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Review Article

Childhood Moyamoya Disease and Moyamoya Syndrome: A Pictorial Review

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Moyamoya disease is an uncommon chronic cerebrovasculopathy, characterized by progressive stenosis of the terminal portion of the internal carotid artery and its main branches, in association with the development of compensatory collateral vessels at the base of the brain. The etiology is unknown, and was originally considered exclusive to East Asia, with particular prevalence in Japan. Moyamoya disease is increasingly diagnosed throughout the world, and represents an important cause of childhood stroke in Western countries. In some cases, similar angiographic features are evident in children with other medical conditions, such as sickle cell disease and Down syndrome. In these instances, the term "moyamoya syndrome" is used. Diagnosing the vasculopathy, excluding possible associated conditions, and planning treatment and follow-up imaging comprise important aspects of clinical management. We review the key imaging features of childhood moyamoya disease and syndrome, present examples of its associations, and discuss new neuroradiologic methods that may be useful in management.

Currie S, Raghavan A, Batty R, Connolly DJA, Griffiths PD. Childhood moyamoya disease and moyamoya syndrome: A pictorial review. Pediatr Neurol 2011;44: 401-413.

Introduction

Moyamoya disease is a chronic cerebrovasculopathy of unknown etiology, characterized by progressive stenosis of the terminal portion of the internal carotid arteries and its main branches. As a result, a compensatory collateral arterial network often develops at the base of the brain [1]. Cerebral arteries contributing to the collateral circulation were first termed "moyamoya" by Suzuki and Takaku in 1969 because of their resemblance to a "puff of smoke" on catheter angiography [2]. Although officially called "spontaneous occlusion of the circle of Willis," moyamoya disease is most commonly used for this idiopathic condition.

Moyamoya syndrome is the term used when radiographic features similar to those of idiopathic moyamoya disease coexist with other medical conditions that may explain the vasculopathy (e.g., sickle cell disease and tuberculous meningitis). As such, moyamoya disease and syndrome represent important causes of cerebrovascular stroke in children, with a peak incidence of disease at age 5 years [3]. Prompt diagnosis and management are crucial in improving long term prognoses. The role of the radiologist is of paramount importance, not only to diagnose the vasculopathy but to confirm or refute the presence of associated abnormalities. We will review the key imaging features of moyamoya disease and syndrome, and provide examples of their associations.

Moyamoya Disease

Japan presents the highest rate of moyamoya disease, with an annual prevalence and incidence estimated at 3.16-10.5 per 100,000 and 0.35-0.94 per 100,000, respectively [3,4]. It is the most common pediatric cerebrovascular disease in that country. In recent years, moyamoya disease has also been observed in most parts of the world, with an increase in reports among American and European populations [5,6]. Studies in the United States suggest an annual incidence of 0.086 per 100,000 (approximately one per million), and the European incidence is estimated at approximately 10% of that in Japan [7-9]. A bimodal age distribution at presentation is

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Received July 28, 2010; accepted February 10, 2011.

doi:10.1016/j.pediatrneurol.2011.02.007 • 0887-8994/$ - see front matter

evident, with the larger juvenile peak at age 5 years, and an adult peak during the fourth decade [3]. The condition accounts for approximately 6% of childhood strokes in Western countries, and half of those are in children aged less than 10 years [10,11]. A female preponderance of approximately 2:1 was reported [4].

Seventy percent to 80% of children with moyamoya disease present with ischemic episodes in the form of transient ischemic attacks or strokes [12] that are frequently recurrent, involving the anterior circulation to the brain because of a predilection of the involvement of the terminal portions of the internal carotid arteries. Posterior circulation events can occur through the involvement of the vertebrobasilar system, but these events are much less common. Signs are often provoked by periods of hyperventilation, e.g., after crying, coughing, straining, or playing on a wind instrument. (The reduced partial pressure of carbon dioxide [$Paco_2$] results in reduced cerebral blood flow because of vasoconstriction. The fall in cerebral blood flow compromises the already reduced cerebral perfusion to the point of causing clinical manifestations, which can include dysarthria, aphasia, hemiparesis, or seizures.) Atypical presenting signs include syncope, paraparesis, visual disturbance, and involuntary movements [13-15]. Children with frontal lobe involvement may also develop long-term intellectual impairment [16,17].

Acute Imaging Presentations

In the emergency setting, diagnosis typically begins with computed tomography to exclude more common childhood pathologies such as tumors and hydrocephalus, rather than stroke. Computed tomography also constitutes a valuable first-line investigation to exclude hemorrhage. Infarction may be detected on early computed tomography via reduced attenuation and a loss of distinction between grey and white matter. In the days after the initial insult, the affected area exhibits progressively lower attenuation, and after 2-3 weeks, a loss of volume may be evident. Children with moyamoya disease may also demonstrate subcortical and deep white matter infarcts resulting from hypoperfusion, but lacunar infarcts are rare in the pediatric age group. Small subcortical hyperdensities are occasionally evident in established areas of stroke, and are likely attributable to dystrophic calcification [18]. However, computed tomography is relatively insensitive in the context of strokes, and many centers choose magnetic resonance imaging as their first-line investigation when faced with the need to sedate a young child. Magnetic resonance imaging can demonstrate subtle subcortical lesions that often go undetected by computed tomography, and it is particularly useful in moyamoya disease, where stroke lesions are typically small and multiple. Acute infarctions are best appreciated as abnormally high signals on diffusion-weighted imaging, in conjunction with low values on apparent diffusion coefficient maps, indicating acute cytotoxic edema.

Established strokes are best visualized in magnetic resonance imaging as low signals on T_1-weighted and high signals on T_2-weighted images, and may be evident in initial imaging after previous unrecognized or unreported strokes. Fluid attenuated inversion recovery sequences are particularly useful in detecting areas of stroke in the cortex or periventricular white matter, which may be missed because of their isointensity to the adjacent cerebrospinal fluid on T_2-weighted images [19]. Leptomeningeal enhancement is reported as characteristic of moyamoya disease, and is related to leptomeningeal vascular engorgement (also known as the "ivy sign"). It is best detected with T_1-weighted or fluid attenuated inversion recovery images after contrast enhancement [20-23]. Magnetic resonance findings similar to the "ivy sign" were also reported in other conditions, however, including subarachnoid hemorrhage, meningitis, brain tumors, meningeal carcinomatosis, Sturge-Weber syndrome, hypotension, and hyperbaric O_2 therapy [24,25].

A recent study compared the magnetic resonance images of children and adults with moyamoya disease who presented with signs of stroke, and demonstrated that certain infarct patterns involved an age-specific preponderance. Gyral and borderzone patterns tended to develop in children, whereas classic territorial patterns were evident after the later teenage years. The authors suggested that these patterns resulted from the selective vulnerability of the cortical gray matter in infants [26].

Diagnosis, Treatment, and Subsequent Imaging

Cerebral angiography is required to diagnose moyamoya disease with confidence. The Research Committee on Spontaneous Occlusion of the Circle of Willis (i.e., moyamoya disease) stated that angiography should demonstrate several findings in patients with no other explanation for vasculopathy [27]:

(1) Stenosis or occlusion at the terminal portions of the internal carotid artery or proximal areas of the anterior or middle cerebral arteries;
(2) Abnormal vascular networks in the arterial territories near the occlusive or stenotic lesions, as observed during the arterial phase; and
(3) Bilateral findings (Fig 1).

In the majority of patients, stenoses involve the anterior circulation. Only in severe cases and late-stage disease does the stenotic process involve the posterior cerebral arteries [28]. Although conventional digital subtraction angiography remains the gold-standard technique, guidelines stipulate that formal cerebral angiography is not mandatory if magnetic resonance imaging and angiography indicate all of the above findings. Typical examples are depicted in Figs 2 and 3. The high diagnostic yield, lack of radiation, and noninvasiveness of magnetic resonance make it an attractive surrogate for conventional angiography in children. However, the possibility of overestimating stenoses, secondary to image quality, should

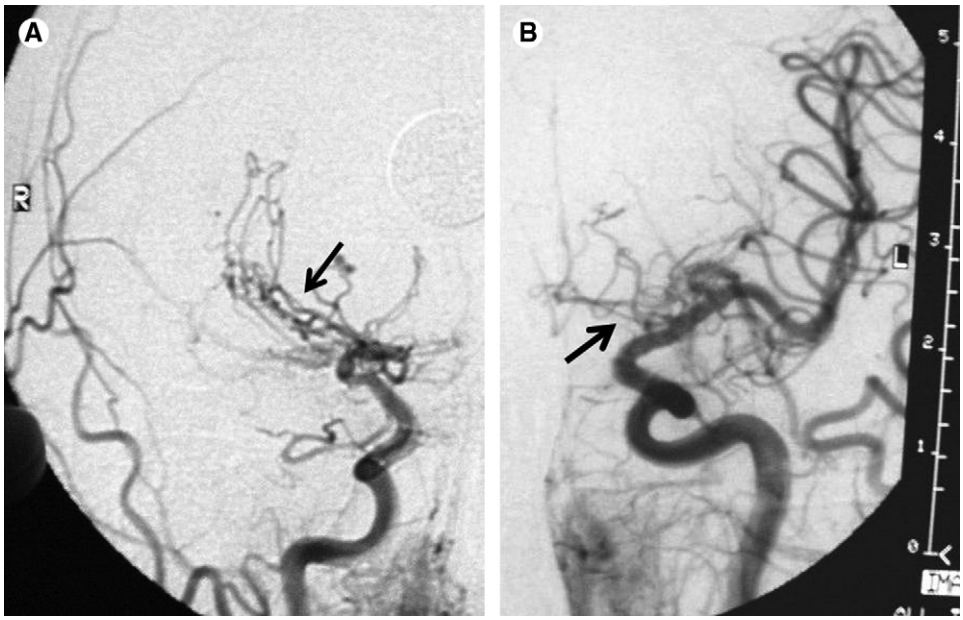

Figure 1. Conventional digital subtraction cerebral angiography of a 7-year-old girl who presented with left hemiparesis. (A) Anteroposterior image of right-sided circulation indicates stenosis at the terminal portion of the right supraclinoid internal carotid artery, proximal middle cerebral artery, and anterior cerebral artery, with a network of abnormal moyamoya collateral vessels (arrow). (B) Anteroposterior image of the left internal carotid artery circulation demonstrates stenosis of the proximal portion of the left anterior cerebral artery (arrow), with poor distal filling. The left internal carotid artery and middle cerebral artery are relatively unaffected.

be borne in mind, and according to previous recommendations, the procedure should be performed at 1.5 T at least [1,29,30]. In addition, although magnetic resonance angiography provides information on major vessel stenoses and basal collaterals, it is less reliable in detecting smaller vessel occlusions compared with conventional angiography. We also emphasize that because similar vascular lesions secondary to other disorders are sometimes indistinguishable from adult moyamoya disease, a diagnosis based on magnetic resonance imaging and magnetic resonance angiography without conventional angiography is recommended only for children. At our institution, computed tomography angiography is not usually performed in children, because magnetic resonance angiography provides similar information without the use of radiation. On occasion, however, we use computed tomography angiography in older children because the delineation of medium-sized arteries is superior to that of magnetic resonance angiography.

The pathognomonic collateral circulation that develops in response to the progressive stenosis of the internal carotid artery and its branches represents both the hypertrophy of

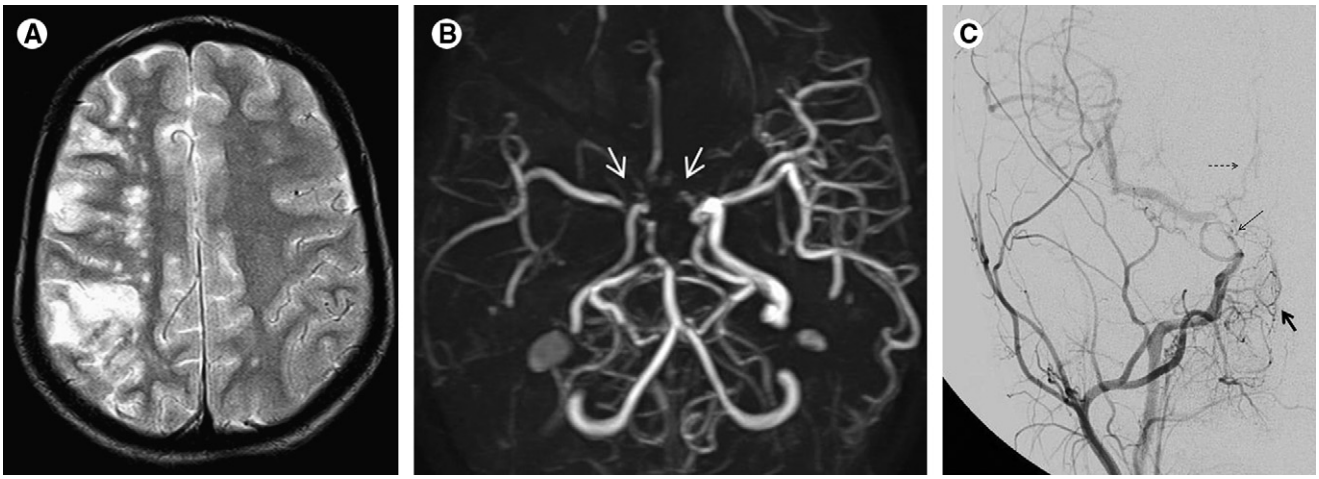

Figure 2. A 15-year-old girl presented acutely with left unilateral monoparesis. (A) Axial T_2-weighted magnetic resonance images indicate acute right middle cerebral artery territory infarct, with several small, focal areas of high signal within the frontal white matter of the centrum semiovale, representing small subcortical infarcts. (B) Magnetic resonance angiography demonstrates narrowing of the right internal carotid artery termination and poor visualization of the anterior cerebral arteries bilaterally (arrows). (C) Preoperative planning digital subtraction angiography confirms terminal stenosis of the right internal carotid artery (thin arrow) and, to a lesser extent, proximal stenosis of the right anterior cerebral artery (dotted arrow) and middle cerebral artery. An extensive network of moyamoya collateral vessels (thick arrow), not detected on magnetic resonance angiography, has formed between the internal and external carotid vessels.

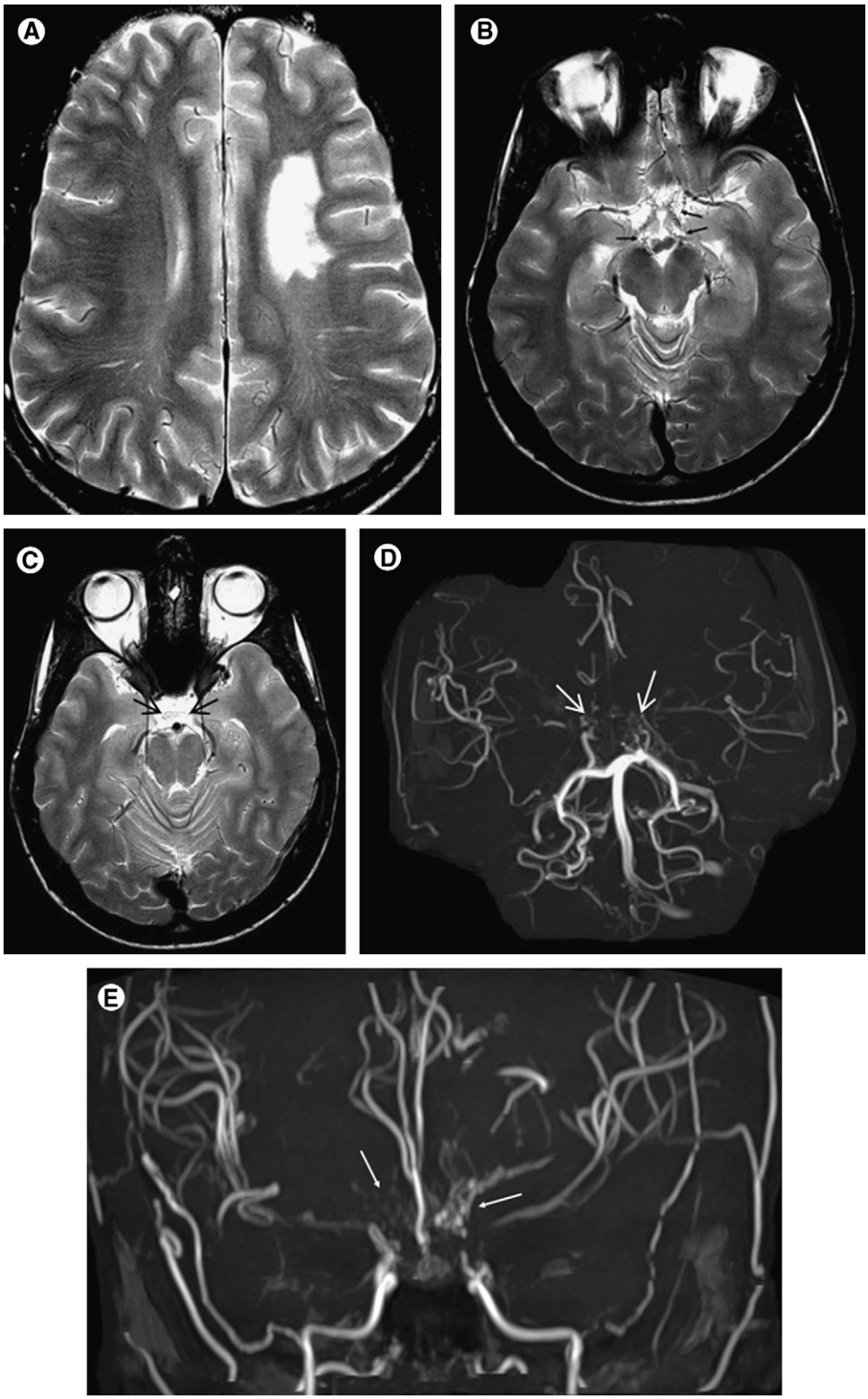

Figure 3. A 6-year-old boy with idiopathic moyamoya disease presented after a left hemispheric infarct. Axial T_2-weighted magnetic resonance images demonstrate established watershed infarction in the left frontal lobe (A), multiple basal moyamoya vessels (B; arrows), and poor visualization of the internal carotid artery terminations bilaterally (arrows) (C). (D) Magnetic resonance angiography reveals bilateral terminal internal carotid artery occlusion (arrows), bilateral middle cerebral artery stenosis, and bilateral proximal anterior cerebral artery occlusion. (E) Small moyamoya vessels are present (arrows). All images were obtained from a 3.0 T machine.

perforator branches and true neoangiogenesis around the circle of Willis [31]. Several collateral pathways were identified, and they exhibit a marked patient-to-patient variability. Common patterns include:

(1) Abnormal dilatation of the perforating arteries, such as the lenticulostriate and thalamoperforating arteries in the basal ganglia and thalami. This pattern is termed "basal moyamoya."
(2) Dilatation of the anterior choroidal and posterior pericallosal arteries.
(3) Dilatation of the anterior and posterior ethmoidal arteries (known as "ethmoidal moyamoya"). These collateral arteries provide pathways mainly from the ophthalmic arteries to the branches of the anterior cerebral arteries.
(4) Collateral circulation from the dural arteries to the pial arteries (known as "vault moyamoya"). This pattern is usually evident in patients with advanced disease.

A six-stage conventional angiographic appearance, indicative of disease progression, has been widely accepted [2]. Moreover, a grading system based on magnetic resonance angiography has been proposed, whereby grading is assigned on the basis of severity of the occlusive changes in the internal carotid artery, the horizontal portions of the anterior, middle, and posterior cerebral arteries, and the flow signals in distal branches of these arteries. These scores correlate well with the six-stage classification, with high sensitivity and specificity [32].

Berry aneurysms are less frequently observed in pediatric moyamoya disease than in the adult form. This finding is reflected in the lower incidence of hemorrhagic stroke among children. In both age groups, Berry aneurysms typically occur around the circle of Willis, although they also originate to a lesser degree from moyamoya collaterals. According to a recent report, the incidence of cerebral aneurysms in association with moyamoya disease is 11% in those under age 20 years [33].

No effective medical therapy is available to treat children with moyamoya disease, so interventions are largely based on surgical revascularization procedures, which are divided into three types: direct, indirect, and combined bypass. Direct bypass procedures (e.g., creating an anastomosis between the superficial temporal artery and a branch of the middle cerebral artery) are often difficult to perform in children because of the small caliber of the vessels. Preoperative digital subtraction angiography is used to discern the course and morphology of donor vessels, which are typically visualized poorly in standard magnetic resonance angiography. However, newer 3.0 T magnetic resonance systems have been used for the selection of bypass arteries, and demonstrate clear visualization of the vessels [34]. Indirect bypass procedures aim to fashion new circulation in the intracranial regions by introducing newly developed vasculature from sutured tissue. These procedures include encephaloduroarteriosynangiosis (the placement of a superficial temporal artery on the dura mater), encephalomyosynangiosis (the laying of temporalis muscle on the surface of the brain), transplantation of the omentum, and more recently, pial synangiosis (involving a superficial temporal artery to the pia mater) [35,36]. Indirect surgery is generally reserved for patients with poor cortical branches, and is thought to provide extensive surgical collaterals in almost all pediatric patients. Combined bypass procedures, which include both direct and indirect bypasses, entail the advantages of both methods, and generally constitute the surgical procedure of choice [37]. Magnetic resonance imaging and angiography can be used postoperatively to determine the patency of grafts and to gauge collateral flow. The evaluation of flow direction is limited in time of flight magnetic resonance angiography, but may be assessed via phase contrast or time-resolved magnetic resonance angiography, although both techniques provide relatively poor spatial resolution [38]. The regression of moyamoya vessels is demonstrated well in T_1-weighted imaging as a reduction in signal voids in the basal ganglia and thalamus [39]. Houkin et al. demonstrated that moyamoya vessels begin to regress 1 month after combined bypass surgery [40]. In the same study, serial magnetic resonance angiography examinations demonstrated how the caliber of the deep temporal and middle meningeal arteries increased to the point of identification on imaging 3 months after surgery, suggesting a reciprocal relationship between neovascularization and the regression of moyamoya vessels.

No data support routine screening for moyamoya disease, and little evidence exists to justify the screening of first-degree relatives of patients with moyamoya disease when a single individual in a family is affected [41]. However, screening may be considered in individuals with relatively common conditions who are at high risk of developing moyamoya syndrome [42-45].

The pathogenesis of moyamoya disease remains unclear. Despite the suggestion of a possible infectious cause, no specific pathogen has been identified [46]. Genetic factors have been considered, particularly in light of the high risk of familial occurrence (in 15% of patients), but candidate genes have not yet been defined [47]. The possibility of an inflammatory etiology is partly supported by the finding of increased concentrations of growth factors and cytokines in the cerebrospinal fluid of patients with the disease, but further research is required [48]. In addition, microthrombi within the stenotic vasculature were postulated to cause endothelial injury, leading to a thickened intima and smooth muscle proliferation [49]. However, because microthrombi are not unique to this condition, that hypothesis does not provide the entire etiologic answer. Moreover, the natural history of moyamoya disease is not fully understood, largely because of the limited number of studies investigating the progression of the disease. Some reports suggest that occlusive lesions in the carotid terminations often worsen

in children [50]. Intellectual quotient scores start to decrease 5 years after the onset of disease [51]. Progressive mental retardation was associated with an early presentation of ischemia (at <4 years of age) [52]. The literature describes children who needed special schooling in their teenage years, and some children required 24-hour care [53]. Other authors think that life expectancy is not significantly reduced [54]. Despite a lack of randomized control trials, anecdotal evidence supports surgical intervention as a means of improving quality of life and reducing further ischemic attacks. Functional or intellectual outcomes were poor in children who were treated conservatively (i.e., without surgery) [53,55]. Recent studies reported that surgical intervention can improve signs, reverse neurologic deficits, prevent further ischemic episodes, allow for normal intellectual development, decrease seizure activity, and lead to the disappearance of involuntary movements [36,56-62]. Recent guidelines of the American Heart Association support the use of surgery to treat moyamoya disease [41].

Table 1. Conditions associated with Moyamoya syndrome

Tuberculosis [75]
Down syndrome [105]
Sickle cell anemia [70]
Neurofibromatosis 1 [106]
Glycogen storage disease, type 1a [107]
Sjögren syndrome [108]
Recurrent thromboembolic events [109]
Radiation [110]
Human immunodeficiency syndrome [77]
Hereditary spherocytosis [111]
Hemophilia [112]
Fanconi's anemia [113]
Oral contraceptives [114]
Head and neck infections [115]
Meningoencephalocele [116]
Williams syndrome [117]
Alagille syndrome [118]
Midaortic syndrome [119]
Primary antiphospholipid syndrome [120]
Noonan syndrome [121]
Hypomelanosis of Ito [122]
Robinow syndrome [123]

Moyamoya Syndrome

The typical neuroradiologic findings in moyamoya disease were reported to coexist with a variety of other medical conditions [63] (Table 1), and we will review some of the more frequently encountered associations. The radiologic intracranial appearances of established moyamoya syndrome are the same as those of moyamoya disease, as are often the clinical signs. The existence of unilateral moyamoya syndrome has been discussed extensively. Several reports of children with a variety of underlying diseases described the typical neuroradiologic findings of moyamoya on one side only. According to a previous report, these patients should be referred to as manifesting unilateral moyamoya syndrome, and they should undergo periodic radiologic follow-up [12]. Three separate studies indicated that the progression to bilateral disease occurs in 44% of patients with unilateral moyamoya, and this progression occurs, on average, between 1.5 and 2.2 years [64-66]. Moreover, this progression is especially evident in children aged <10 years [67,68].

Sickle Cell Disease and Moyamoya Syndrome

Catheter angiograms performed after a stroke in children with sickle cell disease were first reported in 1972 to exhibit a moyamoya pattern [69], and the current quoted risk of moyamoya syndrome in children with sickle cell disease ranges from 20-35% [70]. The identification of patients at high risk of stroke is provided by transcranial Doppler imaging. This noninvasive, portable technique is typically performed with a probe placed over the pterion, to obtain blood velocity measurements of the internal carotid artery and its terminal branches. The American Heart Association recognizes the need for more frequent monitoring of young children (aged 2-10 years) and those with relatively high velocities on transcranial Doppler imaging. Recommendations include annual surveillance of patients with normal transcranial Doppler imaging (time-averaged mean velocity, ≤170 cm/second) and monthly follow-up for children with abnormal transcranial Doppler imaging results (≥200 cm/second). For children with results between these two velocities, transcranial Doppler imaging should be repeated at 3 months (transcranial Doppler imaging, 185-199 cm/second) and 6 months (transcranial Doppler imaging, 170-184 cm/second) [27,41,71]. Examples are depicted in Figs 4 and 5. Although the evidence supporting transcranial Doppler imaging for stroke screening in sickle cell disease did not focus primarily on moyamoya disease, we think that the diagnosis of moyamoya condition is likely to increase as screening continues and subsequent magnetic resonance studies are requested [9].

In sickle cell disease, red blood cells containing hemoglobin S polymerize when they are deoxygenated, and become abnormally adherent to the walls of blood vessels. Subsequent vascular stasis produces platelet aggregation and fibrin deposition, resulting in ischemia and infarction. Continued damage to the blood vessels results in fibrosis and narrowing of the cerebral vasculature, further exacerbating the stenoses, and leading to an eventual progression to occlusion. Collateral vessels are likely to develop at the points of greatest metabolic demand [19].

Down Syndrome and Moyamoya Syndrome

Despite a number of reported cases, a child with Down syndrome is at low risk of developing moyamoya syndrome [71,72]. When it does occur, the age at presentation is

similar to that for moyamoya disease, although a 20-month-old child presenting with seizure and hemiparesis was described [73]. The child referred to our institution is currently under consideration for surgical intervention. The etiologic link between Down syndrome and moyamoya syndrome is largely based on the high incidence of vascular dysplasia in patients with Down syndrome and their greater predisposition to vascular disease [74].

Tuberculous Meningitis and Moyamoya Syndrome

Interestingly, one of the patients with moyamoya disease originally described by Suzuki and Takaku also exhibited tuberculous meningitis. Since then, more cases were reported [75] (Fig 6). The stigmata of tuberculous meningitis resolve, but the vessels continue to demonstrate the moyamoya pattern 2.5 years after the initial presentation. Whether the vessels will return to their normal caliber is unclear. The moyamoya pattern in tuberculous meningitis is attributed to a vasculitis resulting from the bathing of cerebral vessels in an inflammatory gelatinous exudate [76]. Virally induced vasculitis was also postulated for moyamoya syndrome in patients with acquired immunodeficiency syndrome [77].

Many conditions exist in which only one or two cases of moyamoya syndrome were reported as a complication. The underlying cause of a vascular occlusion is usually unknown.

Applying Other Neuroimaging Techniques to Moyamoya Disease and Syndrome

Imaging has been concentrated primarily on diagnosing strokes and the angiographic characteristic findings of moyamoya disease and syndrome. Although these applications are important, they ultimately fail to quantify the effects of the condition on cerebral hemodynamics. Quantitative hemodynamic studies in moyamoya disease and moyamoya syndrome are often necessitated by a discrepancy between the angiographic findings and the clinical severity of disease. For instance, patients with bilateral terminal occlusive internal carotid arteries and innumerable collaterals may remain asymptomatic, whereas others with apparent mild angiographic stenosis may exhibit severe ischemic signs. This disparity likely stems from the physiologic complexity of factors controlling cerebral blood flow (e.g., age, arterial perfusion pressure, intracranial pressure, blood viscosity, $Paco_2$, pH, O_2, and the quality of the remaining cerebral and collateral circulation) [28,78].

A detailed discussion of the pathophysiology governing cerebral blood flow is beyond the scope of this review. However, it is worth briefly revisiting some fundamental concepts, so that quantitative imaging techniques can be appreciated. Cerebrovascular homeostasis is maintained by the process of autoregulation through the interplay between cerebral blood flow, cerebral perfusion pressure, and vascular resistance. Autoregulation maintains cerebral blood flow in the presence of falling cerebral perfusion pressure by the reflex vasodilation of resistance arterioles. However, the brain's capacity for autoregulation is finite, and falls in cerebral perfusion pressure (e.g., in stenotic or occlusive cerebrovascular disease) may result in reduced cerebral blood flow, despite compensatory mechanisms. Beyond the capacity for autoregulation, the body initially attempts to maintain neuronal tissue function by increasing the oxygen extraction fraction. However, further falls in cerebral perfusion pressure result in the eventual exhaustion of compensatory methods, manifesting as ischemia or infarction. Cerebral blood volume, involving arterial, venous, capillary, parenchymal, and pial compartments, can increase with falling cerebral perfusion pressure, which has been attributed to the vasodilatory response [78]. The extent to which these vessels can dilate to maintain cerebral blood flow during a fall in cerebral perfusion pressure is termed the "cerebrovascular reserve." Patients with moyamoya disease tend to be in a state of chronic vasodilation, with little or no cerebrovascular reserve [78].

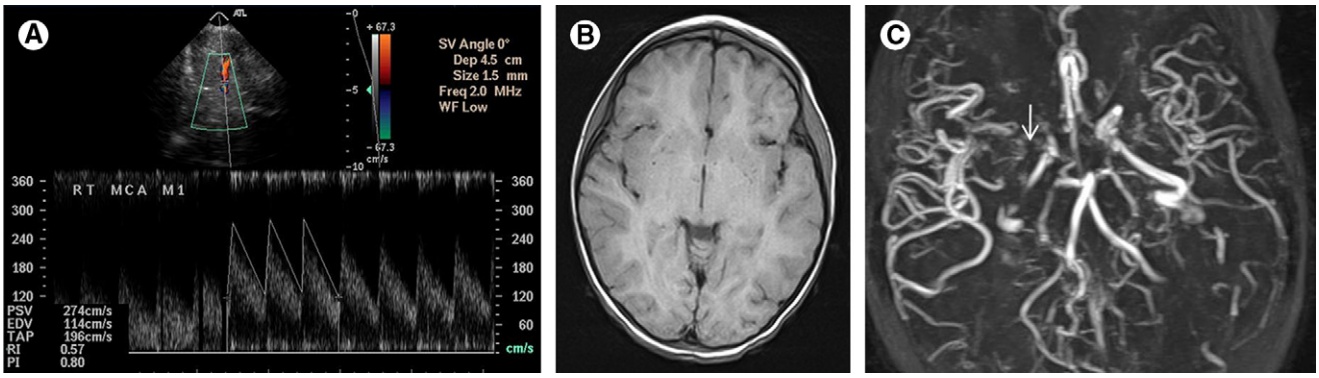

Figure 4. A 5-year-old girl with sickle cell disease presented with increasing episodes of transient ischemic attacks. (A) Transcranial Doppler imaging indicated abnormally high blood flow velocities in both the internal carotid arteries and middle cerebral arteries (right middle cerebral artery [RT MCA M1] demonstrated an average velocity of 196 cm/second). Subsequent magnetic resonance imaging/magnetic resonance angiography revealed numerous signal voids (black dots) in the region of the basal ganglia representing moyamoya vessels (B), significant stenoses at the distal right internal carotid artery, proximal right middle cerebral artery (arrow), and origin of the right anterior cerebral artery and narrowing of the left middle cerebral artery (C). No acute or established parenchymal infarcts were evident.

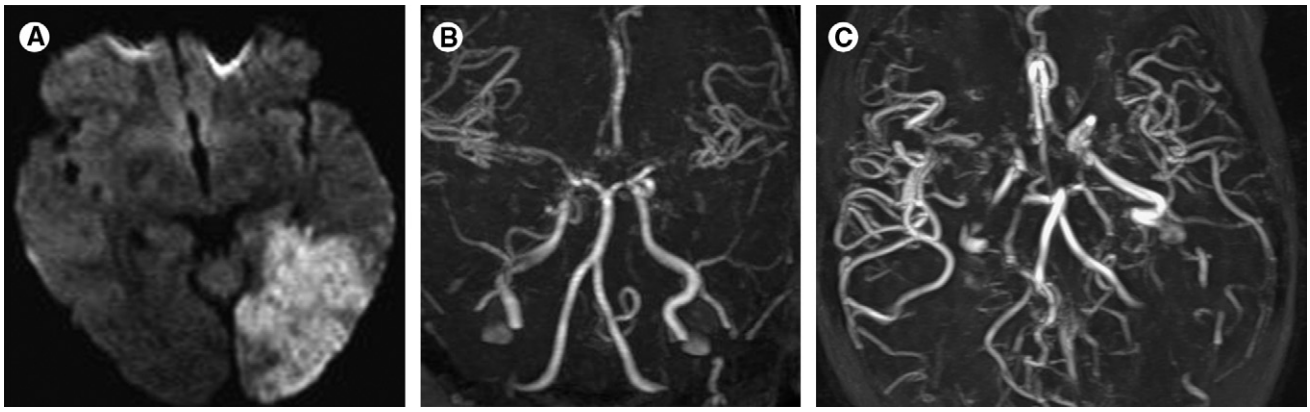

Figure 5. A 9-year-old girl with sickle cell disease and increasing blood flow velocities in the left internal carotid artery and middle cerebral artery on transcranial Doppler imaging during the preceding 4 months presented acutely with visual disturbance. (A) An acute left posterior cerebral artery territory infarct appeared bright on magnetic resonance diffusion-weighted imaging, reflecting restricted diffusion from cytotoxic edema. (B) Magnetic resonance angiography revealed extensive signs of moyamoya disease, with a high level of stenosis in the internal carotid artery terminations bilaterally, and numerous collateral vessels filling the distal middle cerebral artery branches. (C) Both posterior communicating arteries were fetal, which was thought to be the reason for the left posterior cerebral artery territory infarct. The left posterior communicating artery is attenuated because of the infarction.

The cerebrovascular reserve is a relevant indicator of ensuing ischemic stroke in patients with moyamoya disease, and is considered an additional indication for surgery if it is decreased [79,80]. It can be assessed with single-photon emission computed tomography by measuring the cerebrovascular reactivity to a vasodilator such as acetazolamide. Under physiologic conditions, acetazolamide (a carbonic anhydrase inhibitor) increases cerebral blood flow by evoking a shift in the cerebral acid-base balance toward carbonic acidosis. In patients with moyamoya disease, the degree of cerebral vessel dilation after administering acetazolamide is lower in areas of reduced cerebral perfusion pressure, because the cerebral vessels are already dilated [81]. As a result, acetazolamide single-photon emission computed tomography increases the contrast in radioactivity levels between regions of adequate vascular reserve and those of inadequate reserve [82]. This method is widely used throughout the Western world, and is considered the gold-standard technique for studies of cerebral vascular reserve [79].

Acetazolamide is considered safe to administer and is generally well tolerated. Systemic blood pressure, heart and respiratory rates, arterial pH, and arterial CO_2 pressure are unaffected [83]. Moreover, Piepgras et al. reported no acute ischemic sequelae in more than 1000 studies that involved the use of acetazolamide [84].

Positron emission tomography is also widely used to study patients with moyamoya disease [68,85-87]. Measurements of cerebral blood flow, cerebral blood volume, and estimates of the fraction of oxygen consumed by the

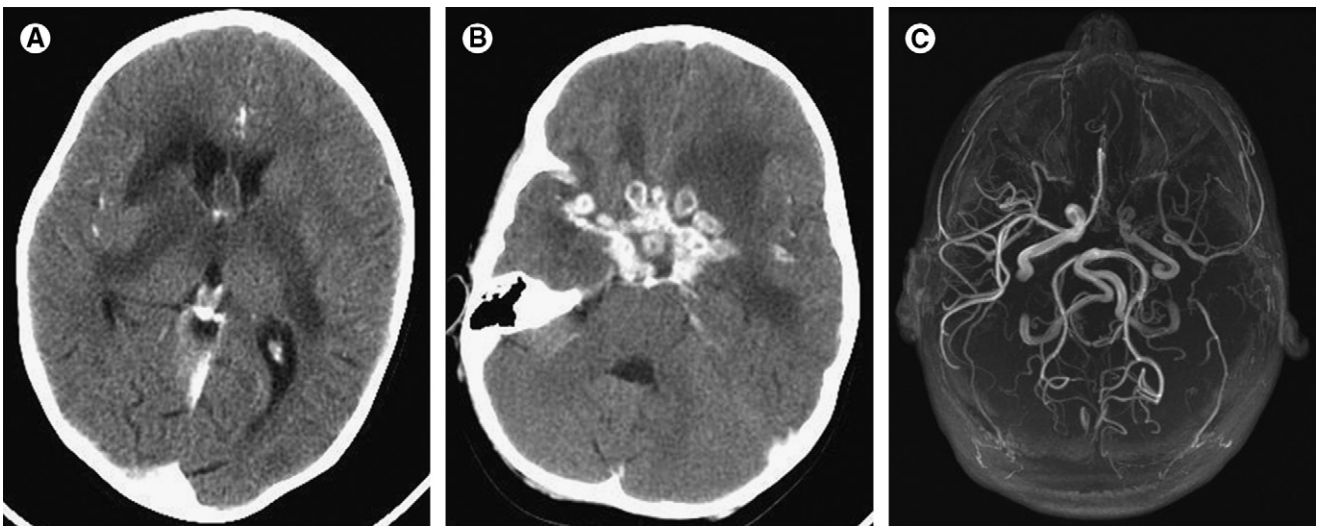

Figure 6. A 3-year-old girl presented with signs of meningism. Initial computed tomography with contrast enhancement (A and B) indicated extensive low attenuation in the regions of the basal ganglia and internal capsules bilaterally, extending to the inferior frontal lobes and temporal lobes. Multiple, irregular, ring-enhancing lesions, consistent with tuberculomata, are present in the suprasellar region and extend along the course of both middle cerebral arteries. Moreover, a focal infarction of the right caudate nucleus and abnormal thickening and enhancement of the pituitary stalk are evident (the patient was diagnosed with diabetes insipidus). In addition, abnormal ependymal enhancement is evident, particularly of the right lateral ventricle, suggesting ventriculitis. (C) Subsequent magnetic resonance angiography revealed terminal stenosis of the left internal carotid artery and proximal stenosis of the left anterior cerebral artery and middle cerebral artery, together with moyamoya collateral vessels.

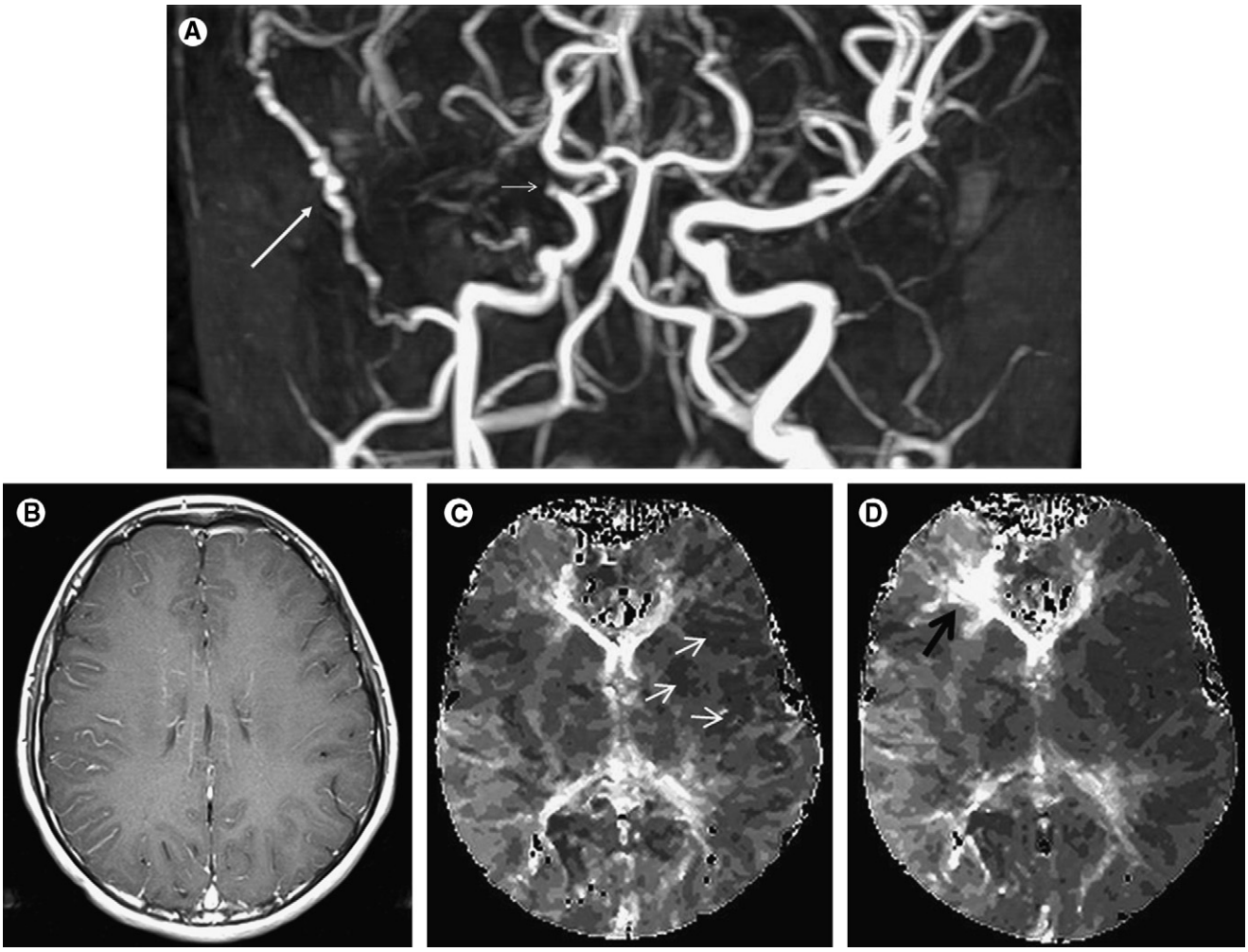

Figure 7. A 5-year-old girl without a remarkable medical history presented with repeated episodes of transient left-sided weakness after episodes of crying. (A) Magnetic resonance angiography demonstrates predominantly right-sided disease, with occlusion of the proximal right middle cerebral artery (small arrow) and established collaterals between distal middle cerebral artery branches and the right superficial temporal artery (large arrow). (B) Axial T_1-weighted, gadolinium-enhanced image reveals right-sided leptomeningeal flow engorgement, i.e., the "ivy-sign." Axial postgadolinium perfusion-weighted imaging mean transit time maps, before and after acetazolamide challenge (C and D, respectively), demonstrate abnormal perfusion of the right hemisphere. Dark areas equate with shorter mean transit times and increased perfusion (indicated as arrows in the normally perfused left hemisphere in C). (D) A normal increase in dark areas follows acetazolamide challenge in the left hemisphere, but with more reduced perfusion on the right (white areas, predominantly right frontal horn periventricular white matter, as indicated by arrow), consistent with the known middle cerebral artery territory vasculopathy.

brain can be obtained. Reduced cerebral blood flow and a raised fraction of oxygen consumption are thought to be hemodynamic indicators of impending cerebral infarctions in moyamoya disease [78]. Single-photon emission computed tomography and positron emission tomography can also help determine the extent of improvement in functional perfusion, and may play a role in predicting outcomes of patients after surgical intervention [41,88].

Ultrasonography was used as a tool for hemodynamic measurement in patients with moyamoya disease [89-91]. Estimations of blood flow volume in the internal carotid artery can provide measurements of hemispheric cerebral blood flow, where reduced cerebral blood flow is used to indicate an impending infarction [92]. Power Doppler was also suggested as a valid method of diagnosis [93] and in the evaluation of direct (bypass patency) and indirect (neoangiogenesis) revascularization [94]. However, this technique is limited because it is operator-dependent and prone to spurious results [92].

Although single-photon emission computed tomography, positron emission tomography, and ultrasound offer important insights into cerebral perfusion, they are not optimal for repeated examinations, and do not provide information about the structural integrity of the hypoperfused brain [95]. Consequently, considerable interest has been invested in developing similar techniques of magnetic resonance in children, using some form of perfusion-weighted imaging. This technique is most frequently performed using fast gradient echo T_2* images, acquired during the injection of a gadolinium bolus. This method of dynamic bolus perfusion-weighted imaging generates parametric maps with a much higher anatomic resolution than in positron emission tomography, and may elucidate focal perfusion abnormalities at the level of each individual gyrus [96]. Although it does not produce quantifiable measures of cerebral blood flow or cerebral blood volume, it does allow for comparisons of cerebral blood volume ratio and mean transit times be-

tween different regions of the brain. Mean transit time is a measure of the mean time for blood to perfuse a region of tissue. It is related to cerebral blood flow and cerebral blood volume according to the central volume principle, i.e., mean transit time = cerebral blood volume/cerebral blood flow [97]. Thus, mean transit time is highly sensitive to hemodynamic disturbances involving changes in both cerebral blood volume and cerebral blood flow, and was implicated as a potentially important indicator of cerebral perfusion abnormalities in patients with moyamoya disease [98,99].

More recently developed methods (e.g., arterial spin labeling) do not require external contrast agents, and may be formally quantifiable. Both dynamic bolus perfusion-weighted imaging and arterial spin labeling can be performed alongside an acetazolamide challenge, to judge cerebrovascular reserve. We are currently using routine magnetic resonance imaging, magnetic resonance angiography, and perfusion-weighted imaging before and after the administration of acetazolamide to investigate children with known moyamoya disease (Fig 7).

Blood oxygen level-dependent magnetic resonance offers a promising new technique for assessing cerebral hemodynamics. It is directed at the assessment of cerebrovascular reserve after a stimulus to induce a change in resting blood flow. Just as acetazolamide may be used as a method of "challenging" the patient, end-tidal $Paco_2$ ($ETco_2$) levels can be manipulated in patients through a rebreathing circuit. At the same time, blood oxygen level-dependent magnetic resonance sequences identical to those used for functional magnetic resonance studies are obtained. Cerebrovascular reactivity maps generated by this method provide spatial, quantitative maps of impaired cerebrovascular reactivity in terms of percent blood oxygen level-dependent signal change per mm Hg change in $ETco_2$, and can be used to assess the extent of exhausted autoregulation [28]. Negative cerebrovascular reserve responses (i.e., decreases in blood oxygen level-dependent magnetic resonance signal) are evident in patients with uncompensated moyamoya disease, and indicate the "steal" phenomenon, whereby in the presence of hypercapnia, blood is diverted away from maximally dilated vascular beds to unimpaired beds that retain the capacity for vasodilation [100-102]. This technique does not involve ionizing radiation and contrast injections, and can be performed in conjunction with other magnetic resonance imaging sequences during a patient's investigation. Moreover, the range of $ETco_2$ required is in the order of that achieved by patients as part of their normal daily activity (30-50 mm Hg) [103]. Limitations, particularly in the pediatric age group, include patient compliance with the rebreathing circuit and the increase in time required for the patient to remain still.

Finally, magnetic resonance spectroscopy should receive mention. Although generally limited to research, it was examined in the context of moyamoya disease. Some authors reported reduced levels of choline, creatine, and *N*-acetyl aspartate in the affected cerebral areas of patients with moyamoya disease. After revascularization surgery, levels of all three metabolites increased [104]. The significance of this alteration is unclear. However, *N*-acetyl aspartate is considered an important marker for healthy neurons.

Conclusions

Although moyamoya disease and syndrome remain rare, their incidence and prevalence are increasing, making them an important cause of pediatric stroke. Prompt diagnosis and appropriate management are crucial in improving the long-term prognoses of patients. Future advances may provide a single imaging tool that can fully characterize the disease process at one sitting. Until then, the assessment of anatomic and cerebrovascular changes will rely on a variety of imaging techniques.

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