Case Report

Cyclophosphamide Treatment of Primary Angiitis of the Central Nervous System in Children: Report of 2 Cases

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ABSTRACT. Primary angiitis of the central nervous system (PACNS) is a rare, idiopathic vasculitis diagnosed most frequently in adults. We describe 2 children presenting with hemiplegia from PACNS treated with cyclophosphamide. Diagnosis in one child was based on abnormal angiography. Oral, but not intravenous (IV), cyclophosphamide was effective in preventing progressive weakness. The second child had unremarkable angiography, but brain biopsy revealed vasculitis; IV cyclophosphamide prevented further weakness. Both cases highlight the importance of early diagnosis and treatment. (J Rheumatol 2006;33:2078–80)

Key Indexing Terms:
CYCLOPHOSPHAMIDE PRIMARY ANGIITIS CHILDREN

Primary angiitis of the central nervous system (PACNS) is a rare, idiopathic vasculitis, diagnosed most frequently in adults[1]. In children, PACNS can result in permanent cerebral damage; potential for survival may be compromised by delayed diagnosis and treatment. No consistent laboratory abnormalities are diagnostic[2]. While neuroimaging and lumbar puncture can be helpful, angiography or brain biopsy is necessary for diagnosis[3]. Early immunosuppressive therapy has improved prognosis[4].

There are few reports of children with PACNS. A series comparing 5 new to 5 previously reported cases suggested that onset can occur at any age, possibly more frequently than previously recognized[5]. A recent study presented 2 patients and reviewed 8 previously reported cases[6]. We describe 2 children with PACNS. The first, diagnosed by abnormal angiography, responded to oral, but not intravenous (IV), cyclophosphamide. The second, diagnosed by brain biopsy when cerebral angiography was unremarkable, responded to IV cyclophosphamide.

CASE REPORTS

Case 1. A previously healthy 5-year-old girl developed transient, mild, right-side weakness and slurred speech. Computed tomography (CT) of the head was normal. One day later, right hemiparesis developed; repeat CT revealed a small infarction of the left globus pallidus with extension to the internal capsule. Magnetic resonance imaging (MRI) showed infarcted areas in the left basal ganglia, including globus pallidus, caudate nucleus, and thalamus. Cerebral angiography was unremarkable. Coagulation studies, lupus anticoagulant, antiphospholipid antibody screens, erythrocyte sedimentation rate (ESR), and complete blood count (CBC) were unremarkable, except for mild lymphopenia. She was discharged with gradually improving strength. Six months later, she developed progressive right hand weakness, but normal ESR and CRP. Cerebral angiogram revealed narrowing of the left internal carotid artery and M1 segment of the middle left cerebral artery (Figure 1).

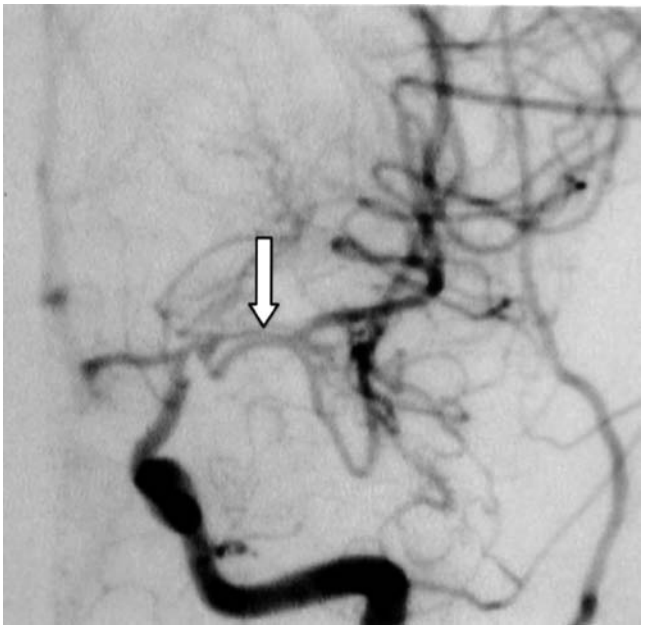

Figure 1. Angiogram, Case 1. Irregularity and narrowing of the M1 segment of the left middle cerebral artery (arrow). The A1 segment of the left anterior cerebral artery is also narrowed, but it is not possible to determine if this is the result of pathology or of congenital atresia.

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Repeat MRI showed no change. Despite IV cyclophosphamide and methylprednisolone, weakness persisted; headaches and left leg weakness developed. Two months later, symptoms and findings improved with a change to oral cyclophosphamide and prednisone. Two years after initial onset, she complained of transient right-side weakness and headaches after a flu-like illness. Cerebral angiography revealed the same findings as previously, with no new abnormalities. Steroids were tapered, and cyclophosphamide was discontinued after 6 months. Verapamil was prescribed; 9 years following the initial episode the child continues taking verapamil with no new symptoms or laboratory or physical findings. She remains physically active and is doing well in school.

Case 2. A 7-year-old girl was admitted with left hemiparesis, posterior, nonradiating neck pain, headache, abdominal pain, and vomiting. Tonic clonic seizures, diagnosed at 2.5 years, were well controlled by anticonvulsant medications. For several months, she complained of headaches and forgetfulness. There was no fever, sleepiness, or trauma. CT scan showed cerebral edema and punctate areas of high attenuation within the right cerebral hemisphere, consistent with calcifications. Low attenuation of the right side with suspected gliosis was noted. MRI revealed right-side white matter changes (Figure 2). ESR, coagulation studies, and CBC were unremarkable, except for mild lymphopenia. Antinuclear antibody (ANA) was positive at 1:5120, nucleolar pattern, with no other autoantibodies or serologic abnormalities suggestive of lupus. Decadron was started. Cerebrospinal fluid (CSF) showed 1 leukocyte/mm^3, glucose 62 mg/dl, protein 17 mg/dl, and negative culture. MR angiogram was unremarkable. Cerebral angiography revealed only subtle irregularity of the lenticulostriate branch of the proximal right cerebral artery. Brain biopsy showed perivascular lymphocytic infiltrate of multiple small vessels (Figure 3). Six days after admission, she noted diplopia, followed by generalized seizures. Ativan, rectal diastat, and IV depakote were given. She was discharged taking oral depakote 250 mg and zantac 75 mg, and started IV cyclophosphamide treatment 750 mg/m^2, monthly oral prednisone 10 mg daily, and depakote 250 mg. Neurologic findings and symptoms resolved completely, and her cyclophosphamide was discontinued after 10 months, with no recurrence for 14 months after onset. Although the ANA has remained high titer, no serologic or physical findings have developed to suggest lupus or related disease.

DISCUSSION

Diagnosis of PACNS is difficult, as presentation varies. The most common presenting symptoms are headaches and focal neurological deficits[5]. Although no diagnostic criteria for PACNS in children have been established, our patients, and most other reported pediatric cases, meet the Calabrese criteria for adults[2]. These criteria require acquired neurological deficit for which other causes have been excluded, and angiographic or histopathological features of CNS angiitis[7].

Childhood PACNS can be classified into 2 groups, based upon involvement of large and medium-size arteries, or of small vessels[6]. Our first patient had large artery involvement, similar to children with PACNS who presented with large arterial ischemic stroke, transient ischemic attacks, and subarachnoid hemorrhage[6]. The risk/benefit ratio for brain biopsy is optimal when PACNS affects small vessels[5]. Our second patient had small-vessel involvement and normal angiography. Gradual symptom progression, after presentation with headaches and focal seizures, and normal CSF and ESR are characteristic of this PACNS category. Resolution of angiography may not detect abnormally involved small vessels. Neuroimaging typically reveals nondiagnostic multiple cerebral lesions, as in our patient[6,8].

Treatment is based on a small series of adult patients and

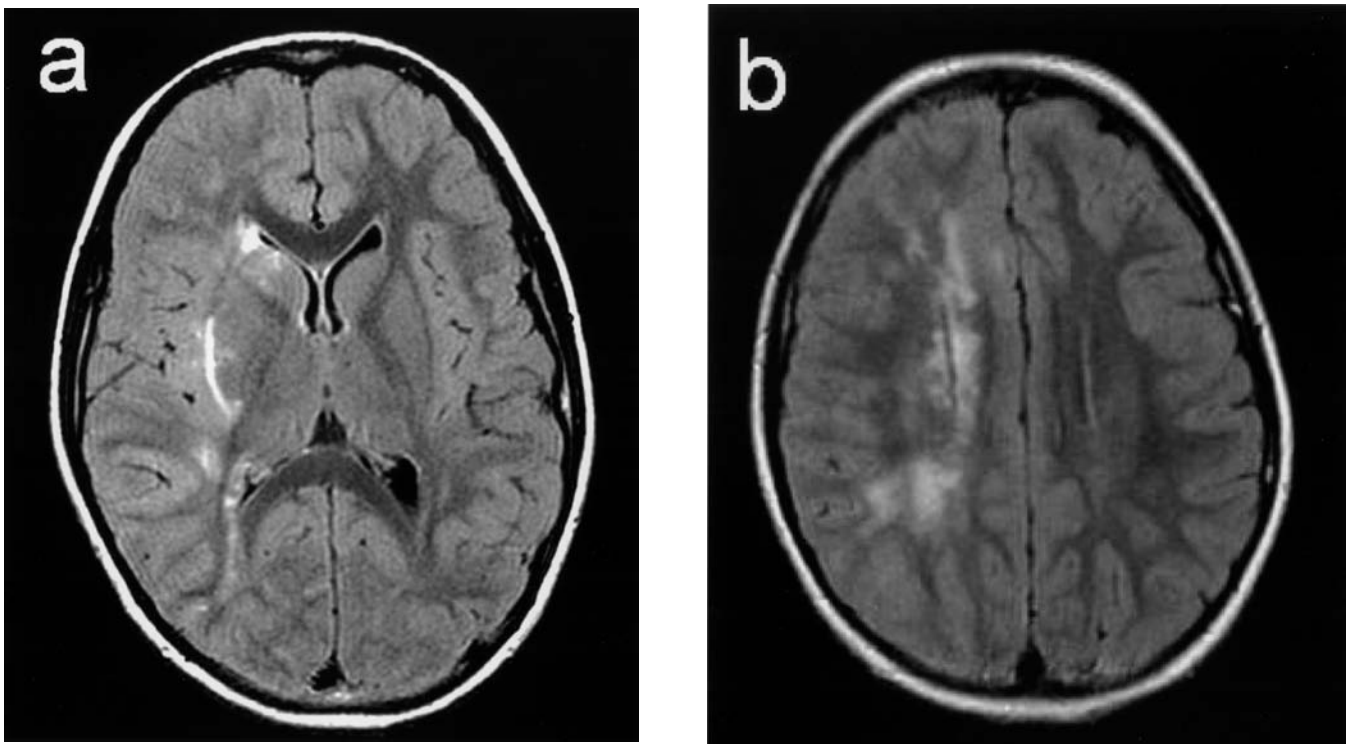

Figure 2. MRI study, Case 2. A. Axial T2 FLAIR (fluid-attenuated-inversion-recovery) image. Multiple sites of T2 hyperintensity in the right hemisphere, including the anterior right caudate head, the right external capsule, and a portion of the right parietal white matter. B. Axial T2 FLAIR image (higher level). Extensive confluent hyperintensity in the white matter of the centrum semiovale of the right hemisphere.

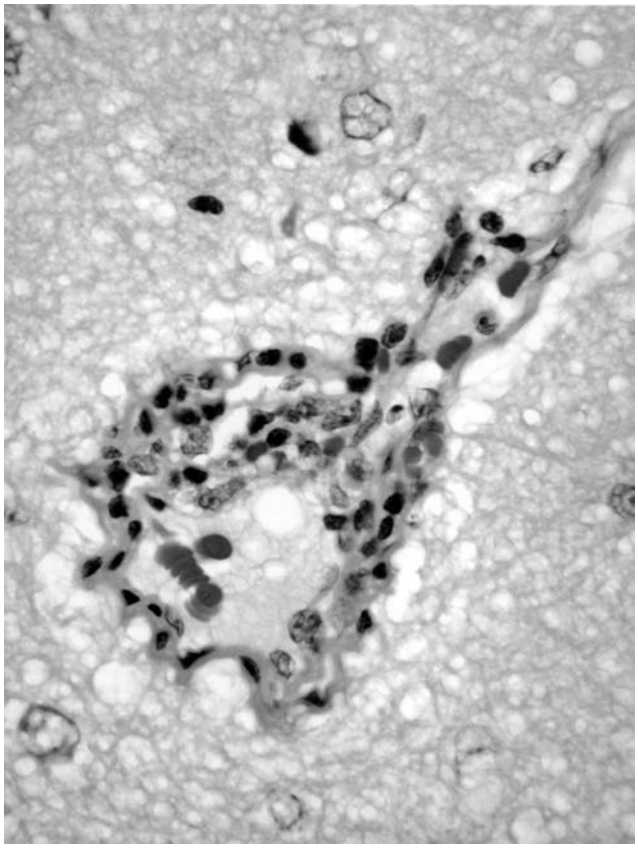

Figure 3. Brain biopsy, Case 2. Small blood vessel with chronic vasculitis, consisting of a significant lymphocytic infiltration of the wall (original magnification 400×).

few pediatric case reports[2]. Corticosteroids and cyclophosphamide improve survival[9]. Pediatric literature frequently reports use of monthly IV cyclophosphamide[2], but oral cyclophosphamide, as we prescribed for our first patient, has been used in children with refractory disease or relapse[6].

The optimal duration of treatment for children with PACNS remains unknown. Outcome is variable; some children experience permanent neurological damage, whereas others have full recovery[2]. Followup is needed to monitor for possible evolution to generalized large-vessel vasculitis or lupus, although both our patients have remained stable. Our experience shows the importance of considering oral cyclophosphamide when IV treatment is ineffective in a child with large-vessel disease.

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