Should infants with perinatal thrombosis be screened for thrombophilia and treated by anticoagulants?

I SAY NO

Shoshana Revel-Vilk, MD MSc
Pediatric Hematology Center,
Pediatric Hematology/Oncology Department,
Hadassah- Hebrew University Hospital, Jerusalem, Israel
Perinatal arterial ischemic stroke (PAIS)

- a condition with acute encephalopathy, seizures, or neurologic deficit presenting in a term or preterm infant before the 29th postnatal day, with brain imaging confirming a parenchymal infarct in the appropriate arterial territory

Presumed perinatal stroke

- Infants who develop neurological deficits attributable to focal infarction later in infancy
- Diagnosis must be based on compatible neuroimaging findings
- Clinical presentation of these children will depend on the age at which they are recognized and the extent of injury
Outcome

- Mortality less than 10%
- Morbidity 60%-70%
  - Motor impairments
  - Abnormal cognitive outcome
  - Post-neonatal epilepsy

Question

- Whether testing for thrombophilia and/or treating with anticoagulation has a beneficial effect on the outcome of children with perinatal arterial ischemic stroke
Etiology

- Synergism of fetal and maternal factors
- Patent foramen ovale (PFO) allows passage of thrombi derived from the placenta or venous circulation, resulting in occlusion of an artery.
Risk factors

- Maternal/intrapartum
  - Infertility, nuliparity, maternal fever, meconium-stained amniotic fluids, chorioamnionitis, pre-eclampsia, intrauterine growth retardation
  - emergency CS, low Apgar score, arterial umbilical cord pH < 7.1
Risk factors

- Infant
  - Hypoglycemia, sepsis/meningitis, dehydration

- Identified in small retrospective case series, do not necessarily reflect a causal relation
Risk factors

- 52 neonates with PAIS

Table 2: Multivariable risk factor analysis of PAIS

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>OR</th>
<th>95% CI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal fever</td>
<td>10.24</td>
<td>1.33 to 78.53</td>
<td>0.03</td>
</tr>
<tr>
<td>Apgar score (5 min) &lt;7</td>
<td>18.06</td>
<td>3.37 to 96.81</td>
<td>0.00</td>
</tr>
<tr>
<td>Hypoglycaemia</td>
<td>12.99</td>
<td>3.20 to 52.56</td>
<td>0.00</td>
</tr>
<tr>
<td>Early-onset sepsis/meningitis</td>
<td>5.82</td>
<td>1.06 to 31.88</td>
<td>0.04</td>
</tr>
</tbody>
</table>

PAIS, perinatal arterial ischaemic stroke.

Other risk factors

- Patent foramen ovale (PFO)
- Congenital heart disease
- Arterial dissection
- Catheterization
- Cardiac surgery
Thrombophilia

- Studies have reported prothrombotic factors in more than half of the children with history of perinatal arterial ischemic stroke
  - Inherited
  - Acquired - APLA
<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Patients (n=91)</th>
<th>Controls (n=182)</th>
<th>ORs/95% CIs</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipoprotein(a) &gt;30 mg/dL</td>
<td>20 (22.0%)</td>
<td>10 (5.5%)</td>
<td>4.84/2.16–10.86</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Factor V 1691GA*</td>
<td>17 (18.7%)</td>
<td>10 (5.5%)</td>
<td>3.95/1.72–9.0</td>
<td>0.0016</td>
</tr>
<tr>
<td>Prothrombin 20210GA</td>
<td>4 (4.4%)</td>
<td>4 (2.2%)</td>
<td>2.04/0.49–8.3</td>
<td>0.44†</td>
</tr>
<tr>
<td>MTHFR 677TT</td>
<td>15 (16.5%)</td>
<td>20 (10.9%)</td>
<td>1.59/0.77–3.29</td>
<td>0.28</td>
</tr>
<tr>
<td>Protein C deficiency type I</td>
<td>6 (6.6%)</td>
<td>……</td>
<td>……</td>
<td>0.0012†</td>
</tr>
<tr>
<td>Total</td>
<td>62 (68.0%)</td>
<td>44 (24.2%)</td>
<td>6.70/3.84–11.67</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values shown are n and (percent).
*Combined with lipoprotein(a) Lp: n=3 (not included in the Lp column) and with anticardiolipin IgG antibodies (n=1).
†Fisher’s exact test.
Table 1. Thrombophilic Risk Factors Among 47 Infants With Perinatal Stroke and Comparison Between Infants With Perinatal Stroke With and Without Available Maternal Information

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>All Infants With Perinatal Stroke, N=47 (%)</th>
<th>Infants With Maternal Information, N=23 (%)</th>
<th>Infants With No Maternal Information, N=24 (%)</th>
<th>*P</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least 1 thrombophilic risk factor</td>
<td>30 (63.8)</td>
<td>14 (60.9)</td>
<td>16 (66.7)</td>
<td>0.67</td>
</tr>
<tr>
<td>Genetic thrombophilia (at least 1)</td>
<td>25 (53.2)</td>
<td>12 (52.2)</td>
<td>13 (54.2)</td>
<td>0.9</td>
</tr>
<tr>
<td>Decreased protein C activity</td>
<td>9 (19.2)</td>
<td>5 (21.7)</td>
<td>4 (16.7)</td>
<td>0.66</td>
</tr>
<tr>
<td>Decreased free protein S</td>
<td>6 (12.8)</td>
<td>2 (8.7)</td>
<td>4 (16.7)</td>
<td>0.43</td>
</tr>
<tr>
<td>FVL mutation</td>
<td>10 (21.3)</td>
<td>6 (26.1)</td>
<td>4 (16.7)</td>
<td>0.43</td>
</tr>
<tr>
<td>FIIG20210A mutation</td>
<td>3 (6.4)</td>
<td>2 (8.7)</td>
<td>1 (4.2)</td>
<td>0.55</td>
</tr>
<tr>
<td>MTHFR C677T</td>
<td>9 (19.2)</td>
<td>5 (21.7)</td>
<td>4 (16.7)</td>
<td>0.66</td>
</tr>
<tr>
<td>Acquired (APLA)</td>
<td>11 (23.4)</td>
<td>6 (26.1)</td>
<td>5 (20.8)</td>
<td>0.68</td>
</tr>
<tr>
<td>Combined genetic and acquired thrombophilia</td>
<td>7 (14.9)</td>
<td>4 (13)</td>
<td>3 (12.5)</td>
<td>0.62</td>
</tr>
</tbody>
</table>

*Comparison of thrombophilia distribution between infants with and without available maternal information.

23 mother-children pairs

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Infants, n=23</th>
<th>Prevalence in Controls</th>
<th>Relative Risk (95% CI)</th>
<th>Mothers, n=22</th>
<th>Prevalence in Controls</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>677T MTHFR homozygote</td>
<td>21.7% (5)</td>
<td>15.1%</td>
<td>1.4 (0.6; 3.5)</td>
<td>13.6% (3)</td>
<td>12.7%</td>
<td>1.1 (0.4; 3.1)</td>
</tr>
<tr>
<td>FVL-Het</td>
<td>26.1% (6)</td>
<td>6.25%</td>
<td>4.2 (1.5; 11.3)</td>
<td>31.8% (7)</td>
<td>3.8%</td>
<td>8.5 (4.1; 17.5)</td>
</tr>
<tr>
<td>FIIG20210A-Het</td>
<td>8.7% (2)</td>
<td>3.6%</td>
<td>2.4 (0.5; 12.5)</td>
<td>9% (2)</td>
<td>4.2%</td>
<td>2.1 (0.5; 7.5)</td>
</tr>
<tr>
<td>Protein C deficiency</td>
<td>21.7% (5)</td>
<td>1.8%</td>
<td>12.2 (2.5; 59.9)</td>
<td>0% (0)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Free protein S deficiency</td>
<td>8.7% (2)</td>
<td>0%</td>
<td>NA</td>
<td>13.6% (3)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Antithrombin deficiency</td>
<td>0% (0)</td>
<td>0%</td>
<td>NA</td>
<td>0% (0)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>APLA</td>
<td>21.7% (5)</td>
<td>5.4%</td>
<td>4.1 (1.4; 12.2)</td>
<td>18.2% (4)</td>
<td>4.7%</td>
<td>3.9 (1.5; 10.0)</td>
</tr>
</tbody>
</table>

Relative risks are presented for infants vs controls (derived from Kenet et al\(^2\)) and for mothers vs controls (derived from Salomon et al\(^1\)), separately. Het indicates heterozygous; NA, not available.
Maternal thrombophilia

- Six mothers with previous TEs
  - Strokes (n=3)
  - TIA during pregnancy (n=1)
  - DVT (n=2)

- One mother had 2 children with PAIS and a previous pregnancy that ended in stillbirth

60 mother-children pairs

Table 6. Prothrombotic factors in 60 mother-child pairs with perinatal arterial stroke

<table>
<thead>
<tr>
<th></th>
<th>Child, n/N (%)</th>
<th>Mother, n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor V Leiden</td>
<td>3/60 (5)</td>
<td>4/52 (8.2)</td>
</tr>
<tr>
<td>Prothrombin 20210</td>
<td>6/58 (10)</td>
<td>2/49 (4.2)</td>
</tr>
<tr>
<td>MTHFR C677T/C677T</td>
<td>13/59 (22)</td>
<td>13/51 (26.5)</td>
</tr>
<tr>
<td>MTHFR C677T/A1298C</td>
<td>6/35 (17)</td>
<td>3/30 (10)</td>
</tr>
<tr>
<td>MTHFR A1298C/A1298C*</td>
<td>2/35 (6)</td>
<td>2/30 (6.7)</td>
</tr>
<tr>
<td>MTHFR C677T/neg</td>
<td>22/59 (37)</td>
<td>18/51 (36.7)</td>
</tr>
<tr>
<td>MTHFR A1298C/neg</td>
<td>1/35 (3)</td>
<td>0/30 (0)</td>
</tr>
<tr>
<td>MTHFR neg/neg</td>
<td>14/59 (2)</td>
<td>13/51 (27.1)</td>
</tr>
<tr>
<td>Low protein C activity</td>
<td>1/51 (2)</td>
<td>0/40 (0)</td>
</tr>
<tr>
<td>Low protein S activity</td>
<td>1/56 (4)</td>
<td>5/42 (12)</td>
</tr>
<tr>
<td>Anticardiolipin antibodies</td>
<td>not available</td>
<td>7/42 (10)</td>
</tr>
<tr>
<td>Lupus anticoagulant</td>
<td>not available</td>
<td>1/27 (3.7)</td>
</tr>
<tr>
<td>B2 glycoprotein antibodies</td>
<td>not available</td>
<td>4/16 (25)</td>
</tr>
<tr>
<td>Lipoprotein(a) &gt;30mg/dL</td>
<td>5/24 (21)</td>
<td>9/24 (33)</td>
</tr>
<tr>
<td>Homocysteine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;10 μm/L mother</td>
<td>7/22 (32)</td>
<td></td>
</tr>
<tr>
<td>&gt;7 μm/L child</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Maternal thrombophilia

- Previous pregnancy loss (n=16)
  - late-term stillbirth (n=3)
- Intrauterine growth restriction (n=3)
- History of previous PE (n=2)
- Family history of thrombosis (n=13)

Meta-analysis

- Six studies for perinatal AIS

- Summary odd ratios
  - factor V G1691A 3.56 (95% CI 2.29-5.53)
  - factor II G20210A 2.02 (95% CI, 1.02 to 3.99)

Does thrombophilia effects outcome?
24 children with perinatal cerebral infarction confirmed by neonatal MRI
10 had at least one prothrombotic risk factor
Hemiplegia was diagnosed in all (5/5) children with FVL compared to 4/20 of children without FVL ($P = .003$)

Neurological outcome

- 47 infants with clinically and radiologically confirmed perinatal arterial ischemic stroke
- 15 children with residual neurological deficit
- Not associated with positive thrombophilia

Recurrence

215 children
Follow-up median 3.5 years (1 to 8 years)

Kurnik K, et al. 2003 Stroke;34:2887-2892

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age, mo</th>
<th>Recurrent Event</th>
<th>Basic Disease</th>
<th>Prothrombotic Risk Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>3</td>
<td>Sinus venous thrombosis</td>
<td>...</td>
<td>Hcy 43 μmol/L*</td>
</tr>
<tr>
<td>Female</td>
<td>6</td>
<td>AIS</td>
<td>...</td>
<td>MTHFR T677T</td>
</tr>
<tr>
<td>Female</td>
<td>6</td>
<td>Sinus venous thrombosis</td>
<td>Mastoiditis</td>
<td>Lipoprotein(a)</td>
</tr>
<tr>
<td>Male</td>
<td>12</td>
<td>AIS</td>
<td>CHD</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>20</td>
<td>AIS</td>
<td>Moyamoya Diarrhea</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>22</td>
<td>Deep venous thrombosis</td>
<td>CHD, central venous line, immobilization</td>
<td>Protein C type I deficiency</td>
</tr>
<tr>
<td>Male</td>
<td>98</td>
<td>AIS</td>
<td>Diarrhea</td>
<td>Lipoprotein(a) MTHFR T677T</td>
</tr>
</tbody>
</table>
Thrombophilia and recurrence

- Recurrence
  - 5/127 (3.9%) with thrombophilia
  - 2/88 (2.3%) without thrombophilia

- No significance difference ($p=0.7$)
- Need to treat 60 neonates with thrombophilia to prevent one event

Kurnik K, et al. 2003 Stroke;34:2887-2892
Recurrence

84 children,
Follow-up median 5.8 years (mean 6 years, range 3 day to 12.4 years)
No recurrence of ischemic stroke (one event of ICH)

Rate of recurrence

- 2.34% (95% CI 0.95%-4.76%) risk of any thrombotic event
- 1.34% (95% CI 0.37%-3.39%) risk of recurrent AIS

Despite the presence of prothrombotic factors, recurrence of arterial ischemic stroke is rare, suggesting a multifactorial cause of PAIS
Role of anticoagulation

- Reduce the risk of extension or embolization
- Reduce the incidence of recurrent thrombosis
Recommendations

2.18. For neonates with a first AIS in the absence of a documented ongoing cardioembolic source, we suggest supportive care over anticoagulation or aspirin therapy (Grade 2C).

2.19. For neonates with a first AIS and a documented cardioembolic source, we suggest anticoagulation with UFH or LMWH (Grade 2C).

2.20. For neonates with recurrent AIS, we suggest anticoagulant or aspirin therapy (Grade 2C).
Answer

- Whether testing for thrombophilia and/or treating with anticoagulation has a beneficial effect on the outcome of children with perinatal arterial ischemic stroke

No!
Testing children for inherited thrombophilia: more questions than answers

Leslie Raffini¹ and Courtney Thornburg²
Ethical issues with genetic testing in pediatrics

- Medical benefit, related to therapy or prevention, should be the primary justification for genetic testing in children and adolescents.
- Thus, prior to testing children for inherited thrombophilia, clinicians should consider whether testing can improve clinical outcomes.
Arterial Ischemic Stroke in an Adolescent With Presumed Perinatal Ischemic Stroke

Kristin Hamilton, MD\textsuperscript{1}, Michael S. Salman, PhD\textsuperscript{1}, Ilan Schwartz, MD\textsuperscript{2}, Patricia J. McCusker, FRCPC\textsuperscript{1}, Jens Wrogemann, FRCPC\textsuperscript{3}, and Mubeen F. Rafay, FCPS\textsuperscript{1}
Abstract
The risk of recurrent ischemic stroke after presumed perinatal stroke and the risk factors for such recurrence are rarely reported. Here, we present an adolescent with a history of presumed perinatal stroke who presented with arterial ischemic stroke recurrence at the age of 15 years. Hereditary thrombophilia screening performed at the time of his stroke recurrence demonstrated protein S deficiency. No evidence-based consensus guidelines on thrombophilia screening in children with presumed perinatal stroke exist, nor has the role of secondary prophylaxis been addressed. There is a risk of stroke recurrence after presumed perinatal stroke, and routine thrombophilia screening may identify those children who are at higher risk for recurrence and who might therefore benefit from secondary prophylaxis. Clear guidelines should be developed to standardize investigations and management of children with presumed perinatal ischemic stroke.
Case report

- 15 y.o., diagnosed with AIS
- Past history - gestational diabetes, hypertension. Emergency CS, Apgar score 4 and 9, PFO. At 17 months - global delay and right-sided hemiparesis. Imaging - presumed perinatal stroke. Not investigated for thrombophilia
Case report

- When he was 3 years age the mother was diagnosed with possible protein S deficiency based on family history of DVT. He was not tested.

How would knowing the diagnosis of PS deficiency effect his management?
Case report

- Based on the family history he was immediately investigated and diagnosed with PS deficiency
- Anticoagulation therapy was immediately started

Should he received anticoagulation from the age of 7 months?? From the age of three years?
Consider testing

- Significant multisystem thrombosis
- Significant family history

- Testing the mother for persistently elevated antiphospholipid antibodies may be considered for predicting recurrence in subsequent pregnancies

An update on thrombophilia and placenta mediated pregnancy complications: What should we tell our patients?

Marc A. Rodger\textsuperscript{a, b, *}

\textsuperscript{a}Thrombosis Program, Division of Hematology, Department of Medicine, University of Ottawa, Ottawa, Ontario, Canada
\textsuperscript{b}Clinical Epidemiology Unit, Ottawa Hospital Research Institute, The Ottawa Hospital, Ottawa, Ontario, Canada
Placenta related complications

- Associations are very week and mainly with severe outcomes

- Preventive therapy with anticoagulation is only beneficial in preventing recurrent severe placenta mediated complications
Perinatal arterial ischemic stroke is related to multifactorial cause

Association with prothrombotic factors do not necessary determine causation

Diagnosis of prothrombotic factors in this setting do not effect short term and/or long term management
Should infants with perinatal thrombosis be screened for thrombophilia and treated by anticoagulants?

I Say No

Shoshana Revel-Vilk, MD MSc
Pediatric Hematology Center,
Pediatric Hematology/Oncology Department, Hadassah-Hebrew University Hospital, Jerusalem, Israel