Original Article

Cerebral Venous Thrombosis in Children

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ABSTRACT

Cerebral venous thrombosis is an important cause of stroke in children. Understanding the natural history of the disease is essential for rational application of new interventions. We retrospectively identified 31 children with cerebral venous thrombosis confirmed by head computed tomography (4 patients) or by magnetic resonance imaging (27 patients). Risk factors, clinical and radiographic features, and neurologic outcomes were analyzed. There were 21 males and 10 females aged 1 day to 13 years (median 14 days). Nineteen (61%) were neonates. The most common risk factors included mastoiditis, persistent pulmonary hypertension, cardiac malformation, and dehydration. The chief clinical features were seizures, fever, respiratory distress, and lethargy. Fifteen patients had infarctions (8 hemorrhagic, 7 ischemic). Protein C and antithrombin III deficiency were the most common coagulopathies among 14 tested patients. On discharge, 11 patients were normal, 17 had residual deficits, and 2 patients died. Twenty-seven patients were followed from 1 month to 12 years (mean 22 months). At follow-up, 11 patients were normal, and 13 patients had development delay. One had residual hemiparesis and cortical visual impairment. Two had other deficits. Neonatal cerebral venous thrombosis is probably more common than previously thought, and outcomes are worse in this group. All children with cerebral venous thrombosis should be tested for coagulation disorders. (*J Child Neurol* 2001;16:574–580).

Cerebral venous thrombosis is increasingly recognized as an important and underdiagnosed cause of morbidity and mortality in children.[1] Previous studies showed that outcome of cerebral venous thrombosis in children included 16% mortality and approximately 22% serious long-term neurologic morbidity.[2]

Diagnosis is often difficult because the symptoms are nonspecific. Cerebral venous thrombosis has been found in infants with respiratory distress, lethargy, and seizures[3,4]; thus, cerebral venous thrombosis should be considered part of the differential diagnosis in newborns who have an unclear etiology for seizures.[5] Infection, trauma, and impaired systemic circulation were associated with cerebral venous thrombosis in the 1930s when Baily and Hass published detailed case reports and autopsy series with pathologic descriptions of cerebral venous thrombosis in children.[6,7] More recent reports have identified inherited and acquired prothrombotic disorders as important risk factors for cerebral venous thrombosis.[8] Earlier diagnosis of cerebral venous thrombosis has been facilitated by the development and availability of sensitive radiographic tests such as computed tomography (CT) and magnetic resonance imaging (MRI) with magnetic resonance angiography and venography.[9] However, the clinical course is still unpredictable and can result in fulminant neurologic dysfunction and death.[10,11]

Treatment options have recently expanded with the advent of MRI and advanced interventional neuroradiologic techniques. In our series, treatment was supportive. All children underwent medical management of intracranial hypertension, seizures, and underlying risk factors.[10] Anticoagulation and local thrombolysis are described in two series,[2,10] and the safety of heparin anticoagulation has been studied, but the efficacy of this therapy has not been systematically studied in the pediatric population. The objective of our study is to describe the natural history of cerebral venous thrombosis in children so that analysis of interventions may subsequently be undertaken.

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PATIENTS, MATERIALS, AND METHODS

Patients

In a retrospective review, we searched patient charts at Riley Hospital for Children, using International Classification of Diseases-9 codes, to identify all patients younger than 18 years diagnosed with cerebral venous thrombosis from 1986 to 1999. Fifty patients were initially identified. We reviewed all charts and radiographs and excluded patients with inconclusive neuroimaging studies or incomplete medical records. Thirty-one patients were included in the study.

Data Collection

The following demographic information was collected for all patients: current age, age at the time of diagnosis, sex, underlying diseases, clinical presentation, and neurologic outcome. The anatomic location of the thrombosis was also noted, and patients were divided into three groups: superior sagittal thrombosis, sigmoid/transverse sinus thrombosis, or multiple sinus thrombosis. Presence of ischemic or hemorrhagic stroke was identified radiographically. Coagulation factor testing was available in 14 patients including protein C, protein S, antithrombin III, factor V Leiden mutation, and antiphospholipid antibodies. Outcomes at the time of discharge and most recent follow-up visit were evaluated based on chart review and pediatric neurology outpatient clinic follow-up notes. We did not examine the incidence of post-thrombotic intracranial hypertension.

Statistical Analysis

Using Fisher's exact test, we compared the incidence of developmental delay in neonates with multiple sinus thrombosis and patients without multiple sinus thrombosis (patients with isolated superior sagittal thrombosis or sigmoid/transverse sinus thrombosis). A contingency table analysis yielded the positive and negative predictive value of multiple sinus thrombosis in neonates for developmental delay.

RESULTS

Patients

The neonate group consisted of 12 boys (63.2%) and 7 girls (36.8%), yielding 61.2% of the total series. The age ranged from 1 to 13 days (mean age 6.8 days; median 14 days). The most common presenting features in neonates were seizures, fever, respiratory distress, and lethargy. Children older than 1 month consisted of 9 boys (75%) and 3 girls (25%), or 38.8% of the series (mean age 62.5 months; median 80.1 months). Older children commonly presented with fever and lethargy but also had classic signs of intracranial hypertension: vomiting, headache, papilledema, and abducens palsy (Table 1).

Table 1. Presenting Features of Children With Cerebral Venous Thrombosis

		Number of Patients	
Clinical Presentation	*%*	*Neonates (n = 19)*	*Non-neonates (n = 12)*
Seizures	55	13	4
Fever	32	3	7
Respiratory distress	29	8	1
Lethargy	26	3	5
Poor oral intake	19	4	2
Vomiting	19	0	6
Headache	16	0	5
Papilledema	13	0	4
VIth nerve palsy	9.6	0	3

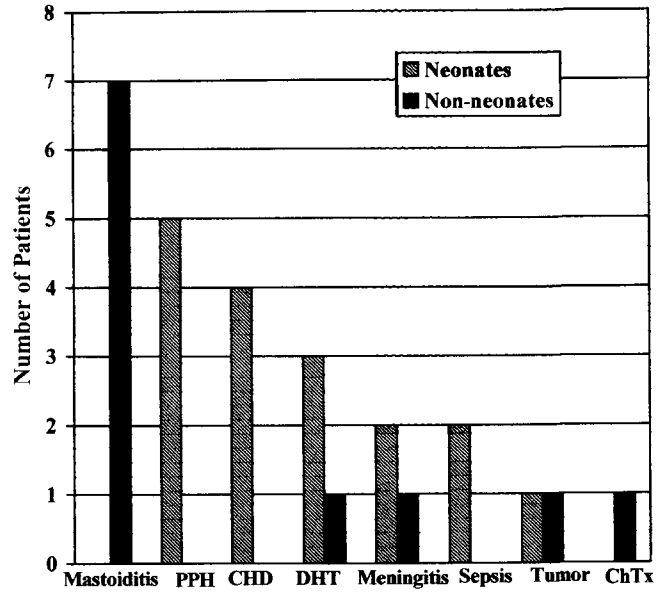

Figure 1. Risk factors in children with cerebral venous thrombosis. PPH = persistent pulmonary hypertension; CDH = congenital heart disease; DHT = dehydration; ChTx = chemotherapy.

Cerebral Venous Thrombosis Risk Factors

Clinical risk factors for cerebral venous thrombosis were found in 24 patients. Among neonates, 14 of 19 had clinical risk factors: persistent pulmonary hypertension (n = 5), congenital heart disease (n = 4), dehydration (n = 3), meningitis (n = 2), sepsis (n = 2), and central nervous system tumor (n = 1). Among older children, 10 of 12 had risk factors: 7 with mastoiditis and 1 each with dehydration, meningitis, central nervous system tumor, and leukemia undergoing L-asparaginase therapy (Figure 1). In 7 children, no definite risk factors were identified.

Radiography

Among the 19 neonates, 9 had superior sagittal thrombosis, 3 had sigmoid/transverse sinus thrombosis, and 7 had

Table 2. Venous Sinus Thrombosis in Neonates and Non-neonates

	Neonates	*Non-neonates*
Sagittal	9	0
Multiple	7	5
Sigmoid/transverse	3	7

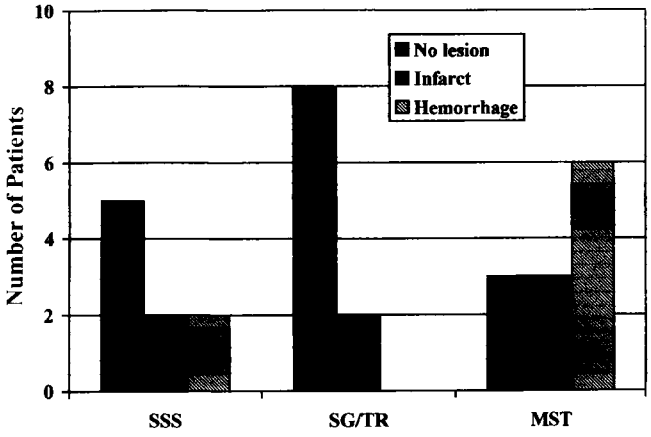

Figure 2. Anatomic location of cerebral venous thrombosis in children. SSS = isolated superior sagittal thrombosis; SG/TR = sigmoid/transverse sinus thrombosis; MST = multiple sinus thrombosis.

multiple sinus thrombosis. In the 12 non-neonates, none had superior sagittal thrombosis, 7 had sigmoid/transverse sinus thrombosis, and 5 had multiple sinus thrombosis (Table 2).

Strokes were identified in 15 patients (Table 3): 11 (58%) of 19 neonates and 4 (33%) of 12 non-neonates. Among non-neonates, there was infarction in 4 patients, with hemorrhagic conversion in 1. Among neonates with multiple sinus thrombosis (n = 7), 5 had hemorrhage, 1 infarcted, and 1 died. In those with sigmoid/transverse sinus thrombosis, 1 infarcted and 2 did not. In those neonates with superior sagittal thrombosis (n = 9), 2 had infarctions and 2 had hemorrhage. In older children with multiple sinus thrombosis (n = 5), 2 had infarct and 1 hemorrhage. Those with sigmoid/transverse sinus thrombosis (n = 7) had 1 cerebral infarction (Figure 2).

Coagulation Studies

Coagulation data were available in 14 children (45.1%) (Table 4). All 7 children with no other identifiable risk factors had coagulation profiles sent. Two of these 7 children had one abnormal coagulation factor, 1 had two abnormal results, and 4 had three abnormalities. One child had a normal coagulation profile. Two of 5 tested for factor V Leiden were abnormal (Figure 3). Five of 7 had abnormal protein C, 2 of 7 had abnormal protein S, and 4 of 7 children had antithrombin III deficiency.

Neurologic Outcome

Neurologic evaluation was performed on discharge from the hospital and compared with the neurologic examination at the time of diagnosis. The examination was classified as normal (n = 12, 38.7%), unchanged from the time of diagnosis (n = 14, 45.1%), and improved from the time of diagnosis (n = 3, 9.7%). Four patients died, all of causes unrelated to cerebral venous thrombosis, and 2 died in hospital. Two patients died of extensive brain tumor, 1 had sepsis, and 1 died of complications of leukemia.

We obtained follow-up evaluations in 27 (87%) patients from 1 month to 12 years (mean 22.3 months; median 5 years). Eleven patients (5 neonates and 6 non-neonates) had complete recovery, and 16 patients had residual neurologic deficit (Table 5). One patient had persistent developmental delay and hemiparesis, and 1 patient had developmental delay and persistent cortical visual loss, both non-neonates.

Table 3. Stroke in Children With Cerebral Venous Thrombosis

	Number of Patients	
	Neonates (n = 19)	*Non-neonates (n = 12)*
No stroke	8	8
Infarction	4	3
Hemorrhage	7	1

Table 4. Coagulation Abnormalities in Children With Cerebral Venous Thrombosis

Coagulation Test	*Abnormal Patients/ Tested Patients (%)*	*Abnormal Results in Patients Without Other Risk Factors*
Protein C deficiency	7/14 (50)	5/7 (71)
Antithrombin III deficiency	5/14 (35)	4/7 (57)
Factor V Leiden mutation	3/9 (33)	2/5 (40)
Protein S deficiency	2/14 (14)	2/7 (29)
Antiphospholipid antibodies	1/8 (13)	0/4 (0)

DISCUSSION

The estimated incidence of cerebral venous thrombosis in children is 0.29 per 100,000 per year, constituting 25% of

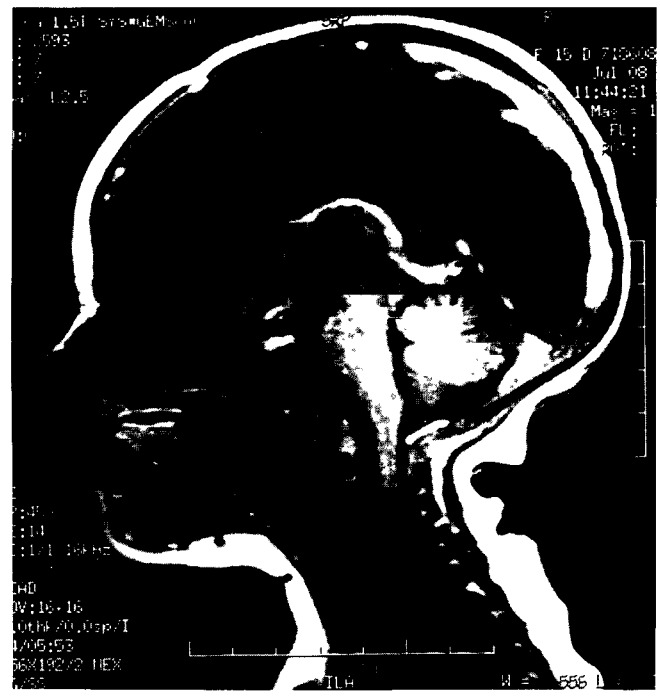

Figure 3. Midline sagittal T_1-weighted contrast-enhanced MRI shows extensive thrombosis of the superficial and deep venous system in a newborn with factor V Leiden gene mutation.

Table 5. Neurologic Outcome in Neonates and Non-neonates

Residual Neurologic Deficit	*Neonates (n = 19) (%)*	*Non-neonates (n = 12) (%)*
None	5 (26.3)	6 (50)
Developmental delay	11 (57.8)	2 (16.7)
VIth nerve deficit	0 (0)	2 (16.7)
Hemiparesis	0 (0)	1 (8.3)
Learning disability	1 (5.3)	0 (0)
Cortical visual loss	0 (0)	1 (8.3)
Death	2 (10.5)	2 (16.7)

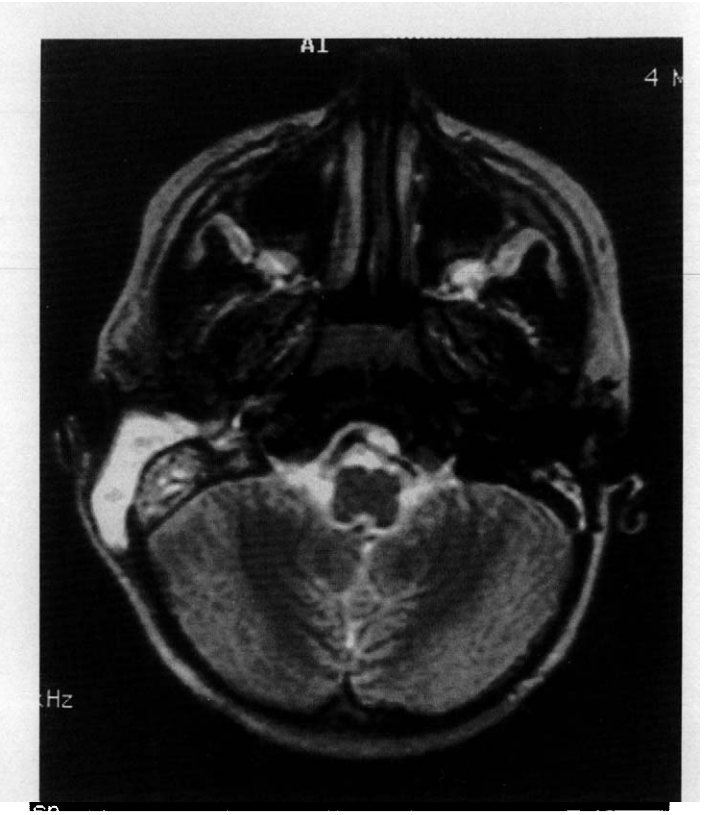

Figure 4. Transverse T_2-weighted MRI shows thrombosis of the right sigmoid/transverse sinus in a 5-year-old boy with mastoiditis. There is no evidence of hemorrhagic or ischemic stroke.

ischemic cerebrovascular disease in the pediatric population.[2,11,12] Cerebral venous thrombosis has been identified as an important cause of death and long-term neurologic deficits in the pediatric population. It is associated with altered cerebral hemodynamics such as shock, dehydration, and congestive heart failure. Mastoiditis and trauma can incite acquired hypercoagulable states locally, and this may compound inherited disorders of coagulation.[13] The presenting clinical picture can vary from minimal nonspecific symptoms such as decreased oral intake and irritability to more ominous neurologic conditions such as lethargy and coma. Seizures, fever, and respiratory distress are common in neonates. In older children, papilledema, focal neurologic deficits, and classically described signs of intracranial hypertension are commonly found in addition to less specific symptoms.[13] Because of the variable and nonspecific presentation, a high index of suspicion is required. Since the introduction of high-resolution CT and MRI scans, the diagnosis of cerebral venous thrombosis is more easily made. However, despite the development and availability of more sophisticated diagnostic tools and earlier detection of the sinus occlusion, there has not been a major change in the prognosis and outcome of children with cerebral venous thrombosis.[19]

The present study involved 31 children ranging from 1 day to 13 years of age. The majority of these patients were neonates (61%), the largest reported series of neonates with cerebral venous thrombosis. This striking age-related finding in our study may be referral bias. Our hospital is a major referral center for tertiary neonatal care in Indiana. Alternatively, cerebral venous thrombosis may have a higher incidence in neonates than previously recognized. This may be the result of high clinical suspicion and aggressive diagnostic evaluation in our institution. The particularities of the coagulation process in neonates may also be an important predisposing factor for thrombotic events, putting this population group at higher risk for cerebral venous thrombosis.

The clinical presentation was dependent on age and risk factors but not gender. As mentioned before, the neonates in our series had predominantly nonspecific symptoms such as seizures, fever, respiratory distress, lethargy, and decreased oral intake. In contrast, older children presented with symptoms suggesting increased intracranial pressure such as headache, papilledema, and abducens nerve palsy.

Mastoiditis was present in 7 patients and was the largest risk factor in non-neonates with cerebral venous thrombosis (n = 7/12, 58%). Children with mastoiditis presented with transverse and/or sigmoid sinus thrombosis and no evidence of cerebral infarction, although VIth cranial nerve neuropathy was found in 3 (Figure 4). They were treated with antibiotics and mastoidectomy. Two patients with mastoiditis had a permanent neurologic deficit (abducens nerve palsy). Mastoiditis complicated by cerebral venous thrombosis is a medical emergency. Although the introduction of antibiotics has markedly reduced its overall incidence, the reported mortality rate is still high, ranging from 18 to 36%.[14] No children in our series succumbed to mastoiditis. The usual presentation is headache, fever, otalgia/otorrhea, papilledema, and abducens nerve palsy.[15] Direct extension of the mastoiditis via emissary veins results in a local inflammatory state. This causes a reactive thrombophlebitis followed by thrombosis within the sinus lumen.[15] Most patients need mastoidectomy and insertion of a transtympanic ventilation tube for drainage of the middle ear infection. Broad-spectrum antibiotics are mandatory.

One child had acute lymphoblastic leukemia and received L-asparaginase. Cerebral venous thrombosis is a well-recognized complication of chemotherapy with L-asparaginase.[16] This drug interferes with protein synthesis, resulting in acquired coagulation protein deficiency, especially antithrombin III.[17] This patient had multisinus thrombosis, received heparin, and died neurologically normal. Cerebral venous thrombosis has been described in children with non-Hodgkins lymphoma and neuroblastoma not treated with L-asparaginase.[18] Some authors suggest that "procoagulant factors" are released with the breakdown of tumor cells since thrombosis occurs most commonly in the first 2 months of therapy. Curiously, noncerebral thrombosis with L-asparaginase has not been described.[18]

The contribution of congenital prothrombotic hemostatic disorders to venous sinus thrombosis in children is important because there is a high incidence of recurrent events in those affected, specific therapies are available, and family members require appropriate screening.[1] Acquired prothrombotic states are associated with surgery, trauma, malignancy, renal disease, and sepsis.[19] Congenital deficiency of antithrombin III, protein C, protein S, and the presence of activated protein C resistance predispose children and young adults to cerebral venous thrombosis, particularly in the presence of an acquired risk factor.[20] All of these protein deficiencies are inherited in an autosomal-dominant fashion, with most heterozygotes being mildly or moderately symptomatic and most homozygotes suffering severe, early-onset forms of hypercoagulability.[20] Several patients in our study had low levels of protein C, protein S, and antithrombin III, isolated or in combination. The presence of multiple coagulation protein deficiencies is more consistent with an acquired than a congenital prothrombotic disorder.[1]

Activated protein C resistance is the coagulation defect most frequently identified in association with cerebral venous sinus thrombosis.[1] Protein C is a plasma zymogen that plays an important role in the inhibition of blood coagulation and promotion of clot lysis.[21] Protein C enzymatically cleaves and inactivates factors V and VII, thus impeding fibrin formation and clot stabilization. The proteolytic activity of protein C is greatly enhanced by its cofactor, protein S. A single missense mutation (R506Q) owing to a G/A transition (G1691A) of the factor V gene results in an amino-acid substitution at the protein C cleavage site that renders this mutant form of factor V resistant to proteolytic degradation by activated protein C.[22] This mutation, called factor V Leiden gene mutation, accounts for 90 to 95% of all activated protein C resistance.[22] In our study, three of nine patients tested were found to be heterozygotes for factor V Leiden mutation. Factor V Leiden mutation occurs in 5 to 7% of the general pediatric population.[23] Heterozygous carriers have a 7-fold increased risk of thrombosis, whereas the risk for homozygous individuals is increased 80-fold.[22] Some authors suggest that factor V Leiden mutation may account for 60 to 70% of familial thrombophilia cases.[24] The impact of factor V Leiden mutation in children with cerebral venous thrombosis seems to be highest in newborns and young infants[25] and may reflect the different physiology of hemostasis, with proportionately lower levels of protein C and protein S frequently observed in this age group.

Antiphospholipid antibody was found in one of our patients (1/8). This is a well-established risk factor for thrombotic events. A variety of effects on platelets, coagulation proteins, and endothelial cells have been ascribed to antiphospholipid antibody and are thought to play an important role in the pathogenesis of antiphospholipid antibody-related thrombosis.[26,27] In a prospective blood bank survey, antiphospholipid antibodies were detected in about 6.5% of normal subjects.[24] Children with antiphospholipid antibodies have a significantly increased risk of arterial and venous thrombosis, of which 50% occur in the central nervous system. Our patient had sagittal sinus thrombosis, was treated with heparin, and is neurologically normal. The prognostic implications of the presence of antiphospholipid antibodies in children are not yet established.

The number of prothrombotic abnormalities in our patients with cerebral venous thrombosis suggests that all patients with cerebral venous thrombosis, despite the presence of obvious clinical risk factors or lack of family history of thrombosis, should undergo coagulation evaluation, including prothrombin time, activated partial thromboplastin time, platelet count, bleeding time, fibrinogen levels, protein C, protein S, antithrombin III, factor V Leiden gene mutation, and antiphospholipid antibodies.[2] In particular, these studies are obligatory in patients with cerebral venous thrombosis and no other risk factors. Our data showed that 6 of 7 patients without other risk factors had some sort of coagulopathy.

The most useful predictors of outcome in children with cerebral venous thrombosis are the site of thrombosis and the presence of stroke, although these are not independent variables. Ischemic and hemorrhagic strokes are usually present in the setting of multiple sinus thrombosis. In our study, the positive predictive value of multiple sinus thrombosis for developmental delay in neonates was 100% (prevalence of multiple sinus thrombosis in neonates was 61%), and the negative predictive value was 64%, showing the high association between multiple sinus thrombosis and developmental delay in the neonatal population. We found that 15 patients (48%) had strokes, 7 patients (22.6%) had ischemic stroke, and 8 patients (25.8%) had intracerebral hemorrhage. Nine patients (60%) with stroke had multiple sinus thrombosis, 4 patients (26%) had isolated superior sagittal thrombosis, and only 2 (14%) had sigmoid/transverse sinus thrombosis. The availability of collateral venous pathways may explain the great variability of the lesions. Patients with multiple sinus involvement complicated by stroke are at greatest risk of persistent neurologic deficit and major functional disability. Bergui et al tried to correlate the site and extent of dural sinus thrombosis with the location and the size of brain lesions in 26 consecutive patients and found no significant correlation.[28] In our series, neonates with multiple sinus thrombosis had a higher incidence of hem-

orrhage and persistent deficits. Eleven patients (11/14) with stroke were neonates, and only 4 (4/12) patients were older than 1 month of age. This is probably owing to the fact that in older children, cerebral venous thrombosis was more often related with mastoiditis and sigmoid sinus/transverse sinus thrombosis. Early hydration, systemic antibiotics, and surgical drainage of infection are the most important steps in the management of children with mastoiditis complicated with cerebral venous thrombosis. Patients with seizures should be treated with anticonvulsants, and intracranial hypertension should be managed aggressively.[29] Systemic anticoagulation and intravascular thrombolysis have been controversial, and efficacy has not been established prospectively in pediatric patients. The guidelines for anticoagulation therapy in children have been directly extrapolated from recommendations for adults.[30,31] Neither the amount of heparin required to maintain the therapeutic level nor the incidence of significant bleeding and recurrent thrombotic complications is known for children with cerebral venous thrombosis.[30] A pilot study (performed in Toronto, Canada) showed that the use of anticoagulants, particularly low molecular weight heparin, is safe in children with cerebral venous thrombosis but was inconclusive with regard to the efficacy of anticoagulation and impact on mortality and long-term neurologic morbidity.[2,32]

Thrombolytic agents such as urokinase and streptokinase promote clot lysis by converting plasminogen to plasmin but also stimulate plasmin-mediated proteolysis of blood coagulation factors.[33] This results in a high risk of catastrophic hemorrhage. The tissue plasminogen activator is clot selective, has a shorter half-life, and produces the lowest levels of fibrinogen degradation products, but no trial has demonstrated acceptable safety in the pediatric population.

CONCLUSION

Cerebral venous thrombosis is a potentially fatal disease and is an important cause of disability in children. It is more common than previously thought and is remarkable for its large spectrum of clinical presentations and unpredictable course. Cerebral venous thrombosis in neonates tends to have worse prognosis compared with older children. Thrombosis of multiple venous sinuses is highly associated with developmental delay in neonates. A thorough hematologic evaluation (protein C, protein S, antithrombin III, antiphospholipid antibodies, factor V Leiden, plasminogen, plasmin, and D-dimer, as well as prothrombin time, partial thromboplastin time, and platelet studies) should be made in every case of cerebral venous thrombosis. Therapy remains controversial. A large multicenter, randomized trial is necessary to elucidate the potential role of anticoagulation or thrombolysis in the management of children with cerebral venous thrombosis.

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