Child Neurology: Primary angiitis of the CNS

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A 9-year-old right-handed girl presented to an outside emergency department (ED) with persistent left-sided weakness after a first-time whole-body seizure. She had no prior fevers or viral prodrome. She then developed left gaze deviation and unresponsiveness. Brain MRI demonstrated multiple T2 hyperintense lesions with contrast enhancement (figure, A and B) but no diffusion restriction. Magnetic resonance angiography (MRA), MRI spine, and EEG were normal and CSF had 1 white blood cell (WBC), normal protein, normal glucose, and no oligoclonal bands. The patient received 5 days of IV Solu-Medrol and then a 2-week oral prednisone taper. Four days after completing steroids, she developed vertical diplopia and was diagnosed with a fourth cranial nerve palsy. The next day she had right head turning, bilateral arm weakness, and slurred speech, which self-resolved within minutes. She re-presented to the ED with seizures. Repeat MRI demonstrated increased T2 lesions; she was started on levetiracetam, IV steroids, and then oral steroids. The initial diagnosis was acute disseminated encephalomyelitis (ADEM).

The patient then presented to the Partners Pediatric MS Center at Massachusetts General Hospital. She complained of fatigue and intermittent headaches but had no further seizures and neurologic examination was normal. Her medical history included eczema as an infant and family history included a half-sibling with seizures but no autoimmunity. C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), von Willebrand Factor (vWF) antigen, antinuclear antibodies (ANA), anti-DNAse, anti-Ro, anti-La, and anti-TPO antibodies, and serum autoimmune encephalitis panel were unremarkable.

Two weeks later, while tapering steroids, the patient developed bilateral arm and left leg weakness; neurologic examination revealed right hypertropia with vertical diplopia and left-sided 4+/5 strength. Imaging revealed increased T2 lesions and increased gadolinium enhancement (figure, C and D) with normal MRA. CSF demonstrated 2 WBCs (60% neutrophils, 30% lymphocytes, 10% monocytes) but normal protein and glucose. CSF oligoclonal bands,

immunoglobulin G (IgG) index, and autoimmune encephalitis panel were negative. Brain biopsy of a right enhancing parietal lobe lesion demonstrated findings consistent with angiography-negative, small vessel CNS vasculitis: endothelial activation, perivascular inflammatory predominant T-cell infiltrate with vascular wall injury along with acute to subacute multiple microinfarctions in the cortex, and white matter gliosis without demyelination (figure, E and F).

The patient received 6 months of IV cyclophosphamide and then mycophenolate mofetil (MMF) maintenance therapy. One month after starting MMF and during steroid taper, left arm weakness and headaches recurred, so she received another IV cyclophosphamide dose. At her most recent follow-up, she has remained clinically stable with normal neurologic examination at 6 months on maintenance therapy and 1 year after diagnosis. Steroids were discontinued without incident.

PRIMARY ANGIITIS OF THE CNS CNS vasculitis, or primary angiitis of the CNS (PACNS), consists of CNS blood vessel inflammation. PACNS occurs in children and adults.^{1,2} The adult criteria include new neurologic symptoms, angiographic or histologic findings for PACNS, and no systemic illnesses associated with PACNS.¹ PACNS is isolated to the brain and spinal cord and secondary CNS vasculitis can occur in other systemic illnesses including autoimmune diseases or infections.² Differential diagnoses include other autoimmune diseases, infections, and genetic or metabolic disorders, which is not discussed in this article.²

PACNS can be divided into angiography-positive, large-medium vessel or angiography-negative, small vessel CNS vasculitis. Angiography-positive PACNS can be further divided into progressive and nonprogressive. Progressive is defined as new areas of stenosis or more than 25% decrease in diameter in the areas of initial stenosis on angiography 3 months after initial imaging.³

CLINICAL PRESENTATION PACNS presents in a variety of ways in children.²⁻⁴ Headaches, seizures, and focal neurologic deficits from strokes are more

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Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

At time of symptom onset, lesions are predominantly in right frontal parietal lobes and pons with minimal left-sided lesions on T2 fluid-attenuated inversion recovery (FLAIR) MRI (A) and T1 contrast-enhancing images (B); 3 months later and at time of biopsy, the right-sided lesions worsened (now including midbrain) along with new left-sided lesions including in basal ganglia on T2 FLAIR MRI (C) and T1 contrast-enhancing images (D). Brain biopsy demonstrates findings consistent with primary angiitis of the CNS, including inflammatory infiltrate of cell wall (black arrows) as seen by hematoxylin & eosin staining (E). The inflammatory infiltrate was predominantly CD3-positive T cells (red arrows) by immunohistochemistry (F).

prominent in PACNS compared to other demyelinating diseases. Other symptoms include encephalopathy, neuropsychiatric symptoms such as behavior or mood changes, fever, fatigue, and nausea.^{2,3} Ischemic strokes are more likely in angiography-positive PACNS whereas angiography-negative PACNS more likely presents with seizures. PACNS should be considered when patients do not follow the typical course for other demyelinating diseases, such as ADEM.

DIAGNOSTIC WORKUP Laboratory and CSF studies.

Initial evaluation for PACNS involves clinical assessments, neuroimaging, and laboratory investigation including blood and CSF. Clinical assessment includes a detailed neurologic examination and survey for systemic illnesses. Neuropsychiatric testing can also be considered. Laboratory testing includes a complete blood count with differential inflammatory markers (CRP, ESR, vWF antigen, ANA, anti-DNAse, anti-Ro, anti-La, and anti-TPO antibodies,

and serum autoimmune encephalitis panel). vWF antigen, a protein derived from endothelial cells, is elevated up to 70% in children with PACNS, more commonly in small vessel PACNS. Conversely, vWF antigen levels are normal in demyelinating disease.² Lumbar puncture should be performed, including opening pressure. CSF studies include cell count with differential, protein, glucose, infectious workup (bacterial, fungal, viral cultures, and serology), oligoclonal banding, IgG index, and CSF autoimmune encephalitis panel. While serum evaluation can be normal, small vessel PACNS and progressive PACNS often have increased ESR or CRP. CSF cell count and protein are often elevated in biopsy-positive patients.^{2,3}

Imaging studies. Given the limitations of CT, MRI is the preferred imaging modality in the workup of a child with suspected PACNS. Neuroimaging should include a brain MRI with contrast and MRA. Imaging findings include multiple T2 lesions and contrast enhancement in all forms of PACNS. In angiography-positive PACNS, narrowing of blood vessels is observed and diffusion-weighted imaging and apparent diffusion coefficient imaging may demonstrate acute ischemia. Gradient echo or susceptibility-weighted imaging is important to guide the decision for antithrombotic therapy. Discordant progression, which is worsening and improvement in different vessels, can be observed in 26%.⁵ If initial workup is supportive of PACNS or if the diagnosis remains unclear, then conventional angiogram should be considered. However, sensitivity of conventional angiography ranges from 40% to 90% and specificity is 30%.⁶

Biopsy. If imaging studies including conventional angiography are normal or unrevealing, brain biopsy can aid diagnosis. In a pediatric study, brain biopsy had a diagnostic yield of up to 70%, with PACNS being the most common diagnosis.⁷ A large meta-analysis of brain biopsies including children demonstrated that the highest diagnostic yield by biopsy in cryptogenic neurologic disease is PACNS.⁶ Biopsy should include leptomeninges and gray and white matter tissues for highest diagnostic yield; lesional and nonlesional biopsies reportedly have similar diagnostic yield⁸ and thus nonlesional biopsy should be considered when lesional is not possible.^{2,8}

TREATMENT Treatment is dependent on PACNS subtype. All patients should be treated with antithrombotic therapy symptomatically as needed, including antiseizure medications and antipsychotics. Vitamin D and calcium should be supplemented during steroid administration. Nonprogressive PACNS is monophasic and treated with steroids. Steroid dosing

is initially pulse methylprednisolone 30 mg/kg/d (maximum 1 g) for 3–5 days, then 3 months of high-dose oral prednisone 2 mg/kg/d for 1 month (maximum 60 mg), 1.5 mg/kg/d for 1 month, and 1 mg/kg/d for 1 month.^{2,3} Antithrombotic therapy is low-molecular-weight heparin for 2 weeks and then low-dose aspirin. Treatment efficacy is assessed clinically and by 3-month follow-up MRI.

For progressive or small vessel PACNS, treatment includes induction and maintenance over 2 years. Treatment is based upon an open-label cohort trial in pediatric PACNS.⁹ Induction involves the first 6 months with 7 pulses of 500–750 mg/m² of IV cyclophosphamide every 4 weeks. Concomitant cotrimoxazole prophylaxis is administered. In addition, prednisone at 2 mg/kg daily (maximum 60 mg) with a taper to 50, 40, 30, 25, and 20 mg daily and then by 2.5 mg every 4 weeks until discontinued is administered. Urinalysis is obtained with each cyclophosphamide dose to monitor for hemorrhagic cystitis. For girls, endocrinology or gynecology should be consulted for consideration of ovarian failure and fertility problems from cyclophosphamide.

Over the next 18 months, maintenance includes 800–1,200 mg/m² (maximum 2,000 mg) mycophenolate mofetil per day (preferred in small vessel PACNS) or 2–3 mg/kg (maximum 150 mg) azathioprine per day (for progressive angiography-positive PACNS). Prednisone should continue to be weaned.^{2,9} During this time, patients are at high risk for infections due to immunosuppression.

PROGNOSIS IN PEDIATRIC PACNS Prognosis is variable in pediatric PACNS. One-third of patients with nonprogressive PACNS have reportedly achieved full neurologic recovery 1 year after diagnosis. However, patients with nonprogressive PACNS were less likely to achieve full recovery if untreated with steroids. For angiography-negative PACNS, rates of recovery at 2 years have been reportedly 50%, with mild residual deficits and cognitive dysfunction in the rest of the patients.^{2,10} Seizures at time of presentation are associated with higher disease activity. Persistent motor deficits are more likely in angiography-positive PACNS whereas lasting cognitive dysfunction is more likely in angiography-negative PACNS. While earlier studies reported a high mortality rate in pediatric PACNS, more recent reports suggest that morbidity and mortality are decreased with earlier recognition and treatment.^{2,10}

DISCUSSION PACNS can mimic other more common diseases such as ADEM; lesions in ADEM are usually bilateral, diffuse, and nonenhancing and resolution is expected in 3 months. Features atypical for ADEM in this patient include headaches, seizures,

steroid dependence, and subsequent worsening lesions. Imaging characteristics atypical for ADEM include unilateral predominance, increased enhancement, and the juxtacortical/cortical pattern of lesions. This case highlights the importance of early diagnosis of PACNS as early treatment leads to improved outcomes in children.

AUTHOR CONTRIBUTIONS

Grace Kim: treating clinician, literature review, clinical review, imaging review, manuscript preparation, editing. Tanuja Chitnis: treating clinician, literature review, clinical review, imaging review, manuscript preparation, editing.

STUDY FUNDING

No targeting funding reported.

DISCLOSURE

G. Kim reports no disclosures relevant to the manuscript. T. Chitnis has served as an advisor for Biogen-Idec, Novartis, Sanofi-Aventis, and Teva Neurosciences. Go to Neurology.org for full disclosures.

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Neurology 2017;89:e268-e271

DOI 10.1212/WNL.0000000000004718

This information is current as of December 4, 2017

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