Primary central nervous system vasculitis: comparison of patients with and without cerebral amyloid angiopathy


Objectives. To describe the clinical features and outcomes of patients with primary central nervous system vasculitis (PCNSV) and cerebral amyloid angiopathy (CAA) from a large cohort of consecutive patients with PCNSV treated at a single institution.

Methods. We identified 101 consecutive patients with PCNSV admitted between January 1983 and December 2003. PCNSV diagnoses were based on findings from a central nervous system (CNS) biopsy (n=31) and conventional angiography (n=70). CNS tissue specimens from 49 cases were examined histologically, and 49 were stained for amyloid deposits. Those with vascular amyloid deposits (CAA) were compared with those without histological evidence of amyloid deposition.

Results. Eight cases (26%) with CNS biopsy specimens positive for PCNSV also showed findings of CAA. Compared with patients with PCNSV only, these patients were older at diagnosis, predominantly male, had a more acute onset, a higher frequency of cognitive dysfunction and showed prominent gadolinium-enhanced leptomeningeal lesions with MRI. Histologically, all had a granulomatous vascular inflammatory pattern. Six patients responded promptly to therapy. Outcomes at last follow-up were similar in the two groups.

Conclusions. PCNSV with CAA appears to form a clinical subset of PCNSV. The vasculitis influences the clinical findings to a greater degree than the presence of amyloid deposits in the vessels.

KEY WORDS: Cerebral amyloid angiopathy, Cerebral angiography, Cerebral biopsy, Primary central nervous system vasculitis, Therapy.

Introduction

Primary central nervous system vasculitis (PCNSV) is an uncommon condition in which vascular inflammatory lesions are limited to the brain and spinal cord [1–4]. Diagnostic criteria include a newly acquired neurological deficit that is unexplained by other processes and angiographic or central nervous system (CNS) biopsy features of vasculitis [2]. Cerebral amyloid angiopathy (CAA) is a disorder characterized by the deposition of amyloid β (Aβ) peptide in the media and adventitia of small- to medium-sized arteries in the cerebral cortex and leptomeninges [5–9]. Deposition may lead to vessel fragility, rupture and subsequent intracerebral haemorrhage [5, 6], or it may cause generalized symptoms such as cognitive impairment [7, 8]. Although vascular inflammation generally is not observed in CAA, coexistence of sporadic CAA and PCNSV has been reported [10–13]. Causal relationships between CAA and vasculitis have not been determined.

Recently, Scolding and coworkers [13] suggested that Aβ-related PCNSV was a distinct clinicopathological entity; they termed it ‘Aβ-related angiitis.’ Their conclusions were based on the combined findings of nine new cases and individual case reports already in the medical literature. Because of the relatively small number of cases studied and the lack of follow-up, the clinical spectrum of Aβ-related PCNSV, its response to treatment and its long-term outcome is still uncertain.

We recently reviewed the medical records of 101 patients with PCNSV at Mayo Clinic (Rochester, MN) over a 21-yr period [4]. CNS biopsies showed the presence of vasculitis in 31 patients.

In this report, we describe the clinical characteristics of a subset of 8 of the 31 biopsy-positive patients who also had vascular deposits of β-amyloid peptide that were consistent with CAA.

Patients and methods

Patients

We used the Mayo Clinic medical records linkage system to obtain a list of all patients with a possible diagnosis of CNS vasculitis between 1 January 1983 and 31 December 2003 [4]. Patients were given a diagnosis of PCNSV if a brain or spinal cord biopsy specimen showed vasculitis (transmural destructive inflammatory infiltrate) or if angiograms showed changes that were highly suggestive of vasculitis (segmental narrowing, dilatation or occlusion affecting multiple cerebral arteries in the absence of proximal vessel changes of atherosclerosis). We excluded patients with vasculitis in organs other than the CNS and those with evidence of other diseases such as SLE and infection. During the period reviewed, 101 patients at Mayo Clinic (Rochester, MN, USA) fulfilled the diagnostic criteria for PCNSV [4]. The Mayo Clinic Institutional Review Board approved this study.

Biopsy specimens were reviewed by two pathologists (D.V.M. and C.G.), and angiograms were reviewed by a neuroradiologist. In cases with an uncertain initial diagnosis, the complete medical record was reviewed again by two rheumatologists (C.S. and G.G.H.) and one neurologist (R.D.B.) to reach a consensus. A standard data collection form was completed for all cases and included information about clinical manifestations at presentation and during follow-up, other medical conditions, findings from laboratory investigations and radiological imaging, response to treatment, number of relapses, follow-up functional status and cause of death. To assess the effect of treatment, we used the treating physician’s global opinion about the response to therapy.

The modified Rankin scale [14] was used to evaluate the functional status at presentation and at the last visit. It is a standardized and commonly used method of evaluating stroke victims by measuring disability or dependence in activities of daily living. The scale consists of seven grades: 0 indicates no signs or symptoms of disability; 1 indicates no significant disability, despite symptoms; 2 indicates slight disability; 3 indicates
intracerebral haemorrhage. Conventional cerebral angiography was performed in five patients, and features of vasculitis were present in two. Brain magnetic resonance angiography was performed in four patients, but none showed evidence of vasculitis. One patient with positive results after conventional cerebral angiography had negative results with brain magnetic resonance angiography.

**Biopsy results**

The 31 patients with histologically proven PCNSV had the following histological patterns: 18 (58.1%) had a granulomatous inflammatory pattern, 8 (25.8%) had a lymphocytic pattern and 5 (16.1%) had an acute necrotizing pattern.

Table 2 shows the results of pathology examinations in the eight with histologically confirmed PCNSV and vascular deposits of Aβ that were consistent with CAA. A granulomatous vasculitis histological pattern was present in all eight patients (Fig. 1). The vasculitis was characterized by transmural mononuclear inflammation with well-formed granulomas and multinucleated giant cells that resulted in vessel wall destruction. In six patients, leptomeningeal and parenchymal involvement was observed; the other two had only leptomeningeal involvement. Infarcts were present in two patients.

**Treatment and outcome**

Table 3 shows details of treatment, follow-up MRI examinations and patient status at the last visit. The median duration of follow-up was 24 months (range 1.5–112 months). All patients were treated with prednisone. The median initial dosage of oral prednisone was 60 mg/day (range 30–150 mg/day). In three patients (Cases 2, 3 and 8), oral prednisone was preceded by a course of intravenous methylprednisolone pulse therapy (two patients received 1 g/day for 3 days; 1 patient received 500 mg/day for 9 days). The median duration of oral prednisone therapy was 6 months (range 1–19 months). Three patients (Cases 2, 4 and 7) initially were treated with corticosteroids only, and five were treated with prednisone and cyclophosphamide (Cases 1, 3, 5, 6 and 8). One patient (Case 6) received monthly pulse intravenous injections of cyclophosphamide, and four patients (Cases 1, 3, 5 and 8) received daily oral doses of cyclophosphamide. The median duration of treatment with cyclophosphamide was 12 months (range 1–17 months).

Two patients had a relapse. Case 4 was treated with oral prednisone (80 mg/day) and improved rapidly. One month later, her neurological examination findings were normal. Eleven months later, the prednisone therapy was discontinued. Six years later, she had a recurrence that was characterized by headache, confusion and expressive aphasia. At the time of recurrence, an MRI examination of the brain showed reappearance of contrast-enhanced meningeal lesions. She was treated again with prednisone (60 mg/day) and was in complete remission 1 month later (neurological and MRI findings were normal).

Case 5 initially was treated with prednisone and cyclophosphamide, and he showed marked improvement in the neurological status during an examination 3 months later. Four months later, prednisone therapy was suspended; 5 months later, his neurological examination showed normal findings, and cyclophosphamide was discontinued at that time. Fourteen months later, he presented with an increased level of confusion. Axial CT images (without contrast enhancement) showed a right-sided frontal intracranial haemorrhage that was considered secondary to CAA. The haematoma was evacuated by craniotomy, and he had a complete neurological recovery. Immunosuppressive therapy was not initiated. Ten months later, his neurological examination had normal findings, and he had no symptoms. At that time, an MRI examination of the brain showed nearly complete resolution of confluent T2-weighted signal abnormalities in the white matter of both cerebral hemispheres. Multiple small deposits of haemosiderin within the
<table>
<thead>
<tr>
<th>Case</th>
<th>Age (yrs)</th>
<th>Sex</th>
<th>Clinical findings</th>
<th>Brain MRI</th>
<th>Cerebral angiography</th>
<th>Brain MRA</th>
<th>Time between symptom onset and diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>66</td>
<td>F</td>
<td>Focal TIA</td>
<td>Haematoma in the inferolateral aspect of the right frontal lobe, multiple zones of ischaemia and secondary haemorrhage of the subcortical white matter of the left frontal lobe and left paracentral gyrus</td>
<td>Subtle areas of bilateral vascular narrowing affecting small branch vessels of the anterior and middle cerebral arteries</td>
<td>Normal</td>
<td>2.5 months</td>
</tr>
<tr>
<td>2</td>
<td>75</td>
<td>M</td>
<td>Subacute dementia, personality change, focal TIA, aphasia</td>
<td>Subcortical infarcts, foci of nodular enhancement present either within the sulci or adjacent cortex</td>
<td>Normal</td>
<td>Not done</td>
<td>2 months</td>
</tr>
<tr>
<td>3</td>
<td>42</td>
<td>M</td>
<td>Headache, paraparesis, sudden change in level of consciousness, aphasia, headache, right homonymous hemianopsia, fever, vomiting</td>
<td>Multiple infarcts involving both cerebral hemispheres and cerebellum</td>
<td>Alternating areas of vasoconstriction and normal-calibre vessels, involving numerous large and medium-sized cerebral arteries</td>
<td>Not done</td>
<td>21 days</td>
</tr>
<tr>
<td>4</td>
<td>63</td>
<td>F</td>
<td>Confusion, cognitive decline, headache, aphasia, visual field defect</td>
<td>Diffuse leptomeningeal enhancement involving the subcortical white matter of both cerebral hemispheres, diffuse leptomeningeal enhancement (greater in the right hemisphere)</td>
<td>Normal</td>
<td>Normal</td>
<td>17 days</td>
</tr>
<tr>
<td>5</td>
<td>60</td>
<td>M</td>
<td>Aphasia with alexia</td>
<td>T₂W signal abnormality involving the subcortical white matter of both cerebral hemispheres, diffuse leptomeningeal enhancement (greater in the right hemisphere)</td>
<td>Not done</td>
<td>Not done</td>
<td>16 days</td>
</tr>
<tr>
<td>6</td>
<td>64</td>
<td>M</td>
<td>Confusion, cognitive decline, personality change, headache, ataxia</td>
<td>Diffuse bilateral leptomeningeal enhancement involving the cerebrum and the cerebellum, multiple infarcts, patchy T₂W white matter signal abnormality</td>
<td>Normal</td>
<td>Not done</td>
<td>1.5 months</td>
</tr>
<tr>
<td>7</td>
<td>57</td>
<td>M</td>
<td>Confusion, cognitive decline, amnestic syndrome, aphasia, headache, papilloedema</td>
<td>Confluent T₂W signal abnormality of the white matter, bilateral linear leptomeningeal enhancement of the cerebral hemispheres, basal ganglia, and pons</td>
<td>Not done</td>
<td>Normal</td>
<td>14 months</td>
</tr>
<tr>
<td>8</td>
<td>84</td>
<td>M</td>
<td>Drowsiness, confusion, cognitive decline, agitated behaviour</td>
<td>Extensive confluent T₂W signal abnormality throughout the frontal and temporal lobes</td>
<td>Not done</td>
<td>Normal</td>
<td>1 month</td>
</tr>
</tbody>
</table>

F: female; M: male; MRA: magnetic resonance angiography; TIA: transient ischaemic attack; W: weighted.
Table 2. Laboratory and pathology findings

<table>
<thead>
<tr>
<th>Case</th>
<th>CSF WBC count (cells/mm³)</th>
<th>Protein (mg/dL)</th>
<th>ESR (mm/h)</th>
<th>Pathology findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(50% lymphocytes, 26% monocytes, 24% neutrophils)</td>
<td>68</td>
<td>77</td>
<td>Granulomatous, leptomeningeal and intraparenchymal marked angiocentric inflammation</td>
</tr>
<tr>
<td>2</td>
<td>(95% lymphocytes, 5% monocytes)</td>
<td>118</td>
<td>25</td>
<td>Granulomatous and leptomeningeal marked angiocentric inflammation</td>
</tr>
</tbody>
</table>
| 3    | (78% lymphocytes, 22% monocytes) | 77 | 11 | First biopsy: multiple infarcts
Second biopsy: granulomatous, leptomeningeal and intraparenchymal marked angiocentric inflammation |
| 4    | (79% lymphocytes, 17% monocytes, 4% neutrophils) | 573 | 22 | Granulomatous, leptomeningeal and intraparenchymal marked angiocentric inflammation |
| 5    | (69% neutrophils, 30% lymphocytes) | 105 | 11 | First biopsy: granulomatous, leptomeningeal and intraparenchymal marked angiocentric inflammation
Second biopsy: same findings |
| 6    | (90% lymphocytes, 10% monocytes) | 97 | 2 | Granulomatous, leptomeningeal and intraparenchymal marked angiocentric inflammation |
| 7    | (96% lymphocytes, 4% monocytes) | 161 | 2 | Granulomatous, leptomeningeal and intraparenchymal marked angiocentric inflammation |
| 8    | (84% lymphocytes, 16% monocytes) | 138 | 22 | Granulomatous, leptomeningeal and intraparenchymal marked angiocentric inflammation |

All biopsy specimens showed Aβ peptide deposits. *All patients underwent an open brain biopsy. CSF: cerebrospinal fluid; WBC: white blood cell.

Discussion

This study was part of an analysis of 101 patients with PCNSV who were seen at our institution over a 21-yr period [4]. We noted that 8 of the 31 patients who had biopsy specimens showing vasculitis also had vascular deposits of Aβ peptide. To determine whether these eight patients had different clinical characteristics, we compared them to 40 other patients with histological specimens that did not show CAA. The median age of patients with CAA was significantly higher at diagnosis (P = 0.002), and gadolinium-enhanced meningeal lesions occurred more frequently (P = 0.05). More patients with CAA showed a granulomatous histopathological pattern (P = 0.01).

Other differences in those with CAA that were not statistically significant included a greater number of men, more acute onset, shorter median period between onset of symptoms to diagnosis, a higher frequency of cognitive disorders at presentation, and fewer relapses or recurrences. More were treated initially with cyclophosphamide or AZA and less frequently with prednisone only. Other similarities between the groups included the Rankin disability score at last follow-up, the therapy duration, and the frequency of patients who had discontinued therapy by the last follow-up visit. Figure 2 shows the similar survival curves of patients with and without CAA (P = 0.60).

Comparison of patients with and without CAA

Table 4 compares the clinical features, treatment, pathology findings and MRI findings of the eight patients with histological evidence of PCNSV and CAA, and the 40 patients with biopsies that did not show CAA. The median age of patients with CAA was significantly higher at diagnosis (P = 0.002), and gadolinium-enhanced meningeal lesions occurred more frequently (P = 0.05). More patients with CAA showed a granulomatous histopathological pattern (P = 0.01).

Other differences in those with CAA that were not statistically significant included a greater number of men, more acute onset, shorter median period between onset of symptoms to diagnosis, a higher frequency of cognitive disorders at presentation, and fewer relapses or recurrences. More were treated initially with cyclophosphamide or AZA and less frequently with prednisone only. Other similarities between the groups included the Rankin disability score at last follow-up, the therapy duration, and the frequency of patients who had discontinued therapy by the last follow-up visit. Figure 2 shows the similar survival curves of patients with and without CAA (P = 0.60).

MRI findings were abnormal in all eight cases of PCNSV with CAA. Findings included infarctions, haemorrhage and gadolinium-enhanced lesions. To further evaluate the possible clinical significance of prominent gadolinium enhancement of the leptomeninges, we have performed a separate analysis of all patients with this finding from the overall cohort of 101 patients [15]. Intracerebral haemorrhage occurred with similar frequencies in both groups.
Like the findings of Scolding et al. [13], our data indicate that the clinical manifestations of PCNSV with CAA more closely resemble those of PCNSV only and are less similar to those of CAA only. Although impaired cognition has been associated with CAA [7, 8], the acute onset, radiological findings and response to immunosuppressive therapy observed in our patients are not typical of sporadic CAA. This suggests that vascular inflammation has a major influence in determining the disease manifestations. The absence of an increased frequency of intracerebral haemorrhage, which frequently is observed in patients with CAA only [5, 6], suggests a less critical role for vascular Aβ deposition in the pathogenesis of this syndrome.

Because reports of Aβ-related PCNSV in the medical literature consist mainly of individual cases, the frequency of vascular deposits of Aβ in PCNSV is uncertain. Our data, derived from the largest cohort reported to date of PCNSV patients from a single institution, showed Aβ peptide deposition in 9 of the 49 patients (18.4%) whose specimens were histologically examined and in 8 of the 31 patients (25.8%) who had biopsy-proven PCNSV. CAA without vasculitis is common in the elderly, and its prevalence increases with age. Evidence of CAA has been identified in 45% of autopsies performed in individuals aged 80–89 yrs, but it was observed in only 4.7–9.0% of autopsies in individuals aged 60–69 yrs [16–19]. At diagnosis, 24 of our 31 patients with

![Fig. 1. Leptomeningeal vasculitis with amyloid angiopathy. (A) Destructive vasculitis with well-formed granulomas involves the small vessels. Others show wall thickening with eosinophilic material (arrows). (Haematoxylin and eosin; × 100.) (B) All vessels show Aβ deposits. (Immunoperoxidase staining for Aβ amyloid; × 100.)](image)

**Table 3.** Treatment, outcome and duration of follow-up

<table>
<thead>
<tr>
<th>Case</th>
<th>Treatment</th>
<th>Follow-up MRI</th>
<th>Status at last follow-up (modified Rankin score)</th>
<th>Follow-up period (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Oral prednisone (initial dosage, 60 mg/day) for 11 months, oral cyclophosphamide (100 mg/day) for 17 months</td>
<td>Partially resolved haematoma, enhancement nearly completely resolved, T2W signal abnormalities involving left frontal lobe and left paracentral gyrus nearly completely resolved</td>
<td>Improved (0)</td>
<td>112</td>
</tr>
<tr>
<td>2</td>
<td>IV methylprednisolone (1 g/day) for 3 days, then oral prednisone (initial dosage, 60 mg/day) for 4 months</td>
<td>Not available</td>
<td>Stable (3)</td>
<td>7</td>
</tr>
<tr>
<td>3</td>
<td>IV methylprednisolone (500 mg/day) for 9 days, then oral prednisone (initial dosage, 150 mg/day) for 1 month, oral cyclophosphamide (150 mg/day) for 1 month</td>
<td>New ischaemic lesions, particularly involving the right frontal lobe and left occipital lobe</td>
<td>Stroke-related fatality (6)</td>
<td>1.5</td>
</tr>
<tr>
<td>4</td>
<td>Oral prednisone (initial dosage, 80 mg/day) for 13 months</td>
<td>Resolution of leptomeningeal enhancement</td>
<td>Improved (1)</td>
<td>87</td>
</tr>
<tr>
<td>5</td>
<td>Oral prednisone (initial dosage, 60 mg/day) for 7 months, oral cyclophosphamide (150 mg/day) for 12 months</td>
<td>Subacute intracerebral haemorrhage in the right frontal lobe, decreased T2W signal abnormality in the white matter of both cerebral hemispheres, multiple small deposits of hemosiderin in the white matter of both cerebral hemispheres and the left cerebellum</td>
<td>Improved (0)</td>
<td>37</td>
</tr>
<tr>
<td>6</td>
<td>Oral prednisone (initial dosage, 30 mg/day) for 2 months, IV cyclophosphamide (1.7 g/month) for 14 months</td>
<td>Resolution of leptomeningeal enhancement, no new infarcts</td>
<td>Improved (1)</td>
<td>15</td>
</tr>
<tr>
<td>7</td>
<td>Oral prednisone (initial dosage, 60 mg/day) for 19 months</td>
<td>Resolution of initial changes</td>
<td>Improved (1)</td>
<td>33</td>
</tr>
<tr>
<td>8</td>
<td>IV methylprednisolone (1 g/day) for 3 days, then oral prednisone (initial dosage, 60 mg/day) for 5 months, oral cyclophosphamide (150 mg/day) for 4 months</td>
<td>Not available</td>
<td>Improved (0)</td>
<td>6</td>
</tr>
</tbody>
</table>

The modified Rankin score is defined as follows: 0: no signs or symptoms of disability; 1: no significant disability, despite symptoms; 2: slight disability; 3: moderate disability; 4: moderately severe disability; 5: severe disability; 6: death. From the onset of symptoms. W, weighted.
Vascular Aβ peptide deposition may trigger a variable inflammatory response. Yamada et al. [20] examined brain specimens of patients with CAA and reported an increased number of perivascular monocytes. However, in most cases, it was so slight that it could be recognized only by immunohistochemical analysis. In a report of 42 cases of pathologically diagnosed CAA, Eng et al. [21] noted seven patients with perivascular inflammation and multinucleated giant cells. This group of seven patients appeared to be pathologically different from our patients, who presented destructive vascular inflammation, and from other patients in published case reports of Aβ-related PCNSV. However, Eng and coworkers’ patients did have a clinical syndrome that resembled PCNSV more than it resembled non-inflammatory CAA. Their patients were younger at presentation when compared with patients with CAA only, the clinical symptoms were subacute cognitive decline or seizure rather than haemorrhagic stroke, and the clinical symptoms and radiological findings improved with immunosuppressive treatment. A variable inflammatory response may account for the clinical features observed in patients with CAA-related PCNSV and CAA-related perivascular inflammation. The inflammatory response to vascular amyloid observed in a transgenic mouse model that develops prominent CAA [22] supports amyloid deposition as the likely trigger of vascular or perivascular inflammation.

The strength of this study was the identification of patients with Aβ-related PCNSV from the largest group of consecutive patients reported to date from a single institution. In this cohort, case ascertainment was well defined and uniform, and clinical follow-up data were available. The retrospective nature of the study and potential selection bias are limitations. By restricting the

histological evidence of PCNSV and five of the eight patients with CAA and PCNSV were younger than 65 yrs. Therefore, the proportion of patients with CAA who were younger than 65 yrs at diagnosis was greater than that observed in general autopsy studies as above (5 of 24; 21%). The median age at diagnosis in our series of patients with PCNSV was 47 yrs [4]. The patients with PCNSV and CAA had an older age at diagnosis (median 63 yrs), but this was considerably lower than that reported for patients with sporadic CAA. The prevalence of CAA observed in our series of PCNSV patients was much higher than we expected, given the age of the patients. This finding strongly argues against the possibility that the association of these two conditions is coincidental.

![Fig. 2. Survival of patients with PCNSV, with and without CAA. Both groups had similar survival curves (P = 0.60).](image)
The present study to cases with pathology samples, we also may have introduced a potential bias towards selection of patients with atypical clinical presentations or more severe disease (such patients may have been more likely to undergo a biopsy). Our study did not elucidate the pathogenesis of PCNSV or CAA.

To summarize, we described a group of patients with PCNSV and CAA. The diagnosis was confirmed by brain biopsy specimens that showed granulomatous vasculitis and vascular deposits of Aβ peptide. When compared with patients who had PCNSV only, those with PCNSV and CAA were older at presentation but younger than patients with CAA and no inflammation. They showed a trend of more acute clinical onset and higher frequency of cognitive dysfunction. MRI findings showed contrast-enhanced meningeal lesions more frequently, and biopsy specimens typically showed granulomatous vasculitis. The eight patients tended to have a monophasic disease course and generally responded well to immunosuppressive treatment.

Acknowledgements

Editing, proofreading, and reference verification were provided by the Section of Scientific Publications, Mayo Clinic.

Disclosure statement: G.H. is a member of a speaker’s bureau for Merck and Abbott. All other authors have declared no conflicts of interest.

References