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Original Article

Cerebrovascular Reactivity and Intellectual Outcome in Childhood Stroke With Transient Cerebral Arteriopathy

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ABSTRACT

BACKGROUND: Hypercapnic-challenge blood oxygen level–dependent magnetic resonance imaging cerebrovascular reactivity (CVR), measures the regional perfusion response to altered carbon dioxide. CVR correlates with the tissue-level microvascular dysfunction and ischemic risk. Among children with arterial ischemic stroke, transient cerebral arteriopathy (TCA) is a frequent, nonprogressive unilateral intracranial arteriopathy, which typically results in basal ganglia infarction and chronic cerebral artery stenosis. Therefore TCA provides a model for studying the consequences of chronic nonprogressive stenosis using CVR and intellectual outcome. We hypothesized that children with TCA and chronic nonprogressive intracranial artery stenosis have impaired CVR distal to the stenosis and associated cognitive impairment. **METHODS:** We studied children with a prior diagnosis of TCA as defined by infarction limited to the basal ganglia, internal capsule, or both; and significant (greater than 50% diameter) residual stenosis of the supraclinoid internal carotid artery, its proximal branches or both. All children had CVR, intellectual function, and infarct volumes quantified. **RESULTS:** We performed CVR studies in five children at mean 8.96 years (3.33 to 14.58 years) poststroke. Impaired CVR was limited to the infarct zone and adjacent white matter in most children. Intellectual function was broadly average in all but one subject. **CONCLUSIONS:** In children with typical TCA, ipsilateral cortical CVR and intellectual function seem to be preserved despite persistent arterial stenosis in the majority. These findings suggest that chronic revascularization strategies in these children may not be indicated and require further exploration in a larger cohort of children.

Keywords: cerebrovascular reactivity, CVR, transient cerebral arteriopathy, outcome, neuropsychology, stroke, arteriopathy

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Introduction

In adults with symptomatic chronic intracranial artery stenosis revascularization procedures including endovascular stent placement and others have been employed to improve the hemodynamic compromise and perfusion distal to the arterial stenosis. Although outcomes have been variable, improvement in neurocognitive outcome has been demonstrated.[1-3]

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Cerebral arteriopathy is present in in 63% of children with arterial ischemic stroke (AIS). These arteriopathies are usually intracranial and characteristically involve the circle of Willis, in particular the distal internal carotid artery (ICA), proximal middle artery (MCA), and anterior cerebral artery (ACA). Childhood arteriopathies are associated with recurrent stroke in up to 66%.[4] Transient cerebral arteriopathy (TCA) is the most frequent cause of arteriopathy associated with childhood stroke.[5] It occurs in 25% of children with stroke and arteriopathy and is characterized by unilateral arteriopathy involving the supraclinoid ICA, its proximal branches or both, and infarction in the territory of the perforator arteries typically sparing the cortex.[6-8] Stenosis can increase in the initial three to six months poststroke; however, beyond six months the course is static or resolving. Recurrent stroke occurs in up to 25% of affected individuals, typically in the first three months after the incident stroke.[3,9] However, at presentation the determination of likelihood of future progression is difficult, even in unilateral arteriopathy. Hence a further revision of the classification of the arteriopathies was proposed by the International Pediatric Stroke Study participants, with the coining of the term "focal cerebral arteriopathy."[5,10] Focal cerebral arteriopathy may be defined as cerebral arterial stenosis not attributed to the specific subtypes, such as dissection, TCA, or moyamoya. This term allows descriptive labeling at the onset of the illness (unlike TCA). Moyamoya occurs in 22% of children with stroke and arteriopathy and is typically bilateral and progressive.[10] With moyamoya, chronic hypoperfusion and recurrent strokes are each posited to contribute to the observed chronic progressive cognitive decline.[11-13] However, the consequence of chronic intracranial arterial stenosis on perfusion distal to the stenosis in TCA is unknown. TCA is therefore a useful model for studying the consequences of chronic nonprogressive arterial stenosis on tissue-level microvascular function distal to the stenosis and cognitive outcome. These factors in turn can elucidate whether consideration of reperfusion strategies are indicated in the medium- to long-term poststroke, in children with TCA, to prevent ongoing ischemia and cognitive demise.

Magnetic resonance (MR) perfusion techniques used in adults include T2* dynamic susceptibility contrast imaging and T1 dynamic contrast enhancement—both of which require a gadolinium contrast agent. The need for contrast is a barrier to dynamic susceptibility contrast and dynamic contrast enhancement imaging in the pediatric population given the safety concerns.[14-16] Arterial spin labeling (ASL) that uses blood water protons as an endogenous contrast agent has been a promising alternative. To date, reliable application of ASL has been limited by steno-occlusive disease specific and developmental age dependent difficulties in determining the appropriate transit time needed for accurate labeling and quantification of perfusion in this population.[17,18] However, Blauwblomme et al.[19] demonstrated its successful use in children with moyamoya.

Cerebrovascular reactivity (CVR) is a marker of brain vascular reserve and is defined as the change in blood flow per unit change in PCO_2. Abnormal CVR is an indicator of tissue-level microvascular dysfunction and tissue at risk of ischemia.[20-22] In moyamoya, CVR demonstrates cortical perfusion deficits[23,24] even in the absence of infarction. Paradoxical reduction in regional blood flow after a vasodilatory stimulus, also known as "steal," is associated with recurrent stroke in the affected vascular area and cortical thinning that reverses toward normal after surgical revascularization.[25-29] CVR in pediatric subjects has been reported to be feasible and informative in children with cerebral arteriopathy, such as moyamoya.[20]

Standardized neuropsychological outcome measures can be used to assess whether cognitive deficits are primarily referable to cortical or subcortical injury. For example, deficits in verbal and visual reasoning are typically associated with cortical injury and deficits in information processing and working memory are associated with with subcortical injury.

We hypothesized that in children with TCA and persistent moderate to severe stenosis, CVR abnormalities as an indicator of tissue-level microvascular dysfunction would be present in cortex distal to the stenosis and not limited to the infarct location. In addition, we hypothesized that children with persistent stenosis would exhibit weaker than expected intellectual function overall, with deficits referable to cortical and subcortical injury.

Methods

Patient population

Clinical and radiographic data of all children enrolled in our institutional Children's Stroke Registry with TCA diagnosed per published criteria[4,6] between 1990 and 2007 were screened. Children with persistent moderate to severe stenosis on conventional angiography of MCA, ACA, or ICA plus infarcts limited to subcortical structures at the time of their follow-up imaging were selected for CVR assessment. Clinical information and repeat standardized intellectual assessments were obtained as part of routine follow-up. The assessment closest to the CVR was chosen for inclusion in this study analysis.[30] The project received institutional research ethics board approval. Informed consent was obtained from all study participants.

Patient definition

Inclusion criteria were based on the published criteria for TCA[6] and included

(1) acute AIS limited to the basal ganglia and adjacent white matter;
(2) unilateral intracranial stenosis or occlusion involving the distal proximal MCA, ACA, or distal ICA as defined by conventional angiography performed within three months of acute stroke;
(3) magnetic resonance imaging/magnetic resonance angiography (MRI/MRA) six or more months from index stroke demonstrating nonprogressive vascular disease;
(4) MRI/MRA $\geq$12 months from index stroke demonstrating stable persistent moderate to severe stenosis of the ICA, MCA, or ACA;
(5) MRI six or more months from index stroke demonstrating no AIS recurrence; and
(6) able to co-operate with awake research MRI and breathe with a face mask in place for minimum 20 minutes.

MRI including CVR

MR imaging was performed on a 3.0 T MRI system using an 8-channel head coil (Philips Healthcare, Best, the Netherlands). Anatomical imaging included standard fluid-attenuated inversion recovery (FLAIR), diffusion-weighted imaging (DWI), three-dimensional time-of-flight (TOF) MRA, and a high-resolution T1-weighted sequence. CVR data were acquired using a T2*-weighted single-shot echo planar imaging (EPI) gradient echo sequence (TR/TE repetition time/echo time 2000/30 milliseconds, FA flip