

Angiography-negative primary angiitis of the central nervous system in childhood

Case report

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Childhood primary angiitis of the CNS is a recently characterized, potentially reversible disease process. A favorable outcome requires early diagnosis and appropriate treatment. The histological findings of childhood primary angiitis of the CNS are characterized by a lymphocytic, nongranulomatous vasculitis. This disorder can lead to neurological deficits, seizures, and strokes. Laboratory and radiographic investigation are part of the evaluation, but are often nonspecific. Conventional angiography can fail to show any abnormality, and biopsy may ultimately be required for diagnosis. Although there can be significant rates of morbidity and mortality if untreated, patients who receive appropriate therapy can experience excellent outcomes, and in many cases will demonstrate near-complete or total clinical and radiographic resolution. The case of a previously healthy 13-year-old girl with new-onset generalized tonic-clonic seizures is presented, with a review of the literature.

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KEY WORDS • primary angiitis of the central nervous system • childhood primary angiitis of the central nervous system • arteriopathy • vasculitis • vascular disorders

IN 1959 Cravioto and Feigin¹⁵ first described a noninfectious granulomatous primary angiitis of the CNS (PACNS). They proposed that their 2 cases and 6 other previously reported cases in the literature represented a unique clinicopathological entity characterized by a granulomatous angiitis with necrosis, giant cells, and lymphocytic infiltration found exclusively in the vessels of the CNS. In 1988 Calabrese and Mallek¹² proposed diagnostic criteria for adult PACNS based on an extensive review of 40 previously reported cases and 8 additional cases of their own. These criteria included the recent onset of headaches, confusion, and unexplained multifocal neurological deficits, angiographic evidence of vasculitis, exclusion of systemic conditions known to cause secondary vasculopathies, and biopsy to confirm vasculitis and exclude neoplasm, infection, and noninflammatory cerebrovascular disease. Using the Calabrese criteria for PACNS, there has been a marked increase in the recognition, diagnosis, and successful treatment of this disease. Similarly, using

the Calabrese criteria has led to an increased recognition and diagnosis of childhood PACNS (cPACNS). Numerous case reports and series of patients with cPACNS have now been published, primarily in the rheumatology literature.^{4,5,19,25,27,29,32}

Early diagnosis followed by aggressive treatment is critical to improve survival and neurological outcome in cPACNS.^{4,8,19,22,23,37} We report a case of biopsy-proven, angiography-negative PACNS in a 13-year-old girl. To our knowledge there are no reports of cPACNS in the neurosurgical literature.

Case Report

History and Examination. This right-handed 13-year-old girl presented to the emergency room after a 5-minute seizure characterized by flailing of her upper extremities, drooling, and a loss of consciousness. Following the seizure she reported an ill-defined numbness in her entire body. Results of her neurological evaluation including funduscopic examination were within normal limits, except for mild scoliosis.

The patient's medical history revealed a positive purified protein derivative test for *Mycobacterium tuberculosis*.

Abbreviations used in this paper: cPACNS = childhood primary angiitis of the CNS; ESR = erythrocyte sedimentation rate; MMF = mycophenolate mofetil; MRA = MR angiography; NAA = N-acetyl-aspartate; vWF = von Willebrand factor.

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sis 2 years prior to admission with treatment noncompliance. She also had a history of asthma. She had traveled in the US and the Caribbean, with animal exposure a few years previously.

Neuroimaging. Admission CT scanning showed a 17 × 19-mm enhancing lesion in the left frontal lobe with surrounding edema and a 5-mm left frontal lobe convexity lesion. The MRI studies showed multifocal enhancing lesions throughout the brain, most pronounced in the left frontal and parietal lobes (Fig. 1). Magnetic resonance spectroscopy revealed elevated choline peaks and decreased *N*-acetylaspartate (NAA) peaks. Results of MR angiography (MRA) were negative, and the 4-vessel angiogram was also negative.

Laboratory Findings. Laboratory results were as follows: white blood cell count 5.6×10^3 cells/ μ l, ESR 6 mm/hour, and C-reactive protein < 0.5 mg/dl. Analysis of CSF showed 7×10^3 cells/ μ l for white blood cells (10% segmented leukocytes, 90% lymphocytes), glucose 47 mg/dl, and protein 34 mg/dl. Based on the recommendations of the infectious disease specialists, extensive testing of CSF for infectious causes, including acid-fast bacillus, fungus, *Cryptococcus*, and cysticercosis, was negative. Serology for an infectious cause was significant only for evidence of a probable past infection with cytomegalovirus and *Bartonella henselae* (causative agent for cat scratch fever). The angiotensin-converting enzyme level was 48 U/L, ruling out sarcoidosis.

Operation. Because of the spectroscopy results the patient was brought to the operating room for definitive diagnosis. Two lesions in the left frontal lobe were excised. Pathological investigation revealed gliosis with focal infarction. Vessels in and around the necrotic areas were thickened, with chronic inflammatory cells surrounding and within the vessel walls. Lymphocytes showed a mixture of CD3 T cells and CD20 B cells, which was consistent with a lymphocytic vasculitis or primary cerebral angiitis (Figs. 2 and 3).

Postoperative Course. The patient was seen by rheumatology and oncology specialists and started on prednisone. Over the ensuing year she remained neurologically intact but became cushingoid. Her follow-up MRI studies have shown marked improvement in the enhancing lesions and no new lesions.

Discussion

Childhood primary angiitis of the CNS has been described primarily in the rheumatological literature.^{4,5,19,27,29,32,41} Since 2006, the Calabrese criteria have been adopted for use in children > 1 month and < 18 years of age.⁵ These criteria are as follows: a newly acquired and otherwise unexplained neurological or psychiatric deficit, angiographic or histological evidence of angiitis limited to the CNS, and the absence of a systemic condition that could cause or mimic findings.¹² The differential diagnosis can be broad and includes primary, inflammatory (such as lupus), and infectious vasculitides. Herpes zoster in particular has been described in association with CNS vasculitis. Demyelinating diseases as well as metabolic disorders such as

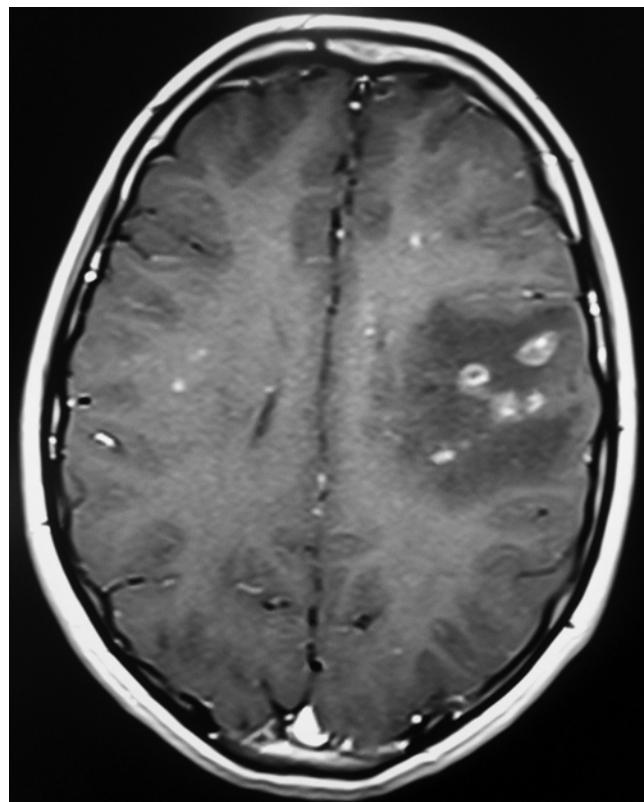


Fig. 1. Preoperative axial T1-weighted MRI study obtained with contrast.

MELAS (mitochondrial encephalopathy with lactic acidosis and strokelike episodes) can also present in a similar fashion to cPACNS.^{10,17,23} Consultation with rheumatological and infectious disease specialists, as in this case, may be helpful during the evaluation. In children who present with a possible diagnosis of cPACNS, the workup should be prompt, and includes a variety of hematological tests, examination of the CSF (primarily to rule out mimicking conditions such as demyelinating disorders), electroencephalography, CT scanning, MRI including MRA, cerebral angiography, and brain biopsy.

Two distinct subtypes of cPACNS have been identified. Angiography-positive cPACNS affects large and medium-sized cerebral blood vessels. Angiography-negative cPACNS affects the small vessels.^{14,17,23} Each has a unique clinical presentation and radiographic appearance. The approach to treatment and outcome also differs between these 2 distinct entities. Although this case represents a case of angiography-negative cPACNS, both clinical entities will be reviewed (Table 1).

Angiography-Positive cPACNS

The typical presentation consists of headache, acute hemiparesis, hemisensory deficits, or fine motor deficits. Electroencephalography most often reveals generalized slow waves.¹² The ESR is the most commonly elevated inflammatory marker, but laboratory abnormalities are insensitive, nonspecific, and incapable of ruling out or diagnosing primary or secondary CNS vasculitis.⁹ Analysis of the CSF reveals pleocytosis and elevated protein in only

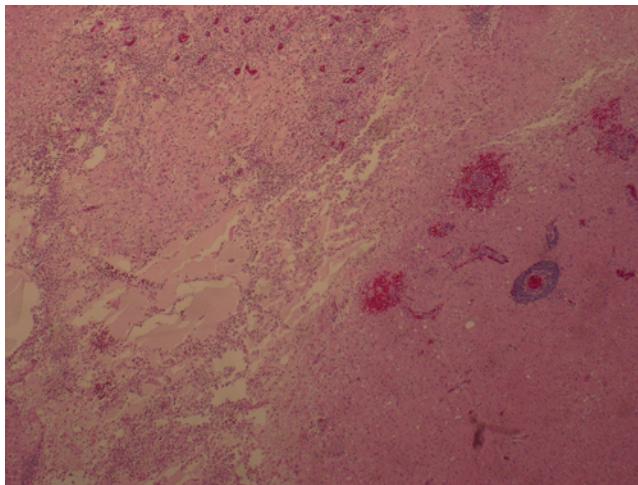


Fig. 2. Photomicrograph of a histopathological section of the lesion. Multiple regions of subacute necrosis with macrophages are present. H & E, original magnification $\times 2$.

30% of cases, and oligoclonal banding is usually absent. Large- to medium-vessel cPACNS is defined by Calabrese criteria as for adult PACNS;¹¹ in most instances the diagnosis hinges on a combination of either positive biopsy results or high-probability vascular imaging, and laboratory testing is largely relegated to detecting the myriad of mimicking conditions, including infections, malignancies, hypercoagulable and embolic states, and other inflammatory diseases.^{9,17}

More recently von Willebrand factor (vWF) antigen, a factor that is released by endothelial cells after vascular injury, has been proposed as a potential biomarker to help diagnose and monitor the effectiveness of the treatment in cPACNS.¹³ In their study of 39 patients with cPACNS (25 with angiography-negative and 14 with angiography-positive disease), Cellucci et al. found that vWF antigen levels were increased at diagnosis in 65% of children and decreased significantly after treatment.

Sensitivity of MRI approaches 100%,^{3,12,20,37} combining neuroimaging with lumbar puncture increases the overall sensitivity, and normal findings on both would have a high negative predictive value.^{9,10} The most specific findings are provided by serial examinations in which multiple foci of ischemia are detected in varying anatomical locations and developing over time. Such studies typically demonstrate areas of acute ischemia with unilateral or bilateral, multifocal, proximal, and supratentorial T2 hyperintensities involving both the gray and white matter.^{3,5,20} Lesions can also manifest as hemorrhages.^{20,32} Leptomeningeal enhancement can occur in the granulomatous variant of PACNS,^{9,20} and vessel-wall enhancement is highly suggestive of inflammation of the vascular wall in cPACNS.^{23,26} Furthermore, approximately 15% of patients with PACNS can present with a masslike lesion, mimicking those often seen in tumor, including vasogenic edema and multifocal Gd enhancement.^{6,34}

The initial report of spectroscopy findings included marked elevations of the glutamate and glutamine peaks, which have been associated with inflammatory disorders, but only minimal elevation of the choline peak, which is

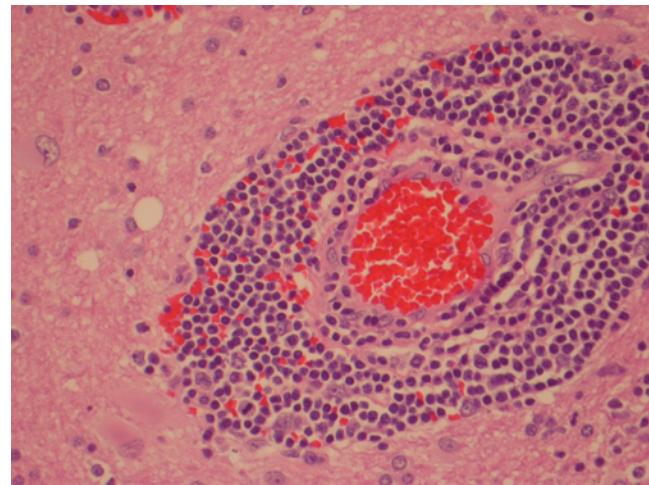


Fig. 3. Photomicrograph of a histopathological section of the lesion. Vessels in and around the area of necrosis are thickened, with chronic inflammatory cells around and in the vessel walls. The lymphocytes present are a mixture of CD3 T cells and CD20 B cells. H & E, original magnification $\times 40$.

typically elevated in aggressive neoplastic processes secondary to increased cell turnover. There was also marked elevation of the lipid peak, which is indicative of destructive processes with release of free lipids from cell membranes, without lactate peak elevation or evidence of gross necrosis, and mild decrease of the NAA peak.³⁴

A second report, however, detected elevation of choline-containing compounds, as well as in the creatine, NAA, and lipid peaks, in contrast to findings from Panchal et al.³⁴ The authors postulate that this may be due to granulomas retaining moderate proliferation potential. There was mild elevation of the glutamate and glutamine peaks, however. It is interesting to note that in the latter case report central necrosis was identified in the gross specimen. These investigators also point out that the low fractional anisotropy value on diffusion tensor imaging lowers the probability of the radiographic lesion being consistent with malignant glioma.⁶ In both cases there was resolution of MRI findings after completion of appropriate therapy.

Conventional angiography or MRA is required for diagnosis of large- to medium-vessel vasculitis. Beading of one or more vessels is often described,^{1,3,12,16,20,32} and there may be vessel stenosis, tortuosity, and occlusion as well. The involved vessels usually, but do not always, correspond to the territory of radiographically confirmed lesions.³ Transient aneurysm formation has been reported,^{3,21,32} and in rare cases the clinical presentation occurs secondary to intracranial hemorrhage.^{7,19,27,32,33,36,37}

Given the positive findings on angiography, brain biopsy is typically not pursued. It should also be kept in mind that there are reports of spinal cord involvement of PACNS.^{16,28,33,42} Reported histological characteristics of granulomatous CNS vasculitis include a transmural infiltrate in which lymphocytes, plasma cells, and histiocytes predominate, with ill-defined granulomas, evidence of giant cells, and areas of vessel wall necrosis. The giant cells may appear eccentrically in any layer of the vessel wall.

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TABLE 1: Comparison of angiography-positive and angiography-negative cPACNS*

Feature	Angio-Positive cPACNS	Angio-Negative cPACNS
presentation	HA; acute hemiparesis; hemisensory deficit; fine motor deficit; stroke (nonprogressive)	systemic symptoms (fever, malaise, flulike symptoms); HA; intractable Sz's; ataxia; cognitive decline; behavior changes; hemiparesis; facial droop; optic neuritis; myelitis
significant laboratory results	ESR can be elevated or normal; CSF may or may not demonstrate elevated protein &/or pleocytosis	ESR can be elevated or normal; CSF may or may not demonstrate elevated protein &/or pleocytosis
MRI findings	unilat or bilat multifocal lesions on T2/FLAIR imaging; leptomeningeal &/or vessel wall enhancement, parenchymal edema, or hemorrhage may be present	unilat or bilat multifocal lesions on T2/FLAIR imaging; leptomeningeal &/or vessel wall enhancement, parenchymal edema, or hemorrhage may be present
angiographic findings	focal areas of stenosis; "beading" or "sausage" pattern	negative (by definition)
pathology & types of lymphocytes present	granulomatous & lymphocytic infiltrate w/ T & B cells	nongranulomatous lymphocytic infiltrate of T > B cells
treatment	progressive: monthly cyclophosphamide & high-dose corticosteroids × 6 mos followed by 18 mos maintenance therapy; nonprogressive: 5 days intravenous methylprednisolone followed by 3 mos tapered oral glucocorticoids; both w/ & w/o antiplatelet therapy (now recommended)	cyclophosphamide induction × 6 mos followed by 18 mos of MMF maintenance therapy w/ or w/o antiplatelet therapy
outcomes	generally excellent, w/ only a minority w/ persistent neurological deficit on completion of therapy	generally excellent, w/ no detectable neurological deficit on completion of therapy

* Angio = angiography; HA = headache; Sz = seizure.

The process can involve both arteries and veins, with the media and adventitia most often affected. Chronic angiitis may demonstrate intimal fibrocellular proliferation, and there may be thrombosis within the vessels.^{15,28} Weakening of the arterial walls secondary to fibrinoid necrosis and leading to aneurysm formation has been postulated to occur.^{21,32,42} Beta-amyloid deposition has been described in a subset of granulomatous adult PACNS.^{30,37}

The initial literature on adult PACNS reported a high mortality rate, and many of the histological studies were performed postmortem.^{12,15} Rapid progression leading to death was also reported in the early pediatric cases.^{27,29,32} Treatment with corticosteroids and cyclophosphamide was initially reported by Cupps et al.,¹⁶ and treatment regimens are now largely based on this paradigm. The early reports of cPACNS, once the diagnosis was recognized, included treatment with high-dose corticosteroids and immunosuppression, usually with cyclosporine.¹⁹ Treatment for progressive angiography-positive cPACNS now commonly consists of induction therapy of monthly intravenous cyclophosphamide in addition to high-dose steroids for 6 months, followed by maintenance treatment with either oral methotrexate or azathioprine for 18 months.^{5,8,27} Mycophenolate mofetil (MMF) is also sometimes used as the oral maintenance therapy, based on a report of 3 children (2 with angiography-negative cPACNS and 1 with angiography-positive cPACNS) who had been weaned off the maintenance steroids, with recurrence of cPACNS; excellent results were obtained using MMF.³⁸ A short course of heparin followed by an antiplatelet agent is frequently given, although anticoagulation for cerebral vessel inflammation remains controversial. Excellent results have been reported in cases of cPACNS treated using this proto-

col.^{3,5} Treatment for nonprogressive angiography-positive cPACNS is also controversial, although patients may benefit from a short course of high-dose steroids and an antiplatelet agent;¹⁷ one group recommends a 5-day course of pulsed intravenous methylprednisolone followed by a 3-month course of tapered oral glucocorticoids, with a low-dose antiplatelet agent.²³

Benseler et al.⁵ reviewed a series of 62 conventional or MRA-positive cases of cPACNS for the purpose of identifying prognostic factors. Presence of neurocognitive dysfunction (as opposed to focal neurological deficit), multifocal parenchymal lesions on T2-weighted MRI, and distal stenosis on angiography were predictive of progressive cPACNS. Other factors associated with worse prognosis identified by Lanthier et al.²⁷ include acute stroke presentation secondary to involvement of large and medium-sized arteries, granulomatous pathology, and delayed treatment.

Angiography-Negative cPACNS

The presentation of small-vessel vasculitis frequently includes systemic features (fever, malaise, and flulike symptoms), headache, intractable seizures, ataxia, cognitive decline, or behavior changes.^{4,17,18,23,24} Hemiparesis or facial droop may be presenting features, and optic neuritis or myelitis may be present.^{23,24,38} The course of presentation can vary over weeks to months, although acute presentations may also occur.¹⁷ Seizures at presentation were found to be associated with higher disease activity, and the presence of seizures, cognitive dysfunction, or visual symptoms is more likely to be found with small-vessel PACNS, whereas motor deficits were more frequently found in medium- to large-vessel PACNS.¹⁴

As for angiography-positive cPACNS, ESR and C-reactive protein may be mildly elevated, and CSF pleocytosis or elevated protein may be present, but again these are neither sensitive nor specific.^{2,4,9,23,24,27,39,40} The C3 complement and vWF antigen may also be elevated.^{23,24} The electroencephalography findings will often be abnormal, but this too is neither specific nor sensitive.^{18,23,24}

T2-weighted MRI studies reveal multifocal hyperintensities in both white and gray matter, which may be unilateral or bilateral.^{17,18,23,24} Diffusion restriction is uncommon but can detect areas of acute ischemia in the deep or subcortical white matter.³¹ Lesions do not typically conform to a large-vessel vascular territory, and Gd enhancement has been postulated to be sensitive for small-vessel PACNS.^{18,35} By definition, angiography is negative;¹⁷ it has been postulated that the affected vessels are smaller than the resolution of the angiogram.^{27,35} Elevated intracranial pressure may be detected.^{4,39}

Biopsy, which is of lower diagnostic yield in adults than in children,^{2,11,17} reveals necrotizing granulomatous lesions in adults,^{28,40} but lesions consisting of segmental, nongranulomatous, intramural infiltration of B and predominantly T lymphocytes involving small arteries, arterioles, capillaries, or venules in children.^{18,24,29,41} Occasional plasma cells, polymorphonuclear cells, and eosinophils may be present.¹⁸ There may be gliosis, calcification, and pallor of myelin staining surrounding the areas of active inflammation.^{4,18,27} Biopsy sampling comes with a high false-negative rate, as high as 25%,¹² and can prove to be nondiagnostic because of the skip-lesion nature of the disease.^{1,11,16} A technically adequate biopsy sample should include the leptomeninges, cortex, and white matter,^{9,10,12,16,17,40} because the leptomeninges often enhance on MRI sequences.⁹ In one review negative biopsy results were reported in cases in which the leptomeninges were not included on the biopsy samples, but PACNS was confirmed on postmortem examination.¹²

Alrawi et al.² have put forth a set of histopathological criteria for angiography-negative small-vessel cPACNS: a minimum of 2 layers of lymphocytes within or around the walls of parenchymal or leptomeningeal and dural vessels; structural alterations of the vessel wall such as prominence of endothelial cells, with or without necrosis; pink neuronal cytoplasm and pyknotic neuronal nuclei with or without pyknotic glial nuclei and astrocytic gliosis; neuronophagia; parenchymal edema; and exclusion of alternate diagnoses. Definitive diagnosis requires fulfillment of all criteria and probable diagnosis requires fulfillment of all criteria except the first.

At the present time there is no standard treatment protocol for angiography-negative cPACNS, although there are reports of generally excellent long-term outcomes with 6 months of cyclophosphamide induction followed by 18 months of MMF maintenance therapy.^{23,24} Azathioprine has also been used for maintenance therapy, but was found to be associated with disease flares, and is not typically used at this time.^{14,24}

Conclusions

Diagnosis of cPACNS is a challenge due to several factors, including its rarity, wide differential diagnoses that

can manifest similarly to cPACNS, and nonspecific laboratory and radiographic findings. Small-vessel cPACNS, in particular, can demonstrate negative results on angiography. The development of newly acquired neurological deficits with rapid progression in a previously healthy child without evidence of infection or malignancy should lead to the clinical suspicion of cPACNS, and in angiography-negative cases, small-vessel cPACNS, keeping in mind that the diagnosis may ultimately be made solely on the basis of biopsy findings. Although there can be significant morbidity and mortality if cPACNS is untreated, patients who receive appropriate therapy can experience excellent outcomes, and in many cases demonstrate near-complete or total clinical and radiographic resolution.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Marlin, Gaskill. Acquisition of data: Marlin, Gaskill. Analysis and interpretation of data: all authors. Drafting the article: all authors. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Park. Administrative/technical/material support: all authors. Study supervision: all authors.

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