Symptomatic Ischemic Stroke in Full-Term Neonates
Role of Acquired and Genetic Prothrombotic Risk Factors

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Background and Purpose—The present multicenter case-control study was prospectively designed to assess the extent to which single and combined clotting factor abnormalities influence the onset of symptomatic ischemic stroke in full-term neonates.

Methods—Lipoprotein (Lp)(a); the factor V (FV) G1691A mutation; the prothrombin (PT) G20210A variant; the methylenetetrahydrofolate reductase (MTHFR) T677T genotype; antithrombin; protein C; protein S; and anticardiolipin antibodies (ACAs) were investigated in 91 consecutively recruited neonatal stroke patients and 182 age- and sex-matched healthy controls.

Results—Sixty-two of 91 stroke patients (68.1%) had at least 1 prothrombotic risk factor compared with 44 control subjects (24.2%) (odds ratio [OR]/95% confidence interval [CI], 6.70/3.84 to 11.67). An increased Lp(a) level (>30 mg/dL) was found in 20 patients and 10 controls (OR/95% CI, 4.84/2.16 to 10.86); FV G1691A was present in 17 patients and 10 controls (OR/95% CI, 3.95/1.72 to 9.0); the PT G20210A variant was detected in 4 patients and 4 controls (OR/95% CI, 2.04/0.49 to 8.3); the MTHFR TT677 genotype was found in 15 patients and 20 controls (OR/95% CI, 1.59/0.77 to 3.29); and protein C type I deficiency was found in 6 neonates. Neither antithrombin deficiency nor protein S deficiency was found in the neonatal patients studied. Acquired IgG ACAs were found in 3 cases. Additional triggering factors, ie, asphyxia, septicemia, maternal diabetes, and perinatally acquired renal venous thrombosis, were reported in 54.0% of patients.

Conclusions—Besides acquired triggering factors, the data presented here suggest that genetic prothrombotic risk factors play a role in symptomatic neonatal stroke. **(*Stroke*. 2000;31:2437-2441.)**

Key Words: factor V ■ lipoproteins ■ neonate ■ prothrombin ■ risk factors ■ stroke

Within the past decade, various genetic defects of proteins that regulate blood coagulation have been discussed as risk factors for venous thromboembolic events in young adults, ie, deep venous thrombosis, recurrent fetal loss, stillbirth, or other pregnancy complications.[1–4] In addition, cardiovascular disease, ie, myocardial infarction or stroke, is the leading cause of death in the developed countries. In some cases, cardiovascular disease is also related to defects within the anticoagulant pathways.[1] In contrast, ischemic cerebrovascular accidents are very rare in children, with an estimated incidence of ≈1 per 100 000 per year.[5–7] Nongenetic risk factors of arterial cerebrovascular accidents in children and adolescents include congenital heart malformations, vascular abnormalities, endothelial damage, infectious diseases, and some rare congenital metabolic dysfunctions.[7,8]

The role of congenital thrombophilic states such as activated protein C resistance,[9] in the majority of cases due to the factor V (FV) G1691A gene mutation[10,11]; antithrombin, protein C, or protein S deficiency[1]; the 20210A allele within the 3′-untranslated region of the prothrombin (PT) gene[12]; and an increased lipoprotein (Lp)(a) level has also been discussed with reference to the common risk factors for venous thrombosis in children and adolescents.[13,14] However, information on these hemostatic defects in symptomatic patients with ischemic stroke during infancy and childhood is limited and controversial. Results of available studies differ, mainly because of differences in the study populations, age groups, or study designs.[15–25]

Very recently, we have shown that an increased Lp(a) level, the FV G1691A mutation, the PT 20210A allele, and

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the homozygous C677T polymorphism in the methylenetetrahydrofolate reductase (MTHFR) gene are significant risk factors for spontaneous stroke in childhood.[23] That study, however, did not include neonatal and child patients with additional acquired risk factors.

In this article, we present the results of a stroke subgroup analysis. It includes symptomatic, full-term neonatal stroke patients only, with respect to inherited prothrombotic risk factors[23] and prospectively defined triggering factors.[7,8,26–29]

Subjects and Methods

Ethics

The present study was performed in accordance with the ethical standards laid down in the updated Declaration of Helsinki and approved by the medical ethics committee at the Westfälische Wilhelms-University, Münster, Germany.

Inclusion Criteria for Subgroup Analysis

Full-term neonates with a first onset of symptomatic ischemic stroke occurring spontaneously or associated with perinatal asphyxia, dehydration, septicemia, patent foramen ovale, birth trauma, maternal diabetes, maternal drug abuse, or infection composed the patient group.[7,8,26–29] In all cases, suspected vascular accidents were confirmed by standard imaging methods (cranial sonography, CT, or MRI) by an independent neuroradiologist as previously described.[23]

Patients

From October 1996 to January 2000, 91 of 273 (33.3%) consecutive white childhood stroke patients from different geographic catchment areas of Germany were enrolled in the study. They fulfilled the inclusion criterion of neonatal stroke defined above. The median age at onset of the first thrombotic episode was 3 days, ranging from newborn to <4 weeks of age (male/female ratio, 1:1.1).

Control Group

With informed parental consent, 182 age- and sex-matched healthy neonates and infants from the same geographic areas served as controls.

Exclusion Criteria

Preterm infants (<37 weeks of gestation)[30] or those affected by stroke associated with arterial catheterization, surgery, metabolic disorders, or congenital heart disease (already presented in Reference 24) were excluded from participation in the study.

Blood Samples

With informed parental consent, blood samples from patients were collected 6 weeks to 3 months (median, 10 weeks) after the acute thrombotic event by peripheral venipuncture into plastic tubes containing 1/10 by volume of 3.8% trisodium citrate or into plastic tubes without additives (Sarstedt). From healthy control neonates, blood samples were drawn during infancy, ie, at a median age of 3 months (range, 6 to 16 weeks). Citrated blood (3 mL) was placed immediately on melting ice. Platelet-poor plasma and serum were prepared by centrifugation at 3000*g* for 20 minutes at 4°C or at room temperature, divided into aliquots into polystyrene tubes, stored at −70°C, and thawed immediately before the assay procedure. For genetic analysis, we obtained venous blood (0.5 mL) in EDTA-treated sample tubes (Sarstedt) from which cells were separated by centrifugation at 3000*g* 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, PT G20210A, and MTHFR C677T genotypes were determined by polymerase chain reaction and analysis of restriction fragments as previously reported.[11,12,31]

Assays for Plasma Proteins

Amidolytic protein C and antithrombin activities were measured on an ACL 300 analyzer (Instrumentation Laboratory) with the use of chromogenic substrates (Chromogenix). Free protein S antigen, total protein S, and protein C antigen were measured by using commercially available ELISA assay kits (Stago). Lp(a) and ACAs (IgM and IgG) were also determined with ELISA techniques (Chromogenix).[13,14,23]

Classification of Risk Cutoff

The type I deficiency state (protein C and antithrombin) was diagnosed when the functional plasma activity and immunological antigen concentration of a protein were repeatedly below the lower age-related limit (for 3 months of age, protein C <20% and antithrombin <30%).[32] A type II deficiency was diagnosed when the functional activity levels were repeatedly low but antigen concentrations were normal. The diagnosis of protein S deficiency was based on reduced free protein S antigen levels combined with a decreased or normal total protein S antigen concentrations (for 3 months of age, <30%).[33] The cutoffs used for ACAs were <11 μg/mL (IgM) and <23 μg/mL (IgG).

Statistics

Prevalences of prothrombotic risk factors in patients and control subjects were calculated by χ^2 analysis or, where relevant, by Fischer's exact test. The significance level was set at 0.05. With respect to the number of different tests applied, Bonferroni's correction was performed. In addition, odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. All statistical analyses, including nonparametric statistics (medians and ranges), were performed by using the MedCalc software package (MedCalc).

Results

Clinical Presentation at Onset of Acute Stroke

Seizures were the leading symptoms in 70 neonates. In 66 patients, focal seizures had occurred, and 4 subjects presented with generalised seizures. Additionally, recurrent apnea was found in 12 full-term neonates, whereas 9 neonates presented with persistent hypotonia.

Location of Thrombosis

At onset of acute stroke, neonates presented with left middle cerebral artery occlusion (n=58), right middle artery occlusion (n=29), or vascular accident of both middle arteries (n=3).One neonate had occlusion of the anterior cerebral artery.

Prothrombotic Risk Factors

Sixty-two of 91 stroke patients (68.1%) were found to have at least 1 prothrombotic risk factor compared with 44 subjects (24.2%) in the control group (OR/95% CI, 6.70/3.84 to 11.67). An increased Lp(a) level (>30 mg/dL) was found in 20 patients and 10 controls (OR/95% CI, 4.84/2.16 to 10.86), FV G1691A in 17 patients and 10 controls (OR/95% CI, 3.95/1.72 to 9.0), the PT G20210A variant in 4 patients and 4 controls (OR/95% CI, 2.04/0.49 to 8.3), the MTHFR TT677 genotype in 15 patients and 20 controls (OR/95% CI, 1.59/0.77 to 3.29), and protein C deficiency in 6 neonates (P=0.0012). Acquired IgG ACAs were measured in 3 neonates 9 weeks after the acute stroke onset. In 3 of the 17 symptomatic patients carrying the heterozygous FV mutation, an increased Lp(a) concentration was diagnosed, and in 1 patient, the FV mutation was

TABLE 1. Distribution of Prothrombotic Risk Factors in Full-Term Neonatal Stroke Patients Versus Healthy Age- and Sex-Matched Controls

	Patients (n=91)	Controls (n=182)	ORs/95% CIs	P
Risk factors				
Lipoprotein(a) >30 mg/dL	20 (22.0%)	10 (5.5%)	4.84/2.16–10.86	<0.001
Factor V 1691GA*	17 (18.7%)	10 (5.5%)	3.95/1.72 –9.0	0.0016
Prothrombin 20210GA	4 (4.4%)	4 (2.2%)	2.04/0.49 –8.3	0.44†
MTHFR 677TT	15 (16.5%)	20 (10.9%)	1.59/0.77 –3.29	0.28
Protein C deficiency type I	6 (6.6%)	...	...	0.0012†
Total	62 (68.0%)	44 (24.2%)	6.70/3.84–11.67	<0.001

Values shown are n and (percent).

*Combined with lipoprotein(a) Lp): n=3 (not included in the Lpcolumn) and with anticardiolipin IgG antibodies (n=1).

†Fisher's exact test.

found in combination with IgG ACAs. The overall distribution of prothrombotic risk factors is shown in Table 1. Antithrombin deficiency, protein S deficiency, or IgM ACAs were not found in the neonatal patients studied. Table 2 shows median (range) values of Lp(a), protein C activity, free protein S antigen, antithrombin activity, and IgG ACAs in patients and controls.

Acquired Triggering Factors

Besides spontaneous ischemic stroke (46%), additional triggering factors, ie, asphyxia (19%), neonatal septicemia (12%), patent foramen ovale (16%), maternal diabetes (3%), antenatal renal venous thrombosis (3%), and fibromuscular dysplasia (1%), were found in the patients investigated.

In 33 of the 49 subjects with additional triggering factors (67.0%), at least 1 prothrombotic risk factor was found. The FV G1691A mutation was found in 13 neonates (asphyxia n=3, septicemia n=2, patent foramen ovale n=5, maternal diabetes n=1, and renal venous thrombosis n=2). An increased Lp(a) level was additionally present in 10 cases (asphyxia n=4, septicemia n=2, patent foramen ovale n=3, and fibromuscular dysplasia n=1) and the MTHFR TT677 genotype in 7 neonates (asphyxia n=2, septicemia n=1, patent foramen ovale n=3, and maternal diabetes n=1). Furthermore, protein C deficiency was found in 2 subjects with asphyxia and in 1 baby with patent foramen ovale.

TABLE 2. Median (Range) of Serum and Plasma Values of Lipoprotein(a), Protein C Activity, Free Protein S Antigen, and Antithrombin Activity in Patients and Controls

	Patients Age 11 (6–16) Weeks (n=91)	Controls Age 12 (6–16) Weeks (n=182)
Lipoprotein(a), mg/dL	8.6 (0–120)	3.6 (0–104)
Protein C, %	51 (8–87)	57 (32–85)
Protein S, %	58 (32–99)	55 (36–95)
Antithrombin, %	86 (55–120)	89 (54–115)
ACA IgG, μg/mL	8 (1–49)	4 (2–12)

Discussion

The present multicenter case-control study was prospectively designed to assess the extent to which single and combined clotting factor abnormalities influence the onset of symptomatic ischemic stroke in full-term neonates. Results of the multicenter subgroup analysis presented here show that symptomatic ischemic stroke in white neonates occurs with an overall incidence of 1.35 per 100 000 live births. This figure is within the range previously reported for the disease.[5,6] Clinically, the majority of symptomatic patients presented with seizures.[34,35] In the affected neonates, the ischemic vascular occlusion was predominantly found within the left hemisphere. This finding is in accordance with previously reported data that a high proportion of infarctions identified in the neonatal period affect the left hemisphere, suggesting a thromboembolic origin.[8,36,37] The patients investigated had a significantly higher overall rate of genetic prothrombotic risk factors (OR, 6.70) than did the healthy age- and sex-matched controls.

As in adults and in childhood patients >6 months of age suffering from spontaneous ischemic stroke, increased Lp(a) is the most important prothrombotic risk factor in the neonatal period.[23,38,39] The heterozygous FV G1691A genotype and protein C deficiency were found in another 6 cases. The heterozygous FV gene mutation has recently been suggested to be an important risk factor for childhood antenatal porencephaly[15] and is associated with a significant OR of 3.95 in neonatal stroke patients. The results reported from this subgroup analysis are in clear contrast to data published by Zenz et al[20] and McColl et al.[22] This discrepancy is due mainly to the small number of investigated cases and the different study designs, and it underlines the need for larger subgroup analyses in childhood patients as well.

However, confirming these reports[20,22] but in contrast to children with spontaneous stroke, the carrier rates of the PT G20210A variant and the homozygous MTHFR 677TT genotype were not significantly increased compared with those in the control subjects. Furthermore, only 4.4% of infants investigated in this study had 2 prothrombotic risk factors.

The FV G1691A mutation was found in combination with either increased Lp(a) or increased ACAs. Comparison of these data with results obtained from childhood patients suffering from thromboembolism beyond infancy revealed a distinctly lower proportion of combined defects in the cohort presented here.[13,14,23] This finding is due mainly to the high proportion of additional acquired risk factors (54%) prospectively defined at baseline. As previously suggested in a small case series, perinatally acquired asphyxia, neonatal septicemia, and stroke associated with an open foramen ovale are the most important triggering factors for symptomatic ischemic stroke in neonates.[26–29]

In summary, the data presented here underline the multifactorial etiology of symptomatic ischemic stroke in neonates. It includes prothrombotic risk factors, acquired underlying conditions, or a combination of acquired and genetic risks. Thus, although an underlying disease is diagnosed in ≈54% of cases, comprehensive screening for prothrombotic risk factors is recommended in children suffering vascular accidents during the neonatal period.

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Appendix: Participants in the Childhood Stroke Study Group

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