Cerebral Venous Thrombosis in Children
A Multifactorial Origin

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Background—The present study was performed to assess the association of prothrombotic risk factors and underlying conditions (infections, vascular trauma, immobilization, malignancies, autoimmune diseases, renal diseases, metabolic disorders, obesity, birth asphyxia, cardiac malformations, and use of prothrombotic drugs) with cerebral venous thrombosis (CVT) in children.

Methods and Results—From 1995 to 2002, 149 pediatric patients aged newborn to <18 years (median 6 years) with CVT were consecutively enrolled. In patients and in 149 age- and gender-matched children with similar underlying clinical conditions but without CVT, the factor V G1691A mutation, the factor II G20210A variant, lipoprotein(a) [Lp(a)], protein C, protein S, antithrombin, and antiphospholipid antibodies, as well as associated clinical conditions, were investigated. Eighty-four (56.4%) of the patients had at least 1 prothrombotic risk factor compared with 31 control children (20.8%; *P*<0.0001). In addition, 105 (70.5%) of 149 patients with CVT presented with an underlying predisposing condition. On univariate analysis, factor V, protein C, protein S, and elevated Lp(a) were found to be significantly associated with CVT. However, in multivariate analysis, only the combination of a prothrombotic risk factor with an underlying condition (OR 3.9, 95% CI 1.8 to 8.6), increased Lp(a) (OR 4.1, 95% CI 2.0 to 8.7), and protein C deficiency (OR 11.1, 95% CI 1.2 to 104.4) had independent associations with CVT in the children investigated.

Conclusions—CVT in children is a multifactorial disease that, in the majority of cases, results from a combination of prothrombotic risk factors and/or underlying clinical condition. (***Circulation***. 2003;108:1362-1367.)

Key Words: pediatrics ∎ lipoproteins ∎ thrombosis

Cerebral venous thrombosis (CVT) in childhood is a serious disease that is being increasingly diagnosed, mainly because of more sensitive diagnostic procedures and increasing clinical awareness of the disease.[1] The clinical presentation shows a wide spectrum of symptoms, eg, seizures, papilledema, headache, lack of consciousness or lethargy, and focal neurological deficits.[1,2]

The origin and pathophysiology of CVT in the pediatric population is still poorly understood, mainly because of its low incidence, which is estimated at 0.67 per 100 000 children.[1] The disease is serious, and predisposing and influencing factors should be unraveled to identify patients at risk and to establish treatment regimens in children. Local or systemic infections,[3–6] vascular trauma,[7] cancer, acute lymphoblastic leukemia, drug toxicity,[8] lupus erythematosus,[9] nephrotic syndrome,[10] dehydration,[11] asphyxia, maternal problems during pregnancy,[12]

Behçet's disease,[2] and metabolic disorders[13–15] have been described as predisposing factors.

Recently published data have suggested that multiple additional factors including prothrombotic risk factors contribute to the symptomatic onset of CVT.[11,16,17] In contrast to childhood venous thrombosis, in which the influence of thrombophilic disorders is now well established, data describing prothrombotic risk factors contributing to the origin of CVT in adults and pediatric patients are still conflicting.[16–29] The present study was performed to assess the role of prothrombotic risk factors in combination with underlying clinical conditions as risk factors for CVT in children.

Methods

Ethics

The present prospective multicenter follow-up study was performed in accordance with the ethical standards established in the updated

TABLE 1.   Characteristics of Patients and Controls

Characteristic	Patients (n=149)	Controls (n=149)	P*
Median age, y (range)	6.0 (neonate–<18)	6.2 (neonate–<18)	0.7
Male/female, n (%)	84 (56.4)/65 (43.6)	89 (59.7)/60 (40.3)	0.64
Underlying conditions, n			
None (idiopathic/healthy)	44	44	
Trauma/immobilization	14	14	
Steroids	33	33	
Infections	44	44	
Other†	14	14	
Prothrombotic risk factors,‡ n (%)	84 (55.4)	31 (20.8)	<0.001
With underlying condition	66	14	
Without underlying condition	18	17	

*χ^2 test.

†Birth asphyxia, diabetes type I, metabolic diseases, nephrotic syndrome, obesity, and oral contraceptives.

‡FV G1691A, FII G20210A, elevated Lp(a), protein C deficiency, protein S deficiency, antithrombin deficiency, and ACAs.

version of the 1964 Declaration of Helsinki and was approved by the medical ethics committee of the University of Münster, Germany.

Inclusion and Exclusion Criteria

With written or oral parental consent, consecutively admitted term neonates and children with newly diagnosed CVT not older than 18 years at onset were enrolled in the study. Preterm infants, patients older than 18 years at onset, children not of Caucasian origin, patients with incomplete clinical or laboratory workup (established prothrombotic risk factors), and subjects lost to follow-up or without parental consent were not enrolled.

Imaging Methods

In all cases, diagnosis was confirmed by standard imaging methods, eg, duplex sonography, computerized tomography (CT) followed by MRI, or magnetic resonance venography/angiography.[1,30,31] Conventional angiography was performed in selected cases to rule out vasculopathy or arterial ischemic stroke.

Underlying Clinical Conditions

Bacterial or viral infections,[3–6] head or vascular trauma, surgery, immobilization or obesity,[17,22,24,32] jugular[33] or subclavian central venous lines,[7,34,35] solid tumors, leukemia and lymphomas,[8] autoimmune diseases,[9] renal diseases,[10] metabolic disorders,[13–15] birth asphyxia,[12] and cardiac malformations were predefined as predisposing clinical conditions.[2] In addition, drugs such as steroids[2,20,22,32] and *Escherichia coli* asparaginase, the use of sympathomimetics, coagulation factor concentrates, or oral contraceptives, and nicotine abuse were classified as underlying conditions. Patients with CVT who did not have one of the criteria stated here were classified as having idiopathic CVT.

Final Study Population

From January 1995 to February 2002, 973 consecutively admitted white pediatric patients from different geographic areas of Germany with symptomatic thromboembolism were enrolled in the German Pediatric Thrombophilia Registry, as described previously.[26] Two hundred five (21.1%) of the 973 children had CVT. Five of these 205 patients died during the acute thrombotic onset, and 12 were excluded because of loss of follow-up. In addition, 38 children with an incomplete prothrombotic workup (established prothrombotic risk factors) and 1 child for whom parental consent to participate in the study was refused were excluded.

Thus, the final patient population comprised 149 children with CVT. With informed written parental consent, 149 age- and gender-matched children with a similar distribution of underlying conditions (healthy children, steroid administration, infectious diseases, trauma, immobilization, obesity, birth asphyxia, metabolic diseases, renal diseases, or the use of oral contraceptives) served as a control group. The controls were enrolled within the same time period and from similar geographic areas as the patients and had received identical treatment regimens (Table 1).

Antithrombotic Therapy

At the discretion of the participating study centers, patients were treated with low-molecular-weight heparin (2- to 4-hour anti-factor Xa level 0.4 to 0.6 IU/mL) or unfractionated heparin (activated partial thromboplastin time increase 1.5- to 2-fold compared with baseline). Acute antithrombotic treatment was performed with unfractionated heparin in 47% of cases, whereas 40% received low-molecular-weight heparin, and 12% underwent no separate antithrombotic therapy in addition to the treatment of the basic disease. For secondary long-term prophylaxis, 73% of cases received low-molecular-weight heparin, 4% received prolonged unfractionated heparin, and 7% were given vitamin K antagonists, whereas no secondary prophylaxis was initiated in 16%. In the majority of children, the anticoagulation agent was administered over a period of 6 months; this period was extended if the underlying predisposing factors for thrombotic events persisted. No child with antithrombotic therapy showed major hemorrhagic side effects.

Outcome Measurements

Acute outcome measurements were defined as patency proved by MRI 3 to 6 months after the acute thrombotic onset.

Laboratory Analyses

The factor V (FV) G1691A and the factor II (FII) G20210A mutations, activated protein C resistance, and levels of protein C, protein S, antithrombin, and anticardiolipin antibodies (ACAs) were investigated as established prothrombotic risk factors with standard laboratory techniques at thromboembolic onset and 3 to 6 months after the acute event (analysis performed in all patients).[26,27] A type I deficiency (antithrombin, protein C) state was diagnosed when functional plasma activity and antigen concentration of a protein (blood sample after 3 to 6 months) were repeatedly found to be below the 50% age-related percentile.[35] A type II deficiency (antithrombin, protein C) was diagnosed by the repeated finding of low

functional activity levels along with normal antigen concentrations. 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, respectively. For ACA cutoff values, >20 IU/mL (IgG) and >11 IU/mL (IgM) were considered abnormal.

As a new prothrombotic risk factor, lipoprotein(a) [Lp(a)] was investigated in 106 of the 149 patients and in the entire control group. 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. Criteria for the hereditary nature of a hemostatic defect were its presence in at least 1 other first- or second-degree family member and/or the identification of a causative gene mutation.

Statistics
Statistical analyses were performed with the StatView 5 software package (SAS Institute Inc). To compare the rate of prothrombotic risk factors between patients and controls, to evaluate an independent contribution of thrombophilia and underlying clinical condition to the onset of CVT, and to adjust for potential cofounders, the ORs together with 95% CIs were estimated from the conditional logistic regression model (PHREG procedure, SAS, version 8).[36] In this model, patients and controls were matched pairwise by disorder. Because of their apparent non-Gaussian distribution, continuous data are presented as medians and ranges and were evaluated by nonparametric statistics with the Wilcoxon Mann-Whitney U test. The frequency distribution of underlying diseases was compared with the χ^2 test or Fisher's exact test. Probability values <0.05 were considered significant. Incidence data were calculated with the German population denominator with respect to age groups per year.

Results

Patient Population
Over a period of 7 years, 65 female and 84 male patients with confirmed CVT were enrolled (Table 1). Forty patients were neonates (<28 days old; female:male ratio 1:1.7). The 109 older children had an age range from 28 days to 18 years with a female:male ratio of 1:1.3. The median age at onset was 72.0 months (range 0 to 192 months) in girls compared with 69.5 months (range 0 to 204 months) in boys. The yearly incidence of CVT was 2.6 per 100 000 in neonates compared with 0.35 per 100 000 in the older children.

Main Neurological Signs at Onset
The majority of children with CVT initially presented with headache, papilledema and vomiting (32.6%), seizures (37.9%; generalized 32.6%, focal 5.3%), drowsiness and confusion (9.5%), isolated cranial nerve palsies (9.5%), coma (4.2%), motor deficits (3.2%), respiratory failure (3.2%), or sensory deficits (1.1%). In 6.3% of cases, CVT without primary neurological disturbances was diagnosed in addition to the underlying diseases, mainly mastoiditis or sinusitis.

Thrombotic Locations
Ninety-three children (62.4%) had suffered thrombosis of the superior sagittal sinus (SSS); in 21 children (14.1%), the thrombosis was localized in a lateral sinus (LS), 3 children (2.0%) showed thrombosis in the straight sinus (STS), and in 10 patients (6.7%), vascular occlusion affected the sigmoid sinus (SS). Two children (1.3%) showed thrombosis within the internal veins. In addition, thrombosis occurred in some patients in more than 1 sinus (SSS and LS, n=8 [5.4%]; SSS and cavernous sinus, n=1 [0.7%]; SSS and SS, n=1 [0.7%];

SS and LS, n=4 [2.7%]; SS and internal jugular vein, n=1 [0.7%]). Three patients (2.0%) had thrombosis of the SSS, LS, and SS, and 2 other children (1.3%) had thrombosis of the SSS and infarction of the central retinal veins.

Underlying Clinical Conditions
Underlying clinical conditions were documented in 105 (70.5%) of the 149 patients. The most frequent clinical risk factors reported were steroid administration (leukemia or lymphoma induction therapy, concomitant with *Escherichia coli* asparaginase, n=27; induction of fetal lung maturation in preterm labor, n=5; colitis ulcerosa, n=1), infectious diseases (mastoiditis, n=14; otitis, n=5; meningitis, n=6; septicemia, n=8; sinusitis, n=5, varicella zoster infection, n=2; infectious gastroenteritis, n=4), trauma (n=10), or immobilization (n=4). Other risk factors were obesity (n=2), birth asphyxia (APGAR <8, hypoxemia, n=2), diabetes (n=2), other metabolic diseases (n=3), nephrotic syndrome (n=1), and the use of oral contraceptives (n=4). In 44 cases (29.5%), no predisposing clinical condition could be identified (Table 1).

Prothrombotic Risk Factors
In 84 (56.4%) of the 149 patients, at least 1 established prothrombotic risk factor was found compared with 31 (20.8%) of the 149 control children. The distribution of single and combined prothrombotic risk factors in patients and controls is shown in Table 2.

On univariate analysis and compared with controls, patients showed significantly higher prevalences of FV G1691A (OR 3.4, 95% CI 1.3 to 9.3), elevated Lp(a) (OR 7.2, 95% CI 3.7 to 14.2), protein C deficiency (OR 14.2, 95% CI 1.6 to 129.3), and protein S deficiency (OR 17.0, 95% CI 1.9 to 151.2). No significant differences were found for frequencies of FII G20210A (OR 3.8, 95% CI 0.8 to 17.3), antithrombin deficiency (P=0.07), or ACAs (OR 8.1, 95% CI 0.8 to 82.4).

The association of prothrombotic risk factors with CVT resulted mainly from underlying prothrombotic risk factors with concomitant underlying diseases. In a multivariate analysis that included all the thrombophilic risk factors significantly associated with CVT in the univariate analysis, only the combination of a prothrombotic risk factor with an underlying condition, elevated Lp(a), and protein C deficiency retained their statistically significant association with CVT (Table 3).

Patency Rates
The primary aim of the present study was to evaluate the interaction of established and new prothrombotic risk factors with underlying condition in young CVT patients. However, information is also available on the 6-month patency rate in a subgroup of patients. When MRI or magnetic resonance angiography was used 6 months after the acute thrombotic onset in 119 children (80%), complete patency was demonstrated in 51 (43%) of 119 cases, partial patency in 49 children (41%), and no patency in 19 infants (16%). No association was found, however, between patency rates, hereditary prothrombotic risk factors, underlying clinical conditions, or therapy used, respectively.

TABLE 2. Distribution of Single and Combined Prothrombotic Risk Factors in Patients and Controls

Prothrombotic Risk	Patients	Controls
Factor V G1691A		
Total	22/149 (14.8%)	8/149 (5.4%)
Single	14/22	8/8
Combined with the following:	8/22	...
FII G20210A	2	...
Lp(a)	5	...
Protein C type I deficiency	1	...
FII G20210A		
Total	7/149 (4.7%)	3/149 (2.0%)
Single	2/7	3/3
Combined with the following:	5/7	...
FV G1691A	2	...
Protein C type I deficiency	1	...
Lp(a) and antithrombin type I deficiency	1	...
ACAs	1	...
Protein C type I deficiency		...
Total	6/149 (4.0%)	1/149 (0.7%)
Single	3/6	1/1
Combined with the following:	3/6	...
FV G1691A	1	...
FII G20210A	1	...
Lp(a)	1	...
Protein S type I deficiency		...
Total	8/149 (5.4%)	1 /149 (0.7%)
Single	7/8	1/1
Combined with the following:	1/8	...
ACAs	1	...
Antithrombin type I deficiency		...
Total	5/149 (3.4%)	...
Single	4/5	...
Combined with the following:	1/5	...
FII G20210A and Lp(a)	1	...
Elevated Lp(a)		
Total	44/106 (41.5%)	17/149 (11.4%)
Single	36/44	17/17
Combined with the following:	8/44	...
FV G1691A	5	
FII G20210A and antithrombin type I deficiency	1	
Protein C type I deficiency	1	
ACAs	1	
ACAs		
Total	6/149 (4.0%)	1/149 (0.7%)
Single	3/6	1/1
Combined with the following:	3/6	...
FII G20210A	1	...
Lp(a)	1	...
Protein S type I deficiency	1	...

TABLE 3.   Conditional Logistic Regression Model

Risk Factor	OR	95% CI
No prothrombotic risk factor or underlying condition	1*	
FV G1691A	2.1	0.8–5.9
FII G20210A	2.3	0.4–11.6
Lp(a) >30 mg/dL	4.1	2.0–8.7
Protein C deficiency	11.1	1.2–104.4
Protein S deficiency	8.8	0.9–85.5
ACAs	3.9	0.3–45.3
Underlying condition† and prothrombotic risk factors‡	3.9	1.8–8.6

To evaluate the independent contribution to the risk of CVT and to adjust for potential confounders, thrombophilic risk factors and the combination of a prothrombotic risk factor with an underlying clinical condition were analyzed.

*Reference.

†Healthy children, steroid administration, infectious diseases, trauma, immobilization, obesity, birth asphyxia, metabolic diseases, renal diseases, and the use of oral contraceptives.

‡FV G1691A, FII G20210A, elevated Lp(a), protein C deficiency, protein S deficiency, antithrombin deficiency, and ACAs.

Discussion

The data presented here suggest that specific clinical conditions and genetic prothrombotic risk factors play an important role in the origin of CVT in pediatric patients. Univariate analysis revealed that the FV mutation, elevated levels of Lp(a), and deficiency states of proteins C and S occurred significantly more frequently in patients than in age-, gender-, and disease-matched controls, whereas frequencies of the FII G20210A variant, antithrombin deficiency, and the presence of ACAs did not differ significantly between the 2 groups. In this context, we wish to emphasize that the prevalence rate of prothrombotic risk factors in the disease-matched control group presented here was no different from that of our healthy pediatric controls published previously.[26,27] However, when all the prothrombotic risk factors significantly associated with CVT on univariate analysis were included in a multivariate statistical model, neither the heterozygous FV G1691A mutation, protein S deficiency alone, nor an underlying clinical condition itself showed any independent association with CVT. In contrast, an elevated Lp(a) concentration and protein C retained their significant association in multivariate analysis in which the combination of prothrombotic risk factors with at least 1 underlying predisposing factor was included. In addition, any combination of a prothrombotic risk factor with an underlying disease had a significant association with CVT. This finding is in agreement with a previous observation that interactions of thrombophilic risk factors with one another or concomitant diseases increase the risk of thromboembolic events in childhood and adolescence.[1,16,17,28]

Although the cohort reported here is one of the largest controlled series of children with CVT, we wish to emphasize that the size of this cohort is still too small to be of statistical power. The possibility of those prothrombotic factors that did not show any significant association with CVT on multivariate analysis also proving to be independent risk factors in larger cohorts cannot be ruled out because of an insufficient sample size.

In summary, the data presented here underline the multifactorial origin of CVT in children. In addition to the combination of an underlying disease with at least 1 prothrombotic risk factor, increased Lp(a) proved to be the most important independent prothrombotic risk factor in pediatric patients with CVT, followed by protein C type I deficiency. Therefore, larger cohorts of children with CVT need to be investigated, or, alternatively, cohorts of pediatric patients from similar ethnic backgrounds need to be pooled to provide more information on possible interactions of further prothrombotic risk factors, eg, antithrombin, ACAs,[1,16] and FII G20210A,[22,23] which did not reach significance levels in the small cohort investigated here.

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