Imaging Review of Common and Rare Causes of Stroke in Children

Giulio Zuccoli, MD,[*] Charles Fitz, MD,[*] Stephanie Greene, MD,[†] Samuel A. Lindner, MD,[‡] Raffaele Nardone, MD,[§] Abdullah S. Khan, MD,[‡] Deepa Rajan, MD,[¶] and Dana D. Cummings, MD, PhD[¶]

Abstract: Vascular injury is increasingly recognized as an important cause of mortality and morbidity in children (29 days to 18 years of age). Since vascular brain injury in children appears to be less common than in adults, the index of suspicion for vascular brain injury is usually lower. In this review article, we describe frequent and rare conditions underlying pediatric stroke including cardioembolic, viral, autoimmune, post-traumatic, and genetic etiologies. Furthermore, we provide a neuroimaging correlate for clinical mimics of pediatric stroke. This review highlights the role of multimodal noninvasive neuroimaging in the early diagnosis of pediatric stroke, providing a problem-solving approach to the differential diagnosis for the neuroradiologist, emergency room physician, and neurologist.

Key Words: *ACTA2*, children, Col4A1 mutation, moyamoya, sickle cells, stroke, vasculitis

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Estimates show that arterial ischemic stroke occurs in approximately 2.4 to 13 cases per 100,000 US children per year.[1,2] In the present review, we discuss a selection of risk factors associated with ischemic brain injury, and aim to provide characteristic neuroimaging of these conditions. Several pathologies are incorporated in this review, and should be included in the differential diagnosis in children presenting with acute neurological symptoms. These include focal and diffuse cerebral ischemia, cardiogenic causes of stroke, hematological, autoimmune, traumatic, infections, and genetic causes of stroke [such as *Col4A1* mutation, *ACTA2* mutations, and cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)].

CARDIAC DISORDERS

Cardioembolic stroke may be due to congenital, acquired, or iatrogenic etiologies. The most frequent congenital causes are cardiomyopathy, congenital heart disease, arrhythmias, and cardiac tumors. Acquired causes include cardiomyopathy, myocarditis, arrhythmias, artificial valves, and endocarditis. Iatrogenic causes include cardiac catheterization, cardiac surgery/cardiopulmonary bypass, carotid ligation and infected mediport (Fig. 1).

Using the large population collected in the prospective International Pediatric Stroke Study, the characteristics, clinical presentations, imaging findings, and early outcomes of children with and without cardiac disorders have been analyzed.[3] Children with stroke secondary to a cardiac disorder more frequently had bilateral strokes in both the anterior and posterior circulation, and had an increased frequency of hemorrhagic transformation compared to children without cardiac disorders. Etiological data were available for 667 children with ischemic stroke (ages 29 days to 19 years). Cardiac disorders were identified in 204 of 667 (30.6%) of patients with arterial ischemic stroke. Congenital cardiac defects were present in 121 of 204 (59.3%). Cardiac disorders were acquired in 40 of 204 (19.6%). An isolated patent foramen ovalis was identified in 31 of 204 cases (15.2%). Compared to other children with stroke, children with cardiac disorders were younger (median age 3.1 vs 6.5 yr), and less likely to present with headache (25.6% vs 44.6%). There were, however, no significant differences in types of clinical presentations including focal deficits, seizures, or recent infection.[1]

Diffusion-weighted imaging (DWI) is the most sensitive modality for diagnosing cytotoxic edema, and also allows for the diagnosis of a cardioembolic strokes in cases with normal computerized tomography (CT) and standard magnetic resonance imaging (MRI) sequences likewise T1- and T2-weighted images.[4] Perfusion MRI, such as by arterial spin labeling (ASL), assesses relative cerebral blood flow and volume, and can detect areas of ischemia during stroke without the use of a contrast agent.[5] ASL perfusion imaging have been demonstrated to correlate with clinical symptoms, acute infarct location, magnetic resonance angiogram (MRA) abnormalities, and follow-up T2 findings.[4] The relationship between ASL and perfusion-weighted imaging has been only studied in adults. ASL uses magnetically labeled arterial water as a freely diffusible tracer instead of contrast, which makes it appealing for use in children. To date, ASL represents the least invasive study to quantitatively and qualitatively evaluate brain perfusion (Fig. 2). Transthoracic echocardiogram can reveal a potential cardiac source of thrombus or right-to-left intracardiac shunting, and is recommended within 48 hours of presentation in all children with acute ischemic stroke.[6]

VIRAL INFECTION

Increasing evidence implicates viral infection as a causal factor in pediatric stroke.[1,7] Stroke in children with active viral infection has been linked to the herpesviruses group herpes simplex virus-1 (HSV-1), HSV-2, varicella-zoster virus, Epstein-Barr virus, cytomegalovirus, and human herpes virus-6.[8] In a recent study by the Vascular Effects of Infection in *Pediatric Stroke* study 57% of children with arterial ischemic stroke showed serology findings consistent with acute herpes virus infection (HSV, either type 1 or 2), whereas only 39% of children showed serology findings reflecting acute varicella-zoster virus infection.[7] Interestingly, most of the affected children did

From the [*]Section of Neuroradiology; [†]Department of Neurosurgery, Children's Hospital of Pittsburgh of UPMC; [‡]Department of Radiology, University of Pittsburgh School of Medicine, Pittsburgh, PA; [§]Department of Neurology, Christian Doppler Klinik, Paracelsus Medical University, Salzburg, Austria; and [¶]Department of Pediatrics, Division of Child Neurology, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA.

Address correspondence to Giulio Zuccoli, MD, Department of Radiology Children's Hospital of Philadelphia 3401 Civic Center Boulevard, Wood Building 2115 Philadelphia, PA 19104 (e-mail: giulio.zuccoli@gmail.com).

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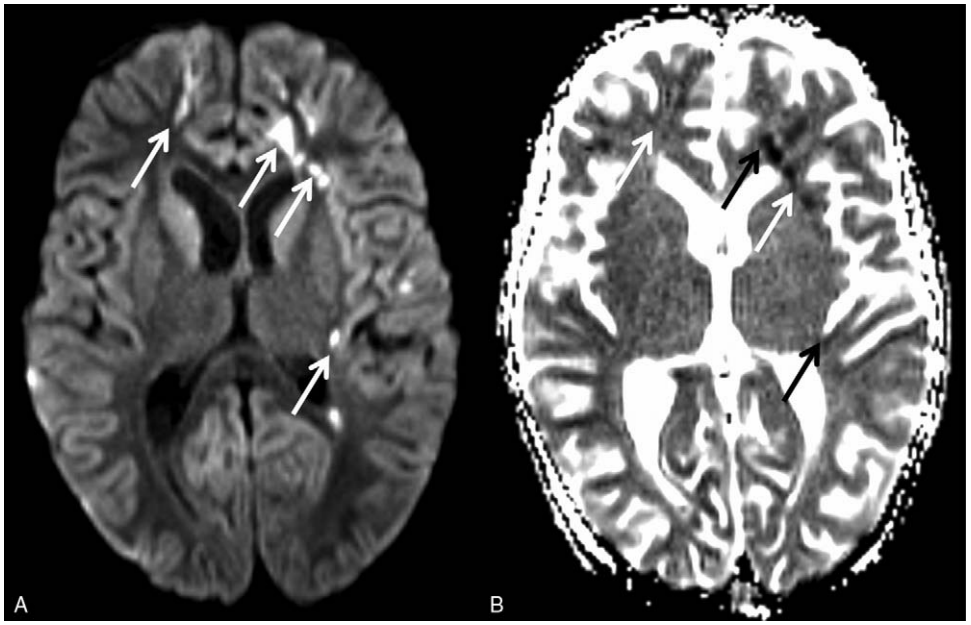

FIGURE 1. Infected emboli. A 3-year-old girl affected by multiple embolic strokes in the left hemisphere from infected mediport (A, diffusion; B, ADC map, arrows).

not have any other symptom related to viral infection.[7] Hence, in otherwise healthy children presenting with stroke a herpesvirus arteritis should be considered. The use of antiviral therapies, however, remains empirical due to the lack of prospective studies in this field.[7]

To date there are no defined diagnostic nor classification criteria for acute viral ischemic stroke in children. Restricted diffusion in a vascular brain territory may reflect acute viral arteritis. Thus, in the absence of other possible etiologies, radiological findings of infarction and stenosis of the cerebral arteries in a child with serological evidence of viral infection should be considered highly suspicious for stroke caused by viral vasculitis[8] (Figs. 3 and 4). The diagnostic workup includes MRI with DWI and ASL imaging, MRA, and cerebrospinal fluid analysis. Cerebral angiography typically demonstrates unilateral stenotic arteriopathy affecting the proximal middle cerebral artery (MCA) and anterior cerebral artery (ACA) and/or distal internal carotid artery (ICA), whereas brain imaging usually reveals infarcts within the lenticulostriate territory, such as the basal ganglia and internal capsule.[9–14] Herpesviruses-related strokes usually present with multifocal cortical involvement, more frequently involving the limbic system and basal ganglia. Although the abnormal appearing brain cortex does not enhance in the early phase of the encephalitis, leptomeningeal enhancement overlying the affected regions may be observed, reflecting meningitis.[8] Perivascular enhancement is a nonspecific finding which may be also observed in bacterial stroke and autoimmune disorders.[15,16]

Other viral infections can cause stroke in children. Human influenza A subtype H1N1 virus induced-ischemic stroke is reported in the literature (Fig. 5).[17–19] As with other viral infections leading to neurologic sequelae, cerebrospinal fluid samples may show pleocytosis or be normal, but polymerase chain reaction may isolate DNA from influenza A subtype H1N1. In suspected cases, MRI can reveal an ischemic area, with MRA used to highlight focal occlusions. Radiographically, La Crosse encephalitis (arbovirus family) may present with neuroimaging findings resembling herpesviruses infection, whereas serological findings of elevated peripheral white counts may suggest a bacterial or enterovirus infection making the diagnosis uncertain till the virus is identified.[20] Neuroimaging findings of La Crosse encephalitis include restricted diffusion involving the basal ganglia, cerebellum, and brain cortex (Fig. 6).

MOYAMOYA

Moyamoya is a progressive arteriopathy affecting the distal ICA and its proximal branches with a less frequent involvement of the posterior branches of the circle of Willis.[21] This arteriopathy can present as an isolated medical condition, with unilateral or more often bilateral disease. It is, however, found in association with systemic disorders such as neurofibromatosis, Down syndrome, or sickle cell anemia (moyamoya syndrome). The ischemia resulting from progressive luminal narrowing predisposes children to transient ischemic attacks and ischemic stroke, which are the most common presentations in affected children. The diagnosis is established by arteriography, which shows the characteristic stenosis in ICA branches and a pathognomonic proliferation and dilation of the lenticulostriate vessels, descriptively similar to a puff of smoke.[22] The 3 angiographic criteria for the diagnosis of moyamoya include (1) stenosis of the distal ICAs along with segments of the proximal ACA and MCA; (2) presence of dilated basal collateral vessels; and (3) bilateral findings of vessel changes.[22]

Although CT angiography (CTA) allows identification of arterial narrowing and the presence of collateral vessels at the base of the brain in the more advanced cases,[23] the use of CT alone is not adequate to confirm the diagnosis of moyamoya; MRI should be performed because of the greater sensitivity for acute stroke and the characteristic vessel changes. Although acute infarcts are well seen with DWI, chronic infarcts are better identified with T1- and T2-weighted imaging. Fluid-attenuated inversion recovery (FLAIR) sequences may demonstrate a linear high signal following a sulcal pattern, whereas postcontrast imaging may demonstrate leptomeningeal enhancement in the same regions, which is thought to reflect decreased vascular reserve.[24] Diminished flow voids in the ICA, MCA, and ACA, and prominent flow voids in the thalamus and basal

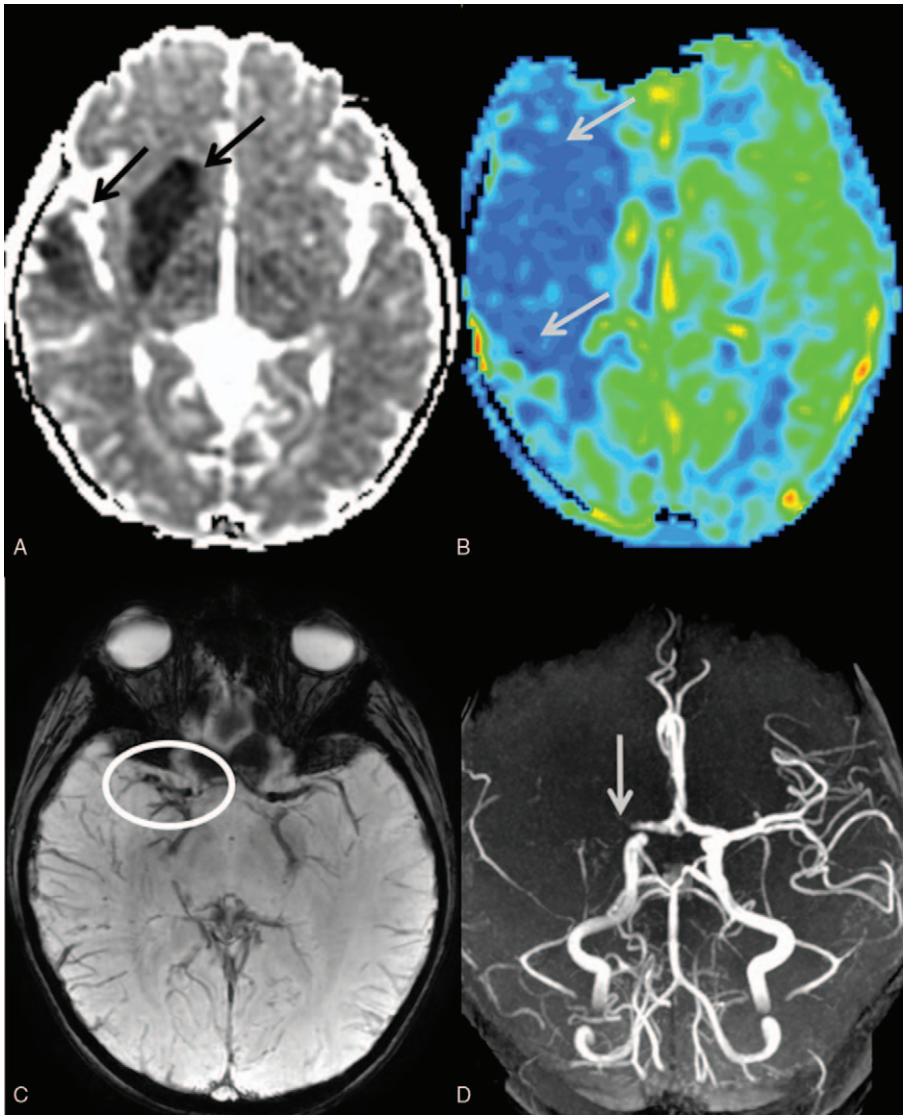

FIGURE 2. Right MCA stroke. A 15-year-old boy with hypoplastic left heart syndrome and congestive heart failure and had right MCA stroke treated with mechanical thrombectomy. Restricted diffusion is noted on ADC map (arrows, A). A larger area of hypoperfusion is identified by ASL imaging (arrows, B). Irregular signal involving the M1 segment of the right MCA consistent with a thrombus is seen on SWI (circle, C). The right MCA is not visualized on 3D-TOF MRA (arrow, D).

ganglia by MRI on T1-weighted images, is a classic sign of moyamoya.[22,25–32] The use of MRA as the primary diagnostic imaging modality for moyamoya syndrome, rather than conventional cerebral angiography, has been proposed.[33–39] However, although MRA readily identifies stenosis of the large arteries, visualization of the lenticulostriate vessels, smaller-vessel occlusions and aneurysms, and extracranial-intracranial spontaneous collateral formation is much less likely than with conventional angiography. The superficial temporal donor arteries cannot be well-characterized on MRA. Angiography further confirms the Suzuki stage. The risk of complications from performing angiography with moyamoya syndrome has been shown to be no higher than the risk of performing angiography in the general population being evaluated for cerebrovascular disease.[25] Thus, conventional angiography remains the criterion standard for the diagnosis of moyamoya. We currently use ASL as a noninvasive tool to assess vascular reserve and in the selection of patients needing revascularization with split duroencephalo-synangiosis (Figs. 7–9).[40]

SICKLE CELL DISEASE

Stroke is one of the most devastating complications of sickle cell disease (SCD).[41]

SCD-associated cerebral vasculopathy is a unique entity reflecting the abnormal interactions between sickled red blood cells and the cerebral arterial endothelium.[42] Children with SCD have a high rate of overt strokes and silent cerebral infarcts. Cardiovascular accident occurs in 11% of patients with homozygous Hemoglobin SS disease before the age of 20 years.[43] Standard care for secondary prevention of strokes in children with SCD includes regular blood transfusion therapy to suppress synthesis of hemoglobin S[44] and to decrease the

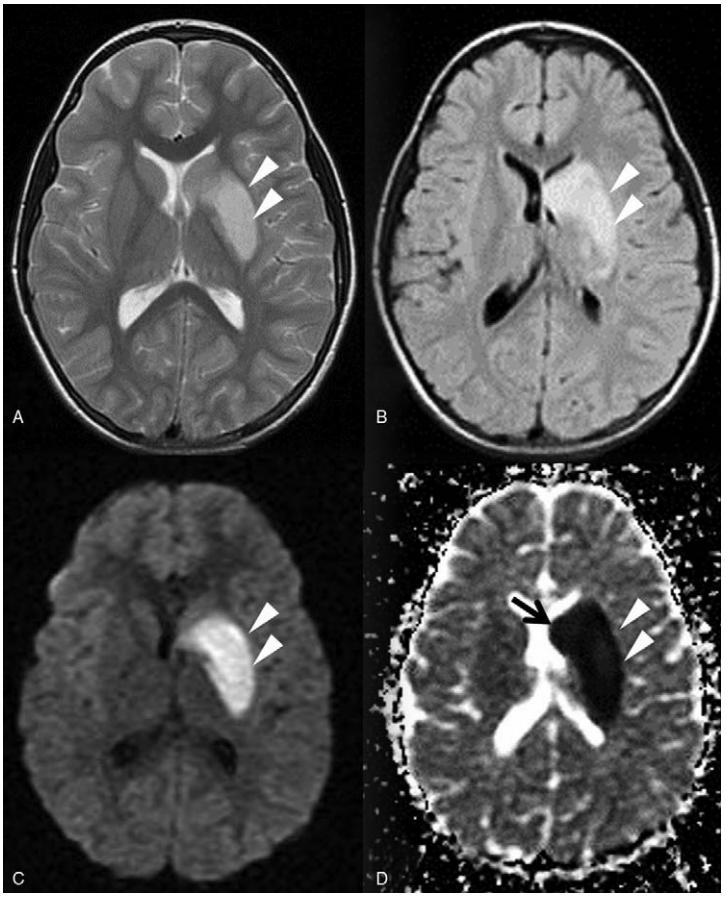

FIGURE 3. Varicella leading to basal ganglia stroke. A 7-year-old girl with varicella infection. A stroke involving the region of the left basal ganglia can be easily depicted T2-flair images (A, B, arrowheads). Restricted diffusion is noted in the basal ganglia on DWI (C, arrowheads) and ADC map (D, arrowheads).

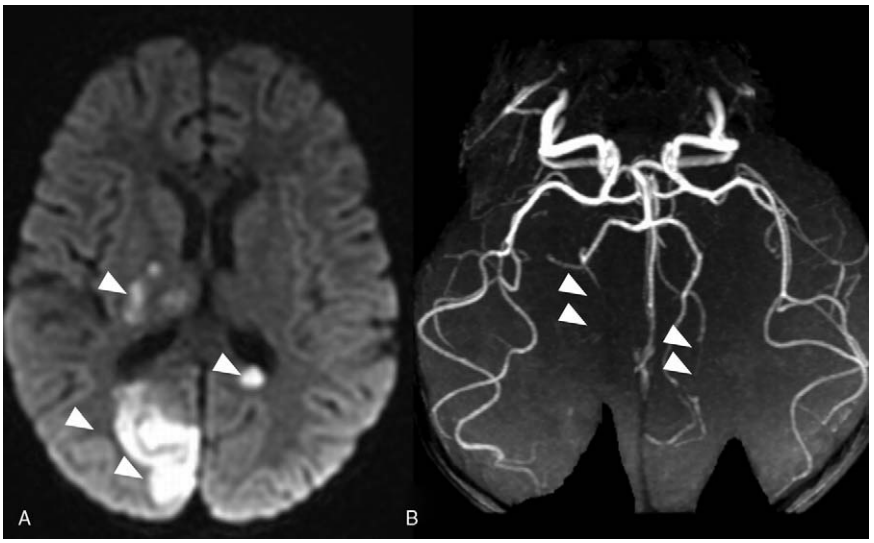

FIGURE 4. Adenovirus vasculitis. A 3-year-old boy with adenovirus infection shows multiple strokes in the posterior circulation (A, arrowheads), and multifocal stenosis of the bilateral right greater than left posterior cerebral arteries (B, arrowheads).

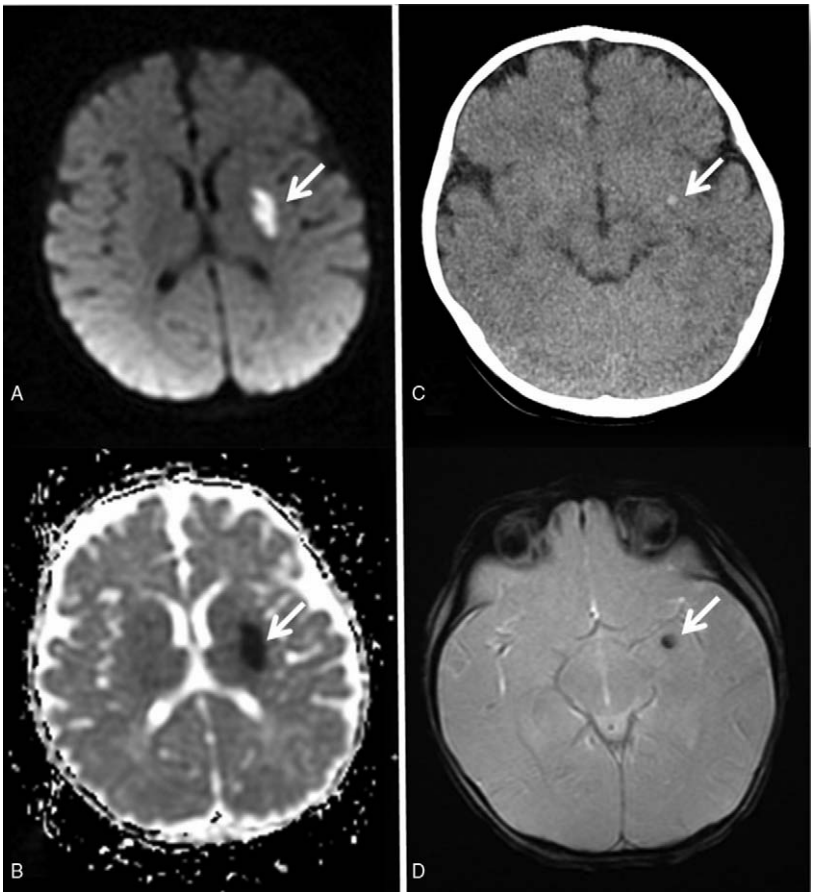

FIGURE 5. H1N1 influenza stroke and micro bleed. A 12-month-old boy affected by H1N1 infection presenting with focal seizures. A stroke is identified on DWI (A, arrow) and ADC map (B, arrow). A focal hemorrhagic focus consistent with petechial hemorrhage is also noted in the left temporal region on CT (C, arrow) and MPGR imaging (D, arrow).

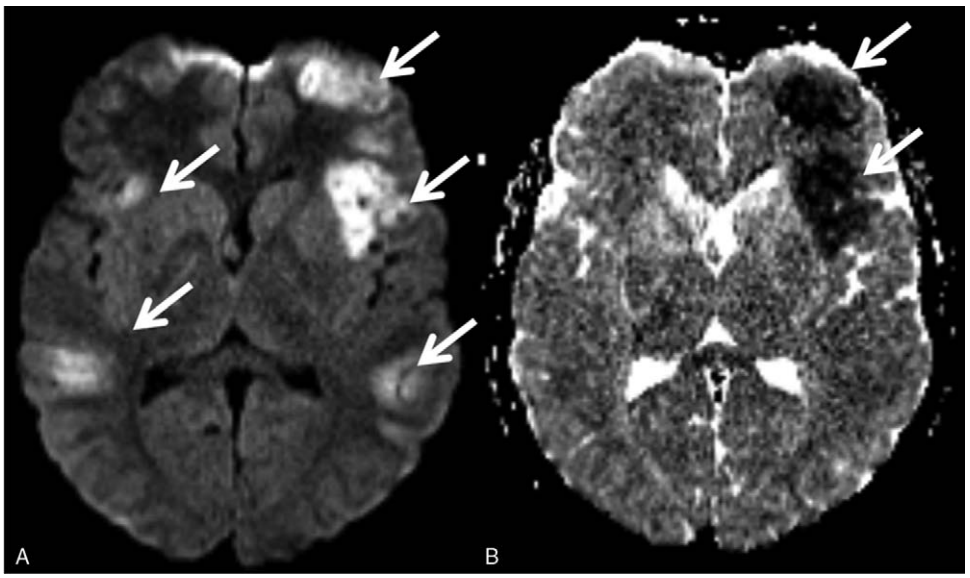

FIGURE 6. La Crosse encephalitis. An 11-years-old girl affected by La Crosse encephalitis. Multifocal cortical infarcts are identified on DWI images with nonterritorial areas of restricted diffusion in the left frontal region (arrows, A).

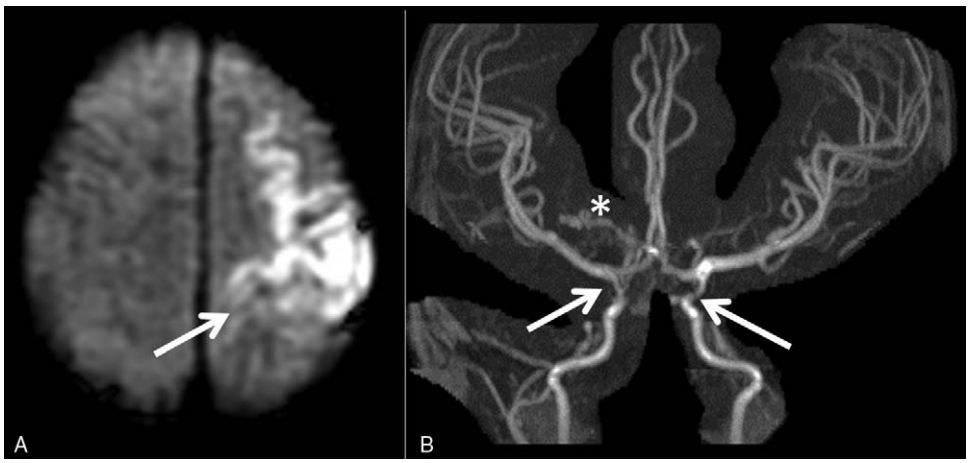

FIGURE 7. Acute moyamoya-related stroke. One-year-old child with moyamoya disease showing left middle cerebral artery infarct on DWI (A, arrow) and narrowing of both cavernous internal carotid arteries on MRA (B, arrows) with collaterals involving the posterior circulation (B, asterisk).

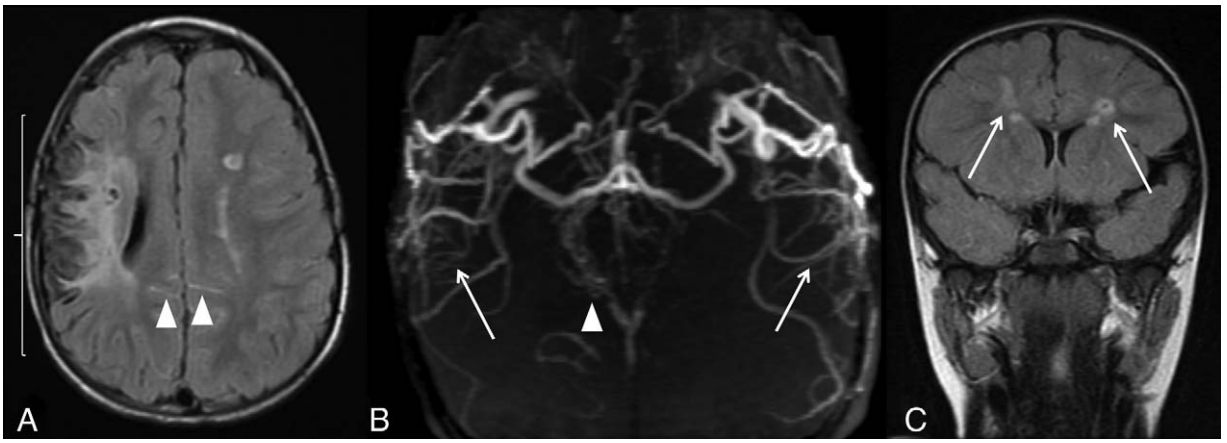

FIGURE 8. Chronic moyamoya: on FLAIR images, atrophy and gliosis in the right middle cerebral artery territory (A, straight bracket), and frontal gliosis (C, arrows) is observed. The Ivy sign reflecting cortical stasis is present (A, arrowheads). MRA shows multiple collaterals in the anterior (B, arrows) and posterior (B, arrowhead) circulation.

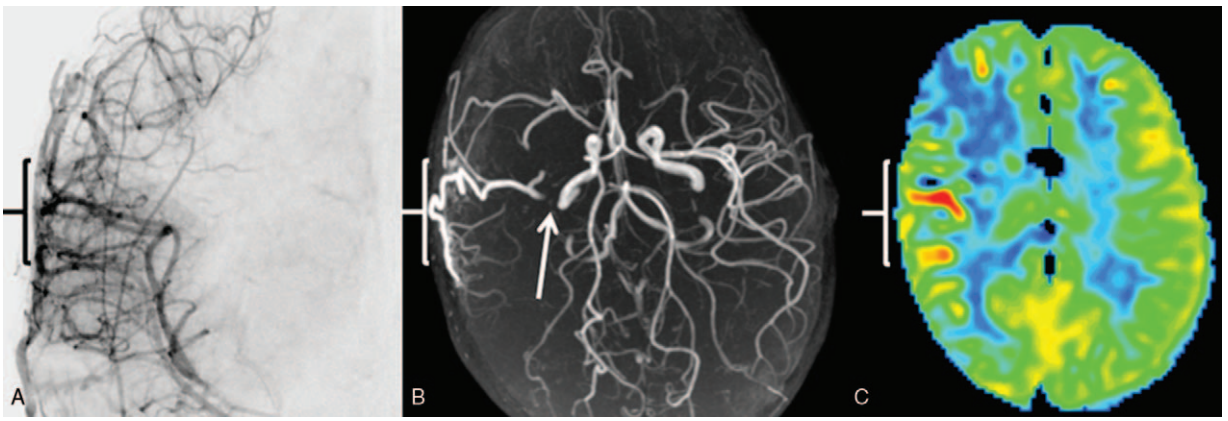

FIGURE 9. Moyamoya status postsynangiosis. Right AP angiogram internal carotid artery injection demonstrating external carotid artery injection shows filling of the middle cerebral branches via the superficial temporal artery following pial synangiosis (A, black straight bracket). Same features are seen on MRA (B, white straight bracket). C, Normal perfusion on pseudocontinuous arterial spin labeling imaging (C, white straight bracket) following synangiosis in the same patient.

fraction of hemoglobin S to <30%. Without transfusion therapy, 67% of these children will have second overt strokes.[45] However, 20% of children have a second stroke despite regular blood transfusion therapy.[44]

In children with SCD, the most common location of hypoxic-ischemic injury is border-zone stroke, which occurs between the ACA and MCA territories (Fig. 10).[41] In a neuroimaging evaluation of 25 patients with a history of stroke, 41% had infarction patterns consistent with major vessel occlusion of the anterior circulation, and 31% had border-zone infarction implicating large-vessel vasculopathy.[46] Cortical-branch occlusion and discrete subcortical infarcts were seen in fewer cases. Among 18 patients with strokes in another study that used MRI exclusively, 16 had border-zone infarcts, 5 had occlusions of an MCA branch, and 4 had basal ganglia infarcts.[47] Noninvasive imaging of the intracranial circulation by MRA and transcranial Doppler (TCD) correlates well with angiography.[46,48,49] Moyamoya collaterals have been reported in 20% to 40% of patients with SCD and stroke (Fig. 11).[50,51] MRI and MRA disclose vasculopathy affecting large and small arteries leading to multifocal stenosis, moyamoya syndrome, silent cerebral ischemia, territorial strokes, and hemorrhages.[52] ASL may be helpful in assessing areas at risk for stroke.[53] Given the positive correlation between MRA and TCD ultrasound, TCD may be used to monitor the effect of transfusion for stroke prevention in SCD.[46,54] To date, only moderate evidence regarding the preventive role of transfusion in preventing stroke is, however, available.[55] One neuropathological review showed border zone strokes in all stroke patients with SCD.[56] A sickling effect of gadolinium on erythrocytes has been shown only in in vitro experiments.[52]

ARTERIAL DISSECTION

A leading cause of cerebrovascular injuries in children that accounts for approximately 20% of pediatric acute ischemic stroke is traumatic craniocervical arterial dissection, of which carotid artery dissection is the most frequent.[57] Collagenopathies, including Ehlers-Danlos syndrome, type IV collagen-related small vessel disease, and osteogenesis imperfecta are additional causes of craniocervical arterial dissections.[58] Disorders with generalized

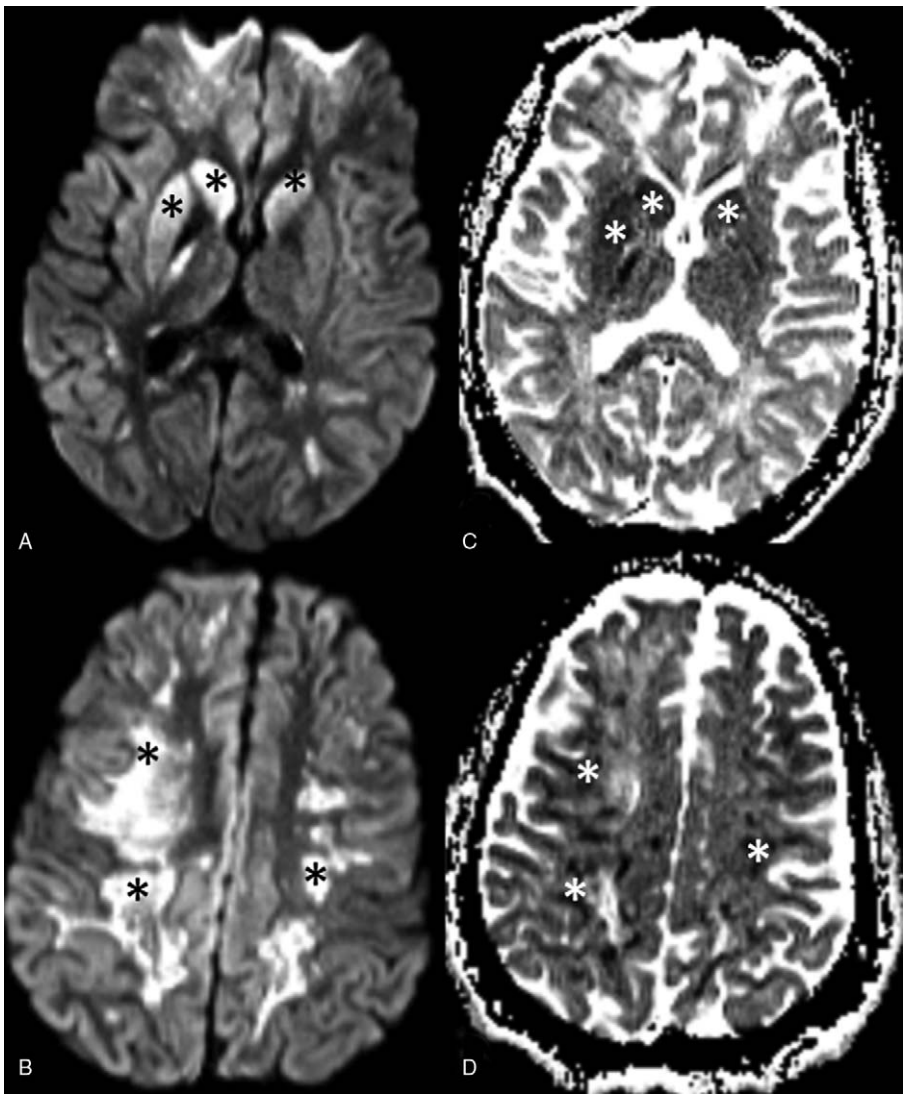

FIGURE 10. Sickle cells crisis. Multifocal infarcts are noted on both DWI (A, B, asterisks) and ADC map imaging (C, D, asterisks) during a sickle cells crisis.

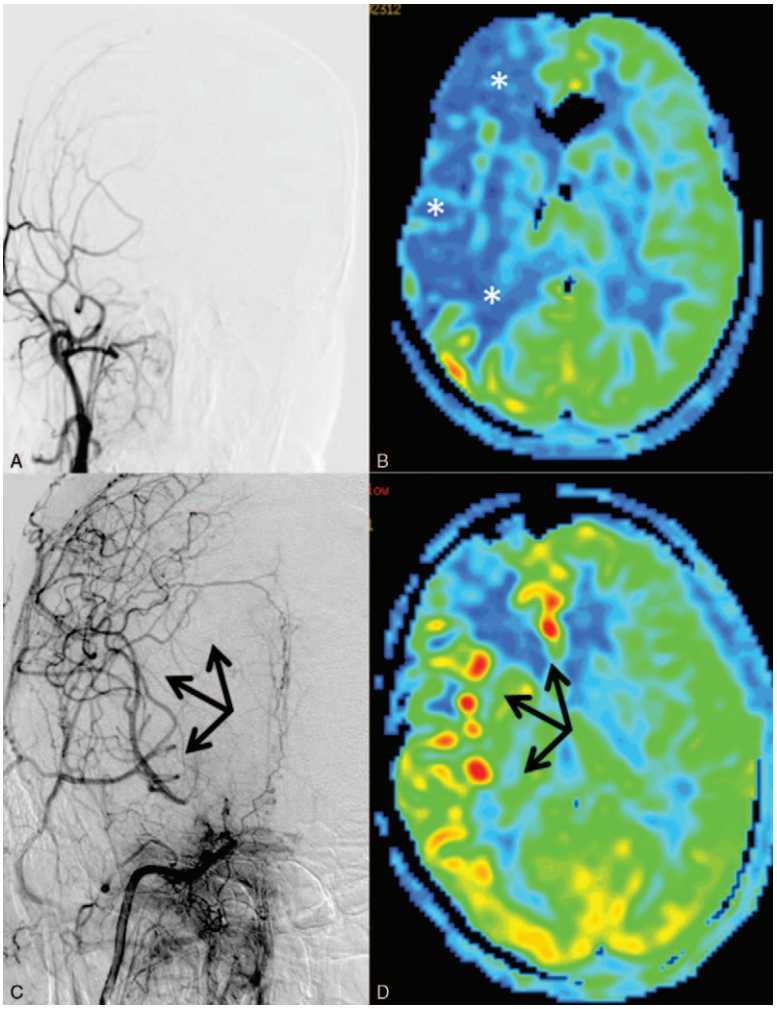

FIGURE 11. Moyamoya collaterals in a sickle cell anemia patient. Patient with sickle cell anemia and moyamoya disease. A, AP angiogram of right common carotid artery demonstrating (B) an absence of filling of the internal carotid artery or its branches and (C, arrows) filling of the middle cerebral artery candelabra by the superficial temporal artery following pial synangiosis. Interval improvement in brain oxygenation as observed on ASL imaging pre- (B, asterisks) and post-pial synangiosis (D, arrows).

connective tissue involvement such as fibromuscular dysplasia have been associated with dissection with and without trauma.[58,59] Post-traumatic carotid artery dissection (PTCAD) represents a mechanical breach in the ICA wall with formation of a subintimal hematoma, and may result in acute arterial ischemic stroke. Most pediatric PTCADs result from a direct blunt or penetrating injury to the ICA, or are secondary to an overstretching of the vessel due to acute hyperextension or excessive rotation of the neck. Subtle insults, such as external manipulation, physical exertion, and contact sports have also been identified as causes of pediatric PTCAD.[57,60] Children are thought to have a higher risk compared to adults because of their weaker neck musculature, higher dependency on ligamentous rather than bony structures, larger heads proportional to necks, and less well-developed protective reflexes.[57,61]

Pediatric PTCAD is rarely diagnosed before the onset of neurological symptoms.[62] The diagnosis of PTCAD in children begins with a careful history and physical examination in a child with a transient ischemic attack or acute ischemic stroke.[63] In children (and in adults), the morbidity from acute ischemic stroke can be significant.[62] Pediatric neuroradiologists should be familiar with neuroimaging findings in children, especially as an acute PTCAD may initially be clinically silent, and PTCAD should be actively excluded in children with head and neck trauma.

Neuroimaging is helpful for the diagnosis of PTCAD, and differs between pediatric and adult patients.[64,65] Noncontrast enhanced CT was shown to be insensitive for PTCAD, but is nevertheless able to show skull base fractures, which are commonly associated with PTCAD.[63] Skull base fractures and subcutaneous pneumocephalus extending along the carotid canal should alert the radiologist to examine the ICA region carefully to rule out PTCAD. Although experience is still limited, CTA was reported to be as sensitive as MRA in detecting PTCAD.[63] CTA may reveal eccentric mural thickening in stenotic regions and a narrowed central or eccentric enhancement from a residual lumen surrounded by a hypodensity from a mural hematoma (Fig. 12).[63,66] A major limitation of CTA is the deleterious effect of ionizing radiation on children, who are at a higher risk than adults of radiation-induced side effects.[67]

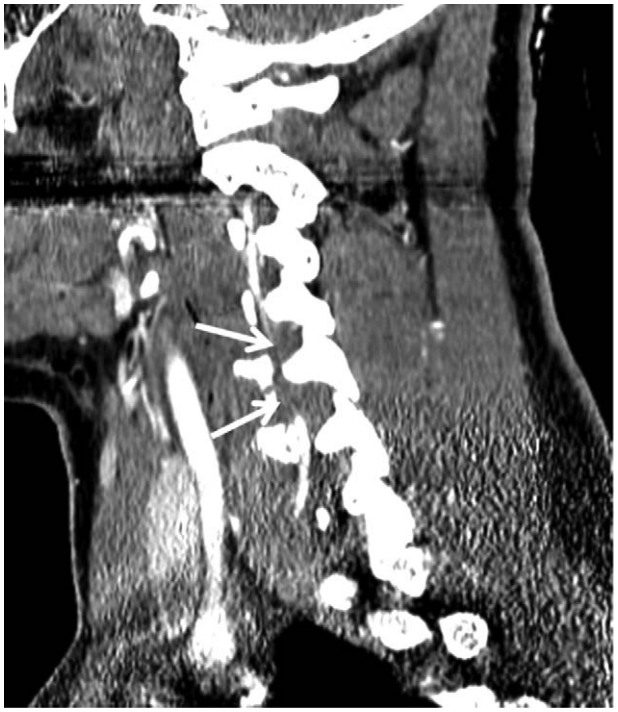

FIGURE 12. CTA findings in post-traumatic dissection. An 11-year-old patient status post motor vehicle accident showing filling defect in the right vertebral artery (arrows) consistent with traumatic dissection.

Considered the diagnostic criterion standard for PTCAD, conventional angiography is very helpful in identifying vascular changes in PTCAD, such as an intimal flap, double lumen, aneurysmal pouch formation, stenosis, and occlusion, but has a few disadvantages in children, including increased exposure to radiation and the need for sedation, the need for sedation, and the technical difficulty of performing angiography in younger children.[65]

Combined MRI and MRA have a high sensitivity in diagnosing PTCAD and are now considered the diagnostic tool of choice in PTCAD.[68] MRI usually includes diffusion-weighted, FLAIR, and T1 images of the brain, and fat saturated T1 or T2 axial imaging through the neck. MRA should include 3D time-of-flight MRA of the head and neck from the aortic arch through the circle of Willis, followed by contrast-enhanced MRA when enhanced MRA when needed. Absence of the normal flow void, or altered luminal signal intensity in and narrowing of the arterial lumen with hematoma within the arterial wall, represent the typical MRI findings.[65] Fat-saturated, noncontrast T1-weighted MRI of head and neck provide ideal visualization of an intramural hematoma. MRA may show a tapered narrowing or occlusion of the dissected vessel (Fig. 13).[65] In children presenting with posterior circulations strokes, dissection of the vertebral artery should always be considered in the differential consideration.[69] A multimodal imaging approach which includes CTA and traditional angiography to better visualize the arterial lumen has been recommended in children with a negative or inconclusive neck MRA, particularly when multiple strokes are identified on DWI.[69] Younger children (<3 years old) are at higher risk for abusive head trauma, with dissection of the extra and intracranial vessels representing a potential neuroradiological presentation of child abuse (Fig. 3).[70]

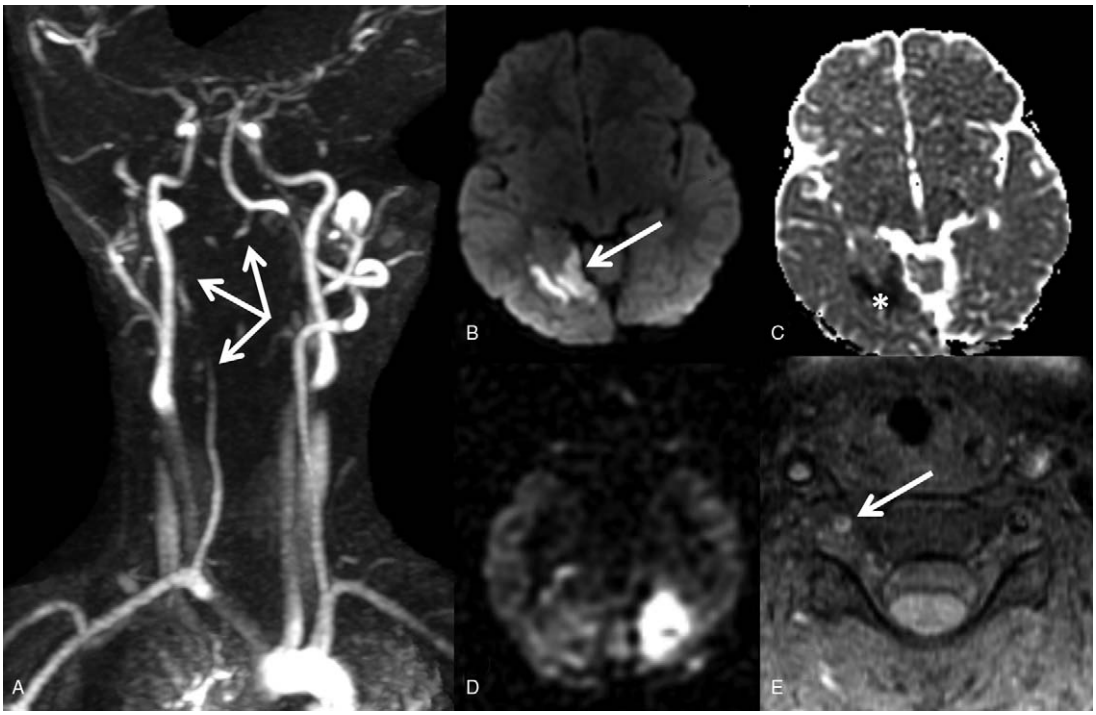

FIGURE 13. Imaging approach to post traumatic dissection. A 4-year-old boy with dissection of the right vertebral artery on neck MRA (A, arrows) resulting in right temporo-occipital junction acute infarct observed at examination time (B, C, asterisks). Rebound reperfusion is noted in the left occipital region (D, asterisk) reflecting another ischemic lesion in the left posterior circulation. The intramural hematoma which is a diagnostic hallmark of arterial dissection is seen on axial T1-fat saturated images (E, arrow).

AUTOIMMUNE VASCULITIS

Vasculitides of the central nervous system (CNS) are a heterogeneous group of disorders characterized by inflammatory changes in the vessel walls. CNS vasculitis can be primary, or secondary to a variety of causes. Primary angiitis of the CNS in children (PACNS) represents a group of idiopathic vasculitides involving small, medium, and large vessels.[71] Affected arteries in medium and large vessel disease are large enough to be differentiated by angiography, whereas angiography studies in small vessel PACNS are typically negative. In these cases, diagnosis can only be confirmed by brain biopsy.[72] PACNS is a distinctive form of vasculitis in the brain and/or spinal cord, with variable clinical manifestations. The natural history of PACNS is often unpredictable, and it may spontaneously resolve, slowly progress, relapse, or rapidly worsen with a fatal outcome.

The clinical criteria for PACNS in adults are (1) an acquired neurologic deficit that remains unexplained after a thorough initial basic evaluation, (2) either classic angiographic or histopathologic features of angiitis within the CNS, and (3) no evidence of systemic vasculitis or any other condition to which the angiographic or pathologic features could be secondary.[73] Most reported pediatric cases fit these criteria. However, compared with adult PACNS, pediatric PACNS is a less well understood clinical entity, because it is only described in case reports and small case series.[74–80]

MRI is the modality of choice in suspected PACNS in children. The MRI findings in PACNS are highly variable in terms of number and size of lesions, as well as the presence of hemorrhage.[73,74] MRI findings at initial presentation may not be typical for stroke, and only exhibit characteristics of subacute and chronic cerebral infarction.[81] There are no pathognomonic MRI findings in angiography-negative PACNS, underscoring the diagnostic limitations of neuroimaging and the need for pathologic correlation.[82] Lesions are usually multifocal, not restricted to a cerebral vessel territory, can be bilateral or unilateral, symmetric or asymmetric, and involve gray matter, white matter, or both.[83] MRI in subacute infarction typically shows hyperintense signal conforming to a laminar pattern on T1-weighted images without contrast, which reflects the resorptive phase of liquefactive cortical necrosis. The main limitation of MRI is its poor specificity in distinguishing vasculitis from cerebral vasoconstriction syndromes. 3-D time of flight (TOF) MRA should be obtained, because it offers higher spatial resolution. Although there are no reports available on perfusion imaging in PACNS, perfusion deficits could be demonstrated using ASL. There is another pattern of PACNS characterized predominantly by multiple petechial-like cortical hemorrhages, with pathologic features of hemorrhagic infarcts.

Angiography is more sensitive than MRA, and remains the criterion standard for identifying lesions in cerebral vasculitis.[84] Angiography is particularly more helpful than MRA in detecting involvement of the posterior circulation and distal cerebral vessels.[81] Although MRA is a reasonable initial modality in the investigation of suspected CNS vasculitis, in cases of abnormal parenchymal MRI

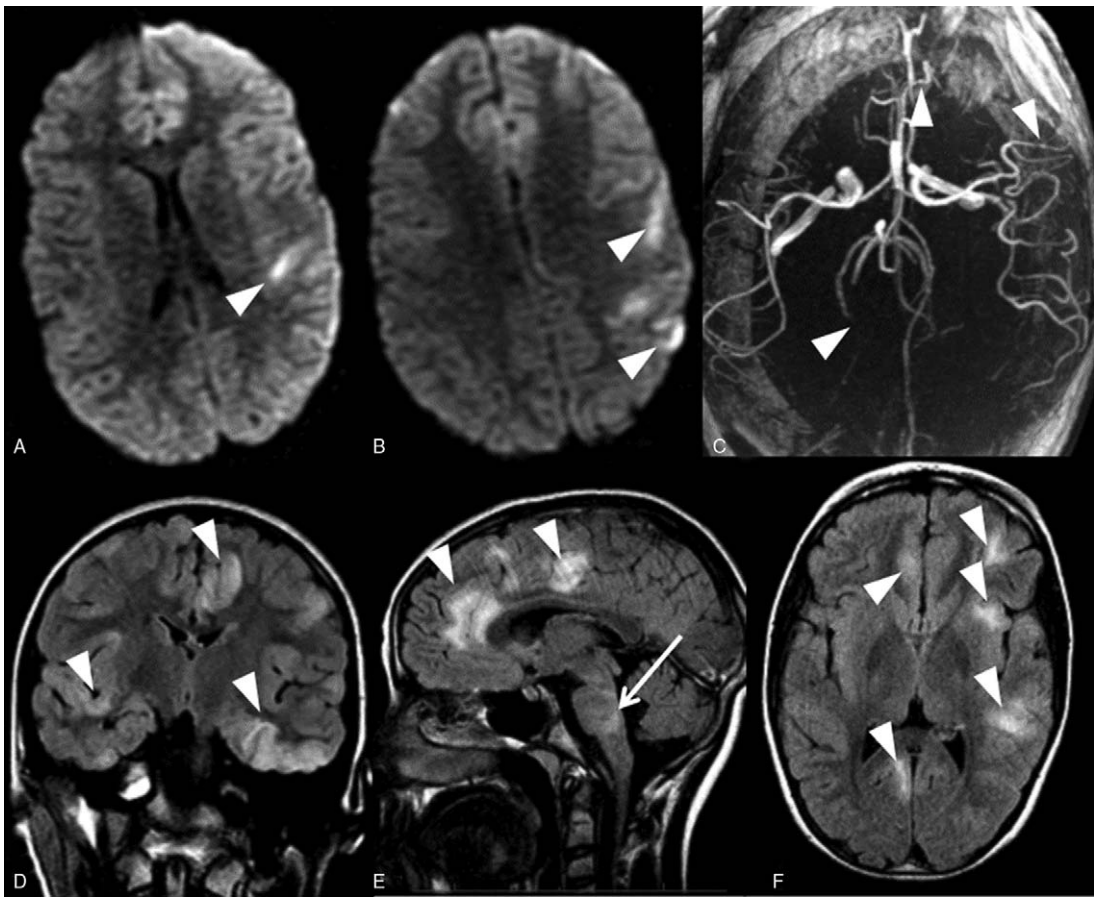

FIGURE 14. PACNS. An 11-year-old boy with PCNS vasculitis. A and B, DWI shows multifocal areas of restricted diffusion in the cortex (arrowheads). MRA shows focal stenosis of the right posterior cerebral artery and areas of arterial beading in the left anterior circulation (C, arrowheads). Multifocal signal abnormalities involving the cortex are seen on FLAIR images (D, E, F, arrowheads). Note is made of involvement of the pons (E, arrow).

and normal MRA, angiography is recommended by the literature.[81] In our Institution we, however, tend to avoid invasive procedures if MRA shows the typical beading appearance of vasculitis (Fig. 14)

CEREBRAL SINOVENOUS THROMBOSIS

Cerebral sinovenous thrombosis (CSVT) affects at least 0.67 per 100,000 new children per year.[85,86] The incidence seems to be declining, because many of the conditions historically associated with CSVT in children, such as cyanotic congenital heart disease or mastoiditis, are now rare or treatable.

The clinical manifestations of CSVT can be life threatening and cause long-term neurological deficits,[87,88] but are also nonspecific and may be subtle. Diagnosis may thus often be delayed or even be missed. CSVT occurs at all ages, and the clinician should consider this diagnosis in a wide range of acute neurological presentations in childhood, including seizures, coma, stroke, headache, and raised intracranial pressure. Non-enhanced CT may not be adequate to exclude CSVT and indications for MRI and MR venogram (MRV) in acute neurological presentations have not been established, because there are little data for evidence-based guidelines. To explore the variety of clinical and neuroradiological presentations and the frequency of associated hematological risk factors, and to determine predictors of outcome, Sebire et al described their experience with children with CSVT at 5 academic centers.[88] The authors compare the clinical presentation of children with infarction or hemorrhage secondary to CSVT with those with arterial ischemic or hemorrhagic stroke. All 42 children had CT, and in 9 patients the diagnosis was made with contrast-enhanced CT. MRI was performed in 33, of whom 31 had MRV. Of the 25 children with parenchymal abnormalities, 24 had cortical involvement. Four of the 42 patients in the study had bilateral hemorrhagic infarcts, and 7 had bilateral bland infarcts. In multiple logistic regression analysis, microcytosis, parietal involvement, and lack of caudate involvement independently predicted CSVT rather than arterial disease. Occipital and thalamic infarcts tended to be more common in CSVT.

In childhood, CSVT is relatively equally distributed across all age groups, except for a higher incidence in neonates.[85] Infarction in the thalami, basal ganglia, and white matter may lead to the typical clinical manifestations of deep cerebral venous thrombosis such as altered consciousness, decerebrate posturing, changes in extrapyramidal tone, and psychiatric symptoms. However, as mentioned above, the clinical presentation of CSVT is highly variable and

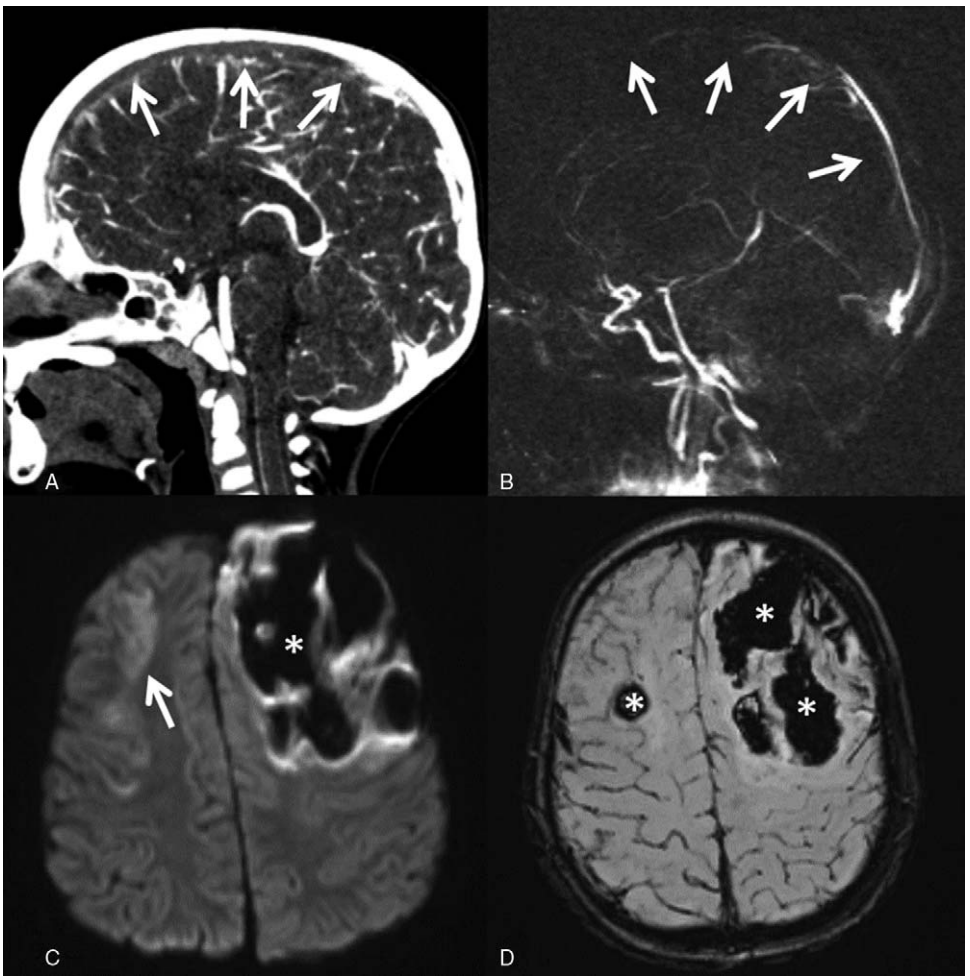

FIGURE 15. Venous infarct. A 3-year-old child presenting with altered mental status. CT angiogram shows a filling defect (A, arrows) in the superior sagittal sinus reflecting thrombosis. Thrombosis is confirmed on 2D TOF MRV (B, arrows). A large artifact reflecting intraparenchymal hemorrhage is seen in the left frontal region on DWI (C, asterisk), and a venous stroke is identified in the right frontal lobe (C, arrow). The bilateral hemorrhages are better seen on SWI (D, asterisks).

ranges from mild symptoms, such as isolated headache, to severe multifocal neurological deficits.

In children with CSVT unenhanced CT scans reveal linear densities in the expected locations of the deep and cortical veins representing acute, hyperdense thrombosis. Contrast-enhanced studies may show the ''empty delta'' sign, which is described as a triangular filling defect in the posterior aspect of the superior sagittal sinus.[85] Post-contrast volumetric T1-weighted images are extremely useful in depicting filling defects in the venous sinuses. Diffusion and perfusion MRI allow the differentiation of cytotoxic and vasogenic edema and show changes in brain oxygenation, but do not differentiate venous from arterial infarction.[89] Absence of flow in the cerebral veins can help establish the diagnosis. Concurrent MRI and MRV studies are useful because they can demonstrate both the infarct and the clot within the vessels. The thrombus is readily recognizable on MRI in the subacute phase, when it is of high signal on the T1-weighted imaging. In the acute phase, the thrombus is isointense on T1-weighted scan and has low signal on T2-weighted images.[89] Acute thrombus is also strikingly hypointense on susceptibility weighted imaging (SWI). SWI may also reveal absent or decreased flow through the emissary veins.[90] MRV is useful in demonstrating an absence of flow in the thrombosed sinus (Fig. 15).

GENETIC CAUSES OF STROKE

Mendelian diseases are also associated with an increased risk of childhood arterial ischemic stroke and cerebral arteriopathy, including CADASIL, pseudoxanthoma elasticum and neurofibromatosis type 1 (NF1). Mutations in genes including COL4A1, *ACTA2*, ATP7A and SLC2A10 have also been implicated in phenotypes of pediatric arterial ischemic stroke, with proposed or elucidated mechanisms such as abnormal vascular smooth muscle proliferation or abnormal response to vascular and endothelial injury.[91]

Several Mendelian diseases cause occlusive and aneurysmal cerebral arteriopathies leading to ischemic and hemorrhagic stroke. Mutations in COL4A1 (Fig. 16), which encodes the alpha chain of type IV collagen found abundantly in vascular basement membranes, leads to reduced stability of these structures.[92] This leads to idiopathic cerebral small vessel disease in children.[93] Associated clinical features include migraines and epilepsy, while neuroradiological features include intracranial hemorrhage and microbleeds, occlusive/aneurysmal cerebral arteriopathy, and porencephaly.[92] Mutations in ABCC6 cause pseudoxanthoma elasticum, which has been proposed to cause secondary calcification of elastic fibers.[94,95] In addition to childhood cutaneous manifestations, arterial ischemic stroke and peripheral vascular disease are common manifestations.[96]

ACTA2, which encodes actin alpha 2, is a main contractile protein in vascular smooth muscle cells. Mutation of the gene disrupts the polymerization of alpha actin into thin filaments, which leads to increased vascular smooth muscle cell proliferation and occlusive disease in small arteries (Fig. 17).[97] Large arteries have shown involvement in a small proportion of cases.[98] Cases with *R179H* gene mutation have demonstrated early severe childhood arteriopathy.[99] Cerebrovascular features include dilation of the proximal ICA, occlusion in the terminal ICA, abnormally straight intracranial arteries, and absent ''moyamoya'' collaterals.[100] Excessive smooth muscle cell proliferation and vascular occlusion is the proposed mechanism in NF1 as well.[101] NF1 causes diffuse cerebral arteriopathy in 6% of affected children.[102]

CADASIL is caused by mutation in *NOTCH3* which normally encodes for a transmembrane receptor involved in the notch signaling pathway expressed in arterial smooth muscle cells.[103] This mutation also causes mainly subcortical white matter infarction in small vessels, although large vessel involvement has also been detected.[104]

The association of stroke and thrombophilia in the pediatric population was previously debated, but supported by observational studies.[105] In a systematic review and meta-analysis, Kenet et al[106] substantiated that thrombophilias are a risk factor for arterial ischemic stroke and cerebral sinovenous thrombosis in neonates and children. The analysis included antithrombin deficiency, protein C deficiency, protein S deficiency, factor 5 G1691A, antiphospholipid antibodies, and others. Among uncombined thrombophilias, protein C deficiency had the highest measured odds ratio at 8.76 (95% CI,

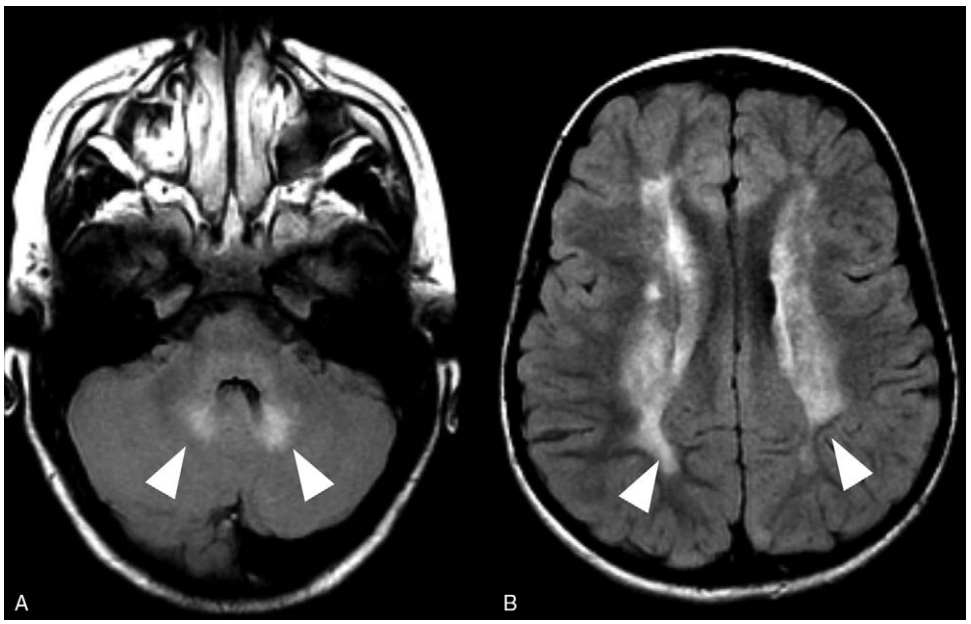

FIGURE 16. COL4A1. Infra- and supratentorial lesions on FLAIR in a 4-year-old patients with COL4A1 mutation reflecting chronic white matter injury.

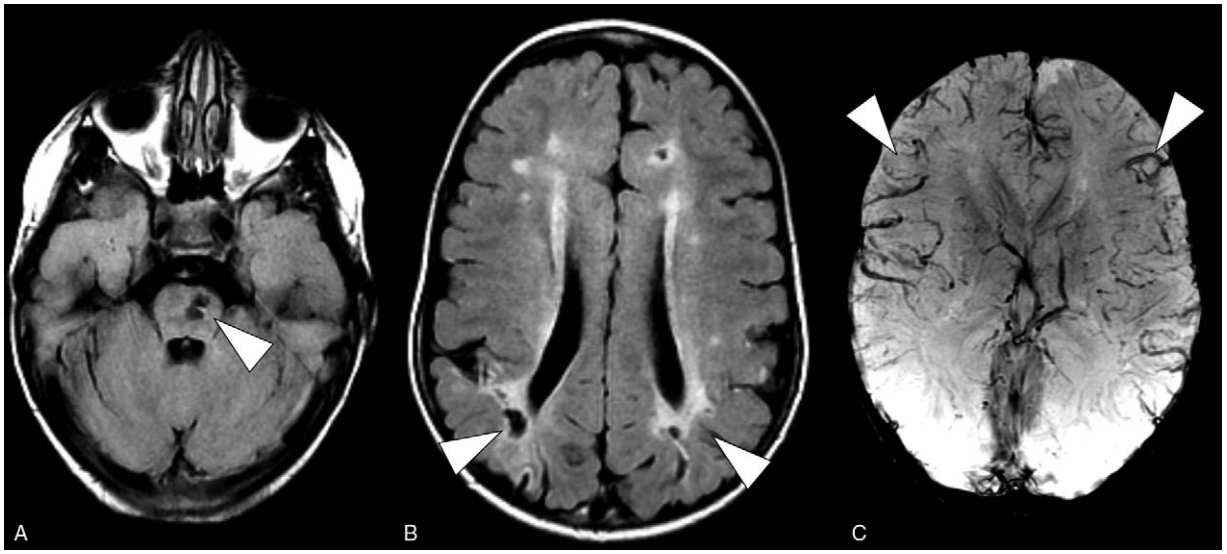

FIGURE 17. *ACTA2* mutation in a 6-year-old boy. A large pontine cavitation (A, arrowhead) and confluent areas of periventricular encephalomalacia (B, arrowheads) more prominent posteriorly. On SWI tortuous cortical veins resembling moyamoya disease are observed (C, arrowheads).

4.53–16.96).[106] Double mutations of the protein C gene frequently result in newborn-onset of intracranial thromboembolism and hemorrhage.[107]

CONCLUSIONS

Given the variety of causes of stroke in childhood clinical information, even family history is more important and varied than in adults. To date there is no specific neuroradiological pattern of pediatric stroke. Although viral causes of stroke are increasingly identified, patterns of injury are overlapping. Appropriate use of multiple MRI sequences is necessary to confirm the vascular nature of the injury and provide guidance for treatment. Although stroke related to well characterized neurogenetic disorders are rare, the characterization of these diseases has provided insights to endothelial and vascular biology that might lead to new future treatment and prevention strategies.

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