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Original Article

Vascular Imaging Outcomes of Childhood Primary Angiitis of the Central Nervous System

Jorina Elbers MD [a,*], Derek Armstrong MD [b], Ivanna Yau NP [c], Susanne Benseler MD [d]

[a] *Division of Child Neurology, Department of Neurology and Neurological Sciences, Stanford University, Stanford, California*
[b] *Department of Diagnostic Imaging, Hospital for Sick Children, Toronto, Ontario, Canada*
[c] *Division of Neurology, Department of Pediatrics, Hospital for Sick Children, Toronto, Ontario, Canada*
[d] *Division of Rheumatology, Department of Pediatrics, Hospital for Sick Children, Toronto, Ontario, Canada*

ABSTRACT

BACKGROUND: Inflammation affecting cerebral blood vessels is a common cause of stroke in children. Arterial abnormalities on vascular imaging are an important risk factor for stroke recurrence. We aimed to describe the vascular imaging outcomes in children with primary angiitis of the central nervous system after 12 months and identify factors associated with vascular progression and stroke recurrence. **METHODS:** We retrospectively analyzed clinical and neuroimaging data from the BrainWorks Registry of children with large-vessel primary angiitis of the central nervous system. Neuroimaging was collected at baseline and at least 12-month follow-up, and vascular outcome was categorized as improved, stable, or progressed based on comparison of magnetic resonance angiography. Univariate clinical and neuroimaging predictors were associated with outcome by Fisher exact test. **RESULTS:** Our study consisted of 27 children; 20 male; median age was 7.92 years (range, two to 15 years). Twelve patients received steroids (44%). Median follow-up time was 16 months (range, 12 to 56 months). Vascular imaging outcome was categorized as improved in 37%, stable in 22%, and progressed in 41% of patients. Discordant progression, defined as progression and improvement occurring simultaneously across multiple vessels, was observed in 26%. Stroke recurred in 15%, occurring exclusively in the group with progression on follow-up imaging ($P = 0.02$). **CONCLUSIONS:** After 12 months, 40% of children with primary angiitis of the central nervous system demonstrated progression on vascular imaging, without apparent clinical or angiographic predictors. Stroke recurrence was associated with vascular progression. Discordant progression is a newly described angiographic finding. Further studies are necessary to determine if this represents a unique characteristic of inflammatory arteriopathies.

Keywords: vasculitis, inflammation, central nervous system, child, angiography, outcome

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Introduction

Pediatric stroke is now a well-recognized cause of childhood morbidity and long-term disability.[1,2] Arteriopathies account for over 50% of childhood stroke cases,[3,4] with a majority presumed to be inflammatory.[3,5] Arteriopathies account for the highest rate of stroke recurrence,[6] with a five-year cumulative recurrence rate of 66%.[7] The rate of stroke recurrence has been correlated to etiology, with a one-year stroke recurrence rate of 32% for children with moyamoya disease, 25% for children with transient cerebral arteriopathy (TCA), and 19% for children with dissection.[6] Recurrent stroke has been also associated with progressive arterial disease[5] and worse neurological outcome.[8]

The terminology for cerebral arteriopathies is evolving. Although disorders such as arterial dissection and moyamoya disease have remained fairly constant in their definitions, arteriopathies due to inflammation have been more difficult to describe. In the absence of biomarkers or pathology, there is often uncertainty in the diagnosis of arteriopathy at presentation, which improves with follow-up

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* Communications should be addressed to: Dr. Elbers; 750 Welch Road; Suite 317; Palo Alto, California 94305.
E-mail address: jelbers@stanford.edu

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vascular imaging.[9] Large-vessel primary angiitis of the central nervous system in children (cPACNS) is a term used to describe inflammation isolated to the central nervous system, which may be transitory[10] or progressive.[11] In a prior study of 62 children with cPACNS, vascular progression after three-month follow-up was observed in 32%, however, this was not associated with stroke recurrence.[11] This study identified bilateral multifocal brain lesions and distal vessel stenosis as predictors of vascular progression after three months. In comparison, another study described the course and outcome of 79 children with proximal, unilateral intracranial arteriopathy.[5] This study further characterized a monophasic, proximal vasculitis, known as TCA. TCA was differentiated from progressive disease according to the timing of progression, with TCA demonstrating interval worsening within 6 months, followed by subsequent improvement or stabilization.[5,10] In this study, 94% of patients demonstrated interval worsening within the first six months, of which 18% had recurrence of stroke or transient ischemic attack (TIA). Progressive arteriopathy occurring after six months in the remaining five patients was associated with arterial occlusion, moyamoya vessels, anterior cerebral artery involvement, and increased risk of stroke recurrence.

Despite the relatively high incidence of inflammatory arteriopathies, and their associated risk of stroke recurrence, only a small number of studies describe the natural history of this arteriopathy in children.[5,11] This observational cohort study describes the vascular imaging outcomes after a minimum of 12 months in children with PACNS, including focal, bilateral, and posterior circulation disease. We aimed to characterize the vascular imaging features at baseline and after a minimum of 12 months and identify the rate and risk factors of vascular progression and stroke recurrence in this population.

Methods

Study population

This observational cohort study was performed among consecutive children diagnosed with large-vessel cPACNS who were enrolled in the Hospital for Sick Children cohort of the BrainWorks registry between January 1, 1998, and December 31, 2013. The BrainWorks Study is an international, multicenter collaborative study to assess the outcomes of children with inflammatory brain diseases. Patients were included if they were between one month and 18 years of age and had a centrally confirmed diagnosis of cPACNS based on criteria established by Calabrese et al.: (1) a newly acquired neurological deficit; (2) cerebral angiographic abnormalities consisting of focal or multifocal beading, stenosis, or occlusion; and (3) the absence of systemic or other condition that could account for these findings.[12] Although the classical definition of adult cPACNS requires digital subtraction angiography (DSA), the risks associated with this procedure limit its use in children. Because magnetic resonance angiography (MRA) was previously found to have similar sensitivity, specificity, and predictive values compared to DSA in children with cPACNS,[13] baseline DSA was not required for inclusion in this study. When performed, DSA was used to support the diagnosis of cPACNS and exclude alternate diagnoses. Patients were included if they had magnetic resonance imaging (MRI) and MRA completed at baseline and at least 12-follow-up, with neuroimaging available for onsite review at the Hospital for Sick Children. Patients were excluded if they had clinical follow-up less than 12 months from presentation, incomplete vascular imaging data set (no baseline MRI, poor image quality), clinical or angiographic features of arterial dissection (history of trauma, intimal flap, or double-lumen on DSA), isolated arterial occlusion on DSA or abnormal echocardiography (as this can indicate cardioembolic occlusion), steroid treatment before baseline angiography, and alternative diagnosis to account for angiographic findings (i.e., acute infection, systemic autoimmune disease, sickle cell disease). Ethics approval was obtained locally from the Hospital for Sick Children Institutional Review Board.

Baseline clinical data collection

Baseline data collection for this study included demographics, clinical presentation, laboratory investigations (erythrocyte sedimentation rate, C-reactive protein, cerebrospinal fluid [CSF] cell count and protein), and varicella zoster virus serology and CSF polymerase chain reaction. Treatment data included antiplatelet agents, anticoagulants, and immunosuppression with both steroids and steroid-sparing agents.

Neuroimaging review

Review of deidentified MRI (on 1.5 or 3 T) and angiography at baseline and at least 12 months was conducted by consensus between two reviewers who were not aware of this: a pediatric neuroradiologist (D.A.), and pediatric neurologist (J.E.) according to a standardized rating scheme. Ischemic lesions on MRI were localized and categorized as acute (restricted on diffusion-weighted imaging) or chronic (hyperintense on T2 Fluid Attenuated Inversion Recovery [FLAIR] in the absence of diffusion restriction). Meningeal or lesion enhancement was noted in patients given gadolinium.

Analysis of angiography included both time-of-flight MRA and DSA, when performed. Angiographic abnormalities were described according to circulation (anterior or posterior) and involved vessels. Angiography was further classified as unilateral intracranial arteriopathy or multifocal and/or posterior arteriopathy. According to previous literature, unilateral intracranial arteriopathy was defined as isolated involvement of the proximal large arteries in the anterior circulation: distal internal carotid artery (dICA), proximal middle cerebral artery (M1), secondary branch of the middle cerebral artery (M2), and/or proximal anterior cerebral artery (A1), secondary branch of the anterior cerebral artery (A2).[5] The presence of additional features including beading, moyamoya collaterals, and clot visualization was noted on DSA. Beading was defined as more than two alternating, short, regularly spaced segments of stenosis with short, normal, or dilated intervening segments.

Vascular imaging outcome

Each arterial lesion on MRA and DSA was measured using visual estimation of the apparent luminal diameter according to North American Symptomatic Carotid Endarterectomy Trial criteria scored as 1 to 4 points: 1 = normal (0% to 9%), 2 = mild stenosis (10% to 29%), 3 = moderate stenosis (30% to 69%), 4 = severe (70% to 99%) or complete occlusion (no flow detected).[14] Embolic occlusion was ruled out according to DSA in patients with apparent occlusion on MRA. The number of affected vessels was also assessed. Vascular outcome was based on comparison of baseline MRA to follow-up MRA and was categorized as improved, stable, or progressed. A patient was considered to have progressed if follow-up imaging showed involvement of new vessels or worsening of an existing flow abnormality by at least one point. Progressive patients were further categorized as discordant if a new or worsening arterial abnormality coexisted with an improved or normalized vessel. If there was no change in flow abnormality or number of involved vessels, the patient was defined as stable. Patients with normal angiography, improved flow, or fewer abnormal vessels, were categorized as improved. Groups were then dichotomized as progressed or not progressed (stable or improved) for analysis of predictors for vascular progression and stroke-recurrence.

Stroke recurrence

Stroke recurrence was determined by central review of clinical follow-up data obtained at least 12 months from stroke presentation and onsite review of follow-up neuroimaging in all patients. In accordance