CEREBRAL SINOVENOUS THROMBOSIS IN CHILDREN

GABRIELLE DEVEBER, M.D., MAUREEN ANDREW, M.D., COLEEN ADAMS, M.B., BRUCE BJORNSON, M.D., FRANCES BOOTH, M.D., DAVID J. BUCKLEY, M.B., CH.B., CAROL S. CAMFIELD, M.D., MICHÈLE DAVID, M.D., PETER HUMPHREYS, M.D., PIERRE LANGEVIN, M.D., E. ATHEN MACDONALD, M.D., AND JANE GILLETT, M.D., FOR THE CANADIAN PEDIATRIC ISCHEMIC STROKE STUDY GROUP*

ABSTRACT

Background Cerebral sinovenous thrombosis in children is a serious disorder, and information is needed about its prevention and treatment.

Methods The Canadian Pediatric Ischemic Stroke Registry was initiated in 1992 at the 16 pediatric tertiary care centers in Canada. Children (newborn to 18 years of age) with symptoms and radiographic confirmation of sinovenous thrombosis were included.

Results During the first six years of the registry, 160 consecutive children with sinovenous thrombosis were enrolled, and the incidence of the disorder was 0.67 case per 100,000 children per year. Neonates were most commonly affected. Fifty-eight percent of the children had seizures, 76 percent had diffuse neurologic signs, and 42 percent had focal neurologic signs. Risk factors included head and neck disorders (in 29 percent), acute systemic illnesses (in 54 percent), chronic systemic diseases (in 36 percent), and prothrombotic states (in 41 percent). Venous infarcts occurred in 41 percent of the children. Fifty-three percent of the children received antithrombotic agents. Neurologic deficits were present in 38 percent of the children, and 8 percent died; half the deaths were due to sinovenous thrombosis. Predictors of adverse neurologic outcomes were seizures at presentation and venous infarcts.

Conclusions Sinovenous thrombosis in children affects primarily neonates and results in neurologic impairment or death in approximately half the cases. The occurrence of venous infarcts or seizures portends a poor outcome. (N Engl J Med 2001;345:417-23.)

CEREBRAL sinovenous thrombosis in children is a rare disorder but one that is increasingly diagnosed because of greater clinical awareness, sensitive neuroimaging techniques, and the survival of children with previously lethal diseases that confer a predisposition to sinovenous thrombosis.[1-3] The literature on sinovenous thrombosis in children consists only of case reports and analyses of small case series.[4-10] Extrapolating the results of studies of adults to children is of limited value because of large age-related differences in the hemostatic, vascular, and neurologic systems. An understanding of the epidemiology of sinovenous thrombosis in children is necessary to define critical clinical settings and develop interventional strategies. The Canadian Pediatric Ischemic Stroke Registry was established to obtain comprehensive prospective epidemiologic data on stroke, including sinovenous thrombosis, in children.

METHODS

Patients

All 16 pediatric tertiary care centers in Canada participated in the registry. Children from birth (with a gestational age of more than 36 weeks) to 18 years of age were eligible for the study if they had radiologically confirmed sinovenous thrombosis. The children were classified as neonates (less than 1 month old) or nonneonates (1 month to 18 years old). A neurologist at each center maintained a prospective list of consecutive children with objectively diagnosed sinovenous thrombosis. A research nurse visited each center at regular intervals, checked the completeness of patient identification by searching the medical-records data base for discharge diagnoses, with the use of the *International Classification of Diseases, Ninth Revision* (ICD-9) codes for sinovenous thrombosis (437.6 and 325),[11] and filled out standardized data-collection forms. The data were entered into a central data base, reviewed for inaccuracies, missing data, and inconsistencies, and corrected according to a review of medical records and discussions with the site investigators. The institutional research-ethics board at each institution approved the study. Data on children with sinovenous thrombosis who were enrolled in the registry between January 1, 1992, and December 31, 1997, are included in this report.

In a substudy, performed to assess the completeness of the ascertainment of cases, the Canadian data base for health information was searched for cases of sinovenous thrombosis in children during the study period, with the use of the same ICD-9 codes for sinovenous thrombosis. Cases in Ontario, the province with the largest population, were matched to those in the registry.

From the Divisions of Neurology (G.D.) and Hematology–Oncology (M.A.), the Population Health Sciences Program, Hospital for Sick Children, Toronto; the Department of Pediatrics, University of Toronto, Toronto (G.D., M.A.); the Department of Pediatrics, University of Calgary, Calgary, Alta. (C.A.); the Department of Pediatrics, University of British Columbia, Vancouver (B.B.); the Department of Pediatrics, University of Manitoba, Winnipeg (F.B.); the Department of Pediatrics, Memorial University, St. John's, Nfld. (D.J.B.); the Department of Pediatrics, Dalhousie University, Halifax, N.S. (C.S.C.); the Department of Hematology–Oncology, Université de Montreal, Montreal (M.D.); the Department of Pediatrics, University of Ottawa, Ottawa, Ont. (P.H.); the Department of Pediatric Neurology, Centre Hospitalier de l'Université Laval, Sainte-Foy, Quebec, Que. (P.L.); the Department of Pediatrics, Queen's University, Kingston, Ont. (E.A.M.); and the Departments of Pediatrics and Clinical Neurosciences, University of Western Ontario, London (J.G.) — all in Canada. Address reprint requests to Dr. deVeber at the Division of Neurology, Hospital for Sick Children, 555 University Ave., Toronto, ON M5G 1X8, Canada.

Other authors were Brandon Meaney, M.D. (Department of Pediatrics, McMaster University, Hamilton, Ont.), Michael Shevell, M.D., C.M. (Department of Neurology, Pediatrics, and Neurosurgery, McGill University, Montreal), D. Barry Sinclair, M.D. (Department of Pediatrics, University of Alberta, Edmonton), and Jerome Yager, M.D. (Department of Pediatrics, University of Saskatchewan, Saskatoon).

*Other members of the study group are listed in the Appendix.

Clinical Features

Basic demographic information was recorded, as well as neurologic manifestations of sinovenous thrombosis, which were classified as seizures, diffuse neurologic signs, and focal neurologic signs.

Risk Factors

Findings that were recorded as risk factors included disorders of the head and neck (including local infection), acute systemic illness, chronic systemic disease, and prothrombotic disorders. Standard assays for prothrombotic disorders were used at each center, including activity assays for antithrombin, protein C, protein S, and the lupus anticoagulant; immunologic assays for anticardiolipin antibody; and molecular assays for the presence of factor V Leiden and the G20210A mutation in the prothrombin gene.

Radiologic Evaluation

Sinovenous thrombosis was confirmed by computed tomography (CT), magnetic resonance imaging (MRI) with or without magnetic resonance venography (MRV), conventional angiography, or transfontanel power Doppler ultrasonography. The results of MRI, with the results of MRV when available, were compared with the results of CT or those of power Doppler ultrasonography when both sets of data were available.

The location of the thrombosis was classified as superficial or deep. The presence and nature of parenchymal lesions were noted. Infarcts were classified as nonhemorrhagic or hemorrhagic. Extraparenchymal hemorrhages were classified as subdural, subarachnoid, or intraventricular.

Treatment

The use of antithrombotic agents, other medical therapies, and surgery was recorded. Overt clinical bleeding requiring transfusion therapy, bleeding viewed as excessive and prompting the cessation of anticoagulant therapy, and confirmed bleeding into the central nervous system were considered to be major episodes of bleeding. Recurrent thrombosis was defined as a confirmed thrombotic event within or outside the central nervous system.

Neurologic Outcome

The neurologic outcome, based on the assessment at the last follow-up visit, was classified as normal (no neurologic deficits) or abnormal (one or more neurologic deficits). Neurologic deficits and death due to sinovenous thrombosis were classified as adverse outcomes. Seizures were classified as adverse outcomes only if they occurred after discharge from the acute care hospital and were treated with anticonvulsant agents.

Statistical Analysis

The incidence of sinovenous thrombosis was calculated on the basis of the Canadian population of persons 18 years of age or younger.[12] The following variables were tabulated: patient enrollment in each province, age at the time of presentation, sex, neurologic manifestations, risk factors, radiologic findings, treatment, adverse outcomes, and cause of death.

Statistical analyses were performed with the use of Stat-View 5.1.[13] Univariate analyses were performed with the chi-square test or Fisher's exact test for categorical data and with Student's t-test for continuous data. Potentially important differences between neonates and nonneonates were tested for each of the variables noted above. Univariate analyses were also performed to identify predictors of an adverse outcome; variables included in these analyses were age, sex, presence or absence of seizures, presence or absence of infarcts, location of thrombosis, involvement of single or multiple sinuses, and presence or absence of treatment with antithrombotic agents. Multivariate analyses were planned if more than three variables were found to be significantly associated with an adverse outcome ($P<0.05$) in the univariate analyses.

RESULTS

Patients

A total of 160 consecutive children with sinovenous thrombosis were enrolled in the registry: 69 neonates and 91 nonneonates. The geographic distribution of the patients reflected that of the general population in Canada, with Ontario having the largest number of patients (52 percent). The substudy showed that the registry included 97 percent of the children who were classified as having an ICD-9 code for sinovenous thrombosis in the Ontario health-information data base. The incidence of sinovenous thrombosis was 0.67 case per 100,000 children per year (95 percent confidence interval, 0.55 to 0.76). Information was available for more than 95 percent of the children unless otherwise indicated.

Demographic and Clinical Characteristics

Forty-three percent of the children were neonates, and 54 percent were less than one year old (Fig. 1); 54 percent were male and 46 percent were female. Seizures were more common and both focal and diffuse neurologic signs less common in neonates than in nonneonates (Table 1).

Risk Factors

Risk factors were present in all but four patients (2 percent) and were related to age (Table 2). Acute systemic illnesses were present in 84 percent of neonates; the most frequent illnesses were perinatal complications (in 51 percent) and dehydration (in 30 percent). The perinatal complications included hypoxia at birth (in 30 cases), premature rupture of membranes

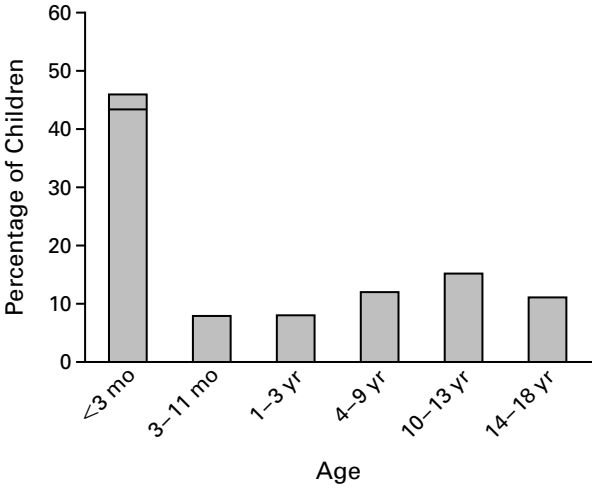

Figure 1. Age Distribution among 160 Children with Sinovenous Thrombosis.

The portion of the first bar below the horizontal line indicates infants less than one month old.

TABLE 1. NEUROLOGIC MANIFESTATIONS OF SINOVENOUS THROMBOSIS IN 160 CHILDREN.*

NEUROLOGIC MANIFESTATION	TOTAL (N=160)	NEONATES (N=69)	NONNEONATES (N=91)	P VALUE†
	no. of children (%)			
Seizures				
Any	93 (58)	49 (71)	44 (48)	0.006
Generalized	42 (26)	19 (28)	23 (25)	
Not specified	29 (18)	16 (23)	13 (14)	
Focal	27 (17)	17 (25)	10 (11)	
None	63 (39)	17 (25)	46 (51)	
Diffuse neurologic signs				
Any	122 (76)	40 (58)	82 (90)	<0.001
Decreased level of consciousness	70 (44)	25 (36)	45 (49)	
Headache	54 (34)	0	54 (59)	
Jittery movements	27 (17)	14 (20)	13 (14)	
Papilledema	20 (12)	0	20 (22)	
None	34 (21)	26 (38)	8 (9)	
Focal neurologic signs				
Any	68 (42)	20 (29)	48 (53)	0.004
Hemiparesis	21 (13)	4 (6)	17 (19)	
Visual impairment	16 (10)	0	16 (18)	
Cranial-nerve palsies	15 (9)	5 (7)	10 (11)	
Ataxia	6 (4)	0	6 (7)	
Speech impairment	6 (4)	0	6 (7)	
Hemisensory loss	3 (2)	0	3 (3)	
Other	26 (16)	17 (25)	9 (10)	
None	88 (55)	46 (67)	42 (46)	

*Data were available for more than 95 percent of children in all categories. Children may have had more than one neurologic manifestation. All percentages were calculated with a denominator of 160 for the total group, 69 for neonates (<1 month old), and 91 for nonneonates (1 month to 18 years old).

†P values (two-sided) are for comparisons between neonates and nonneonates. Headache, visual impairment, ataxia, speech impairment, and hemisensory loss were excluded from the statistical analysis because they are generally not observed in one of the age groups.

TABLE 2. RISK FACTORS FOR SINOVENOUS THROMBOSIS.*

RISK FACTOR	TOTAL (N=160)	NEONATES (N=69)	NON-NEONATES (N=91)	P VALUE†
	no. of children (%)			
Head and neck disorder	46 (29)	11 (16)	35 (38)	<0.001
Infection	28 (18)	7 (10)	21 (23)	
Other	20 (12)	5 (7)	15 (16)	
Acute systemic illness				
Any	86 (54)	58 (84)	28 (31)	<0.001
Dehydration	40 (25)	21 (30)	19 (21)	
Perinatal complications	38 (24)	35 (51)	3 (3)	
Bacterial sepsis	15 (9)	11 (16)	4 (4)	
None	69 (43)	9 (13)	60 (66)	
Chronic systemic disease				
Any	58 (36)	3 (4)	55 (60)	<0.001
Connective-tissue disease	22 (14)	1 (1)	21 (23)	
Hematologic disorder	20 (12)	2 (3)	18 (20)	
Cancer	12 (8)	0	12 (13)	
Cardiac disease	8 (5)	0	8 (9)	
Disorder requiring indwelling catheter	8 (5)	0	8 (9)	
None	97 (61)	62 (90)	35 (38)	
Prothrombotic state	50 (41)	10 (20)	40 (54)	<0.001
Prothrombotic disorder	39 (32)	10 (20)	29 (39)	
Procoagulant drug	14 (11)	0	14 (19)	
Other	29 (18)	8 (12)	21 (23)	
None	4 (2)	1 (1)	3 (3)	

*For all risk factors except prothrombotic disorders, data were available for more than 95 percent of the children. Children may have had more than one risk factor. The percentages were calculated with a denominator of 160 for the total group, 69 for neonates (<1 month old), and 91 for nonneonates (1 month to 18 years old). Data on prothrombotic disorders were available for 123 of the 160 children (77 percent): 49 neonates and 74 nonneonates.

†P values (two-sided) are for comparisons between neonates and nonneonates. Perinatal complications, connective-tissue disease, and cancer were excluded from the statistical analysis because they are generally not observed in one of the age groups.

(in 4), maternal infection (in 4), placental abruption (in 2), and gestational diabetes (in 2). Head and neck disorders were common in nonneonates (38 percent), and in both neonates and nonneonates, the majority of these disorders (61 percent) were infections. Chronic systemic diseases were also common in nonneonates (present in 60 percent) and were diverse in nature.

Tests for prothrombotic disorders were performed in 123 of the 160 patients (77 percent), of whom 39 (32 percent) had abnormal results. The most frequent abnormality was the presence of anticardiolipin antibody (in 10 children), with IgG titers ranging from 15 to 60 IgG phospholipid units per milliliter. Other abnormalities included decreased levels of protein C (in nine children), antithrombin (in seven), protein S (in five), fibrinogen (in two), and plasminogen (in one) and the presence of a lupus anticoagulant (in four), factor V Leiden (in three), and the G20210A prothrombin-gene mutation (in one). The deficiencies of antithrombin, protein C, and protein S were in many cases caused by an acquired disorder such as liver disease, the nephrotic syndrome, or disseminated intravascular coagulation. Procoagulant drugs were given to 14 children: 11 received asparaginase, and 3 received oral contraceptives.

Radiologic Findings

CT was performed in 153 children (96 percent), MRI with or without MRV in 114 (71 percent), and conventional angiography in 13 (8 percent), with power Doppler ultrasonography in 12 neonates (8 percent). Among the 104 children who underwent CT and MRI, CT did not reveal sinovenous thrombosis in 17 children (16 percent). Power Doppler ultrasonography detected sinovenous thrombosis in 10 of the 12 neonates who underwent both power Doppler ultrasonography and MRI.

Figure 2 shows the structures that were most frequently involved. The location of the thrombosis was superficial in 137 children (86 percent) and deep in 60 (38 percent), with no significant differences between neonates and nonneonates (Table 3). Multiple

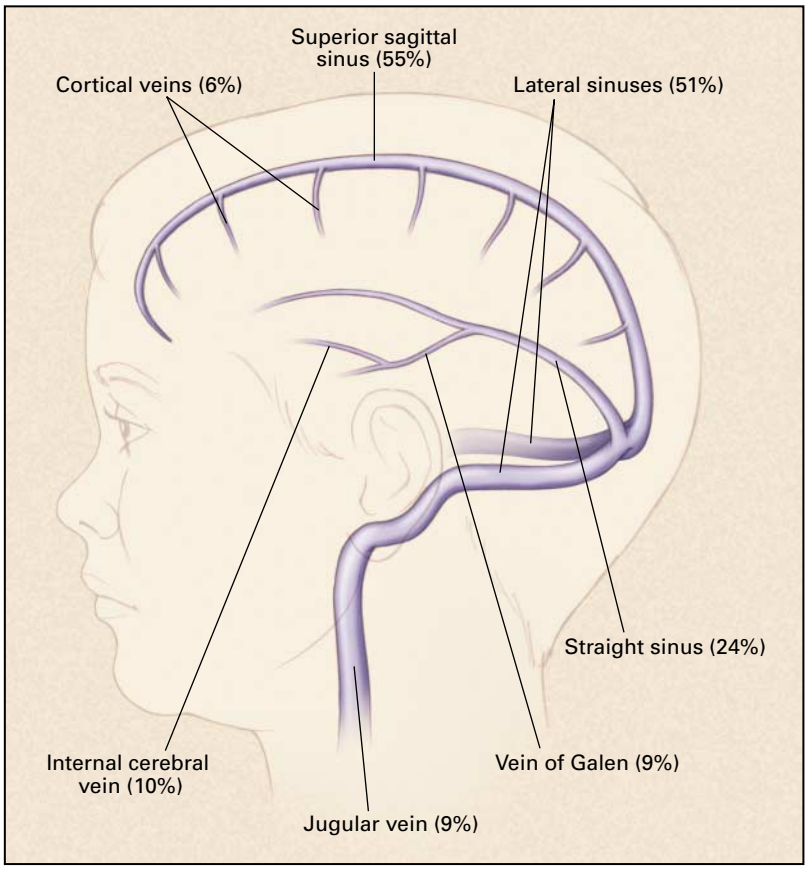

Figure 2. Lateral View of the Cerebral Sinovenous System.
The structures that are most susceptible to sinovenous thrombosis in children are shown, with the relative frequency of involvement given in parentheses. A patient may have multiple sites of involvement.

sinuses were involved in 78 children (49 percent). The lateral sinus was more frequently involved in nonneonates than in neonates (60 percent vs. 39 percent) ($P=0.01$).

Cerebral parenchymal infarcts were present in 66 children (41 percent): 29 neonates and 37 nonneonates. The infarcts were nonhemorrhagic in 21 of the 66 children and hemorrhagic in 45. Twenty-four neonates (35 percent) had hemorrhagic infarcts, as compared with 21 nonneonates (23 percent, $P=0.05$). Parenchymal lesions other than infarcts were present in 11 children; the lesions included brain tumors, arteriovenous malformations, and multifocal white-matter lesions. Extraparenchymal hemorrhage was present in 14 children (9 percent).

Treatment

Antithrombotic therapy was given to 85 children (53 percent): 25 neonates (36 percent) and 60 nonneonates (66 percent) (Table 4). Most children were treated for three months, and none died or had neurologic deterioration because of hemorrhagic complications. Fifty-one neonates (74 percent) required anticonvulsant therapy, as compared with 38 nonneonates (42 percent). Surgical procedures, performed in 21 children (13 percent), consisted of mastoidectomy and shunt placement.

Outcome

The neurologic outcome could be assessed in 143 children (89 percent): 61 of 69 neonates (88 percent) and 82 of 91 nonneonates (90 percent). The mean interval from thrombosis to the last follow-up visit was 1.6 years (range, 0.05 to 5.2). Of these 143 children, 77 (54 percent) were normal, 54 (38 percent) had neurologic deficits, and 12 (8 percent) had died. The neurologic deficits were motor impairment in 80 percent of cases, cognitive impairment in 10 percent, developmental delay in 9 percent, speech impairment in 6 percent, visual impairment in 6 per-

TABLE 3. LOCATION OF THROMBOSIS.*

LOCATION	TOTAL (N=160)	NEONATES (N=69)	NON-NEONATES (N=91)	P VALUE†
	no. of children (%)			
Superficial	137 (86)	55 (80)	82 (90)	1.03
Superior sagittal sinus	88 (55)	43 (62)	45 (49)	
Lateral sinus	82 (51)	27 (39)	55 (60)	
Cortical vein	10 (6)	2 (3)	8 (9)	
Deep	60 (38)	27 (39)	33 (36)	0.83
Straight sinus	39 (24)	21 (30)	18 (20)	
Internal cerebral vein	16 (10)	7 (10)	9 (10)	
Vein of Galen	14 (9)	8 (12)	6 (7)	
Jugular vein	14 (9)	1 (1)	13 (14)	

*Data were available for more than 95 percent of children in all categories. Children may have had thrombosis in more than one location. All percentages were calculated with a denominator of 160 for the total group, 69 for neonates (<1 month old), and 91 for nonneonates (1 month to 18 years old).

†P values (two-sided) are for comparisons between neonates and nonneonates.

TABLE 4. TYPE OF TREATMENT.*

TREATMENT	TOTAL (N=160)	NEONATES (N=69)	NON-NEONATES (N=91)	P VALUE†
	no. of children (%)			
Antithrombotic therapy	85 (53)	25 (36)	60 (66)	<0.001
Low-molecular-weight heparin	50 (31)	20 (29)	30 (33)	
Unfractionated heparin	35 (22)	6 (9)	29 (32)	
Oral anticoagulant	39 (24)	1 (1)	38 (42)	
Aspirin	9 (6)	0	9 (10)	
Urokinase	1 (1)	0	1 (1)	
Other medical therapy	142 (89)	63 (91)	79 (87)	0.62
Antibiotics	94 (59)	47 (68)	47 (52)	
Anticonvulsants	89 (56)	51 (74)	38 (42)	
Corticosteroids	31 (19)	2 (3)	29 (32)	
Chemotherapy for underlying tumor	7 (4)	0	7 (8)	
Other	31 (19)	10 (14)	21 (23)	
Surgery	21 (13)	3 (4)	18 (20)	0.008

*Data were available for more than 95 percent of children in all categories. Children may have received more than one type of treatment. All percentages were calculated with a denominator of 160 for the total group, 69 for neonates (<1 month old), and 91 for nonneonates (1 month to 18 years old).

†P values (two-sided) are for comparisons between neonates and nonneonates. Chemotherapy was excluded from the statistical analysis because it generally does not apply to neonates.

cent, and other impairments in 26 percent. Of the 12 deaths, 6 were attributable to sinovenous thrombosis and the remainder were attributable to other associated diseases. Predictors of adverse neurologic outcomes included seizures at presentation in nonneonates (P=0.02) and the presence of infarcts (nonhemorrhagic or hemorrhagic) in neonates and nonneonates (P=0.03). Seizures were present at follow-up in 12 neonates (20 percent) and 9 nonneonates (11 percent, P=0.22). Nineteen children (13 percent) had symptomatic recurrent thrombosis: 5 neonates (8 percent) and 14 nonneonates (17 percent, P=0.19). Recurrent thrombosis was cerebral in 12 children and noncerebral in 7.

DISCUSSION

The Canadian Pediatric Ischemic Stroke Registry was the source of the data for this large, population-based study of the epidemiology of sinovenous thrombosis during childhood. The incidence of sinovenous thrombosis was 0.67 case per 100,000 children per year, and neonates were the most commonly affected age group. There were age-related differences in the neurologic manifestations of sinovenous thrombosis, and specific risk factors were identified, including head and neck infections and prothrombotic states. Venous infarcts and the occurrence of seizures predicted a poor neurologic outcome.

The registry data pose several methodologic issues that need to be addressed. First, a potential limitation of the data is bias in case ascertainment. Our substudy, however, showed that the registry data accounted for 97 percent of children with sinovenous thrombosis in Ontario, where the majority of the patients lived. Second, the patient cohort was divided into neonates and nonneonates rather than into patients with septic and those with nonseptic sinovenous thrombosis, which is the conventional classification. The validity of the registry classification was supported by the striking differences between the neonatal and nonneonatal groups, and analyses of the registry data according to the presence or absence of sepsis did not reveal any significant differences (data not shown).

Third, testing for prothrombotic disorders was not required, and neither factor V Leiden nor the G20210A mutation in the prothrombin gene had been discovered in the early years of the registry. However, 77 percent of the children were tested, and the results were similar to those in smaller studies in which consecutive children were tested.[14,15] Fourth, one of the limitations of any registry is a lack of standardized data on the long-term outcome. Despite this limitation, data on the neurologic outcome were available for 89 percent of the children in the Canadian registry, and the findings were similar to those in a smaller, hospital-based cohort study.[16]

The main neurologic manifestations of sinovenous thrombosis in the nonneonates in our study were similar to those reported in adults[17]: a decreased level

of consciousness, headache, focal neurologic signs such as hemiparesis, and cranial-nerve palsies. In contrast, the primary neurologic manifestations in the neonates were seizures and diffuse neurologic signs. The increased frequency of seizures in this group may reflect the general propensity of infants to have seizures. The frequency of seizures and diffuse neurologic signs means that clinicians must have a high index of suspicion for sinovenous thrombosis in neonates.

The risk factors for sinovenous thrombosis in our study were age dependent, were frequently multiple, and were often different from those reported in adults.[17,18] Perinatal complications, of which hypoxic encephalopathy was most common, predominated in the neonates. Head and neck infections, such as otitis media, mastoiditis, and sinusitis, predominated in preschool children, whereas chronic diseases such as connective-tissue disorders were more frequent in older children. Risk factors that are common in adults, such as pregnancy,[19] cancer,[20,21] and use of oral contraceptives,[22] were rare in our study. Idiopathic sinovenous thrombosis represented only 3 percent of cases, as compared with an estimated 10 to 25 percent of cases in adults.[17]

Prothrombotic states may cause or contribute to sinovenous thrombosis in both adults and children. In adults, the frequency of prothrombotic disorders is 15 to 21 percent; the G20210A prothrombin-gene mutation and the presence of factor V Leiden are the most common genetic disorders.[23-25] In children with sinovenous thrombosis, the frequency of prothrombotic disorders is 12 to 50 percent, and the presence of anticardiolipin antibody is the most common acquired disorder.[14,15,26-30] In our study, 32 percent of the children who underwent testing for prothrombotic disorders had at least one abnormality; the presence of anticardiolipin antibody was the most common acquired disorder, and the presence of factor V Leiden was the most common genetic disorder. Other prothrombotic disorders were due to underlying diseases. Whether acquired prothrombotic disorders cause sinovenous thrombosis in children or are merely associated with it remains to be determined.

The registry offered a unique opportunity to compare the accuracy of the various radiographic tests used to diagnose sinovenous thrombosis in children. Although CT scans were obtained in 96 percent of the children, they detected the disorder in only 84 percent of the children who also underwent MRI with MRV. Previous studies have suggested that CT scans may also have false positive results in neonates because of an increased hematocrit, a decreased density of unmyelinated white matter, and slower venous flow — factors that may result in radiographic findings that mimic the dense-triangle sign.[31] Transfontanel power Doppler ultrasonography is a powerful tool for the noninvasive diagnosis and monitoring of neonatal sinovenous thrombosis.[32] At this time, the optimal technique for establishing the diagnosis in children is MRI with MRV.

The use of anticoagulant therapy in adults with sinovenous thrombosis is based on data from four clinical trials that showed an improved neurologic outcome with this treatment.[33-36] The extrapolation of these results to children with sinovenous thrombosis, particularly neonates, is problematic, because the ratio of efficacy to safety may differ from that in adults. The registry data show that anticoagulants are frequently used in children with sinovenous thrombosis, especially in nonneonates (66 percent). Although the potential benefit of anticoagulants in children with sinovenous thrombosis cannot be determined from the registry data, the results of our study suggest that anticoagulant therapy is not associated with serious hemorrhage in selected patients and that such therapy warrants further evaluation, particularly in neonates.

The long-term neurologic outcome of sinovenous thrombosis in children is unclear.[9,10] The best available estimate is that after a mean of 2.1 years, 77 percent of neonates and 52 percent of nonneonates are neurologically normal.[16] Our findings are consistent with those estimates. Long-term follow-up of affected children is very important, especially in neonates, since the onset of signs of neurologic injury is delayed in this age group. Given the increasing incidence of sinovenous thrombosis in children, the variations in treatment, and the adverse outcomes in half the children with this disorder, studies are needed to identify more effective immediate and secondary preventive therapies.

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The following investigators also participated in the study: **Canada** — *Alberta:* S. Lee, B. Prieur; *British Columbia:* S. Kent, J.A.R. Tibbles; *Manitoba:* P.J. McCusker; *Newfoundland:* S. Penney; *New Brunswick:* D.C. Meek; *Nova Scotia:* E. Woods; *Ontario:* M. Adams, A.K.C. Chan, S.N. Christie, R.M. Curtis, T. Domi, M.P. Flavin, L.F. Jardine, J.A. Julian, D.L. Keene, S. Lanthier, D.L. MacGregor, S. Mayank, L. Mitchell, J. Tu, L. Wylie; *Quebec:* B.G. Lemieux; **Australia** — P. Monagle.

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