Stroke in Children
First Steps on the Road to Intervention

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Stroke in the infant and child, although not a new entity, is increasingly being recognized as one of the most common causes of morbidity in childhood, with reasonably consistent incidence figures of 2 to 3 per 100,000 population and suggested rates as high as 13 per 100,000.1,2 Importantly, stroke recurrence rates in children of 6% to as high as 40% have been reported in recent literature,3,4 most commonly in those with arteriopathy. In addition, the cause of stroke in childhood differs substantially from that in the adult and is far more heterogeneous, evolving over a period of time in which there is rapid development of the brain and vasculature. As a result, identification of stroke in children remains a challenge even for the tertiary care health professional,5 likely resulting in an underestimation of the overall incidence of this debilitating event. The significance of the article by Amlie-Lefond et al6 in this issue of Circulation is its recognition of the importance of the determination of predictive markers that are associated with arterial ischemic stroke and arteriopathy.

The International Pediatric Stroke Study (IPSS) group should be congratulated for its accomplishment in bringing together a large number of international pediatric centers and establishing the foundation for this and future studies that will bring clarity to the cause, pathogenesis, and treatment of childhood stroke. The study by Amlie-Lefond et al6 makes several important points. Of the 667 cases of pediatric arterial ischemic stroke, 545 of the patients (81%) had vascular imaging completed. Within this group, the type of vascular imaging varied considerably, with magnetic resonance angiography being the most common, followed by conventional angiography and computed tomography angiography. Of the 525 patients for whom results were known, 277 (53%) had recognized arteriopathy, consistent with other previously published studies. However, once again, the incidence of arteriopathy may well have been underestimated. In this regard, not all children with stroke had vascular imaging performed. Moreover, magnetic resonance angiography as the predominant modality, particularly given that 42% of the children were <5 years of age, may not be the angiographic technique of choice.7

Paramount to the findings of Amlie-Lefond et al is the fact that those children with sickle cell anemia had a 3- to 4-fold increased risk for the development of arteriopathy in both univariate and multivariate analyses. Although this finding may seem intuitive, a substantial percentage of patients with sickle cell anemia do not develop arteriopathy. The annual incidence of stroke in children with sickle cell anemia is 1%. Those with evidence of vasculopathy on transcranial Doppler is 10%. Transfusion therapy in this high-risk group of children has shown a 9% absolute and 92% relative risk reduction in the first 2 years of follow-up. Overall, recurrent stroke has been decreased from 70% in this population to 13%.8 Hence, there may be an alternative etiopathogenetic pathway that these individuals follow. Additionally, the finding of an association between arteriopathy in the sickle cell disease population leading to stroke in this age group provides an opportunity not only for enhancing prevention but also for acute management.

Recent upper respiratory tract infection and early school age (5 to 9 years) were the other risk factors shown to be significantly correlated with arteriopathy. As pointed out by the authors, infection has been associated with stroke in the pediatric population, particularly in association with varicella9,10 and as part of a multifactorial association.11 The concept of an infectious burden in association with age is intriguing and provides a narrowed “region of interest” when one looks at risk factors in the general population of children presenting with focal symptoms to the emergency room. However, the study has deficiencies that weaken the findings of the IPSS group. The study included both retrospective and prospective collection of data, which results in a bias of reported results because of the absence of a priori determination of which data to collect. The data that were collected were informally obtained from parents or guardians, not from a formally validated, universally used (multilingual) questionnaire. Thus, determination of the presence of an upper respiratory tract infection may not have been carried out in the same way at each center but instead relied on parental recall. The neuroimaging studies performed to document arteriopathy occurred during 2003 to 2007. Not all centers used the same diagnostic imaging technique, and as pointed out, the sensitivity of techniques differs not only within institutions but as a result of interobserver variability. Most important is the fact that the study did not create a central adjudication committee to review and determine the presence of arteriopathy in all imaging studies. All of these limitations affect the validity of the following findings: the prevalence of arteriopathy in children with arterial ischemic
stroke and the association of sickle cell anemia, upper respiratory tract infection, and early school age as predictors of arteriopathy.

Despite the limitations outlined here and recognized by the authors, this article provides important information regarding the association of predictors of arteriopathy in those children with arterial ischemic stroke. Whether one can refer to these associations as predictive of arteriopathy needs further clarification in larger prospective multicenter studies, currently planned within the IPSS. In this regard, the incidence of stroke in children likely remains underestimated despite current epidemiological data. The present study provides the background necessary to identify those children presenting with focal deficits that require neuroimaging to determine the presence of stroke. This should lead to subsequent angiography in children with those biomarkers identified in this study of sickle cell disease, upper respiratory tract infection, and young age (5 to 9 years) for the determination of arteriopathy. The importance lies in identifying those children most likely to experience recurrence and indicating the subsequent need for further studies determining the safety and efficacy of secondary prophylaxis.

The IPSS group has done an outstanding job of initiating a large multicenter approach to childhood stroke. The article by Amlie-Lefond provides first important steps in more specifically identifying a cohort of children at risk for arteriopathy and hence subsequent recurrence. Given the heterogeneity of causes for stroke in infancy and childhood, such markers are necessary to move forward in the development of therapeutic interventions that are age specific, safe, and efficacious.

Disclosures
Dr Massicotte is a consultant for Boehringer Ingelheim, Bristol Myers Squibb, Eisai, Sanoﬁ-Aventis, Bayer, Levitronix, Eli Lilly, and Berlin Heart and is a member of the IPSS. Dr Yager is a member of the IPSS.

References
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Circulation. 2009;119:1361-1362; originally published online March 2, 2009;
doi: 10.1161/CIRCULATIONAHA.108.829069
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://circ.ahajournals.org/content/119/10/1361

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