Prothrombotic Disorders in Infants and Children With Cerebral Thromboembolism

Gabrielle deVeber, MD; Paul Monagle, MBBS; Anthony Chan, MBBS; Daune MacGregor, MD; Rosalind Curtis, MD; Sharon Lee, BSc; Patricia Vegh; Margaret Adams; Velma Marzinotto, BScN; Michael Leaker, MD; M. Patricia Massicotte, MD; David Lillicrap, MD; Maureen Andrew, MD

Background: To our knowledge, the contribution of prothrombotic conditions to cerebral thromboembolism has never been prospectively studied in a large series of pediatric patients.

Methods: The Hospital for Sick Children, Toronto, Ontario, established a program in January 1992 to diagnose and treat children (term newborn to 18 years old) with arterial ischemic stroke or sinovenous thrombosis. The routine evaluation for prothrombotic conditions included plasminogen, antithrombin, protein C, free protein S, activated protein C resistance, IgG and IgM anticardiolipin antibody, and lupus anticoagulant. We analyzed samples taken within 2 years of the event. We report results on patients seen from January 1, 1992, to January 1, 1997.

Results: Ninety-two patients (47 males and 45 females) entered the program during the study interval. Patients ranged from newborn to 18 years in age. Arterial ischemic stroke occurred in 78% of patients while sinovenous thrombosis occurred in 22%. All were tested for prothrombotic disorders. One or more abnormal results were present in 35 (38%) of the 92 patients. The majority (21/35) had multiple abnormal test results. The abnormal test results were anticardiolipin antibody (33%), plasminogen (9.5%), activated protein C resistance (9%), protein C (7%), antithrombin (12.5%), lupus anticoagulant (8%), and free protein S (11.5%). Male sex predicted the presence of prothrombotic abnormalities (relative risk, 1.7; 95% confidence interval, 1.2-2.5), but stroke type (relative risk, 0.8; 95% confidence interval, 0.7-1.1), age group, and presence of other risk factors did not predict abnormal testing.

Conclusions: A significant proportion (38%) of children with cerebral thromboembolism had evidence of prothrombotic conditions. In particular, there was a predominance of children with anticardiolipin antibody (33%). These data support a recommendation that children with cerebral thromboembolism be evaluated for prothrombotic disorders.

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Thrombosis in the central nervous system occurs in both the sinovenous system (sinovenous thrombosis) and in the arterial system (arterial ischemic stroke). The diagnosis of cerebral thrombosis in children has been facilitated by the development and availability of sensitive and safe radiographic tests such as computed tomographic scans and magnetic resonance imaging with magnetic resonance angiography. The widespread use of these radiographic tests in children’s hospitals has contributed to an increasing awareness of thrombotic disease in the central nervous system.

At the same time that our ability to diagnose central nervous system thrombosis has increased, our understanding of blood coagulation and both congenital and acquired defects that present risk factors for thrombotic disease has significantly improved. The contribution of both quantitative and qualitative abnormalities in coagulation and fibrinolysis to extracerebral thrombosis has been delineated in adult patients and is being assessed in pediatric patients. However, little is known about the association between coagulation abnormalities and cerebral thrombotic events in children. Detecting acquired and congenital prothrombotic disorders is important because this information can influence both initial and long-term therapies. In addition, family studies are indicated if a child has a congenital prothrombotic disorder. Affected patients and family members require counseling regarding risk factors for thrombosis, the need for intermittent prophylaxis in the presence of acquired risk factors, and medical care by physicians knowledgeable about their disease.

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**SUMMARY**

The purpose of this study was to describe the presence of both acquired and congenital prothrombotic disorders in a consecutive cohort of pediatric patients with arterial ischemic stroke and sinovenous thrombosis. The study included 92 children evaluated during a 5-year period. Seventy-three had arterial ischemic stroke and 19 had sinovenous thrombosis. Laboratory assays were performed to evaluate the presence of thrombotic conditions. The results showed that children with prothrombotic conditions had a higher risk of thrombosis compared to those without. The study highlights the importance of identifying prothrombotic disorders in pediatric patients with thrombotic conditions.

**RESULTS**

There were 92 children evaluated during the 5-year study period. Seventy-three had arterial ischemic stroke and 19 had sinovenous thrombosis. All patients underwent labo-
The formation of a clot (thrombus) depends on a complex interaction between the coagulation and fibrinolytic systems. Congenital deficiencies of antithrombin and activated protein C resistance were the most frequent abnormalities. The median age of the children with sinovenous thrombosis was 10 years (range, newborn to 18 years). The Figure shows the distribution of the entire cohort by age and stroke type. There was no significant difference in the ratio of normal to abnormal coagulation tests when analyzed by different age groups. In particular, prothrombotic abnormalities were not more likely in older infants and children (1 month to 18 years) compared with newborns (<1 month) (P = .42; RR, 1.45; 95% CI, 0.6-3.4).

The associated conditions in patients with arterial ischemic stroke and sinovenous thrombosis varied. In children with arterial ischemic stroke, cardiac disease was the most common underlying disease. In children with sinovenous thrombosis, dehydration was the most common precipitating factor. There was insufficient power in our study to determine whether there were any differences in underlying causes for patients with or without a prothrombotic disorder.

A positive family history for thrombotic disorders was present in only 1 of the 35 children with a prothrombotic abnormality, a child with a transient anticardiolipin antibody positivity. Four of the 57 patients with negative prothrombotic testing had family histories suggestive of a congenital prothrombotic disorder.

The contribution of acquired and congenital prothrombotic hemostatic disorders to thrombotic stroke in children is unknown but important to determine because of the potential risk of recurrent events, availability of specific therapies and need to screen family members. This analysis of the first 92 consecutively evaluated patients from a single institutional program showed that acquired prothrombotic hemostatic conditions exist in a large proportion of children with thrombotic stroke while congenital prothrombotic disorders are rare. Prothrombotic abnormalities were found in patients in all age groups, with both stroke types, and whether there were additional risk factors or a family history suggesting a coagulation abnormality.

The Table provides the results for the 35 patients with positive testing for a prothrombotic disorder. The presence of anticardiolipin antibody in 23 patients (33%) was the most frequent abnormality. Twelve children had anticardiolipin antibody as a single abnormality. The remainder of the children with anticardiolipin antibody also had other abnormalities, including protein S deficiency (n = 3), plasminogen deficiency (n = 2), lupus anticoagulants (n = 2), activated protein C resistance (n = 2), antithrombin deficiency (n = 1), and plasminogen and antithrombin deficiencies (n = 1). Of the remaining patients, many had combined deficiencies of coagulation proteins, including antithrombin and protein S (n = 2), antithrombin and protein C (n = 2), antithrombin and plasminogen (n = 1), antithrombin, protein C, protein S, and plasminogen (n = 2), and antithrombin, protein C, and protein S (n = 2). Two children had lupus anticoagulant and activated protein C resistance. The average interval from event to sample was 8 months (range, 1 day to 4.5 years). Of the 44 abnormal samples, 6 were taken within 1 week of the clinical event. The remainder were obtained between 7 days and 1 month (n = 10), 1 to 3 months (n = 5), 3 to 6 months (n = 4), and 6 months to 4.5 years (n = 19) after the clinical event. In patients with anticardiolipin antibody in whom samples were available from multiple time points, the results went from initially normal to abnormal in 1 patient and initially abnormal to normal in 4 patients.

Male sex was associated with positive prothrombotic testing (P = .01; RR, 1.7; 95% CI, 1.2-2.5). Of the 35 patients with positive prothrombotic testing, 25 (71%) had arterial ischemic stroke and 10 (29%) had sinovenous thrombosis (Figure). The distribution was not significantly different to that in the 57 patients with negative prothrombotic testing (48 [84%] with arterial ischemic stroke and 9 [16%] with sinovenous thrombosis) (P = .19; RR, 0.8; 95% CI, 0.7-1.1).

The median age of children with arterial ischemic stroke was 4.9 years (age range, newborn to 15 years). The median age of the children with sinovenous thrombosis was 10 years, newborn to 18 years). The Figure shows the distribution of the entire cohort by age and stroke type. There was no significant difference in the ratio of normal to abnormal coagulation tests when analyzed by different age groups. In particular, prothrombotic abnormalities were not more likely in older infants and children (1 month to 18 years) compared with newborns (<1 month) (P = .42; RR, 1.45; 95% CI, 0.6-3.4).

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bin, protein C, protein S, and the presence of activated protein C resistance predispose young adults to cerebral and noncerebral thrombotic events, particularly in the presence of an acquired risk factor for thrombosis. These deficiencies have all been described in adults with sinovenous thrombosis,12-14 and deficiencies of plasminogen, protein C, and protein S have been reported in adults with arterial ischemic stroke.15-18 Activated protein C resistance occurs in 5% of the white population,19 which increases the risk of thrombosis whether it is attributable to the factor V Leiden mutation or not.20 Deficiencies in the fibrinolytic system, for example congenital deficiency of plasminogen, also result in thrombotic complications.21

In children with stroke, deficiencies of protein C, protein S, and antithrombin,22-29 and activated protein C resistance23 have been reported, although one retrospective case series30 reported no association of these abnormalities with childhood stroke. In our study, activated protein C resistance was found at only a slightly increased incidence compared with the general population.21 The frequency of other congenital prothrombotic conditions is difficult to determine from our study because not all patients were investigated for all abnormalities, follow-up testing was incomplete, and family studies were not performed in most cases. Further studies will be required to confirm the relative frequency of congenital prothrombotic disorders in children with stroke.

Acquired deficiencies of protein C and protein S associated with clinical thrombosis occur in patients with sepsis and viral infections such as varicella.31-33 Our patients frequently had combinations of deficiencies in protein C, protein S, antithrombin, and plasminogen. The presence of multiple coagulation protein deficiencies is more consistent with an acquired than a congenital prothrombotic disorder. Because cerebral thromboses, especially arterial ischemic strokes, are usually associated with smaller thrombi than noncerebral thromboses, plasma concentrations of coagulation proteins are less likely to be significantly decreased. The multiple abnormalities in our patients were unlikely to be attributable to the sinovenous thrombosis or arterial ischemic stroke per se since the mean interval from event to testing was 8 months and abnormal hemostatic results within 1 week of the stroke event were considered to be indeterminate and subsequently repeated. Our results suggest that acquired deficiencies of coagulation proteins are present in children following thromboembolic stroke, but their causative role remains to be determined.

Antiphospholipid antibodies consist of both lupus anticoagulant and anticardiolipin antibody, and are a heterogeneous group of antibodies that react with proteins, platelets, phospholipids, and interfere with functional coagulation tests.34 The presence of antiphospholipid antibodies is the most common acquired prothrombotic state in cerebral35 and noncerebral34,36 thrombosis in adults. Children with antiphospholipid antibodies and systemic lupus erythematosus have a significant risk of arterial or venous thrombosis, of which 50% occur in the central nervous system,37,38 and antiphospholipid antibodies have been increasingly reported in children with cerebral ischemia.39 The increased prevalence of antiphospholipid antibodies in our large cohort confirms the association between antiphospholipid antibodies and cerebrovascular disease in children. In our study antiphospholipid antibodies were found in children of all ages who did not have systemic lupus erythematosus as a primary diagnosis. Further studies are needed to confirm the importance of transient and persistent antiphospholipid antibodies and the prognostic implications of each. Whether antiphospholipid antibodies are involved in the pathogenesis of stroke remains to be proven.

In conclusion, to our knowledge, this is the first large prospective cohort study of prothrombotic abnormalities in children with arterial ischemic stroke or sinovenous thrombosis. The presence of prothrombotic abnormalities in infants and children at all ages, in both arterial ischemic stroke and sinovenous thrombosis, with and without additional risk factors or a family history suggesting a coagulation disorder suggests that all children with these forms of stroke should be evaluated for prothrombotic abnormalities. Further studies are required to define the pathogenic significance of these prothrombotic abnormalities. Finally, large prospective follow-up studies will be needed to determine if the recurrence risk of sinovenous thrombosis or arterial ischemic stroke is increased in children with prothrombotic abnormalities.

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Reprints: Gabrielle deVeber, MD, Division of Neurology, Hospital for Sick Children, 555 University Ave, Toronto, Ontario, Canada M5G 1X8 (e-mail: deveber@sickkids.on.ca).

REFERENCES


