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.
(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 Giulio 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
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>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>AIS (100,000/y)</th>
<th>Total (ischemic plus hemorrhagic stroke) (100,000/y)</th>
</tr>
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<tbody>
<tr>
<td>United States (Rochester) [4]</td>
<td>1965–1974</td>
<td>0.63</td>
<td>2.52</td>
</tr>
<tr>
<td>Sweden (Linköping) [171]</td>
<td>1970–1979</td>
<td>2.1</td>
<td></td>
</tr>
<tr>
<td>Japan (Tohoku) [18]</td>
<td>1974–1989</td>
<td>0.2</td>
<td>–</td>
</tr>
<tr>
<td>France (Dijon) [19]</td>
<td>1985–1993</td>
<td>7.9</td>
<td>13</td>
</tr>
<tr>
<td>United States (Cincinnati) [172]</td>
<td>1988–1989</td>
<td>1.2</td>
<td>2.7</td>
</tr>
<tr>
<td>United States (California)</td>
<td>1991–2000</td>
<td>1.2</td>
<td>2.3</td>
</tr>
<tr>
<td>Australia (Victoria) [29]</td>
<td>1993–2001</td>
<td>1.8</td>
<td>–</td>
</tr>
<tr>
<td>China (Hong Kong) [32]</td>
<td>1998–2001</td>
<td>2.1</td>
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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 (≥0.09%) of descending corticospinal tracts DWI signal abnormality, and percentage of peduncle involvement (≥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

<table>
<thead>
<tr>
<th>Study</th>
<th>Years</th>
<th>N</th>
<th>Motor abnormality (%)</th>
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<tbody>
<tr>
<td>Sran and Baumann [68]</td>
<td>1975–86</td>
<td>17</td>
<td>24</td>
</tr>
<tr>
<td>Fujimoto et al [69]</td>
<td>1980–89</td>
<td>18</td>
<td>28</td>
</tr>
<tr>
<td>Sreenan et al [60]</td>
<td>1983–97</td>
<td>46</td>
<td>48</td>
</tr>
<tr>
<td>Mercuri et al [40]</td>
<td>1991–96</td>
<td>22</td>
<td>27</td>
</tr>
<tr>
<td>Lee et al [43]</td>
<td>1997–2002</td>
<td>36</td>
<td>58</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td></td>
<td>45</td>
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<thead>
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<th>Study</th>
<th>Years</th>
<th>N</th>
<th>Motor abnormality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lanksa et al [174]</td>
<td>1976–88</td>
<td>42</td>
<td>76</td>
</tr>
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<td>De Schryver et al [31]</td>
<td>1976–95</td>
<td>37</td>
<td>59</td>
</tr>
<tr>
<td>Steinlin et al [79]</td>
<td>1985–99</td>
<td>16</td>
<td>63</td>
</tr>
<tr>
<td>Barnes et al [29]</td>
<td>1993–2001</td>
<td>95</td>
<td>42</td>
</tr>
<tr>
<td>Brower et al [72]</td>
<td>1996</td>
<td>36</td>
<td>61</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td></td>
<td>67</td>
</tr>
</tbody>
</table>
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 palsy 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].
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 \( \frac{15\%}{24} \) 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 3

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

**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 \( \sim 15\% \) 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
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 thromboembolic 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, hypercholesterolemia/hyperlipidemia, diabetes, and smoking have very little role in pediatric AIS. Although multiple risk factors have

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Focal seizures (%)</th>
<th>Generalized seizures (%)</th>
<th>Subtle/Apnea (%)</th>
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<tbody>
<tr>
<td>Levy et al [62]</td>
<td>7/7</td>
<td>43</td>
<td>57</td>
<td>0</td>
</tr>
<tr>
<td>Clancy et al [66]</td>
<td>10/11</td>
<td>100</td>
<td>0</td>
<td>10 (also with focal seizures)</td>
</tr>
<tr>
<td>Filipek et al [175]</td>
<td>7/7</td>
<td>86</td>
<td>14</td>
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<tr>
<td>Sran &amp; Baumann [68]</td>
<td>14/17</td>
<td>86</td>
<td>14</td>
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<td>Fujimoto et al [69]</td>
<td>14/18</td>
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<td>Estan &amp; Hope [21]</td>
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<td>67</td>
<td>25</td>
<td>8</td>
</tr>
<tr>
<td>Jan &amp; Camfield [70]</td>
<td>7/7</td>
<td>86</td>
<td>0</td>
<td>14</td>
</tr>
<tr>
<td>Sreenan et al [60]</td>
<td>42/46</td>
<td>40</td>
<td>24</td>
<td>36</td>
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<tr>
<td>Totala</td>
<td>306/340</td>
<td>74</td>
<td>17</td>
<td>9</td>
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*aTotals more than 100% as one patient had focal seizures and subtle seizures.*
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 peri-
natal 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 cerebro-
vascular imaging was performed, abnormalities were present in 79% [28] and 
78% [75] of patients, respectively. A population-based cohort study in Califor-
nia 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 clas-
sify 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.
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<th>CARDIAC</th>
<th>ARTERIOPATHIES</th>
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<td>Congenital CHD</td>
<td>Vasculitis Primary</td>
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<td>– Primary</td>
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<td>Iron deficiency anemia</td>
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*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 catheterization (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 hemoglobinopathy 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 ≥ 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 (≥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 antiviral 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 azathioprine 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 cardi oembolic 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 1 or 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


