

Pediatric Arterial Ischemic Stroke

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KEYWORDS

- Pediatric stroke • Pediatric arterial ischemic stroke
- Neonatal stroke

Arterial ischemic stroke (AIS) is a rare, but increasingly recognized, disorder in children. Research in this area suggests that risk factors, outcomes, and even presentation are different from those of adult stroke. In particular, prothrombotic abnormalities and large vessel arteriopathies that are nonatherosclerotic seem to play a large role in the pathogenesis of childhood AIS. The purpose of this review is first to examine the epidemiology and etiologies of neonatal and childhood AIS and then provide a detailed discussion of approaches to the clinical characterization, diagnostic evaluation, and management of this disorder in pediatric patients. Long-term outcomes of recurrent AIS and neuromotor, speech, cognitive, and behavioral deficits are considered. Emphasis is on available evidence underlying current knowledge and key questions for further investigation.

CHARACTERIZATION

AIS is characterized by a clinical presentation consistent with stroke combined with radiographic evidence of ischemia or infarction in a known arterial distribution. Unless otherwise specified, throughout this article the term, “stroke,” is used synonymously with AIS. AIS in pediatrics is divided into two main categories: neonatal AIS and childhood (non-neonatal) AIS. Neonatal AIS is defined as any ischemic stroke occurring within the first 28 days of life and is subdivided further into prenatal, perinatal, and postnatal. Acute perinatal stroke usually presents with neonatal seizures during the first week of life. This differs from a presumed prenatal stroke, which typically presents at 4 to 8 months of life with an evolving hemiparesis.¹ Because of the difficulty in

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determining the exact timing of presumed prenatal AIS, some investigators combine the two classifications as presumed prenatal/perinatal AIS. In contrast to neonatal stroke, childhood AIS typically presents with sudden onset of focal neurologic symptoms and signs and (given the broad differential diagnosis) requires an MRI of the brain with diffusion-weighted images to confirm the diagnosis of AIS (AIS presentation discussed later).

EPIDEMIOLOGY

The incidence of neonatal AIS recently is estimated at approximately 1 in 4000 live births annually.² Similar estimates are provided by the United States National Hospital Discharge Survey, which recently published an incidence of 18 neonatal strokes per 100,000 births per year.³ Childhood AIS is less common than neonatal stroke, occurring one third to one tenth as often. The incidence of childhood stroke is approximately 2 to 8 in 100,000 per year in North America.^{4,5} Before the advent of MRI techniques, a Mayo Clinic retrospective analysis of cases in Rochester, Minnesota, in the late 1970s yielded an incidence of 2.5 strokes per 100,000 children per year.⁶ Although pre-MRI data likely underestimate the incidence of AIS because of the low sensitivity of CT for ischemia, more recent retrospective analyses using medical record review are subject to well-documented inaccuracies engendered by the *International Statistical Classification of Diseases, 9th Revision* coding.⁷ In addition, given the low index of suspicion for cerebrovascular events in children, the true incidence of pediatric AIS likely remains underdiagnosed.

ETIOLOGY

The etiology of neonatal and childhood AIS is in many instances poorly understood, largely owing to the low incidence of the disease in the pediatric population and the lack of sufficient multicenter data on causal factors. The traditional ischemic stroke risk factors in adults, such as hypertension, atherosclerosis, diabetes, smoking, obesity, and hypercholesterolemia, are infrequent among neonates and older children who have AIS. In some instances of childhood AIS, such as congenital heart disease, sickle cell disease, and arterial dissection, the etiology readily is understood. For instance, with regard to cardiac risk factors, the Canadian Pediatric Stroke Registry found heart disease in 25% of patients who had pediatric AIS,⁸ whereas the prevalence of patent foramen ovale (PFO) in patients who had cryptogenic stroke was 40% to 50% compared with 10% to 27% in the general population.^{9,10} Some additional important risk factors for childhood AIS are identified, including vasculopathy, infection, head and neck trauma, previous transient ischemic attack (TIA) (defined as a focal neurologic deficit lasting less than 24 hours), and prothrombotic disorders.^{11–21} Often more than one risk factor is identified. Nevertheless, in the majority of childhood AIS cases, the etiology remains unclear, resulting in a broad subgroup of idiopathic childhood AIS.

Increasingly, arteriopathy (characterized by a disturbance of arterial blood flow within the vessel) is identified as a prevalent risk factor for childhood AIS, occurring in as many as 50% to 80% of cases.^{13,22} Often this arteriopathy is secondary to dissection of carotid or vertebral arteries, which accounts for 7% to 20% of all cases of childhood AIS,^{12,22} and may be caused by neck manipulation or head and neck trauma^{23–26} (although this association may be influenced by recall bias) and in rare cases may be related to underlying connective tissues disorders (eg, collagen defects).²⁷ Nondissective arteriopathy also is related to certain infections. For example, there is a threefold increased risk for AIS within 1 year of acute varicella

zoster virus (VZV) infection in childhood.²⁸ Postvaricella arteriopathy typically exhibits a characteristic pattern of intracranial narrowing of the internal carotid artery (ICA), middle cerebral artery (MCA), and anterior cerebral artery (ACA), classically causing basal ganglia infarctions.²⁹

Increasingly, however, angiographic studies in childhood AIS identify MCA, ICA, and ACA arteriopathy without a known infectious or alternative cause; such cases consequently are characterized as idiopathic arteriopathies (Fig. 1),¹³ A minority of these cases represent early moyamoya syndrome (defined as stenosis in the terminal portion of the ICAs bilaterally with the formation of tenuous collateral arteries, producing the classic angiographic “puff of smoke”) or possible moyamoya syndrome (recently characterized as unilateral stenosis in the terminal segment of an ICA with collaterals or the presence of bilateral stenosis of the terminal portion of the ICAs without collaterals) (Fig. 2).¹² Moyamoya, in turn, may be associated with sickle cell

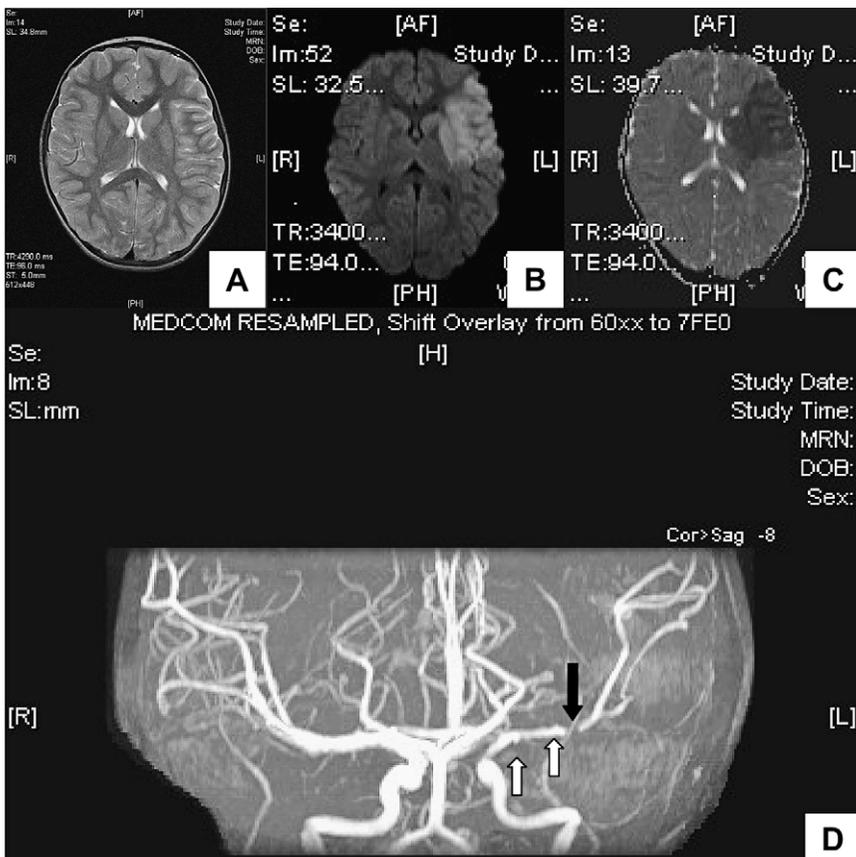


Fig. 1. Idiopathic arteriopathy. A previously healthy 6-year-old boy who had acute-onset right hemiparesis and aphasia. MRI T2 sequences (A) are unrevealing 5 hours after onset, but diffusion-weighted imaging (B) and ADC mapping (C) demonstrate cytotoxic edema, consistent with AIS in the left MCA territory. From the same examination, an anterior-posterior MRA (slightly oblique) image (D) demonstrates irregularity of the distal left ICA, extending to the proximal MCA (white arrows). There also seems to be an occlusion in the proximal MCA (black arrow).

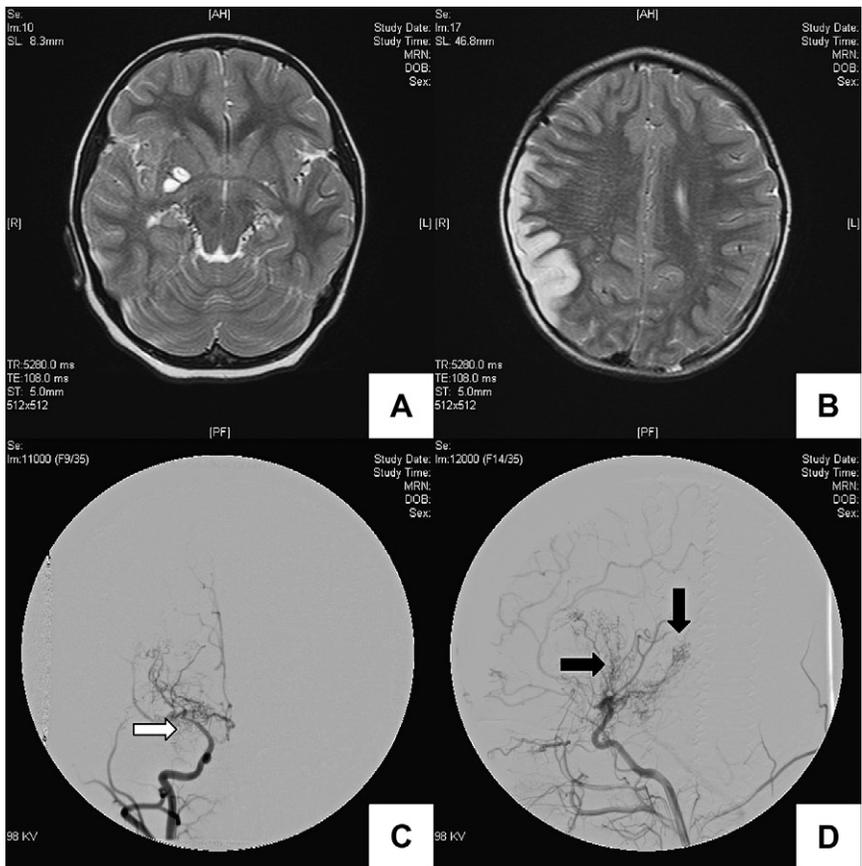


Fig. 2. Moyamoya in a 4-year-old boy who has trisomy 21. MRI demonstrates multifocal infarctions on T2 sequencing; one image reveals an old right-sided basal ganglia infarction (A), whereas another illustrates a subacute right parietal infarction (B). Follow-up angiogram of the right anterior circulation demonstrates ICA narrowing (*white arrow*) and the classic puff-of-smoke appearance of collateral circulation (*black arrows*) on anterior (C) and lateral (D) images.

anemia, trisomy 21, a history of cranial irradiation for malignancy,³⁰ or fibromuscular dysplasia; in many cases, however, moyamoya is of unclear etiology. In the majority of idiopathic arteriopathies, in which there is no progression to moyamoya, the phenomenon is termed, “transient cerebral arteriopathy,” in cases of a monophasic transient lesion that resolves or stabilizes within 6 months, and “chronic cerebral arteriopathy” in progressive cases.¹² An elucidation of the etiology of these currently idiopathic arteriopathies will enhance the understanding of childhood stroke and may have an impact on future therapeutic management and outcomes in these patients.

Thrombophilia may contribute to AIS risk via arterial thrombosis or cerebral embolism of a venous thrombus through a cardiac lesion with right-to-left shunt. Thrombophilia risk factors in pediatric AIS include antiphospholipid antibodies,^{19,20} anticoagulant deficiencies,²¹ and hyperhomocysteinemia.^{31,32} Protein C is the most commonly associated anticoagulant deficiency, although in cases of AIS (and venous thromboembolism [VTE]) after acute varicella infection, antibody-mediated acquired

protein S deficiency seems prevalent.³³ It is likely that anticoagulant deficiencies are acquired most commonly secondary to viral-mediated inflammation, as is the case in varicella. As in VTE, however, severe congenital anticoagulant deficiencies also may be contributory. Although homozygosity for factor V Leiden or prothrombin G20210A polymorphism is a strong risk factor for thrombotic events, it remains unclear whether or not the factor V Leiden or prothrombin G20210A variant in heterozygous form confers a meaningful increase in the risk for pediatric AIS.^{18–21} Greatly elevated homocysteine levels classically are associated with metabolic disorders, such as homocystinuria (resulting from cystathionine β -synthase deficiency), and mild to moderately elevated levels also occur in homozygous carriers of the methylenetetrahydrofolate reductase mutation (MTHFR C677T). Among heterozygotes, the latter cause of hyperhomocysteinemia is evident particularly in countries where routine folate supplementation of the diet is not undertaken. Another prothrombotic trait, elevated lipoprotein(a) concentration, is associated with increased odds of otherwise idiopathic (ie, apart from thrombophilia) childhood AIS.¹⁸ Other suspected blood-based risk factors for pediatric AIS, supported thus far by evidence from case series or case-control studies, include iron deficiency anemia,³⁴ polycythemia, and thrombocytosis.³⁵

Given that focal arteriopathy is an uncommon finding in neonatal AIS, stroke etiology is less clear for this group than for childhood AIS. Nevertheless, congenital cardiac anomalies are established risk factors, and thrombophilia investigation has provided additional meaningful contributions. Similar thrombophilic risk factors are identified for neonatal AIS as for childhood stroke, including factor V Leiden, protein C deficiency, and elevated lipoprotein(a).³⁶ The possibility of vertical transmission of prothrombotic molecular entities or vasoconstrictive agents (eg, antiphospholipid antibodies or cocaine, respectively) also is important to consider in the etiology of neonatal AIS but has not been studied systematically. In addition, maternal pregestational and gestational factors, such as infertility, placental infection, premature rupture of membranes, and preeclampsia, in the past few years have been found independently associated with neonatal AIS.³⁷ Recent birth registry data are further suggestive of maternal vascular disease risk factors contributing to neonatal AIS, given the finding of an association with the development of seizures in term neonates (a common manifestation of neonatal AIS);³⁸ however, further work is necessary to establish this potential risk factor. In addition, emerging data suggest a combination of maternal- and fetal-specific molecular risk factors in the development of placental pathology may be worthy of additional study regarding perinatal stroke risk.³⁹

CLINICAL PRESENTATION

The clinical presentation of AIS differs greatly among presumed prenatal, perinatal, postnatal, and childhood stroke. Within each classification, further variance of presentation exists and depends largely on the territory, extent, and timing of ischemia. The most common presentation for presumed prenatal stroke is evolving hemiparesis at 4 to 8 months of life.¹ Typically, the hand is more involved than the arm, because of the high incidence of MCA distribution infarction, and the left hemisphere is affected more commonly than the right.³⁶ Perinatal AIS has a similar predilection for the left MCA but often presents with focal neonatal seizures during the first week of life. Postnatal stroke may present similarly to perinatal AIS; in other instances, its presentation is like that of childhood stroke (discussed later).

The clinical presentation of childhood AIS is less stereotypical than that of pre- and perinatal AIS and is more dependent on the territory of ischemia. As a general rule,

patients who have small- to medium-sized events present with sudden-onset focal neurologic deficits (such as hemiparesis, visual field deficits, aphasia, cranial nerve palsies, dysphagia, and unilateral ataxia) without major alterations of consciousness. Focal neurologic deficit in the presence of preserved consciousness can aid in the diagnosis, as many more common pediatric illnesses, such as complex partial and generalized seizures or encephalitis, often have alteration of awareness. Larger strokes tend to have multiple deficits and alteration of consciousness. As discussed previously, a history of head or neck trauma, recent varicella infection, and the presence of sickle cell disease or cardiac disease may aid in understanding the underlying etiology. A recent single-center retrospective series of AIS in non-neonatal children found that a nonabrupt pattern of neurologic symptoms or signs (including those in whom the maximum severity of symptoms or signs developed more than 30 minutes from the time of symptom onset, the presentation of symptoms or signs was waxing and waning, or the presentation was preceded by recurrent transient symptoms or signs with intercurrent resolution) often was associated with findings of arteriopathy on diagnostic neuroimaging.⁴⁰

Strokes of metabolic etiology frequently manifest a progressive course of stroke-like episodes. Often, there is a family history of early-onset strokes, early-onset dementia, or severe migraines. A classic example of a metabolic stroke occurs in mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS). MELAS is caused by mitochondrial DNA defects encoding tRNA involved in the generation of ATP and the majority of cases (80%) have the mt3243 mutation.⁴¹ In addition to a maternal history of migraine and stroke, there often is a history of short stature, diabetes, hearing loss, occipital lobe seizures, and optic atrophy.⁴¹ The presentation often is characterized by stroke-like episodes with complete resolution of neurologic function. Over time, however, neurologic deficits persist, often in the form of hemianopia.⁴² Acute lesions observed by MRI can be distinguished from typical AIS by virtue of their paradoxical bright appearance on apparent diffusion coefficient (ADC) maps. In cases of a family history of cryptogenic stroke or atypical presentation of stroke, other inherited disorders (eg, non-MELAS mitochondrial DNA defects, organic acidemias, lysosomal diseases, severe congenital thrombophilias, and cerebral autosomal dominant arteriopathy with subcortical infarctions and leukoencephalopathy [CADASIL]), should be considered.⁴¹

DIAGNOSTIC EVALUATION

Diagnostic evaluation of pediatric AIS is more extensive than in adult stroke because of the broad differential diagnosis at presentation and the higher incidence of arteriopathies in childhood AIS. In a child presenting with an acute focal neurologic deficit, multiple alternative etiologies must be considered, including hypoglycemia, prolonged focal seizures, prolonged postictal paresis (Todd's paralysis), acute disseminated encephalomyelitis, meningitis, encephalitis, and brain abscess.⁴³ For this reason, MRI brain with diffusion-weighted images is becoming the radiographic modality of choice in most cases of childhood AIS. Acutely, CT can rule out hemorrhage, tumor, and abscess and may be an appropriate first-line evaluation in some cases. Typically, this needs to be followed by an MRI with diffusion-weighted images to assess for cytotoxic edema, the hallmark of acute ischemia (see **Fig. 1**). The use of perfusion-weighted imaging largely is experimental in children⁴⁴ but as acute interventions become more available in childhood AIS, this modality likely will be used increasingly as a means by which to identify potentially preservable territories of at-risk functioning brain. Furthermore, the pattern of infarction also may be suggestive of etiology. For

example, a case of multiple infarctions in separate arterial distributions likely is thromboembolic, findings of occipital and parietal strokes that cross vascular territories may suggest MELAS, a distribution between vascular territories is consistent with watershed infarction suggestive of a hypotensive etiology, and a pattern of small multifocal lesions at the gray-white junction is suspicious for vasculitis.

Although routine CT and MRI evaluate for ischemia, hemorrhage, mass/mass effect, and other non-AIS pathologies, vascular imaging (magnetic resonance angiography [MRA], CT angiography [CTA], or conventional angiography) can demonstrate arteriopathy, including dissection, stenosis, irregular contour, or intra-arterial thrombosis of the head and neck. Typically, MRA or CTA is the modality used as first-line arterial imaging, unless MRI reveals a pattern consistent with small vessel vasculitis, in which case conventional angiography is indicated. If MRA or CTA suggests moyamoya or atypical vasculature, conventional angiography is warranted, as MRA or CTA may underestimate or overestimate the degree of disease.⁴⁵

An additional important component of diagnostic imaging in pediatric AIS is echocardiography with peripheral venous saline injection. In addition to disclosing a septal defect and other congenital cardiac anomalies, echocardiography with saline injection may disclose a small lesion, including a PFO that otherwise may not be detected by conventional transthoracic echocardiography. The prevalence of PFO in patients who have cryptogenic stroke is 40% to 50% compared with 10% to 27% in the general population.^{9,10} The use of Doppler imaging during echocardiography assists in determining the direction of shunt through a lesion, although the prognostic significance of the direction of shunt is not well established in pediatric stroke.

At a minimum, diagnostic laboratory evaluation in pediatric acute AIS involves a complete blood count, toxicology screen, complete metabolic panel, erythrocyte sedimentation rate/C-reactive protein (ESR/CRP) to assess for biochemical evidence of systemic inflammation that may suggest vasculitis or infection in the etiology of AIS, β -hCG testing in postmenarchal women, fasting lipid profile, and a comprehensive thrombophilia panel (**Box 1**). Further investigation into metabolic, genetic, infectious, or rheumatologic diseases should be considered in cases of atypical presentation. In the setting of arteritis, arthritis, or elevated ESR/CRP, rheumatologic evaluation should be considered and include testing of antinuclear antibodies and rheumatoid factor. In childhood AIS with encephalopathy of unclear etiology, nonarterial distribution, or other multisystem disorders of unclear etiology (eg, hearing loss, myopathy, or endocrinopathy), testing should include lactate and pyruvate to screen for metabolic disorders and mitochondrial DNA testing for MELAS and related disorders. A lumbar puncture is indicated if infectious signs and symptoms are present and in other inflammatory states of unclear etiology. If cerebrospinal fluid (CSF) abnormalities are present, further infectious work-up and routine chemistries and blood counts are warranted. It may be prudent to test routinely for VZV, herpes simplex virus (HSV), enterovirus, and other known viral etiologies in the CSF when a lumbar puncture is performed in addition to performing routine bacterial cultures.

Because the etiology and pathogenesis of childhood AIS often are unclear at the time of diagnosis, thrombophilia testing during the diagnostic evaluation of AIS should be comprehensive (see **Box 1**). Given the association between recurrence of neonatal AIS and thrombophilia,⁴⁶ a similar investigation is warranted in neonatal AIS. A particularly important issue of thrombophilia testing specific to neonatal AIS involves antiphospholipid antibody (APA) testing (see **Box 1**). When APAs are positive in neonates who have AIS, it is informative to evaluate for APA in the mothers, as many case reports have identified vertical (ie, transplacental) transmission of IgG APA in association with neonatal AIS.⁴⁷

Box 1**Suggested diagnostic laboratory evaluation in children who have acute arterial ischemic stroke**

Complete blood count

Comprehensive metabolic panel (including hepatic indices)

ESR

CRP

Antinuclear antibody screen

Disseminated intravascular coagulation screen^a

Thrombophilia panel^b

Urine toxicology screen

Urine β -hCG (in postmenarchal woman)

Viral evaluation (if suspected by clinical presentation or if cerebral arteriopathy is demonstrated)^c

Metabolic disease screening (if suspected by clinical presentation)^d

Mitochondrial DNA mutational analyses (if suspected by clinical presentation)

^a Includes prothrombin time, activated partial thromboplastin time, fibrinogen, and D-dimer.

^b Includes protein C activity, free protein S antigen or protein S activity, antithrombin activity, factor VIII activity, factor V Leiden mutation, prothrombin 20,210 mutation, homocysteine concentration (\pm methylenetetrahydrofolate reductase mutations), antiphospholipid antibody evaluation (lupus anticoagulant testing [eg, dilute Russell's viper venom time or StaClot-LA], anticardiolipin IgG and IgM levels, anti- β 2-glycoprotein I IgG and IgM levels), and lipoprotein(a) concentration.

^c Consider blood titers of VZV, HSV, Epstein-Barr virus (EBV), enterovirus, and parvovirus; blood viral culture; CSF viral culture; CSF VZV, HSV, EBV, enterovirus, and parvovirus testing by polymerase chain reaction (PCR); *Helicobacter pylori* testing; and enteroviral PCR from oral and rectal swabs.

^d Includes blood lactate concentration, blood pyruvate concentration, serum carnitine concentration, urine organic acids profile, and serum amino acids profile.

TREATMENT

Initial management of childhood stroke should emphasize supportive measures, such as airway stabilization, administration of oxygen, maintenance of euglycemia, and treatment of seizures if they are present. Currently there are no randomized controlled trials on which to base management of medical therapies in childhood or neonatal AIS, with the exception of AIS in the setting of sickle cell disease. Guidelines exist from the American College of Chest Physicians (ACCP)⁴⁸ and the Royal College of Physicians,⁴⁹ with recommendations based on consensus, cohort studies, and extrapolation from adult studies.

Most commonly, childhood AIS is treated with antithrombotic agents, such as aspirin or heparins (unfractionated heparin [UFH] or low-molecular-weight heparin [LMWH]), unless a stroke is a complication of sickle cell anemia. The ACCP recommendations suggest treatment of all nonsickle cell childhood AIS with UFH or LMWH for 5 to 7 days and until cardioembolic stroke and dissection are excluded. For cases of cardioembolic stroke or dissection, the ACCP recommends anticoagulation for 3 to 6 months. After discontinuation of anticoagulation in all patients who have childhood AIS, long-term aspirin therapy is recommended. These ACCP recommendations are based on grade 2C data.⁴⁸ In contrast, the Royal College of Physicians

recommends initial treatment with aspirin rather than anticoagulation in all childhood AIS. A nonrandomized prospective cohort study of low-dose LMWH versus aspirin in the treatment of AIS (ie, as secondary AIS prophylaxis) in children detected no significant difference in the cumulative incidence of recurrent AIS or significant side effects between these two therapies.⁵⁰

Treatment of stroke in sickle cell disease is based largely on clinical experience and retrospective analysis. Recommendations (from ACCP)⁴⁸ include exchange transfusion to reduce hemoglobin S to levels less than 30% for acute stroke and maintaining a long-term transfusion program after initial stroke. Based on results from the Stroke Prevention Trial in Sickle Cell Anemia (STOP), which showed that regular transfusions can prevent primary stroke in high-risk children who have sickle cell anemia and whose transcranial Doppler time-averaged maximum velocities exceed 200 cm per second,⁵¹ ACCP also recommends primary prevention of AIS through annual transcranial Doppler screening for arteriopathy in children who have sickle cell disease and are older than 2 years.

Pediatric AIS with moyamoya syndrome usually is treated with surgical intervention. Anticoagulation and antiplatelet agents are considered possible therapies but typically are temporizing measures before surgery. Given heightened risks for recurrent AIS and bleeding, neurosurgical approaches at revascularization (including indirect means, such as encephaloduroarteriomyosyngiosis [EDAMS], and direct means, such as superficial temporal artery branch to MCA branch bypass) generally are preferred as first-line therapy.^{52,53} Given the bleeding risk inherent in moyamoya, long-term antithrombotic therapy perhaps best is reserved for children who have appropriately defined “possible moyamoya” in the absence of recurrent symptoms or recurrent AIS/TIA despite appropriate surgical intervention.

Case reports and case series describe the use of systemic intravenous and selective interventional arterial thrombolytic therapy in acute childhood stroke, in many instances used beyond the 3- to 6-hour window from symptom onset for which safety and efficacy is established in adult trials.^{54–57} Bleeding risks, efficacy, and outcomes are defined poorly in these studies, making it difficult to assess risk-benefit considerations of this therapy. A multicenter collaborative clinical trial approach with stringent uniform exclusion criteria ultimately will be required to address whether or not adult evidence for a beneficial role of systemic tissue plasminogen activator administration in the immediate period after onset of AIS and the optimal time window for this intervention also apply to children.

In contrast to childhood stroke, neonatal stroke usually is treated acutely with supportive measures only. Antiplatelet therapy and anticoagulation rarely are used, given the low risk for recurrence (cumulative incidence of approximately 3% at a median follow-up duration of 3.5 years).⁴⁶ In the largest follow-up series to date evaluating recurrence in neonatal AIS, all of the recurrent events were associated with an identifiable prothrombotic or cardiac risk factor.⁴⁶ Therefore, most neonates who have AIS unlikely benefit from anticoagulation or antiplatelet therapy when these risk factors are evaluated and excluded appropriately. In the event that a potent thrombophilic risk factor is identified, antithrombotic therapy should be considered on a case-by-case basis.

Long-term management of childhood and neonatal AIS ideally should be coordinated by a multidisciplinary team that has pediatric stroke expertise and includes a neurologist, hematologist, rehabilitation physician (along with physical, occupational, and speech therapy services), and neuropsychologist. Children who have hemiparesis should be considered for constraint therapy, a method in which the unaffected arm is restrained, thereby training use of the paretic arm. Recent studies have

demonstrated a potential benefit of this therapy.⁵⁸ Furthermore, the impact of rehabilitative and neuropsychologic interventions on the neuromotor and academic progress and future needs of patients who have pediatric AIS should be reassessed regularly during extended follow-up. Finally, attention should be given to assessing and monitoring the psychologic impact of AIS on patients and their families.

OUTCOMES

Recurrent AIS is one of the principal outcomes for which current medical therapies are undertaken (ie, secondary stroke prophylaxis), and the risk for recurrence after non-neonatal AIS varies between approximately 20% and 40% at a fixed follow-up duration of 5 years.^{17,59} Certain risk factors in the childhood population are associated with a higher recurrence risk. A recent United States population-based cohort study demonstrated a 66% recurrence risk in children who have abnormal vascular imaging as compared with a negligible recurrence risk in AIS victims who have normal vascular imaging at presentation.⁶⁰ Previously, a large multicenter German prospective cohort study of childhood AIS demonstrated a similar increased risk for recurrence in AIS patients who had vasculopathy.⁶¹ It has become clear, therefore, over the past several years that arterial abnormalities impart an increased risk for recurrence. Patients who have moyamoya, in particular, are at greatly increased risk for recurrent AIS and persistent neurologic deficits.^{17,22,62}

The risk of recurrent AIS also seems to increase with the number of AIS risk factors.⁵⁹ In particular, elevated serum levels of lipoprotein(a), congenital protein C deficiency, and vasculopathy are independent risk factors for recurrent AIS.⁶¹ Some studies also suggest a possible relationship between anticardiolipin IgG antibodies and recurrence, although this association has not reached statistical significance.⁶³

Neuromotor, language, and cognitive outcomes of childhood and neonatal AIS are highly variable and dependent on stroke size, comorbid conditions, and age at diagnosis. Long-term sequelae include residual neurologic deficits (especially hemiparesis), learning disabilities, seizures, and cognitive impairments. The magnitude of these outcomes and their prediction are less clear in childhood AIS than neonatal stroke, perhaps because of the greater heterogeneity in stroke subtypes and distributions (primarily MCA territory) in the former group. A few cohort study analyses indicate that 30% of survivors of childhood AIS have normal motor function at an average follow-up of 6 months to 2.5 years.^{22,64} The cumulative incidence of seizure after childhood AIS seems to be 25% to 33% and of behavioral concerns from 29% to 44% at 5 to 7 years of follow-up.^{65,66}

In neonatal AIS, the risk for recurrence is approximately 0% to 3% at an average follow-up of 3.5 to 6 years.^{46,59} As discussed previously, recurrence in neonatal AIS seems confined primarily to patients who have prothrombotic abnormalities and congenital heart disease.⁴⁶ Much evidence has emerged recently with regard to prediction of outcomes in neonatal AIS. An abnormal background on early neonatal encephalography and an ischemia distribution that includes the internal capsule, basal ganglia, and the surrounding cortex are associated with the development of hemiplegia or asymmetry of tone without hemiplegia.^{67,68} Acute findings on MRI are predictive of hemiparesis in several series. The presence of signal abnormalities in the posterior limb of the internal capsule or the cerebral peduncles on magnetic resonance with diffusion-weighted imaging and ADC mapping in neonatal acute AIS is associated with the development of unilateral motor deficit.^{69,70} Most recently, abnormal signal in the descending corticospinal tract on magnetic resonance with diffusion-weighted imaging in neonates who have AIS has been evaluated; the

percentage of cerebral peduncle affected and the total length of descending corticospinal tract involved correlates with the development of hemiparesis.⁷¹

Expressive speech impairments were noted in 12% of perinatal/neonatal and 18% of non-neonatal AIS cases in a single study.⁵³ As for neuropsychologic outcomes, cognitive or behavioral deficits were discerned in 3% to 14% of children who had neonatal AIS at an average follow-up of 2 to 6 years.^{68,72}

Despite important work to date in the field, prediction of outcomes and risk stratification in neonatal and childhood stroke remain largely in their infancy. Given the current limited knowledge of prognostic factors in pediatric AIS, it is hoped that within the next few years, large multicenter cohort analyses will permit further risk stratification, laying the foundation for interventional clinical trials.

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REFERENCES

1. Golomb MR, MacGregor DL, Domi T, et al. Presumed pre- or perinatal arterial ischemic stroke: risk factors and outcomes. *Ann Neurol* 2001;50(2):163–8.
2. Nelson K, Lynch JK. Stroke in newborn infants. *Lancet Neurol* 2004;3:150.
3. Lynch JK, Hirtz DG, DeVeber G, et al. Report of the National Institute of Neurological Disorders and Stroke workshop on perinatal and childhood stroke. *Pediatrics* 2002;109:116–23.
4. Kittner SJ, Adams RJ. Stroke in children and young adults. *Curr Opin Neurol* 1996;9:53–6.
5. Giroud M, Lemesle M, Gouyon JB, et al. Cerebrovascular disease in children under 16 years of age in the city of Dijon, France: a study of incidence and clinical features from 1985 to 1993. *J Clin Epidemiol* 1995;48:1343–8.
6. Schoenberg BS, Mellinger JF, Schoenberg DG, et al. Cerebrovascular disease in infants and children: a study of incidence, clinical features, and survival. *Neurology* 1978;8:763–8.
7. Golomb MR, Garg BP, Saha C, et al. Accuracy and yield of ICD-9 codes for identifying children with ischemic stroke. *Neurology* 2006;67:2053–5.
8. DeVeber G. Risk factors for childhood stroke: little folks have different strokes! *Ann Neurol* 2003;52(3):167–73.
9. Wu LA, Malouf JF, Dearani JA, et al. Patent foramen ovale in cryptogenic stroke. *Arch Intern Med* 2004;164:950–6.
10. Lechat P, Mas MJ, Lascault P, et al. Prevalence of patent foramen ovale in patients with stroke. *N Engl J Med* 1988;318:1148–52.
11. Chabrier S, Lasjaunias P, Husson B, et al. Ischaemic stroke from dissection of the craniofacial arteries in childhood: report of 12 patients. *Eur J Paediatr Neurol* 2003;7:39–42.
12. Sebire G, Fullerton H, Riou E, et al. Toward the definition of cerebral arteriopathies in childhood. *Curr Opin Pediatr* 2004;16:617–22.
13. Danchaivijitr N, Cox TC, Saunders DE, et al. Evolution of cerebral arteriopathies in childhood arterial ischemic stroke. *Ann Neurol* 2006;59:620–6.
14. Shaffer L, Rich PM, Pohl KRE, et al. Can mild head injury cause ischaemic stroke? *Arch Dis Child* 2003;88:267–9.

15. Kieslich M, Fiedler A, Heller C, et al. Minor head injury as cause and co-factor in the aetiology of stroke in childhood: a report of eight cases. *J Neurol Neurosurg Psychiatry* 2002;73:13–6.
16. Ganesan V, Prengler M, McShane MA, et al. Investigation of risk factors in children with arterial ischemic stroke. *Ann Neurol* 2003;53:167–73.
17. Ganesan V, Prengler M, Wade A, et al. Clinical and radiological recurrence after childhood arterial ischemic stroke. *Circulation* 2006;114:2170–7.
18. Nowak-Göttl U, Sträter R, Heinecke A, et al. Lipoprotein (a) and genetic polymorphisms of clotting factor V, prothrombin, and methylenetetrahydrofolate reductase are risk factors of spontaneous ischemic stroke in childhood. *Blood* 1999;94:3678–82.
19. Kenet G, Sadetzki S, Murad H, et al. Factor V Leiden and antiphospholipid antibodies are significant risk factors for ischemic stroke in children. *Stroke* 2000;31:1283–8.
20. Sträter R, Vielhaber H, Kassenböhmer R, et al. Genetic risk factors of thrombophilia in ischaemic childhood stroke of cardiac origin. A prospective ESPED survey. *Eur J Pediatr* 1999;158(Suppl 3):S122–5.
21. Haywood S, Liesner R, Pindora S, et al. Thrombophilia and first arterial ischaemic stroke: a systematic review. *Arch Dis Child* 2005;90:402–5.
22. Chabrier S, Husson B, Lasjaunias P, et al. Stroke in childhood: outcome and recurrence risk by mechanism in 59 patients. *J Child Neurol* 2000;15:290–4.
23. Rubinstein SM, Peerdeman SM, van Tulder MW, et al. A systematic review of the risk factors for cervical artery dissection. *Stroke* 2005;36:1575–80.
24. Patel H, Smith RR, Garg BP. Spontaneous extracranial carotid artery dissection in children. *Pediatr Neurol* 1995;13:55–60.
25. Reess J, Pfandl S, Pfeifer T, et al. Traumatic occlusion of the internal carotid artery as an injury sequela of soccer. *Sportverletz Sportschaden* 1993;2:88–9.
26. Tekin S, Aykut-Bingol C, Aktan S. Case of intracranial vertebral artery dissection in young age. *Pediatr Neurol* 1997;16:67–70.
27. Brandt T, Orberk E, Weber R, et al. Pathogenesis of cervical artery dissections. Association with connective tissue abnormalities. *Neurology* 2001;57:24–30.
28. Askalan R, Laughlin S, Mayank S, et al. Chickenpox and stroke in children. *Stroke* 2002;32:1257–62.
29. Lanthier S, Armstrong D, Doni T, et al. Post-varicella arteriopathy of childhood. *Neurology* 2005;64:660–3.
30. Bowers DC, Liu Y, Leisenring W, et al. Late-occurring stroke among long-term survivors of childhood leukemia and brain tumors: a report from the childhood cancer survivor study. *J Clin Oncol* 2006;24:5277–82.
31. van Beynum IM, Smeitink JAM, den Heijer M, et al. Hyperhomocysteinemia. A risk factor for ischemic stroke in children. *Circulation* 1999;99:2070–2.
32. Cardo E, Vilaseca MA, Campistol J, et al. Evaluation of hyperhomocysteinemia in children with stroke. *Eur J Paediatr Neurol* 1999;3:113–7.
33. Josephson C, Nuss R, Jacobson L, et al. The varicella autoantibody syndrome. *Pediatr Res* 2001;50:345–52.
34. Maguire JL, deVeber G, Parkin PC. Association between iron-deficiency anemia and stroke in young children. *Pediatrics* 2007;120:1053–7.
35. Alvarez-Larran A, Cervantes F, Bellosillo B, et al. Essential thrombocythemia in young individuals: frequency and risk factors for vascular events and evolution to myelofibrosis in 126 patients. *Leukemia* 2007;21:1218–23.
36. Kirton A, deVeber G. Cerebral palsy secondary to perinatal ischemic stroke. *Clin Perinatol* 2006;33(2):367–86.

37. Lee J, Croen LA, Backstrand KH, et al. Maternal and infant characteristics associated with perinatal arterial stroke in the infant. *JAMA* 2005;293:723.
38. Hall DA, Wadwa RP, Goldenberg NA, et al. Maternal cardiovascular risk factors for term neonatal seizures: a population-based study in Colorado 1989–2003. *J Child Neurol* 2006;21:795–8.
39. Sood R, Zogg M, Westrick RJ, et al. Fetal and maternal thrombophilia genes cooperate to influence pregnancy outcomes. *J Exp Med* 2007;204:1049–56.
40. Braun KPJ, Rafay MF, Uiterwaal CSPM, et al. Mode of onset predicts etiological diagnosis of arterial ischemic stroke in children. *Stroke* 2007;38:298–302.
41. Pavlakis SG, Kingsley PB, Bialer MG. Stroke in children: genetic and metabolic issues. *J Child Neurol* 2000;15:308–15.
42. Hirano M, Pavlakis SG. Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS): current concepts. *J Child Neurol* 1994;9:4–13.
43. Shellhaas R, Smith SE, O'Tool E, et al. Mimics of childhood stroke: characteristics of a prospective cohort. *Pediatrics* 2006;118:704.
44. Gadian DG, Calamante F, Kirkham FJ, et al. Diffusion and perfusion magnetic resonance imaging in childhood stroke. *J Child Neurol* 2000;15:279–83.
45. Bernard TJ, Mull BR, Handler MH, et al. An 18-year-old man with fenestrated vertebral arteries, recurrent stroke and successful angiographic coiling. *J Neurol Sci* 2007;260:279–82.
46. Kurnik K, Kosch A, Sträter R, et al. Recurrent thromboembolism in infants and children suffering from symptomatic neonatal arterial stroke. A prospective follow-up study. *Stroke* 2003;34:2887–93.
47. Boffa MC, Lachassinne E. Review: infant perinatal thrombosis and antiphospholipid antibodies: a review. *Lupus* 2007;16:634–41.
48. Monagle P, Chan A, Massicotte P, et al. Antithrombotic therapy in children: the Seventh ACCP Conference on Antithrombotic and Thrombotic Therapy. *Chest* 2004;126(Suppl 3):645S–87S.
49. Paediatric Stroke Working Group. Stroke in childhood: Clinical guidelines for diagnosis, management and rehabilitation. Royal College of Physicians; 2004. Available at: http://www.rcplondon.ac.uk/pubs/books/childstroke/childstroke_guidelines.pdf. Accessed February 25, 2008.
50. Sträter R, Kurnik K, Heller C, et al. Aspirin versus low-dose molecular-weight heparin: antithrombotic therapy in pediatric ischemic stroke patients. A prospective follow-up study. *Stroke* 2001;32:2554–8.
51. Adams R, McKie V, Hsu L, et al. Prevention of a first stroke by transfusion in children with abnormal results of transcranial Doppler ultrasonography. *N Engl J Med* 1998;339:5–11.
52. Ozgur BM, Aryan HE, Levy ML. Indirect revascularization for paediatric moyamoya disease: the EDAMS technique. *J Clin Neurosci* 2006;13:105–8.
53. Khan N, Schuknecht B, Boltshauser E, et al. Moyamoya disease and Moyamoya syndrome: experience in Europe; choice of revascularization procedures. *Acta Neurochir (Wien)* 2003;145:1061–71.
54. Amlie-Lefond C, Benedict SL, Benard T, et al. Thrombolysis in children with arterial ischemic stroke: initial results from the International Paediatric Stroke Study [abstract]. *Stroke* 2007;38:485.
55. Golomb MR, Rafay M, Armstrong D, et al. Intra-arterial tissue plasminogen activator for thrombosis complicating cerebral angiography in a 17-year-old girl. *J Child Neurol* 2003;18:420–3.
56. Benedict SL, Ni OK, Schloesser P, et al. Intra-arterial thrombolysis in a 2-year-old with cardioembolic stroke. *J Child Neurol* 2007;22:225–7.

57. Thirumalai SS, Shubin RA. Successful treatment for stroke in a child using recombinant tissue plasminogen activator. *J Child Neurol* 2000;15:558.
58. Taub E, Griffin A, Nick J, et al. Pediatric CI therapy for stroke-induced hemiparesis in young children. *Dev Neurorehabil* 2007;10:3.
59. Lanthier S, Carmant L, David M, et al. Stroke in children. The coexistence of multiple risk factors predicts poor outcome. *Neurology* 2000;54:371–8.
60. Fullerton HJ, Wu YW, Sidney S, et al. Risk of recurrent childhood arterial ischemic stroke in a population-based cohort: the importance of cerebrovascular imaging. *Pediatrics* 2007;119:495–501.
61. Sträter R, Becker S, von Eckardstein A, et al. Prospective assessment of risk factors for recurrent stroke during childhood—a 5-year follow-up study. *Lancet* 2002;360:1540–5.
62. Nagata S, Matsushima T, Morioka T, et al. Unilaterally symptomatic moyamoya disease in children: long-term follow-up of 20 patients. *Neurosurgery* 2006;59: 830–6.
63. Lanthier S, Kirkham FJ, Mitchell LG, et al. Increased anticardiolipin antibody IgG titers do not predict recurrent stroke or TIA in children. *Neurology* 2004;62: 194–200.
64. Steinlin M, Pfister I, Pavlovic J, et al. The first three years of the Swiss Neuropaediatric Stroke Registry (SNPSR): a population-based study of incidence, symptoms and risk factors. *Neuropediatrics* 2005;36:90–7.
65. DeSchryver EL, Kappelle LJ, Jennekens-Schinkel A, et al. Prognosis of ischemic stroke in childhood: a long term follow up study. *Dev Med Child Neurol* 2000;42: 313–8.
66. Steinlin M, Roellin K, Schroth G. Long-term follow-up after stroke in childhood. *Eur J Pediatr* 2004;163:245–50.
67. Mercuri E, Rutherford M, Cowan F, et al. Early prognostic indicators of outcome in infants with neonatal cerebral infarction: a clinical electroencephalogram, and magnetic resonance imaging study. *Pediatrics* 1999;103:1–15.
68. Mercuri E, Barnett A, Rutherford M, et al. Neonatal cerebral infarction and neuro-motor outcome at school age. *Pediatrics* 2004;113:95–100.
69. De Vries LS, Van der Grond J, Van Haastert IC, et al. Prediction of outcome in new-born infants with arterial ischaemic stroke using diffusion-weighted magnetic resonance imaging. *Neuropediatrics* 2005;36:12–20.
70. Boardman JP, Ganesan V, Rutherford MA, et al. Magnetic resonance image correlates of hemiparesis after neonatal and childhood middle cerebral artery stroke. *Pediatrics* 2005;115:321–6.
71. Kirton A, Shroff M, Visvanathan T, et al. Quantified corticospinal tract diffusion restriction predicts neonatal stroke outcome. *Stroke* 2007;38:974–80.
72. deVeber GA, MacGregor D, Curtis R, et al. Neurologic outcome in survivors of childhood arterial ischemic stroke and sinovenous thrombosis. *J Child Neurol* 2000;15:316–24.