patients who had angiography-positive PCNSV. Although they had more relapses, they were less frequently treated initially with immunosuppressive agents. MacLaren and colleagues¹² also noted more frequent relapses in patients they designated as having small vessel disease. However, of the 12 patients they studied, only 1 of the 6 cases of small vessel PCNSV had brain biopsy results that confirmed the diagnosis.

In 2005, Benseler and coworkers¹ reported on 4 children with angiography-negative, biopsy-confirmed small vessel PCNSV that they considered a new disease entity belonging to the spectrum of childhood PCNSV. Neurocognitive dysfunction was the most frequent neurologic deficit at diagnosis, CSF abnormalities were present in all patients, and immunosuppressive therapy led to an excellent neurologic outcome. A lymphocytic vasculitis of the small arterial vessels was the histologic finding observed on brain biopsy in the 4 children. Although the histologic pattern was different from the one we observed, the pediatric and our adult forms of angiography-negative PCNSV had similar clinical findings.

The identification of 8 patients with angiography-negative PCNSV in our consecutive series of 101 cases diagnosed by predefined criteria provides an estimate of the relative frequency of this subset. However, the retrospective nature of our larger series with the potential for referral bias is a limitation.

In conclusion, we describe a group of patients with PCNSV whose angiograms were normal but findings on brain biopsy were positive. These findings suggest that the vasculitis was limited to small vessels beyond the resolution of conventional angiography. These patients had the following characteristics more frequently than patients with angiography-positive PCNSV: 1) cognitive dysfunction at presentation; 2) greater CSF abnormalities, in particular a marked elevation in total protein level; and 3) meningeal or parenchymal enhancing lesions present at MRI.

REFERENCES

- Benseler SM, deVeber G, Hawkins C, Schneider R, Tyrell PN, Aviv RI, Armstrong D, Laxer RM, Silverman ED. Angiography-negative primary central nervous system vasculitis in children: a newly recognized inflammatory central nervous system disease. *Arthritis Rheum.* 2005;52:2159–2167.
- Calabrese LH, Duna GF, Lie JT. Vasculitis in the central nervous system. *Arthritis Rheum.* 1997;40:1189–1201.
- Calabrese LH, Gragg LA, Furlan AJ. Benign angiopathy: a distinct subset of angiographically defined primary angitis of the central nervous system. *J Rheumatol.* 1993;20:2046–2050.
- Calabrese LH, Mallek JA. Primary angitis of the central nervous system: report of 8 new cases, review of the literature, and proposal for diagnostic criteria. *Medicine (Baltimore).* 1988;67:20–39.
- Cloft HJ, Phillips CD, Dix JE, McNulty BC, Zagardo MT, Kallmes DF. Correlation of angiography and MR imaging in cerebral vasculitis. *Acta Radiol.* 1999;40:83–87.
- Duna GF, George T, Rybicki L, Calabrese LH. Primary angitis of the central nervous system (PACNS): an analysis of unusual presentations. *Arthritis Rheum.* 1995;38:S340.
- Hajj-Ali RA, Furlan A, Abou-Chebel A, Calabrese LH. Benign angiopathy of the central nervous system: cohort of 16 patients with clinical course and long-term follow-up. *Arthritis Rheum.* 2002; 47:662–669.
- Harris KG, Tran DD, Sickels WJ, Cornell SH, Yuh WT. Diagnosing intracranial vasculitis: the roles of MR and angiography. *AJNR Am J Neuroradiol.* 1994;15:317–330.
- Hassan AS, Trobe JD, McKeever PE, Gebarski SS. Linear magnetic resonance enhancement and optic neuropathy in primary angitis of the central nervous system. *J Neuroophthalmol.* 2003;23:127–131.
- Hurst RW, Grossman RI. Neuroradiology of central nervous system vasculitis. *Semin Neurol.* 1994;14:320–340.
- Kadkhodayan Y, Alreshaid A, Moran CJ, Cross DT III, Powers WJ, Derdeyn CP. Primary angitis of the central nervous system at conventional angiography. *Radiology.* 2004;233:878–882.
- MacLaren K, Gillespie J, Shrestha S, Neary D, Ballardie FW. Primary angitis of the central nervous system: emerging variants. *QJM.* 2005;98:643–654.
- Moore PM. Diagnosis and management of isolated angitis of the central nervous system. *Neurology.* 1989;39:167–173.
- Negishi C, Sze G. Vasculitis presenting as primary leptomeningeal enhancement with minimal parenchymal findings. *AJNR Am J Neuroradiol.* 1993;14:26–28.
- Parisi JE, Moore PM. The role of biopsy in vasculitis of the central nervous system. *Semin Neurol.* 1994;14:341–348.
- Rucker JC, Biousse V, Newman NJ. Leptomeningeal enhancement and venous abnormalities in granulomatous angitis of the central nervous system. *J Neuroophthalmol.* 2003;23:148–150.
- Salvarani C, Brown RD Jr, Calamia K, Christianson TJH, Weigand SD, Miller DV, Giannini C, Meschia JF, Huston J III, Hunder GG. Primary central nervous system vasculitis: analysis of 101 cases. *Ann Neurol.* 2007;62:442–451.
- Shoemaker EI, Lin ZS, Rae-Grant AD, Little B. Primary angitis of the central nervous system: unusual MR appearance. *AJNR Am J Neuroradiol.* 1994;15:331–334.
- Sulter G, Steen C, De Keyser J. Use of the Barthel Index and modified Rankin Scale in acute stroke trials. *Stroke.* 1999;30:1538–1541.