Recurrent Thromboembolism in Infants and Children Suffering From Symptomatic Neonatal Arterial Stroke: A Prospective Follow-Up Study

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Background and Purpose—The present study was performed to evaluate the rate of recurrent symptomatic thromboembolism with respect to prothrombotic risk factors and underlying clinical conditions.

Methods—In a series of 215 consecutively enrolled neonates with arterial ischemic stroke (AIS), the factor V G1691A mutation, factor II G20210A variant, methylenetetrahydrofolate reductase (MTHFR) T677T genotype, lipoprotein (Lp) (a), antithrombin, protein C, protein S, and anticardiolipin antibodies (ACA) were investigated. Patient median follow-up was 3.5 years (range, 1 to 8 years).

Results—During follow-up, 7 infants and children (3.3%) showed recurrent symptomatic thromboembolism (AIS, n = 4; venous sinus thrombosis, n = 2; deep vein thrombosis of the leg, n = 1). The factor V mutation, factor II variant, elevated Lp(a) > 30 mg/dL, protein C deficiency, and protein S or antithrombin deficiency were associated with first stroke onset. In 5 of 7 cases (71.4%), prothrombotic risk factors [MTHFR T677T, elevated Lp(a), hyperhomocysteinemia, protein C deficiency] were involved at the time of recurrence. Furthermore, a second thromboembolic event was triggered additionally by underlying diseases (71%), eg, cardiac malformation and immobilization, diarrhea, mastoiditis, and moyamoya syndrome.

Conclusions—Data shown here give evidence that symptomatic recurrent thromboembolism is not common in children with neonatal AIS. The risk of a second event, however, is increased when underlying diseases occur and prothrombotic risk factors are involved. (Stroke. 2003;34:2887-2893.)

Key Words: infant, newborn • lipoproteins • protein C deficiency • stroke • thromboembolism
The rate of a second stroke reported is ≈20%, ranging from 8% in children with no identified underlying disorder to 42% in pediatric patients with multiple risk factors. We therefore investigated in a prospective study the relevance of underlying prothrombotic risk factors and organic and metabolic diseases to a second symptomatic thromboembolic event in white term infants and children initially suffering from neonatal AIS.

**Subjects and Methods**

**Ethics**

The present study was performed in accordance with the ethics standards laid down in a relevant version of the 1964 Declaration of Helsinki and approved by the medical ethics committee at the Westfälische Wilhelms-University (Muenster, Germany).

**Inclusion Criteria**

Surviving white term neonates, including neonates previously reported, with a first onset of symptomatic AIS occurring spontaneously or associated with birth asphyxia, dehydration, septicemia, patent foramen ovale or congenital heart disease, birth trauma, maternal diabetes, maternal drug abuse, or perinatal/postnatal infection were prospectively enrolled. In all cases, suspected vascular accidents were confirmed by standard imaging methods (cranial sonography, CT, MRI) by an independent neuroradiologist as previously described.

**Study End Point**

Clinically suspected recurrent symptomatic thromboembolism, e.g., arterial or venous thrombosis, confirmed by MRI imaging, MR angiography, conventional angiography (arterial events), venography, compression sonography, CT, or spiral CT (venous events) was defined as the study end point.

**Patients**

From October 1994 to January 2003, 215 consecutive white neonatal AIS patients (100% white: 89% German, 5.1% Turkish, 1.4% Greek, 1.4% Serbian, 0.9% Spanish) from different geographic catchment areas of Germany were enrolled in the study. Median age at first thrombotic onset was 3 days (range, from 1 to 28 days; 120 males).

**Clinical Presentation at Acute Stroke Onset**

Seizures were the leading symptoms in neonates with a first AIS onset. In 156 patients (72.6%), focal seizures had occurred; 9 subjects (4.2%) presented with generalized seizures. Additionally, recurrent apnea was found in 28 full-term neonates (13.0%); 22 neonates (10.2%) presented with persistent hypotonia.

**Thrombosis Location**

At AIS onset, neonates presented with left middle cerebral artery occlusion (n=129; 60.0%), right middle cerebral artery occlusion (n=65; 30.2%), or vascular accident of both cerebral middle arteries (n=13; 6.0%). The anterior cerebral artery was affected in 5 neonates (2.5%), and vascular territory of the thalamus was occluded in 3 (1.4%) additional cases.

**Underlying Diseases**

In 117 of 215 neonates (54.4%), additional triggering factors found at first stroke onset were as follows: birth asphyxia (5-minute APGAR score <5; umbilical artery pH at birth <7.2; heart rate, <80 bpm; n=41; 19.1%), septicemia (n=26; 12.1%), persistent patent foramen ovale and/or congenital heart disease (n=34; 15.8%), maternal diabetes (n=6; 2.8%), renal venous thrombosis (n=7; 3.3%), and cerebral vasculopathies (dissection, fixed stenosing vasculopathy, congenital moyamoya; n=3; 1.4%). In contrast, no triggering exogenous factor was found in 98 cases (45.6%).

**Acute Antithrombotic Treatment**

Because of the individual decisions of the participating study centers, no antithrombotic treatment was performed in most cases (n=155; 72.1%); in 12 neonates (5.6%), unfractionated heparin (activated partial thromboplastin time prolongation times 1.5 to 2) was administered over a period of 10 to 14 days; 39 infants (18.1%) received prophylactic doses of low-molecular-weight heparin (4-hour anti-factor Xa activity, 0.2 to 0.4 IU/mL); and 9 subjects (4.2%) received aspirin (2 to 4 mg/kg) over a period of 3 to 6 months.

**Blood Samples**

With informed written or oral parental consent, blood samples were collected from patients at AIS onset (ACA) and 3 to 6 months after the acute event by peripheral venipuncture into plastic tubes containing 1/10 by volume of 3.8% trisodium citrate or into plastic tubes without additives (Sarstedt). Citrated blood (3 mL) was placed immediately on melting ice. Platelet-poor plasma and serum were prepared by centrifugation at 3000g for 20 minutes at 4°C or at room temperature, divided into aliquots in polystyrene tubes, stored at −70°C; and thawed immediately before the assay procedure. For genetic analysis, venous blood (0.5 mL) was obtained in EDTA-treated sample tubes (Sarstedt), from which cells were separated by centrifugation at 3000g for 15 minutes. The buffy coat layer was then removed and stored at −70°C, pending DNA extraction by a spin column procedure (Qiagen).

**Assays for Genotyping**

The FV G1691A, prothrombin G20210A, and MTHFR C677T genotypes were determined by polymerase chain reaction and analysis of restriction fragments as previously reported.

**Assays for Plasma Proteins**

Amidolytic protein C and antithrombin activities were measured on an ACL 300 analyser (Instrumentation Laboratory) using chromogenic substrates (Chromogenix). Free protein S antigen, total protein S, and protein C antigen were measured with commercially available enzyme-linked immunosorbent assay kits (ELISA; Stago). Factor VIIIIC was measured with the BCS (Dade-Behring) with factor VIII–deficient plasma (Dade-Behring, Germany). Lp(a) and ACA (IgM and IgG) were determined with ELISA techniques (Chromogenix).

**Total fasting plasma homocysteine levels** were measured in EDTA plasma by high-performance liquid chromatography with reverse-phase separation and fluorescent detection. Separation conditions of 0.24 mmol/L acetate, 1-mL/min flow rate, and a reverse-phase column C18 Xterra (150×39 mm, Waters) have been used. Coefficients of variation between days were 2.2% and 3.5%.

**Classification of Risk Cutoff**

Type I deficiency state (protein C, antithrombin) was diagnosed when functional plasma activity and immunological antigen concentration of a protein were repeatedly found to be below the lower age-related limit (3 months: protein C <20%, antithrombin...
TABLE 1. Distribution of Single (n=96) and Combined* (n=31) Prothrombotic Risk Factors in Full-Term Neonatal AIS Patients at Onset (n=215) and in Recurrent Thromboembolism (n=7)

<table>
<thead>
<tr>
<th>Prothrombotic Risk Factor</th>
<th>Neonatal Stroke Onset</th>
<th>Recurrent Thromboembolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall distribution of single and combined prothrombotic risk factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Factor V G1691A total</td>
<td>32/215</td>
<td></td>
</tr>
<tr>
<td>Alone</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>And lipoprotein(a) &gt;30 mg/dl</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>And MTHFR TT</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>And antithrombin/protein C deficiency</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>And protein C/protein S deficiency</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>And Hcy &gt;10 μmol/L</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Factor II G20210A total</td>
<td>8/215</td>
<td></td>
</tr>
<tr>
<td>Alone</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>And lipoprotein(a) &gt;30 mg/dL</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>And MTHFR TT</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>And protein C deficiency</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>MTHFR T677T total</td>
<td>28/215</td>
<td></td>
</tr>
<tr>
<td>Alone</td>
<td>12</td>
<td>1/7</td>
</tr>
<tr>
<td>And lipoprotein(a) &gt;30mg/dL</td>
<td>5</td>
<td>1/7</td>
</tr>
<tr>
<td>And protein C deficiency</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>And Hcy &gt;10 μmol/L</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>And others*</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Hcy &gt;10 μmol/L total</td>
<td>9/48</td>
<td></td>
</tr>
<tr>
<td>Alone</td>
<td>5</td>
<td>1/7</td>
</tr>
<tr>
<td>And lipoprotein(a) &gt;30mg/dL</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>And others*</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Lipoprotein(a) &gt;30 mg/dL total</td>
<td>45/148</td>
<td></td>
</tr>
<tr>
<td>Alone</td>
<td>29</td>
<td>1/7</td>
</tr>
<tr>
<td>And antithrombin deficiency</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>And protein C deficiency</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>And factor VIIIC &gt;150%</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>And others*</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Protein C deficiency total</td>
<td>9/215</td>
<td></td>
</tr>
<tr>
<td>Alone</td>
<td>4</td>
<td>1/7</td>
</tr>
<tr>
<td>And others*</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Protein S deficiency total</td>
<td>1/215</td>
<td></td>
</tr>
<tr>
<td>Alone</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>And others*</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Antithrombin deficiency total</td>
<td>1/215</td>
<td></td>
</tr>
<tr>
<td>Alone</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>And others*</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Factor VIIIC &gt;150% total</td>
<td>6/75</td>
<td></td>
</tr>
<tr>
<td>Alone</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>And others*</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>ACA total</td>
<td>19/215</td>
<td></td>
</tr>
<tr>
<td>Alone</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Interaction of prothrombotic risk factors and basic diseases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prothrombotic risk without basic disease</td>
<td>62/215 (28.8%)</td>
<td>1/7 (14.3%)</td>
</tr>
<tr>
<td>Prothrombotic risk and basic disease</td>
<td>65/215 (30.2%)</td>
<td>4/7 (57.1%)</td>
</tr>
</tbody>
</table>

Additionally, the interaction between prothrombotic risk factors and basic diseases are shown.

ACA indicates anticardiolipin antibodies; Hcy, homocysteine; MTHFR, methylenetetrahydrofolate reductase.

*Combined prothrombotic risk factors were mentioned at first appearance in the Table.
TABLE 2. **Patient Characteristics at the Time of Recurrent Thromboembolism**

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

AIS indicates arterial ischemic stroke; CHD, congenital heart disease; Hcy, homocysteine; LMWH, low-molecular-weight heparin; MTHFR, methylenetetrahydrofolate reductase; UFH, unfractionated heparin.

* MTHFR C677T genotype.

<30%). The diagnosis of protein S deficiency was based on reduced free protein S antigen levels combined with decreased or normal total protein S antigen concentrations (3 months: <30%). Serum levels of Lp(a) >30 mg/dL were considered elevated, and 28 kringle IV was used as the cutoff for the definition of small apolipoprotein(a) isoforms. The cutoffs (above the age-related 90th percentile) used at 3 to 6 months after the acute stroke onset were >150% of normal for factor VIIIC and >10 μmol/L for fasting total homocysteine concentrations.

**Statistical Analysis**

All statistical analyses were performed with the StatView 5 software package (SAS Institute Inc). The probability of recurrent IS as a function of time was determined with Kaplan-Meier method. Because of their seemingly nongaussian distribution, continuous data are presented as medians and ranges.

**Results**

**Recurrent Symptomatic Thromboembolism**

After a first neonatal AIS, patient median follow-up was 3.5 years (range, 1 to 8 years). Within a median follow-up time of 12 months (range, 3 to 98 months), 7 surviving infants and children (3.3%) with a first neonatal AIS experienced a second symptomatic event. The Figure shows that with increasing time the slope of the Kaplan-Meier cumulative hazard plot becomes slightly flatter, suggesting that the risk of recurrence decreases with time from initial stroke onset.

**Thromboembolic Location at Recurrence**

At recurrence, 4 of 7 infants and children presented with a second AIS (left middle cerebral artery, n=2; right middle cerebral artery, n=2). Two infants showed venous cerebral vascular occlusion (superior sagittal sinus, transversal sinus), and 1 child suffered deep vein thrombosis of the leg.

**Clinical Presentation at Recurrence**

Seizures and/or focal neurological symptoms were the leading symptoms in infants and children with recurrent AIS and in the 3-month-old boy with sinus venous thrombosis. Vomiting and headache were found in the 6-month-old girl with mastoiditis and sinus venous thrombosis, and the 22-month-old girl presented with a swollen blue leg caused by central line–associated thrombosis after cardiac surgery and immobilization.

**Prothrombotic Risk Factors**

The overall distribution of prothrombotic risk factors diagnosed at first AIS and recurrent thromboembolism is shown in Table 1. At first stroke onset, 157 prothrombotic risk factors were found in 127 of 215 neonates (59.1%; single, n=96; combined, n=31), and no prothrombotic risk factor was found in 88 infants (40.1%). During symptomatic recurrent thromboembolism, 5 of 7 infants and children (71.4%) suffered inherited thrombophilia.

Table 2 summarizes thromboembolic locations, time of recurrence, underlying conditions, and associated prothrombotic risk factors. In addition, the duration of antithrombotic treatment performed after the first stroke onset is shown, together with the administered drugs. Interestingly, most children, 4 of 7 (57.1%), showed a combination of inherited prothrombotic risk factors and underlying basic diseases. As shown in Table 2, no patient developed recurrent thromboembolism during the period of prophylactic antithrombotic treatment. Interestingly, early recurrence at 3 and 6 months had been recorded in 3 infants who did not receive antithrombotic therapy after the first AIS onset.

**Discussion**

Results of the multicenter analysis presented here show that symptomatic thromboembolism in white neonates occurs at the low rate of 3.3%, which is within the rate reported previously for the disease but lower than in our recently reported series of white infants and children >6 months of age.

Interestingly, most symptomatic patients with recurrence presented with thromboembolic events in the central nervous system, eg, AIS or sinovenous thrombosis. As demonstrated in the Figure and in Table 2, 4 of 7 patients suffered a second thromboembolic event within the first year of life, suggesting that the rate of symptomatic recurrence is lower beyond infancy.

Whereas increased Lp(a) and the homozygous MTHFR T677T genotype, elevated homocysteine, and confirmed protein C type I deficiency were involved during a second symptomatic thromboembolism, the heterozygous FV G1691A gene mutation, FII G20210A variant, deficiency states of antithrombin and protein S, or elevated factor VIIIC
and ACA were not associated with recurrent thromboembolism in the infants and children investigated here. Because of the small number of cases involved, however, no conclusion can be drawn at present as to whether the prothrombotic risk factors involved during recurrence or vice versa play a significant role with respect to recurrent thromboembolic vascular accidents. In addition to inherited thrombophilia, acquired risk factors (71%) prospectively defined at the beginning of the study were found at the second vascular accident; in 4 children, they were combined with at least 1 inherited prothrombotic risk factor.

Interestingly, no infant or child with recurrent thromboembolism in the cohort presented here was under antithrombotic therapy at the time of recurrence. This is of major importance, and the question of secondary preventive anticoagulation in risk situations—eg, diarrhea, cardiac surgery, presence of central venous lines, and infectious diseases—has to be discussed in further multicenter studies in infants and children who have previously suffered neonatal stroke.

In summary, data presented here underline the multifactorial cause of recurrent symptomatic ischemic thromboembolism as a rare event in patients with neonatal AIS. Because of the small number of cases available in this white age group, further multicenter and international studies are urgently needed to clarify in an evidence-based model the unanswered questions, eg, rate of recurrence, thrombosis locations, involvement of prothrombotic risk factors, underlying clinical conditions, and the preventive use of different secondary antithrombotic treatment modalities.13,16,39,40

Appendix

Participants in the Childhood Stroke Study Group
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Editorial Comment

Specificities of the Neonatal Stroke

In this issue of Stroke, Kurnik and collaborators report the largest cohorts in the literature of children who presented with symptomatic arterial ischemic stroke in the neonatal period.1 The study provides 2 major findings. First, it confirms, on a large scale, that many biological alterations are stroke risk factors in the neonatal period. Indeed, 127 out of the 215 neonates have a prothrombotic state. Even in the absence of a control group, the range of these disturbances (notably factor V Leiden mutation with an incidence of 15% and protein C deficiency with 4%) is clearly greater than in the general population. It is also higher than the rate of thrombophilia usually discovered in non-neonates with arterial ischemic stroke.2 Although the prothrombotic condition is in general constitutional, the stroke rarely recurs. Only 4 of the 215 children had a second arterial ischemic stroke after a median follow-up of 3.5 years. Among them, 1 had congenital heart disease and 1 had congenital moyamoya disease, 2 conditions also at risk for recurrence of stroke in non-neonates. By comparison, studies concerning non-neonate children with arterial ischemic stroke reveal a rate of recurrence of 7% to 22% in the same span of follow-up.3–5

These facts advocate envisaging some characteristics of the fetus or the newborn that predispose them to cerebral arterial ischemic events, especially in a context of thrombophilia. The first hypothesis is a lesion of cervicocephalic arteries during childbirth. Roessmann and Miller report the autopsy of a newborn who had a traumatic birth and a cerebral infarct.6 The inner layers of a median cerebral artery were injured by the attempted forceps delivery, which led to occlusion. Charollais et al also described a pathological report of a carotid occlusion in a newborn which led to occlusion. Charollais et al also described a pathological report of a carotid occlusion in a newborn which led to occlusion.
although symptomatic during the neonatal age, occur in the
days preceding the birth.8,9

The second etiologic hypothesis regards the role of the
maternofetal vascular interface, ie, the placenta. Hyperco-
agulability, carried by either the mother or the fetus, is a
cause of abnormal vascular development, vessel occlusion,
and placental infarctions, which affect the maternofetal
circulation.10–13 Such placental injuries have been de-
scribed in cases of neonatal stroke. In addition, the fetal
circulation implies that a clot, which has formed in the
placenta and migrates, will preferentially embolize through
the foramen ovale in the cerebral vasculature. Some anatomic
and arteriographic reports support this embolic theory.8,14,15

Another matter of debate relates to the outcome of the
children, notably the issue of cognitive and motor develop-
ment. One of the best prognostic factors is the extent and the location
of the lesions on magnetic resonance imaging.16 Nevertheless,
the children’s outcome varies considerably between the studies.
The duration of the follow-up explains some of these discrep-
ancies. Some sequelae (notably subtle cognitive deficits) of
perinatal cerebral traumas may appear only after years of
neurological follow-up. Also in the field of neonatal stroke, the
longer the follow-up, the worse the neurological evolution. For
example, in the Sran and Baumann’s report, 4 of 7 children
followed for <2.5 years have a normal neurologic status versus
only 3 of 9 followed for >2.5 years.17 In another small series, 1
out of 8 children (the youngest: 1.4 years) has normal develop-
ment. In older children, concentration, speech, perception,
and intelligence were significantly poorer than in control groups.18

In the absence of a known physiopathological mecha-
nism, only supportive care is provided to the newborns. If
the traumatic hypothesis were confirmed, analysis of
pregnancy and delivery modalities would allow for obstet-
ric situations with a stroke risk to be determined and, as
a consequence, preventive interventions achieved. In se-
lected newborns, early detection of arterial occlusion and,
in the event of it occurring, treatment by anticoagulant or
fibrinolytic agents is also conceivable. If the placento-
embolic theory is verified, there is an opportunity to
reduce the incidence of neonatal stroke by prophylactic
therapy of the thrombophilia during pregnancy.19 Determi-
nation of early indicators of neurological disabilities would
lead to personalized follow-up and rehabilitation pro-
grams. Further prospective studies with evaluation of
delivery conditions, maternal and children’s thrombophilia
screening, systematic vascular exploration of the newborn,
and long-term neurological and neuropsychological follow-up are on the way, aimed at answering these issues
and elaborating therapeutic trials.

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Editorial Comment—Specificities of the Neonatal Stroke
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