Unilateral Relapsing Primary CNS Vasculitis
Description of 3 Cases From a Single-Institutional Cohort of 216 Cases

Carlo Salvarani, MD, Gene G. Hunder, MD, Caterina Giannini, MD, PhD, John Huston III, MD, and Robert D. Brown, MD

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Abstract

Objectives
To define the frequency and characteristics of patients with unilateral relapsing involvement in a cohort of patients with adult primary CNS vasculitis (PCNSV).

Methods
We retrospectively studied a cohort of 216 patients with PCNSV seen at the Mayo Clinic, Rochester, MN from 1983 to 2022. Twenty-five patients (19.8%) had at least 2 flares. Three of them (1.4%) had unilateral relapsing vasculitis. We described these 3 patients and compared them with the entire cohort of 216 patients.

Results
All 3 patients had angiography-negative and biopsy-positive PCNSV with granulomatous-necrotizing and lymphocytic vasculitides and amyloid beta-related angiitis. The main manifestation at diagnosis and during flares was seizures. Unilateral lesions with gadolinium enhancement were the main MRI finding. Spinal fluid examination at diagnosis was normal in 2 patients. All had multiple flares (from 4 to 10) and were treated with long-term high-dose prednisone and numerous traditional immunodepressive drugs, and one received rituximab for steroid resistance. All 3 patients had slight disability with mild cognitive impairment at last follow-up.

Discussion
Unilateral relapsing involvement represents a rare subset of PCNSV with peculiar characteristics and can be observed in all neuropathologic patterns.
Introduction

Some cases of unilateral primary CNS vasculitis (PCNSV) with relapsing disease involving the same brain hemisphere have been described.1–5 Recently, AbdelRazek et al. described 3 cases and reviewed the literature identifying 4 additional cases.1–5

We reviewed all cases of PCNSV evaluated at the Mayo Clinic from 1983 to 2022 to identify patients presenting with unilateral relapsing PCNSV. We evaluated the prevalence, clinical findings, imaging, and clinical course of this subgroup of patients.

Methods

In this study, we extended our earlier PCNSV cohort of 191 consecutive patients seen at Mayo Clinic, Rochester, MN over a 35-year period to 40 years, from 1983 to 2022.6 Using the same previously predefined criteria, we identified 25 additional patients; therefore, 216 patients with PCNSV seen at the Mayo Clinic from 1983 to 2022 were included in this series.6–8

Standard Protocol Approvals, Registrations, and Patient Consents

The study was approved by the Mayo Clinic Institutional Review Board. Written informed patient consent to perform this study was received by all patients.

Data collected for all cases included comprehensive information about clinical findings, laboratory tests, imaging, CNS biopsy or autopsy, therapies, flares, follow-up functional status, and cause of death. Relapse was defined as a recurrence of or increase in symptoms or evidence of worsening of existing lesions and/or new lesions on subsequent MRI examinations while the patient received no medication or received a stable dosage of medication. Patients with relapse led to an increase in therapy. Cerebral biopsy specimens were reviewed by one neuropathologist (CG). Angiograms and MRIs were reviewed by a neuroradiologist. For this study, we specifically identified those patients with at least 2 flares and imaging at diagnosis and at follow-up showing vasculitis confined to one cerebral hemisphere.

Data Availability

Anonymized data not published within this article are available by request.

Results

Of 216 patients with PCNSV, we identified 3 patients (1.4%) with unilateral relapsing PCNSV. Twenty-five of 216 patients (19.8%) had at least 2 flares. Cerebral angiogram was performed at diagnosis in 17 of 25 patients and 12 of 17 (70.6%) had changes highly suggestive of vasculitis (smooth-wall segmental narrowing, dilatation, or occlusion affecting multiple cerebral arteries in the absence of proximal vessel changes consistent with atherosclerosis) involving both cerebral hemispheres in 11 patients. Only one patient had angiographic lesions confined to one hemisphere, but brain MRI showed involvement of both hemispheres. Cerebral biopsy was performed in 18 of 25 patients and showed vasculitis in 14 patients (77.8%).

Table shows the characteristics of the 3 patients with unilateral relapsing PCNSV. One of these cases was previously reported.9 All 3 patients had angiography-negative and biopsy-positive PCNSV. One patient had amyloid beta-related angiitis (ABRA) while the other 2 patients had granulomatous-necrotizing and lymphocytic vasculitides, respectively (Figure 1). The inflammation was transmural, and no evidence of encephalitis was found. Hemisphere involvement occurred on the left in 2 and on the right in one. In all 3 patients, the main presenting clinical manifestation at diagnosis and at the time of flares was seizures, often associated with headaches. All had multiple flares (from 4 to 10) and were treated with different traditional immunodepressive drugs and rituximab (RTX) for steroid resistance. They received long-term treatment (more than 2 years) with fixed high-dose prednisone (PDN) (in one 40 mg/daily, in the other 2 20 mg/daily) because the vasculitic process flared when the PDN dose was reduced. Case 1 had flares during oral cyclophosphamide (Cyc) and azathioprine (AZA) therapies; in this patient, mycophenolate mofetil (MMF) was successful in allowing reduction of prednisone. Case 2 was resistant to AZA, CYC, MMF, and methotrexate (MTX), and only the introduction of RTX while receiving MTX permitted lowering of the PDN dosage. In case 3, only pulse CYC therapy (6 pulses) was able to reduce the PDN daily dosage while AZA and MMF failed.

Table shows the brain MRI findings of the patients at diagnosis and during the disease course. Patient 1 had lesions characterized by prominent leptomeningeal enhancement while the other 2 patients had cerebral lesions with gadolinium enhancement. In all 3 patients, the vasculitic process was confined to the same cerebral hemisphere at diagnosis and during the flares and at the last available brain MRI performed 35 months, 167 months, and 65 months after the diagnosis, respectively (Figure 2). All 3 patients at last follow-up had slight disability with mild cognitive impairment; one case also had mild left hemiparesis.

Erythrocyte sedimentation rate and blood immunologic and coagulation studies were normal in all 3 patients at diagnosis. Viral and fungal serologic and cultural surveys in blood and spinal fluid were negative. In situ hybridization for varicella zoster virus was negative in the biopsy with a granulomatous-necrotizing pattern. Spinal fluid examination at diagnosis was normal in patients 1 and 2 while in patient 3 a mild elevation of protein concentration (54 mg/dL; normal 14–45 mg/dL) was noted. Morphologic evaluation and/or immunocytochemical studies and/or flow cytometric immunophenotyping were negative in spinal fluid in all 3 patients.

Discussion

Patients with unihemispheric relapsing vasculitis represent a very rare subset of adult PCNSV. Recently, AbdelRazek et al. described 3 cases and reviewed the literature, identifying 4
<table>
<thead>
<tr>
<th>Case</th>
<th>Age (y)/sex</th>
<th>Clinical findings at presentation and during flares</th>
<th>Imaging at diagnosis and during flares</th>
<th>Type of biopsy</th>
<th>Histologic findings</th>
<th>Vascular lesions at DSA/MRA</th>
<th>Treatment</th>
<th>Relapse/ recurrence (n)</th>
<th>Follow-up time (mo)</th>
<th>MRS presentation/ last follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Case 1</strong></td>
<td>73/M</td>
<td>At diagnosis: Seizures. 4 flares characterized by seizures and 2 also had increased leptomeningeal enhancement.</td>
<td>At diagnosis: Leptomeningeal enhancement in the posterior left frontal and anterior left parietal lobes with sulcal effacement and several focal areas of white matter signal abnormality in the same areas. First and third flares: Progressed leptomeningeal enhancement, degree of nodularity and sulcal effacement in the same areas.</td>
<td>Stereotactic</td>
<td>ABRA (granulomatous)</td>
<td>Absent PDN, AZA, MMF</td>
<td>4</td>
<td>41</td>
<td>1/2</td>
<td></td>
</tr>
<tr>
<td><strong>Case 2</strong></td>
<td>25/F</td>
<td>At diagnosis: Seizures, headaches, confusion. 8 flares characterized by seizures and/or new enhancing lesions.</td>
<td>At diagnosis: Approximately 5.5 cm in maximal diameter area of increased T2 signal in the subcortical white matter of the left frontal lobe extending into the underlying left centrum semiovale. Approximately 1.2 cm × 2.3 cm heterogeneous enhancement is seen centrally within this T2 area of abnormality. Additional smaller areas of T2 signal in the subcortical white matter of the paramedian left frontal lobe with some associated enhancement following administration of gadolinium. Additional enhancement in the superior left frontal lobe with a perivascular appearance. Flares: Progression of the extent of the T2 signal abnormality and degree of enhancement within the left frontal lobe.</td>
<td>Stereotactic</td>
<td>Granulomatous and necrotizing</td>
<td>Absent PDN, AZA, CYC, MMF, MTX, RTX</td>
<td>8</td>
<td>167</td>
<td>1/2</td>
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<tr>
<td><strong>Case 3</strong></td>
<td>20/F</td>
<td>At diagnosis: Seizures, left hemiparesis, headaches, confusion. At least 10 flares characterized by left focal motor seizures and headaches</td>
<td>At diagnosis and during the follow-up: waxing and waning unilateral right cerebral hemispheric process with new areas of T2 hyperintensity and enhancement appearing at different times and other lesions regressing. Mostly, the process involves the right cerebral hemispheric white matter, including periventricular, deep, and subcortical areas. Some of the more chronic lesions are T1 hypointense and have associated volume loss.</td>
<td>Stereotactic</td>
<td>Lymphocytic</td>
<td>Absent PDN, MMF, AZA, CYC</td>
<td>10</td>
<td>89</td>
<td>2/2</td>
<td></td>
</tr>
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</table>

Abbreviations: ABRA = Aβ-related angiitis; AZA = azathioprine; CYC = cyclophosphamide; DSA = digital subtraction angiography; MMF = mycophenolate mofetil; MRA = magnetic resonance angiography; MRS = Modified Rankin Score; MTX = methotrexate; ND = not done; PCNSV = primary CNS vasculitis; PDN = prednisone; RTX = rituximab.

* These drugs allowed a reduction in the PDN daily dosage without flares.
additional cases. However, there are no data on the frequency of this subset. In our clinical series of 216 adult patients with PCNSV, we observed this condition in 3 (1.4%) patients. Interestingly, one of the 12 angiography-positive patients with relapsing vasculitis had unilateral angiographic involvement at diagnosis; however, brain MRI at diagnosis and during flares showed bihemispheric lesions.

AbdelRazek et al. described the characteristics of the 7 cases. There were several similarities between our patients and those reported by AbdelRazek et al. In both series, all patients presented with seizures, had several clinical and/or radiologic flares (at least 4) in the same hemisphere in which vasculitis occurred at diagnosis, and conventional angiogram and/or magnetic resonance angiography were negative for typical findings of vasculitis. Therefore, small cortical/leptomeningeal vessels were predominantly involved. Other similarities were the normal or mildly abnormal spinal fluid, the absence of response to several traditional immunosuppressants, the need to use long-term high-dose prednisone for maintenance of remission, and the cognitive impairment as the most frequent outcome at last follow-up. Cerebral lesions with gadolinium enhancement were the predominant lesions on MRI in both series with unilateral volume loss at follow-up MRI observed in one of our patients and in 4 of 7 cases described by AbdelRazek et al. All patients were diagnosed with brain biopsy. The 2 series were different in the reported neuropathologic pattern. Lymphocytic vasculitis was reported in all 7 cases described by AbdelRazek et al. while we noted lymphocytic vasculitis in one case, one with granulomatous-necrotizing vasculitis, and one with ABRA. Therefore, unilateral involvement may be an expression of all types of inflammation observed in PCNSV.

In the differential diagnosis, Rasmussen encephalitis (RE) was considered in some of the described cases and in our case 3. However, most RE cases present in childhood, gadolinium-enhancing lesions are very rare, and histopathologically this condition is an encephalitis characterized by mild perivascular inflammation prevalently constituted by T lymphocytes, but not by the transmural vessel inflammation typical of vasculitis. Therefore, the diagnosis of RE was excluded in our case.

Interestingly, AbdelRazek et al. speculated on possible interhemispheric differences in the modulation of immune function predisposing to the asymmetric inflammatory response between the 2 brain hemispheres observed in patients with unilateral relapsing PCNSV, but this hypothesis remained to be demonstrated.

In conclusion, unilateral relapsing involvement represents a rare subset of adult PCNSV with unique characteristics and may be observed in all pathologic vasculitic patterns.

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Disclosure
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Publication History

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Appendix Authors

<table>
<thead>
<tr>
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<th>Location</th>
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<tbody>
<tr>
<td>Carlo Salvarani, MD</td>
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Initial MRI brain imaging in February 2003 demonstrated broad zones of increased T2 signal on T2 FLAIR (A) and multiple focal enhancing lesions (B). Follow-up imaging in May 2007 showed evolution of the T2 changes (C) with no evidence of enhancing lesions (D). Subsequent examination in April 2009 again demonstrates scattered T2 abnormalities (E) confined to the right hemisphere with new foci of enhancement (arrows, F).

Appendix (continued)

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</table>

References


Figures

**Figure 2 Case 3 With Right Hemisphere Relapsing PCNSV**


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