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Drs Lo and Kumar discuss the unlabeled/investigational use of antithrombotic and thrombolytic agents in children with stroke.

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# Arterial Ischemic Stroke in Children and Young Adults

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## ABSTRACT

**Purpose of Review:** This article reviews risk factors, recurrence risk, evaluation, management, and outcomes of arterial ischemic stroke in children and young adults.

**Recent Findings:** The risk for recurrence and mortality appear to be low for neonatal and childhood stroke. Most children have relatively mild deficits, but those who have greater neurologic deficits, poststroke epilepsy, or strokes early in life are at risk for lower overall cognitive function. Stroke recurrence and long-term mortality after stroke in young adults are greater than originally thought. Cognitive impairments, depression, and anxiety are associated with higher levels of poststroke unemployment and represent targets for improved poststroke care. Poststroke care in young adults involves more than medical management. Self-reported memory and executive function impairments may be more severe than what is detected by objective measures. Assessment of possible cognitive impairments and appropriate management of psychological comorbidities are key to maximizing the long-term functional outcome of stroke survivors.

**Summary:** Childhood and young adult stroke survivors survive for many more years than older patients with stroke. To ensure that these survivors maximize the productivity of their lives, neurologists must not only optimize medical management but also recognize that impairments in cognition and mood may be remediable barriers to long-term functional independence.

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## INTRODUCTION

This article reviews risk factors, recurrence risk, evaluation, management, and outcomes of arterial ischemic stroke in children and young adults. In particular, recent insights in risk factors and recurrence risks in children, the implications for secondary prevention of stroke in children, and a detailed emphasis on poststroke outcomes are highlighted.

## EPIDEMIOLOGY

Ischemic stroke is uncommon in children beyond the neonatal period. One population-based estimate in California that combined a search of medical re-

ports with brain imaging reports determined an incidence of 2 per 100,000 to 4 per 100,000 in children 1 month to 18 years of age.<sup>1</sup> The group with the highest incidence of ischemic stroke is neonates, where the estimated incidence ranges from 1 in 4400 to 1 in 7700 live births.<sup>2,3</sup> Strokes also occur in utero. While the incidence is unknown, the US prevalence of cerebral palsy is 3.1 per 1000 children eight years of age.<sup>4</sup> Unilateral spasticity accounts for 19% to 35% of the total, and many of these cases are due to in utero stroke.

Ischemic stroke in young adults is estimated to account for 15% of all cases.<sup>5</sup>

Whether the incidence is changing is unclear. Evidence from epidemiologic studies in the United States suggests that the prevalence may be rising, while a study in Sweden found no evidence for a changing incidence. A study of a US national hospital discharge database found that from the years 1995/1996 to 2007/2008, the prevalence of individuals 15 to 34 years of age discharged with ischemic stroke increased by 30%, and the prevalence of individuals 35 to 44 years of age discharged with ischemic stroke increased by 37%.<sup>6</sup> Consistent with this finding was a population-based study in the greater Cincinnati-Northern Kentucky region that found the proportion of all types of strokes occurring in adults 20 to 50 years of age significantly increased from 13% to 19% from 1993/1994 to 2005.<sup>7</sup> In contrast, a population-based study from Gothenburg, Sweden, found no change in the incidence of ischemic stroke from 1987 to 2006 for adults 20 to 54 years of age.<sup>8</sup>

An in-depth discussion of the global aspects of stroke is beyond the scope of this review; however, it is important to note that 89% of strokes in children and 78% of strokes in young and middle-aged adults occur in low- and middle-income nations.<sup>9</sup> Furthermore, 63% of first-time ischemic strokes and 80% of first-time hemorrhagic strokes occur in low- and middle-income countries.<sup>10</sup> The high frequency of stroke in low- and middle-income countries is a significant social burden.

### DELAYS IN DIAGNOSIS

The relative rarity of ischemic stroke in children and young adults contributes to delays in diagnosis.<sup>11,12</sup> A 2014 study from the United Kingdom documented the delays for children that occur at every step, with a median total delay of 24 hours between symptom onset and diagnosis.<sup>13</sup> This delay in diagnosis far exceeds the therapeutic window for

treatment with IV thrombolysis or mechanical thrombectomy. A major contributor to delayed diagnosis in children is the wide range of stroke mimics that have to be considered in the differential diagnosis.<sup>14</sup> In a study of children presenting to an emergency department with the sudden onset of brain dysfunction,<sup>15</sup> migraine, seizures, and Bell's palsy were the most commonly identified diagnoses (Table 8-1). Stroke was the fourth most common diagnosis but only accounted for 7% of cases.<sup>15</sup> In contrast, in one study of adults with acute focal neurologic dysfunction, stroke accounted for 69% of attacks,

**TABLE 8-1** Stroke Mimics in Children by Frequency<sup>a</sup>

- ▶ Migraine
- ▶ Seizures/epilepsy
- ▶ Bell's palsy
- ▶ Conversion disorder
- ▶ Miscellaneous neurologic disorders
- ▶ Miscellaneous non-neurologic disorders
- ▶ Syncope
- ▶ Headache not otherwise specified
- ▶ Encephalopathy
- ▶ Cerebellitis
- ▶ Central nervous system (CNS) demyelination
- ▶ Peripheral nerve disorder
- ▶ CNS infection
- ▶ Drug intoxication
- ▶ CNS tumors
- ▶ Cord demyelination

<sup>a</sup> Data from Mackay MT, et al, *Neurology*.<sup>15</sup> [neurology.org/content/82/16/1434.short](http://neurology.org/content/82/16/1434.short).

### KEY POINTS

- In children, the group with the highest incidence of ischemic stroke is neonates, where the estimated incidence ranges from 1 in 4400 to 1 in 7700 live births.
- Strokes also occur in utero. While the incidence is unknown, the US prevalence of cerebral palsy is 3.1 per 1000 children at eight years of age. Unilateral spasticity accounts for 19% to 35% of the total, and many of these cases are due to in utero stroke.
- The relative rarity of ischemic stroke in children and young adults contributes to delays in diagnosis.

**KEY POINT**

■ The striking difference between stroke in children and young adults is the pattern of identified risk factors and associated diseases.

while seizures, sepsis, and toxic/metabolic conditions accounted for much of the remainder.<sup>16</sup> Therefore, when an acute brain attack is assessed in a child, many more alternative diagnoses must be considered than in an adult. Ideally, some type of recognition tool would help distinguish strokes from stroke mimics in children.<sup>15</sup> To date, no such tool has been developed. The authors found that an adult stroke tool did not distinguish children who had acute stroke from those who had acute facial or limb weakness due to other causes.<sup>17</sup>

Young adults who present with strokes may encounter similar delays in diagnosis when stroke is not considered because of their age. In one prospective series, 57 individuals 16 to 50 years of age had acute stroke. Of these, eight

were misdiagnosed and seven were initially released from emergency evaluation before stroke was diagnosed. What can delay stroke diagnosis further is a nonlocalizing presentation or if the symptoms are atypical or nonspecific, such as isolated acute vestibular symptoms.<sup>18</sup>

**RISK FACTORS AND RECURRENCE RISK**

The striking difference between stroke in children and young adults is the pattern of identified risk factors and associated diseases (Table 8-2).<sup>19-21</sup> In the Vascular Effects of Infection in Pediatric Stroke (VIPS) study of 355 children who had arterial ischemic stroke after the neonatal period, 30% had congenital or acquired cardiac disease, 36% had definite vascular disease

**TABLE 8-2 Risk Factors and Comorbidities for Stroke in Children and Young Adults<sup>a</sup>**

Pediatric <sup>b</sup>		Young Adult <sup>c</sup>	
<b>Definite Arteriopathy</b>	36%	<b>Well-Documented Risk Factors</b>	
Arterial dissection	7%	Tobacco smoking	56%
Transient cerebral arteriopathy	7%	Physical inactivity	48%
Moyamoya (primary or secondary)	10%	Hypertension	47%
Genetic or syndromic arteriopathy	2%	Dyslipidemia	35%
Secondary vasculitis	4%	High LDL cholesterol	42%
Fibromuscular dysplasia	1%	Low HDL cholesterol	28%
Not further classified	5%	Obesity	22%
<b>Cardiac Diseases</b>	30%	Diabetes mellitus	10%
Congenital heart disease	18%	Cardiovascular disease	9%
Acquired heart disease	6%	Coronary heart disease	4%
Isolated patent foramen ovale	6%	Congestive heart failure	1%
Stroke at cardiac surgery <72 hours	3%	Myocardial infarction	3%
Other cardiac disease	12%	Peripheral arterial disease	2%
		Valvular disease	2%
		Atrial fibrillation	2%

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**TABLE 8-2 Risk Factors and Comorbidities for Stroke in Children and Young Adults<sup>a</sup>** *Continued from page 160*

Pediatric <sup>b</sup>		Young Adult <sup>c</sup>	
<b>Other Chronic Disorders</b>		<b>Potentially Modifiable Risk Factors</b>	
Sickle cell anemia	4%	High-risk alcohol consumption	33%
Down syndrome	3%	Migraine, lifetime history	27%
Other genetic syndrome	5%	Sleep $\leq 6$ hours per night	18%
Migraine	3%	Obstructive sleep apnea	3%
Prothrombotic state	3%		
Oral contraceptives (girls)	6%		
Indwelling catheter	3%		
Iron deficiency anemia	2%		
Brain tumor	1%		
Aneurysm	1%		
PHACES syndrome/hemangioma	1%		
Hematologic malignancy	1%		
L-Asparaginase therapy	1%		
Connective tissue disease	1%		
<b>Acute systemic illness</b>			
Fever lasting >48 hours	12%		
Systemic sepsis or bacteremia	6%		
Dehydration	5%		
Shock	9%		
Viral gastroenteritis	1%		

HDL = high-density lipoprotein; LDL = low-density lipoprotein; PHACES = posterior fossa malformations, hemangioma, arterial anomalies, cardiac defects, eye anomalies, and sternal defects.

<sup>a</sup> Subcategories are not mutually exclusive.

<sup>b</sup> Pediatric data from Wintermark M, et al, *Stroke*.<sup>19</sup> [stroke.ahajournals.org/content/45/12/3597.long](http://stroke.ahajournals.org/content/45/12/3597.long).

<sup>c</sup> Adult data from von Sarnowski B, et al, *Stroke*.<sup>21</sup> [stroke.ahajournals.org/content/44/11/1119.long](http://stroke.ahajournals.org/content/44/11/1119.long).

(arteriopathy), 10% had suspected arteriopathy, and 18% had acute fever or systemic sepsis.<sup>19</sup> The risk factors seen in older adults (hypertension, hyperlipidemia, smoking, and diabetes mellitus) were not commonly found in this age range. In comparison, in a large European cross-sectional study of 3331 young adults with first-time ischemic stroke, 17% had cardioembolic disease, 13% had cervical artery dissec-

tion, 12% had small vessel occlusion, 9% had large-artery atherosclerosis, and 9% had other identified causes (not dissection), followed by thrombophilias, antiphospholipid antibody syndrome, systemic vasculitis, migraine with aura, and others.<sup>22</sup> Young adults have a substantial number of potentially modifiable risk factors<sup>20,21</sup> that are similar to those common in older adults (Table 8-2). The presence of these modifiable risk

factors offers opportunities for secondary prevention in young adults, while the opportunities for secondary prevention in children are far more limited.

The difference in presumed risk factors is even more pronounced in neonates. The identification of stroke risk factors in neonates has been limited, but pregnancy, particularly in the months just before delivery, is a relatively hypercoagulable state.<sup>23</sup> This may contribute to clotting in the placenta, which, in turn, might serve as a source of embolus to the fetus/newborn. A 2016 case-control study of infants with neonatal arterial ischemic stroke found that their mothers had experienced more intrapartum complications when compared with controls.<sup>24</sup> Prolonged rupture of membranes (21% versus 2%), fever (14% versus 3%), thick meconium (25% versus 7%), prolonged second stage (31% versus 13%), and tight nuchal cord (15% versus 6%) occurred more frequently in the mothers whose infants had stroke. The presence of more than one intrapartum complication was asso-

ciated with an increasing odds ratio for stroke in the infant. Circulating anticoagulant proteins are normally low in the fetus and do not rise to adult levels until 1 year of age.<sup>25</sup> This combination of temporary procoagulant states has been proposed to contribute to neonatal arterial ischemic stroke (**Case 8-1**).<sup>26</sup>

The risk factor profiles influence the type of stroke mechanistic evaluation for different age ranges and the strategies used for secondary prevention. A key question is the rate of stroke recurrence for children and young adults. In the VIPS study mentioned previously, 278 subjects were followed for at least 1 year after the incident stroke. Of these subjects, 40 (14%) had a recurrent stroke that occurred at a median of 23 days after the incident stroke. The risk factors associated with the highest 1-year risk of recurrence were definite arteriopathy (N = 127), with recurrence risk of 21%; possible arteriopathy (N = 34), with recurrence risk of 12%; cardioembolic stroke (N = 65), with a recurrence risk of 8.1%; and idiopathic stroke (N = 90),

### Case 8-1

A 7-year-old girl had 1 week of upper respiratory tract symptoms, then 5 days of high fever. She was treated with an antibiotic for pharyngitis, but became increasingly sleepy and confused. Reevaluation determined meningismus and an altered mental state. A blood culture from her initial evaluation grew *Streptococcus pneumoniae*. She was given fluids and antibiotics and transferred to the authors' institution for treatment of sepsis.

On arrival, she was hypotensive and obtunded; she was intubated and given fluids, vasopressors, and broad-spectrum antibiotics. An echocardiogram identified a large vegetation on the mitral valve. A lumbar puncture showed bacterial meningitis. Her neurologic examination while sedated and intubated was remarkable for meningismus, limited arousal to painful stimulation, equal movements of all limbs, and hyperactive symmetric tendon reflexes.

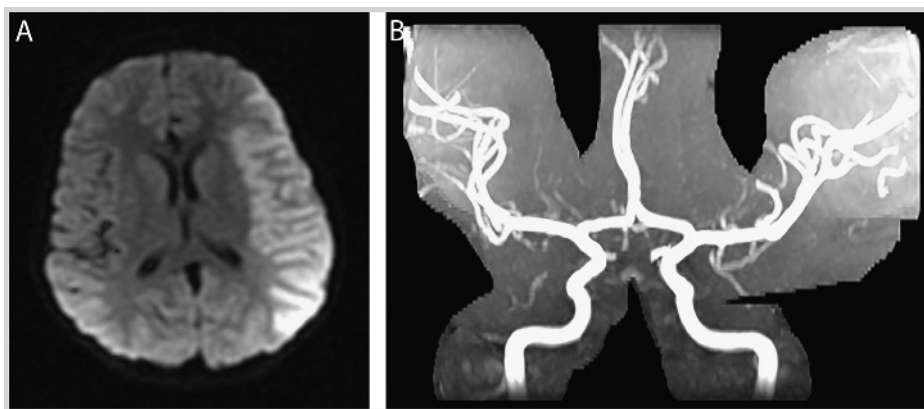
A brain MRI was obtained on the third hospital day for the mitral valve vegetation, showing abnormal diffusion in the territory of the left middle cerebral artery (MCA) but no occlusion of the major cerebral arteries (**Figure 8-1**). Repeat neurologic examination noted limited pain arousal, no right arm movement, decreased right face and leg movement, and hyperactive tendon reflexes on her right. The risk for acute recurrent embolic stroke necessitated emergency replacement of the mitral valve. She received no anticoagulation until the third postoperative day when warfarin was started. A follow-up CT scan showed cerebral edema with mild midline shift to the right. The patient's sepsis improved so she could be extubated, off sedation, and followed clinically.

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Over several weeks, movement improved in the right leg but not in the right arm or hand. She denied any abnormal or diminished sensation on her right. Her mother reported her saying yes once and laughing with her brothers, but otherwise she had no language production. Her mother felt the child was more emotional than she was prestroke.

She had ongoing problems following discharge, including receptive and expressive language deficits, slow processing, easy frustration, increased impulsivity, and difficulty persisting on cognitive tasks. She could walk under supervision up to 150 feet but needed a wheelchair for long distances. She could grasp with her right hand for a short time and pick up small blocks and puzzle pieces. She required assistance to zip or snap her jacket and pants and tie her shoes.



**FIGURE 8-1** Imaging of the patient in Case 8-1. *A*, Diffusion restriction on brain MRI in the distribution of the left middle cerebral artery consistent with extensive acute infarction. *B*, Intracranial magnetic resonance angiography (MRA) shows patent proximal segment of the left middle cerebral artery without evidence of large vessel occlusion.

**Comment.** Detection of acute stroke may be difficult in patients who are sedated because of severe acute systemic illness. Although acute revascularization strategies have been proposed in children, applications may be constrained by clinical events. Acute stroke in children presents with similar issues as in young adults; large MCA infarcts require close observation for malignant MCA syndrome. From a rehabilitation perspective, multiple challenges exist in children as they have a much longer lifespan than an adult who is elderly. How the potential for neural plasticity can best be harnessed in a child, how long rehabilitation should be pursued for children poststroke, and whether long-term interventions offer sustained benefits are questions yet to be answered.

with a recurrence risk of 4.5%.<sup>27</sup> For those children with definite arteriopathy, those with moyamoya had a 1-year recurrence risk of 32% (N = 34), those with transient cerebral arteriopathy had a 25% recurrence risk (N = 25), those with arterial dissection had a 19% recurrence risk (N = 26), and those with vasculitis secondary to acute infections had a 6.7% recurrence risk (N = 15). In children, the risk of recurrence is most strongly linked

with underlying nonatherosclerotic cerebrovascular disease. In neonatal stroke, the immediate recurrence risk appears to be very low, unless a congenital heart lesion associated with cardiogenic embolism or a hypercoagulable disorder associated with systemic thrombosis exists.<sup>28</sup>

In young adults, the problems of recurrence are very different, for increased risk exists not only for recurrent cerebral ischemia but also for myocardial

#### KEY POINT

- In neonatal stroke, the immediate recurrence risk appears to be very low, unless a congenital heart lesion associated with cardiogenic embolism or a hypercoagulable disorder associated with systemic thrombosis exists.

**KEY POINT**

■ Brain imaging is essential in children to confirm the presence of an ischemic stroke and to rule out a hemorrhagic stroke, but each modality has benefits and disadvantages to consider.

ischemia and death. In a Finnish study of 807 patients, the 5-year cumulative recurrence rate for ischemic stroke or myocardial infarction (nonfatal and fatal) was 11.5%.<sup>29</sup> Predictors of recurrence were type 1 diabetes mellitus, large artery atherosclerosis, heart failure, previous transient ischemic attack (TIA), and increasing age. Similarly, in a Dutch study of 446 patients with ischemic stroke, the 20-year risk of recurrent ischemic stroke was 19.4%.<sup>30</sup> Patients who had atherothrombotic, cardioembolic, or lacunar stroke had increased risk for recurring stroke. These findings were similar to an Italian study of 1867 young adults with first ischemic stroke. The 10-year cumulative risk for a composite end point of ischemic stroke, TIA, or myocardial infarction was 14.7%. Factors that increased the risk of these events included migraine with aura, family history of stroke, discontinuation of antiplatelet or antihypertensive medication, or antiphospholipid antibodies.

**EVALUATION**

The risk factor and recurrence profiles suggest that the evaluation for a child should be somewhat different from that for an adult. In a child, the diagnostic approach should focus on identification of possible factors that might lead to short-term recurrence, such as a cardiac source for embolism.<sup>31,32</sup> A vasculopathy may lead to further strokes from progressive stenosis or thromboembolism, so vascular imaging of the brain and neck is important to identify intracranial and extracranial pathology. ECG and echocardiogram (transesophageal when appropriate) also should be performed when a child has a first-time arterial ischemic stroke. In contrast, atherosclerosis is not known to play a significant role in pediatric arterial ischemic stroke, although lipid profiles are not systematically pursued in children. Doppler evaluations looking for carotid artery

stenosis are not routinely ordered. Atrial fibrillation is distinctly uncommon in children, so extended cardiac rhythm monitoring is not routinely performed in children with cryptogenic stroke.

Brain imaging is essential to confirm the presence of an ischemic stroke and to rule out a hemorrhagic stroke, but each modality has benefits and disadvantages to consider (Table 8-3).<sup>31</sup> CT is fast and readily available and is sensitive for hemorrhage but has low sensitivity for acute ischemia within the first 6 hours of symptom onset. MRI is sensitive to acute ischemia but is less readily available, and younger children may not be able to lie still for a complete study without general anesthesia. Some pediatric centers have developed minimum-sequence MRI protocols to reduce the scanning time when looking for an acute stroke. Such a protocol would include diffusion-weighted imaging, a fluid-attenuated inversion recovery (FLAIR) sequence, a gradient recalled echo (GRE) or susceptibility-weighted imaging (SWI) sequence, and time-of-flight MRA of the head and neck.<sup>33</sup> If the patient does not have a stroke, however, such a limited protocol may be insufficient to characterize other pathology. Magnetic resonance vascular imaging avoids radiation exposure, but the resolution limits the ability to look at medium and small cerebral vessels. CT angiography can be performed quickly, and the resolution approaches that of catheter angiography, but the amount of radiation has generated a debate about its use in young children, particularly if longitudinal follow-up is needed. Catheter angiography is the gold standard and is sensitive to small vessel disease, such as is found in vasculitis, but involves the risks of an invasive procedure and is less feasible for longitudinal follow-up. For children who have a pattern of venous infarcts,

**TABLE 8-3** Benefits and Disadvantages of Neuroimaging Techniques in Children With Suspected Stroke<sup>a</sup>

Stroke Imaging Modalities	Advantages for Infants and Young Children	Limitations for Infants and Young Children
CT brain	Fast; sufficient for hemorrhage; readily available at all hours	Radiation exposure; insensitive to acute ischemic change
MRI brain	Sensitive to early ischemic change; higher resolution than CT scan	Not readily available at some hospitals during nights, weekends, holidays; complete MRI study frequently requires sedation/anesthesia in younger children; some hospitals have protocols with limited sequences specific for stroke; implanted hardware/devices pose potential restrictions and safety concerns handled case by case
CT angiography	Fast; approaches catheter angiography in resolution	Significant radiation burden; requires postprocessing
CT venography	Fast; can localize and grade diseased venous segments	Significant radiation burden; requires postprocessing
CT perfusion	Can provide absolute and relative measures of perfusion in local regions of hemisphere	Significant radiation burden; requires postprocessing; negligible pediatric experience at present
MR angiography	Can localize and grade diseased vascular segments; no radiation exposure so can be used serially	Same limitations as MRI; resolution not as sensitive as CT angiography or catheter angiography; requires postprocessing
MR venography	Can localize and grade diseased venous segments; no radiation exposure so can be used serially	Same limitations as MRI; requires postprocessing; very susceptible to technical artifact; hypoplastic sinuses may mimic thrombotic occlusion
MR perfusion	Can provide measures of perfusion to identify regions at hemodynamic risk; no radiation exposure so can be used serially	Same limitations as MRI; requires postprocessing; emerging experience in children
SPECT perfusion	Acetazolamide challenge can demonstrate areas where perfusion varies with challenge; can be used to anticipate regions at risk for infarction	Requires radionuclide exposure; younger children require sedation/anesthesia; requires postprocessing; limited availability at pediatric centers
Catheter angiography	Gold standard	Invasive; typically requires sedation; does not provide perfusion data

CT = computed tomography; MR = magnetic resonance; MRI = magnetic resonance imaging; SPECT = single-photon emission computed tomography.

<sup>a</sup> Data from Moharir M, Deveber G, Continuum (Minneapolis, Minn).<sup>31</sup> [journals.lww.com/continuum/Fulltext/2014/04000/Pediatric\\_Arterial\\_Ischemic\\_Stroke.14.aspx](http://journals.lww.com/continuum/Fulltext/2014/04000/Pediatric_Arterial_Ischemic_Stroke.14.aspx).

SWI is a powerful tool to identify large venous or sinus thromboses. Magnetic resonance venous imaging can identify regions of diminished flow, but then hypoplastic vessels must be distinguished from occluded vessels.

### THROMBOPHILIA EVALUATION AND CONTROVERSIES

Thrombophilia is the association between laboratory markers of congenital or acquired abnormalities in the coagulation system and an increased



risk of arterial and venous thromboembolic events. Deficiencies in the endogenous anticoagulants were described in the 1960s (antithrombin) and the 1980s (protein C and protein S). More recently, point mutations in the factor V gene (*F5*) *R506Q* and factor II gene, (*F2*) *G20210A* were identified and found to be more prevalent than the previously described deficiencies in natural anticoagulants.<sup>34</sup> Other defects, including dysfibrinogenemia, elevated factor VIII activity (FVIII:C), elevated lipoprotein (a), and hyperhomocysteinemia, have since been associated with arterial ischemic stroke (Table 8-4). The prevalence of an identifiable thrombophilia

in children with arterial ischemic stroke is estimated to range from 20% to 50%.<sup>35</sup> However, given that most pediatric arterial ischemic strokes occur in the setting of multiple risk factors, the exact significance of identifying a thrombophilia on the eventual neurologic outcome, treatment selection, and duration of therapy remains unclear.

The association between thrombophilia and perinatal arterial ischemic stroke is difficult to estimate given the physiologically low levels of endogenous anticoagulants in neonates.<sup>36</sup> A 2010 meta-analysis of six studies estimated a 3.56-fold (95% confidence interval 1.02–3.99) increased risk of heterozygosity for *F5* *R506Q*, and a 2.02-fold (95% confidence interval 1.02–3.99) increased risk of heterozygosity for *F2* *G20210A* in perinatal arterial ischemic stroke/cerebral sinus venous thrombosis.<sup>37</sup> The association between thrombophilia and risk of recurrent stroke following perinatal arterial ischemic stroke is unknown.

Two systematic reviews assessed the relationship between thrombophilia and childhood-onset stroke (Table 8-5).<sup>37–39</sup> Interestingly, these reviews arrived at contradictory conclusions. Haywood and colleagues reviewed 18 case-control studies published between 1996 and 2002 investigating the association between thrombophilia and childhood-onset stroke (1 month to 18 years of age). Only protein C deficiency was statistically associated with childhood-onset stroke (odds ratio 6.5; 95% confidence interval 3–14.3).<sup>38</sup> Kenet and colleagues performed a more recent meta-analysis of 22 studies (published between 1970 and 2009) and concluded that all thrombophilias, except for antithrombin and protein S deficiencies, were statistically associated with pediatric stroke.<sup>37</sup> Different inclusion criteria for the two analyses likely explain the different results. However, these results should be

**TABLE 8-4 Common Thrombophilias Detected During Laboratory Testing**

<p>► <b>Congenital</b></p> <p>Deficiency of natural anticoagulants</p> <ul style="list-style-type: none"> <li>Antithrombin deficiency</li> <li>Protein C deficiency</li> <li>Protein S deficiency</li> </ul> <p>Blocking anticoagulant effect</p> <ul style="list-style-type: none"> <li>Factor V Leiden (<i>F5</i>) <i>R506Q</i> mutation</li> </ul> <p>Elevated levels of procoagulant proteins</p> <ul style="list-style-type: none"> <li>Prothrombin (<i>F2</i>) <i>G20210A</i> mutation</li> <li>Elevated factor FVIII level</li> </ul> <p>Others</p> <ul style="list-style-type: none"> <li>Hyperhomocysteinemia</li> <li>Elevated lipoprotein (a)</li> </ul>
<p>► <b>Acquired</b></p> <p>Antiphospholipid antibody syndrome</p>

**TABLE 8-5** Associations Between Thrombophilia and Childhood-onset Arterial Ischemic Stroke From Selected Meta-analyses and Cohort Studies<sup>a</sup>

Thrombophilia	Prevalence	Incident Childhood Arterial Ischemic Stroke Odds Ratio (95% Confidence Interval)	Recurrent Childhood Arterial Ischemic Stroke Odds Ratio (95% Confidence Interval)
Factor V R506Q <sup>b</sup>	~1:20	3.7 (2.8–4.9) <sup>37</sup> 1.2 (0.8–1.9) <sup>38</sup>	0.3 (0.4–2.3) <sup>39</sup>
Prothrombin G20210A <sup>b</sup>	~1:50	2.6 (1.7–4.1) <sup>37</sup> 1.1 (0.5–2.3) <sup>38</sup>	1.8 (0.2–15.0) <sup>39</sup>
Antithrombin deficiency <sup>b</sup>	~1:2000–5000	3.3 (0.7–15.5) <sup>37</sup> 1 (0.3–3.7) <sup>38</sup>	NA
Protein C deficiency <sup>b</sup>	~1:500	11.0 (5.1–23.6) <sup>37</sup> 6.5 (3–14.3) <sup>38</sup>	10.7 (2.5–45.8) <sup>39</sup>
Protein S deficiency <sup>b</sup>	~1:500	1.5 (0.3–6.9) <sup>37</sup> 1.1 (0.3–3.8) <sup>38</sup>	0.6 (0.05–6.4) <sup>39</sup>
Hyperhomocysteinemia	NA	1.4 (0.5–3.5) <sup>38</sup>	NA
Elevated lipoprotein (a)	NA	6.5 (4.5–9.6) <sup>37</sup>	2.8 (1.1–7.5) <sup>39</sup>
Elevated FVIII:C	NA	NA	NA
≥2 Genetic traits	NA	18.8 (6.5–54.1) <sup>37</sup>	NA
APLA syndrome	variable	7 (3.7–13.1) <sup>37</sup>	NA

APLA = antiphospholipid antibody; FVIII:C = factor VIII activity; NA = not available.

<sup>a</sup> Selected meta-analyses were of incident arterial ischemic stroke and cohort studies were of recurrent arterial ischemic stroke.

<sup>b</sup> Heterozygous trait.

interpreted cautiously since the studies analyzed were small and observational, the relationship between the timing of thrombophilia testing and stroke was often not clear, and data linking stroke with certain thrombophilias were reported only from a single group.

In stark contrast to multiple case-control and cohort studies investigating the association between thrombophilia and incident stroke, few studies have evaluated the association of thrombophilia with recurrent childhood arterial ischemic stroke. A prospective German study of 301 infants and children (7 months to 18 years of age) found 20 children (6.6%) had a recurrent stroke during a median follow-up

of 44 months. Elevated lipoprotein (a) (relative risk 4.4; 95% confidence interval 1.9–10.5) and congenital protein C deficiency (relative risk 3.5; 95% confidence interval 1.1–0.6) were associated with an increased risk of recurrent stroke.<sup>39</sup> A retrospective study from the Great Ormond Street Hospital examined 212 children with arterial ischemic stroke (21 days to 19 years of age). After a median follow-up of 2.2 years, 79 children (37%) had clinical recurrence (TIA 46, arterial ischemic stroke 29, death with reinfarction 4). In 115 children who had no acquired risk factors for stroke, the prothrombin *F2 G20210A* mutation was associated with a significantly increased risk of

**KEY POINT**

■ The authors offer thrombophilia testing to patients with childhood-onset stroke, particularly when other risk factors are not identified and after discussing risks and benefits of such testing with the patient and family. Testing is typically done acutely and repeated at 3 months if specific abnormalities are identified.

stroke (hazard ratio 7.89; 95% confidence interval 1.78–34.92).<sup>40</sup> These differing results indicate that large prospective studies are needed to clarify the association between thrombophilia and stroke recurrence in children.

**RELEVANCE OF THROMBOPHILIA TESTING IN PEDIATRIC ARTERIAL ISCHEMIC STROKE**

Although studies and meta-analyses have indicated an association between congenital/acquired thrombophilia and pediatric stroke, the exact impact of thrombophilia on risk of recurrence and clinical outcome, the economic effectiveness of testing, and the psychological impact of a thrombophilia diagnosis upon patient and family are unclear. Except for very specific clinical scenarios (eg, antiphospholipid antibody syndrome), the results of thrombophilia testing rarely impact treatment selection or duration of therapy. The proposed potential benefits of testing (guidance of testing in family members, informed decisions on future estrogen therapy in girls, and guidance of thromboprophylaxis recommendations for future high-risk situations) are not evidence based and have not been shown to improve outcomes.<sup>34</sup>

Interestingly, the ambiguity surrounding thrombophilia testing is reflected in the divergent recommendations made by international consensus guidelines. In 2002, the perinatal/pediatric subcommittee of the International Society on Thrombosis and Haemostasis (ISTH) recommended that all children with arterial or venous thrombosis be tested for genetic and acquired thrombotic states, including complete blood cell count, antithrombin activity, protein C activity, free and total protein S antigen, *F5 R506Q* and *F2 G20210A* mutation testing, *MTHFR T677T* and/or fasting homocysteine, lipoprotein (a), lupus anticoagulant, anticardiolipin antibody, and

sickle cell screen/hemoglobin electrophoresis.<sup>41</sup> Similarly, the 2008 American Heart Association guidelines concluded that it was reasonable to test for common prothrombotic conditions in childhood-onset stroke, even when other risk factors for stroke are identified.<sup>42</sup> In contrast, in 2010 the British Committee for Standards in Haematology suggested that testing for heritable thrombophilia was not indicated in children with stroke.<sup>43</sup> Similarly, the 2012 American College of Chest Physicians (ACCP) guidelines do not recommend changing the duration or intensity of anticoagulation based on the presence or absence of an identifiable thrombophilia.<sup>44</sup>

In the absence of robust evidence or consistent guidelines, it is difficult to make recommendations on thrombophilia testing in pediatric arterial ischemic stroke. At the authors' institution, thrombophilia testing is offered to patients with childhood-onset stroke, particularly when other risk factors are not identified and after discussing risks and benefits of such testing with the patient and family. Testing is typically done acutely and repeated at 3 months if specific abnormalities are identified. Given the low risk of recurrence, acute testing is rarely offered in cases of perinatal arterial ischemic stroke (with the exception of arterial ischemic stroke in the setting of neonatal purpura fulminans). Risks and benefits of thrombophilia testing are usually discussed with families at 1-year follow-up and testing is performed for specific cases, such as in patients with a strong family history of thrombosis or when a patient is perceived to be at high risk for recurrent thrombotic events (eg, complex congenital heart disease) in which there might be a role of future thromboprophylaxis during high-risk situations. Standard thrombophilia testing at the

authors' center includes antiphospholipid antibodies (ie, lupus anticoagulant, IgG and IgM isotype anticardiolipin antibodies, IgG and IgM isotype  $\beta$ 2 glycoprotein-I antibodies), *F5 R506Q* and *F2 G20210A* mutation analysis, antithrombin activity, protein C and protein S activity, fibrinogen level, D-dimer, FVIII:C, fasting lipoprotein (a), and homocysteine level. Given that recent evidence suggests that polymorphisms in the *MTHFR* gene do not result in elevated levels of homocysteine and are not, by themselves, associated with an increased risk of thrombosis, we no longer test for *MTHFR* variants.<sup>45</sup>

### **FURTHER DIAGNOSTIC EVALUATIONS**

In some instances, the acute clinical setting provides obvious clues for the cause of the stroke, eg, ischemic strokes detected concurrent with extracorporeal membrane oxygenation or cortical venous infarcts occurring with bacterial meningitis. In such patients, the extent of the evaluation may be more tailored and less protocol driven. Typically, though, the cause of the stroke is not apparent at onset, so a lumbar puncture should be considered, especially if the patient is febrile. Additionally, a history of varicella should be sought, and a serum varicella titer should be considered. Screens for autoimmune disease, such as an erythrocyte sedimentation rate, antinuclear antibody, and complement profile, should be considered, particularly when multiple organ systems appear to be affected. A large number of genetic disorders are associated with stroke in children, such as neurofibromatosis type 1 or trisomy 21 syndrome, but clinical clues that the patient has a genetic disorder or a neurocutaneous syndrome usually exist. Disorders of mitochondrial function can be difficult to diagnose,<sup>46</sup> but

they should be suspected when characteristic periventricular infarcts are seen coupled with multisystem impairment (eye, hearing, cardiac, hepatic, renal) or lactic acidosis. A 2015 consensus statement described in detail the steps to evaluate suspected mitochondrial disease.<sup>46</sup>

The necessary diagnostic testing in children who sustain a perinatal stroke is less clear. Since mother and fetus are in relatively prothrombotic states close to term,<sup>23</sup> screening tests for thrombophilia may be abnormal, but it is not clear that these abnormalities translate into increased risk for future strokes or specific management of future pregnancies. Echocardiography to evaluate for congenital heart lesions is appropriate. Imaging evaluation of the cervical vessels, particularly in those children who experienced a traumatic birth, is also appropriate.

The diagnostic evaluation for an initial stroke in the young adult is similar to that for the older adult. Illicit drug use should be considered as a possible cause for stroke in the young adult. In a case-control study of young adults with stroke, acute cocaine use, particularly in the smoked form, was associated with a nearly eightfold increase in stroke risk.<sup>47</sup> The role of a patent foramen ovale as a cause for stroke is still being debated, but a large randomized trial in patients who had cryptogenic stroke and patent foramen ovale comparing device closure with medical management found no difference in stroke recurrence between the two groups.<sup>48</sup> Genetic disorders are rare causes of ischemic stroke but should be considered in young adults when an obvious cause cannot be found and particularly when clinical features suggest a diagnosis. Fabry disease; cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) and the recessive form,

cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL); *COL4A1* and *TREX1* mutations; mitochondrial disorders, such as mitochondrial encephalomyopathy, lactic acidosis, and strokelike episodes (MELAS)<sup>5</sup>; Marfan syndrome; and Ehlers-Danlos syndrome type IV can all present with stroke in a young person whose underlying diagnosis was not previously recognized.<sup>49</sup> In patients with cryptogenic stroke, additional cardiac rhythm monitoring may be indicated. Recent advances in cardiac telemetry have shown that paroxysmal atrial fibrillation may occur intermittently and can be missed even with 24-hour monitoring; these patients have a higher risk for stroke than patients without atrial fibrillation.<sup>50</sup>

### ACUTE MANAGEMENT

The acute management of stroke in young adults is not fundamentally different from that in older adults. Since those details are covered extensively elsewhere in this issue, they will not be addressed here. Instead, acute management will focus upon aspects germane to children.

The majority of neonates with symptomatic arterial ischemic stroke present with seizures, so the initial management involves seizure monitoring and acute treatment with antiepileptic drugs.<sup>28</sup> About one-third require resuscitation and almost one-quarter have systemic illness, so cardiorespiratory stabilization and treatment of associated systemic illness are critical to acute management. A source for recurrent cardioembolism and sustained prothrombotic states occur in less than 20%, so routine antithrombotic treatment is not recommended unless one of these conditions is identified.<sup>31</sup>

After the neonatal period, initial management involves basic supportive care:

adequate oxygenation, assurance of airway integrity, and maintenance of adequate hydration while avoiding hypotonic fluids. Blood pressure should be maintained to ensure adequate cerebral perfusion, and hypotension should be avoided. Mild hypertension can be tolerated to preserve cerebral perfusion as long as blood pressures are not severely elevated. If severely elevated blood pressures must be lowered, treatment should be gradual to avoid precipitous hypotension that could impair cerebral perfusion. Depending upon the size and location of the acute ischemic infarct, monitoring for malignant MCA infarction syndrome, aspiration risk, or herniation risk are warranted. Patients with small cortical infarcts are less likely to need intensive observation once an aspiration risk has been excluded, while patients with large MCA infarcts or cerebellar or brainstem infarcts need intensive observation until the acute cerebral edema has resolved.

If a child has acute stroke from sickle cell anemia, acute transfusion or exchange transfusion with the guidance of a hematologist is the treatment of choice.<sup>51</sup> If the source of a stroke is unknown and cervical vessel dissection, focal arteriopathy, or cardiac embolism are suspected, anticoagulation with unfractionated heparin/low-molecular-weight heparin or antiplatelet therapy with aspirin are appropriate for acute management.<sup>44</sup> At the authors' institution, ongoing anticoagulation is preferred for patients with extracranial dissection and cardioembolic stroke (with low-molecular-weight heparin or vitamin K antagonist [warfarin]). The duration of anticoagulation therapy is about 3 months for cardioembolic stroke and 6 weeks to 3 months for patients with extracranial dissection (based on follow-up radiologic assessment).<sup>44</sup> Once dissection and embolism have been excluded, we tend to

offer antiplatelet therapy (aspirin) for secondary prophylaxis for a minimum of 2 years. Thrombophilias that are clinically significant must be distinguished from population polymorphisms, and their treatment should involve the input of a hematologist.

Patients who have moyamoya disease or moyamoya syndrome (when the vasculopathy occurs in association with diseases such as sickle cell disease, neurofibromatosis type 1, or trisomy 21 syndrome) are candidates for surgical revascularization, such as the indirect pial synangiosis or the direct superficial temporal artery-MCA anastomosis (Case 8-2).<sup>52</sup> The timing of such surgery is a matter of neurosurgical judgment, particularly with the indirect pial synangiosis<sup>52</sup>; if a sufficient degree of cerebral ischemia does not exist, there may be insufficient stimulus for vascular proliferation to occur. On the other hand, if clinical progression occurs with recurring strokes or TIAs, cognitive decline, or radiologic evidence of steady vascular occlusion, the natural history is progressive deterioration if no intervention occurs. When the patient is stable without clinical or radiologic evidence of progression, it is difficult to determine when to operate.

In selected circumstances, children with acute stroke may be candidates for IV thrombolysis and endovascular thrombectomy.<sup>33,53</sup> Publication bias toward positive results was likely for reports of IV thrombolysis in children,<sup>54</sup> and the same may be true for reports of endovascular revascularization. Obstacles that limit acute thrombolysis in children are the delays in diagnosis and the need to distinguish a stroke mimic from a stroke. If an older adolescent has a confirmed acute arterial ischemic stroke and is within the time frame for IV thrombolysis (4.5 hours) or endovascular thrombectomy (6 hours), thrombolysis is reasonable if published

inclusion and exclusion criteria are rigorously followed and the patient is managed according to well-established protocols.<sup>33</sup> Thrombolysis in younger children should be pursued with great caution. Despite isolated case reports of successful endovascular thrombectomy in very young children, careful technical consideration should be given to what stent retrievers can be safely used in small cerebral vessels. At the authors' institution, endovascular thrombectomy in preteen children is not an option. Furthermore, since definite vasculopathy is a significant cause of ischemic stroke in children, neurointerventionalists must be keenly aware that they may be dealing with a very abnormal cerebrovascular system.

IV thrombolysis is most effective if a team follows a developed protocol where key groups (emergency department, radiology, pharmacy, and intensive care) have well-identified tasks. This is particularly true for endovascular thrombectomy. Not only must the interventionalist be experienced with cerebrovascular disease, but the anesthesia and catheterization laboratory teams must be able to work safely and effectively with children. If these elements cannot be assembled within the requisite time frames, it is far safer to provide supportive care rather than work outside existing guidelines. One should not feel compelled to work outside guidelines simply because a child is involved.

## SECONDARY PREVENTION

Since the recurrence risk for most neonatal arterial ischemic stroke appears to be low,<sup>31</sup> neonates are not typically treated with antithrombotic agents. Neonates who have had stroke may have few focal neurologic signs in the acute phase. Long-term management requires monitoring the infants for the later appearance of motor and

### KEY POINT

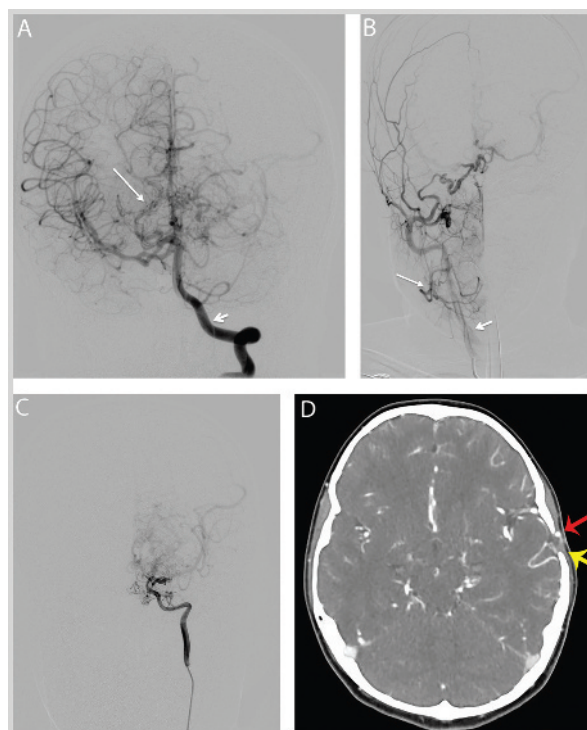
- Since the recurrence risk for most neonatal arterial ischemic stroke appears to be low, neonates are not typically treated with antithrombotic agents.

**Case 8-2**

A 7-year-old girl presented with long-standing headaches that became more severe and frequent. When she developed a headache with right hand numbness, a brain MRI was performed and thought to show an arteriovenous malformation. Magnetic resonance angiography (MRA) and catheter angiography showed enlarged vertebral and basilar vessels, right internal carotid artery occlusion, left middle cerebral artery (MCA) stenosis, and numerous collateral vessels consistent with moyamoya disease, Suzuki stage III to IV (the Suzuki stages range from I to VI, with the higher score indicating a greater severity of stenosis) (Figures 8-2A, 8-2B, and 8-2C). Scattered punctate T2 and fluid-attenuated inversion recovery (FLAIR) positive areas in the deep white matter suggested prior ischemic injury. She was initially treated with aspirin and soon had a left pial synangiosis; the right side was not addressed because of the prominent collateral supply from the posterior circulation.

Eighteen months after the pial synangiosis, she developed recurring headaches, nausea, and vomiting that varied in frequency. Topiramate 1.5 mg/kg/d was prescribed without change in headache frequency. Two years after her initial presentation, she reported an episode of right hand numbness similar to her original presentation. Her neurologic examination remained normal. CT angiography showed stable moyamoya pattern and a stable left external carotid artery branch supplying the synangiosis (Figure 8-2D). Magnetic resonance perfusion in the left hemisphere showed 10% lower perfusion than the right, but no focal area of decreased perfusion. The headaches continued with variable right hand numbness. Adding clopidogrel yielded no change, so 3 to 4 months after the headaches and right hand numbness recurred, topiramate was increased to 5 mg/kg/d and the headaches promptly decreased. She remained free of severe headache for the following 9 months.

**Comment.** This case illustrates that moyamoya can occur without any identifiable risk factors. Monitoring disease progression in children can be challenging because of the need for monitoring over many years and the limited tools to predict which areas at risk will progress to infarction. Indirect revascularization (such as a pial synangiosis where the superficial temporal artery is sutured to the pia mater) is technically more feasible in young children, but to be successful, a pial synangiosis must be performed where sufficient cerebral ischemia exists to promote the proliferation of collateral vessels. Patients with moyamoya syndrome may also have migraine, which can be extremely difficult to distinguish from the patient's moyamoya symptoms. This child's response to an adequate trial of topiramate suggests that her headaches were more likely to be migraine than moyamoya-related symptoms.



**FIGURE 8-2** Imaging of the patient in Case 8-2. *A*, Catheter angiogram, left vertebral artery injection. The *long arrow* identifies moyamoya collateral vessels. The *short arrow* illustrates that this is a left vertebral artery injection filling the right middle cerebral artery and both anterior cerebral arteries via a large right posterior communicating artery. *B*, Catheter angiogram, right common carotid artery injection. Absent flow into the internal carotid artery (*short arrow*) and collateral flow via the middle meningeal artery (*long arrow*) to the supraclinoid right internal carotid artery are seen. *C*, Catheter angiogram, left internal carotid artery injection. Severe stenocclusive disease and prominent moyamoya collateral vessels are seen. *D*, CT angiogram. The *red arrow* identifies the external carotid artery branch supplying the anastomosis. The *yellow arrow* identifies the craniotomy defect.

tone deficits and delayed developmental milestones as well as providing appropriate interventions when those problems appear. A small proportion of infants will develop epilepsy, but reliable predictors of poststroke epilepsy have not been established.

In children who sustained a stroke after the neonatal period, treatment to prevent recurrent stroke varies with the associated condition. In the VIPS study, children who had definite arteriopathy, especially those with moyamoya disease/syndrome, had the highest recurrence risks; thus, children with moyamoya disease/syndrome warrant long-term monitoring and long-term treatment with antithrombotic medication, in particular antiplatelet agents. Those who have moyamoya disease are likely candidates for revascularization surgery,

although timing of the surgery, as mentioned previously, is a complex problem. In contrast to adults,<sup>55</sup> in the VIPS study, a 19% stroke recurrence risk was seen in the small number of children with cervical artery dissection. These limited data suggest that children should be treated with anti-thrombotic agents to prevent acute recurrence until the dissection has resolved.<sup>44</sup> Children with stable focal arteriopathy should be treated with antiplatelet agents, but the duration is uncertain (**Case 8-3**). One case series of 79 children noted that of the 74 with nonprogressive arteriopathy, 13 had recurrent stroke or TIA<sup>56</sup> over a median follow-up of 1.4 years. The VIPS study showed that the 1-year recurrence risk was low, 4.5 %, for children without an identified cause for the initial stroke

#### KEY POINT

- In children who sustained a stroke after the neonatal period, treatment to prevent recurrent stroke varies with the associated condition.

### Case 8-3

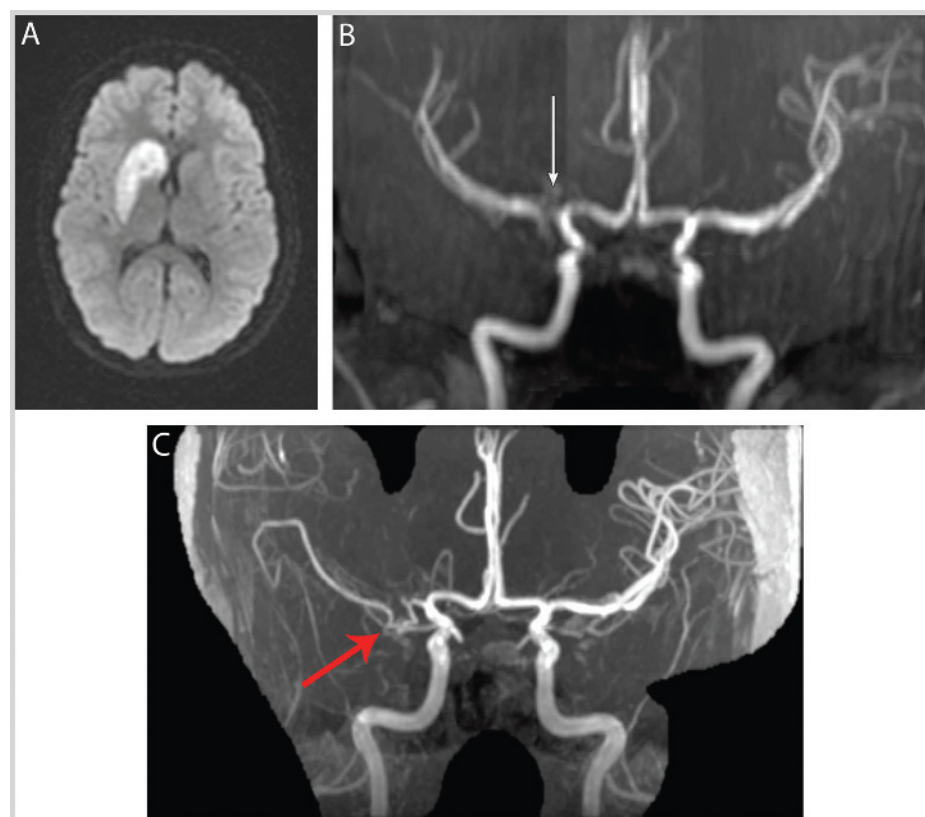
A 12-year-old girl presented with a 2-day history of headache. She became difficult to awaken and then appeared disoriented. She was noted to have left-sided facial droop, drooling, and numbness as well as weakness in her left arm and leg. Brain MRI showed an acute infarction in the right basal ganglia (**Figure 8-3A**). Further history revealed that she had been started on an oral contraceptive 10 days earlier. Family history was notable for deep venous thrombosis in the paternal grandmother when she was in her forties; there was no family history of strokes or clotting disorders. Evaluation for thrombophilia and an echocardiogram were normal. Antinuclear antibody was slightly elevated but was considered a nonspecific finding. A magnetic resonance angiogram (MRA) showed arterial stenosis within the proximal M1 segment of the right middle cerebral artery, confirmed by a catheter angiogram (**Figure 8-3B**). She was treated with aspirin.

She was readmitted 5 times soon after initial presentation for recurring right frontal headache, transient unsteadiness, or recurrence of the left-sided face and arm weakness coupled with intermittent paresthesia and numbness. Each episode cleared within 24 hours, and no new diffusion changes were noted on subsequent MRIs. In between these episodes, her neurologic examination was notable only for stable mild weakness of her left foot extensors.

Since clinical suspicion was that the events reflected recurrent hemispheric TIAs, dipyridamole was added to the aspirin. Angioplasty and bypass were considered but eventually not recommended. A single-photon emission computed tomography (SPECT) perfusion scan showed no areas of reversible hypoperfusion, and her MRA remained stable 5 months after initial presentation. She was treated with topiramate and the episodes of headache and left-sided sensory symptoms stopped, although mild headaches continued 3 to 4 times per week and she had a severe activity-limiting headache 2 to 3 times per month. About 3 years after original presentation, she developed severe depression requiring treatment but eventually responded to antidepressants and counseling. A follow-up MRA 5 years after her incident stroke showed complete occlusion of the original focal stenosis at the mid right M1 segment (**Figure 8-3C**). The distal M1 segment beyond the stenosis was reconstituted by an inferior collateral loop that had evolved.

*Continued on page 174*



*Continued from page 173*

**FIGURE 8-3** Imaging of the patient in Case 8-3. *A*, Diffusion-weighted MRI sequence demonstrates the subcortical location of the original infarction in the right basal ganglia. *B*, Intracranial magnetic resonance angiography (MRA) demonstrates an area of focal signal abnormality in the proximal right middle cerebral artery consistent with focal stenosis (*arrow*). *C*, Intracranial MRA demonstrates absence of flow in the proximal right middle cerebral artery suggestive of complete occlusion with reconstitution of the distal segments from a collateral vessel (*red arrow*).

**Comment.** This case illustrates the focal nonatherosclerotic arteriopathy that can occur in children. The patient did not have risk factors for moyamoya syndrome. The vasculopathy did not progress to a moyamoya type, but the focal stenosis eventually progressed to become complete. This case also illustrates that behavior/mood complications can occur in children and adolescents, just as in young adults.

(ie, idiopathic stroke). The duration of antithrombotic treatment in these children is uncertain, although a small study found no recurrence after 2 years following idiopathic stroke without arteriopathy.<sup>57</sup> Children with cardiac disease who have potential for further cardioembolism should be treated with an antithrombotic agent until the risk for embolism has resolved.<sup>44</sup> For chil-

dren who have had stroke due to sickle cell disease, long-term transfusion therapy is necessary to reduce recurrence; stopping long-term transfusion therapy results in an increased risk of stroke recurrence.<sup>58</sup> If the stroke occurred in association with an acute provocation, such as central nervous system infection, cardiac surgery/catheterization, or traumatic fat embolism, long-term

antithrombotic treatment is probably unnecessary unless a cause for thromboembolism persists.

Young adults have a significant risk of recurrent stroke and other cardiovascular events. As noted earlier, one prospective European cohort study found the 20-year cumulative risk of ischemic stroke recurrence was 19.4%, and the 20-year cumulative risk was 32.8% for any vascular event (including TIA, myocardial infarction, stroke).<sup>30</sup> One prospective multicenter European study found that young adults with stroke had a number of modifiable risk factors,<sup>21</sup> such as smoking (55%), physical inactivity (48.2%), hypertension (46.6%), dyslipidemias (34.9%), obesity (28.0%), and diabetes mellitus (10.3%). Secondary stroke prevention thus involves encouraging the same lifestyle changes as in older adults: avoiding smoking, increasing physical activity, making dietary modifications to achieve weight loss, and avoiding recreational drugs, especially cocaine. Aggressive treatment of hypertension, dyslipidemias, and diabetes mellitus are also obvious targets. These secondary prevention measures are particularly important in young adults because of their longer potential lifespan and the significant risk of recurring vascular events over that longer lifespan. Whether statin therapy is warranted in young adults who have stroke from non-atherosclerotic events (such as cardiac embolism) is uncertain.<sup>5</sup>

## OUTCOMES AND LONG-TERM MANAGEMENT

The challenge for managing patients who have had stroke, particularly as neonates or young children, is identifying those who have risks for significant sequelae that might respond to appropriate intervention. A proportion will have significant sequelae, but not all.

## Outcomes After Neonatal Stroke

Relatively few long-term follow-up studies of neonatal arterial ischemic stroke have been conducted, and the results can be somewhat contradictory because of differing follow-up periods. A 2015 prospective study of 100 neonates with arterial ischemic stroke reported that at 2 years of age, 39% had cerebral palsy and 31% had delayed mental performance of variable magnitude.<sup>3</sup> Significant associations existed between normal development and absence of cerebral palsy and epilepsy. In a study of 31 school-aged children who had neonatal MCA infarcts, 28 had normal IQs; of this group, three had IQs in the low normal range.<sup>59</sup> Another three had extremely low IQs, but they also had hemiplegia or epilepsy. Lesion size did not correlate with IQ.

## Outcomes After Stroke in Children

Similar to neonates, few studies of long-term outcome after stroke have been conducted in older children. The largest to date is a prospective cohort study from Switzerland that had follow-up data for 95 children for an average of 7 years after the incident stroke.<sup>60</sup> Mortality was 14% overall; those children who died in the first 6 months expired from the stroke, while those who expired later died from a range of diseases, including infection, leukemia, and cardiac disease. Of the children studied, 6% had a recurrent stroke. Fifty-five percent had a hemiparesis, although most (49% of those affected) were mild in severity, and 21% had speech impairments, but again, most (59% of those affected) were mild. Parents reported that 15% of the children had some type of psychological or psychiatric disorder.

These investigators examined the relationship between poststroke deficits

## KEY POINTS

- Secondary stroke prevention in young adults involves encouraging the same lifestyle changes as in older adults: avoiding smoking, increasing physical activity, making dietary modifications to achieve weight loss, and avoiding recreational drugs, especially cocaine. Aggressive treatment of hypertension, dyslipidemias, and diabetes mellitus are also obvious targets. These secondary prevention measures are particularly important in young adults because of their longer potential lifespan and the significant risk of recurring vascular events over that longer lifespan.
- Similar to neonates, few studies of long-term outcome after stroke have been conducted in older children.
- In a prospective cohort study of 7 years of follow-up data for children after a stroke, mortality was 14% overall, and 6% had a recurrent stroke. Fifty-five percent had a hemiparesis, although most (49% of those affected) were mild in severity, and 21% had speech impairments, but again, most (59% of those affected) were mild. Parents reported that 15% of the children had some type of psychological or psychiatric disorder.

**KEY POINTS**

- Interest is growing in the outcome of young adults who have had stroke, but the number of studies with long-term follow-up is relatively small.
- A Dutch study of outcomes 9 years after the incident stroke found that 10% of young adult ischemic stroke survivors were functioning at a modified Rankin Scale score of 3 to 5 and 27% were dead. As a group, stroke survivors performed worse than controls in objective measures of processing speed, working and immediate memory, delayed memory, attention, and executive function. Depressive symptoms were present in 16% of men and 23% of women, compared with 6% in controls. Anxiety was present in 15% of men and 29% of women, compared with 12% of controls.

and cognitive outcomes.<sup>61</sup> Total IQ for the entire stroke group was not significantly different from population norms; however, distinct subgroups had significantly lower IQs. Total IQ was significantly lower in children who had more severe neurologic impairment, poorer function as measured by a modified Rankin Scale (mRS) score of 2 or more, or acute seizures with the incident stroke or poststroke epilepsy. In specific cognitive domains, children who had infarcts involving both cortical and subcortical regions had significantly lower verbal IQ and poorer working memory and performance speed. Working memory and processing speed were significantly poorer in children who had more severe neurologic impairment or poorer mRS scores.

Our own work is consistent with this finding.<sup>62</sup> In a case-control study of children who had stroke compared with controls, most of the children who had stroke had mild neurologic deficits. Greater neurologic impairment correlated with lower total IQ and reduced processing speed, adaptive behavior, and social participation. In summary, while childhood stroke survivors typically have normal cognitive function, certain subgroups will be at risk for greater cognitive impairment, and physicians should anticipate the need for greater assistance in these subgroups.<sup>63</sup>

Interest is growing in the outcome of young adults who have had stroke, but the number of studies with long-term follow-up is relatively small. One large prospective Dutch study examined a number of outcomes 9 years after the incident stroke in individuals aged 18 to 50 years. These investigators found that 10% of ischemic stroke survivors functioned at an mRS score of 3 to 5 and 27% were dead.<sup>64</sup> Greater age and higher National Institutes of Health Stroke Scale scores at stroke onset were associated with greater odds

of a poorer mRS score. Poststroke epilepsy occurred in 16% of survivors, and epilepsy was significantly associated with a poorer mRS score.<sup>65</sup> The investigators assessed subjective reports of memory and executive function impairment in the survivors and compared them with objective measures of these cognitive functions.<sup>66</sup> Stroke survivors reported subjective memory (86%) and executive function (67%) impairments at rates significantly greater than in stroke-free controls, but the magnitude of these self-reported impairments did not correlate with the magnitude of objective measures of memory or executive function. As a group, however, stroke survivors performed worse than controls in objective measures of processing speed, working and immediate memory, delayed memory, attention, and executive function.<sup>67</sup> When cognitive impairment was compared with mRS score, only impaired working memory was associated with poorer mRS scores.<sup>68</sup>

In this same cohort, depression and anxiety occurred in a significant proportion of survivors. Depressive symptoms were present in 16% of men and 23% of women, compared with 6% in controls.<sup>69</sup> Anxiety was present in 15% of men and 29% of women, compared with 12% of controls. Lower educational level and unemployment were significantly associated with depressive symptoms and anxiety. Stroke survivors reported higher levels of fatigue (41%) when compared with controls (18%); fatigue was significantly associated with poorer functional outcome on the mRS.<sup>70</sup> When survivors of ischemic and hemorrhagic stroke (89% were ischemic strokes) were compared with the general Dutch population regarding partial or full unemployment, 26% to 33% of men and women 34 to 54 years of age were unemployed, compared with 5% to 9% of the general population.<sup>71</sup>

Greater initial severity of stroke and longer duration of follow-up were significantly associated with higher likelihood of unemployment.

## CONCLUSION

The recent outcome studies in childhood and young adult stroke demonstrate two general points. Most of these stroke survivors will have longer life expectancy compared with traditional stroke survivors. Since young adults have an appreciable long-term risk of stroke recurrence and cardiovascular mortality, careful management of modifiable risk factors, such as smoking, hypertension, and obesity, are important for young adults because of their additional years of exposure. Beyond medical management, poststroke care for children and young adults requires attention to more global aspects of function, and impairments can be long term. Patients who have greater neurologic deficits are more likely to have multiple comorbidities and thus are easier to target for assistance, but neurologists should recognize that impairments in attention and working memory, which are potentially remediable, and impairments in mood and anxiety may serve as obstacles to greater functional independence.

## USEFUL WEBSITES

### Children's Hemiplegia and Stroke Association

[chasa.org](http://chasa.org)

### International Alliance for Pediatric Stroke

[iapediatricstroke.org/home.aspx](http://iapediatricstroke.org/home.aspx)

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