

Evolving Pediatric Cerebral Arteriopathy on Neuroimaging

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Abstract

Background: Progressive cerebral arteriopathies are not an uncommon cause of ischemic stroke in children. The clinical and radiological distinction between various cerebral arteriopathies remains a challenge and topic of controversy for physicians.

Methods: We report an 11-year-old girl who presented with a left subcortical ischemic stroke.

Results: An 11-year-old girl presented with a progressive right hemiparesis. Her neuroimaging showed diffusion restriction and T2 signal abnormalities in the left basal ganglia with normal magnetic resonance and CT angiography. Subsequent MRA and cerebral catheter angiography at 9 days post-stroke revealed medium and large vessel stenoses of bilateral distal anterior cerebral arteries, proximal and distal segment of left middle cerebral artery, and distal left internal cerebral artery.

Conclusion: This case demonstrates the uncertainties and challenges related to ischemic stroke due to cerebral arteriopathies and the importance of early evaluation with cerebral catheter angiogram with unidentified ischemic stroke etiology and normal initial non-invasive angiography.

Keywords: Stroke; Cerebrovascular disorders; Brain ischemia; Cerebral infarction; Neuroimaging; Cerebral angiography

Introduction

Cerebral inflammatory arteriopathies can be either focal [such as unilateral Focal Cerebral Arteriopathy (FCA), Transient Cerebral Arteriopathy of Childhood (TCA), Post-Varicella Angiopathy (PVAR) or other idiopathic stenosis] or diffuse [such as Primary Angitis of the Central Nervous System (PACNS) or secondary angiitis of the central nervous system secondary to other systemic inflammatory vasculitides]. The distinctions between primary angiitis of the central nervous system and transient cerebral arteriopathy are sometimes controversial. The transient cerebral arteriopathy is generally considered to be a unilateral self-limiting monophasic, presumably inflammatory, arteriopathy with lack of progression beyond six months [1,2]. Primary angiitis of the central nervous system is a diffuse and progressive inflammatory vasculitis of central nervous system [3,4]. While the pathophysiologic cause remains elusive, it is hypothesized that the inflammatory changes in the medium and small sized arteries lead to occlusion or stenosis of the affected arteries or their branches with resultant thromboembolism and cerebral ischemia. For example, proximal middle cerebral artery and anterior cerebral artery involvement secondarily occlude the origin of the perforator vessels and can lead to distal thrombembolism or reduction in the flow of perpendicularly-oriented perforator vessels [2,5]. In addition, limited literature exists with regards to early evolution of primary angiitis of the central nervous system on serial parenchymal neuroimaging in children [5,6].

Case Report

An eleven-year-old, previously healthy, right-handed girl presented with progressive right hemiparesis over 10 minutes while playing soccer. There was no head or body trauma when she fell to the ground. There was no prior personal or family history of chicken pox exposure, stroke, myocardial infarction, blood clotting disorders or migraine. She initially presented to the local emergency room with slurred speech, decreased level of consciousness, right hemiparesis and left choreoathetotic movements. Initial head Computed Tomography (CT) within 2-hours after symptom onset was normal. She was transferred to our center, the only tertiary care pediatric hospital in the region. Repeat head computed tomography at 8 hours after initial onset of symptoms was consistent with an acute infarct involving the left lentiform nucleus (putamen more than globus pallidus) (Figure 1A). Her cerebral computed tomography angiogram was normal (Figure 1B). Her initial investigations revealed normal complete blood count, C3, C4 and CRP, ESR and serum electrolytes, urea, creatinine, lactate, liver function tests, PTT and INR. The family was reluctant to start anticoagulation with heparin therapy so oral aspirin was started. Magnetic resonance imaging brain on diffusion-weighted imaging at 21 hours post-stroke demonstrated acute infarcts in the left corpus striatum and in a gyrus in the left parietal lobe (Figure 1C and 1D). Magnetic resonance angiogram was normal. Stroke work-up including complete blood count, serum lactate, hypercoagulability screen, vasculitis work-up, infectious work-up including cerebrospinal fluid analysis and transthoracic echocardiogram were normal with intact atrial and ventricular septa. By day 3 post-stroke, the patient's choreoathetotic movements had stopped and only minimal right-sided

face, arm and leg weakness were detectable. Her speech, level of consciousness and cognitive function returned to baseline. The patient complained of new-onset headaches and worsening hemiparesis and a repeat head computed tomography was performed. A small hemorrhagic transformation of ischemic stroke was noted (Figure 2A) and her computed tomography angiogram was again normal (Figure 2B). Aspirin was held for 48 hours and restarted after repeat computed tomography head on day 5 demonstrated stable hemorrhage with lack of progression. Over the next few days, the patient had progressive right leg weakness. An angiogram on day 9 post-stroke showed stenosis and luminal irregularities in the distal bilateral anterior cerebral arteries, predominantly the right anterior cerebral artery, distal and proximal M1 segment of left middle cerebral artery, and the distal left Internal Cerebral Artery (ICA) termination (Figure 3). Repeat brain magnetic resonance angiogram within 48-hours of the cerebral catheter angiogram demonstrated similar abnormalities. The possibility of Transient Cerebral Arteriopathy of Childhood (TCA) was raised but considering bilateral involvement with angiographic evidence of significant luminal abnormalities and rapid progression, and lack of other systemic inflammatory disease or markers, the clinical and the angiographic findings were considered to be most consistent with progressive angiography positive primary angiitis of the central nervous system rather than transient cerebral arteriopathy [3,4]. The patient was started on oral prednisone. There was no further clinical progression and patient was discharged from the hospital on day 12 post-stroke on oral prednisone and aspirin.

A repeat brain magnetic resonance imaging within 2-weeks of patient's last neuroimaging showed new areas of T2 hyperintensity with restricted diffusion in the parasagittal cortex of the left frontal lobe, subcortical white matter of the parasagittal right frontal lobe and genu of the left corpus callosum (Figure 4A and 4B). The magnetic resonance angiogram showed subtle progression of narrowing involving the supraclinoid portion of the left internal cerebral artery, M1 segment of the left middle cerebral artery and the A2 segments of both left and right anterior cerebral arteries (Figure 4C and 4D). There were no new clinical deficits on examination at that time, except for persistent subtle right hemiparesis. A brain biopsy was considered but not done due to the presence of obvious progressive vascular and parenchymal abnormalities and the invasive nature of the procedure. Due to the rapid progression of her parenchymal and vascular disease (in spite of oral prednisone), the patient was started on treatment with monthly intravenous cyclophosphamide and the prednisone dose was tapered down gradually. No other medications were given. Follow-up brain magnetic resonance imaging at 4 and 12 months post-stroke and after 7 cycles of cyclophosphamide did not reveal any new parenchymal or vascular changes. Previously demonstrated arterial narrowing remained unchanged in appearance (Figure 5).

Seven years post stroke, the patient continues to do well with only mild right hemiparesis. Her strength is 5/5 in all muscle groups with the exception of slow rapid finger and foot tap on the right side. She has no difficulty with tiptoe walking or jumping but has difficulty with heel walking on the right side. Her tone is mildly increased in the right Achilles tendon. Her reflexes are +2 symmetric except the +3 knee jerk on right with an extensor plantar response on the right side. She has mild foot slap and the tendency to bring her right arm into the flexed position with the hand fisted. Interestingly, the patient remains right-handed for most tasks including writing and eating but demonstrates increased left-hand preference for certain tasks. A formal psychology assessment indicated mild dyslexia, (which was known to be present

prior to stroke) and marked attention difficulties which were attributed to her strokes.

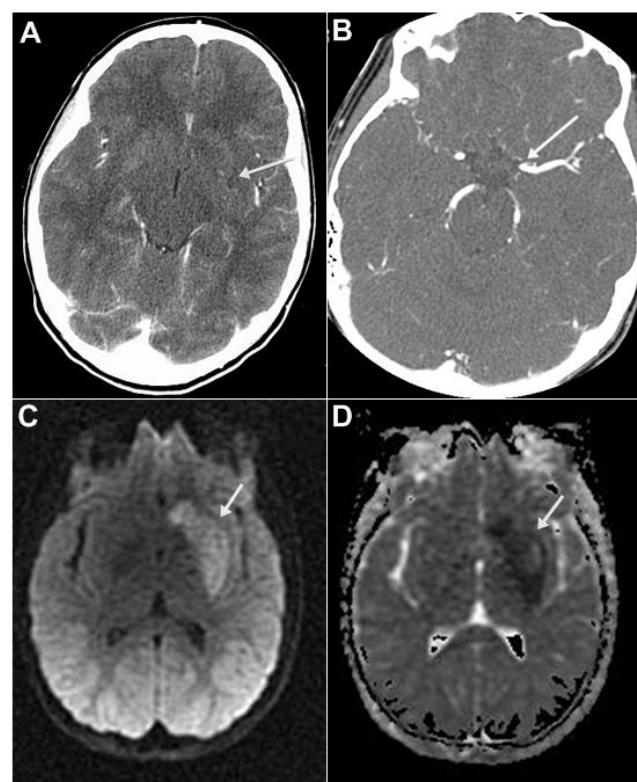


Figure 1: Axial Computed Tomography (CT) of the brain, 8 hours post-stroke **[A:** Hypodense changes involving the inferior aspect of the left lentiform nucleus enhanced head scan; **B:** Axial post-infusion Computed Tomographic Angiography (CTA) of the brain demonstrating the absence of a left middle cerebral artery abnormality; **C and D:** Axial Magnetic Resonance Imaging (MRI) of the brain, 21 hours post-stroke demonstrates restricted diffusion in the left globus pallidus and putamen on Diffusion-Weighted Imaging (DWI) and corresponding Apparent Diffusion Imaging (ADC map) consistent with acute ischemic infarction].

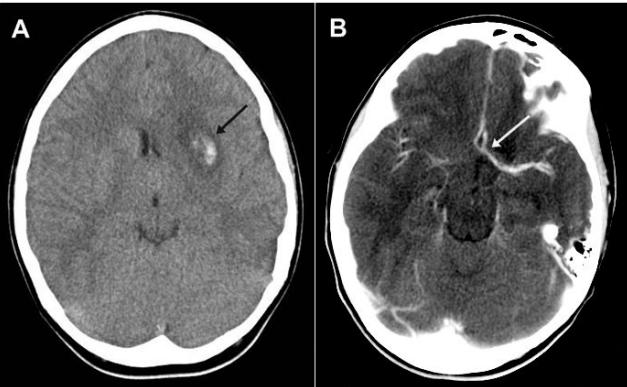


Figure 2: Axial CT of the brain, 3 days post-stroke [A: Small hemorrhagic transformation in the left corpus striatum infarct; B: CTA showing normal left MCA and bilateral Anterior Cerebral Arteries (ACA)].

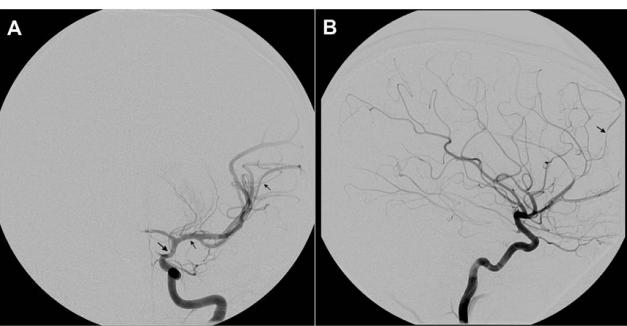


Figure 3: Cerebral angiogram 9 days post-stroke [A: Irregular vascular caliber seen in the left internal carotid artery and the proximal (M1) segment and distal branch of the left middle cerebral artery (arrows); B: Narrowing of the distal right anterior cerebral artery is noted (arrows)].

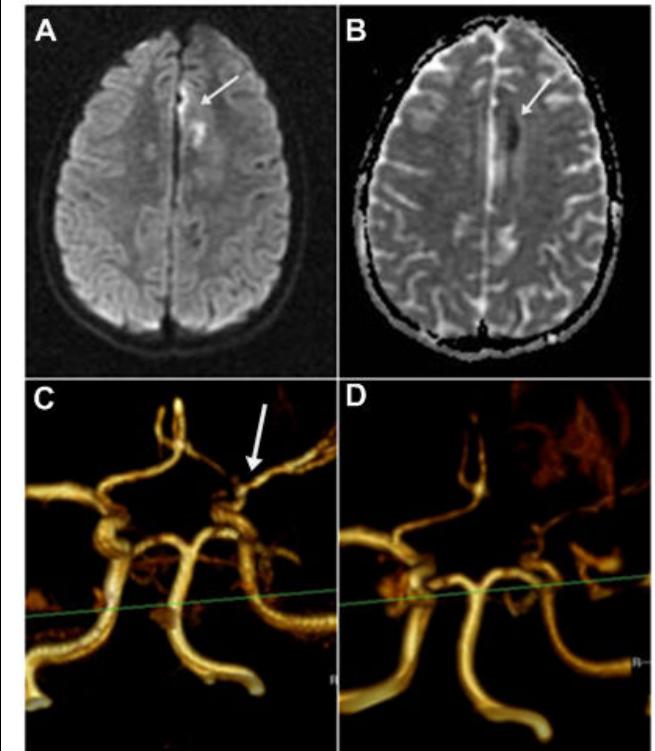


Figure 4: Axial MRI of the brain, 1 month post-stroke [A: Diffusion-weighted imaging and the corresponding apparent diffusion imaging; B: demonstrating new areas of restricted diffusion in the left frontal lobe consistent with acute ischemic infarction; C and D: 3D reconstruction of time-of-flight Magnetic Resonance Angiography (MRA) of the brain demonstrating worsening of the narrowing of the left middle cerebral artery].

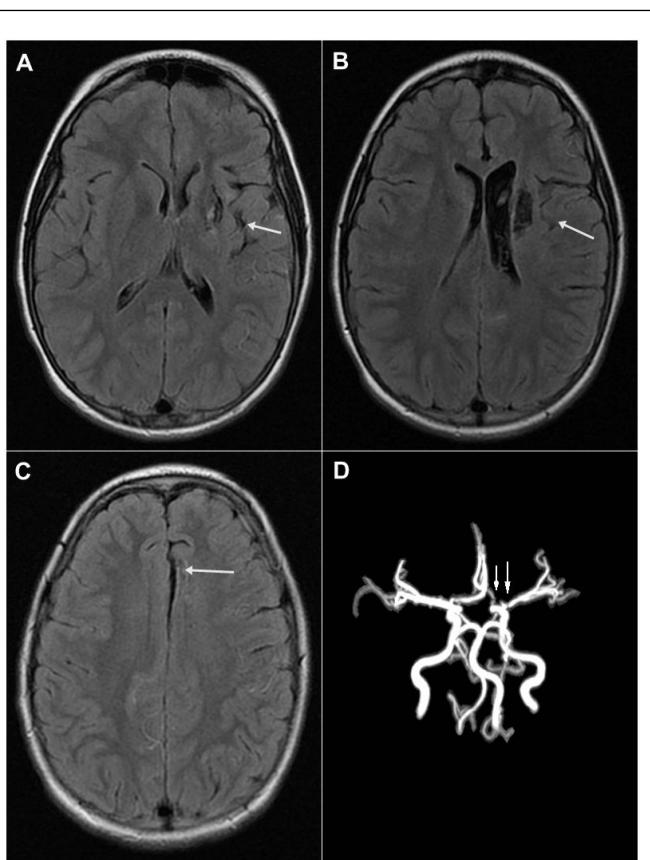


Figure 5: Axial MRI of the brain, 12 month post-stroke [A: Areas of cystic gliosis seen within the left parasagittal frontal lobe, left extreme capsule, left head of caudate nucleus, and within the right parasagittal frontal lobe region. The associated ex-vacuo dilatation of the left lateral ventricle and left sylvian fissure is also noted; B: Time-of-flight magnetic resonance angiography of the brain demonstrating stable narrowing of the left internal carotid artery and left middle cerebral artery (arrows)].

Discussion

Our patient was initially suspected to have transient cerebral arteriopathy as up to 19% of patients with transient cerebral arteriopathy have been reported to have transient worsening of arteriopathy before stabilization of the disease [1]. Transient cerebral arteriopathy is typically a unilateral arteriopathy with or without evidence of apparent progression (skip lesions) which typically involves anterior circulation [1,2]. It is speculated to involve contiguous arterial branches involving posterior circulation on the same side. In our patient, the presence of bilateral arteriopathy, particularly distant and contralateral involvement of the anterior cerebral arteries, with resultant multifocal recurrent parenchymal cerebral infarctions were considered to be atypical for transient cerebral arteriopathy or other Focal Cerebral Arteriopathies (FCA). Moreover, anterior cerebral artery involvement is reportedly more frequent in patients with primary angiitis of the central nervous system [1]. Therefore, a diagnosis of progressive angiography-positive primary angiitis of the central nervous system was presumed and the patient was treated accordingly.

Primary angiitis of the central nervous system has been categorized into three primary forms: angiography-positive progressive, angiography-positive non-progressive and angiography-negative small vessel vasculitis [4]. In the presence of angiography positive angiitis of the central nervous system, a brain biopsy is not required since a diagnosis of central nervous system angiitis on brain biopsy does not alter the treatment of central nervous system angiitis. While angiography-negative primary angiitis of the central nervous system is typically diagnosed via brain biopsy, angiography-positive disease is frequently diagnosed without pathologic confirmation to avoid an invasive procedure as in our patient [4,7]. Although her maximal symptoms were present within the first few hours of stroke onset, and the neurologic injuries were visible within the first 24 hours of neuroimaging, the parenchymal and vascular radiographic abnormalities developed progressively over the course of a very short period (over days instead of months) which is infrequently described [6].

It is reported in the literature that individuals with angiography-positive primary angiitis of the central nervous system have primarily medium and large-vessel involvement [5,8]. At the onset of symptoms, our patient's non-invasive cerebral angiography did not demonstrate any vascular abnormalities. While this may suggest that computed tomography and/or magnetic resonance angiogram done early in the process are possibly not sensitive enough to identify early abnormalities, we postulate that initial small vessel involvement may predate medium and large vessel abnormalities. While angiography-positive progressive primary angitis of the central nervous system are known to have medium and large vessel involvement, the clear documentation of significant small vessel involvement prior to large vessel involvement via either invasive or non-invasive cerebral angiography is novel.

While some autoimmune conditions, (Kawasaki disease, polyarteritis nodosa) have a predilection for small and medium cerebral vessel involvement, other diseases, predominantly affects medium and large vessels, such as post-varicella arteriopathy, or angiography-positive primary angiitis of the central nervous system. However, this distinction may not always be absolute. There is no fundamental reason why small vessels cannot be involved prior to large vessels in an inflammatory cerebral vasculitis. Brain biopsies of children with angiography-negative small-vessel primary angiitis of the central nervous system have demonstrated multifocal, vascular and perivascular, predominantly T-lymphocytic inflammatory, infiltration [3,7,9,10]. These findings are not significantly different from angiography-positive primary angiitis of the central nervous system or other inflammatory vasculitides involving medium and large vessels. While granulomatous changes have been reported more frequently in cerebral vasculitis involving medium and large vessels, these changes are more likely reflective of the extent and duration of illness rather than a fundamental difference in pathophysiology. Our patient's eventual response to prednisone and cyclophosphamide is consistent with the hypothesis that progressive angiitis of the central nervous system is an inflammatory phenomenon.

This case demonstrates the uncertainties and challenges related to pediatric arterial ischemic stroke, in particular stroke due to cerebral arteriopathies, and its etiologies and importance of early evaluation with cerebral catheter angiogram with unidentified stroke etiology and normal initial non-invasive angiography. In addition, close clinical and neuroradiological follow-up should be considered for pediatric stroke patients, especially in children with what appears to be atypical and

inconsistent with a diagnosis of an arteriopathy or inflammatory vasculitis.

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