

Primary Angiitis of the Central Nervous System in Children: 5 Cases

KERRY T. GALLAGHER, BRACHA SHAHAM, ANDREAS REIFF, ANNE TOURNAY, J. PABLO VILLABLANCA, JOHN CURRAN, MARVIN D. NELSON Jr, BRAM BERNSTEIN, and DAVID J. RAWLINGS

ABSTRACT. We describe 5 children who meet criteria for primary angiitis of the central nervous system (PACNS). All patients presented with headache and/or focal neurologic deficits and exhibited clinical and/or radiographic evidence of disease progression. Two patients had disease progression prior to combined treatment with cyclophosphamide and corticosteroids; one progressed while receiving intravenous cyclophosphamide and stabilized after a change to daily oral dosing; one progressed after discontinuing therapy after less than 12 months and improved after retreatment; and one progressed on steroid therapy alone but was lost to followup. Children who have frequent or severe headaches or focal neurologic deficits should be carefully evaluated and those meeting criteria for PACNS should be treated aggressively. (J Rheumatol 2001;28:616–23)

Key Indexing Terms:

CENTRAL NERVOUS SYSTEM VASCULITIS
COMPUTER TOMOGRAPHIC ANGIOGRAPHY

STROKE

JUVENILE MIGRAINE
CYCLOPHOSPHAMIDE

Primary angiitis of the central nervous system (PACNS) is a rare form of vasculitis described primarily in middle aged adults¹. To date only 5 children with this condition have been reported (Table 1)²⁻⁵. We describe 5 additional children who meet criteria for the diagnosis of PACNS based upon: unexplained neurologic deficits, angiographic abnormalities typical of vasculitis, and exclusion of other potential etiologies⁵. The treatment and outcome of these patients is described. Our experience suggests that CNS vasculitis

occurs more frequently in children than previously recognized and that combined therapy with corticosteroids and cyclophosphamide may improve disease control.

CASE REPORTS

Patient 1. An 11-year-old boy presented with a possible seizure and altered mental status. Examination revealed right hemiparesis and aphasia. Magnetic resonance image (MRI) revealed an infarct in the head of the caudate nucleus and left putamen extending into the corona radiata. Magnetic resonance angiogram (MRA) revealed extracranial tapering of the proximal left internal carotid artery. Coagulation studies including prothrombin time, partial thromboplastin time, protein C, protein S, antithrombin-3, factor 5 Leiden mutation analysis, urine homocysteine level, and anticardiolipin antibodies were normal. Diluted Russell viper venom test was 1.36 (normal < 1.2) and was considered clinically insignificant. Antinuclear antibody (ANA) was negative. Erythrocyte sedimentation rate (ESR), echocardiogram, and electrocardiogram were normal. Cerebrospinal fluid (CSF) had 0 white blood cells (WBC), 88 red blood cells (RBC), normal protein and glucose. Bacterial and viral cultures were negative. Urine toxicology screen was negative. He was initially treated with aspirin (81 mg daily) and discharged after clinical improvement with the diagnosis of cerebral vascular accident (CVA) of unclear etiology. Five days after discharge he was readmitted with confusion and increased right-side weakness. A computed tomography (CT) scan showed new hypodensities in the left thalamus and left parietal white matter. MRA showed decreased flow in the left internal carotid artery (ICA), tapering of the left proximal ICA with no distal flow. The aspirin dose was increased to 162 mg daily and he was discharged with an outpatient angiogram scheduled to rule out a carotid dissection. Two days later he developed aphasia and increased right hemiparesis. A CT scan showed hypodense areas in the left frontal area and improvement of hypodensities in the left parietal area. An angiogram revealed multiple focal segmental narrowing with high grade stenosis of the left cavernous, supraclinoid, and proximal ophthalmic portions of the internal carotid artery, diminished filling of the middle cerebral artery (MCA), and filling of the anterior cerebral artery (ACA) primarily by collaterals from the posterior circulation. CSF antineuronal

From the Departments of Rheumatology and Radiology, Children's Hospital Los Angeles; and the Departments of Allergy, Immunology and Rheumatology, Neurology, and Radiology, Mattel Children's Hospital at UCLA, Los Angeles, California, USA.

Dr. Rawlings is recipient of a McDonnell Scholar Award; a Leukemia and Lymphoma Society Scholar Award; UCLA Child Health, HHMI, and Pennington Research Awards; and the Joan J. Drake Grant for Excellence in Cancer Research. The Pediatric Rheumatology training programs at UCLA and CHLA are supported, in part, by a grant from the Joseph Drown Foundation and the Southern California Chapter of the Arthritis Foundation.

K.T. Gallagher, MD, Assistant Professor of Pediatrics; B. Shaham, MD, Assistant Professor of Pediatrics; A. Reiff, MD, Assistant Professor of Pediatrics; B. Bernstein, MD, Professor of Pediatrics, Department of Rheumatology; M. Nelson, MD, Associate Professor of Radiology, Department of Radiology, Children's Hospital Los Angeles; A. Tournay, MD, Assistant Professor of Pediatrics, Department of Neurology; J. Curran, MD, Associate Professor of Radiology; J.P. Villablanca, MD, Assistant Professor of Radiology, Department of Radiology; D.J. Rawlings, MD, Associate Professor of Pediatrics, Department of Allergy, Immunology and Rheumatology, Mattel Children's Hospital.

Address reprint requests to Dr. D.J. Rawlings, Division of Pediatric Allergy, Immunology and Rheumatology, Mattel Children's Hospital at UCLA, 22-387 MDCC, 10833 Le Conte Avenue, Los Angeles, CA 90095. E-mail: drawlings@mednet.ucla.edu

Submitted May 24, 2000 revision accepted September 7, 2000.

and CSF and serum antiribosomal P antibodies were normal. Serum antineuronal antibody was 9 Mean Intensity Fluorescence units (normal < 5). Rapid plasma reagent, antineutrophil cytoplasmic antibody, and repeat ANA were normal. Serum complement, cryoglobulins, immunoglobulin levels, and CSF IgG synthesis and oligoclonal bands were normal. He was treated with a 3 day pulse of 1 g/day methylprednisolone followed by 1 g monthly, prednisone 0.5 mg/kg/day, and bimonthly intravenous cyclophosphamide at 10 mg/kg/dose. Two months later serum antineuronal antibody was 7 MIF and was subsequently normal. Cyclophosphamide was changed to monthly dosing, methotrexate (MTX) was begun at 15 mg weekly, and prednisone was slowly tapered. Fourteen months after beginning treatment, corticosteroid therapy was discontinued and MTX was tapered. Twelve months after clinical remission, cerebral angiogram showed moderate stenosis at the distal left ICA and occlusion of the proximal ACA with no new areas of stenosis. Cyclophosphamide was discontinued 19 months after presentation. He was last evaluated 21 months after treatment began and was asymptomatic except for mild residual facial paresis and pronator drift. He continued ASA 81 mg daily and MTX 5 mg weekly.

Patient 2. An 8-year-old girl developed severe headache and emesis from presumed viral gastroenteritis. Over a 2 week period she became progressively “dizzy” and fell, hitting the right side of her head. Examination noted combativeness but was otherwise unremarkable. CT scan revealed a left parietal-occipital hemorrhage that extended into the lateral ventricle. The CSF had elevated red blood cells but no white cells, normal protein, and negative viral, bacterial, and fungal cultures. An angiogram showed focal segmental stenoses of the left ACA, midbasilar artery, right posterior cerebral artery (PCA), and right ICA. There was occlusion of the distal left PCA and focal stenosis or occlusion of the angular branch of the left MCA. ESR was 17 mm/h and peripheral white blood cell count was 26,200 with 95% neutrophils, 4% lymphocytes, and 1% monocytes. Chest radiograph, lower extremity arterial Doppler, echocardiogram, serologic and coagulation investigation (as described for Patient 1) were all normal. She was diagnosed with acute CNS vasculitis and discharged without treatment after clinical recovery. Six days later she developed a generalized tonic-clonic seizure, aphasia, and right hemiplegia, and CT scan showed a new left frontal hemorrhage. She was treated with phenytoin and 2 mg/kg/day of prednisolone. Within a week her speech returned but she remained hemiplegic and was transferred to our institution for rehabilitation and management. Treatment with intravenous cyclophosphamide was initiated but discontinued after a single dose because of uncertainty of the diagnosis, including the rare association of hemorrhagic stroke with vasculitis. She was discharged after completing inpatient rehabilitation. A repeat angiogram was recommended but was not obtained. She continued low dose prednisone and a MRI 6 months after initial presentation showed new signal abnormalities in the right frontal area. Treatment was not modified by the referring physicians and she has since been lost to followup.

Patient 3. A 5-year-old boy presented with 5 months of intermittent severe headaches, emesis, and vertigo initially diagnosed as juvenile migraine. MRI revealed abnormal signal intensity in the right pons and right cerebellum and MRA suggested decreased caliber of the left vertebral artery. CSF had 1 WBC, 0 RBC, normal levels of protein and the inflammatory marker β_2 -microglobulin, negative viral serologies, and negative cultures for bacteria, fungus, mycoplasma and viruses. Angiogram showed multiple areas of stenosis and occlusions in the vertebrobasilar system bilaterally, including bilateral extracranial vertebral artery stenosis (Figure 1A, 1B). Complete blood count (CBC), ESR, urine organic acids, and serological and coagulation tests (as in Patient 1) were normal. Prednisone at 2 mg/kg/day, IV cyclophosphamide 10 mg/kg bimonthly, aspirin 81 mg/day, and warfarin for anticoagulation were initiated. Repeat angiogram 8 weeks later, after prednisone taper to 1 mg/kg/day, showed right vertebral artery occlusion at the site of previous narrowing, decreased filling of the basilar artery, and no improvement in the left midvertebral artery stenosis. Oral cyclophosphamide therapy was begun. Repeat angiogram 3 months later showed improvement in both the right vertebral occlusion and distal basilar

narrowing. Cyclophosphamide was decreased to 3 doses per week. Angiogram 3 months later (10 months after initiation of therapy) showed increased stenosis at the distal basilar artery. Narrowing was also observed in the right superficial temporal artery, but biopsy of that vessel was normal. Daily cyclophosphamide was restarted and an angiogram 3 months later remained unchanged. Cyclophosphamide was tapered, MTX (10 mg week) added, and prednisone changed to alternate day dosing. Angiogram 15 months after initiation of therapy showed improved filling of the basilar artery via the vertebral circulation (Figure 1C). CT angiography obtained concurrently correlated well with the angiogram (Figure 1D) and was therefore used for further followup studies. Two years after initiation of therapy, CT angiography shows continued improvement (Figure 1E, 1F) and he is asymptomatic with a normal neurologic examination. He continues warfarin and aspirin therapy.

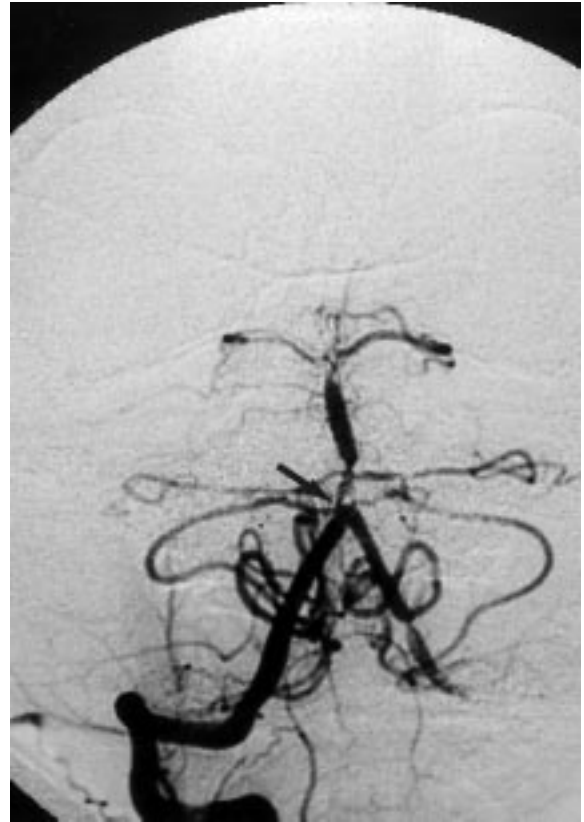
Patient 4. A 7-year-old girl presented to a local emergency department with a history of mild headaches and acute onset of a more severe headache with left-side weakness. CT scan showed a right frontotemporal infarct. Empiric treatment with dexamethasone and acyclovir was initiated. Carotid duplex and echocardiogram were normal. MRI showed infarction of the right basal ganglia, internal capsule, and frontotemporal areas, and MRA showed decreased flow in the right MCA. An angiogram obtained 1 week later showed narrowing at the right supraclinoid ICA, proximal ACA and MCA, and left ICA. Investigation revealed normal cerebrospinal fluid with negative viral and bacterial cultures. ANA was 1:1280; however, further serologic and coagulation investigations (as in Patient 1) was normal. The ESR was 29 mm/h. Prednisone 2 mg/kg/day and aspirin 81 mg were initiated and she was transferred for rehabilitation. Repeat ANA was 1:320, anti-dsDNA antibody was 176 IU/ml (normal < 100), complements were normal, and she has never met additional criteria for systemic lupus erythematosus. Prednisone (2 mg/kg/day) was continued and IV cyclophosphamide (10 mg/kg bimonthly) was initiated. She regained significant function of her left lower extremity but continued to have flaccid severe paresis of the upper extremity. Her ANA titer became negative, dsDNA antibodies remained mid-positive, and serum complement remained normal. Seven months after presentation cyclophosphamide was discontinued because of difficult venous access and azathioprine was begun at about 2 mg/kg/day. Repeat angiogram 12 months after presentation showed improved focal luminal narrowing at the distal right ICA and irregularities of the M2 segment of the right MCA, and continued focal narrowing of the left distal ICA. She was hydrated intravenously overnight and then underwent CT angiography, revealing reduced caliber right MCA consistent with the old infarct. Seven days later she developed a severe headache, disorientation, and worsening of her left hemiparesis. A CT scan showed no new lesions and CSF was normal including antineuronal and ribosomal-P protein antibodies. White blood cell count and ESR were normal. A central venous catheter was placed and she received 3 doses of methylprednisolone 30 mg/kg, cyclophosphamide 10 mg/kg, and ASA 162 mg daily. Her examination results returned to baseline and she continues cyclophosphamide (10 mg/kg) and methylprednisolone (30 mg/kg) every 3 weeks and daily ASA. She has remained asymptomatic for 12 months and continues to make progress in physical therapy.

Patient 5. Patient 5 was almost 8 years old when she developed acute right-side headache and general tonic-clonic seizure, followed by a dense hemiplegia and dysarthria. Laboratory studies included a normal CBC and Westergren sedimentation rate of 15 mm/h. MRI showed right parietal insular cortex and basal ganglia infarcts (Figure 2A). An angiogram showed an irregular segment of the cavernous and supraclinoid portions extending to the M1 segment of the right MCA, and occlusion and narrowing of the A1 segment of the right ACA (Figure 2B). She was transferred for rehabilitation. Echocardiogram, chest radiograph, CSF including cultures, serologic and coagulation investigation (as in Patient 1) were normal. Prednisone was begun at 1.3 mg/kg divided TID for possible vasculitis. Angiogram 3 weeks later showed significant interval progression with tapering and occlusion of the right ICA, poor filling of the ACA and

A



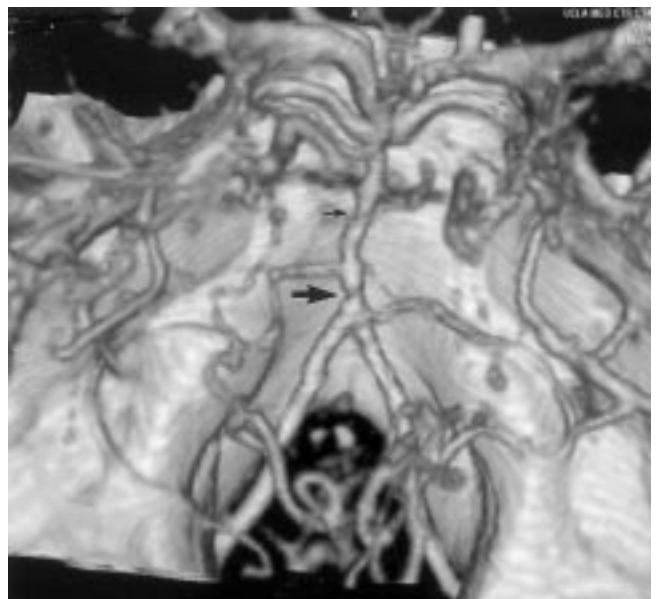
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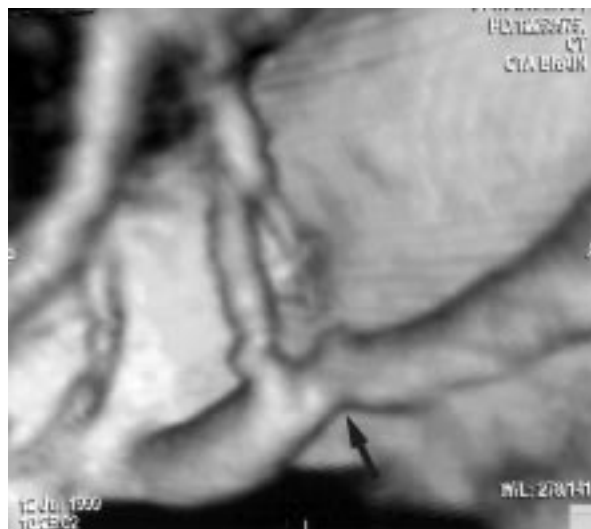


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F

Figure 1. A. Cerebral angiogram in Patient 3: lateral view of left vertebral artery in the neck revealing segmental obstruction (arrow) with collateral filling of distal artery. B. Cerebral angiogram: anteroposterior (AP) view of posterior circulation (right vertebral injection) shows marked focal narrowing of the proximal (arrow) and distal basilar artery. C. Cerebral angiogram: AP view of posterior circulation (right vertebral injection) shows improvement in proximal (arrow) and distal basilar artery narrowing. D. CT angiogram, posterior projection showing proximal (large arrow) and distal (small arrow) basilar artery narrowing. E. High magnification CT angiogram views of left vertebral artery, mediolateral projection, obtained before and (F) one year after treatment, showing interval improvement in focal narrowing of left vertebral artery (arrow) at the site of a posterior inferior cerebellar artery fenestration.

MCA and PCA (Figure 2C). Therapy was changed to methylprednisolone 1 g/day for 3 days followed by 1 g every 3 weeks, IV cyclophosphamide at 10 mg/kg every 3 weeks, and aspirin 81 mg daily. Four months later she began a slow taper of methylprednisolone. Nine months after presentation a repeat angiogram showed occlusion of the right ACA and M1 segment of the MCA, with no new occlusions or narrowing. CT angiogram also showed only the previous occlusions. Cyclophosphamide and methylpred-

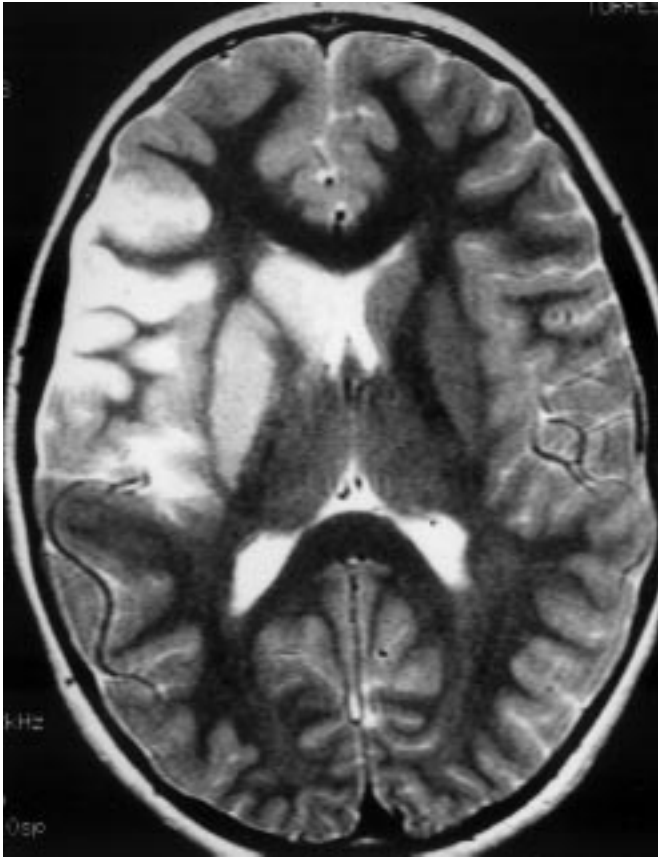
nisolone were discontinued. One year later she continues to gain strength in her left extremities but has required treatment for impulsive and aggressive behavior with methylphenidate hydrochloride.

DISCUSSION

We describe 5 pediatric patients who meet criteria for angiographically defined PACNS. Table 1 summarizes the clinical presentation, therapy, and courses of these patients and the 5 previously reported cases of childhood PACNS. Four of our 5 patients had an acute presentation, 3 with ischemic infarcts and one with hemorrhage. Three patients had a history of headaches, one with mild, intermittent complaints, one with 2 weeks of severe complaints, and one with an initial diagnosis of juvenile migraine. Two of the 5 previously reported cases in children had also been diagnosed with migraines and 4 presented with focal deficits.

These cases underscore the difficulty of making a definitive diagnosis of PACNS. Because a range of disorders may mimic the appearance of vasculitis on angiogram, several authors recommend the use of leptomeningeal and/or brain biopsy to establish this diagnosis. Alternative etiologies include diffuse atherosclerosis, reversible vasospasm, and lymphoproliferative disease. Each of these is poorly documented in the pediatric literature. Infection remains an important potential etiology and evaluation for infection including human immunodeficiency virus and varicella-zoster virus are required in this population as well as in adults. The sensitivity of biopsy is limited (50–75%) because of the skip nature of vasculitis^{6,7}. Superficial temporal artery biopsy was performed in one of our patients (Patient 3) because of narrowing on angiography, but was normal. Because of the improbability of other etiologies in children with a normal infectious, autoimmune, and coagulation evaluation, and the potential risks of brain biopsy, we elected to treat our patients without a histologic diagnosis. While definitive diagnosis of CNS vasculitis requires a positive biopsy, the risk/benefit ratio for biopsy is most optimal in individuals with predominantly small vessel abnormalities. Such individuals were not represented in this series.

All 5 patients had MRI changes consistent with infarction. Three had completely normal CSF studies, one had a transient CSF pleocytosis, and one had evidence of CNS bleed. Stone and colleagues report a sensitivity of 100% with the combination of MRI and lumbar puncture in CNS vasculitis that has been diagnosed by angiography⁸. The specificity and sensitivity of this approach, however, remain unclear because only 3/12 patients in that study had PACNS. At present, angiography remains the gold standard for the radiologic diagnosis of CNS vasculitis. When performed by an experienced neuroradiologist this procedure is relatively safe. In 2 recent series of adults evaluated for possible CNS vasculitis, there were no deaths or neurologic deficits lasting greater than 48 h^{9,10}. Patient 4 had a repeat MCA stroke more than one week after conventional and CT angiography. This was not considered related to the imaging procedures



A



B

Figure 2. A. MRI T2 weighted axial image in Patient 5 showing extensive infarction in the deep nuclear and cortical territory of the right middle cerebral artery. B. Cerebral angiography: right common carotid injection reveals occlusion of the majority of the right MCA branches (arrow). Only the posterior parietal branch of the MCA remains patent (arrowheads). The right anterior cerebral artery is also not visible. C. Cerebral angiography: right common carotid injection showing complete occlusion of the right MCA (large arrow). There is filling of the right posterior cerebral artery (small arrow) through a patent right posterior communicating artery (arrowhead). The previous patent parietal branch of the MCA is now not visible.

because it occurred beyond the expected time period for such complications.

At present, monitoring of abnormalities due to continued inflammation within CNS vessels requires serial angiography. In addition, relying on the development of new clinical changes is difficult to justify in patients whose initial presentation was a CVA. For these reasons, repeat angiography were recommended in all and were obtained in 4/5 of our patients. Patient 3 was evaluated using serial angiography because of the severity of stenosis at a critical location. Overall, these angiographic studies revealed gradual improvement over time in association with therapy. CT



C

Table 1. Presentation, treatment, and outcome of current and previously reported PACNS pediatric cases.

| Patient | Age, yrs, | Presenting Symptoms | Duration | CSF | MRI/A | Angiogram at Diagnosis | Treatment | Clinical Outcome |
|---------|-----------|--|--------------------------------|-----------------------|--|--|---|--------------------------|
| 1 | 11 | Seizure, hemiparesis | Acute | 88 rbc, 0 wbc nl pro | ↓ ICA | Segmental narrowing L ICA, ↓ filling MCA, ACA | Steroids, CTX, ASA, MTX | Minimal hemiparesis |
| 2 | 8 | HA, dizziness, falling | 2 wks | 2130 rbc 0 wbc nl pro | Par-occ bleed (CT) | Segmental narrowing L ACA, Bas, R PCA & ICA, occ L PCA, angular br L MCA | Steroids | Hemiparesis |
| 3 | 5 | HA, emesis, vertigo | 5 mo | nl | 3 small infarcts, focal basilar stenosis | B Vert, Bas Stenoses/occ | Steroids CTX, ASA, warfarin, MTX | Asymptomatic |
| 4 | 7 | HA, hemiparesis | Subacute HA, acute hemiparesis | nl | BG, IC, Frontotemp infarcts, ↓ MCA | Narrowing B ICA, R ACA, & MCA | Steroids, CTX, AZT, ASA RPT steroid, CTX | Hemiparesis |
| 5 | 7 | HA, seizure, hemiparesis | Acute | nl | Frontopar, BG infarcts | Irregular R MCA, narrowing R ACA | Steroids, CTX, ASA | Hemiparesis, impulsivity |
| 6* | 5 | Recurrent hemiparesis, aphasia | 2 mo | nl | BG infarct | L MCA beading | Steroids, 4 mo | Asymptomatic |
| 7* | 12 | HA, emesis | Chronic migraines, acute ↑ | nl | Parietal bleed | Focal segmental narrowing ant & post circ | Steroids 12+ mo CTX 18 mo | Asymptomatic |
| 8* | 8 | Facial hemiparesis. HA, hemianesthesia, diplopia | 3/7 mo | nl | Multi hyperintense signals | nl | Steroids 6 weeks RPT Tx? 14 mo CTX? 14 mo | Deceased |
| 9* | 12 | Hemiparesis nystagmus, hemianesthesia | 3 days | N/A | N/A | Stenosis, ectasia B, PCA, MCA | Steroids | Asymptomatic |
| 10 | 10 | HA, aphasia, hemiparesis confusion | 4 wks | N/A | N/A | Stenosis, ectasia B, MCA | None | Asymptomatic |

nl: normal, B: bilateral, Par: parietal, Bas: basilar, Occ: occipital, temp: temporal, BG: basal ganglia, IC: internal capsule, MCA: middle cerebral artery, ACA: anterior cerebral artery, PCA: posterior cerebral artery, ICA: internal carotid artery, CTX: cyclophosphamide, MTX: methotrexate, AZT: azathioprine, ASA: acetylsalicylic acid, ↑: increase, ↓: decrease, N/A: not available.

*Previous reports in the literature, see references 2,3,4,5.

angiography is a safer alternative to conventional angiography for neurovascular imaging, as it does not require arterial puncture or intraarterial catheter manipulation¹¹. Two of our patients exhibited excellent correlation in the findings between CT angiography and cerebral angiography. CTA has recently been shown to have sensitivity and specificity

equal to digital subtractive angiography in the detection of small vascular lesions¹². However, the resolution with CTA is lower and is limited by poor visualization of very small arteries¹³. CTA also has the potential limitation of showing arteries and veins in the same image. We advocate the use of conventional angiography in the initial diagnosis of all

patients and for followup of vasculitis involving the distal circulation. CTA is appropriate for followup of patients with large and medium-size vessel involvement, although further studies are required to fully establish its role in the evaluation and monitoring of CNS vasculitis.

Our observations suggest that, in contrast to adult patients, both cerebral hemorrhage and posterior circulation involvement may be more common in childhood PACNS. Two of the 10 cases reviewed presented with hemorrhagic strokes and 3/10 had posterior circulation involvement. One of our patients presented with isolated posterior circulation disease. Isolated posterior circulation vasculitis represents a unique diagnostic challenge because of similarities with occlusive disease of the vertebrobasilar system. Eight children have been reported with this entity, 2 secondary to sepsis, 2 with history of trauma, and 5 from unknown causes¹⁴⁻¹⁶. In one case report, atlantoaxial subluxation causing occlusion at C1-2 bilaterally led to bilateral vertebral artery occlusion, basilar artery abnormalities, and hind-brain stroke. These findings were similar to the initial abnormalities in Patient 3, who had no history of trauma and a stable cervical spine.

There have been no controlled therapeutic trials in PACNS. Cupps, *et al* first reported improved survival with the combination of corticosteroids and cyclophosphamide¹⁷. All our patients received corticosteroids, and 4/5 received cyclophosphamide. Patient 5 was initially treated only with corticosteroids and exhibited significant angiographic progression 3 weeks later. Patient 2 received a less aggressive regimen including low dose prednisone (7.5 mg/day) and a single dose of cyclophosphamide because of uncertainty with the diagnosis. She progressed, then was lost to followup. Patient 4 exhibited continued angiographic abnormalities 4 months after cyclophosphamide was discontinued, and clinical deterioration that responded to retreatment with cyclophosphamide. Patient 3 had angiographic progression while taking bimonthly cyclophosphamide that stabilized following initiation of daily oral dosing. The optimal duration of therapy in PACNS also remains unclear. Alhalabi and Moore performed serial angiography on 19 adult patients with PACNS and found continued improvements in angiograms in patients treated longer than one year¹⁰. Two of our patients were transitioned from cyclophosphamide to MTX after 12 and 19 months, respectively, based on its potential benefit in other vasculitides¹⁸. One of these patients is now off all immunosuppressive therapy, and both remain clinically and radiographically stable. As noted, one patient who received less than 8 months of cyclophosphamide therapy relapsed. Together, our experience suggests that optimal management for pediatric PACNS should consist of combined corticosteroid and cytotoxic therapy in association with careful angiographic (or possibly CT angiography) monitoring for a minimum of 12 months.

Finally, Calabrese, *et al* have proposed the classification of benign angiopathy of the CNS (BACNS) for patients with a vasculitic picture on angiogram and normal or mildly abnormal CSF studies¹⁹. These authors suggest that such findings correlate with a monophasic, benign clinical course despite an initial presentation with focal neurologic deficits, and therefore they suggest use of less aggressive immunosuppression in this clinical context. Four of our 5 patients had normal CSF studies and thus would have met criteria for BACNS. It should be noted, however, that large vessel involvement, vessel occlusion, and/or unilateral disease (present in 2 of 5 our patients) are rarely reported in adults with BACNS. In further contrast to the observations in adults, each of these patients exhibited radiographic disease progression, and 2 exhibited clinical progression prior to any therapy. Thus, while a normal CSF and focal neurologic deficit may be associated with a monophasic course in adults, this is unlikely to be the case in children. The benign nature of this disorder in adults has also recently been questioned²⁰. Our experience, in association with previous case reports, suggests that PACNS in children is associated with a significant potential for morbidity and mortality. Children with frequent or severe headaches and/or focal neurologic deficits should be thoroughly evaluated. Patients meeting criteria for PACNS should be treated aggressively.

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