Cerebrovascular Disorders in Children

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Cerebrovascular disorders are an important cause of mortality and chronic morbidity in children. International incidence rates for childhood stroke (*ie*, from 30 days to 18 years of age) have ranged from 1.3 to 13 per 100,000 children. Ischemic stroke is probably more common than hemorrhagic stroke in children. The clinical presentation of stroke in children varies according to age and location of the stroke. Over 100 risk factors for stroke in children have been reported, but in up to one third of cases no cause is identified. The management and prevention of stroke in children is not well studied and current recommendations are based on adult studies, nonrandomized trials, or expert opinion. Over half of children with stroke will develop lifelong cognitive or motor disability and up to one third will have a recurrent stroke. This review briefly describes the epidemiology, risk factors, evaluation, treatment, and outcome of stroke in children.

Introduction

Stroke is an important cause of mortality and chronic morbidity in children. Cerebrovascular disorders are among the top 10 causes of death in children. In the United States in 2001, over 28,000 years of potential life were lost to stroke in individuals under 25 years of age. Of the hundreds of children who suffer a stroke each year, more than half will have permanent motor or cognitive disability. Perinatal stroke develops between 28 weeks of gestation and 1 month of age, whereas childhood stroke occurs later, between 30 days and 18 years of age.

Recent improvements in imaging techniques have led to increased detection and characterization of stroke in children and have contributed to increases in the reported incidence and prevalence of the disorder. The first population-based study of stroke in children, done in the 1970s, found an incidence of 2.52 per 100,000 children for all stroke types [1]. Subsequent studies based on more widespread use of neuroimaging have identified higher rates of stroke in children.

The clinical presentation of stroke in children varies according to age, underlying cause, and stroke location. The most common presentations include hemiplegia and seizure in ischemic stroke, headache and vomiting in hemorrhagic stroke, and headache and decreased level of consciousness in children with cerebral venous thrombosis.

The causes of stroke in children have changed over time. In the past, bacterial meningitis was a common cause of ischemic stroke in children. Today, cardiac disorders, blood disorders, vasculopathies, and viral infections are more common causes.

The treatment and prevention of stroke in children is not well studied. Other treatments for childhood stroke are based on adult studies, nonrandomized trials, or expert opinion. Future prevention studies are needed, because up to 30% of children with ischemic stroke will have a recurrence.

The outcome of children after stroke varies among studies due to differences in follow-up time, functional measures, stroke type, and population studied. More than 50% of survivors develop some neurologic or cognitive problem, and 5% to 20% of affected children die.

This review is restricted to cerebrovascular disorders that occur between 30 days and 18 years of age, and it briefly describes the epidemiology, risk factors, evaluation, treatment, and outcome of arterial ischemic stroke, hemorrhagic stroke, and cerebral venous thrombosis in children. Perinatal stroke is not discussed here, but detailed information is available elsewhere [2].

Arterial Ischemic Stroke

Epidemiology

Arterial ischemic stroke (AIS) is defined as an acute focal neurologic deficit lasting more than 24 hours with neuroimaging evidence of cerebral infarction. The incidence of childhood AIS, as reported by population-based studies and hospital discharge surveys, ranges from 0.6 to 7.9 per 100,000 children. The first study to report the incidence of childhood stroke in the United States was based in Rochester, MN and estimated the rate of AIS at 0.6 per 100,000 children [1]. Since then, recent studies within and outside the United States have found higher rates of AIS in children (Table 1) [3–6]. Hospital discharge studies of stroke in children have found similar incidence rates as compared with population-based studies and have provided important information on gender, ethnicity, and stroke subtype differences. A study of hospital discharges for stroke in children in Califor-

Table 1. International age-specific incidence rates of stroke in children

Study (years), country	Subjects, *n*	Age range	Incidence rate AIS	Incidence rate HS	Incidence rate AIS + HS
Beran-Koehn (1955–1994), USA	13	0–14 y	1.3	1.1	2.3
Schoenberg (1965–1974), USA	4	0–14 y	0.6	1.9	2.5
Eeg-Olofsson (1970–1979), Sweden	5	0–14 y	-	-	2.1
Satoh (1974–1989), Japan	54	0–15 y	0.2	-	-
Broderick (1988–1989), USA	16	0–15 y	1.2	1.5	2.7
Giroud (1985–1993), France	28	0–16 y	7.9	5.1	13
Earley (1988–1991), USA	35	0–14 y	0.58	0.71	1.29
DeVeber (2000), Canada	820	30 d to 18 y	2.6	-	0.7
Lynch (1979–2000), USA	1377	30 d to 18 y	7.8*	4.1*	11.9*
Fullerton (1991–2000), USA	2278	30 d to 19 y	1.2*	1.1*	2.3*
Al-Sulaiman (1991–1996), Saudi Arabia	31	0–11 y	-	-	29.7†

*Based on a hospital discharge database.
†Hospital frequency rate.
AIS—arterial ischemic stroke; HS—hemorrhagic stroke.

nia from 1991 to 2000 yielded an incidence rate of AIS at 1.2 per 100,000 children per year [7•]. A review of data from the National Hospital Discharge Survey (NHDS), a continuous survey of hospital discharges throughout the United States, revealed that from 1979 through 2000 the mean rate of hospitalization for children diagnosed with AIS was 7.8 per 100,000 children per year [8]. In these two studies, childhood AIS hospitalization rates were greater for male patients than female patients, for blacks than whites, and for ischemic than hemorrhagic stroke. The mean age at hospitalization in the NHDS study was 7.6 years (median, 7.0), which is slightly higher than ages reported in other cohort studies [9,10••].

The clinical presentation of AIS is related to the age of the child and location of the stroke. In the 1st year of life, infants with stroke typically present with seizures, hypotonia, or apnea. Some infants with stroke may not manifest symptoms early in life, but are diagnosed retrospectively when evidence of hemiparesis or postneonatal seizures leads to later evaluation and neuroimaging. Older children with stroke present with focal neurologic deficits, usually hemiplegia and/or seizures.

Mechanism

The determination of the mechanism of AIS may require extensive investigation. Etiologic evaluations of childhood stroke vary among institutions and are often limited. The mechanisms by which AIS occurs in children include thromboembolism from the heart or an intracranial or extracranial vessel; acute, transient, or progressive arteriopathy; and other rare causes. A recent study of 185 children with AIS found that 79% of cases had abnormal cerebral arterial imaging, predominantly occlusion or stenosis of the terminal internal carotid artery (ICA) or proximal middle cerebral artery (MCA). In the remaining cases, the mechanism of stroke was undetermined [10••].

Risk factors

Over 100 risk factors for stroke in children have been reported [11]; however, the extent of the evaluation is often limited and no risk factors are identified in one third of cases. The most frequently reported risk factors for AIS in children are cardiac disorders, hematologic disorders, metabolic disorders, vascular disorders, and infection [12••,13].

Cardiac disorders

Cardiac disorders, identified in up to 50% of strokes in case series, are the most common risk factor for stroke in children [14]. In the Canadian Pediatric Ischemic Stroke Registry (CPISR) [6], cardiac disease was identified in 25% of children with AIS. Cardiac disorders were the most common risk factor among children hospitalized with AIS in the United States from 1979 to 2000 (27% of all cases) [8]. Several cardiac disorders are associated with stroke in children: congenital heart disease, intracardiac defects, cardiac procedures, and acquired heart disease. Cardiac disorders can lead to the development of intracardiac thrombi that may embolize to the brain or can lead to thrombosis in cyanotic patients with anemia [15]. Congenital heart disease (CHD) was the most common risk factor among children hospitalized with stroke in California from 1991 to 2000 [7•]. The incidence of CHD is one per 125 live births [16]. In the United States, early treatment and improved surgical techniques for cardiac disorders have increased survival rates and reduced cerebrovascular events [17]: the percentage of ischemic strokes due to cardiac disorders decreased 76% among children hospitalized with ischemic stroke between the years 1979 and 2000 [8]. The risk of stroke in children with CHD is related to the underlying abnormality, diagnostic and surgical procedures, and associated genetic or acquired factors that predispose children to thrombosis. Silent infarction may also occur as demonstrated by neuroimaging studies that revealed permanent neurologic damage in infants undergoing cardiac surgery for CHD [18]. A pre- and postoperative magnetic resonance imaging (MRI) study of 24 infants undergoing pediatric surgery revealed that 67% of cases developed new lesions or worsening of preoperative lesions [17].

Hematologic and metabolic disorders

Blood disorders were the second most common risk factor recorded among children hospitalized with AIS in the United States from 1979 to 2000. Several blood disorders are associated with AIS in children and include sickle cell disease (SCD) and genetic and acquired coagulation abnormalities. SCD is the most common risk factor for stroke in black children. Children with SCD (hemoglobin SS) have a risk of stroke over 200 times that of healthy children. Cohort studies have shown that 22% percent of children with SCD have evidence of silent infarction [19•], and 10% percent will develop symptomatic stroke by 14 years of age [20]. The recurrence risk of stroke in children with SCD is extremely high: as many as 66% will have a recurrence by 9 years [21], and even among children who receive the best medical therapy the recurrence rate is 22% [20]. Sickle cell-related stroke is primarily associated with large vessel disease, but small vessel involvement is also reported. A study of 34 children with AIS and SCD reported greater involvement of large arteries (59%) than small vessels (32%) [10••]. In contrast, a study of 146 children with SCD found that among children with vasculopathy, 69% had small vessel disease whereas only 31% had large vessel disease [22]. The large vessel vasculopathy observed in SCD primarily involves the distal ICA and proximal anterior cerebral artery (ACA) and MCA and may progress to an angiographic pattern of moyamoya disease [23]. The mechanism by which stroke develops in children with SCD is unclear, but the extent of resulting brain injury is correlated to the degree of vasculopathy [22].

Deficiencies or mutations in coagulation and metabolic factors can lead to thrombosis. Several coagulation and metabolic abnormalities have been evaluated in children with AIS, but there has been a wide variation in the prevalence of these abnormalities among international cohorts. Several case-control studies, utilizing hospital-based adult and population-based child controls, have shown an association between coagulation abnormalities and AIS [24–26], whereas others studies yielded negative results [27–30]. The most consistent associations between AIS and coagulation and metabolic abnormalities have been reported primarily in European populations for protein C deficiency, elevated lipoprotein (a), and the factor V Leiden mutation [26,30,31]. Case-control studies of protein S and antithrombin deficiency, anticardiolipin antibodies, and the prothrombin 20210A and MTHFR mutation have shown mixed results. The variation in the prevalence of these mutations is likely due to the range and timing of investigations, small sample sizes, and population admixture and stratification [10••]. The risk of AIS seems to be greatest among children with a combination of genetic factors, as multiple factors are associated with a heightened risk of thrombosis and recurrence [9,12••].

Vascular disorders

Vasculopathies, including moyamoya syndrome, arterial dissection, and hypoplastic vessels, were identified in 23% of children with AIS in a recent cohort study [10••]. Moyamoya syndrome is a chronic noninflammatory occlusive intracranial vasculopathy that accounts for a small percentage of AIS in children. The etiology of moyamoya is unknown, but has been associated with a number of systemic disorders. Diagnosis is based on an angiographic finding of bilateral stenosis of the ICA and the development of an extensive collateral network with the appearance of a "puff of smoke." Moyamoya is seen primarily in Japanese patients, but has been reported in all ethnic groups. Children with moyamoya typically present with an acute neurologic deficit and may develop headache, seizures, involuntary movements, and cognitive changes. Arterial dissection is a common cause of stroke in young adults and children. A review of case series published over a 34-year period found that most children with dissection are male and present with symptoms of hemiplegia and headache [32•]. The mean age at diagnosis is around 8 to 11 years of age. Unlike adults, intracranial dissection occurs more frequently in children. Arterial dissection has been associated with a variety of conditions, but most cases are due to trauma. Diagnosis is based on magnetic resonance angiography (MRA) or conventional angiography abnormalities. There may be a long segment of narrowing, a double-barrel lumen, an intimal flap, a tapering occlusion, dissecting aneurysm, and/or distal embolization.

Infectious disorders

Observational studies have shown a strong and consistent association between acute infection and stroke in adults. Childhood AIS has been reported as a complication of meningitis, encephalitis, brain abscess, and sepsis; in addition, there have been several recent reports linking childhood AIS with varicella, HIV, infection with *Mycoplasma pneumoniae*, and parvovirus B19 infections. Infection likely leads to cerebral ischemia via multiple mechanisms. Infection can lead to thrombosis via a systemic inflammatory response, a hypercoagulable state, and/or direct invasion of the endothelium. During serious infection, there is a rapid destruction of protein C and antithrombin III, both of which normally inhibit coagulation. Infection also produces endothelial injury and a release of inflammatory cytokines, which lead to the downregulation of thrombomodulin. Decreased levels of activated protein C and increased levels of D-dimer and C4b binding protein have also been observed in patients with stroke [33]. Meningitis and encephalitis were among the most common risk factors in children hospitalized with stroke in California from 1991 to 2000 [7•]. The prevalence of AIS in children with bacterial meningitis has been reported as high as 27% [34]. Several studies have described a link between varicella infection and AIS. A case-control study of children with idiopathic AIS found a history of varicella infection within the past 9 months in 64% of cases and 9% of control subjects [35]. The prevalence of stroke among children with varicella has been estimated at one per 6500 to 15,000 children [36,37]. The majority of strokes occur within the first 4 months after infection, and children typically present with hemiplegia. Varicella infection can produce a transient cerebral angiopathy that affects the distal ICA and proximal cerebral artery and may lead to intracranial arterial stenosis and subcortical infarction. The recurrence rate of transient ischemic attack (TIA) and AIS among children with varicella related AIS has been reported as high as 45% [37].

Evaluation

There are no published consensus guidelines on the evaluation of AIS in children, but systematic approaches have been recommended [38,39]. The evaluation should identify the etiology and rule out other nonvascular causes that mimic stroke (postictal paralysis, migraine, hypoglycemia, and alternating hemiplegia). The history should include questions regarding head and neck trauma, unexplained fever or recent infection (varicella in last 12 months), drug ingestion, developmental delay, blood disorders, and associated headache. A careful family and birth history should also be taken, with special attention to neurologic disease, premature vascular disease, hematologic disease, and mental retardation. A comprehensive evaluation of children with stroke should also include hematologic, metabolic, and angiographic studies, as recent evidence suggests that the identification of multiple risk factors predicts worse long-term outcome (Fig. 1) [9].

Cranial imaging procedures for AIS include MRI, computed tomography (CT), and ultrasonography. Although CT is usually the first imaging test employed and is useful for differentiating hemorrhage from AIS, conventional T1 and T2, with diffusion-weighted MRI, is a preferable choice. Diffusion-weighted MR imaging (DWI) is particularly sensitive to detection of early infarction, even when standard techniques do not detect abnormalities. In addition to DWI, several new MRI techniques have been used for the evaluation of AIS in children, including perfusion, gradient echo, and fluid attenuated inversion recovery imaging [40]. MRA is also useful for detecting occlusion and hypoplastic vessels [41] and should be considered especially in the evaluation of children with suspected arterial dissection. Conventional angiography is recommended when MRI fails to identify an etiology.

Transcranial Doppler (TCD) is useful in sickle cell-related stroke and can be performed at the bedside. Children with SCD who have a peak mean velocity greater than 200 cm within the terminal ICA or proximal MCA are at an increased risk for stroke [42].

Echocardiography should be performed in all children with AIS, and transesophageal echocardiography and a bubble (agitated saline) study may also be indicated. More extensive diagnostic testing should be performed in children with no readily identifiable cause of stroke. These exams may include cerebrospinal fluid analysis, tests for metabolic disorders and vasculitis, and hemoglobin electrophoresis.

Treatment

There have been no randomized, clinical trials for the acute treatment or secondary prevention of AIS in children. Current treatment recommendations are based on small nonrandomized trials, adult stroke studies, case series, or expert opinion.

Acute treatment

The acute management of children with AIS should include aggressive treatment of infection, fever, blood pressure, hypo- and hyperglycemia, and seizures to limit ischemic damage. Hypothermia and a number of neuroprotective agents have been studied in adults, but the utility in children is unclear [43]. There are several reports of children receiving thrombolytic agents for AIS [44–46], but these drugs have not been evaluated in children. Thrombolytic therapy is recommended for childhood AIS in special situations, but should only be considered at institutions able to support its complications [47]. Decompressive hemicraniectomy for large unilateral stroke has been used in adults and may be warranted in children [48]. Acute exchange transfusion should be considered in children with sickle cell-related AIS.

Current treatment strategies at the Hospital for Sick Children in Toronto, Canada are to treat with anticoagulation (low molecular weight heparin or unfractionated heparin) unless contraindicated (hemorrhage, hypertension, or large infarct) for the first 7 days. Following this, the majority of patients are switched to acetylsalicylic acid (3 to 5 mg/d) or in cases of cardiogenic embolism or dissection, to coumadin for several months and then to acetylsalicylic acid. The decision is individualized based on the underlying etiology or the stroke (DeVeber, Personal communication) [49].

Primary prevention

The Stroke Prevention in Sickle Cell Study Project (STOP) [50] evaluated the efficacy of serial blood transfusions in children at a high risk of stroke. The STOP trial was terminated early due to positive results showing a 92% reduction in stroke in the treatment arm compared with standard therapy [50]. Chronic transfusion therapy is indicated in children with SCD and intracranial stenosis as identified by TCD. Blood transfusions are performed every 3 to 4 weeks to maintain hemoglobin S levels below 30%. Early surgical treatment has been shown to decrease the risk of stroke among children with congenital heart disease. Whereas stroke was not a primary outcome in a recent

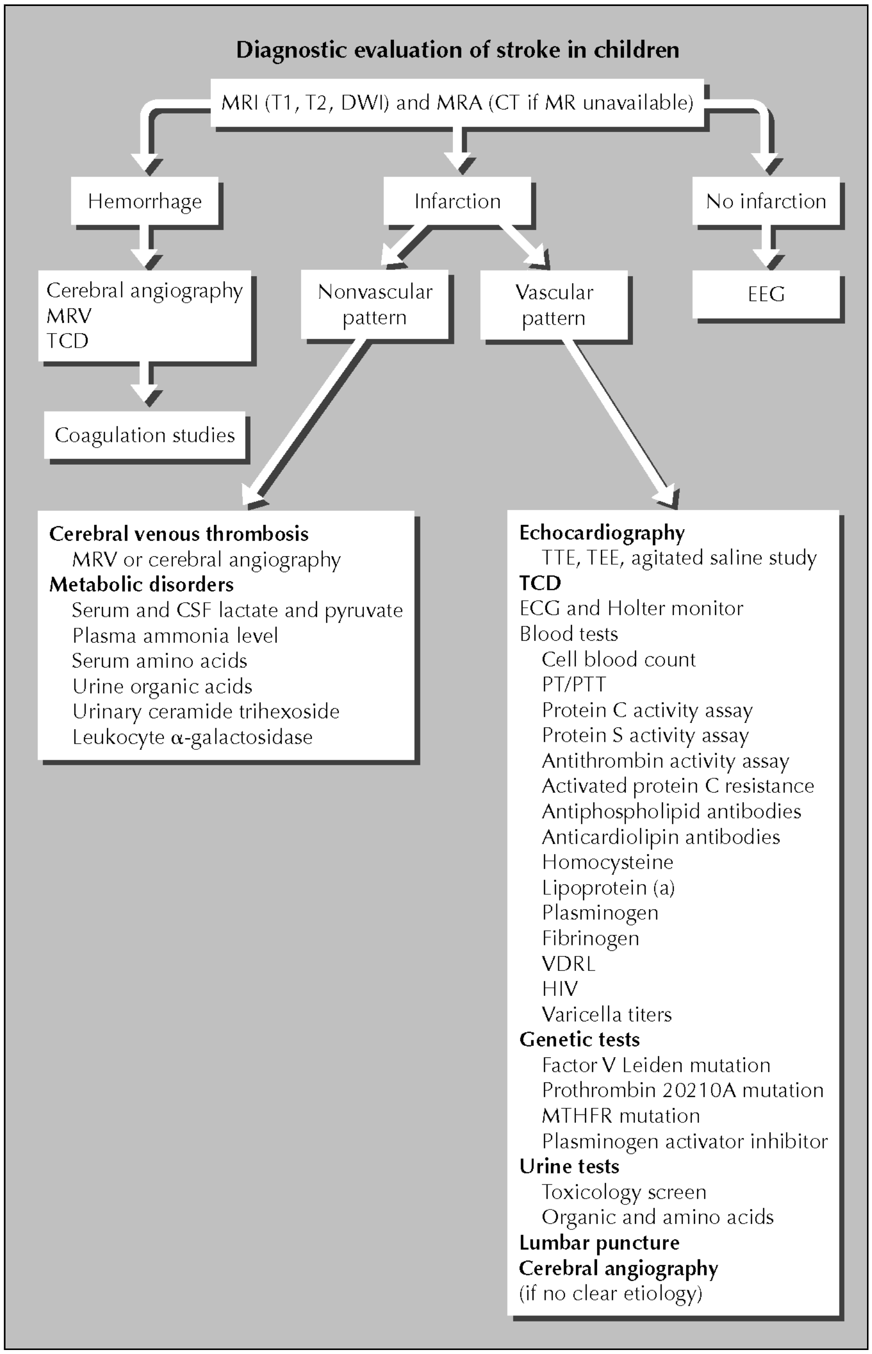

Figure 1. Diagnostic evaluation of stroke in children. (CSF—cerebrospinal fluid; CT–computed tomography; DWI—diffusion-weighted imaging; EEG—electroencephalogram; MRA—magnetic resonance angiography; MRI—magnetic resonance imaging; MRV—magnetic resonance venography; PT—prothrombin time; PTT—partial thromboplastin time; TCD—transcranial Doppler; TEE—transesophageal echocardiography; TTE—transthoracic and transesophageal color-flow Doppler echocardiography.)

study of children undergoing heart surgery with deep hypothermic circulatory arrest, preoperative treatment with allopurinol was shown to reduce seizures, coma, and death [51].

Secondary prevention

There have been no secondary prevention trials for AIS in children. Based on adult studies and the underlying pathophysiology of the stroke, antiplatelet and antithrombotic agents are sometimes prescribed in children with AIS. Although there is limited evidence to support its use in children, anticoagulation may be indicated in AIS associated with extracranial arterial dissection, prothrombotic disorders, cardiac disease, severe intracranial stenosis, and recurrent stroke while on antiplatelet therapy. Most experts support the use of anticoagulation for 3 to 6 months, with a follow-up evaluation at this time to determine the need for long-term anticoagulation or a switch to antiplatelet therapy.

In children with moyamoya-related AIS, surgical therapy may be beneficial, although there are no randomized trials to support surgery [52]. Treatment with antiplatelet agents should also be considered, as many children will have an associated prothrombotic disorder. Chronic exchange transfusion or hydroxyurea should be considered in children with sickle cell-related AIS [53,54]. B-vitamin and folate supplementation has been recommended for children with the MTHFR mutation [55].

Outcome and recurrence

The outcome of children after stroke varies among studies due to differences in the duration of follow-up, functional measures, stroke type, and population studied. Combined data from several selected studies of AIS in children over the past 25 years (n=1197) revealed that on average, 35% of children were neurologically normal, 55% developed cognitive or motor problems, and 10% died by the outcome evaluation period. In addition to motor and cognitive problems, children with AIS are at risk for developing chronic seizures and psychiatric disorders.

Factors associated with an abnormal outcome (cognitive, motor, or death) in children with AIS include clinical presentation, stroke subtype, underlying cause, and size of infarct. Children that present with an altered level of consciousness and/or seizures have a higher risk of death and an abnormal outcome. Children with hemorrhagic stroke have a higher mortality rate as compared with AIS and cerebral venous thrombosis. Children with stroke of unknown etiology tend to have a better prognosis as compared with AIS due to other causes. Children with complete MCA strokes and infarct volumes greater than 10% of intracranial volume have a worse outcome than those with lesions in other vascular territories and smaller infarct volumes [56].

Up to one half of children with AIS will develop recurrent seizures, and almost two thirds will develop a psychiatric disorder. A large series of children with AIS revealed that 29% developed recurrent seizures after stroke [57]. Recurrent seizures are more common among children with cortically based strokes and those who present with seizures more than 2 weeks after stroke. A cross-sectional study of 29 children with stroke (21 with AIS, eight with hemorrhagic stroke) identified a psychiatric disorder in 59% of cases. The most common psychiatric disorders included attention-deficit hyperactivity disorder, personality change disorder, and anxiety disorders. A family history of psychiatric disease and neurologic severity were independent predictors of post-stroke psychiatric disorders [58].

The case fatality rate for AIS is reported as high as 21% [59]. The mortality rate due to stroke in children aged 1 to 15 years was 0.6 per 100,000 children in the United States in 2001 [60]. The mortality rate in children due to AIS is higher in male patients than female patients and in blacks compared with whites [61].

The recurrence rate of stroke in children ranges from 6% to 30% [9,62,63], and most recurrences develop in the first 6 months [12••]. A study of combined data from Germany, Canada, and the United Kingdom of 565 patients with AIS revealed a recurrence rate of 10% after several years of follow-up [64]. The recurrence rate of AIS is highest among children with recurrent TIA, underlying vascular disorders (stenosis, moyamoya, vasculitis, sickle cell disease, arterial dissection, and fibromuscular dysplasia), and metabolic and coagulation abnormalities (MTHFR homozygosity, elevated homocysteine, elevated anticardiolipin antibodies, elevated lipoprotein (a), and protein C deficiency). The presence of multiple risk factors can increase the risk of recurrence several-fold. Despite antithrombotic therapy, 10% of children with AIS will develop a recurrent stroke [65••].

Hemorrhagic Stroke

Epidemiology

Hemorrhagic stroke (HS) is defined as an acute focal neurologic deficit lasting more than 24 hours with neuroimaging evidence of intracranial hemorrhage not associated with ischemic infarction. Traumatic intracranial hemorrhage and hemorrhagic conversion of ischemic stroke are typically excluded from studies of HS in children. The epidemiology of HS in children is based primarily on small case series and case reports. The incidence of HS in children is estimated at 1.5 to 5.1 per 100,000 children per year (Table 1). Several population-based studies of stroke in children, based on less than 40 cases each, reported HS to be more common than AIS in children. More recent estimates from hospital discharges in California and the entire United States revealed hospitalization rates of HS at 1.5 to 6.4 per 100,000 children, rates that are less than AIS.

Most studies of HS have shown a slight male predominance, with a median age at diagnosis around 7 to 8 years of age. Similar to childhood AIS, HS is more common in male children than female children, and more common in blacks than whites [7•,8]. The clinical presentation of HS is related to the location and size of hemorrhage. The most common symptoms include headache, vomiting, decreased level of consciousness, focal neurologic deficits, and seizures.

The majority of cases of HS in children are intraparenchymal, but the intraventricular, subdural, and subarachnoid space may also be involved. Most HS in children are supratentorial, and the basal ganglia are rarely involved. Three large series of children with HS revealed that over 80% of the hemorrhages were in the cortical region and less than 10% involved the basal ganglia [5,66,67].

Risk factors

Several risk factors for HS have been identified in children, including vascular malformations, blood disorders, and malignancy.

Vascular malformations, including arteriovenous malformations (AVMs), aneurysms, and cavernous malformations, are the most common risk factor for HS in children. Vascular malformations have been identified in 20% to 85% of children with HS in case series. AVMs account for the majority of vascular malformations in children with HS. The development of an AVM is due to failure in the formation of the capillary bed between primitive arteries and veins in the brain. The incidence of AVM in children is estimated at one to three per 100,000, and approximately 10% to 20% of all AVMs will become symptomatic during this period. The average probability of a first hemorrhage is 2% to 4% per year, with a recurrence risk as high as 25% by 5 years of age [68].

Around 1% to 2% of aneurysms will become symptomatic during childhood. Aneurysms in children are typically associated with other vascular lesions or chronic disorders. Cavernous malformations can also lead to HS in children, and one third are familial.

Blood disorders, including thrombocytopenia, leukemia, SCD, and coagulopathies, have been identified in 10% to 30% of children with HS in reported series. Acquired thrombocytopenia and coagulopathies were the most common blood risk factors in a recent series of 68 children with HS [69].

Intracranial tumors have been identified in 2% to 25% of children with HS in reported case series. HS is occasionally the presenting feature of malignancy in children. The intracranial neoplasms that most commonly present with HS in children include medulloblastomas and primitive neuroectodermal tumors [11].

Evaluation

The evaluation of HS in children should determine the underlying etiology, as many of the causes are treatable. The history should include questions regarding headache, blood disorders, and drug ingestion. A careful family and birth history should also be taken, with special attention to neurologic disease, premature vascular disease, hematologic disease, and a history of brain abscess and vascular skin lesions.

Neuroimaging studies for HS include CT, MRI/MRA, and conventional angiography. CT is the diagnostic test of choice in the initial evaluation. Children with unexplained hemorrhage should have a four-vessel angiogram. The optimal time for angiography is unclear, and the test may need to be repeated; some children may have a normal angiogram in the acute period despite an underlying cause.

Treatment

The treatment for HS in children depends on the underlying etiology and the condition of the child. The proper characterization of the cause is essential to determine the best therapy. Guidelines for the treatment of spontaneous intracerebral hemorrhage in adults should be considered in children [70]. In general, the acute management of children with HS should include aggressive treatment of blood pressure, infection, fever, seizures, and intracranial pressure. There have been no randomized, clinical trials in children to determine which treatments improve long-term outcome. Although surgical removal of intracranial hematoma is controversial in adults, surgical removal is recommended in children with moderate or larger lobar hemorrhages who are clinically worsening [70]. A recent study of 34 children with HS revealed that 29% of children received hematoma evacuation, 17% required a ventriculoperitoneal shunt, and 32% received no intervention [66]. Of the children that received hematoma evacuation (n=10), four had a favorable outcome or mild deficits, and the remaining developed severe deficits or died [66]. The treatment for vascular malformations includes surgery, endovascular embolization, and radiosurgery.

Outcome

The outcome of children after HS has varied among studies due to differences in duration of follow-up, outcome measures, and population studied. Combined data from several selected studies of HS in children over the past 25 years (n=418) revealed that 38% of children were neurologically normal, 41% had cognitive or motor abnormalities, and 20% died by the outcome evaluation period.

Cerebral Venous Thrombosis

Epidemiology

Cerebral venous thrombosis (CVT) is defined as an acute onset of systemic or focal neurologic symptoms consistent with cerebral venous thrombosis and neuroimaging evidence of thrombosis within cerebral veins or venous sinuses. CVT produces an obstruction of venous drainage that can lead to increased venous pressure, increased intracranial pressure, cerebral edema, hemorrhage, and venous infarction [71]. The epidemiology of CVT has been assessed with limited evidence from selected case series and case reports. The incidence of CVT in children is estimated at 0.4 to 0.6 per 100,000 children per year and is highest in the 1st year of life [72••,73]. Data from a large German series revealed that CVT is more common among male patients and occurs at a median age of 6 years [73]. There are no data regarding ethnic differences for CVT in children. The clinical presentation of CVT is related to the course and location of thrombus formation, underlying anatomy of the sinuses, and age of the patient [74]. The presentation in children is often subtle, but the most common symptoms include headache, decreased level of consciousness, seizures, and hemiparesis. The majority of thromboses are located within the lateral and superior sagittal sinus, and up to half of cases involve multiple sinuses [72••].

Risk factors

A number of risk factors are linked to the development of CVT, including prothrombotic disorders, connective tissue disorders, dehydration, head and neck infections, hematologic disorders, procoagulant drugs, and cancer. In the two largest studies of CVT in children, prothrombotic abnormalities were present in at least half of the cases and many had multiple risk factors [62,73]. The combination of a prothrombotic risk factor and an underlying clinical condition known to predispose to thrombosis substantially increases the risk of CVT in children [73].

Evaluation

The diagnosis of CVT is often challenging due to the variability of clinical and radiologic findings. Neuroimaging is essential to detect the location, age, and extent of thrombus and underlying abnormalities, and to provide information regarding treatment and prognosis [75]. Diagnostic imaging procedures for CVT include MRI, MR venography (MRV), digital subtraction angiography, CT, and ultrasonography. Conventional T1 and T2 weighted MRI with MRV is the current recommendation for the diagnosis of CVT in children. DWI and T2*/susceptibility-weighted imaging sequences have been useful in the detection of CVT in adults but have not been used extensively in childhood CVT [75,76]. If MRI is unavailable or not possible for a sick child, multislice CT with CT venography should be considered and is comparable with gadolinium enhanced MRV. Ultrasonography is typically employed in neonates and is most useful for detecting decreased or absent flow in the superior sagittal sinus [71].

Treatment

There are no established guidelines for the treatment of CVT in children. Infection, fever, dehydration, and seizures, along with other underlying risk factors, should be treated aggressively. Anticoagulation is recommended for CVT in adults and may be indicated for use in children [77]. In two recent series, the majority of children with CVT were treated with anticoagulant regimens of varying duration, and none developed bleeding complications [62]. Thrombolytic therapy has been recommended for children with CVT who progressively worsen despite adequate anticoagulation [71]. However, at present, there is insufficient evidence to recommend thrombolytic therapy as first-line treatment in adults or children [78].

Outcome

The outcome of children after CVT has varied among case series due to differences in treatment, outcome measures, and duration of follow-up.

Neuroimaging studies have found that over time there is a complete resolution of the affected vessel in 40% to 60% of cases, whereas 30% to 40% will have partial resolution, and 13% to 16% will have no improvement. Data from the CPISR, which included 82 non-neonates with CVT, revealed that 51% were normal, 39% had neurologic deficits, 10% died, and 17% suffered a recurrence of CVT by the outcome evaluation period.

Conclusions

Cerebrovascular disorders are an important cause of mortality and chronic morbidity in children, and are an emerging area for clinical research. The clinical presentation of stroke varies according to age and location, and may be subtle. Ischemic stroke is probably more common than hemorrhagic stroke in children, but this has not been confirmed in all studies. Several risk factors for stroke in children have been reported, but frequently no cause is identified. Recent improvements in neuroimaging have contributed to a better understanding of the underlying mechanisms of stroke in children, but much work remains. Over half of children with stroke will develop lifelong cognitive or motor disability and up to one third will have a recurrent stroke. International collaborations are currently underway to provide more information on risk factors and outcome, to develop a consensus on evaluation, and to establish a network for future prevention and treatment studies.

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References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Schoenberg BS, Mellinger JF, Schoenberg DG: **Cerebrovascular disease in infants and children: a study of incidence, clinical features, and survival.** *Neurology* 1978, **28**:763–768.
2. Nelson KB, Lynch JK. **Stroke in newborn infants.** *Lancet Neurology* 2004, In press.
3. Broderick J, Talbot GT, Prenger E, *et al.*: **Stroke in children within a major metropolitan area: the surprising importance of intracerebral hemorrhage.** *J Child Neurol* 1993, **8**:250–255.
4. Giroud M, Lemesle M, Gouyon JB, *et al.*: **Cerebrovascular disease in children under 16 years of age in the city of Dijon, France: a study of incidence and clinical features from 1985 to 1993.** *J Clin Epidemiol* 1995, **48**:1343–1348.
5. Earley CJ, Kittner SJ, Feeser BR, *et al.*: **Stroke in children and sickle-cell disease: Baltimore-Washington Cooperative Young Stroke Study.** *Neurology* 1998, **51**:169–176.
6. DeVeber G, and the Canadian Ischemic Stroke Study Group: **Canadian Pediatric Stroke Registry: analysis of children with arterial ischemic stroke [abstract].** *Ann Neurol* 2000, **48**:526.
7.• Fullerton HJ, Wu YW, Zhao S, Johnston SC: **Risk of stroke in children: ethnic and gender disparities.** *Neurology* 2003, **61**:189–194.

This study of a hospital discharge database provided information on all first admissions of children aged 1 month to 19 years in the state of California from 1991 to 2000 (n=2278). The study found that rates of hospitalization for stroke are higher among male children than female children, blacks than whites, and for ischemic compared with hemorrhagic stroke patients.

8. Lynch JK: **The hospitalization of childhood stroke in the United States, 1979–2000 [abstract].** *Stroke* 2003, 34:287.
9. Lanthier S, Carmant L, David M, *et al.*: **Stroke in children: the coexistence of multiple risk factors predicts poor outcome.** *Neurology* 2000, **54**:371–378.

10.•• Ganesan V, Prengler M, McShane MA, *et al.*: **Investigation of risk factors in children with arterial ischemic stroke.** *Ann Neurol* 2003, **53**:167–173.

This was a large cohort study of children with stroke from a single pediatric center in the United Kingdom over a 22-year period. The children in this study were evaluated for a number of risk factors for ischemic stroke. The study found that cerebral arterial abnormalities, varicella infection, anemia, and recent trauma and infection are common among children with arterial ischemic stroke.

11. Roach ES, Riela AR: *Pediatric Cerebrovascular Disorders*, edn 2. Armonk, NY: Futura Publishing Company; 1995.
12.•• Strater R, Becker S, von Eckardstein A, *et al.*: **Prospective assessment of risk factors for recurrent stroke during childhood—a 5-year follow-up study.** *Lancet* 2002, **360**:1540–1545.

This large German cohort study of children with arterial ischemic stroke (n=301) evaluated the risk of recurrent stroke over a median period of 7 years. The study found that the risk of recurrent stroke was 7% and was increased in children with elevated lipoprotein(a), protein C deficiency, and children with stroke of a vascular origin.

13. Kirkham FJ, Prengler M, Hewes DK, Ganesan V: **Risk factors for arterial ischemic stroke in children.** *J Child Neurol* 2000, **15**:299–307.
14. Lanska MJ, Lanska DJ, Horwitz SJ, Aram DM: **Presentation, clinical course, and outcome of childhood stroke.** *Pediatr Neurol* 1991, **7**:333–341.
15. Kumar K: **Neurological complications of congenital heart disease.** *Indian J Pediatr* 2000, **67**:S15–S19.
16. Strauss A, Toth B, Schwab B, *et al.*: **Prenatal diagnosis of congenital heart disease and neonatal outcome--a six years experience.** *Eur J Med Res* 2001, **6**:66–70.
17. Mahle WT, Tavani F, Zimmerman RA, *et al.*: **An MRI study of neurological injury before and after congenital heart surgery.** *Circulation* 2002, **106**:I109–I114.
18. Miller G, Mamourian AC, Tesman JR, *et al.*: **Long-term MRI changes in brain after pediatric open heart surgery.** *J Child Neurol* 1994, **9**:390–397.
19.• Pegelow CH, Macklin EA, Moser FG, *et al.*: **Longitudinal changes in brain magnetic resonance imaging findings in children with sickle cell disease.** *Blood* 2002, **99**:3014–3018.

This cohort study (n=415) of children with SCD recruited from 1978 to 1988 evaluated the prevalence, location, and recurrence of silent brain abnormalities. The study found a 22% rate of MRI abnormalities among children with SCD. The abnormalities were predominantly in the frontal and parietal region.

20. Scothorn DJ, Price C, Schwartz D, *et al.*: **Risk of recurrent stroke in children with sickle cell disease receiving blood transfusion therapy for at least five years after initial stroke.** *J Pediatr* 2002, **140**:348–354.
21. Powars D, Wilson B, Imbus C, *et al.*: **The natural history of stroke in sickle cell disease.** *Am J Med* 1978, **65**:461–471.
22. Steen RG, Emudianughe T, Hankins GM, *et al.*: **Brain imaging findings in pediatric patients with sickle cell disease.** *Radiology* 2003, **228**:216–225.
23. Adams RJ: **Stroke prevention and treatment in sickle cell disease.** *Arch Neurol* 2001, **58**:565–568.
24. Akar N, Akar E, Deda G, *et al.*: **Factor V1691 G-A, prothrombin 20210 G-A, and methylenetetrahydrofolate reductase 677 C-T variants in Turkish children with cerebral infarct.** *J Child Neurol* 1999, **14**:749–751.
25. Kenet G, Sadetzki S, Murad H, *et al.*: **Factor V Leiden and antiphospholipid antibodies are significant risk factors for ischemic stroke in children.** *Stroke* 2000, **31**:1283–1288.
26. Nowak-Gottl U, Strater R, Heinecke A, *et al.*: **Lipoprotein (a) and genetic polymorphisms of clotting factor V, prothrombin, and methylenetetrahydrofolate reductase are risk factors of spontaneous ischemic stroke in childhood.** *Blood* 1999, **94**:3678–3682.
27. Hagstrom JN, Walter J, Bluebond-Langner R, *et al.*: **Prevalence of the factor V leiden mutation in children and neonates with thromboembolic disease.** *J Pediatr* 1998, **133**:777–781.
28. Bonduel M, Sciuccati G, Hepner M, *et al.*: **Factor V Leiden and prothrombin gene G20210A mutation in children with cerebral thromboembolism.** *Am J Hematol* 2003, **73**:81–86.
29. McColl MD, Chalmers EA, Thomas A, *et al.*: **Factor V Leiden, prothrombin 20210G-->A and the MTHFR C677T mutations in childhood stroke.** *Thromb Haemost* 1999, **81**:690–694.
30. Zenz W, Bodo Z, Plotho J, *et al.*: **Factor V Leiden and prothrombin gene G 20210 A variant in children with ischemic stroke.** *Thromb Haemost* 1998, **80**:763–766.
31. Strater R, Vielhaber H, Kassenbohmer R, *et al.*: **Genetic risk factors of thrombophilia in ischaemic childhood stroke of cardiac origin. A prospective ESPED survey.** *Eur J Pediatr* 1999, **158(suppl 3)**:S122–S125.
32.• Fullerton HJ, Johnston SC, Smith WS: **Arterial dissection and stroke in children.** *Neurology* 2001, **57**:1155–1160.

This literature review of case series published from 1966 to 2000 described the clinical characteristics of children with arterial dissection and stroke. The review reported that arterial dissection-related stroke is most often intracranial in location, associated with trauma, and more common in males.

33. Lindsberg PJ, Grau AJ: **Inflammation and infections as risk factors for ischemic stroke.** *Stroke* 2003, **34**:2518–2532.
34. Snyder RD, Stovring J, Cushing AH, *et al.*: **Cerebral infarction in childhood bacterial meningitis.** *J Neurol Neurosurg Psychiatry* 1981, **44**:581–585.
35. Sebire G, Meyer L, Chabrier S: **Varicella as a risk factor for cerebral infarction in childhood: a case-control study.** *Ann Neurol* 1999, **45**:679–680.
36. Ichiyama T, Houdou S, Kisa T, *et al.*: **Varicella with delayed hemiplegia.** *Pediatr Neurol* 1990, **6**:279–281.
37. Askalan R, Laughlin S, Mayank S, *et al.*: **Chickenpox and stroke in childhood: a study of frequency and causation.** *Stroke* 2001, **32**:1257–1262.
38. Kirkham FJ: **Stroke in childhood.** *Arch Dis Child* 1999, **81**:85–89.
39. Riela AR, Roach ES: **Etiology of stroke in children.** *J Child Neurol* 1993, **8**:201–220.
40. Zimmerman RA, Haselgrove JC, Wang Z, *et al.*: **Advances in pediatric neuroimaging.** *Brain Dev* 1998, **20**:275–289.
41. Koelfen W, Wentz U, Freund M, Schultze C: **Magnetic resonance angiography in 140 neuropediatric patients.** *Pediatr Neurol* 1995, **12**:31–38.
42. Adams RJ, McKie VC, Carl EM, *et al.*: **Long-term stroke risk in children with sickle cell disease screened with transcranial Doppler.** *Ann Neurol* 1997, **42**:699–704.
43. Inamasu J, Ichikizaki K, Matsumoto S, *et al.*: **Mild hypothermia for hemispheric cerebral infarction after evacuation of an acute subdural hematoma in an infant.** *Child Nerv Syst* 2002, **18**:175–178.
44. Thirumalai SS, Shubin RA: **Successful treatment for stroke in a child using recombinant tissue plasminogen activator.** *J Child Neurol* 2000, **15**:558.
45. Noser EA, Felberg RA, Alexandrov AV: **Thrombolytic therapy in an adolescent ischemic stroke.** *J Child Neurol* 2001, **16**:286–288.
46. Golomb MR, Rafay M, Armstrong D, *et al.*: **Intra-arterial tissue plasminogen activator for thrombosis complicating cerebral angiography in a 17-year-old girl.** *J Child Neurol* 2003, **18**:420–423.
47. Younkin DP: **Diagnosis and treatment of ischemic pediatric stroke.** *Curr Neurol Neurosci Rep* 2002, **2**:18–24.
48. Lee MC, Frank JI, Kahana M, *et al.*: **Decompressive hemicraniectomy in a 6-year-old male after unilateral hemispheric stroke. Case report and review.** *Pediatr Neurosurg* 2003, **38**:181–185.
49. Andrew M, DeVeber G: *Pediatric Thromboembolism and Stroke Protocols*, edn 2. Hamilton, Ontario: BC Decker; 1999.
50. Adams RJ, McKie VC, Hsu L, *et al.*: **Prevention of a first stroke by transfusions in children with sickle cell anemia and abnormal results on transcranial Doppler ultrasonography.** *N Engl J Med* 1998, **339**:5–11.

51. Clancy RR, McGaurn SA, Goin JE, *et al.*: **Allopurinol neurocardiac protection trial in infants undergoing heart surgery using deep hypothermic circulatory arrest.** *Pediatrics* 2001, **108:**61–70.
52. Houkin K, Kuroda S, Nakayama N: **Cerebral revascularization for moyamoya disease in children.** *Neurosurg Clin North Am* 2001, **12:**575–84.
53. Wang WC, Kovnar EH, Tonkin IL, *et al.*: **High risk of recurrent stroke after discontinuance of five to twelve years of transfusion therapy in patients with sickle cell disease.** *J Pediatr* 1991, **118:**377–382.
54. Sumoza A, de Bisotti R, Sumoza D, Fairbanks V: **Hydroxyurea (HU) for prevention of recurrent stroke in sickle cell anemia (SCA).** *Am J Hematol* 2002, **71:**161–165.
55. Cardo E, Monros E, Colome C, *et al.*: **Children with stroke: polymorphism of the MTHFR gene, mild hyperhomocysteinemia, and vitamin status.** *J Child Neurol* 2000, **15:**295–298.
56. Ganesan V, Ng V, Chong WK, *et al.*: **Lesion volume, lesion location, and outcome after middle cerebral artery territory stroke.** *Arch Dis Child* 1999, **81:**295–300.
57. Yang JS, Park YD, Hartlage PL: **Seizures associated with stroke in childhood.** *Pediatr Neurol* 1995, **12:**136–138.
58. Max JE, Mathews K, Lansing AE, *et al.*: **Psychiatric disorders after childhood stroke.** *J Am Acad Child Adolesc Psychiatry* 2002, **41:**555–562.
59. Wang LH, Young C, Lin HC, *et al.*: **Strokes in children: a medical center-based study.** *Zhonghua Min Guo Xiao Er Ke Yi Xue Hui Za Zhi* 1998, **39:**242–246.
60. Arias E, Anderson RN, Kung HC, *et al.*: **Deaths: final data for 2001.** *Natl Vital Stat Rep* 2003, **52:**1–115.
61. Fullerton HJ, Chetkovich DM, Wu YW, *et al.*: **Deaths from stroke in US children, 1979 to 1998.** *Neurology* 2002, **59:**34–39.
62. DeVeber G, Monagle P, Chan A, *et al.*: **Prothrombotic disorders in infants and children with cerebral thromboembolism.** *Arch Neurol* 1998, **55:**1539–1543.
63. Chabrier S, Husson B, Lasjaunias P, *et al.*: **Stroke in childhood: outcome and recurrence risk by mechanism in 59 patients.** *J Child Neurol* 2000, **15:**290–294.
64. Kirkham F, DeVeber G, Chan AK, *et al.*: **Recurrent stroke: the role of prothrombotic disorders [abstract].** *Ann Neurol* 2003, **54:**S110.
65.•• Strater R, Kurnik K, Heller C, *et al.*: **Aspirin versus low-dose low-molecular-weight heparin: antithrombotic therapy in pediatric ischemic stroke patients: a prospective follow-up study.** *Stroke* 2001, **32:**2554–2558.

This large, German, multicenter, prospective follow-up study evaluated the risk of recurrent stroke among children with AIS treated with prophylactic acetylsalicylic acid (4 mg/kg/d) or low-dose low molecular weight heparin. This was a nonrandomized study and children were followed-up from 8 to 48 months. The study found that there was no difference in the rates of recurrent stroke among children treated with with acetylsalicylic acid or low molecular weight heparin.

66. Meyer-Heim AD, Boltshauser E: **Spontaneous intracranial haemorrhage in children: aetiology, presentation and outcome.** *Brain Dev* 2003, **25:**416–421.
67. Livingston JH, Brown JK: **Intracerebral haemorrhage after the neonatal period.** *Arch Dis Child* 1986, **61:**538–544.
68. Fults D, Kelly DL: **Natural history of arteriovenous malformations of the brain: a clinical study.** *Neurosurgery* 1984, **15:**658–662.
69. Al Jarallah A, Al Rifai MT, Riela AR, Roach ES: **Nontraumatic brain hemorrhage in children: etiology and presentation.** *J Child Neurol* 2000, **15:**284–289.
70. Broderick JP, Adams HP Jr, Barsan W, *et al.*: **Guidelines for the management of spontaneous intracerebral hemorrhage: a statement for healthcare professionals from a special writing group of the Stroke Council, American Heart Association.** *Stroke* 1999, **30:**905–915.
71. Shroff M, deVeber G: **Sinovenous thrombosis in children.** *Neuroimaging Clin North Am* 2003, **13:**115–138.
72.•• DeVeber G, Andrew M: **Cerebral sinovenous thrombosis in children.** *N Engl J Med* 2001, **345:**417–423.

This large, Canadian, multicenter, prospective cohort study described the clinical features, risk factors, treatment, and outcome of children with CVT. The study found that CVT is most common in neonates and is associated with a systemic illness. Most children with CVT are treated with antithrombotic therapy and half of them developed neurologic impairment or died.

73. Heller C, Heinecke A, Junker R, *et al.*: **Cerebral venous thrombosis in children: a multifactorial origin.** *Circulation* 2003, **108:**1362–1367.
74. Huisman TA, Holzmann D, Martin E, Willi UV: **Cerebral venous thrombosis in childhood.** *Eur Radiol* 2001, **11:**1760–1765.
75. Lovblad KO, Bassetti C, Schneider J, *et al.*: **Diffusion-weighted MR in cerebral venous thrombosis.** *Cerebrovasc Dis* 2001, **11:**169–176.
76. Selim M, Fink J, Linfante I, *et al.*: **Diagnosis of cerebral venous thrombosis with echo-planar T2*-weighted magnetic resonance imaging.** *Arch Neurol* 2002, **59:**1021–1026.
77. deVeber G, Chan A, Monagle P, *et al.*: **Anticoagulation therapy in pediatric patients with sinovenous thrombosis: a cohort study.** *Neurology* 1998, **51:**1622–1628.
78. Canhao P, Falcao F, Ferro JM: **Thrombolytics for cerebral sinus thrombosis: a systematic review.** *Cerebrovasc Dis* 2003, **15:**159–166.