Moyamoya disease is an unremitting cerebrovascular occlusive disorder of unknown etiology that is becoming more widely recognized as a cause of stroke in pediatric and adult patients. In fact, moyamoya disease accounts for ≥ 6% of strokes in children. If left untreated, it can lead to devastating, permanent neurological disability. It is characterized by progressive narrowing (and, ultimately, occlusion) of the terminal ICA and proximal middle and anterior cerebral arteries and the nearly simultaneous formation of dilated intracranial ICA tributaries at the base of the brain in response to ICA stenosis. These arteries, the so-called moyamoya vessels, traverse the basal ganglia and thalamus, and provide collateral blood flow to areas of hypoperfused brain distal to the narrowed vessels. Takeuchi and Shimizu were the first to describe this disease in the Japanese literature in 1957 as a case of “hypoplasia of the bilateral internal carotid arteries.” Kudo subsequently introduced it to the English literature in 1968 when he described it as a “spontaneous occlusion of the circle of Willis.” Finally, in 1969, Suzuki and Takaku used the term, “moyamoya,” a Japanese expression signifying “something hazy, like a puff of cigarette smoke drifting in the air,” to describe and define this disease process because of the distinctive angiographic appearance of the dilated collateral arteries that develop at the base of the brain in this disorder. Moyamoya disease may be idiopathic or occur in association with other syndromes. In the literature, moyamoya disease typically refers to the idiopathic form of the arteriopathy, whereas moyamoya syndrome signifies cases in which the characteristic angiographic findings occur in association with other pathological processes such as neurofibromatosis, sickle cell anemia, Down syndrome, and prior cranial irradiation. These distinctions are important to keep in mind when analyzing outcome data from the literature since most if not all outcome studies are from Japan and other Asian countries. These studies include only those patients with the idiopathic form of moyamoya disease. In contrast, outcome studies from the Western hemisphere include patients with moyamoya disease and those with moyamoya syndrome. Despite the distinctions between the idiopathic and syndrome-associated forms, their angiographic and clinical courses are nearly identical.
Since its initial discovery, moyamoya disease has been studied extensively, and there are now >1200 publications describing various facets of this disorder and its management. Despite this, significant controversy remains regarding its etiology, pathogenesis, diagnosis, and treatment, including indications for treatment. Nevertheless, recent advances in research, diagnosis, and operative techniques emphasize the significance of a multidisciplinary approach to the management and further study of this disorder to improve the long-term outcome for patients with moyamoya disease. This review provides a comprehensive discussion of moyamoya disease in children, with an emphasis on the most effective surgical treatment options.

**Epidemiology**

Moyamoya disease occurs worldwide, however, the greatest incidence continues to be in East Asia. For instance, in Japan, the idiopathic form of this disease occurs annually in ≥0.35–0.54 per 100,000 population (that is, 0.35 in 1994 and 0.54 in 2003). In contrast, the incidence in Europe is ~one-tenth the incidence in Japan. Moyamoya disease affects both males and females; however, in most series there is a consistent female preponderance, with females being affected nearly twice as often as males. In addition, there is a bimodal age distribution, with patients typically presenting either in the 1st or 4th decade of life. For those presenting within the 1st decade, ischemic events such as TIAs or strokes are more common. In contrast, adult patients more commonly present with hemorrhage. Because of this, the time to diagnosis is typically longer in pediatric patients. For those presenting within the 1st decade, ischemic events such as TIAs or strokes are more common. In contrast, adult patients more commonly present with hemorrhage. Because of this, the time to diagnosis is typically longer in pediatric patients. Finally, there is a relatively high incidence of familial occurrence, which accounts for ~15% of patients.

**Clinical Presentation**

Children with moyamoya disease typically present with evidence of cerebral ischemia, and ~80% demonstrate TIAs (40%) or cerebral infarction (40%). Of these, ~80% have extremity weakness or paralysis as the initial finding. Some patients present with ischemic events precipitated by crying, coughing, blowing, or hyperventilation since such activities lead to hypocapnia-induced vasoconstriction of the normal cerebral blood vessels, which in turn causes a transient reduction in CBF in an already compromised cerebral circulation. Patients can also present with headaches (likely resulting from dilation of meningeal and leptomeningeal collateral vessels), seizures (including somatosensory focal seizures), involuntary movements of the extremities, and/or a progressive decline in neurocognitive function. Although cerebral hemorrhage can be seen on presentation, it occurs only rarely in children. In contrast, 40–65% of adult patients present with hemorrhage, especially in the basal ganglia (40%), thalamus (15%), or ventricular system (30%). Symptoms related to posterior circulation ischemia, such as visual field defects, decreased visual acuity, transient blindness, scintillating scotomas, diplopia, ataxia, and vertigo, are uncommon presenting features in both children and adults. However, when they do occur, they are observed more often in children.

Although most patients present with bilateral involvement, up to 18% of patients have angiographically documented unilateral involvement. In children, unilateral involvement typically progresses to bilateral involvement within 1–2 years. For example, in 1 study, 33 (14%) of 235 patients presented with unilateral moyamoya disease. Of these, 33% progressed to bilateral angiographic disease, on average, within 2.2 years, suggesting that all patients with unilateral disease should be observed closely for disease progression.

Multiple clinical associations have been observed in patients with moyamoya disease. Such associations may represent significant risk factors for the development of this disorder as well as for disease progression in patients with unilateral disease. These include prior cranial irradiation; tumors, such as optic gliomas, craniopharyngiomas, and pituitary tumors; genetic disorders, such as Down syndrome, neurofibromatosis (with or without hypothalamic-optic pathway tumors), Fanconi anemia, and sickle cell anemia and other hemoglobinopathies; collagen vascular disorders, such as Marfan syndrome, Ehler-Danlos, and homocystinuria; Graves disease; congenital cardiac disease; renal artery stenosis; infections, such as tuberculous meningitis and leptospirosis; atherosclerosis; and fibromuscular dysplasia.

**Pathology**

In moyamoya disease, stenotic changes initially appear in the intracranial ICAs distal at the level of their bifurcation. Later, the stenosis progresses to involve the proximal anterior and MCAs. During subsequent stages, the posterior circulation may also become involved. Histological analyses of the stenotic arteries reveal endothelial hyperplasia and fibrocellular thickening of the intima; tortuosity or undulation and sometimes even duplication of the internal elastic lamina and attenuation of the media. Affected vessels lack inflammatory changes, suggesting that inflammation does not play a major causative role in vessel pathology.

Concomitant with stenosis, moyamoya vessels (that is, dilated perforating ICA tributaries) develop at the base of the brain in response to chronic ischemia. This intense compensatory recruitment of new vessels provides collateral blood flow to areas of hypoperfused brain distal to the narrowed vessels. These collateral vessels can be categorized as follows: 1) intracerebral anastomoses, which arise from basal and convexity perforating arteries that penetrate brain parenchyma and Anastomose at the external angle of the lateral ventricles; 2) dilated basal collateral networks, which develop directly from circle of Willis vessels and perforating carotid artery–basilar artery anastomoses; 3) cortical-leptomeningeal end-to-end anastomoses, which form over the surface of the brain at watershed areas of the major cerebral artery territories; 4) dural networks, which arise from dural vessels and perfuse ischemic brain through anastomoses with the cortical leptomeningeal system; and 5) extracranial
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networks, which arise from transdural vessels and connect scalp arteries to the cortical leptomeningeal system. The dural and extracranial arterial networks (vault moyamoya vessels) collateralize the anterior and middle cerebral circulations through vascular connections that form at the sagittal and transverse sinuses, falk, and tentorium. These vessels are particularly evident in areas where openings exist between skull, dura, arachnoid, and brain, such as around the venous sinuses or at the skull base where cranial nerves exit the calvaria (for example, at the cribiform plate).

Histologically, moyamoya vessels exhibit thin walls, mural fibrin deposits, fragmentation of the elastic lamina, and microaneurysm formation. Such changes may predispose these vessels to rupture, making them a possible source of hemorrhage, especially in adults. In addition, typical saccular aneurysms, many of which are located in posterior circulation vessels (with the basilar tip being the most common), are seen more frequently in adults with moyamoya than in the general population. Saccular aneurysms and pseudoaneurysms, which can develop along peripheral portions of perforating moyamoya vessels and the anterior and posterior choroidal arteries, also represent potential sources of hemorrhage. The incidence of aneurysms in children with moyamoya disease is ~1%, whereas that in adults is ~6.2%. Finally, AVMs can occur in patients with moyamoya disease, typically in the MCA territory, but the relationship between AVMs and moyamoya disease remains unknown.

Pathogenesis and Etiology

Although the pathogenesis and etiology of moyamoya disease remain unknown, genetic and acquired or environmental factors have been implicated in this disease process. The following observations support a role for genetic factors in the pathogenesis of moyamoya disease. The incidence of moyamoya disease is highest in, although not confined to, individuals of Japanese origin. Moyamoya disease has a high incidence of familial occurrence, with a familial incidence in Japan of 7–12%. Moyamoya disease frequently occurs in association with genetically transmitted disorders, including neurofibromatosis, sickle cell anemia, autoimmune disorders, and Down syndrome. Antidouble stranded DNA antibodies and several HLA antigens have also been observed in patients with moyamoya disease.

Chromosome linkage analyses provide further support for genetic factors in the etiology of moyamoya disease. For example, a linkage study using markers on chromosome 6, where the HLA gene resides, identified an allele that appears to be linked with moyamoya disease. In another study, the observation that the characteristic cerebrovascular abnormalities of moyamoya disease are sometimes seen in neurofibromatosis Type 1, of which the causative gene (that is, NFI) has been assigned to 17q11.2, led to microsatellite linkage analyses to ascertain whether a gene related to moyamoya disease is also located on chromosome 17. Such analyses detected a gene for familial moyamoya disease on 17q. Besides 17q, microsatellite linkage analyses have shown linkages between moyamoya disease and markers located on 3p, 6q, and 8q. Interestingly, a locus for Marfan syndrome, a connective tissue disorder characterized by skeletal and cardiovascular anomalies, maps to 3p as does the von Hippel–Lindau disease tumor suppressor gene, which is responsible for the vascular tumor, hemangioblastoma. The gene product of the moyamoya gene mapping to 3p, although it has not yet been characterized, likely is fundamental to the formation and maintenance of vascular wall homeostasis. At present the significance of these findings is not entirely certain; however, the eventual molecular characterization of moyamoya disease will likely provide valuable insights into the etiology of this disorder as well as its treatment (for example, gene therapy).

Besides genetic factors, evidence supports a role for acquired or environmental factors in the pathogenesis of moyamoya disease. The observation of moyamoya pathology as a delayed response in patients following irradiation of the skull base for treatment of tumors of the head and neck, especially hypothalamic-optic pathway gliomas and craniopharyngiomas, suggests a role for environmental factors. Infection has also been proposed as a cause based on the observation in some patients of an infectious illness prior to the onset of moyamoya disease. Moreover, the altered expression of certain mitogens, adhesion molecules, and angiogenic factors and/or alterations in cellular responses to growth factors and cytokines (small secreted proteins that mediate and regulate immunity, inflammation, and hematopoiesis) in vascular cells may play a crucial role in the development of moyamoya pathology (in particular, intimal thickening and media thinning) by affecting vascular endothelial or smooth muscle cell proliferation or migration. For example, caspase-3, a cysteine protease essential for programmed cell death, is elevated in MCA specimens from patients with moyamoya disease. This suggests a potential role for caspase-3-dependent apoptosis in attenuation of the media that can be seen in the stenotic vessels in patients with moyamoya disease. Furthermore, several studies have shown that bFGF, an angiogenic substance, is elevated in assays of dura and scalp arteries in patients with moyamoya disease as well as in the CSF of children with moyamoya disease, sampled at the time of revascularization surgery. Increased levels of bFGF may play a role in stenosis or in the neovascular response that occurs spontaneously and following cerebral revascularization procedures in patients with moyamoya disease. Although we still do not fully understand the specific mechanisms underlying the pathogenesis and etiology of moyamoya disease, genetic and environmental factors likely play significant roles in the underlying disease process.

Natural History and Prognosis

The natural history of moyamoya disease is still not fully understood; however, it is clear that the rate of disease progression is variable. For example, some patients exhibit a rapidly progressive course with multiple strokes and significant disability within the 1st year of diagnosis. Others demonstrate a more gradual disease progres-
sion, with neurological deficits accumulating slowly over many years and often with prolonged symptom-free intervals. Despite the course, the disease inevitably progresses in untreated patients with angiographic and clinical worsening over time. Stability occurs only after development of sufficient leptomeningeal or transdural collateral vessels. Until then, patients are at risk for developing ischemic symptoms.

A previous study investigated the prognosis of 27 children with moyamoya disease treated conservatively. That study revealed that ischemic symptoms, such as TIAs, occurred most often during the first 4 years and then tended to decline over time. In contrast, intellectual deterioration and neurological deficits increased with time; 50–65% of children exhibited a considerable decline in cognitive function. Several factors determine the overall prognosis of patients with moyamoya disease. These include the following: 1) the rapidity and extent of vascular occlusion; 2) the ability to develop effective collateral circulation; 3) the age at onset of symptoms; 4) the severity of presenting neurological deficits and degree of disability; and 5) the extent of infarction seen on CT or MR imaging studies at the time of initial presentation. As expected, patients presenting with fixed neurological deficits related to stroke tend to have poorer functional outcomes, with increased difficulty with activities of daily living. Moreover, the extent of disease at the time of diagnosis is a more important prognostic indicator than the age at onset of symptoms. For example, children who present with bilateral strokes tend to be developmentally delayed at long-term follow-up, regardless of their age, whereas those with multiple small infarcts or a large nondominant stroke often are educable and capable of leading independent and productive lives. Furthermore, if surgical revascularization is performed prior to infarction, the prognosis tends to be excellent in the face of severe angiographic changes. However, if left untreated, the angiographic process and clinical symptoms invariably progress, leading to clinical deterioration and possible irreversible neurological deficits.

**Diagnosis**

Although it is relatively uncommon, moyamoya disease must be considered in any child who presents with symptoms of cerebral ischemia (for example, TIAs manifesting as episodes of hemiparesis, speech disturbance, sensory impairment, involuntary movement, and/or visual disturbance), especially if the symptoms are precipitated by physical exertion, hyperventilation, or crying. Imaging plays a key role in the diagnostic evaluation of these patients. A head CT is typically the first study obtained. In patients with moyamoya disease, the head CT scan frequently shows areas of hypodensity consistent with infarct in cortical watershed zones, basal ganglia, deep white matter, or periventricular regions. The head CT may also reveal hemorrhage, most commonly in the basal ganglia (40%), ventricular system (30%), and thalamus (15%). Atrophy of the affected hemisphere is frequently seen in patients who have had severe stroke, and gyral enhancement can also be observed after contrast administration.

Magnetic resonance imaging and MR angiography are helpful in the diagnosis of moyamoya disease because they provide greater parenchymal and vascular detail. Magnetic resonance imaging typically reveals diminished flow voids in the ICA, MCA, and ACA and prominent flow voids in the basal ganglia and thalamus from dilated moyamoya vessels that traverse these regions to supply hypoperfused brain distal to the occluded vessels. Such flow voids are virtually diagnostic of moyamoya disease. Magnetic resonance imaging may also demonstrate multiple, small, asymptomatic areas of cerebral infarction, which are typically found in watershed regions between the cortical areas vascularized by the ACA and MCA. Likewise, diffusion weighted, perfusion echo planar, and gradient echo MR imaging techniques are useful for evaluating cerebral ischemia, with diffusion weighted imaging leading to significantly earlier detection of ischemic lesions in patients with moyamoya disease.

Magnetic resonance angiography is very useful for diagnosing moyamoya disease, with previous studies showing a sensitivity of 73% and a specificity of 100%. Sensitivity increases to 92% when MR angiography is combined with MR imaging or when MR angiography is performed with selective maximum intensity projection. Because of its excellent diagnostic yield and noninvasiveness, some have suggested that MR angiography be used instead of conventional cerebral angiography for the diagnosis of moyamoya disease. However, the smaller moyamoya collaterals are visualized more clearly with conventional cerebral angiography, which is still the gold standard for diagnosing moyamoya disease. Bilateral selective ECA and ICA injections and a vertebrabasilar artery injection are essential to define the extent of preexisting collaterals from the extracranial circulation, to document areas of cerebral hypoperfusion, and to identify any coexisting aneurysms or AVMs.

Moyamoya disease progresses through the following 6 characteristic angiographic stages: 1) stenosis of distal intracranial ICAs, often bilaterally; 2) formation of moyamoya collateral vessels at the base of the brain; 3) further prominence of moyamoya vessels as stenosis of the anterior circulation progresses; 4) severe stenosis or occlusion of the entire circle of Willis along with narrowing of the dilated moyamoya vessels and formation of extracranial collateral networks; 5) enlargement of extracranial collateral vessels; and 6) occlusion of the distal ICAs, disappearance of the basal moyamoya vessels, and cerebral vasculization from extracranial sources only. Cerebral angiography allows visualization of extracranial collateral networks and extracranial anastomotic sources such as the anterior branch of the middle meningeal artery, maxillary artery, and ophthalmic artery (for example, through the cribiform plate to supply the undersurface of the frontal lobe and through the falx to supply the ACA distribution).

Electroencephalography can be helpful in the diagnostic workup of pediatric patients with moyamoya disease. In ~50% of children with moyamoya disease, electroencephalography will show a hyperventilation-in-
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duced diffuse pattern of monophasic slow waves (that is, buildup) followed by a characteristic “re–buildup” phenomenon.17,123 This re–buildup phenomenon occurs after hyperventilation has stopped and involves the appearance of slow waves after disappearance or attenuation of ordinary buildup. This electroencephalography finding, which is characteristic of moyamoya disease, is thought by some to occur as a consequence of decreased arterial CO₂ tension, which causes vasoconstriction of previously maximally dilated normal cerebral vessels and leads to cerebral ischemia.99,105 Other investigators have proposed that cerebral hypoxia occurs after the cessation of hyperventilation and that this plays an essential role in the appearance of the re–buildup phenomenon.15,55 In conjunction with this, vasodilation in normal brain areas, which occurs in response to increasing PaCO₂ after the cessation of hyperventilation has been hypothesized to induce a possible steal response in cerebral areas suffering from chronic hemodynamic stress. This produces even more profound hypoperfusion in these already ischemic cerebral areas and possibly explains the clinical symptoms initiated by hyperventilation in patients with moyamoya disease.75

Techniques used to evaluate CBF are also very helpful in the diagnosis and management of moyamoya disease. Such techniques, which include Xe-enhanced CT, PET, and SPECT, can identify regional perfusion instability prior to treatment and ascertain the extent of improvement of functional perfusion following therapy.50,62,74,108 Single photon emission CT, with and without acetazolamide/CO₂ vasodilatory challenge, is a particularly useful technique that assesses cerebrovascular reserve and helps to predict the likelihood of further disease progression. Occlusion of the major cerebral arteries in patients with moyamoya produces chronic hemodynamic stress. In response to this stress, the cerebral blood vessels supplying ischemic areas vasodilate maximally in an attempt to preserve CBF and compensate for reduced cerebral perfusion. This leads to abnormal vasoreactivity to vasodilatory stimuli, such as hypercapnia or acetazolamide. Consequently, CBF in chronically hypoperfused areas challenged with a vasodilatory stimulus often is paradoxically diminished.75,76

This occurs because the unaffected vessels, which vascularize chronically ischemic areas through leptomeningeal collaterals or poorly developed collaterals from the circle of Willis, promptly dilate in response to vasodilatory stimuli, thereby effectively reducing CBF to areas with an impaired vascular response.

Treatment Options

Some patients with moyamoya disease stabilize clinically without intervention; however, this usually occurs only after they have experienced a significant, debilitating neurological disability. Following a major stroke or hemorrhage, children with moyamoya disease frequently are left with permanent neurological impairment.78,89-41 Consequently, early diagnosis and prompt, appropriate surgical management are of utmost importance.58 Currently, there is no definitive medical treatment to halt the progression or stabilize the course of moyamoya disease. Multiple surgical procedures designed to augment CBF distal to the occluded carotid arteries have been successful in treating moyamoya disease. Although objective evidence from randomized controlled clinical trials suggesting improved function following these procedures is still lacking, several studies examining the long-term outcome in children with moyamoya disease following revascularization surgery strongly suggest that surgical revascularization improves cerebral hemodynamics and reduces the incidence of subsequent ischemic events. In pediatric patients who have undergone surgical revascularization for treatment of symptomatic moyamoya disease, TIA’s rapidly decrease or disappear and strokes rarely recur.16,17,29,34,51,115

Because stroke can occur and lead to severe neurological impairment, it is unwise to wait for evidence of ischemic symptoms before recommending surgery.89,90 Moreover, if surgical revascularization is performed before infarction occurs, patients with moyamoya disease who present with TIAs will frequently have excellent outcomes. Patients with angiographic evidence of moyamoya disease are candidates for surgery. Angiographic criteria include the following: 1) stenosis or occlusion of the distal portion of the intracranial ICA and the proximal portions of the ACA and MCA; 2) an abnormal vascular network seen during the arterial phase near the stenosed or occluded vessels; and 3) bilateral involvement.18 If the degree of hypoperfusion on angiography does not appear critical but one suspects symptomatic moyamoya, then a CBF study such as SPECT with acetazolamide challenge should be done to look for reduced cerebral perfusion reserve as an additional indication for surgical treatment. Once the diagnosis has been established, surgery is recommended before further ischemic symptoms and related complications develop. Early diagnosis and prompt surgical revascularization over a wide area are crucial to achieving a good long-term outcome with improved intellectual function.78 If a patient has neurological deficits related to a prior stroke, the decision to operate should be based on the presence of other cortical areas at risk for stroke and on the patient’s quality of life if further neurological deficits were to develop.

Options for Medical Treatment

Currently, there is no known medical treatment capable of reversing, halting, or stabilizing the relentless progression of the arteriopathic process in moyamoya disease. Nevertheless, 2 types of medication play a role in the treatment of this disorder: aspirin and calcium channel blockers. Aspirin is taken daily and continued indefinitely to avoid ischemic symptoms owing to possible emboli from microthrombus formation at sites of arterial stenoses.78,89,90 Patients < 6 years of age receive 80 mg/day; the dose is gradually increased up to 300 mg/day in adolescents. Patients are monitored for side effects, such as easy bruising, bleeding, and gastrointestinal irritation, and the aspirin dose is adjusted as needed.

Calcium channel blockers are also effective in treating certain symptoms in patients with moyamoya disease, such as persistent postoperative TIAs and intractable headaches. Although the mechanism of action is
unknown, calcium channel blockers seem to be effective in reducing the frequency and severity of refractory TIAs in patients with moyamoya disease. Moreover, they can be used to treat headaches in children with moyamoya disease. Headaches can occur before and after revascularization surgery and can be very difficult to treat. Because of their antimigraine pharmacotherapeutic effect, calcium channel blockers are effective in relieving intractable headaches in patients with moyamoya disease.

Although currently there is no evidence that medical management alters the clinical course or outcome of individuals with moyamoya disease, future treatment will likely include the use of medical therapy. Plausible examples of potential medical therapies include the use of the following: topical or systemic angiogenic growth factors to induce neovascularization; gene therapy to target genetically determined conditions that occur in association with moyamoya disease; and additional novel therapies that block or alter the arteriopathic disease process.

**Options for Surgical Treatment**

To date there are no prospective randomized controlled clinical trials to determine the efficacy of surgical revascularization in the treatment of moyamoya disease. Nevertheless, there are a number of studies in the literature that provide strong support for surgical treatment. Revascularization surgery is generally recommended for patients with recurrent or progressive cerebral ischemic events and associated reduced cerebral perfusion reserve. Numerous operative techniques have been described. At the present time, there is no standardized surgical approach for the treatment of moyamoya disease in children, and numerous surgical procedures have been used in a variety of combinations. Such techniques aim to prevent further ischemic injury by increasing collateral blood flow to hypoperfused areas of cortex, with most using the external carotid circulation as a donor supply.

Revascularization procedures can be divided into 3 main groups: indirect (nonanastomotic) bypass techniques, direct (anastomotic) bypass techniques, and indirect and/or direct bypass techniques combined. Indirect bypass techniques include pial synangiosis, EDAS, EMS (temporalsis muscle with its rich blood supply is sutured to the dura mater), encephaloduroarteriomyosynangiosis (EDAMS), ribbon EDAMS, encephalogleoynangiosis (EGS), encephalogleoynangiosis (EGMS), omental transplantation, bifrontal encephalogleoperiosteal synangiosis (EGPS), and multiple bur hole surgery, with opening of dura and arachnoid over affected areas, as well as a combination of ≥ 1 of these techniques. One of the biggest criticisms of the indirect techniques has been that the beneficial effects are not immediate because it takes ≥ 3–4 months for collaterals to develop, and during that time there is a risk of perioperative ischemic stroke. The most commonly used direct bypass techniques are the ECA-ICA anastomoses, which involve anastomosis of the STA or the OA to the MCA either in isolation or in combination with a variety of indirect bypass techniques.

Numerous studies have reported on the technical aspects, indications, pitfalls, and efficacy of direct and indirect revascularization techniques for the prevention of ischemic symptoms in patients with moyamoya disease. In general, these studies have documented good to excellent angiographic and clinical results, including good collateralization of the MCA territory, reduction in the size of the basal collateral vessels, improved CBF, and partial or complete resolution of ischemic symptoms. Increased levels of angiogenic factors, such as bFGF, which is elevated in the CSF in patients with moyamoya disease, likely contribute to the effectiveness of both indirect and direct revascularization techniques by enhancing the formation and in-growth of new blood vessels from extracranial sources. Evidence suggests that essentially any surgically created pathway that traverses the skull, dura, and arachnoid will permit formation of cortical collaterals.

**The STA-MCA Bypass.** Direct (anastomotic) bypass techniques, such as the STA-MCA or OA-MCA bypass, which depend on the patency and suitability of the donor vessel, were the first revascularization procedures used in the treatment of moyamoya disease. Such procedures provide the greatest amount of immediate collateral blood flow of any of the revascularization procedures, and excellent angiographic and clinical results have been observed. With regard to the STA-MCA anastomosis, this technique has been shown to improve the progressive natural history, angiographic appearance, and CBF abnormalities associated with moyamoya disease. Moreover, STA-MCA anastomosis is effective in patients in whom prior indirect revascularization procedures have failed. Although this type of direct revascularization procedure has a distinct advantage over indirect revascularization procedures by providing immediate high-flow revascularization to ischemic brain regions, there are limitations to its widespread use in children. First, the small diameters of the STA and MCA in children make it technically very challenging to accomplish a successful anastomosis that supplies meaningful blood flow to the operated hemisphere. Second, the risk of intraoperative stroke is increased related to the temporary MCA occlusion required for anastomosis and also to the potential damage that can occur to existing transdural anastomoses between the distal STA and cortical arteries. Third, unless the proximal MCA circulation is relatively intact, the amount of blood flow to the entire MCA territory that can be achieved by STA-MCA bypass is severely limited. Based on the fact that published postoperative angiograms have demonstrated collateral circulation derived from scalp and meningeal arteries, which is difficult to distinguish from collateral circulation provided by the surgical anastomosis, the actual role of the anastomosis in the perfusion of the MCA distribution is often tough to determine. Finally, in multiple studies in the literature (especially from Japan), the STA-MCA bypass technique is frequently combined with an indirect technique, such as EMS, in which the inner surface of a partially freed flap of temporalsis muscle is applied to the brain surface after creating multiple openings in the arachnoid. The need to combine techniques suggests that STA-MCA
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The EDAS Procedure. The indirect (nonanastomotic) revascularization technique that is most commonly used to treat moyamoya disease in children is the EDAS procedure.67,69 In this technique, the intact STA (usually parietal STA branch or other scalp donor artery such as the OA or the anterior STA branch) is sutured by its adventitia into a linear opening in the dura subjacent to a small elliptical craniotomy.69 Although early reports in the literature described good to excellent results with this technique,66 subsequent studies have criticized the EDAS technique because of insufficient collateral flow on postoperative angiograms and persistence of ischemic symptoms.6,111 Nevertheless, at least in children, the amount of collateralization that develops and the clinical benefit that can be derived from EDAS alone are roughly the same as those observed from STA-MCA bypass combined with EMS.57

Pial Synangiosis. Another widely used indirect revascularization procedure is pial synangiosis,2,30,87–91,94 This technique, which represents a modification of the EDAS procedure, can be used to treat moyamoya disease in children and adults. Pial synangiosis allows for greater induction of extradural collateral vessels by placing the donor scalp artery in direct contact with the pial vasculature stripped of its meningeal coverings.2,34,38 A retrospective case study evaluating 143 consecutive pediatric patients with moyamoya disease treated with pial synangiosis and followed for an average of 5.1 years (the largest moyamoya revascularization surgery series in the western hemisphere)59 showed that patients treated with pial synangiosis stop having strokes and TIAs and have an excellent long-term prognosis.59 This study provided strong evidence that indirect revascularization from pial synangiosis “halts what is normally a relentless clinical deterioration in the untreated patient.”91

The pial synangiosis technique involves the following steps (Fig. 1). A scalp donor artery (most commonly the posterior/parietal branch of the STA) is dissected with a cuff of galea and a large craniotomy bone flap is turned in the region subjacent to the artery (Fig. 1A). The dura is opened in a stellate fashion, making 6 incisions without disrupting potential meningeal collateral vessels, to increase the surface area of dura exposed to the pial surface and thereby enhance formation of collateral vessels from the dural vascular supply (Fig. 1B). The arachnoid is opened widely over the cortical surface exposed by the dural opening. The intact donor artery is sutured by its galeal cuff directly to the pial surface using several interrupted 10-0 nylon sutures (Fig. 1C). Cerebral angiograms obtained 1 year after pial synangiosis showed excellent MCA collateralization from the donor artery as well as from other meningeal and scalp arteries close to the craniotomy site. In the study by Scott et al.,90 65% of the 195 hemispheres studied showed synangiosis-induced filling of more than two-thirds of the MCA circulation, and 25% showed synangiosis-induced filling of at least one-third of the MCA circulation. More importantly, patients with moyamoya disease who have undergone pial synangiosis have demonstrated an excellent neurological outcome with complete resolution or a significant reduction in the frequency and severity of TIAs during the 1st postoperative year as well as an extremely low incidence of new strokes.2,83,91

Omental Transplantation. Another indirect revascularization technique occasionally used in the treatment of moyamoya disease is intracranial transplantation of the omentum. This involves tunneling an intact omental flap from the abdomen and placing it on the surface of the brain or anastomosing a free flap of omentum via the gastroepiploic artery and vein end-to-end with the superficial temporal artery and vein, respectively.23,30,38 Omental transplantation is typically reserved for treatment of moyamoya disease after a direct or other indirect revascularization procedure has failed to alleviate ischemic symptoms or for revascularization of the frontal pole or medial cortical surface. Omental transplants also provide...
good collateralization and resolution of ischemic symptoms.2,3,10

Multiple Bur Holes. The multiple cranial bur hole technique is an additional indirect technique that can be used to treat moyamoya disease.11,12 Until recently, this technique has been used in combination with other techniques, such as the STA-MCA bypass, EMS, EDAS, or pial synangiosis, to provide supplemental collateralization, especially to the frontal and occipital lobes, which typically are not well vascularized by these other techniques.95 Unfortunately, the rate of collateral development as determined by postoperative angiography is variable.95 However, a recent study has provided evidence for the use of multiple cranial bur holes bilaterally as the sole treatment for moyamoya disease in children without the use of supplementary revascularization procedures.84 In this study of 14 patients (24 hemispheres), a bilateral retrocoronal scalp incision was made, and the scalp flaps were retracted widely anteriorly and posteriorly to expose the frontal, parietal, temporal, and occipital regions bilaterally. Ten to 24 small triangular flaps of pericranium were then elevated ~ 3 cm apart and bur holes were drilled at each site. The dura, arachnoid, and pia were opened, and the periosteal flap was placed in contact with the cortical surface. Postoperative angiograms obtained 8–12 months after surgery in this small series of patients showed good collateralization of the ischemic brain, and there were no ischemic events postoperatively.

In a recent review of the literature designed to determine the evidence base for the efficacy of surgical revascularization for the treatment of moyamoya disease in children,10 57 of 1260 studies met criteria for review, and all were retrospective case studies. This review included data from 1448 patients, of whom 1322 were pediatric patients (< 21 years of age), with a total of 2218 hemispheres operated either with direct techniques (4%), indirect techniques (73%, all considered as a single group), or a combination of direct and indirect techniques (23%). In this analysis, 51.2% of patients became completely asymptomatic with resolution of TIA signs and no neurological signs, 35.5% showed definite clinical improvement, 10.5% showed no change, and 2.7% exhibited deterioration, developing new infarcts. Postoperative angiography showed collateralization of ≥ one-third of the MCA territory (good collateralization) in 83% of indirect procedures (including all types) as well as in 6 of 7 direct procedures and 97 of 101 combined procedures. When the indirect procedure group was compared with pooled data from the direct and combined procedure groups, good collateralization was seen significantly more often in the direct/combined group. However, there was no statistically significant difference in the rate of positive outcomes among the 3 groups of techniques.

Conclusions

Moyamoya disease, although relatively uncommon, is a widely recognized cause of stroke in children and must be considered in the differential diagnosis of any child who presents with symptoms of cerebral ischemia, especially if the symptoms are precipitated by physical exertion, hyperventilation, or crying. If left untreated, moyamoya disease will inevitably progress and can lead to devastating, permanent neurological impairment. Fortunately, excellent long-term prognosis is achievable with prompt diagnosis and appropriate surgical management.

Revascularization surgery is recommended for the treatment of most patients. Currently, there are no randomized controlled trials to determine the efficacy of surgical revascularization; however, numerous studies have provided strong support for surgical intervention. Numerous operative techniques have been described. To date, there is no standardized surgical approach for the treatment of moyamoya disease in children, and numerous surgical procedures have been used in a variety of combinations with variable effectiveness.12,16,17,20,29,34,48,54,81,91,113 Future investigations are needed to clarify the etiology, pathogenesis, diagnosis, and treatment, including indications for treatment, of this disorder to improve the long-term outcome for patients with moyamoya disease.

Disclaimer

The author reports no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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