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Authors
McCrea, Nadine
Fullerton, Heather J
Ganesan, Vijeya

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Genetic and Environmental Associations With Pediatric Cerebral Arteriopathy

Insights Into Disease Mechanisms

Nadine McCrea, MB; Heather J. Fullerton, MD; Vijeya Ganesan, MD

See related article, p 230, 233, 240, 249 and 266

Mechanisms underlying childhood arterial ischemic stroke (AIS) are heterogeneous and poorly understood but critical for the development of targeted interventions. Current evidence suggests interplay between (mostly) rare genetic risk factors and common environmental exposures. Here, we explore this interplay in relation to cerebral arteriopathies associated with childhood AIS.

Background

Most childhood AIS is associated with nonatherosclerotic cerebral arteriopathy[1,2]—a term encompassing any pathological abnormality of the arterial circulation. This nonspecific terminology reflects the paucity of knowledge regarding underlying mechanisms. In 2014, the VIPS study (Vascular Effects of Infection in Pediatric Stroke) defined arteriopathy as the imaging appearance of an in situ arterial abnormality (stenosis, irregularity, occlusion, banding, pseudoaneurysm, and dissection flap) not attributable to an exogenous thrombus (eg, cardioembolism) and not considered a normal developmental variant.[3] It further defined arteriopathy subtypes using the 2004 consensus-based definitions described by Sébire et al[4] and the 2012 CASCADE criteria (Childhood AIS Standardized Classification and Diagnostic Evaluation).[5] These definitions use radiological and clinical characteristics to categorize patients; however, biomarkers separating distinctive arteriopathy subtypes are still lacking.

Arteries are maintained by dynamic processes responsive to genetic and local signals. Congenital arteriopathies could reflect abnormal arterial development, whereas acquired arteriopathy could arise from disruptions in vascular homeostasis, for example, endothelial injury, repair, and angiogenesis.[6]

Overall, arteriopathy increases AIS recurrence risk, which varies with subtype.[7] Diagnosis can be challenging—even with rigorous review, arteriopathy diagnosis could not be adjudicated in 34 of 355 cases.[3] Careful phenotyping is important; for example, a pattern initially called moyamoya had distinctive features in *ACTA2* mutations (Figure 1).[8] It is not meaningful to consider all arteriopathies or AIS as a single group because they likely have different pathogeneses, disease course, and treatments.

Environmental associations with childhood AIS include infection and trauma. Clinically trivial viral infection and minor trauma are ubiquitous in childhood, yet AIS is rare—so additional factors, such as genetic predisposition, are likely to be important. Inflammation is likely to play a variety of roles in childhood AIS subtypes. Although monogenic causes of childhood AIS are rare, single-gene associations with arteriopathy provide important mechanistic insights. Increasingly, it appears that, in many of these, the interaction between genetic predisposition and environmental factors is necessary to produce the ultimate disease phenotype.

Genetic Association With Childhood Cerebral Arteriopathy

The Table and Table I in the online-only Data Supplement summarize single-gene mutations associated with pediatric cerebral arteriopathy and highlight concurrent phenotypic features.

Moyamoya

Moyamoya is a rare, severe, and often progressive cerebral arteriopathy, defined radiologically by occlusive disease of the terminal internal carotid arteries with basal collaterals.[9] Moyamoya is divided into moyamoya disease (MMD—primary or isolated) and moyamoya syndrome (MMS; secondary to another disease, often genetic). Children with moyamoya are at risk of AIS, whereas adults are more prone to hemorrhagic stroke. Moyamoya is arguably the most malignant pediatric cerebral arteriopathy phenotype, with the highest risk of AIS recurrence.[7,10]

The strong ethnic bias (in East Asians) and 15% familial cases strongly implicate a genetic basis. Linkage studies have identified several HLA alleles associated with MMD

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From the Department of Neurology, Great Ormond Street Hospital for Children NHS Foundation Trust, London (N.M.); Department of Neurology, University of California, San Francisco (H.J.F.); and Clinical Neurosciences, UCL Great Ormond Street Institute of Child Health, London (V.G.).

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Correspondence to Vijeya Ganesan, MD, Clinical Neurosciences, UCL Great Ormond St Institute of Child Health, London, WC1N 1EH, UK. Email v.ganesan@ucl.ac.uk

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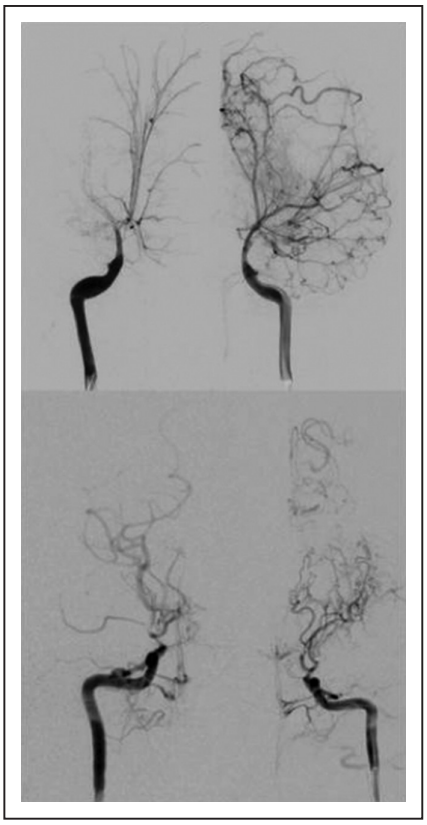

Figure 1. Contrasting appearances of ACTA2 and moyamoya disease. Catheter cerebral angiograms (frontal projection) with right and left internal carotid artery (ICA) injections. **Top** row from a patient with R179H mutation in *ACTA2* showing the typical appearances of proximal ICA ectasia, distal ICA occlusive disease, and twig-like distal ICA branches. There are no basal moyamoya collaterals. In contrast, the **bottom** row shows images from an otherwise healthy girl with moyamoya disease. There is marked occlusive disease of both terminal ICAs with moyamoya collaterals.

in East Asians: HLA-B35, HLA-B51, HLADRB1*04:05, DQB1*05:02, and *04:01. MMS is also seen in trisomy 21, Turner syndrome, sickle cell disease, and neurofibromatosis type 1 (NF1); other associations are summarized in the Table.

The p.R4810K in *RNF213* polymorphism is associated with MMD in Japanese and Koreans.[11,12] Because Japanese prevalence of MMD is 6/100 000, compared with 1% carrier rate of p.R4810K, additional factors must be required to produce moyamoya in carriers.[12,13] *RNF213* p.R4810K polymorphisms have been reported in small numbers of East Asian patients with other genetic diagnoses, which predispose to MMS, including NF1 and trisomy 21; thus *RNF213* may act as an additional modifier.[14,15] Evidence from *RNF213* knockouts suggests that loss of function could result in vascular fragility and susceptibility to hemodynamic stress and other insults.[16] Additional postulated mechanisms include a proinflammatory effect resulting in endothelial cell dysfunction and proliferation of smooth muscle cells with vascular stenosis.[17]

Neurofibromatosis Type 1

NF1—an autosomal dominant tumor-suppressor syndrome caused by mutations in the *NF1* gene—is associated with MMS and other large-vessel arteriopathies (aneurysm and arterial stenosis).[18,19] *NF1* encodes for neurofibromin—a Ras pathway inhibitor. Children with NF1 have an increased risk of stroke, with odds ratios of 8.1 for hemorrhagic stroke and 3.4 for AIS.[20] Radiotherapy for optic glioma is an additional risk factor, but even discounting this cerebral arteriopathy has been reported in 2.5% to 6% of NF1 patients.[21] Patients with asymptomatic MMS may show radiological progression and could benefit from antiplatelet therapy or revascularization.[22]

Neurofibromin is expressed in vascular endothelial cells, is a regulator of macrophage function, and is likely to have a role in pathogenesis. NF1 patients without arteriopathy have elevated levels of inflammatory cells and cytokines linked to vascular disease; thus, they may be susceptible to vascular disease, but a second hit may be required to generate arteriopathy.[23]

Most cases of MMS in NF1 are reported in whites, and this also implicates additional genetic predisposition to MMS in NF1. *RNF213* mutations have been reported in a small group of Korean patients with NF1 and MMS, and this may be a gene modifier.[14]

Mutations Causing Smooth Muscle Cell Dysfunction

ACTA2

α-Actin (encoded by *ACTA2*) forms a major part of the vascular smooth muscle cell contractile apparatus. Heterozygous *ACTA2* mutation carriers are at risk of vascular disorders, including aortic aneurysm and dissection, with high attendant mortality.[24] Heterozygous Arg179 *ACTA2* mutations are associated with a distinctive cerebrovascular phenotype[8] with proximal dilatation of carotid arteries and widespread distal occlusive arteriopathy. Unlike moyamoya, basal collaterals are absent and intracranial arteries are abnormally straight and broom like (Figure 1). Clinical features of smooth muscle dysfunction include congenital mydriasis and patent ductus arteriosus, pulmonary hypertension, bladder and bowel dysfunction, and livedo reticularis. It is notable that the vascular phenotype may be influenced by regional differences in arterial structure, namely dilatation of (proximal) elastin-containing segments of the internal carotid artery and stenosis in (distal) elastin-deficient segments.[25] We speculate this may be an example of the local environment interacting with genetic background.

MYH11

Disruptions in the smooth muscle MYH11 (myosin heavy chain 11), also part of the smooth muscle cell contractile apparatus, are associated with thoracic aortic aneurysm or aortic dissection and patent ductus arteriosus. The *MYH11* phenotype has been expanded to include moyamoya-like occlusive cerebrovascular disease.[26]

Both dominantly inherited disorders carry attendant genetic implications for family members and aortic screening.

Mutations Affecting Vascular Basement Membranes: *COL4A1* and *COL4A2*

COL4A1 and *COL4A2* sit head-to-head on chromosome 13q34, encoding the α1 and α2 chains of type IV collagen—the main component of vascular basement membranes.

Table. Diagnostic Clues in Single Gene Causes of Pediatric Cerebral Arteriopathy

		Genetic Mutation (Disease Name Given Below if Different)
History		
Family history	Stroke	AD conditions: *COL4A1*, *COL4A2*, *NF1*, *NOTCH3*, *SLC2A10*, and *JAG1*
		AR conditions: *HBB*
	Cardiac disease/TAAD	AD conditions: *ACTA2* and *MYH11*
	Neurocutaneous	AD conditions: *NF1*
	Consanguinity (or negative family history)	AR conditions: *GUCY1A3*, *CECR1*, *HTRA1*, *SAMHD1*, *PCNT*, *ABCC6*, and *HBB*
	Sickle cell trait	*HBB*
	Maternal inheritance	XLR conditions: *CBS*, *GLA*, *ATP7A*, and *BRCC3/MTCP1*
Neurological symptoms	Migraine	*COL4A1*, *COL4A2*, and *NOTCH3*
	Congenital hemiplegia	*COL4A1* and *COL4A2*
	Developmental delay	*BRCC3/MTCP1*, *ELN*, *JAG1*, *SAMHD1*, *PCNT* (motor), *ATP7A*, *CBL*, and *HBB*
	Neuropathies	*CECR1* and *HBB*
	Seizures	*NF1*, *ATP7A*, *SAMHD1*, and *HBB*
	Neurofibromata	*NF1*
	Behavioral/psychiatric	*NOTCH3* and *HTRA1*
	Encephalopathy and regression	*SAMHD1* and *ATP7A*
	Acroparesthesia	*GLA*
Other	Intermittent fever	*CECR1*
	Achalasia	*GUCY1A3*
	Vaso-occlusive crises, anemia, and acute chest syndrome	*HBB*
Examination		
Musculoskeletal	Tall stature	*CBS*
	Short stature	*BRCC3/MTCP1*, *PCNT*, and *HBB*
	Scoliosis	*NF1*
	Contractures and arthropathy	*SAMHD1* and *HBB*
	Joint laxity	*ATP7A* and *SLC2A10*
	Arachnodactyly	*SLC2A10*
	Cramps	*COL4A1* and *COL4A2*
Skin	Livedo reticularis	*ACTA2*, *GUCY1A3*, and *CECR1,*
	Raynaud syndrome	*GUCY1A3* and *SAMHD1*
	Chilblains	*SAMHD1*
	Axillary and inguinal freckling	*NF1*
	Café-au-lait spots	*NF1* and *PCNT*
	Increased laxity	*ABCC6*
	Angiokeratoderma	*GLA*
	Pallor and jaundice	*HBB*
Hair	Alopecia	*HTRA1*
	Sparse and friable	*ATP7A*
	Premature hair graying	*BRCC3/MTCP1*
Eyes	Cataracts	*COL4A1*, *COL4A2*, *BRCC3/MTCP1*, and *GLA*
	Retinal tortuosity	*COL4A1* and *COL4A2*
	Congenital mydriasis (pupils fixed and dilated)	*ACTA2*
	Optic glioma and lisch nodules	*NF1*
	Peau d'orange angioid streaks	*ABCC6*
	Neovascularisation and hemorrhage	*ABCC6* and *HBB*
	Posterior embryotoxon	*JAG1*
	Dislocated lens	*CBS*
Facial dysmorphism	Hypertelorism, long philtrum, and mild ptosis	*BRCC3/MTCP1* and *CBL*
	Small upturned nose, long philtrum, wide mouth, full lips, and small chin	*ELN*
	Microcephaly and abnormal teeth	*PCNT*
Abdomen	Splenomegaly	*HBB*
Systemic investigation findings		
Cardiovascular	Arrhythmia	*COL4A1*, *COL4A2*, and *GLA*
	Supravalvular aortic stenosis	*ELN*
	PDA	*ACTA2*, *MYH11*, and *JAG1*
	TAAD	*ACTA2*, *MYH11*, and *CBS*
	Coronary artery disease	*ACTA2*, *BRCC3*, and *GLA*
	Pulmonary hypertension	*ACTA2*

(*Continued*)

Table. Continued

(*Continued*)

Table. Continued

		Genetic Mutation (Disease Name Given Below if Different)
	Peripheral pulmonary stenosis	*JAG1*
	Dilated cardiomyopathy	*BRCC3/MTCP1*
	LVH, high output heart failure	*HBB*
	Systemic hypertension	*BRCC3/MTCP1*, *GUCY1A3*, and *CECR1*
	Peripheral artery disease	*ABCC6*
Renal	Cysts	*COL4A1* and *COL4A2*
	Hematuria and renal failure	*COL4A1*, *COL4A2*, and *HBB*
	Proteinuria and renal tubular dysfunction	*GLA*
	Bladder dysfunction	*ACTA2*
Hepatic	Cholestasis and bile duct paucity	*JAG1*
Skeletal X rays	Sphenoid dysplasia	*NF1*
	Butterfly vertebrae	*JAG1*
	Spondylosis deformans	*HTRA1*
	Skeletal dysplasia	*PCNT*
Blood investigations	Low platelets	*GUCY1A3*
	Raised HbF on hemoglobin electrophoresis	*HBB*
	Raised inflammatory markers and hypogammaglobulinaemia	*CECR1*
	Raised creatine kinase	*COL4A1* and *COL4A2*
Brain imaging		
	Porencephaly	*COL4A1* and *COL4A2*
	Infarction and hemorrhage	*COL4A1*, *COL4A2*, *ATP7A*, *GLA* (PCAIS more common), *CECR1* (lacunar infarcts), *ABCC6* (lacunar infarcts), and *HBB*
	White matter signal abnormalities preceding symptom onset	*NOTCH3* and *HTRA1*
	Unidentified bright objects and hamartomas	*NF1*
	Basal ganglia calcification and leukoencephalopathy	*SAMHD1*
	Craniosynostosis and Chiari malformation	*SLC2A10*
Arterial imaging		
	MM and aneurysm or stenosis	*COL4A1*, *COL4A2*, *NF1*, *GUCY1A3*, *JAG1*, *SAMHD1*, *PCNT*, and *HBB*
	MM or stenosis	*ELN*
	MM-like with absent basal collaterals and abnormally straight intracranial arteries	*ACTA2*
	MM-like, straight intracranial arteries, and profuse basal collaterals	*MYH11*
	MM	*BRCC3/MTCP1*
	MM with posterior circulation involvement	*GUCY1A3*
	Tortuous cerebral arteries	*ATP7A*
	Intra and extracranial dissections and aneurysms	*SLC1A10*

(*Continued*)

ABCC6 indicates pseudoxanthoma elasticum; AD, autosomal dominant; AR, autosomal recessive; ATP7A, Menke disease; CBS, Homocysteinuria; CECR1, adenosine deaminase 2 (ADA2) deficiency; ELN, Williams syndrome; GLA, Fabry disease; HBB, sickle cell disease; HTRA1, Cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL); JAG1, Alagille syndrome; MM, moyamoya; NF1, Neurofibromatosis type 1; NOTCH3, Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL); PCAIS, posterior circulation arterial ischemic stroke; PCNT, Microcephalic osteodysplastic primordial dwarfism type II; PDA, patent ductus arteriosus; SAMHD1, Aicardi-Goutieres syndrome; SLC2A10, arterial tortuosity syndrome; TAAD, thoracic aorta aneurysm and dissection; and XLR, X linked recessive.

Autosomal dominant mutations in *COL4A1* result in variable clinical manifestations, including pediatric cerebral small vessel disease. *COL4A2* mutations produce the same phenotype that includes both ischemic and hemorrhagic stroke. Presentation may be with early-onset hemiparesis, porencephaly, and seizures or with stroke later in childhood or adulthood. Familial heterogeneity is common.[27]

Hemorrhage risk is lifelong and often has an environmental trigger, such as minor trauma.[28,29] Although there is no specific treatment, diagnosis is useful because patients can be counseled to avoid contact sports and anticoagulation, and mothers of affected fetuses could undergo planned cesarean section to reduce hemorrhage risk related to birth trauma.

Deficiency of Adenosine Deaminase 2

Deficiency of adenosine deaminase 2 (ADA2) is a rare pediatric genetic arteriopathy caused by loss-of-function recessively inherited mutations in *CECR1* (cat eye syndrome chromosome region, candidate 1), resulting in an autoinflammatory vasculitis. Deficiency of adenosine deaminase 2 leads to abnormal endothelial and leukocyte development and differentiation.[30] A polyarteritis nodosa-like presentation is common. Systemic inflammatory features include livedoid rash, intermittent fevers, hypertension, raised inflammatory markers, and hypogammaglobulinaemia. Neurological features include lacunar and hemorrhagic stroke, peripheral, and cranial neuropathies.[30,31] As many mutations in *CECR1* have been described, with wide

phenotypic variation, pathogenesis should be confirmed by ADA2 functional enzyme assay.[31] Anti–TNF-α therapy is useful because ADA2 functions as an important regulator of immune development.[31]

Environmental Associations With Childhood AIS and Cerebral Arteriopathy

Although genetic disorders may confer susceptibility to arteriopathy, environmental factors like infection and trauma may be important second hits to express the phenotype or to precipitate AIS in a child with a preexisting arteriopathy. The VIPS study has provided major insights into the role of infection and inflammation in AIS and arteriopathy. This was a rigorous, National Institutes of Health–funded international study of 355 prospectively enrolled children with AIS and 354 age-matched controls, including review of clinical and radiographic information, serum sampling, and follow-up for at least 1 year;[32] findings will be discussed below.

Inflammation in Childhood Cerebral Arteriopathy and AIS

Inflammation is triggered by tissue injury from any cause, such as infection, when inflammatory cells helpfully destroy infected host cells in a transient and localized response. Inflammation becomes pathological when it is disproportionate to the tissue injury, occurring at a distant site, or of prolonged duration.[33] Inflammation contributes to AIS pathogenesis through several mechanisms. Circulating immune mediators can trigger activation of the coagulation system and platelet aggregation, promoting thrombus formation. This could compound other AIS risk factors: for example, inflammation could promote intracardiac clot formation in a child with congenital heart disease. Inflammation can also mediate arterial endothelial injury, disrupting vascular homeostasis, potentially leading to arteriopathy. Infection has been associated with impaired vascular endothelial function in children.[34] In turn, impaired endothelial function may be associated with recurrent AIS in cerebral arteriopathy—circulating indices of endothelial function in a cohort of children with AIS and cerebral arteriopathy were different between those with a monophasic course compared with recurrent AIS. Children with recurrent AIS had significantly higher markers of endothelial injury, thought to reflect ongoing vessel wall damage,[35] as well as biomarkers of impaired endothelial repair response.[36] Ischemia itself is a trigger for inflammatory cascades in the brain, resulting in cell death and further inflammation, exacerbating the ischemic injury.[37]

Laboratory and Imaging Biomarkers of Inflammation in Pediatric Cerebral Arteriopathy

The VIPS study hypothesized that children with arteriopathic AIS would have a distinct pattern of inflammatory biomarkers compared with children with cardioembolic or idiopathic AIS and that these would predict arteriopathy progression and recurrent AIS. Elevated inflammatory biomarkers in AIS suggest the presence of ongoing inflammation,[38,39] although could be a result of downstream effects of ischemia. To minimize the effects of AIS itself, the VIPS study analyses were adjusted for infarct size, seizures, and timing of sample collection. The study found that serum levels of 3 of the 4 inflammatory biomarkers measured differed by AIS pathogenesis. The cardioembolic group had higher concentrations of high-sensitivity C-reactive protein and myeloperoxidase than other groups; the cardioembolic and arteriopathic groups had higher serum amyloid A than the idiopathic group. In the arteriopathic group, higher high-sensitivity C-reactive protein and serum amyloid A predicted recurrent AIS.[40] Although speculative, these differences in biomarkers could reflect the varied role of inflammation in AIS, for example, prothrombotic in children with structural heart disease or promoting endothelial injury in arteriopathy, as discussed above.

Classification of arteriopathy currently relies on luminal imaging techniques—magnetic resonance angiography, computed tomographic angiography, and digital subtraction angiography, which give little information on the disease process in the arterial wall. Vessel wall imaging is an emerging technique that directly images the arterial wall using high-resolution magnetic resonance imaging. Vessel wall enhancement may represent inflammation,[41] and, although requiring validation, vessel wall imaging may help predict progressive arteriopathy in childhood AIS.[42] Further work is needed to fully understand the investigative role of vessel wall imaging in childhood.

Infection, Vaccination, and Childhood AIS

Although unsurprisingly central nervous system and systemic infection are associated with AIS, there is now clear evidence that trivial viral infection transiently increases risk of childhood AIS. Up to one-third of cases of pediatric AIS report infection in preceding weeks.[1,43,44] In the VIPS cohort, infection in the week preceding stroke (or interview for controls) conferred a 6-fold increased risk of AIS. Infections were mostly upper respiratory tract, and were common across all stroke subtypes, with a low use of vasoactive cold remedies.[45] A 6-fold increase in AIS risk still results in a low absolute risk, so additional factors are likely to be involved.

Interestingly, the VIPS study found that undervaccination was an independent risk factor for AIS in an age-adjusted multivariate logistic regression model; odds ratio, 8.2.[45] This is despite most infections being identified as upper respiratory tract, which are not vaccinated against. Vaccination could have a broader immune benefit which affects the inflammatory response, or it may indirectly prevent additional infections.[46]

Further research in the VIPS II study will attempt to better understand the paradox of a common risk factor like childhood infection and a rare outcome like childhood AIS. It will use next-generation sequencing for broad, unbiased detection of pathogens, testing the hypothesis that unusual combinations of infections, or unusual strains of infection, explain this exposure paradox. It will also use multiplex bead array testing to measure serum levels of 16 immune mediators, testing the hypothesis that the paradox is explained by an abnormal inflammatory response to infection.[47]

Specific Bacterial Infections

Severe bacterial infections can be complicated by AIS because of activation of the coagulation cascade, septic emboli, vascular tissue injury, and inflammation. Bacterial meningitis can result in a secondary vasculitis as the basal cerebral arteries are exposed to purulent exudate and direct spread of inflammation. Although vaccinations have dramatically reduced the incidence of bacterial meningitis in developed countries, *Salmonella* species and *Streptococcus pneumoniae* were the most common cause of pediatric meningitis complicated by AIS in 1 large prospective study.[48] Stroke is a common complication of tuberculous meningitis, occurring in one-third of cases because of a particularly aggressive inflammatory/infectious basal vasculopathy.[49] Other bacterial agents reportedly associated with stroke include *Mycoplasma pneumonia*, *Borrelia burgdorferi*, *Haemophilus influenza*, and *Chlamydia pneumoniae*.[33]

Specific Viral Infections

Post-varicella zoster (VZV) arteriopathy typically affects previously healthy young children, 3 to 4 months after chickenpox infection (within 12 months to fit diagnostic criteria). VZV infects the trigeminal nerve and from there gains access to cerebral vessels, directly invading vessel walls causing an inflammatory response, with enhancement on vessel wall imaging, CSF pleocytosis, and lymphocytic infiltration on biopsy.[37] The radiological pattern is of focal stenosis of the proximal middle cerebral artery and basal ganglia infarction.[50] This is in contrast to VZV vasculitis, largely described in adults, which occurs after VZV reactivation (herpes zoster). VZV vasculitis presents with more diffuse neurological features, has a less consistent angiographic pattern, often with patchy multifocal involvement.[33] Less commonly aneurysms and dissection occur. VZV DNA or, more helpfully, anti-VZV antibodies in CSF aid diagnosis. Anti-inflammatory and antiviral treatment (corticosteroids and acyclovir) are recommended. In children with the typical clinical and radiographic findings of post-varicella arteriopathy, CSF studies are not always performed, and evidence for benefit of treatment of positive findings of VZV DNA or antibodies is lacking. The overlap between these entities remains open (Figure 2).

The VIPS study performed herpesvirus serologies in 326 acute AIS cases, including 187 paired acute and convalescent samples. Serological evidence of acute herpesvirus infection doubled the risk of AIS, across all subtypes (even after adjusting for age, race, and socioeconomic status). Almost half of the children with paired samples had serological evidence of acute herpesvirus infection. Herpes simplex virus type 1 was most common, and most infections were asymptomatic.[51] This association could be partly explained by similar mechanisms to VZV arteriopathy. In addition, a common mechanism

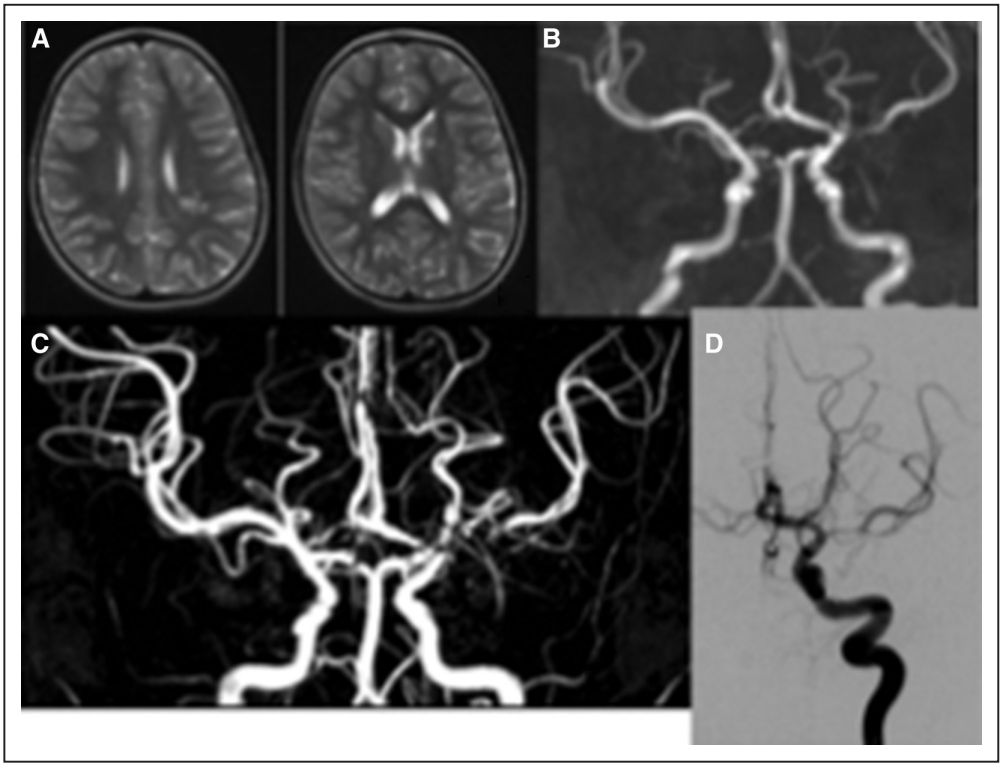

Figure 2. Arteriopathy following varicella zoster (VZV) infection. Axial T2-weighted brain MRI (**A**) and time of flight MRA (**B**) of the circle of Willis from an 8-y-old girl who presented with transient right-sided weakness. She had uncomplicated chickenpox 3 mo earlier. **A** shows multifocal areas of infarction in the territory of the left middle cerebral artery (MCA); **B** shows a focal area of flow abnormality in the proximal left MCA. She was otherwise well with no systemic markers of inflammation. **A**, Diagnosis of focal cerebral arteriopathy was made, and she was treated with aspirin (5 mg/kg per d). Two weeks later, she presented with a more profound episode of right hemiparesis and dysphasia. There was no change on brain MRI; however, the MRA (**C**) showed a more extensive abnormality in the left MCA, confirmed on catheter angiography that also revealed occlusion of the right A1 segment (**D**). CSF examination showed no cells but a positive VZV PCR and VZV IgG. She was treated with intravenous acyclovir for 2 wk and then oral acyclovir for 3 mo in total. She had no further clinical events; reimaging was stable and repeat CSF examination unremarkable.

across AIS subtypes is theorized: inflammatory endothelial injury promoting cardiac thrombus or cerebral arteriopathy.

Stroke occurring in children with HIV 1 infection is likely to be multifactorial in origin. Direct HIV1 infection of the arterial wall may cause arteriopathy. AIS may also result from opportunistic infection, drug effects (toxicity, dyslipidemia, and atherosclerosis), prothrombotic factors, and inflammatory components.[52]

Other viral infections, such as parvovirus, enterovirus, and influenza A, have been reported in the setting of childhood AIS. It is likely that some associated viruses contribute to stroke risk via common mechanisms, activating both proinflammatory and prothrombotic pathways.

Trauma

Significant head trauma (requiring medical attention) in the previous week conferred an almost 40-fold increased odds of AIS compared with matched controls without trauma exposure in a large population-based study. More severe trauma was more strongly linked to AIS.[44] Mechanisms of AIS after major head trauma may be carotid or vertebral artery trauma or dissection, or vasospasm.[53]

Arterial dissection and AIS after minor head trauma may be because of a more complex interplay of factors, such as local inflammation of blood vessels primed by infection or genetic predisposition. Although several rare hereditary connective tissue disorders (eg, Marfan syndrome and Ehlers-Danlos type IV) confer a particularly high risk of dissection, electron microscopy of skin biopsies in patients with arterial dissection reveals a high proportion with structural abnormalities of collagen fibrils and elastic fibers.[54,55] Patients with cervical arterial dissection are also more likely to have clinically detectable connective tissue abnormalities, such as joint laxity or hyperextension.[56] Case-control studies in adults provide evidence of an association between minor acute infection and arterial dissection.[57,58] Taken together, these studies support the hypothesis that environmental exposures like trauma and infection can act as triggers for arteriopathy (in this case, dissection) in the genetically predisposed.

A distinctive clinical phenotype of basal ganglia infarction after minor injury has been reported in infants, postulated to result from vasospasm in lenticulostriate perforator arteries.[59] Lenticulostriate artery mineralization has been described in 1 cohort,[60] possibly reflecting an underlying vulnerability, but has not been replicated elsewhere.

Treatment

Recurrence rates in childhood AIS with arteriopathy are high, despite antithrombotic therapy. In VIPS, 21% of children with definite arteriopathy had a recurrence (the highest in moyamoya), compared with 4.5% with idiopathic AIS and 8.1% for cardioembolism.[7] Improved management of arteriopathy, including prevention of recurrence, is a priority in childhood AIS.

As we have illustrated, inflammation appears to be a key mechanism of AIS and recurrence and, therefore, may underlie arteriopathy progression or recurrence. Anti-inflammatory therapies are an obvious therapeutic target, but there are safety concerns in the context of recent infection. Although anecdotally corticosteroids have been used in post-varicella arteriopathy, and focal cerebral arteriopathy of childhood, a recent systematic review of 34 studies concluded that robust evidence of efficacy is lacking.[61] A recent physician survey concluded that a clinical trial of corticosteroids in focal cerebral arteriopathy of childhood is a priority (with concomitant use of acyclovir in post-varicella arteriopathy).[62] However, a recent analysis of 84 UK AIS cases did not find a high recurrence rate in focal cerebral arteriopathy of childhood.[63] The variable recurrence rate in different cohorts, and in different AIS subtypes, challenges the concept of grouping all AIS cases together for an interventional trial. Rigorous identification of homogenous disease entities and mechanism-specific trials in subgroups would be a more logical approach.

Therapies that inhibit smooth muscle cell proliferation is another potential avenue to explore in pediatric cerebral arteriopathy, particularly in those with genetic smooth muscle dysfunction syndromes, for example, imatinib or statins may have a modifying effect.[8,64]

Improving rates of routine childhood vaccination should be encouraged as a primary stroke prevention method. Varicella-zoster vaccination is recommended by the World Health Organization in counties who assess a significant public health burden from VZV[65]; however, it is not part of the UK routine vaccine schedule.

VIPS II will test for a large number of immune mediators to delineate the pathway of inflammation in different AIS subtypes.[47] Understanding the inflammatory response better could lead to more targeted immunotherapy in future. This study also aims to advance understanding of the role of specific pathogens in arteriopathy, which could also guide treatment with antibiotics or antiviral therapy.

Conclusions

We have outlined some single-gene disorders that are associated with pediatric AIS to illustrate multifactorial pathogenesis of arteriopathy and the interplay between genetic and environmental factors. The latter are common, for example, minor infection or trauma. Inflammation is an important mechanistic final common pathway. A trial of corticosteroids in focal cerebral arteriopathy of childhood is planned, but a one-size-fits-all approach to pediatric AIS trials should be applied with caution because different phenotypes have varying disease trajectories, further varying between cohorts. Further defining specific arteriopathy subtypes, and disease-specific targets for trials, should be an immediate priority.

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None.

References

1. Ganesan V, Prengler M, McShane MA, Wade AM, Kirkham FJ. Investigation of risk factors in children with arterial ischemic stroke. *Ann Neurol*. 2003;53:167–173. doi: 10.1002/ana.10423

2. Fullerton HJ, Wu YW, Sidney S, Johnston SC. Risk of recurrent childhood arterial ischemic stroke in a population-based cohort: the importance of cerebrovascular imaging. *Pediatrics*. 2007;119:495–501. doi: 10.1542/peds.2006-2791
3. Wintermark M, Hills NK, DeVeber GA, Barkovich AJ, Bernard TJ, Friedman NR, et al; VIPS Investigators. Clinical and imaging characteristics of arteriopathy subtypes in children with arterial ischemic stroke: results of the VIPS study. *AJNR Am J Neuroradiol*. 2017;38:2172–2179. doi: 10.3174/ajnr.A5376
4. Sébire G, Fullerton H, Riou E, deVeber G. Toward the definition of cerebral arteriopathies of childhood. *Curr Opin Pediatr*. 2004;16:617–622.
5. Bernard, Manco-Johnson MJ, Lo W, MacKay MT, Ganesan V, DeVeber G et al. Towards a consensus-based classification of childhood arterial ischemic stroke. *Stroke* 2012;43:371–377. doi: 10.1161/STROKEAHA.111.624585
6. Chappell JC, Bautch VL. Vascular development: genetic mechanisms and links to vascular disease. *Curr Top Dev Biol*. 2010;90:43–72. doi: 10.1016/S0070-2153(10)90002-1
7. Fullerton HJ, Wintermark M, Hills NK, Dowling MM, Tan M, Rafay MF, et al; VIPS Investigators. Risk of recurrent arterial ischemic stroke in childhood: a prospective international study. *Stroke*. 2016;47:53–59. doi: 10.1161/STROKEAHA.115.011173
8. Munot P, Saunders DE, Milewicz DM, Regalado ES, Ostergaard JR, Braun KP, et al. A novel distinctive cerebrovascular phenotype is associated with heterozygous Arg179 ACTA2 mutations. *Brain*. 2012;135(pt 8):2506–2514. doi: 10.1093/brain/aws172
9. Suzuki J, Takaku A. Cerebrovascular "moyamoya" disease. Disease showing abnormal net-like vessels in base of brain. *Arch Neurol*. 1969;20:288–299.
10. Ganesan V, Prengler M, Wade A, Kirkham FJ. Clinical and radiological recurrence after childhood arterial ischemic stroke. *Circulation*. 2006;114:2170–2177. doi: 10.1161/CIRCULATIONAHA.105.583690
11. Kamada F, Aoki Y, Narisawa A, Abe Y, Komatsuzaki S, Kikuchi A, et al. A genome-wide association study identifies RNF213 as the first Moyamoya disease gene. *J Hum Genet*. 2011;56:34–40. doi: 10.1038/jhg.2010.132
12. Liu W, Morito D, Takashima S, Mineharu Y, Kobayashi H, Hitomi T, et al. Identification of RNF213 as a susceptibility gene for moyamoya disease and its possible role in vascular development. *PLoS One*. 2011;6:e22542. doi: 10.1371/journal.pone.0022542
13. Kuriyama S, Kusaka Y, Fujimura M, Wakai K, Tamakoshi A, Hashimoto S, et al. Prevalence and clinicoepidemiological features of moyamoya disease in Japan: findings from a nationwide epidemiological survey. *Stroke*. 2008;39:42–47. doi: 10.1161/STROKEAHA.107.490714
14. Phi JH, Choi JW, Seong MW, Kim T, Moon YJ, Lee J, et al. Association between moyamoya syndrome and the RNF213 c.14576G>A variant in patients with neurofibromatosis type 1. *J Neurosurg Pediatr*. 2016;17:717–722. doi: 10.3171/2015.10.PEDS15537
15. Chong PF, Ogata R, Kobayashi H, Koizumi A, Kira R. Early onset of moyamoya syndrome in a Down syndrome patient with the genetic variant RNF213 p.R4810K. *Brain Dev*. 2015;37:822–824. doi: 10.1016/j.braindev.2014.12.006
16. Hu J, Luo J, Chen Q. The susceptibility pathogenesis of Moyamoya disease. *World Neurosurg*. 2017;101:731–741. doi: 10.1016/j.wneu.2017.01.083
17. Koizumi A, Kobayashi H, Hitomi T, Harada KH, Habu T, Youssefian S. A new horizon of moyamoya disease and associated health risks explored through RNF213. *Environ Health Prev Med*. 2016;21:55–70. doi: 10.1007/s12199-015-0498-7
18. Rosser TL, Vezina G, Packer RJ. Cerebrovascular abnormalities in a population of children with neurofibromatosis type 1. *Neurology*. 2005;64:553–555. doi: 10.1212/01.WNL.0000150544.00016.69
19. Rea D, Brandsema JF, Armstrong D, Parkin PC, deVeber G, MacGregor D, et al. Cerebral arteriopathy in children with neurofibromatosis type 1. *Pediatrics*. 2009;124:e476–e483. doi: 10.1542/peds.2009-0152
20. Terry AR, Jordan JT, Schwamm L, Plotkin SR. Increased risk of cerebrovascular disease among patients with neurofibromatosis type 1: population-based approach. *Stroke*. 2016;47:60–65. doi: 10.1161/STROKEAHA.115.011406
21. Kinori M, Hodgson N, Zeid JL. Ophthalmic manifestations in neurofibromatosis type 1. *Surv Ophthalmol*. 2018;63:518–533. doi: 10.1016/j.survophthal.2017.10.007
22. Lin N, Baird L, Koss M, Kopecky KE, Gone E, Ullrich NJ, et al. Discovery of asymptomatic moyamoya arteriopathy in pediatric syndromic populations: radiographic and clinical progression. *Neurosurg Focus*. 2011;31:E6. doi: 10.3171/2011.10.FOCUS11228
23. Lasater EA, Li F, Bessler WK, Estes ML, Vemula S, Hingtgen CM, et al. Genetic and cellular evidence of vascular inflammation in neurofibromin-deficient mice and humans. *J Clin Invest*. 2010;120:859–870. doi: 10.1172/JCI41443
24. Regalado ES, Guo DC, Prakash S, Bensend TA, Flynn K, Estrera A, et al; Montalcino Aortic Consortium. Aortic disease presentation and outcome associated with ACTA2 Mutations. *Circ Cardiovasc Genet*. 2015;8:457–464. doi: 10.1161/CIRCGENETICS.114.000943
25. Masuoka T, Hayashi N, Hori E, Kuwayama N, Ohtani O, Endo S. Distribution of internal elastic lamina and external elastic lamina in the internal carotid artery: possible relationship with atherosclerosis. *Neurol Med Chir (Tokyo)*. 2010;50:179–182.
26. Keylock A, Hong Y, Saunders D, Omoyinmi E, Mulhern C, Roebuck D, et al. Moyamoya-like cerebrovascular disease in a child with a novel mutation in myosin heavy chain 11. *Neurology*. 2018;90:136–138. doi: 10.1212/WNL.0000000000004828
27. Kuo DS, Labelle-Dumais C, Gould DB. COL4A1 and COL4A2 mutations and disease: insights into pathogenic mechanisms and potential therapeutic targets. *Hum Mol Genet*. 2012;21(R1):R97–R110. doi: 10.1093/hmg/dds346
28. Vahedi K, Kubis N, Boukobza M, Arnoult M, Massin P, Tournier-Lasserve E, et al. COL4A1 mutation in a patient with sporadic, recurrent intracerebral hemorrhage. *Stroke*. 2007;38:1461–1464. doi: 10.1161/STROKEAHA.106.475194
29. Majersik JJ. single gene causes of stroke. *Semin Neurol*. 2017;37:351–365. doi: 10.1055/s-0037-1603952
30. Zhou Q, Yang D, Ombrello AK, Zavialov AV, Toro C, Zavialov AV, et al. Early-onset stroke and vasculopathy associated with mutations in ADA2. *N Engl J Med*. 2014;370:911–920. doi: 10.1056/NEJMoa1307361
31. Caorsi R, Penco F, Grossi A, Insalaco A, Omenetti A, Alessio M, et al. ADA2 deficiency (DADA2) as an unrecognised cause of early onset polyarteritis nodosa and stroke: a multicentre national study. *Ann Rheum Dis*. 2017;76:1648–1656. doi: 10.1136/annrheumdis-2016-210802
32. Fullerton HJ, Elkind MS, Barkovich AJ, Glaser C, Glidden D, Hills NK, et al. The vascular effects of infection in pediatric stroke (VIPS) Study. *J Child Neurol*. 2011;26:1101–1110. doi: 10.1177/0883073811408089
33. Moraitis E, Ganesan V. Childhood infections and trauma as risk factors for stroke. *Curr Cardiol Rep*. 2014;16:527. doi: 10.1007/s11886-014-0527-y
34. Charakida M, Donald AE, Terese M, Leary S, Halcox JP, Ness A, et al; ALSPAC (Avon Longitudinal Study of Parents and Children) Study Team. Endothelial dysfunction in childhood infection. *Circulation*. 2005;111:1660–1665. doi: 10.1161/01.CIR.0000160365.18879.1C
35. Eleftheriou D, Ganesan V, Hong Y, Klein NJ, Brogan PA. Endothelial injury in childhood stroke with cerebral arteriopathy: a cross-sectional study. *Neurology*. 2012;79:2089–2096. doi: 10.1212/WNL.0b013e3182752c7e
36. Eleftheriou D, Ganesan V, Hong Y, Klein NJ, Brogan PA. Endothelial repair in childhood arterial ischaemic stroke with cerebral arteriopathy. *Cerebrovasc Dis Extra*. 2015;5:68–74. doi: 10.1159/000381963
37. Steinlin M. Neuroinflammation in ischemic pediatric stroke. *Semin Pediatr Neurol*. 2017;24:201–206. doi: 10.1016/j.spen.2017.08.006
38. Bernard TJ, Fenton LZ, Apkon SD, Boada R, Wilkening GN, Wilkinson CC, et al. Biomarkers of hypercoagulability and inflammation in childhood-onset arterial ischemic stroke. *J Pediatr*. 2010;156:651–656. doi: 10.1016/j.jpeds.2009.10.034
39. Buerki SE, Grandgirard D, Datta AN, Hackenberg A, Martin F, Schmitt-Mechelke T, et al; Swiss Neuropediatric Stroke Registry Study Group. Inflammatory markers in pediatric stroke: an attempt to better understanding the pathophysiology. *Eur J Paediatr Neurol*. 2016;20:252–260. doi: 10.1016/j.ejpn.2015.12.006
40. Fullerton HJ, deVeber GA, Hills NK, Dowling MM, Fox CK, Mackay MT, et al; VIPS Investigators. Inflammatory biomarkers in childhood arterial ischemic stroke: correlates of stroke cause and recurrence. *Stroke*. 2016;47:2221–2228. doi: 10.1161/STROKEAHA.116.013719
41. Bley TA. Imaging studies in the diagnosis of large vessel vasculitis. *Clin Exp Rheumatol*. 2007;25(1 suppl 44):S60–S61.
42. Stence NV, Pabst LL, Hollatz AL, Mirsky DM, Herson PS, Poisson S, et al. Predicting progression of intracranial arteriopathies in childhood stroke with vessel wall imaging. *Stroke*. 2017;48:2274–2277. doi: 10.1161/STROKEAHA.117.017922
43. Mackay MT, Wiznitzer M, Benedict SL, Lee KJ, Deveber GA, Ganesan V; International Pediatric Stroke Study Group. Arterial ischemic stroke risk factors: the International Pediatric Stroke Study. *Ann Neurol*. 2011;69:130–140. doi: 10.1002/ana.22224

44. Hills NK, Johnston SC, Sidney S, Zielinski BA, Fullerton HJ. Recent trauma and acute infection as risk factors for childhood arterial ischemic stroke. *Ann Neurol*. 2012;72:850–858. doi: 10.1002/ana.23688
45. Fullerton HJ, Hills NK, Elkind MS, Dowling MM, Wintermark M, Glaser CA, et al; VIPS Investigators. Infection, vaccination, and childhood arterial ischemic stroke: results of the VIPS study. *Neurology*. 2015;85:1459–1466. doi: 10.1212/WNL.0000000000002065
46. Press CA, Wainwright MS. Preventable pediatric stroke via vaccination? *Pediatr Neurol Briefs*. 2015;29:76. doi: 10.15844/pedneurbriefs-29-10-3
47. Fullerton HJ. The Vascular effects of Infection in Pediatric Stroke (VIPS II) Study. Grantome. http://grantome.com/grant/NIH/R01-NS104094-01 2015. Accessed 1st March 2018.
48. Chang CJ, Chang WN, Huang LT, Chang YC, Huang SC, Hung PL, et al. Cerebral infarction in perinatal and childhood bacterial meningitis. *QJM*. 2003;96:755–762.
49. Farinha NJ, Razali KA, Holzel H, Morgan G, Novelli VM. Tuberculosis of the central nervous system in children: a 20-year survey. *J Infect*. 2000;41:61–68. doi: 10.1053/jinf.2000.0692
50. Miravet E, Danchaivijitr N, Basu H, Saunders DE, Ganesan V. Clinical and radiological features of childhood cerebral infarction following varicella zoster virus infection. *Dev Med Child Neurol*. 2007;49:417–422. doi: 10.1111/j.1469-8749.2007.00417.x
51. Elkind MS, Hills NK, Glaser CA, Lo WD, Amlie-Lefond C, Dlamini N, et al; VIPS Investigators*. Herpesvirus infections and childhood arterial ischemic stroke: results of the VIPS study. *Circulation*. 2016;133:732–741. doi: 10.1161/CIRCULATIONAHA.115.018595
52. Legido A, Lischner HW, de Chadarevian JP, Katsetos CD. Stroke in pediatric HIV infection. *Pediatr Neurol*. 1999;21:588.
53. Chamoun RB, Mawad ME, Whitehead WE, Luerssen TG, Jea A. Extracranial traumatic carotid artery dissections in children: a review of current diagnosis and treatment options. *J Neurosurg Pediatr*. 2008;2:101–108. doi: 10.3171/PED/2008/2/8/101
54. Brandt T, Hausser I, Orberk E, Grau A, Hartschuh W, Anton-Lamprecht I, et al. Ultrastructural connective tissue abnormalities in patients with spontaneous cervicocerebral artery dissections. *Ann Neurol*. 1998;44:281–285. doi: 10.1002/ana.410440224
55. Hausser I, Müller U, Engelter S, Lyrer P, Pezzini A, Padovani A, et al. Different types of connective tissue alterations associated with cervical artery dissections. *Acta Neuropathol*. 2004;107:509–514. doi: 10.1007/s00401-004-0839-x
56. Giossi A, Ritelli M, Costa P, Morotti A, Poli L, Del Zotto E, et al. Connective tissue anomalies in patients with spontaneous cervical artery dissection. *Neurology*. 2014;83:2032–2037. doi: 10.1212/WNL.0000000000001030
57. Guillon B, Berthet K, Benslamia L, Bertrand M, Bousser MG, Tzourio C. Infection and the risk of spontaneous cervical artery dissection: a case-control study. *Stroke*. 2003;34:e79–e81. doi: 10.1161/01.STR.0000078309.56307.5C
58. Grau AJ, Brandt T, Buggle F, Orberk E, Mytilineos J, Werle E, et al. Association of cervical artery dissection with recent infection. *Arch Neurols*. 1999;56:851–856.
59. Buompadre MC, Arroyo HA; Stroke Group. Basal ganglia and internal capsule stroke in childhood–risk factors, neuroimaging, and outcome in a series of 28 patients: a tertiary hospital experience. *J Child Neurol*. 2009;24:685–691. doi: 10.1177/0883073808330163
60. Lingappa L, Varma RD, Siddaiahgari S, Konanki R. Mineralizing angiopathy with infantile basal ganglia stroke after minor trauma. *Dev Med Child Neurol*. 2014;56:78–84. doi: 10.1111/dmcn.12275
61. Edwards HB, Mallick AA, O'Callaghan FJK. Immunotherapy for arterial ischaemic stroke in childhood: a systematic review. *Arch Dis Child*. 2017;102:410–415. doi: 10.1136/archdischild-2016-311034
62. Steinlin M, O'callaghan F, Mackay MT. Planning interventional trials in childhood arterial ischaemic stroke using a Delphi consensus process. *Dev Med Child Neurol*. 2017;59:713–718. doi: 10.1111/dmcn.13393
63. Stacey A, Toolis C, Ganesan V. Rates and risk factors for arterial ischemic stroke recurrence in children. *Stroke*. 2018;49:842–847. doi: 10.1161/STROKEAHA.117.020159
64. Ziedén B, Olsson AG. The role of statins in the prevention of ischemic stroke. *Curr Atheroscler Rep*. 2005;7:364–368.
65. World Health Organization. Varicella and herpes zoster vaccines: WHO position paper, June 2014. *Wkly Epidemiol Rec*. 2014;89:265–287.

KEY WORDS: arteries ■ biomarkers ■ consensus ■ mutations ■ stroke