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ADVANCES IN PEDIATRICS

Pediatric Stroke: Past, Present and Future

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The past two decades have seen a renewed interest and focus in pediatric stroke. Although pediatric stroke in its various guises (acute infantile hemiplegia, hemiplegic cerebral palsy, and apoplexy) was described as early as the 15th century, it is only more recently that a systematic effort has been made to better define the epidemiology and etiology of pediatric stroke, classify pediatric stroke types, and move toward randomized controlled therapeutic and prevention trials. Although relatively uncommon compared with many other childhood diseases, pediatric stroke carries with it a disproportionately high morbidity and long-term personal and societal cost. Improved and safer noninvasive imaging modalities, and an increasing awareness of pediatric stroke amongst physicians, have allowed for better ascertainment data, which is reflected in the increased incidence in recent years. With more children surviving once-fatal and incurable disease (eg, congenital heart disease [CHD] and malignancies), the incidence of pediatric stroke is likely to increase as neurologic morbidity, in particular stroke, is a well-known sequela of many of these disorders.

This review focuses on arterial ischemic stroke (AIS) in childhood and the perinatal period and does not address other stroke mechanisms such as primary hemorrhagic stroke or sinus venous thrombosis. A brief historical review describes the basis of current knowledge on the incidence, epidemiology, etiology, outcome, and recurrence risk in pediatric stroke, and recent developments in treatment and research are highlighted.

HISTORICAL CONTEXT

The concept of pediatric AIS is defined as any clinical neurologic presentation, including seizure, associated with radiographic evidence of ischemia, infarction, or encephalomalacia in an arterial vascular distribution corresponding to the neurologic deficit or presentation. Acute infarction in confirmed by a hypodensity on computerized tomography (CT) scan in a vascular distribution, or by a diffusion-weighted image abnormality on magnetic resonance imaging

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(MRI) study. One exception to this definition is the nonvascular distribution of stroke seen in metabolic disorders such as mitochondrial encephalopathy, lactic acidosis, and stroke (MELAS).

Pediatric stroke was reported in the earliest medical literature as part of case descriptions or clinical series under synonyms such as "cerebral apoplexy," "acute infantile hemiplegia," "acute hemiplegia of childhood," "congenital hemiplegia," and "hemiplegic cerebral palsy." In the absence of imaging studies, and little in the way of pathology, the common denominator was simply the appearance of a hemiplegia in a child. Developmental malformations, tumors, postseizure edema or paralysis, and infectious processes such as cerebral abscesses were all undoubtedly included in this group. With the use of cerebral angiography in children in the late 1950s and early 1960s, radiographic documentation of intracranial vasculopathies was confirmed as the mechanical or etiologic cause of acute hemiplegia in selective children, although the pathophysiology remained elusive [1,2]. CT scans and subsequent MRI and magnetic resonance angiography (MRA) allowed a noninvasive means to image the brain and clarify the nature of the cause of the hemiplegia, although not necessarily the etiology and pathophysiology.

Although the description of stroke has its origins in antiquity in the discussions of Hippocrates and Galen, one of the first documented cases of pediatric stroke in the medical literature may be that of Thomas Willis (1621–1675) in the 17th century [3]. He described a case of neonatal seizures resulting in death within the first month of life of a newborn who was the fourth child of a mother who had already lost 3 previous children in the neonatal period under similar circumstances. At autopsy, Willis described hemorrhage in the brain, but different translations of his original work have raised uncertainty as to the exact site. Although some authors have suggested this was a case of childhood stroke [4], others have argued this case was one of infanticide secondary to a whiplash or shaking injury [3]. Irrespective, a decade or so later, in 1672, Willis did describe a case of suspected venous infarction in a child secondary to presumed septic thrombosis of a cerebral sinus [3].

The 17th century was dominated by the neuroanatomists; however, clinical neurology remained limited by a lack of understanding of the functional anatomy of the brain. Although Willis was the first to realize the clinical importance of the circle or arteries at the base of the brain, subsequently named for him, Gabriel Fallopius (1523–1562) was the first to describe its existence in 1561, and illustrations appeared in the anatomic works of Guilio Casserio (1545–1605) in 1632 and Johann Vesling (1595–1598) in 1647. The presence of the motor cortex was first suggested around this time by Robert Boyle (1627–1691), who described a case of reversible monoplegia ("dead palsy of the arm") following the elevation of a depressed skull fracture in a patient. Advances in understanding of stroke during the 18th century included Giovanni Battista Morgagni's (1682–1771) assertion that lesions occur in the brain opposite the site of hemiplegia (confirmed by anatomically accurate postmortem findings), which was correlated by the works of Emanuel Swedenborg (1688–1772), who described the correct location

and regional representation of the motor cortex in the brain. Experimental neurophysiology was introduced by François Pourfour de Petit (1664–1741), whose work in dogs confirmed that the removal of part of the brain resulted in a paralysis on the opposite side of the body. He is also credited with describing the decussation of the pyramidal tracts. The neuropathological basis for apoplexy was also first documented during this era by Giovanni Battista Morgagni, who provided pathologic evidence that the lesion in apoplexy was on the opposite side of the hemiplegia, and Matthew Baillie (1761–1823), who first described cerebral hemorrhage as the consequence of disease of the blood vessels of the brain (but did not recognize the contribution of vascular disease to ischemia of the brain) [5].

It was only during the 19th century that neuropathology started providing some understanding of disease process and with it functional neuroanatomy. The etiologic basis of stroke, which up until that time mostly consisted of hemiplegia on the basis of apoplexy from intracerebral hemorrhage, began to be better delineated by Moritz Heinrich Romberg (1795–1873), who brought structure to the field of neurology by classifying diseases into "neuroses of sensibility" and "neuroses of motility," Jean-Martin Charcot (1825–1893), who clinically demonstrated cerebral localization, and whose work in "cerebral hemiplegia" included defining the blood supply of the brain (especially the internal capsule and basal ganglia), and John Hughlings Jackson (1835–1911), who introduced the concept of paralysis generally resulting from vascular disturbances in the territory of the middle cerebral artery and who studied cerebrovascular disease [5].

That ischemia rather than "vascular congestion" was the cause of "anemia" of the brain and apoplexy was first suggested by John Cheyne (1777–1836) in 1812 after postmortem studies in apoplexy survivors showed cystic cavities or encephalomalacia. Almost 50 years before, Gerard van Swieten (1700–1772) had suggested emboli as a cause of apoplexy in a case of "polyps" in the heart travelling to the arteries in the brain. Rudolf Virchow (1821–1902) demonstrated the role of vascular occlusion producing cerebral infarction in 1856 [5].

Pediatric stroke, in particular, owes much of its origins to the seminal works of Osler [6], Sachs [7], Freud [8], Gowers [9], and Taylor [10], who wrote early monographs on cerebral palsy, which included hemiplegic forms of cerebral palsy. In 1884, Strümpell postulated primary encephalitis (polioencephalitis acuta) as the infectious basis for acquired hemiplegic cerebral palsy, believing this was akin to anterior poliomyelitis of the spinal cord, although there was not much anatomic or pathologic evidence to support this. Gowers was one of the first to emphasize cerebral thrombosis as a cause of hemiplegia in children, but believed it was usually caused by small vessel disease (venous occlusion). Osler and Freud also considered thrombosis as a cause of infantile hemiplegia, but stressed the importance of emboli as a cause. Osler, Sachs, and others believed that a few cases of infantile hemiplegia were secondary to convulsions resulting in cerebral hemorrhage. Taylor further emphasized the vascular nature of acquired infantile hemiplegia. In another influential early work, Ford and Schaffer [11] suggested the possibility that embolus and

thrombosis of major arteries result from acute infectious and postinfectious causes in a substantial number of cases of infantile hemiplegia, and that coagulation abnormalities associated with the infectious process may also contribute to the vascular lesions. They also emphasized noninfectious causes apart from cardiac emboli, which they had excluded from their series of nearly 70 cases. They provided a more comprehensive classification as to the etiologic basis of pediatric AIS than had existed, and refuted the position of Strümpell (as did Sachs, Freud, and others) that all cases of acquired infantile hemiplegia were caused by a primary infection of the brain based on a detailed review of the literature. In 1948, Wyllie [12] provided a synopsis of the theories of the pathogenesis of acute infantile hemiplegia based on a review of the literature at that time. Although the first reported cases of surgical intervention for epilepsy in infantile hemiplegia occurred around the turn of the 20th century [7], Krynauw in 1950 presented the first detailed series of hemispherectomy in children for intractable epilepsy [13]. The pathology of the resected specimens in several of his cases detailed infarcts caused by vascular ischemia. Although there have been numerous other contributions to the field of pediatric AIS, the monumental and comprehensive work by Gold and colleagues for the Strokes in Children Study Group in the 1970s needs to be acknowledged [14–17].

EPIDEMIOLOGY

Incidence

The published incidence of pediatric AIS (Table 1) has varied from as low as 0.2/100,000 children/y [18] to as high as 7.9/100,000 children/y [19]. The first North American population-based study of pediatric stroke from 1965 to 1974 found an incidence rate of 0.63/100,000 children/y. Many of the earlier incidence studies were hampered by selection bias and poor imaging modalities in determining stroke. Perhaps the best data, and largest cohort of patients, comes from the prospective Canadian Ischemic Stroke Registry, which showed an incidence of AIS in childhood to be 3.3/100,000 children/y. The highest incidence occurs in the neonatal period with estimates as high as 20–30/100,000 newborns/y. This is equivalent to approximately 1/4000–5000 live births/y [20–23], although a population-based epidemiologic study from Switzerland using MRI confirmation of neonatal AIS showed a higher incidence of 1:2300 live births [24]. Perinatal ischemic stroke (occurring between 20 weeks' gestation and 28 days' postnatal life) comprises approximately 25% to 30% of all AISs in children [25,26] and occurs primarily in term infants [21].

Demographics

AIS occurs more commonly amongst males than females in neonatal and childhood forms [26–30], and has a higher incidence amongst blacks [27]. The reason for the latter remains unclear and cannot be attributed to sickle cell disease (SCD) or trauma alone [27]. Ischemic stroke is more common than hemorrhagic stroke. The mean age of childhood presentation is 4 to 6 years

Table 1
Incidence of arterial ischemic stroke in children

Study	Year	AIS (/100 000/y)	Total (ischemic plus hemorrhagic stroke) (/100,000/y)
United States (Rochester) [4]	1965–1974	0.63	2.52
Sweden (Linköping) [171]	1970–1979		2.1
Japan (Tohoku) [18]	1974–1989	0.2	–
France (Dijon) [19]	1985–1993	7.9	13
Unites States (Cincinnati) [172]	1988–1989	1.2	2.7
Unites States (California) [27]	1991–2000	1.2	2.3
Canada [87]	1992–1998	3.3	6
Australia (Victoria) [29]	1993–2001	1.8	–
China (Hong Kong) [32]	1998–2001		2.1
Switzerland [30]	2000–2002	2.1	–

of age [25,28–32] although detailed analysis of 1187 cases from the International Pediatric Stroke Study (IPSS) group showed a slightly older age of 6.8 years for boys and 7.4 years for girls [26].

Mortality

Pediatric stroke remains one of the top 10 causes of death in childhood, with a mortality rate of 0.6/100,000 pediatric strokes/y [33]. This rate is significantly higher during the first year of life with a mortality of 5.3/100,000/y [34]. A review of pooled data on 18 AIS studies in the past 30 years showed that approximately 9% of children who suffered from AIS died [35]. Earlier studies suggested mortality was higher in males [27], although the more recent IPSS cohort did not find any gender differences in case fatality [26]. Mortality is also higher in black children [36].

Morbidity

More than half of the survivors of pediatric stroke develop some neurologic or cognitive deficit or impairment, and epilepsy is a sequela in just more than a quarter of these survivors. Data regarding outcome have been impaired by the lack of standardization of deficits and because they are descriptive. Nonetheless, studies have been consistent in showing some form of motor deficit in about two-thirds of childhood stroke survivors (Table 2). Motor outcome appears slightly better following neonatal stroke, with just under half having a residual motor deficit (Table 2). This finding is of significance as the deficit results in a lifetime of disability and impairment, with associated economic costs (such as physical and occupational therapy, orthotics, and orthopedic surgery) [37]. Two-thirds of all neonatal strokes are left hemispheric and most often involve middle cerebral artery (MCA) territory [38,39]. Neuroimaging findings may help to predict motor developmental outcome following neonatal stroke. Studies from the Hammersmith group in London suggest the need for concomitant involvement of cerebral hemisphere, internal capsule

Table 2
Motor outcome for AIS in selective pediatric stroke studies

Study	Years	N	Motor abnormality (%)
Neonatal			
Sran and Baumann [68]	1975–1986	17	24
Fujimoto et al [69]	1980–1989	18	28
Sreenan et al [60]	1983–1997	46	48
Golomb et al [173]	1989–2006	111	68
Mercuri et al [40]	1991–1996	22	27
DeVeber et al [25]	1995–1999	33	64
Lee et al [43]	1997–2002	36	58
Mean			45
Childhood			
Schoenberg et al [4]	1965–1974	38	94
Lanska et al [174]	1976–1988	42	76
De Schryver et al [31]	1976–1995	37	59
Steinlin et al [79]	1985–1999	16	63
Giroud et al [19]	1985–1993	17	65
Salih et al [81]	1992–2003	90	81
Barnes et al [29]	1993–2001	95	42
DeVeber et al [25]	1995–1999	90	67
Brower et al [72]	1996	36	61
Mean			67

and basal ganglia for resultant hemiplegia in neonatal stroke [40]. Others, however, have suggested that stroke size/volume is more strongly predictive of motor outcome [41–43]. More recently, diffusion-weighted (DWI) MRI signal abnormalities of the ipsilateral cerebral peduncle and posterior limb of the internal capsule were strongly correlated with subsequent Wallerian degeneration and resultant hemiplegia [44]. This finding was refined by a study from Canada [45], showing a correlation between increased motor impairment and length ($>$20 mm) and volume ($\geq$0.09%) of descending corticospinal tracts DWI signal abnormality, and percentage of peduncle involvement ($\geq$25%) [45].

Cognitive, behavioral, and emotional deficits also commonly occur in children following stroke. A leftward shift in the mean intelligence quotient (IQ) has been described in some [46] but not all studies [47]. There appears to be a difference between performance and verbal IQ, with children performing better in the latter following stroke [46,48]. This difference appears to be unrelated to the side of the infarct [49–52] and appears independent of the motor disability itself [50]. However, cognitive outcome was better following left-sided stroke than right-sided stroke [48,53]. Expressive language is more severely affected than receptive language [25,46]. Less-favorable cognitive outcome was associated with stroke onset in children younger than 5 years [46,53–55] and older than 10 years [53]. There was no gender difference [51]. Despite the relevant preservation of global IQ, specific learning disabilities are not uncommon [54]. In a study of 39 pre- or perinatal focal infarcts (hemorrhagic

and ischemic), no behavioral or emotional difficulties relative to matched control patients were found. This finding was true irrespective of hemisphere involved, involvement of frontal lobes, or the presence or absence of seizures [56], in contradistinction to earlier studies that suggested that behavioral, emotional, and social skills are impaired following neonatal stroke [46,50]. Social and attention difficulties were seen as a consequence of ischemic stroke, independent of early family adversity [55,57]. The presence of epilepsy as a consequence of stroke negatively affects the degree of cognitive impairment, although specific hemispheric involvement appears unrelated [31,49,58].

There are limited data concerning the incidence of visual field deficits and sensory impairment following pediatric stroke [42,47,59–61]. The first report of hemianopsia with infantile hemiplegia was that of Freud [7].

> ''The association of epilepsy with infantile cerebral palsies is perhaps the gravest feature of these diseases.''
>
> —B. Sachs 1890 [7]

Data regarding the incidence and risk for the development of epilepsy as a sequela of pediatric stroke have been impaired by there being few prospective studies, small sample size, selection bias, differing definitions and terminology in the classification of epilepsy, and short-term follow-up. Between 12% and 18% of all neonatal seizures are associated with cerebral infarction [21,62–64], with 80% to 90% presenting within 48 to 72 hours of stroke onset. Conversely, more than 80% of all perinatal strokes presenting in the newborn period present with seizures (Table 3). The remainder present with encephalopathy [60,65], hypotonia [39], or focal neurologic features. In an autopsy series of 592 infants, 5.4% were found to have AISs and none showed focal neurologic features during the newborn period; however, 17% had neonatal seizures. The majority of seizures (74%) tend to be focal (Table 4), but generalized and subtle seizures, including apnea, may occur. Electrographic seizures may occur in the absence of clinical findings [66,67]. The seizures are usually easy to control [47,68,69] and typically last 3 to 5 days [69,70]. Prognostically, the presence of an abnormal background on electroencephalogram (EEG) has been associated with subsequent development of hemiplegia, although EEG seizures or epileptic discharges with normal background were not [71]. This study was limited by the use of only 2-channel recording EEGs in most cases. The reported risk for subsequent epilepsy has varied from 0% to 50% depending on the nature of the study, with a ''mean'' of 22% (Table 3) for all studies. Studies in which hemorrhagic and ischemic stroke could not be differentiated or studies in which ischemic stroke included AIS and sinus venous thrombosis have been excluded from analysis in Tables 3 and 5.

Acute/symptomatic seizures occur in ~30% of childhood stroke (Table 5). Seizures may also occur despite deeper (basal ganglia/thalamic) infarcts [72]. Epilepsy occurs as a neurologic sequela in ~28% of childhood strokes (Table 5). Seizures or altered level of consciousness at presentation are associated with increased mortality at 6 months or unfavorable outcome [42]. Cortical involvement is a risk for subsequent epilepsy [73].

Table 3
Seizures and epilepsy in neonatal arterial ischemic stroke

Study	Year	N	Seizures and epilepsy (%)
Clancy et al [66]	1985	11	Acute 91
Levy et al [62]	1985	7	Acute 100 Epilepsy 14
Filipek et al [175]	1987	7	Acute 100 Epilepsy 29
Sran and Baumann [68]	1988	17	Acute 82 Epilepsy 21
Fujimoto et al [69]	1992	18	Acute 78 Epilepsy 0
Koelfen et al [176]	1993	8	Epilepsy 50
Trauner et al [47]	1993	29	Acute 31 Late: 34 Epilepsy 21
Estan and Hope [21]	1997	12	Acute 100 Epilepsy 0
Jan and Camfield [70]	1998	7	Acute 100 Epilepsy 0
Mercuri et al [71]	1999	24	Acute 100 Epilepsy 0
Sreenan et al [60]	2000	46	Acute 91 Epilepsy 46
Golomb et al [177]	2001	22	Acute 0 Late 14 Epilepsy 23
Kurnik et al [39]	2003	215	Acute 77
Ramaswamy et al [65]	2004	5	Acute 100
Steinlin et al [30]	2005 (prospective)	23	Acute 83
Lee et al [43]	2005	34	Acute 80 Late 14 Epilepsy 39
Golomb et al [173]	2007	111	Epilepsy 42
Mean			Acute 81 Epilepsy 22

Recurrence

The mechanism and etiology of childhood stroke strongly influence recurrence risk. Recurrence rate for childhood AIS has varied between 6% and 37% [25,31,32,42,74–84]. Many studies are limited by short-term follow-up, and others include clinical recurrence (transient ischemic attacks [TIAs]) and radiographic confirmation of stroke recurrence [25,77,80]. The best of these studies would suggest a stroke recurrence risk of ~15% to 20%. Risk factors for recurrence include vascular abnormalities as the cause for the initial stroke [78–80,84], and prothrombotic risk factors, either individually (elevated lipoprotein (a) and protein C deficiency) [78] or as part of multiple risk factors [39,76,80,85]. AIS recurrence risk appears highest in the first 6 months after

Table 4
Seizure semiology at presentation in acute neonatal seizures secondary to arterial ischemic stroke

Study	N	Focal seizures (%)	Generalized seizures (%)	Subtle/Apnea (%)
Levy et al [62]	7/7	43	57	0
Clancy et al [66]	10/11	100	0	10 (also with focal seizures)
Filipek et al [175]	7/7	86	14	0
Sran & Baumann [68]	14/17	86	14	0
Fujimoto et al [69]	14/18	86	14	0
Estan & Hope [21]	12/12	67	25	8
Jan & Camfield [70]	7/7	86	0	14
Sreenan et al [60]	42/46	40	24	36
Kurnik et al [39]	193/215	73	4	13
Total[a]	306/340	74	17	9

[a]Totals more than 100% as one patient had focal seizures and subtle seizures.

initial stroke presentation [78,84]. Clinically, silent infarcts were detected in more than 10% of patients on repeat neuroimaging studies in one series [80]. The issue of silent infracts is being assessed as part of a multicentered study on SCD (Silent Cerebral Infarct Multicenter Transfusion [SIT] Trial), and children with SCD are also known to be at increased risk for stroke recurrence, despite blood transfusions [86].

Recurrence risk data for a repeat AIS in perinatal AIS are poor, with only 2 studies specifically addressing this issue. Both showed a low recurrence risk of 1.8% [39] and 1.2% [84], respectively, although the risk for any thromoembolic event (systemic or cerebral venous sinus thrombosis) was slightly higher at 3.3%.

ETIOLOGY

> The trigger that fires the explosion, the convulsion and hemiplegia, is not pulled however, until some time after birth [12].

The basic mechanism of AIS in childhood, like that in adults, includes embolus (cardiac or artery-artery) and in situ thrombosis or occlusion. Perhaps the biggest difference, however, between adult and pediatric stroke, lies in the risk factors and causes of AIS. Unlike adult stroke, degenerative vascular disease (atherosclerosis) and chronic degenerative risk factor diseases such as hypertension, hypercholestolemia/hyperlipidemia, diabetes, and smoking have very little role in pediatric AIS. Although multiple risk factors have

Table 5
Seizures and epilepsy in childhood arterial ischemic stroke

Study	Year	N	Age (months/ years)	Seizures and epilepsy (%)
Isler [74]	1984	87	<1 y to >10 y	Epilepsy 50
Lanska et al [174]	1991	42	Birth to 13 y	Epilepsy 19
Yang et al [73]	1995	56	1 mo to 7 y	Acute 54 Epilepsy 30
Giroud et al [99]	1997	31	Mean 10.25 y	Acute 35 Epilepsy 36
De Schryver et al [31]	2000	37	3 mo to 4 y	Acute 22 Epilepsy 26
Ganesan et al [46]	2000	90	3 mo to 15 y	Acute 33 Epilepsy 15
Lanthier et al [76]	2000	46	1 mo to 18 y	Epilepsy 12
Delsing et al [42]	2001	31	2 mo to 14.3 y	Acute 19
Barnes et al [29]	2004	95	Birth to 19 y	Epilepsy 7
Steinlin et al [30]	2005 (prospective)	40	1 mo. to 16 y	Acute 20
Salih et al [81]	2006	104	1 mo. to 12 y	Epilepsy 58
Mean				Acute 31 Epilepsy 28

been identified in pediatric stroke, the understanding of pathogenesis remains limited in many instances, especially in focal cerebral arteriopathy, one of the larger etiologic groups for pediatric AIS. Despite recent advances in pediatric AIS, approximately one-quarter to one-third of all childhood strokes remain "idiopathic" [35,46,75,84,87], and this number is even greater for perinatal AIS. This may, in part, be accounted for by a nonstandardized approach and limitations in the evaluation and assessment of etiologic causes of AIS in the various studies. In 2 larger studies, for example, in which detailed cerebrovascular imaging was performed, abnormalities were present in 79% [28] and 78% [75] of patients, respectively. A population-based cohort study in California showed 5-year cumulative recurrence stroke risk rate in children of 66% in those with abnormal vascular imaging studies, versus no recurrences among children with normal vascular imaging studies [84]. Attempts to accurately classify the etiology for AIS are therefore important to allow correct treatment and establish potential recurrence risk. This is especially true for cardioembolic sources of stroke and progressive arteriopathies such as moyamoya disease and primary progressive central nervous system (CNS) vasculitis.

The commonest etiologic categories for pediatric AIS include arteriopathies, cardiac disease (congenital and acquired), hematological disease, and infection. Multiple risk factors are often present at the time of stroke, including acute or chronic disease and prothrombotic states (primary or secondary). Table 6 lists some of the more common causes of childhood AIS.

Table 6
Risk factors and causes of childhood AIS

CARDIAC

Congenital
- CHD
- Cardiomyopathy
- Cardiac tumors
- Arrhythmias

Acquired
- Cardiomyopathy
- Carditis
- Arrhythmias
- Artifical valves
- Endocarditis

Iatrogenic
- Cardiac catheterization
- Cardiac surgery/cardiopulmonary bypass
- Carotid ligation

HEMATOLOGIC

Hemagloniopathies
- SCD
- Thalassemia

Thrombophilia
- – Primary
- – Secondary

Iron deficiency anemia
Thrombocytopenia

INFECTIOUS

Meningitis
- Viral, bacterial, fungal

Encephalitis

ARTERIOPATHIES

Vasculitis
Primary
- Primary angiiitis of the CNS

Secondary
- Postinfectious
  - Varicella
  - Other
- Infectious
  - Encephalitis
  - Meningitis
- Associated with collagen vascular disease or systemic vasculitides

VASCULOPATHIES

Transient/focal cerebral arteriopathy[a]
Down syndrome
Fabry disease
NF1
PHACE syndrome
SCD
Moyamoya disease (primary)
Moyamoya syndrome (secondary)
- Down syndrome
- NF1
- SCD
- William syndrome
- Postcranial irradiation

Fibromusuclar dysplasia
Vasospams
- Migraine

Dissection

OTHER

Trauma
- Dissection
- Fat/air embolus

Toxins/Drugs
- Cocaine
- L-aspariginase
- Oral contraceptive pill

Metabolic
- Shock/dehydration
- Carbohydrate deficient glycoprotein syndrome
- Fabry disease
- Homocysteinuria
- MELAS

[a]Cause is uncertain.

Cardiac disorders

CHD is one of the most common birth defects in the United States, and the annual number of infants born with complex CHD is just more than 6500 [88]. Hypoplastic left heart syndrome and tetralogy of Fallot account for nearly 2500 (almost 40%) of these cases; neurologic dysfunction, including stroke, is the major extracardiac complication in the survivors. In a prospective study in infants undergoing cardiopulmonary bypass surgery, 8% had evidence of stroke before surgery, with a further 19% developing new infarcts after surgery [89]. Stroke relating to CHD is usually embolic and may result from mural thrombus in a dyskinetic atrium or ventricle, clot, or vegetation from an abnormal heart valve, or as a consequence of cardiopulmonary bypass. The latter may result from air embolus from open intracardiac procedures, prosthetic patches, or from particulate microemboli from the bypass circuit itself (artificial surfaces, tubing, filters, and aerators). Moyamoya disease has rarely been described in association with CHD [90,91]. Embolic infarcts from cardiomyopathy are usually the result of hypokinetic cardiac wall motion with subsequent clot formation or of cardiac arrhythmias. In an autopsy series of 84 brains in children who died following heart transplantation, cerebral infarct was the most common finding of the CNS, occurring in 34% of the autopsy cases [92]. Stroke following Fontan repair was reported in 2.6% of a large retrospective series from Boston [93], with higher incidences (5.5%–20%) reported in other smaller series [94–98]. Risk factors for the development of embolic stroke following the Fontan procedure include pulmonary artery banding and residual pulmonary artery stump following ligation of the pulmonary artery [93,97]. Other mechanisms for stroke in cardiac disease include septic emboli from infective endocarditis, paradoxic emboli through a persistent patent foramen ovale or atrial septal defect, emboli secondary to cardiac arrhythmias, iatrogenic emboli following cardiac catherization (atrial balloon septostomy or traumatic dissection), and thrombosis from polycythemia in chronic cyanotic CHD.

Stroke from cardiac disease accounts for approximately 20% to 30% of childhood stroke [27,29,30,32,42,76,87,99,100], although some series have shown a lower frequency of less than 20% [46,83]; this percentage is lower in perinatal stroke. Additional prothrombotic risk factors were identified in a cohort of children with cardiac disease suffering stroke compared with age-matched controls [100]. These risk factors included elevated lipoprotein(a) levels, protein C deficiency, anticardiolipin antibodies, and combined prothrombotic disorders.

Hematologic disorders

SCD, an autosomal recessive disorder, is the most common hemaglobinopathy associated with childhood AIS. Historically, the association between SCD and cerebrovascular disease was first made by Sydenstricked in 1923 [101]. Subsequently, Greer and Schotland [102] and Portnoy and Herion [103] emphasized the high prevalence of cerebrovascular disease among SCD patients. The incidence of stroke in children with SCD is estimated at

7% to 11% [104–107]. Arterial ischemic infarction accounts for the majority of stroke subtypes in childhood. The incidence of ischemic stroke was highest in patients younger than 20 years (0.44/100 patient-years); conversely, the rate of hemorrhage was highest in patients 20 to 29 years of age (0.44/100 patient-years) and was low in children [107]. Silent infarction has been found in up to 22% of children with SCD and was associated with an increased risk of new stroke [108]. The majority of strokes are seen in the setting of homozygous SCD, as opposed to sickle trait or the sickle thalassemias. The precise mechanism by which SCD produces infarction is unknown, although several theories have been proposed. Initial thoughts placed emphasis on small vessel disease [109,110]; however, current views have shifted in favor of large arterial disease [111,112] being the cause of most clinically evident cerebrovascular syndromes. In all likelihood, several factors are implicated in the production of stroke in these patients [113–117]. On angiography, the most commonly affected sites are the supraclinoid internal carotid arteries (ICAs), and the proximal MCAs and anterior cerebral arteries (ACAs). Progressive narrowing of vessels may lead to moyamoya syndrome [118].

The Stroke Prevention Trial in Sickle Cell Anemia (STOP) [119] was a landmark study and showed the first successful preventive strategy in reducing stroke risk in a susceptible population. It showed a 92% reduction of first stroke in children with SCD in the treatment arm (blood transfusion to reduce hemoglobin S values to less than 30%) compared with standard therapy arm if their transcranial Doppler (TCD) ultrasound velocity was more than 200 cm/s in the ICA or MCA. The STOP II trial was designed to see whether children on a regular exchange transfusion protocol for 30 months or more following initial abnormal TCD studies (velocities $\geq$ 200 cm/s) could safely stop their transfusion therapy (because of the risks of long-term transfusion and iron overload). This trial was also halted prematurely because 2 children who had discontinued transfusion therapy suffered strokes, and because there was an unacceptably high rate of TCD reversion back to high risk ($\geq$ 200 cm/s) [120]. The SIT Trial in SCD is enrolling patients with silent cerebral infarcts who are to be randomized to receive blood transfusion therapy or observation (standard care) for 36 months to assess if this will improve progressive neurologic complications [121]. Pilot safety and feasibility trials of low-dose aspirin and overnight respiratory support in SCD have also begun [122].

Thrombophilias

The incidence of prothrombotic disorders in pediatric AIS is estimated at between 20% and 50% [123–126]; however, the strength of its association in the etiology of pediatric AIS remains uncertain. The prothrombotic risk factors most strongly associated with pediatric AIS include protein C deficiency, elevated lipoprotein(a) levels, factor V Leiden mutation (G1691A), prothrombin gene mutation (G20210A), methylenetetrahydrofolate reductase mutation (TT677), and

antiphospholipid antibodies [124–129]. Most increase the odds ratio for stroke by 2- to 10-fold [125,126]. Multiple prothrombotic risk factors were found in 10% of patients in one study [125]. Elevated lipoprotein(a) and protein C deficiency are risk factors for recurrent AIS in childhood [78].

Arteriopathies

The arteriopathies, as a group, comprise an important part of pediatric AIS (Table 6). Improved vascular imaging has shown abnormalities of the vessel wall in approximately 80% in some series [28,130], although the incidence has not been so high in other studies, varying from 17% to 53% [75,78,84,131]. Vascular abnormalities are a significant risk for recurrent AIS [78]. The presence of an arterial abnormality does not, however, imply an understanding of the mechanism/pathophysiology or etiology. MRA is a readily available and sensitive tool for assessing the intracranial and extracranial vessels, but requires sedation in younger children unable to lie still for a prolonged period of time. This problem can be overcome by using CT angiography (CTA), however, CTA requires large-bore intravenous access for rapid administration of contrast and exposes the child to high levels of irradiation and potential adverse reaction to the iodide contrast. The sensitivity of MRA in detecting extracranial dissection can be increased by obtaining fat-saturated views. MRA is not sensitive for small vessel disease and may overestimate the degree of stenosis [132]. Formal 4-vessel cerebral angiography (CA) remains the "gold standard" for imaging vessels, especially if the diagnosis remains uncertain, the MRA is "equivocal", or small vessel disease such as vasculitis is a concern. Studies have shown that MRA in pediatric AIS may be as sensitive as CA for large vessel disease [132].

Vasculopathies

The noninflammatory vasculopathies are a heterogeneous group of disorders. The more common vasculopathies seen in pediatric AIS include moyamoya disease and syndrome, dissection, SCD (see discussion earlier in this article), neurofibromatosis, and transient cerebral arteriopathy (TCA).

Moyamoya disease is a disorder of multiple progressive intracranial occlusions of the large cerebral arteries (ICA, MCA, ACA) with compensatory development of lenticulostriate collaterals. Less commonly, the posterior circulation (basilar artery, posterior communicating arteries) may be involved. "Moyamoya" was first used to describe this appearance of collateral networks at the base of the brain in 1969 [133] and comes from the Japanese expression for something "hazy, just like a puff of cigarette smoke drifting in the air." Although the etiology is unknown, familial cases have suggested autosomal dominance inheritance with incomplete penetrance. Genomic imprinting may be associated with the disease as affected mothers are more likely to produce late-onset or asymptomatic female offspring [134]. To date, 3 gene loci have been identified through linkage studies and mapped to chromosome 3p [135], chromosome 17q25 [136], and chromosome 8q23 [137]. A high incidence of moyamoya disease is found in people of

Asian descent, especially Japanese, although it has now been recognized worldwide. It accounts for only about 6% of childhood strokes in Western counties [138] and occurs more frequently in females.

Moyamoya syndrome is differentiated from primary or idiopathic moyamoya disease as it develops secondary to an underlying disorder (acquired or genetic). It is sometimes referred to as "secondary" moyamoya syndrome and has been described in persons with Down syndrome, SCD, William syndrome, neurofibromatosis, and less commonly in other phakomatoses (hypomelanosis of Ito and tuberous sclerosis) [139].

Children with moyamoya disease and/or syndrome typically present with symptoms secondary to an acute ischemic infarct or with seizures; hemorrhagic stroke is more common in adults. There is a high risk of recurrence, and progressive cognitive decline secondary to chronic cerebral hypoperfusion may occur [140]. Treatment to restore the cerebral circulation and avoid recurrent stroke has focused on surgical revascularization options. This typically includes "direct" procedures, ie, the direct anastomosis of an extracranial to intracranial vessel, versus "indirect" procedures in which the superficial temporal artery typically is placed directly on the surface of the brain. The procedure appears to be safe, although perioperative stroke may occur in about 4.5%, and effective, with most treated patients deriving symptomatic benefit [141].

Dissection

Arterial dissection results from a tear in the intimal wall of the blood vessel. This may affect the anterior or posterior circulation, and may be intracranial or extracranial. Symptoms typically result from an artery-artery embolism arising from the site of the intimal tear, but may also occur secondary to thrombosis and complete occlusion of the dissected vessel. Dissection accounts for 7.5% to 20% of AIS in children [28,75,142]. Mean age of presentation is 8 to 11 years [142,143]. Intracranial dissection occurs more commonly in pediatric AIS than in adult stroke, and usually affects the anterior circulation, whereas posterior circulation dissection more commonly involves the extracranial vessels (especially at the C1-C2 vertebral body level) [143]. Arterial dissection differs from adult dissection in several other ways, including an increased frequency in boys (even when trauma is excluded), lack of preceding warning symptoms (such as headache or neck pain), and frequent lack of significant head or neck trauma [143]. Trauma, when present, usually results in an extracranial dissection. Predisposing factors for dissections such as fibromuscular dysplasia or connective tissue disease are rare. There is often a delay in onset of symptoms following dissection, and children almost universally present with signs and symptoms of ischemia, specifically hemiplegia or hemisensory deficits, although seizures at onset, cranial neuropathies, ataxia, visual disturbances, or headache may occur. Angiographic features include a string sign, luminal flap, aneurysmal dilatation, double lumen sign, or short, smooth tapering stenosis or occlusion of the affected vessel. Although conventional CA remains the gold standard, MRA, complemented by fat-saturated T1 views

and CTA can often confirm the diagnosis [138]. Recurrence risk is variable and occurs in about 10% to 12.5% [142,143] but this may be an underestimate since most children are treated with antiplatelet or anticoagulation therapy (for 3–6 months). There are no studies showing superiority of one treatment compared with the other, or superiority of treatment versus nontreatment, in arterial dissection in childhood. In a systematic review of the literature involving 118 reported cases of pediatric AIS from 79 studies, the majority of fatalities occurred in patients not receiving anticoagulation, and complications (specifically hemorrhage) occurred in only 2 patients (1 with a fatal intracranial hemorrhage, and 1 with a large gastrointestinal hemorrhage) [143]. The recent American Heart Association (AHA) guidelines for the treatment of stroke in infants and children [138] give a class III recommendation, (ie, not recommended) to the use of anticoagulation for intracranial dissection (because of concern about possible subarachnoid hemorrhage).

Neurofibromatosis

Neurofibromatosis type 1 (NF1) is an autosomal dominant disorder involving mutations of the NF gene on chromosome 17q11. It affects 1 in 3000 individuals and is a progressive, multisystem disease with complications that can affect any part of the body. NF1 vasculopathy is well recognized and manifests as stenosis, occlusion, arteriovenous fistula, or aneurysm of the large and medium-sized arteries. A 2.5% incidence of NF1 vasculopathy was found in a cohort of 316 pediatric patients with NF1 who underwent brain MRI studies [144]. A recent study from Canada found a minimum prevalence rate of NF1 vasculopathy, amongst a cohort of 419 children with confirmed NF1, of 6% [145]. The incidence of stroke in NF1 vasculopathy is unknown. The most frequently documented vascular abnormality is renal artery stenosis with resultant hypertension [146]. Intracranial occlusive arterial disease is the most common neurovascular manifestation of neurofibromatosis and occurs predominantly in younger patients [146,147]. This disease usually involves the anterior circulation and may be bilateral in about half the cases, resulting in moyamoya syndrome. It may follow intracranial irradiation for optic glioma [148]. The pathogenesis of the vasculopathy in NF1 patients remains to be fully elucidated. Familial occurrence of cerebral vasculopathy in NF1 is rare [149].

Recently, a case of a brainstem stroke in a child with NF2 was reported concurrent with a gastrointestinal illness [150]. No obvious cause for the stroke was found, and what relationship, if any, the NF2 had on the stroke is uncertain. Unlike NF1, vasculopathy is not a known manifestation of NF2.

TCA

TCA describes an idiopathic, nonprogressive focal or segmental, unilateral stenosis of the distal (supraclinoid) ICA or proximal MCA/ACA [151–153], resulting in a lenticulostriate infarction. It appears to be a monophasic event, although angiographic data have shown that the stenosis may worsen in a 3- to 6-month period, with persistent focal narrowing of the vessel in a significant number of patients [151,153]. A recurrence rate of TIA or stroke has been

reported in up to 18% in some series [153]. This term has been used interchangeably with focal arterial stenosis in childhood. TCA is one of the most common causes of vasculopathy in pediatric AIS, accounting for about 20% to 30% of cases [131,153,154]. The pathophysiology is still not fully understood but a postinfectious inflammatory mechanism has been proposed given the strong association between TCA and a preceding varicella infection (postvaricella angiopathy), and the natural history, which initially involves a progressive course with subsequent stabilization on angiogram [28,130, 151,153,155,156]. An angiographic TCA appearance has also been associated with other infectious agents [138,153]. Whether the introduction of the varicella vaccine into childhood immunizations will show a significant reduction in the incidence of stroke from TCA remains to be seen. Further studies are needed to determine the optimal treatment for this condition given the frequency, recurrence risk, and outcome. Whether immunosuppressive agents, with or without antivital medication, affect outcome and recurrence is not known. Similarly, it is unclear whether adjunctive antiplatelet or anticoagulation therapy during the acute phase or the long term is necessary.

Vasculitis

Inflammatory vasculitis may occur as an isolated phenomenon affecting the cerebral arteries (primary angiitis of the CNS) or may be part of a collagen vascular disease, systemic vasculitides, or an infectious or postinfectious process (Table 6).

Primary Angiitis of the CNS

Childhood primary angiitis of the CNS (cPACNS) is a rare, noninfectious, progressive arteriopathy isolated to the cerebral vessels without systemic involvement. It is associated with high recurrence rate, morbidity, and mortality. In a recent review [153] it accounted for 6% of all arteriopathies in childhood AIS. It often presents with a more indolent course of headaches, academic or cognitive decline, and encephalopathy compared with the transient cerebral arteriopathies (discussed earlier in this article), which present acutely with ischemic symptoms, typically hemiplegia. It may involve large- to medium-sized blood vessels, or small distal blood vessels [157]. The small vessel involvement can readily be missed on MRA or CTA although MRI shows evidence of ischemic infarct. The hallmark on CA is beading (segmental vessel narrowing with poststenotic dilatation). In contradistinction to adult PACNS, in which angiographic findings are typically bilateral and asymmetrical, angiographic findings in cPACNS are usually unilateral, proximal, and multifocal [158]. Angiogram may be normal [159]. Cerebrospinal fluid analysis may show an elevated opening pressure, mild lymphocytosis, or elevated protein, but may also be normal. Brain biopsy, including dura, may be necessary for diagnosis but given the patchy nature of involvement of the brain can give a false-negative result. A nongranulomatous vasculitis may be found rather than the typical necrotizing granulomatous vasculitis seen in adult

PACNS [157,160]. Systemic inflammatory markers may be present but are nonspecific and not necessary for diagnosis.

Differentiating progressive cPACNS from a TCA or moyamoya syndrome can be difficult but is important for determining treatment. The presence of multifocal parenchymal lesions, neurocognitive dysfunction, and distal stenosis were important predictive markers in one series [161]. Treatment of cPACNS involves immunosuppressive agents, including steroids and pulse cyclophosphamide, in the acute phase [138], with maintenance immunosuppressive therapy such as azothioprine or mycophenolate mofetil for a prolonged period [157]. The concomitant use of anticoagulation or antiplatelet therapy during the acute phase and for a few months thereafter to prevent in situ thrombosis from vessel inflammation is controversial. Given the rarity of this condition, no formal studies of optimal therapy have been conducted.

Treatment

Evidence-based prevention strategies and treatments for pediatric stroke are lacking, with only 1 randomized control trial [119] in SCD and AIS. In recent years 3 guidelines have been published that address for the first time management and treatment issues in pediatric stroke [138,162,163]. However, many of the recommendations are based on small nonrandomized trials, case series, extrapolation from adult data, or expert consensus opinion. For specific treatment recommendations, readers are referred to these guidelines and other reviews that have been published recently [35,164,165]. The most recent and comprehensive guideline from the AHA also provides protocols for the use of unfractionated heparin (UH), low molecular weight heparins (LMWH) and warfarin in childhood AIS [138].

Initial acute supportive measures for childhood AIS are much the same as in adult stroke and include maintenance of normal oxygenation, control of systemic hypertension (although the specific targeted range and level of "permissible" hypertension is unclear given concerns for lowering perfusion pressure), and normalization of serum glucose [138]. Fever should be controlled. Hyperthermia has been associated with increased secondary injury in multiple animal models of stroke [164]. Seizures should be aggressively treated. There is no evidence to support the use of supplemental oxygen in the absence of hypoxemia or antiepileptic medication prophylactically in the absence of clinical or electrical seizures. None of the 3 guidelines recommend the use of acute thrombolysis with intraarterial or intravenous tissue plasminogen activator (t-PA) in childhood AIS. The recent AHA guidelines [138] give a class III recommendation, that is, it is not recommended or should not be used outside a clinical trial. The use of anticoagulation in acute AIS is also controversial, with differing opinions between the guidelines. There appears to be consensus for its use acutely and indefinitely in children with a cardioembolic source of their stroke if the underlying cardiac reason for their stroke cannot be surgically corrected. The use of anticoagulation in extracranial dissection acutely and for 3 to 6 months is also generally accepted, although

the AHA guidelines include the alternative use of antiplatelet agents instead of anticoagulation. Anticoagulation is not recommended for intracranial dissection (see section on dissection earlier in this article). The *Chest* guidelines [163] recommend UH or LMWH for up to a week while the cause of the stroke is determined, whereas the UK guidelines [162] recommend aspirin. Anticoagulation is not recommended for neonatal AIS in the absence of a cardioembolic source. Exchange transfusions and hydration to keep sickle hemoglobin less than 30% is recommended for acute AIS in SCD.

For secondary prevention in AIS of unknown etiology or in vasculopathy not caused by vasculitis, moyamoya, or dissection, all 3 guidelines recommend the use of aspirin, given the risk of recurrence. Doses vary from 1 to 3 mg/kg in the UK guidelines to 2 to 5 mg/kg in the *Chest* guidelines. The length of treatment is uncertain. There are no specific recommendations on the use of aspirin for secondary stroke prevention in thrombophilias.

FUTURE

> The physician is no longer content, or at least should not be, to make the diagnosis of apoplexy; of hemiplegia, or of paraplegia, in the adult. It is his aim to determine whether the special form of paralysis be due to hemorrhage, thrombosis, embolism, tumor, abscess, or what not. In short, he studies the symptoms of each case with special reference to pathology of the disease. And so with infantile palsies: it is not enough to recognize spastic hemiplegia, diplegia or paraplegia, but the attempt should be made to determine the special morbid condition underlying each form.
>
> —B. Sachs 1898 [7]

Much remains to be learned about pediatric AIS. Despite more than a century of descriptive studies in pediatric AIS, approximately one-third to one-quarter of strokes remain idiopathic. Etiology and risk factors in pediatric AIS are diverse, with no one risk factor predominating, hence each requires a different research approach [87]. The rarity of pediatric AIS, diverse causes, and mimics of stroke have affected the development of rational and effective treatment strategies. The application of adult data to pediatric stroke is not always appropriate because of intrinsic differences in the pathophysiology, etiology, and risk aversion in pediatric stroke. Vasculopathy in pediatric stroke is common, but does not involve the degenerative risk factors or processes of adult stroke, namely atherosclerosis and hypertension, but rather, healthy vessels and robust collateral circulation. Developmental differences in the coagulation system and issues related to birth also affect pediatric AIS. Since the 1990s, research work has provided improved epidemiologic and population-based data regarding pediatric stroke. Efforts have been made to standardize pediatric stroke classification [152], and advances in imaging have allowed for improved diagnostic yield and better classification of etiology, although not necessarily pathophysiology, of pediatric AIS. A monumental, ongoing unfunded international collaboration for data collection and cooperation in pediatric stroke has been

established: the IPSS consortium [26] (http://app3.ccb.sickkids.ca/cstrokestudy). These are necessary first steps toward the development of standardized diagnostic and evaluation protocols and toward randomized controlled trials for therapeutics and intervention in the treatment and prevention of pediatric AIS. The IPSS has also led to the development and establishment of pediatric stroke centers throughout the world that will promote increasing awareness of pediatric stroke (which remains an ongoing problem), more rapid and comprehensive evaluation of AIS, improved outcomes, and age-appropriate clinical research. The first such trial in pediatric stroke funded by the US National Institutes of Health (NIH) is under way; it is investigating the application of a modified pediatric NIH stroke scale in acute AIS and is based at the Children's Hospital of Philadelphia with the participation of several centers throughout the United States and Canada.

Several obstacles still exist with respect to potential treatment studies for pediatric AIS. Despite the increased awareness of pediatric stroke, delays in presentation and evaluation persist. A study from Stony Brook, New York [166] showed a mean delay in symptom onset to medical contact in AIS of 43 hours (median of 20 hours) and a further 7-hour delay (mean) in the diagnosis of AIS. These findings were confirmed in a more recent study from Toronto in which only 20% of childhood AIS cases were diagnosed within 6 hours [167]. Further confounding the time to diagnosis are the stroke mimics that frequently occur in pediatrics, including migraine (hemiplegic, ophthalmic, and confusional forms), seizures (with resultant Todd paralysis), demyelinating disorders (especially acute disseminating encephalomyelitis), and functional disorders [168,169]. The insensitivity of CT scan and the need for MRI/MRA in pediatric stroke is therefore essential, and brings with it its own set of difficulties, as sedation is often required in children. These problems are magnified in perinatal AIS, in which there is often a paucity of symptoms in the newborn period apart from seizures, and diagnosis is often made only at 4 to 6 months of age when asymmetry in reaching or use of the hands is first noted. New therapies for acute intervention in AIS have become available in adult stroke, but their application and suitability for pediatric stroke still needs to be assessed. Three treatment guidelines for pediatric AIS have recently been published, but these are limited because they are based on small nonrandomized trials, case series, extrapolation from adult data, or expert consensus opinion [138,162,163]. Nonetheless, these publications serve as a foundation for future studies and provide some guidelines in an otherwise difficult area. Among the problems associated with primary stroke prevention strategies in pediatrics are the multitude of causes that may give rise to stroke, many of which are uncommon or rare. However, primary stroke prevention measures are well established for the two largest categories of childhood AIS (SCD and cardiac disease). It remains to be seen whether the implementation of varicella vaccination into the immunization schedule of children reduces the incidence of postvaricella angiopathy, one of the more common causes of TCA in childhood AIS. Evidence for the efficacy of treatment for secondary prevention of

recurrence of childhood AIS is lacking, apart from some specific disease entities such as moyamoya. Given the recurrence risk of childhood AIS is ~15% to 20%, depending on the cause, this is an important area for future research.

Although the way forward is difficult for pediatric stroke given the multiple challenges outlined in this article, the lack of funding, and the small number of physicians working in this area, the future is bright given the dedication of purpose of collaboration, such as the IPSS and European collaborative groups, and the advances in the field in the last 1or 2 decades. Ongoing population-based prospective studies are needed with respect to etiology, incidence, recurrence risk, and outcome. Standardized diagnostic and therapeutic algorithms need to be developed so that evaluation and treatment of pediatric AIS is more readily available to all physicians caring for pediatric stroke. This may lead to reduced lifetime morbidity and a reduction in the associated costs for survivors of pediatric stroke. Standardized definitions, classification of stroke subtype, and outcomes are crucial for treatment studies. In this regard, outcome instruments such as the pediatric stroke outcome measure [25] have been helpful, but validated measures of cognitive and behavioral outcomes relating to pediatric stroke are needed. As Kirkham [170] has pointed out, case-controlled studies are preferable to minimize selection bias, but given the difficulty (often for ethical reasons) in obtaining a control group, another option is for studies to use data pooling. Although some early work has been performed to assess the direct cost of pediatric AIS, more information is needed to address the indirect costs of pediatric AIS in the hope of improving funding for research into childhood stroke by showing the burden of pediatric AIS not just to the individual, but to society as a whole. Most children with stroke have vascular abnormalities on imaging and a better understanding is needed of the mechanisms behind this. t-PA is being used in childhood AIS despite a lack of evidence showing safety or even efficacy and this needs to be urgently evaluated in a study. Other future studies will need to focus on small cohorts of homogenous at-risk stroke populations to address possibilities of primary stroke prevention, such as the vasculopathy associated with NF1, and silent strokes seen in CHD. The potential role and application, if any, of newer technologies such as vascular stenting or angioplasty remain to be elucidated in pediatric AIS.

References

[1] Wisoff HS, Rothballer AB. Cerebral arterial thrombosis in children. Review of literature and addition of two cases in apparently healthy children. Arch Neurol 1961;4:258–67.
[2] Bickerstaff ER. Aetiology of acute hemiplegia in childhood. Br Med J 1964;2:82–7.
[3] Williams AN. Winner of the young physician's section of the Gowers' prize 2000. Too good to be true? Thomas Willis–neonatal convulsions, childhood stroke and infanticide in seventeenth century England. Seizure 2001;10:471–83.
[4] Schoenberg BS, Mellinger JF, Schoenberg DG. Cerebrovascular disease in infants and children: a study of incidence, clinical features, and survival. Neurology 1978;28:763–8.
[5] Garrison FH. Garrison's history of neurology. Revised and enlarged with a bibliography of classical, original and standard works in neurology. Springfield (IL): Charles C. Thomas; 1969.

[6] Osler W. Infirmary for nervous diseases (Philadelphia, PA.). The cerebral palsies of children: a clinical study from the infirmary for nervous diseases, Philadelphia. London: H.K. Lewis; 1889.
[7] Sachs B, Peterson F. A study of cerebral palsies of early life, based upon an analysis of one hundred and forty cases. J Nerv Ment Dis 1890;17:295–332.
[8] Freud S. Infantile cerebral paralysis. Translated by Lester A. Russin. Coral Gables (FL): University of Miami Press; 1968.
[9] Gowers W. In: Gowers Sir WR, Taylor James, editors. A manual of diseases of the nervous system. 3rd edition. London: J. & A. Churchill; 1899.
[10] Gowers WR. A manual of diseases of the nervous system. Volume II: Diseases of the brain and cranial nerves, general and functional diseases of the nervous system. 2nd edition. Philadelphia: P. Blakiston's Son and Co; 1907.
[11] Ford FR, Schaffer AJ. The etiology of infantile acquired hemiplegia. Arch Neurol Psychiatr 1927;18:323–47.
[12] Wyllie WG. Acute infantile hemiplegia. Proc R Soc Med 1948;41:459–66.
[13] Krynauw RA. Infantile hemiplegia treated by removing one cerebral hemisphere. J Neurol Neurosurg Psychiatr 1950;13:243–67.
[14] Report of the Joint Committee for Stroke Facilities. IX. Strokes in children. 1. Epidemiology of strokes in children. Stroke 1973;4:835–58.
[15] Report of the Joint Committee for Stroke Facilities. IX. Strokes in children. 1. Neuropathology of strokes in children. Stroke 1973;4:859–70.
[16] Report of the Joint Committee for Stroke Facilities. IX. Strokes in children. 1. Diagnosis and medical treatment of strokes in children. Stroke 1973;4:871–94.
[17] Report of the Joint Committee for Stroke Facilities. IX. Strokes in children. 2. Stroke 1973;4: 1007–52.
[18] Satoh S, Shirane R, Yoshimoto T. Clinical survey of ischemic cerebrovascular disease in children in a district of Japan. Stroke 1991;22:586–9.
[19] 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;48:1343–8.
[20] Perlman JM, Rollins NK, Evans D. Neonatal stroke: clinical characteristics and cerebral blood flow velocity measurements. Pediatr Neurol 1994;11:281–4.
[21] Estan J, Hope P. Unilateral neonatal cerebral infarction in full term infants. Arch Dis Child Fetal Neonatal Ed 1997;76:F88–93.
[22] Lynch JK, Hirtz DG, DeVeber G, et al. Report of the National Institute of Neurological Disorders and Stroke workshop on perinatal and childhood stroke. Pediatrics 2002;109: 116–23.
[23] Lee J, Croen LA, Backstrand KH, et al. Maternal and infant characteristics associated with perinatal arterial stroke in the infant. JAMA 2005;293:723–9.
[24] Schulzke S, Weber P, Luetschg J, et al. Incidence and diagnosis of unilateral arterial cerebral infarction in newborn infants. J Perinat Med 2005;33:170–5.
[25] deVeber GA, MacGregor D, Curtis R, et al. Neurologic outcome in survivors of childhood arterial ischemic stroke and sinovenous thrombosis. J Child Neurol 2000;15: 316–24.
[26] Golomb MR, Fullerton HJ, Nowak-Gottl U, et al, International Pediatric Stroke Study Group. Male predominance in childhood ischemic stroke findings from the International Pediatric Stroke Study. Stroke 2009;40:52–7.
[27] Fullerton HJ, Wu YW, Zhao S, et al. Risk of stroke in children: Ethnic and gender disparities. Neurology 2003;61:189–94.
[28] Ganesan V, Prengler M, McShane MA, et al. Investigation of risk factors in children with arterial ischemic stroke. Ann Neurol 2003;53:167–73.
[29] Barnes C, Newall F, Furmedge J, et al. Arterial ischaemic stroke in children. J Paediatr Child Health 2004;40:384–7.

[30] Steinlin M, Pfister I, Pavlovic J, et al. The first three years of the Swiss neuropaediatric stroke registry (SNPSR): a population-based study of incidence, symptoms and risk factors. Neuropediatrics 2005;36:90–7.
[31] De Schryver EL, Kappelle LJ, Jennekens-Schinkel A, et al. Prognosis of ischemic stroke in childhood: a long-term follow-up study. Dev Med Child Neurol 2000;42:313–8.
[32] Chung B, Wong V. Pediatric stroke among Hong Kong Chinese subjects. Pediatrics 2004;114:e206–12.
[33] Arias E, Anderson RN, Kung HC, et al. Deaths: final data for 2001. Natl Vital Stat Rep 2003;52:1–115.
[34] Lynch JK, Nelson KB. Epidemiology of perinatal stroke. Curr Opin Pediatr 2001;13: 499–505.
[35] Lynch JK, Han CJ. Pediatric stroke: what do we know and what do we need to know? Semin Neurol 2005;25:410–23.
[36] Fullerton HJ, Chetkovich DM, Wu YW, et al. Deaths from stroke in US children, 1979 to 1998. Neurology 2002;59:34–9.
[37] Lo W, Zamel K, Ponnappa K, et al. The cost of pediatric stroke care and rehabilitation. Stroke 2008;39:161–5.
[38] Miller V. Neonatal cerebral infarction. Semin Pediatr Neurol 2000;7:278–88.
[39] Kurnik K, Kosch A, Strater R, et al. Recurrent thromboembolism in infants and children suffering from symptomatic neonatal arterial stroke: a prospective follow-up study. Stroke 2003;34:2887–92.
[40] Mercuri E, Barnett A, Rutherford M, et al. Neonatal cerebral infarction and neuromotor outcome at school age. Pediatrics 2004;113:95–100.
[41] 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.
[42] Delsing BJ, Catsman-Berrevoets CE, Appel IM. Early prognostic indicators of outcome in ischemic childhood stroke. Pediatr Neurol 2001;24:283–9.
[43] Lee J, Croen LA, Lindan C, et al. Predictors of outcome in perinatal arterial stroke: a population-based study. Ann Neurol 2005;58:303–8.
[44] De Vries LS, Van der Grond J, Van Haastert IC, et al. Prediction of outcome in new-born infants with arterial ischaemic stroke using diffusion-weighted magnetic resonance imaging. Neuropediatrics 2005;36:12–20.
[45] Kirton A, Shroff M, Visvanathan T, et al. Quantified corticospinal tract diffusion restriction predicts neonatal stroke outcome. Stroke 2007;38:974–80.
[46] Ganesan V, Hogan A, Shack N, et al. Outcome after ischaemic stroke in childhood. Dev Med Child Neurol 2000;42:455–61.
[47] Trauner DA, Chase C, Walker P, et al. Neurologic profiles of infants and children after perinatal stroke. Pediatr Neurol 1993;9:383–6.
[48] Pavlovic J, Kaufmann F, Boltshauser E, et al. Neuropsychological problems after paediatric stroke: two year follow-up of Swiss children. Neuropediatrics 2006;37:13–9.
[49] Vargha-Khadem F, Isaacs E, van der Werf S, et al. Development of intelligence and memory in children with hemiplegic cerebral palsy. The deleterious consequences of early seizures. Brain 1992;115(Pt 1):315–29.
[50] Goodman R, Yude C. IQ and its predictors in childhood hemiplegia. Dev Med Child Neurol 1996;38:881–90.
[51] Hogan AM, Kirkham FJ, Isaacs EB. Intelligence after stroke in childhood: review of the literature and suggestions for future research. J Child Neurol 2000;15:325–32.
[52] Max JE. Effect of side of lesion on neuropsychological performance in childhood stroke. J Int Neuropsychol Soc 2004;10:698–708.
[53] Aram DM, Eisele JA. Intellectual stability in children with unilateral brain lesions. Neuropsychologia 1994;32:85–95.
[54] Lansing AE, Max JE, Delis DC, et al. Verbal learning and memory after childhood stroke. J Int Neuropsychol Soc 2004;10:742–52.

[55] Max JE, Robin DA, Taylor HG, et al. Attention function after childhood stroke. J Int Neuropsychol Soc 2004;10:976–86.
[56] Trauner DA, Nass R, Ballantyne A. Behavioural profiles of children and adolescents after pre- or perinatal unilateral brain damage. Brain 2001;124:995–1002.
[57] Laucht M, Esser G, Baving L, et al. Behavioral sequelae of perinatal insults and early family adversity at 8 years of age. J Am Acad Child Adolesc Psychiatry 2000;39:1229–37.
[58] Fitzgerald KC, Williams LS, Garg BP, et al. Epilepsy in children with delayed presentation of perinatal stroke. J Child Neurol 2007;22:1274–80.
[59] Tizard JP, Paine RS, Crothers B. Disturbances of sensation in children with hemiplegia. J Am Med Assoc 1954;155:628–32.
[60] Sreenan C, Bhargava R, Robertson CM. Cerebral infarction in the term newborn: Clinical presentation and long-term outcome. J Pediatr 2000;137:351–5.
[61] Kirton A, Deveber G, Pontigon AM, et al. Presumed perinatal ischemic stroke: vascular classification predicts outcomes. Ann Neurol 2008;63:436–43.
[62] Levy SR, Abroms IF, Marshall PC, et al. Seizures and cerebral infarction in the full-term newborn. Ann Neurol 1985;17:366–70.
[63] Aso K, Scher MS, Barmada MA. Cerebral infarcts and seizures in the neonate. J Child Neurol 1990;5:224–8.
[64] Tekgul H, Gauvreau K, Soul J, et al. The current etiologic profile and neurodevelopmental outcome of seizures in term newborn infants. Pediatrics 2006;117:1270–80.
[65] Ramaswamy V, Miller SP, Barkovich AJ, et al. Perinatal stroke in term infants with neonatal encephalopathy. Neurology 2004;62:2088–91.
[66] Clancy R, Malin S, Laraque D, et al. Focal motor seizures heralding stroke in full-term neonates. Am J Dis Child 1985;139:601–6.
[67] Scher MS, Wiznitzer M, Bangert BA. Cerebral infarctions in the fetus and neonate: maternal-placental-fetal considerations. Clin Perinatol 2002;29:693–724, vi–vii.
[68] Sran SK, Baumann RJ. Outcome of neonatal strokes. Am J Dis Child 1988;142:1086–8.
[69] Fujimoto S, Yokochi K, Togari H, et al. Neonatal cerebral infarction: symptoms, CT findings and prognosis. Brain Dev 1992;14:48–52.
[70] Jan MM, Camfield PR. Outcome of neonatal stroke in full-term infants without significant birth asphyxia. Eur J Pediatr 1998;157:846–8.
[71] Mercuri E, Rutherford M, Cowan F, et al. Early prognostic indicators of outcome in infants with neonatal cerebral infarction: a clinical, electroencephalogram, and magnetic resonance imaging study. Pediatrics 1999;103:39–46.
[72] Brower MC, Rollins N, Roach ES. Basal ganglia and thalamic infarction in children. Cause and clinical features. Arch Neurol 1996;53:1252–6.
[73] Yang JS, Park YD, Hartlage PL. Seizures associated with stroke in childhood. Pediatr Neurol 1995;12:136–8.
[74] Isler W. Stroke in childhood and adolescence. Eur Neurol 1984;23:421–4.
[75] Chabrier S, Husson B, Lasjaunias P, et al. Stroke in childhood: outcome and recurrence risk by mechanism in 59 patients. J Child Neurol 2000;15:290–4.
[76] Lanthier S, Carmant L, David M, et al. Stroke in children: the coexistence of multiple risk factors predicts poor outcome. Neurology 2000;54:371–8.
[77] Ganesan V, Chong WK, Cox TC, et al. Posterior circulation stroke in childhood: risk factors and recurrence. Neurology 2002;59:1552–6.
[78] 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;360:1540–5.
[79] Steinlin M, Roellin K, Schroth G. Long-term follow-up after stroke in childhood. Eur J Pediatr 2004;163:245–50.
[80] Ganesan V, Prengler M, Wade A, et al. Clinical and radiological recurrence after childhood arterial ischemic stroke. Circulation 2006;114:2170–7.
[81] Salih MA, Abdel-Gader AG, Al-Jarallah AA, et al. Outcome of stroke in Saudi children. Saudi Med J 2006;27(Suppl 1):S91–6.

[82] Sofronas M, Ichord RN, Fullerton HJ, et al. Pediatric stroke initiatives and preliminary studies: what is known and what is needed? Pediatr Neurol 2006;34:439–45.
[83] Gokben S, Tosun A, Bayram N, et al. Arterial ischemic stroke in childhood: risk factors and outcome in old versus new era. J Child Neurol 2007;22:1204–8.
[84] Fullerton HJ, Wu YW, Sidney S, et al. Risk of recurrent childhood arterial ischemic stroke in a population-based cohort: the importance of cerebrovascular imaging. Pediatrics 2007;119:495–501.
[85] Barreirinho S, Ferro A, Santos M, et al. Inherited and acquired risk factors and their combined effects in pediatric stroke. Pediatr Neurol 2003;28:134–8.
[86] 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;140:348–54.
[87] deVeber G, Roach ES, Riela AR, et al. Stroke in children: recognition, treatment, and future directions. Semin Pediatr Neurol 2000;7:309–17.
[88] Centers for Disease Control and Prevention (CDC). Improved national prevalence estimates for 18 selected major birth defects–United States, 1999–2001. MMWR Morb Mortal Wkly Rep 2006;54:1301–5.
[89] Mahle WT. Neurologic and cognitive outcomes in children with congenital heart disease. Curr Opin Pediatr 2001;13:482–6.
[90] Lutterman J, Scott M, Nass R, et al. Moyamoya syndrome associated with congenital heart disease. Pediatrics 1998;101:57–60.
[91] Ganesan V, Kirkham FJ. Noonan syndrome and moyamoya. Pediatr Neurol 1997;16: 256–8.
[92] McClure CD, Johnston JK, Fitts JA, et al. Postmortem intracranial neuropathology in children following cardiac transplantation. Pediatr Neurol 2006;35:107–13.
[93] du Plessis AJChang AC, Wessel DL, et al. Cerebrovascular accidents following the Fontan operation. Pediatr Neurol 1995;12:230–6.
[94] Mathews K, Bale JF Jr, Clark EB, et al. Cerebral infarction complicating Fontan surgery for cyanotic congenital heart disease. Pediatr Cardiol 1986;7:161–6.
[95] Day RW, Boyer RS, Tait VF, et al. Factors associated with stroke following the Fontan procedure. Pediatr Cardiol 1995;16:270–5.
[96] Rosenthal DN, Friedman AH, Kleinman CS, et al. Thromboembolic complications after Fontan operations. Circulation 1995;92:II287–93.
[97] Chun DS, Schamberger MS, Flaspohler T, et al. Incidence, outcome, and risk factors for stroke after the Fontan procedure. Am J Cardiol 2004;93:117–9.
[98] Barker PC, Nowak C, King K, et al. Risk factors for cerebrovascular events following Fontan palliation in patients with a functional single ventricle. Am J Cardiol 2005;96:587–91.
[99] Giroud M, Lemesle M, Madinier G, et al. Stroke in children under 16 years of age. Clinical and etiological difference with adults. Acta Neurol Scand 1997;96:401–6.
[100] 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):S122–5.
[101] Sydenstricked VP, Mulherin WA, Houseal RW. The AJDC archives. August 1923. Sickle cell anemia. Report of two cases in children, with necropsy in one case. by V.P. Sydenstricked [sic], W.A. Mulherin and R.W. Houseal. Am J Dis Child 1987;141:612–5.
[102] Greer M, Schotland D. Abnormal hemoglobin as a cause of neurologic disease. Neurology 1962;12:114–23.
[103] Portnoy BA, Herion JC. Neurological manifestations in sickle-cell disease, with a review of the literature and emphasis on the prevalence of hemiplegia. Ann Intern Med 1972;76: 643–52.
[104] Powars D, Wilson B, Imbus C, et al. The natural history of stroke in sickle cell disease. Am J Med 1978;65:461–71.

[105] Adams RJ, McKie VC, Brambilla D, et al. Stroke prevention trial in sickle cell anemia. Control Clin Trials 1998;19:110–29.
[106] Balkaran B, Char G, Morris JS, et al. Stroke in a cohort of patients with homozygous sickle cell disease. J Pediatr 1992;120:360–6.
[107] Ohene-Frempong K, Weiner SJ, Sleeper LA, et al. Cerebrovascular accidents in sickle cell disease: rates and risk factors. Blood 1998;91:288–94.
[108] Pegelow CH, Macklin EA, Moser FG, et al. Longitudinal changes in brain magnetic resonance imaging findings in children with sickle cell disease. Blood 2002;99:3014–8.
[109] Baird RL, Weiss DL, Ferguson AD, et al. Studies in sickle cell anemia. xxi. Clinico-pathological aspects of neurological manifestations. Pediatrics 1964;34:92–100.
[110] Hess DC, Adams RJ, Nichols FT 3rd. Sickle cell anemia and other hemoglobinopathies. Semin Neurol 1991;11:314–28.
[111] Stockman JA, Nigro MA, Mishkin MM, et al. Occlusion of large cerebral vessels in sickle-cell anemia. N Engl J Med 1972;287:846–9.
[112] Gerald B, Sebes JI, Langston JW. Cerebral infarction secondary to sickle cell disease: arteriographic findings. AJR Am J Roentgenol 1980;134:1209–12.
[113] Francis RB Jr. Platelets, coagulation, and fibrinolysis in sickle cell disease: their possible role in vascular occlusion. Blood Coagul Fibrinolysis 1991;2:341–53.
[114] Tam DA. Protein C and protein S activity in sickle cell disease and stroke. J Child Neurol 1997;12:19–21.
[115] Tuohy AM, McKie V, Manci EA, et al. Internal carotid artery occlusion in a child with sickle cell disease: case report and immunohistochemical study. J Pediatr Hematol Oncol 1997;19:455–8.
[116] French JA 2nd, Kenny D, Scott JP, et al. Mechanisms of stroke in sickle cell disease: sickle erythrocytes decrease cerebral blood flow in rats after nitric oxide synthase inhibition. Blood 1997;89:4591–9.
[117] Solovey A, Lin Y, Browne P, et al. Circulating activated endothelial cells in sickle cell anemia. N Engl J Med 1997;337:1584–90.
[118] Adams RJ. Stroke prevention and treatment in sickle cell disease. Arch Neurol 2001;58: 565–8.
[119] 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.
[120] Adams RJ, Brambilla D, Optimizing Primary Stroke Prevention in Sickle Cell Anemia (STOP 2) Trial Investigators. Discontinuing prophylactic transfusions used to prevent stroke in sickle cell disease. N Engl J Med 2005;353:2769–78.
[121] Vendt BA, McKinstry RC, Ball WS, et al. Silent cerebral infarct transfusion (SIT) trial imaging core: application of novel imaging information technology for rapid and central review of MRI of the brain. J Digit Imaging 2009;22(3):326–43.
[122] Kirkham FJ, Lerner NB, Noetzel M, et al. Trials in sickle cell disease. Pediatr Neurol 2006;34:450–8.
[123] deVeber G, Monagle P, Chan A, et al. Prothrombotic disorders in infants and children with cerebral thromboembolism. Arch Neurol 1998;55:1539–43.
[124] Heller C, Becker S, Scharrer I, et al. Prothrombotic risk factors in childhood stroke and venous thrombosis. Eur J Pediatr 1999;158(Suppl 3):S117–21.
[125] 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;94:3678–82.
[126] 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;31:1283–8.
[127] 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;80:763–6.

[128] Chan AK, deVeber G. Prothrombotic disorders and ischemic stroke in children. Semin Pediatr Neurol 2000;7:301–8.
[129] Lynch JK, Han CJ, Nee LE, et al. Prothrombotic factors in children with stroke or porencephaly. Pediatrics 2005;116:447–53.
[130] Danchaivijitr N, Cox TC, Saunders DE, et al. Evolution of cerebral arteriopathies in childhood arterial ischemic stroke. Ann Neurol 2006;59:620–6.
[131] Amlie-Lefond C, Bernard TJ, Sebire G, et al. Predictors of cerebral arteriopathy in children with arterial ischemic stroke: results of the International Pediatric Stroke Study. Circulation 2009;119:1417–23.
[132] Husson B, Rodesch G, Lasjaunias P, et al. Magnetic resonance angiography in childhood arterial brain infarcts: a comparative study with contrast angiography. Stroke 2002;33:1280–5.
[133] Suzuki J, Takaku A. Cerebrovascular ''moyamoya'' disease. Disease showing abnormal net-like vessels in base of brain. Arch Neurol 1969;20:288–99.
[134] Mineharu Y, Takenaka K, Yamakawa H, et al. Inheritance pattern of familial moyamoya disease: autosomal dominant mode and genomic imprinting. J Neurol Neurosurg Psychiatr 2006;77:1025–9.
[135] Ikeda H, Sasaki T, Yoshimoto T, et al. Mapping of a familial moyamoya disease gene to chromosome 3p24.2-p26. Am J Hum Genet 1999;64:533–7.
[136] Mineharu Y, Liu W, Inoue K, et al. Autosomal dominant moyamoya disease maps to chromosome 17q25.3. Neurology 2008;70:2357–63.
[137] Sakurai K, Horiuchi Y, Ikeda H, et al. A novel susceptibility locus for moyamoya disease on chromosome 8q23. J Hum Genet 2004;49:278–81.
[138] Roach ES, Golomb MR, Adams R, et al. Management of Stroke in Infants and Children: A Scientific Statement from a Special Writing Group of the American Heart Association Stroke Council and the Council on Cardiovascular Disease in the Young. Stroke 2008;39:2644–91.
[139] Kirkham FJ, Hogan AM. Risk factors for arterial ischemic stroke in childhood. CNS Spectr 2004;9:451–64.
[140] Imaizumi C, Imaizumi T, Osawa M, et al. Serial intelligence test scores in pediatric moyamoya disease. Neuropediatrics 1999;30:294–9.
[141] Fung LW, Thompson D, Ganesan V. Revascularisation surgery for paediatric moyamoya: a review of the literature. Childs Nerv Syst 2005;21:358–64.
[142] Rafay MF, Armstrong D, Deveber G, et al. Craniocervical arterial dissection in children: clinical and radiographic presentation and outcome. J Child Neurol 2006;21:8–16.
[143] Fullerton HJ, Johnston SC, Smith WS. Arterial dissection and stroke in children. Neurology 2001;57:1155–60.
[144] Rosser TL, Vezina G, Packer RJ. Cerebrovascular abnormalities in a population of children with neurofibromatosis type 1. Neurology 2005;64:553–5.
[145] Rea D, Brandsema JF, Armstrong D, et al. Cerebral arteriopathy in children with neurofibromatosis type 1. Pediatrics 2009; [epub ahead of print].
[146] Schievink WI, Michels VV, Piepgras DG. Neurovascular manifestations of heritable connective tissue disorders. A review. Stroke 1994;25:889–903.
[147] Sobata E, Ohkuma H, Suzuki S. Cerebrovascular disorders associated with von Recklinghausen's neurofibromatosis: a case report. Neurosurgery 1988;22:544–9.
[148] Hilal SK, Solomon GE, Gold AP, et al. Primary cerebral arterial occlusive disease in children. II. Neurocutaneous syndromes. Radiology 1971;99:87–94.
[149] Erickson RP, Woolliscroft J, Allen RJ. Familial occurrence of intracranial arterial occlusive disease (moyamoya) in neurofibromatosis. Clin Genet 1980;18:191–6.
[150] Ng J, Mordekar SR, Connolly DJ, et al. Stroke in a child with neurofibromatosis type 2. Eur J Paediatr Neurol 2009;13(1):77–9.
[151] Chabrier S, Rodesch G, Lasjaunias P, et al. Transient cerebral arteriopathy: a disorder recognized by serial angiograms in children with stroke. J Child Neurol 1998;13:27–32.

[152] Sebire G, Fullerton H, Riou E, et al. Toward the definition of cerebral arteriopathies of childhood. Curr Opin Pediatr 2004;16:617–22.
[153] Braun KP, Bulder MM, Chabrier S, et al. The course and outcome of unilateral intracranial arteriopathy in 79 children with ischaemic stroke. Brain 2009;132(Pt2):544–57.
[154] Braun KP, Rafay MF, Uiterwaal CS, et al. Mode of onset predicts etiological diagnosis of arterial ischemic stroke in children. Stroke 2007;38:298–302.
[155] Sebire G, Meyer L, Chabrier S. Varicella as a risk factor for cerebral infarction in childhood: a case-control study. Ann Neurol 1999;45:679–80.
[156] Askalan R, Laughlin S, Mayank S, et al. Chickenpox and stroke in childhood: a study of frequency and causation. Stroke 2001;32:1257–62.
[157] Elbers J, Benseler SM. Central nervous system vasculitis in children. Curr Opin Rheumatol 2008;20:47–54.
[158] Aviv RI, Benseler SM, DeVeber G, et al. Angiography of primary central nervous system angiitis of childhood: conventional angiography versus magnetic resonance angiography at presentation. AJNR Am J Neuroradiol 2007;28:9–15.
[159] Benseler SM, deVeber G, Hawkins C, et al. Angiography-negative primary central nervous system vasculitis in children: a newly recognized inflammatory central nervous system disease. Arthritis Rheum 2005;52:2159–67.
[160] Lanthier S, Lortie A, Michaud J, et al. Isolated angiitis of the CNS in children. Neurology 2001;56:837–42.
[161] Benseler SM, Silverman E, Aviv RI, et al. Primary central nervous system vasculitis in children. Arthritis Rheum 2006;54:1291–7.
[162] Paediatric Stroke Working Group, Royal College of Physicians of London, Clinical Effectiveness and Evaluation Unit. Stroke in childhood: clinical guidelines for diagnosis, management and rehabilitation. London: Royal College of Physicians, Clinical Effectiveness and Evaluation Unit; 2004.
[163] Monagle P, Chalmers E, Chan A, et al. Antithrombotic therapy in neonates and children: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). Chest 2008;133:887S–968S.
[164] Carpenter J, Tsuchida T, Lynch JK. Treatment of arterial ischemic stroke in children. Expert Rev Neurother 2007;7:383–92.
[165] Bernard TJ, Goldenberg NA, Armstrong-Wells J, et al. Treatment of childhood arterial ischemic stroke. Ann Neurol 2008;63:679–96.
[166] Gabis LV, Yangala R, Lenn NJ. Time lag to diagnosis of stroke in children. Pediatrics 2002;110:924–8.
[167] Rafay MF, Pontigon AM, Chiang J, et al. Delay to diagnosis in acute pediatric arterial ischemic stroke. Stroke 2008.
[168] Shellhaas RA, Smith SE, O'Tool E, et al. Mimics of childhood stroke: characteristics of a prospective cohort. Pediatrics 2006;118:704–9.
[169] Braun KP, Kappelle LJ, Kirkham FJ, et al. Diagnostic pitfalls in paediatric ischaemic stroke. Dev Med Child Neurol 2006;48:985–90.
[170] Kirkham F, Sebire G, Steinlin M, et al. Arterial ischaemic stroke in children. Review of the literature and strategies for future stroke studies. Thromb Haemost 2004;92:697–706.
[171] Eeg-Olofsson O, Ringheim Y. Stroke in children. Clinical characteristics and prognosis. Acta Paediatr Scand 1983;72:391–5.
[172] 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;8:250–5.
[173] Golomb MR, Saha C, Garg BP, et al. Association of cerebral palsy with other disabilities in children with perinatal arterial ischemic stroke. Pediatr Neurol 2007;37:245–9.
[174] Lanska MJ, Lanska DJ, Horwitz SJ, et al. Presentation, clinical course, and outcome of childhood stroke. Pediatr Neurol 1991;7:333–41.

[175] Filipek PA, Krishnamoorthy KS, Davis KR, et al. Focal cerebral infarction in the newborn: a distinct entity. Pediatr Neurol 1987;3:141–7.
[176] Koelfen W, Freund M, Konig S, et al. Results of parenchymal and angiographic magnetic resonance imaging and neuropsychological testing of children after stroke as neonates. Eur J Pediatr 1993;152:1030–5.
[177] Golomb MR, MacGregor DL, Domi T, et al. Presumed pre- or perinatal arterial ischemic stroke: risk factors and outcomes. Ann Neurol 2001;50:163–8.