The A's and B's of the ABC's of stroke mechanisms and recurrence in pediatric ischemic stroke

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Arterial ischemic stroke in children is rare, estimated at 2 per 100,000 children per year,[1] but carries a relatively high risk of both recurrent stroke and lifelong neurologic morbidity.[2] Ischemic stroke mechanisms in both adults and children can be conceptually broken down into the "ABC's": arterial, blood, and cardiac. The mechanism of the stroke is important as therapeutic decisions and recurrent risk can vary by etiology. Arterial mechanisms (vasculopathies) are among the most common identified risk factors in childhood stroke, and differ dramatically from those seen in adults. They are traditionally divided into inflammatory (e.g., vasculitis, infectious) and noninflammatory (e.g., focal cerebral arteriopathy, moyamoya, dissection) processes. Little is known about the underlying pathophysiology of one of the most common of these vasculopathies, an entity referred to as focal cerebral arteriopathy (FCA). In fact, much controversy exists concerning the definitions and diagnostic criteria for FCA, and how or if these disorders fit into the spectrum of primary CNS angiitis in childhood.[3] Complicating matters, over half of pediatric arterial ischemic stroke patients have more than one risk factor.[4] Novel research strategies have been greatly needed to shed new light on the underlying pathomechanisms of vascular disorders in childhood ischemic stroke.

In this issue of *Neurology*®, Eleftheriou et al.[5] have done just that. They present the results of a single center, cross-sectional study with acute ischemic stroke with noninflammatory cerebral arteriopathy to determine whether pediatric stroke recurrence is associated with markers of vascular endothelial injury. These authors found, in a cohort of 46 children with stroke and arteriopathy, that there were 10 children (22%) with recurrent strokes at a median of 7 months after index stroke, and 36 children without recurrence at a median of 11 months after index stroke. The children with recurrent stroke had increased markers of circulating endothelial cells (CEC), increased annexin V + microparticles (MP), and increased MP-mediated thrombin generation. The implications are that persistent endothelial injury, platelet activation, and excessive thrombin generation could be important mechanisms for recurrent ischemic stroke in children with arteriopathy.

The major strength of this study, which sets it apart from most of the literature to date in childhood stroke, is that the authors have tackled the underlying pathomechanisms of arteriopathy by examining circulating markers of vascular injury and thrombin activation as they relate to stroke recurrence. The inclusion of healthy age-matched controls and a comparison group of children with vascular anomalies without stroke add to the strength of their observations. Another strength of the study was that the investigators adjusted from time of stroke event to blood tests, and created sensitivity, specificity, and likelihood ratios for CEC and stroke recurrence.

While this groundbreaking study advances our understanding of arteriopathy in childhood stroke, caution is warranted in interpreting the results, as the authors have appropriately stated in their discussion. Their finding of increased CECs in acute ischemic stroke vs controls does not necessarily inform us of causation. It was striking, though, that, when compared to acute ischemic stroke without recurrence, CEC levels with recurrence were approximately 4 times higher. A CEC level of 64 appeared to be the differentiating cutpoint whereby higher levels were associated with recurrence and lower levels were associated with no recurrence.

Unfortunately, radiographic diagnosis of cerebral arteriopathy is generally nonspecific regarding mechanism, as stenosis, beading, and other constrictive/dilative processes can be due to multiple causes. MRI-based cerebral angiography vs catheter angiography was performed on the basis of physician discretion. Reliance on MRI to characterize arteriopathies was acknowledged by the authors as a limitation inherent to research in childhood stroke, where the added procedural risk and radiation exposure of catheter angiography precludes

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its use on a large scale. Hence, children with likely disparate diseases were included in this single study group. Nonetheless, finding biomarkers that could predict increased risk of a second stroke in children is extremely important and worthy of further study.

Braun et al.[6] evaluated the long-term evolution of pediatric unilateral cerebral arteriopathy, classifying them as progressive or transient. Only 6% of children had progressive arteriopathy over a mean follow-up of 1.4 years, and 18% of those with a transient arteriopathy had a recurrent stroke or TIA. Progressive arteriopathy was associated with recurrence. Ganesan et al.[7] found previous TIA, bilateral infarction, prior diagnosis of immunodeficiency, and leukocytosis were independently associated with reinfarction.

While cause and effect of these elevated circulating biomarkers cannot be distinguished based on this cross-sectional study design, designing prospective studies using these putative markers will be the next necessary study to validate these results. Because approximately 1 in 4 children with cerebral arteriopathy had a recurrent stroke, we clearly need better prevention strategies than current empiric therapy with antiplatelets, anticoagulants, or steroids. We need further elucidation of the mechanisms underlying the arteriopathies. The importance of this line of investigation is further illustrated by the need to clarify the role of inflammation and its treatment in children with stroke due to isolated cerebral arteriopathy. A large literature in adult and experimental stroke exists on the importance of inflammation and altered immune responses, both local and systemic.[8,9] As with many aspects of the pathophysiology of cerebral ischemia, inflammatory processes are multiple, complex, and time-dependent, and some exacerbate injury whereas others promote recovery. Lessons learned from negative results of clinical trials of corticosteroids and immune modulation in adults should serve as cautionary tales for childhood stroke. We have much to learn about basic pathophysiology, and the study by Eleftheriou et al.[5] is a step in the right direction.

DISCLOSURE

The authors report no disclosures relevant to the manuscript. **Go to Neurology.org for full disclosures.**

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