Unilateral Relapsing Primary Angiitis of the CNS
An Entity Suggesting Differences in the Immune Response Between the Cerebral Hemispheres

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Neurol Neuroimmunol Neuroinflam 2021;8:e936. doi:10.1212/NXI.0000000000000936

Abstract

Objective
To determine whether studying patients with strictly unilateral relapsing primary angiitis of the CNS (UR-PACNS) can support hemispheric differences in immune response mechanisms, we reviewed characteristics of a group of such patients.

Methods
We surveiled our institution for patients with UR-PACNS, after characterizing one such case. We defined UR-PACNS as PACNS with clinical and radiographic relapses strictly recurring in 1 brain hemisphere, with or without hemiatrophy. PACNS must have been biopsy proven. Three total cases were identified at our institution. A literature search for similar reports yielded 4 additional cases. The combined 7 cases were reviewed for demographic, clinical, imaging, and pathologic trends.

Results
The median age at time of clinical onset among the 7 cases was 26 years (range 10–49 years); 5 were male (71%). All 7 patients presented with seizures. The mean follow-up duration was 7.5 years (4–14.1 years). The annualized relapse rate ranged between 0.2 and 1. UR-PACNS involved the left cerebral hemisphere in 5 of the 7 patients. There was no consistent relationship between the patient’s dominant hand and the diseased side. When performed (5 cases), conventional angiogram was nondiagnostic. CSF examination showed nucleated cells and protein levels in normal range in 3 cases and ranged from 6 to 11 cells/μL and 49 to 110 mg/dL in 4 cases, respectively. All cases were diagnosed with lesional biopsy, showing lymphocytic type of vasculitis of the small- and medium-sized vessels. Patients treated with steroids alone showed progression. Induction therapy with cyclophosphamide or rituximab followed by a steroid sparing agent resulted in the most consistent disease remission.

Conclusions
Combining our 3 cases with others reported in the literature allows better clinical understanding about this rare and extremely puzzling disease entity. We hypothesize that a functional difference in immune responses, caused by such discrepancies as basal levels of cytokines, asymmetric distribution of microglia, and differences in modulation of the systemic immune functions, rather than a structural antigenic difference, between the right and left brain may explain this phenomenon, but this is speculative.

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Go to Neurology.org/NN for full disclosures. Funding information is provided at the end of the article.

The Article Processing Charge was funded by the authors.

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Primary angiitis of the CNS (PACNS) was first recognized in 1959 and is characterized by idiopathic inflammation of arteries of the brain, spinal cord, and leptomeninges.1 The size of the afflicted vessels carries significant diagnostic and prognostic consequences. Disease of predominately small- and medium-sized vessels is often missed by CT angiography, magnetic resonance angiography, and conventional angiography and rather diagnosed with brain biopsy. In such cases, small infarctions are more typical and are associated with a more favorable prognosis overall. Angiitis of large-sized vessels is more likely to have diagnostic angiographic findings and leads to large territorial infarctions and a less favorable prognosis.2 Our understanding is limited regarding the factors that lead to this difference in the size of the afflicted vessels between different individuals.

Despite the well-known functional differences between the right and left hemispheres of the brain, studies identifying the transcribed RNA in different regions of the brain do not demonstrate a significant difference in gene expression between the 2 hemispheres.3 Moreover, evidence of asymmetries of total arterial supply between the right and left brain is, similarly, lacking.4 These data render a readily available explanation for chronic or relapsing asymmetric brain disease difficult to ascertain. In large case series reporting on PACNS, relapsing vasculitis in only 1 hemisphere is not described.2,5 Salavarani et al. reported unilateral findings in 8.8% of patients diagnosed by brain biopsy and in 11.5% of patients diagnosed by angiogram, but did not identify whether further relapses continued to focus on the same hemisphere.2

Here, we report the diagnostic approach, clinical course, and treatment of 3 cases of unilateral relapsing PACNS (UR-PACNS). In addition, we review the literature and summarize the previously reported cases. We also explore how this disease entity can indicate hemispheric differences in immune response mechanisms.

Methods

The index case (case 1) was identified through its presentation in our institution’s (Massachusetts General Hospital, Boston) weekly neuroimmunology faculty meeting. At that time, other colleagues (M.M., J.M.H. and Y.G.) present at that meeting identified the similar presentation of the patients (cases 2 and 3) who they were following clinically. We queried our Research Patient Data Registry to search for additional patients with UR-PACNS within the last 5 years (January 2015–December 2019). Although 145 patients (53.7% female; average age 54.3, SD 16.9) were seen at Massachusetts General Hospital for suspected cerebral vasculitis, during that time, we did not identify any additional UR-PACNS cases. In our search, UR-PACNS was defined as biopsy-proven PACNS with ≥2 relapses after the initial onset, strictly confined to 1 cerebral hemisphere, with or without relative atrophy of that hemisphere. Relapses were defined as a new clinical neurologic manifestation with brain MRI demonstrating at least 1 new lesion with gadolinium enhancement. If there was no gadolinium enhancement, a relapse could still be recorded if it had been judged by the clinician to be so. We identified 3 such patients, described below in detail. To further characterize this entity, we performed an indexed literature search through PubMed for similar reports using the key words “unilateral, unihemispheric, PACNS, vasculitis, and angiitis” and their synonyms in varying combinations. The references within the identified publications were also reviewed for pertinent studies. This resulted in 4 additional cases.6–9 The 7 cases were combined to review demographic, clinical, imaging, and pathologic trends.

Data Availability

Upon appropriate request, the corresponding author can provide deidentified data, e.g., normal serum and CSF tests.

Standard Protocol Approvals, Registrations, and Patient Consents

The authors received written informed consent for research publication from the 3 patients included in the study.

Case Descriptions

Case 1

A 23-year-old right-handed Caucasian woman with a history of migraine headaches and cocaine and alcohol abuse presented in April 2003 with a generalized tonic-clonic seizure. This also coincided with an increased frequency and severity of her headaches. Her migraine history started at age 13 years and was consistent with sporadic hemiplegic migraine, where headaches were associated with transient (~2 hours) weakness of the right arm and leg. Her MRI (4/2003) showed strictly left hemispheric multiple periventricular and deep white matter T2 hyperintense foci, some with faint contrast enhancement (figure 1, A and B) without diffusion-weighted imaging (DWI) changes. CSF analysis was normal without oligoclonal bands. EEG showed intermittent left temporal slowing in the theta and delta range, but no epileptiform activity. She was started on antiepileptic drug (AED) therapy, eventually accumulating 3 AEDs over the course of 4 years for both nonepileptic and 17 epileptic events characterized as

Glossary

ABRA = amyloid beta-related angiitis; AED = antiepileptic drug; DWI = diffusion-weighted imaging; PACNS = primary angiitis of the CNS; UR = unilateral relapsing; VZV = Varicella zoster virus; WBC = white blood cell.
right arm tonic partial onset seizures with secondary tonic-clonic generalization. Five years after presentation, her neurologic examination was only remarkable for slightly slowed finger-tap speed and alternating movements with the right hand. A formal neuropsychiatric evaluation showed low-normal performance in the executive function and language domains. She was on 1 AED with good seizure control but without a formal diagnosis.

Over the course of the 14 years following her initial presentation, she had 11 more brain MRIs exhibiting progressive unihemispheric atrophy, and a total of 3 clinical relapses associated with new gadolinium-enhancing T2 lesions. All relapses presented clinically with focal or generalized seizure and headache. The first occurred 6 years and 4 months after presentation (figure 1, E and F), and she was started on mycophenolate mofetil for presumed CNS vasculitis without angiographic or pathologic confirmation. The second occurred 7 years and 3 months after presentation; AED regimen was adjusted. Mycophenolate was discontinued 12 years after presentation, which was followed by the third relapse occurring 13 years and 3 months after presentation (figure 1, G and H). Cerebral angiogram was normal, but lesional biopsy showed nongranulomatous, non-necrotizing lymphocytic vasculitis (figure 3). Mycophenolate was restarted, and she received 2 cycles of rituximab 1 g infusions (6 months apart). She has had no further relapses until her last follow-up 14 years after presentation, at which point her neurologic examination was not significantly changed from that documented above, 5 years after presentation. Additional studies included 2 further unremarkable CSF studies (5 years and 13 years 3 months after presentation), unremarkable MRI of the cervical and thoracic spine (3 years from presentation), and serum autoimmune and genetic testing (table 1).

Case 2

A 19-year-old left-handed Caucasian woman presented with a secondarily generalized tonic-clonic seizure that commenced with focal right lower extremity numbness and paresthesia. Brain MRI demonstrated left frontal and parietal multifocal cortical and subcortical T2 hyperintense lesions with contrast enhancement (figure 2, A and B). CSF analysis showed lymphocytic pleocytosis (white blood cell [WBC] 8 cells/μL; 93% lymphocytes, 6% monocytes, and 1% polymorphonuclear cells) and positive CSF oligoclonal bands. She had weakly positive serum antinuclear antibody (1:40). Her laboratory values were otherwise unremarkable (table 1). She was commenced on levetiracetam 500 mg twice daily. One month later, she developed episodes of right upper and lower extremity numbness and paresthesia lasting up to 3 hours. Brain MRI demonstrated interval progression of patchy nodular enhancement within the left cerebellar hemisphere and interval growth of a rounded lesion within the left mesial temporal lobe. She was treated with IV methylprednisolone 1,000 mg daily for 3 days. At follow-up 2 months later, there was interval improvement of symptoms and lesions on brain MRI, although small residual foci of enhancement remained (figure 2, C and D).

Ten months after initial presentation, she developed a prolonged episode of right-sided numbness. Brain MRI showed enhancing lesions in the left temporal, frontal, and parietal lobes. Her dose of levetiracetam was increased to 750 mg twice daily. Twelve months after presentation, she underwent brain biopsy that demonstrated inflammatory and reactive changes, as well as a necrotic focus, consistent with small vessel lymphoplasmacytic vasculitis (figure 3). She was commenced on prednisone 60 mg daily for 6 weeks followed by taper and mycophenolate
1,000 mg twice daily. Her dose of levetiracetam was also increased to 1,000 mg twice daily postoperatively for worsening right-sided numbness. Four years after initial presentation, she has not had new symptoms or worsening on MRI. She remains on the same therapeutic regimen and continues to have occasional focal seizures.

**Case 3**

A healthy 26-year-old right-handed Chinese man presented to the emergency department in March 2012 with generalized tonic-clonic seizure after an aura of abnormal vision as if witnessing a 3D movie. Brain MRI showed patchy T2 lesions in the right temporal and occipital lobes with multiple nodular and patchy areas of enhancement. CT angiogram of the head was unremarkable apart from showing a common blood supply to both thalami (artery of Percheron). Lumbar puncture opening pressure was 105 mmH2O, with mild pleocytosis (8 WBC/μL) and normal protein (44 mg/dL). Autoimmune encephalitis and ganglioside spectrum antibody panels of CSF were negative. CSF immunoglobulin G index was 0.96 (normal 0.32–0.6). *Cryptococcus*, cysticercosis antibody, *Mycobacterium tuberculosis* PCR, and bacteria were not detected in CSF. Other normal serum tests are summarized in table 1.

### Table 1 Clinical Features

| 1: 2002 Derry et al. | 2: 2009 Damasceno et al. | 3: 2011 Ho et al. | 4: 2016 Johnson et al. | 5: 2020 AbdelRazek et al. #1 | 6: 2020 AbdelRazek et al. #2 | 7: 2020 AbdelRazek et al. #3 |
|----------------------|--------------------------|------------------|-----------------------|-------------------------------|-------------------------------|-------------------------------|
| **Age at clinical onset/sex/race** | | | | | | |
| 10/M | 35/M | 49/M/Hispanic | 30/M | 23/F/Caucasian | 19/F/Caucasian | 26/M/Chinese |
| **Handedness** | No mention | Right | No mention | Right | Right | Left | Right |
| **Follow-up duration, y** | 11.75 | 10 | 4 | 4 | 14.1 | 4 | 5 |
| **Presenting symptoms** | L focal motor seizure, L hemiparesis, and R-sided headache | Generalized seizure, R hemiparesis, and expressive aphasia | R focal seizure, R hemiparesis, and aphasia | R hemiparesis, hemianopia, nonfluent aphasia, and seizures | Generalized tonic-clonic seizure | R focal seizure with secondarily generalized tonic-clonic seizure | Generalized tonic-clonic seizure |
| **Treatments and responses** | Deteriorated on dexamethasone; stable on CYC | Failed steroids, azathioprine, and beta-interferon 1a | Steroids and CYC very successful with near-complete resolution | Pulse steroids, CYC/rituximab induction and MPM maintenance controlled disease for 4 y | Relapse on MPM, followed for 1 y on rituximab without relapse | Steroids, MPM largely successful | Deteriorated on pulse steroids and stable for 1 y on MPM |
| **Eventual cognitive deficits** | No | Yes (aphasia and problem solving) | No | Yes (moderate nonfluent aphasia) | Low-normal executive function and language domains | No | Mild (MMSE 30 and MoCA 26 2 y after onset) |
| **Eventual motor deficits** | L hemiplegia | R hemiparesis | No | Mild R hemiparesis | No | No | R hemiparesis |
| **Eventual sensory deficits** | Hemianopia | No mention | No mention | No mention | No | No | No mention |
| **Seizure is the presenting symptom** | Yes | Yes | Yes | Yes (first seizure during the first hospitalization) | Yes | Yes | Yes |
| **Headache with relapses** | Yes | No mention | Yes | Yes | Yes | No | No |
| **No. of relapses** | At least 3 | At least 3 | At least 4 | At least 3 | 3 | At least 4 | 4 |
| **Annualized relapse rate** | 0.26 | 0.3 | 1 | 0.75 | 0.21 | 1 | 0.8 |

Abbreviations: CYC = cyclophosphamide; MMSE = Mini-Mental State Examination; MoCA = Montreal Cognitive Assessment; MPM = mycophenolate mofetil.
Ten months after presentation, he gradually developed numbness in his left upper limb. Thirteen months after presentation, his left upper and lower limbs were weak. He could not hold light objects. When walking, he felt as if his left lower limb was treading on cotton. He was admitted to a hospital in Beijing, China. Examination showed reduced muscle tone of left upper limb. His left hand showed weakness and incoordination described as thalamic hand. Distal muscle strength of the left upper limb was 4/5, and proximal was 5−/5; the left lower limb was 4/5 proximally and distally. Hoffman sign was present in both hands, and his left toes showed positive Pussepp sign. Brain MRI, 14 months after presentation, showed radiographic progression with patchy T2 lesions in the right thalamus, temporal lobe, frontal lobe, occipital lobe, basal ganglia region, midbrain, and pons. Multiple nodular and patchy enhancement signals were seen in the right cerebral hemisphere. Brain MRI 3 months later (17 months after presentation) showed further progression with all lesions, old and new, remaining strictly confined to the right hemisphere (figure 2, E–G). Lesional biopsy from the superficial right occipital lobe of about 1.5 cm block of subcortical, cortical, and leptomeningeal tissue was performed. Clinical pathologic diagnosis of primary angiitis of the CNS was made (figure 3). The patient was commenced on methylprednisolone pulse therapy 1,000 mg/d for 5 days with subsequent oral taper. Despite this, he continued to have gradual clinical and radiographic progression.

Four years and 2 months after initial presentation, his left arm and leg strength had deteriorated further with worsened spasticity. He complained of cognitive deficits, although his Mini-Mental State Examination was 30/30, and Montreal Cognitive Assessment was 26/30. Brain MRI showed further progression with new lesions in the right thalamus, midbrain, upper pons, temporal lobe, occipital lobe, frontal lobe, and basal ganglia region. There was significant atrophy of the right hemisphere and right brainstem (figure 2H). There were new enhancing lesions in the left thalamus. Immunosuppressive therapy with mycophenolate 200 mg twice daily was prescribed accompanied with prednisone 8 mg daily. Ten months later (5 years after presentation), the follow-up brain MRI showed stability with no new lesions, although significant unilateral brain atrophy including the brainstem remained evident.

**Results**

In addition to the 3 cases we present in this report, there have been 4 prior distinct case reports of biopsy-proven UR-PACNS in patients aged 10, 30, 35, and 49 years at the time of clinical onset (table 1). Although 2 case series from one academic center reported on unilateral intracranial arteriopathy in 93 children,10,11 the disease entity described in these pediatric neurology case series differs from UR-PACNS. These reports describe a largely transient monophasic arteriopathy. In the first report, only 5 of 79 children had relapsing arteriopathy, and only 1 of these 5 remained unilateral at follow-up and was thought to be related to neuroborreliosis and not PACNS.10 In the second report, none of the 14 cases with unilateral arteriopathy had a relapse after a median 8.8-year follow-up and appeared to be monophasic in character.11

**Demographics, Clinical Course, and Response to Therapy**

In the 7 cases that have been reported to date, 3 of whom from this study, the median age at time of clinical onset was 26 years (range 10–49 years); 5 were male (71%); the mean follow-up duration was 7.5 years (4–14.1 years); the mean annualized relapse rate was 0.62 (0.2–1), defined as the average number of clinical relapses with new MRI changes per year. All 7 patients presented with seizures; this is likely related to the small caliber size of the inflicted blood vessels, which tend to...
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Conventional cerebral angiogram was performed in 4 of
Neuroimaging
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sants showed disease progression. Mycophenolate mofetil
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of the 7 cases with seizures, a cortical epiphenomenon
more likely to occur with distal vasculitis. Of interest, 2
patients showed asymmetry of the caliber size of the in-
tracranial vessels, one on conventional angiogram and the
other on magnetic resonance angiogram. All patients
showed recurring gadolinium-enhancing strictly unilateral
lesions. In the 3 cases we present, none had DWI restricted
diffusion, whereas in the prior 4 cases, there was no specific
comment on this. In case 3, only, there was infratentorial
involvement, above the level of fiber decussation. This case
also showed contralateral thalamic involvement late in the
disease, which we believe was related to the common
vasculature of both thalami, artery of Percheron, seen on
CT angiogram. Table 2 summarizes neuroimaging
findings.
In 4 of the 7 cases, there was progressive unilateral volume
loss such as that seen in Rasmussen encephalitis, including the
midbrain in 1 patient (case 3 of this report). We note that
early induction therapy with a strong immunosuppressant was
absent in these cases. One case had evidence for subtle volume
loss between onset and the
first radiographic disease relapse
ecting that single hemi-
be cortical and thus more likely to induce seizure activity. Two
of the cases presented with focal unilateral arm and leg con-
vulsions without generalization; in 3 cases, there was associ-
ated aphasia; and 4 had hemiparesis not related to Todd
paralysis at presentation. Throughout their clinical course, all
patients had several clinical and radiographic relapses, 4 pa-
tients with headache as a prominent feature, which is the most
common symptom in PACNS, occurring in 60% of cases. At
the end of the reported follow-up duration, 4 patients had
cognitive deficits (language and problem solving), 3 patients
had hemiparesis, and 1 had hemiplegia and hemianopia
without a deficit in cognition.

The 7 patients varied in response to immunomodulatory
therapy as detailed in table 1. Cyclophosphamide and ritux-
imab were successful in suppressing disease relapses whenever
used (4 of the 7 cases). Patients who did not receive early
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midbrain in 1 patient (case 3 of this report). We note that
early induction therapy with a strong immunosuppressant was
absent in these cases. One case had evidence for subtle volume
loss between onset and the first radiographic disease relapse
(2 years and 9 months apart), which may indicate subclinical
baseline chronic inflammation affecting that single hemi-
sphere with superimposed acute inflammatory episodes
causing clinical relapse (case 1 of this report).

Laboratory Investigations
Extensive workup for systemic markers of infectious or
autoimmune/rheumatologic disease was unremarkable in all
patients. The specific workup in each case differed, outlined in

Figure 3 Histopathologic Findings in Cases 1, 2, and 3

Findings were similar in all 3 patients, consisting of varying amounts of perivascular and parenchymal
chronic inflammation, tissue necrosis, and reactive
glialosis. Small sized vessels demonstrated trans-
mural inflammation, but fibrinoid necrosis was not a
prominent finding. No granulomas or microglial
nodules were identified. Microscopic examination
for Case 1 demonstrated multifocal perivascular
inflammatory infiltrates (A, H&E, ×400) composed
of mature lymphocytes, many of which were CD8+
T cells (B, CD8 IHC, ×400), rare plasma cells, and
some macrophages (C, CD68 IHC). Similar peri-
vascular inflammatory infiltrates were seen in Case
2, with more prominent spillage into the adjacent
parenchyma (D, H&E, ×100), with occasional obliti-
erated vessels (D insert, H&E, ×400) and focal tissue
necrosis (not shown). Most inflammatory cells
were also T cells (E, CD3 IHC, ×400) with scattered B
cells (F, CD20 IHC, ×400). Case 3 demonstrated in-
flammatory infiltrates within the vascular walls of
medium-sized leptomeningeal vessels in addition
to small-sized parenchymal vessels (G, H&E, ×100),
composed of many T cells (H, CD3 IHC, ×100)
with an additional component of plasma cells (I, CD138
IHC, ×100). The lack of leptomeningeal involvement
in Cases 1 and 2 however may be due to limited
sampling with a smaller biopsy size in comparison
with Case 3. In all cases, there were no histopath-
ologic findings to suggest any process different
from PACNS. H&E = hematoxylin and eosin; IHC =
immunohistochemistry; PACNS = primary angitis
of the CNS.
Table 2 Laboratory and imaging features

| 1: 2002 Derry et al. | 2: 2009 Damasceno et al. | 3: 2011 Ho et al. | 4: 2016 Johnson et al. | 5: 2020 AbdelRazek et al. | 6: 2020 AbdelRazek et al. #1 | 7: 2020 AbdelRazek et al. #3 |
|----------------------|--------------------------|------------------|------------------------|---------------------------|-------------------------------|-----------------------------|
| **CSF analysis**     |                          |                  |                        |                           |                               |                             |
| Positive OCB, protein 110 mg/dL, otherwise normal | 6 WBC/μL, no OCB, protein 68 mg/dL, and negative VZV DNA | Unremarkable | 11 WBC/μL, 87% lymphocytes, protein 50 mg/dL, 2 OCBs, and negative DNA for VZV, HSV, EBV, and CMV | Normal WBC, protein. Immunostain on brain biopsy for VZV is negative. | Positive OCB, 6 WBC/μL, 96% lymphocytes, protein 49 mg/dL, and negative VZV DNA | 8 WBC/μL and protein 44 mg/dL |
| Conventional angiogram diagnostic of vasculitis (other angiography done) | No (although showed R MCA and its branches of smaller caliber than L) | No (but showed L MCA and R MCA aneurysms) | No mention (MRA showed small caliber of R MCA, ACA, and PCA compared with L) | No | Not performed (although CTA head and neck normal) | Not performed (CTA normal, artery of Percheron seen) |
| **Parenchymal lesion vascular distribution** | R MCA and PCA | L MCA and ACA at least | L MCA | L MCA and PCA | L MCA | LACA, MCA, and PCA | R MCA and PCA |
| Gadolinium enhancement | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Lesion DWI positivity | No mention | No mention | No mention | No mention | No | No | No |
| Hemiatrophy on follow-up MRI | Yes | Yes | No | No | No | No | Yes |
| **Pathologic variant** | Lymphocytic | Lymphocytic | Lymphocytic | Lymphocytic | Lymphocytic | Lymphocytic | Lymphocytic |
| Inflamed artery caliber | Small | Small | Small | Small and medium | Small | Small | Small and medium |
| **Diagnosis made by biopsy or angiogram** | Lesional biopsy | Lesional biopsy | Lesional biopsy | Lesional biopsy | Lesional biopsy | Lesional biopsy | Lesional biopsy |

Abbreviations: ACA = anterior cerebral artery; CMV = cytomegalovirus; CTA = CT angiography; DWI = diffusion-weighted imaging; EBV = Epstein-Barr virus; HSV = herpes simplex virus; MCA = middle cerebral artery; MRA = magnetic resonance angiography; OCB = oligoclonal band; PCA = posterior cerebral artery; VZV = varicella zoster virus; WBC = white blood cell.

table 2. Noteworthy, CSF examination was overall unremarkable or mildly abnormal. Nucleated cells and protein levels were normal in 3 cases (<6 cells/μL and <46 mg/dL) and ranged from 6 to 11 cells/μL and 49 to 110 mg/dL in the remaining 4 cases, respectively. Oligoclonal bands were mentioned to be positive in 3 cases. Varicella zoster virus (VZV) PCR from CSF was reported to be negative in 3 cases, and immunostaining for VZV on the brain biopsy was negative in a fourth case.

Neuropathology

All 7 cases were diagnosed as PACNS by brain biopsy. Two cases had a nondiagnostic first brain biopsy, one on presentation with a positive biopsy 3 years later, and the second 6 years into the disease with a positive biopsy 2 years after that. The pathologic findings in all 7 cases were consistent with lymphocytic vasculitis of the small- and medium-sized vessels, without evidence of granulomatous or significant vessel wall necrotizing components. In our 3 cases, the most salient finding was transmural and perivascular inflammation, with evidence of ischemic injury from small vessel involvement, most prominent in case 2 (figure 3). No particular finding on biopsy explained the unilateral nature of the vasculitis. Amyloid staining was not performed in any case, likely given the young age (under 50 years) in all patients, the absence of granulomatous changes in all cases, which amyloid beta-related angiitis (ABRA) classically shows, and that ABRA almost exclusively occurs in older patients. VZV immunohistochemical stain was performed in 2 cases (cases 1 and 2) and was negative.

Discussion

The most striking feature of these patients’ presentation was the laterality of their clinical and neuroimaging findings. Although the occurrence of lesions in 1 hemisphere repeatedly may be due to chance, not only did patients have multiple relapses in only 1 hemisphere but also most of the relapses had multiple lesions. For example, in case 3 of this article,
there were at least 10 new enhancing lesions over the course of 4 relapses; thus, the chance of random lateral occurrence would be 0.001 (using the formula $0.5^n$ where $n =$ number of lesions). Similar statistical chance was demonstrated in all 7 cases included here.

In detailed databases of human brain transcriptomes, no difference in the transcribed protein between the 2 hemispheres of the brain was displayed, despite the well-known differences in functional organization between the dominant and nondominant hemispheres.3,12 This does not rule out absence of the brain was displayed, despite the well-known differences in functional organization between the dominant and nondominant hemispheres.3,12 This does not rule out the possibility of overlapping of functional immune properties may have predisposed to the persistence of unihemispheric vasculitis.24 Indeed, case 1 and case 3 otherwise fulfill the diagnostic criteria. We note that the biopsy results for these cases most prominently suggest perivascular inflammation and do not demonstrate the typical microglial nodules seen with Rasmussen encephalitis. Furthermore, Rasmussen encephalitis commonly presents with seizures in childhood that progress to epilepsy partialis continua. It is possible, however, that Rasmussen encephalitis and UR-PACNS lie on a spectrum of related disorders especially as some Rasmussen biopsies have suggested dual pathology including perivascular lymphocytosis.25 We also note here that anti–myelin oligodendrocyte glycoprotein encephalitis has been reported to mimic CNS vasculitis in histopathologic samples.26 Unfortunately, serum testing for this was not commercially available during the time frame of follow-up of these patients, and thus, this is a limitation to our report.

In patients with a high diagnostic suspicion of PACNS, we advocate for early brain biopsy. If an initial biopsy is nondiagnostic, and high suspicion remains, we advocate for a second targeted lesional biopsy during disease relapse, ideally including meninges, cortex, and white matter. Two of the 7 cases we reviewed here were diagnosed on the second brain biopsy. Based on current experience from this case series, early induction therapy with cyclophosphamide (15 mg/kg every 2 weeks for 3 doses and then every 3 weeks for 3–6 doses)27,28 is advised, followed by maintenance therapy with a steroid sparing agent such as methotrexate (20–25 mg/wk) or mycophenolate (1–2 mg/kg daily). Rituximab (375 mg/m² once a week for 4 doses or 1,000 mg twice, 2 weeks apart; each dose being successful in 1 of the 7 cases) in lieu of cyclophosphamide or as maintenance therapy is also favorable in many cases.28,29 In addition, a 3- to 5-day course of IV pulse glucocorticoid therapy during an acute relapse is recommended. Clinical and neuroimaging (brain MRI with contrast) follow-up should be performed once every 1–2 years or more frequently as needed.

**Study Funding**
No targeted funding reported.

**Disclosure**
M.A. AbdelRazek reports no conflict of interest. J.M. Hillis participates in research funded by GE Healthcare and is an investor in Elly Health. Y. Guo, M. Martinez-Lage, and T. Gholipour report no conflict of interest. J. Sloane has served on advisory boards for Biogen, Genentech, Celgene, EMD Serono, Teva, and Genzyme; he has grant funding from Biogen, Genentech, EMD Serono, and the National MS Society. T. Cho reports no conflict of interest. M. Matiello is an advisory board member for Alexion, Genentech, and VielaBio; he is funded by the Clinician-Teacher Development Award by the Mass General Hospital Center for Diversity and Inclusion. Go to Neurology.org/NN for full disclosures.
5. de Boysson H, Zuber M, Naggara O, et al. Primary angiitis of the central nervous system: description of the first fifty-two adults enrolled in the French cohort of patients with primary vasculitis of the central nervous system. Arthritis Rheumatol 2014;66:1315–1326. doi: 10.1002/art.38340.

6. Derry C, Dale RC, Thom M, Miller DH, Giovannini G. Unihemispheric cerebral vasculitis mimicking Rasmussen’s encephalitis. Neurology 2002;58:327–328. doi: 10.1212/wnl.58.2.327.

7. Damasceno A, Franca M Jr, Queiroz LS, Candes F, Nucci A, Damasceno BP. Adult onset unihemispheric vasculitis resembling Rasmussen encephalitis. Neurologist 2009;15:285–288. doi: 10.1097/NRL.0b013e31818c7e4.

8. Ho MG, Chai W, Vinters HV, et al. Unilateral hemispheric primary angiitis of the central nervous system. J Neurol 2011;258:1714–1716. doi: 10.1007/s00415-011-5993-1.

9. Johnson MA, Jakubek GA, Howley JS. Unihemispheric cerebral vasculitis: case report and review of literature. J Neurol Sci 2016;368:32–34. doi: 10.1016/j.jns.2016.06.049.

10. Braun KP, Bulder MM, Chabrier S, et al. The course and outcome of unilateral intracranial arteriopathy in 79 children with ischemic stroke. Brain 2009;132:544–557. doi: 10.1093/brain/awn311.

11. Bulder MM, Braun KP, Leeuw JW, et al. The course of unilateral intracranial arteriopathy in young adults with arterial ischemic stroke. Stroke 2012;43:1890–1896. doi: 10.1161/STROKEAHA.112.653212.

12. Johnson MB, Kawasawa YI, Mason CE, et al. Functional and evolutionary insights into human brain development through global transcriptome analysis. Neuro 2009;69:494–509. doi: 10.1152/jneurosci.00306.2009.

13. Louveau A, Smirnov I, Keynes TJ, et al. Structural and functional features of central nervous system lymphatic vessels. Nature 2015;523:337–341. doi: 10.1038/nature14432.

14. Geschwind N, Behan P. Left-handness: association with immune disease, migraine, and developmental learning disorder. Proc Natl Acad Sci USA 1982;79:5097–5100. doi: 10.1073/pnas.79.16.5097.

15. Neveu PJ. Asymmetrical brain modulation of the immune response. Brain Res Brain Res Rev 1992;17:101–107. doi: 10.1016/0169-1688(92)90010-j.

16. Neveu PJ. Cerebral lateralization and the immune system. Int Rev Neurobiol 2002;52:303–323. doi: 10.1016/S0077-7842(02)70146-4.

17. Fu QJ, Shen YQ, Mao MX, Dong J, Neveu PJ, Li KS. Brain interleukin asymmetries and paw preference in mice. Neuroscience 2003;116:639–647. doi: 10.1016/j.neuroscience.2003.02.076.

18. Meador KJ, Loring DW, Ray PG, Holman SW, Vasquez BR, Neveu PJ. Role of cerebral lateralization in control of immune processes in humans. Ann Neurol 2004;55:840–844. doi: 10.1002/ana.20105.

19. Shen YQ, Hébert G, Lin LY, et al. Interleukine-1beta and interleukine-6 levels in stratum and other brain structures after MPTP treatment: influence of behavioral lateralization. J Neuroimmunol 2005;158:14–25. doi: 10.1016/j.neuroimmunol.2004.06.011.

20. Shen YQ, Hébert G, Moez E, Li KS, Neveu PJ. Asymmetrical distribution of brain interleukin-6 depends on lateralization in mice. Neuroimmunomodulation 2005;12:189–194. doi: 10.1159/000084882.

21. Steiner J, Mawrin C, Ziegeler A, et al. Distribution of HLA-DR-positive microglia in schizophrenia reflects impaired cerebral lateralization. Acta Neuropathol 2006;112:305–316. doi: 10.1007/s00401-006-0908-0.

22. Wu HM, Lu CS, Huang CC, et al. Asymmetric involvement in sporadic Creutzfeldt-Jakob disease: clinical, brain imaging, and electroencephalographic studies. Eur Neurol 2010;64:75–103. doi: 10.1159/000315148.

23. Li P, Ensink E, Lang S, et al. Hemispheric asymmetry in the human brain and in Parkinson’s disease is linked to divergent epigenetic patterns in neurons. Genome Biol 2020;21:61. doi: 10.1186/s13059-020-01960-1.

24. Bien CG, Granata T, Antozzi C, et al. Pathogenesis, diagnosis and treatment of Rasmussen encephalitis: a European consensus statement. Brain 2005;128(pt 3):311–329. doi: 10.1093/brain/awh415.

25. Hart YM, Andermann F, Robitaille Y, Laxer KD, Rasmussen T, Davis R. Double Rasmussen encephalitis: a European consensus statement. Brain 2005;128(pt 3):311–329. doi: 10.1093/brain/awh415.

26. Patterson K, Iglesias E, Nasrallah M, et al. Anti-MOG encephalitis mimicking small vessel CNS vasculitis. Neurol Neuroimmunool Neuroflam 2019;6:e538. doi: 10.1212/NXN.0000000000000358.

27. de Groot K, Harper L, Jayne DR, et al. Pulse versus daily oral cyclophosphamide for intracranial arteriopathy in 79 children with ischaemic stroke. Brain 2009;132:544–557. doi: 10.1093/brain/awn311.

28. Mukhtyar C, Guillevin L, Cid MC, et al. EULAR recommendations for the management of primary small and medium vessel vasculitis. Ann Rheum Dis 2009;68:310–317. doi: 10.1136/ard.2008.088096.

29. Stone JH, Merkle PA, Spiess R, et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. N Engl J Med 2010;363:221–232. doi: 10.1056/NEJMoa090905.