Arterial Ischemic Stroke in Children: Baby Steps

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Editorial

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Baby Steps

Alan D. Michelson, MD

Arterial ischemic stroke (AIS) in a child can have devastating, lifelong sequelae.[1] Given the infrequency of AIS (approximately 3 per 100 000 children[1]), primary prevention is probably not feasible in the absence of a known risk factor. However, the prevention of recurrent AIS in childhood, ie, secondary prevention, may be feasible. How can recurrent childhood AIS be prevented? Current consensus guidelines on the use of antiplatelet and anticoagulant therapy for AIS in children are not based on randomized controlled trials (RCTs).[2,3] Detailed knowledge of the rates and predictors of AIS recurrence in children is essential before appropriate RCTs can be designed and before rational treatment guidelines can be promulgated. The article by Ganesan et al[4] in this issue of *Circulation* provides new information in this regard.

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Clinically Apparent and Clinically Silent Recurrences After First Childhood AIS

Ganesan et al[4] gathered longitudinal data on the rates of and risk factors for clinical and radiological recurrence of AIS in 212 children at a single large referral center (Great Ormond Street Hospital for Children, London, UK). Acute AIS was defined as an acute focal neurological deficit with evidence of cerebral infarction in an arterial distribution on brain imaging, irrespective of clinical symptoms. Children presenting with hemorrhagic stroke, congenital hemiplegia, or asymptomatic (silent) infarction were excluded. Patients were allocated to 1 of 2 mutually exclusive groups: those with a recognized medical diagnosis before AIS (prior diagnosis group) and those without such a diagnosis (previously healthy group). Patients underwent repeat neuroimaging (magnetic resonance imaging or computerized tomography [CT]) at the time of clinical recurrence or, if asymptomatic, at least a year after AIS. Cox and logistic regression analyses were used to explore the relationships between risk factors and clinical and radiological recurrence. Of the 212 patients with AIS, 97 were in the prior diagnosis group. Seventy-nine of the 212 (37%) had a clinical recurrence (29, stroke; 46, transient ischemic attack [TIA]; 4, death with reinfarction) between 1 day and 11.5 years (median 267 days) later. After 5 years, only 59% of patients were free of recurrence. Moyamoya disease shown by angiography and low birth weight were independently associated with clinical recurrence in the whole group. Genetic thrombophilia was associated with clinical recurrence in previously healthy patients independently of the presence of moyamoya disease. Sixty of 179 patients who underwent repeat neuroimaging had radiological reinfarction, which was clinically silent in 20 patients. Previous TIA, bilateral infarction, prior diagnosis (specifically immunodeficiency), and leukocytosis were independently associated with radiological reinfarction. Previous TIA and leukocytosis were also independently associated with clinically silent reinfarction.

This longitudinal study by Ganesan et al[4] demonstrates that both clinically apparent and clinically silent recurrences are common after first AIS in childhood. Some[5,6] but not all[7] previous large studies of childhood AIS have reported a lower incidence of clinical recurrence. For example, a previous large (301 patient) prospective study of childhood AIS by Sträter et al[5] reported a lower clinical recurrence rate of 6.6%, but this study included a smaller proportion of children with preexisting diagnoses; also, unlike the study by Ganesan et al,[4] it excluded children with previous vascular events (including TIAs) and, importantly, sickle cell disease (which is associated with a very high rate of recurrent AIS).

The greatest strength of the study by Ganesan et al[4] is that 179 (84%) of the 212 children with AIS, including 103 who remained asymptomatic, underwent repeat neuroimaging (magnetic resonance imaging or CT) at least a year after AIS. Most previous studies of childhood stroke have not performed repeat imaging in unselected consecutive patients. A major finding from the study by Ganesan et al[4] is that 20 (19%) of the 103 children who remained asymptomatic after their initial AIS had reinfarction identified on reimaging. Clinically silent reinfarction has not previously been reported in children with AIS, other than in those with sickle cell disease or moyamoya disease.[8] The relatively high incidence of silent reinfarction reported by Ganesan et al[4] might be important therapeutically because it has previously been suggested that in children with sickle cell disease, treatment (in this case, long-term transfusion therapy) may be effective in the prevention of silent infarcts.[9] Thus, silent reinfarction, which may result in major cognitive loss,[10] could be an important end point, in addition to clinical recurrence, in future RCTs of secondary prevention treatments in pediatric AIS.

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Evidence-Based Guidelines for the Treatment of AIS in Children

Children with AIS are often treated with antiplatelet agents (aspirin or clopidogrel) or anticoagulants (heparin or warfarin). Attempts at evidence-based guidelines for the treatment of AIS in children remain empiric, however, because of the lack of RCT data.[2,3] The effects of treatment on AIS recurrence rates cannot be determined from the study by Ganesan et al[4] because patients were not randomized to treatment versus no treatment. The only treatment for childhood AIS that is supported by a RCT is long-term transfusion therapy in sickle cell disease.[11] Pediatric treatment guidelines for AIS[2,3] are largely extrapolated from recommendations for adults, in whom AIS is much more common and in whom numerous large RCTs have therefore been performed. However, the most common underlying pathophysiology of adult AIS (atherosclerosis) is profoundly different from those in childhood AIS (congenital heart disease, sickle cell disease, prothrombotic abnormalities in the hemostatic system, mechanical injury with arterial dissection, local inflammatory arteriopathy, and moyamoya disease).[1,12]

Only RCTs building on the data of pediatric outcome studies such as that by Ganesan et al[4] will result in truly evidence-based guidelines for the treatment of childhood AIS. Although rare, the incidence of AIS in children is similar to that of brain tumors,[2] and coordinated multicenter RCTs of pediatric brain tumors have been successfully undertaken.[13] The formation of national and international networks focused on pediatric stroke research are steps in the right direction.[14]

Disclosures

None.

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