Thrombophilia and Pediatric Stroke

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Thrombophilia refers to a systemic predisposition to thrombosis, including stroke. Thrombophilia may be genetic (eg, factor V Leiden) or acquired (eg, antiphospholipid antibodies). Approximately 60% of thrombosis risk is attributable to genetic factors. Thrombosis is a disease for which there is a relatively well-defined management strategy in adults but less so in children. Thrombophilia is not a disease but a susceptibility to thrombosis, and its management strategy is less well defined in adults and not at all defined in children. Currently, the role of thrombophilia in pediatric stroke is poorly characterized.

The extensive published literature on stroke in adult patients cannot be assumed to apply to children because common underlying mechanisms of adult stroke, such as atherosclerosis, hypertension, smoking, atrial fibrillation, and diabetes mellitus, are infrequently involved in pediatric stroke. Known underlying mechanisms of pediatric stroke include perinatal placental thromboembolic events through a physiologically patent foramen ovale, congenital heart disease, sickle cell disease, arterial dissection, trauma, infection, inflammation, immobilization, dehydration, metabolic syndromes, moyamoya, and vasculitis. An increasing number of large pediatric centers now have dedicated multidisciplinary stroke services, which include neurology, hematology, neuroradiology, interventional radiology, neurosurgery, and physical, occupational, and speech therapists. Stroke as a diagnosis should be restricted to patients with cerebral infarction (see Figure, top). Multiple additional conditions with predisposition to stroke or cerebral vasculopathy may also be seen by these multidisciplinary groups, including cerebral sinus venous thrombosis (CSVT) (see Figure, bottom), moyamoya, vasculitis, transient ischemic attacks, complex migraines, and nontraumatic intracranial hemorrhage.

The incidence of pediatric arterial ischemic stroke (AIS) from 1988 to 1999 was stable (6.4 per 100,000), whereas a reduced mortality rate from 18% to 9% was reported in the same period. Venous thromboembolic events, including CSVT, are occurring at an increasing rate in children; this increase is attributable to improved survival of critically ill children, increased use of invasive measures for intensive care, and increased awareness by practitioners. Improved care of patients with single-ventricle congenital heart problems and increased use of cardiopulmonary bypass in children would be expected to increase stroke risk.

In this edition of Circulation, Kenet et al report a meta-analysis of the role of multiple thrombophilias as risk factors for pediatric AIS and CSVT. Given the absence of randomized controlled clinical trials in pediatric stroke, this meta-analysis by many of the world’s leaders in pediatric stroke is particularly welcome—the well-known limitations of meta-analyses notwithstanding. Because of the relative infrequency of pediatric stroke compared with adult stroke, only international collaborations such as reported in this article will move the field forward. The study by Kenet et al is by far the most comprehensive analysis to date of the effect of thrombophilia on pediatric stroke. This systematic review and meta-analysis encompasses observational studies from 1970 through 2009 in children from birth to 18 years of age. The meta-analysis includes 1764 patients (1526 AIS and 238 CSVT) and 2799 control subjects. Because of the paucity of data on pediatric stroke outcomes and recurrent stroke, the data are restricted to first presentations of AIS and CSVT.

The pathophysiologies of AIS and CSVT (see Figure) are distinct; therefore, the relative role of thrombophilia in these 2 settings may be different. Indeed, the Table shows reanalyzed data from Kenet et al to highlight the fact that the odds ratios for AIS and CSVT differ with each thrombophilia. For example, both antithrombin and protein S deficiencies are associated more with CSVT than AIS, whereas protein C deficiency is associated more with AIS than CSVT. However, caution in interpreting these data is suggested by the unexpected finding that ≥2 genetic thrombophilia traits are less associated with CSVT than antithrombin deficiency alone (see Table). Similar to the distinction between AIS and CSVT pathophysiology, a prenatal venous infarct, a neonatal arterial ischemic stroke, and a stroke in an older child also likely differ in underlying mechanism. However, there are insufficient data in the article by Kenet et al or elsewhere in the literature to assess the possibly differing role of thrombophilia in these subgroups.

Although the study by Kenet et al is an important new study, a number of methodological issues limit the interpretation of the authors’ conclusion that thrombophilias are risk factors for pediatric stroke:

1. The available studies for review and meta-analysis are small and observational.
2. The reliability of the odds ratios reported for pediatric stroke is critically dependent on the quality of the 2799 normal control subjects in the individual studies. How-
ever, the quality of these normal control subjects is not discussed by Kenet et al. How were these control subjects obtained? Were the control subjects matched by age and ethnic group?

3. The relationship between the timing of the stroke and the timing of the blood sample for thrombophilia testing is not disclosed. Although prothrombotic mutations and lipoprotein(a) contribute consistently to thrombosis risk, acquired transient deficiencies of antithrombin, protein C, or protein S and the presence of antiphospholipid antibodies do not. This is a potentially important confounding factor because thrombosis can, for example, result in transient, acquired low levels of antithrombin, protein C, and/or protein S. What is the significance of a low protein C level hours after a pediatric stroke—cause, effect, or epiphenomenon? Thrombophilia assays were presumably performed after stroke presentation to investigate its origin. Therefore, the conclusion that thrombophilias are risk factors for first pediatric stroke is limited to inherited thrombophilias, including lipoprotein(a). In contrast, the data provided demonstrate an association only between acquired thrombophilias and pediatric stroke.

4. Although the methylenetetrahydrofolate reductase mutation is generally considered to be relevant only to thrombosis in the setting of an elevated serum homocysteine, neither serum nor urine homocysteine was reported because of a paucity of data.

5. Lipoprotein(a) data are limited to 4 studies from a single research group.

6. Antiphospholipid antibodies were not evaluated as stringently as updated diagnostic criteria for antiphospholipid antibody syndrome and rarely included anti-β2 glycoprotein 1 antibodies. This is a particularly important issue in children, in whom transient antiphospholipid antibody titers are commonly found after even mild viral infections. It is unknown whether these transient antiphospholipid antibodies confer an increased thrombotic risk to these children.

There are numerous unanswered questions with regard to the clinical indications, if any, for thrombophilia testing in pediatric patients who have had a stroke. Should all children

### Table. Odds Ratios for Initial AIS Versus CSVT

<table>
<thead>
<tr>
<th>Thrombophilia</th>
<th>Odds Ratio (95% Confidence Interval) for AIS</th>
<th>Odds Ratio (95% Confidence Interval) for CSVT</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥2 Genetic traits</td>
<td>18.75 (6.49–54.14)</td>
<td>6.12 (0.87–43.07)</td>
</tr>
<tr>
<td>Protein C deficiency</td>
<td>11.0 (5.13–23.59)</td>
<td>6.30 (1.56–25.40)</td>
</tr>
<tr>
<td>Antiphospholipid antibodies</td>
<td>6.95 (3.67–13.14)</td>
<td>*</td>
</tr>
<tr>
<td>Lipoprotein(a) elevation</td>
<td>6.53 (4.46–9.55)</td>
<td>*</td>
</tr>
<tr>
<td>Factor V Leiden</td>
<td>3.70 (2.82–4.85)</td>
<td>2.74 (1.73–4.34)</td>
</tr>
<tr>
<td>Antithrombin deficiency</td>
<td>3.29 (0.70–15.48)</td>
<td>18.41 (3.25–104.29)</td>
</tr>
<tr>
<td>Factor II G20210A</td>
<td>2.60 (1.06–4.08)</td>
<td>1.95 (0.93–4.07)</td>
</tr>
<tr>
<td>MTHFR thermolabile</td>
<td>1.58 (1.20–2.08)</td>
<td>*</td>
</tr>
<tr>
<td>Protein S deficiency</td>
<td>1.49 (0.32–6.92)</td>
<td>5.27 (1.53–18.21)</td>
</tr>
</tbody>
</table>

Data were retabulated from the article by Kenet et al. MTHFR indicates methylenetetrahydrofolate reductase. *Insufficient data.

![Figure. AIS (top) and CSVT (bottom). Top left, Magnetic resonance angiogram. Top right, Axial T2 magnetic resonance image. Bottom left, Sagittal T1 magnetic resonance image. Bottom right, Time-of-flight magnetic resonance venography. Arrows highlight abnormalities.](image-url)
with a personal history of AIS or CSVT or those with a strong family history of thrombosis be evaluated for thrombophilia? Should the thrombophilia panel be different for neonatal strokes than for those strokes occurring later in childhood or for AIS versus CSVT? With the exception of substituting fasting homocysteine testing for methylenetetrahydrofolate reductase genotyping, are the thrombophilia traits discussed by Kenet et al the appropriate panel? How should we approach other putative thrombophilias such as elevated factors VIII, IX, or XI; elevated D-dimer; inflammatory markers; and newly discovered polymorphisms? Once identified, which abnormalities should affect acute stroke management or secondary prophylaxis? Genome-wide association studies are finding new genes that carry modest thrombosis risk. Individually, these modest thrombophilias have questionable clinical significance, although they may be informative in combination. Of note, in many cases, transient acquired risk factors are more potent than modest genetic thrombophilias; thus, improved prophylaxis strategies may reduce thrombosis in individual patients.

Antithrombotic treatment guidelines have been proposed for children with AIS and CSVT. Although these guidelines are widely followed, they are based largely on expert opinion rather than controlled data and have not been rigorously validated. Only randomized controlled trials can result in true evidence-based guidelines for the treatment of childhood AIS and CSVT. Although rare, the incidence of AIS in children is similar to that of pediatric brain tumors, and coordinated multicenter randomized controlled trials of pediatric brain tumors have been successfully undertaken. The formation of national and international networks focused on pediatric stroke research has been an important first step. Nevertheless, the internationally authored article by Kenet et al does not address the merits of different treatment for neonates and children with thrombophilia. Therefore, the question remains: Of what clinical use is thrombophilia testing if it does not alter management? It is to be hoped that future research will address this question. For now, participation in the International Pediatric Stroke Study is encouraged to allow uniform collection of comprehensive data, including thrombophilia testing, for all children with stroke.

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Disclosures

None.

References


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