REVIEW ARTICLE

MEDICAL PROGRESS

Moyamoya Disease and Moyamoya Syndrome

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The moyamoya syndrome is a cerebrovascular condition that predisposes affected patients to stroke in association with progressive stenosis of the intracranial internal carotid arteries and their proximal branches. Reduced blood flow in the major vessels of the anterior circulation of the brain leads to compensatory development of collateral vasculature by small vessels near the apex of the carotid, on the cortical surface, leptomeninges, and branches of the external carotid artery supplying the dura and the base of the skull. In rare cases, this process also involves the posterior circulation, including the basilar and posterior cerebral arteries.

First described in 1957 as "hypoplasia of the bilateral internal carotid arteries,"[1] the characteristic appearance of the associated network of abnormally dilated collateral vessels on angiography was later likened to "something hazy, like a puff of cigarette smoke,"[2] which, in Japanese, is *moyamoya* (Fig. 1). Although "spontaneous occlusion of the circle of Willis" has recently been suggested as an alternative to the more evocative name "moyamoya," the *International Classification of Diseases* recognizes "moyamoya" as the specific name for this condition.[3]

Patients with the characteristic moyamoya vasculopathy who also have well-recognized associated conditions (described below) are categorized as having the moyamoya syndrome, whereas patients with no known associated risk factors are said to have moyamoya disease. By definition, the pathognomonic arteriographic findings are bilateral in moyamoya disease, although the severity can differ between sides.[2] Patients with unilateral findings have the moyamoya syndrome, even if they have no other associated risk factors.[3] However, contralateral disease eventually develops in up to 40% of patients initially presenting with unilateral findings.[4,5] When used alone, without the distinguishing modifier of "disease" or "syndrome," "moyamoya" refers solely to the distinctive findings on cerebral arteriography, independently of the cause.

Epidemiologic Features

Originally considered to affect predominantly persons of Asian heritage, moyamoya has now been observed throughout the world in people of many ethnic backgrounds, including American and European populations.[6,7] The incidence peaks in two age groups: children who are approximately 5 years of age and adults in their mid-40s.[8-11] There are nearly twice as many female patients as male patients.[8,9,12] Moyamoya is the most common pediatric cerebrovascular disease in Japan, with a prevalence of approximately 3 cases per 100,000 children.[8,9,13] The incidence among all patients with moyamoya in Europe appears to be about 1/10th of that observed in Japan.[14] Results from a 2005 American review suggest an incidence of 0.086 case per 100,000 persons.[15] Reported incidence-rate ratios are 4.6 for Asian Americans, 2.2 for blacks, and 0.5 for Hispanics, as compared with whites.[15]

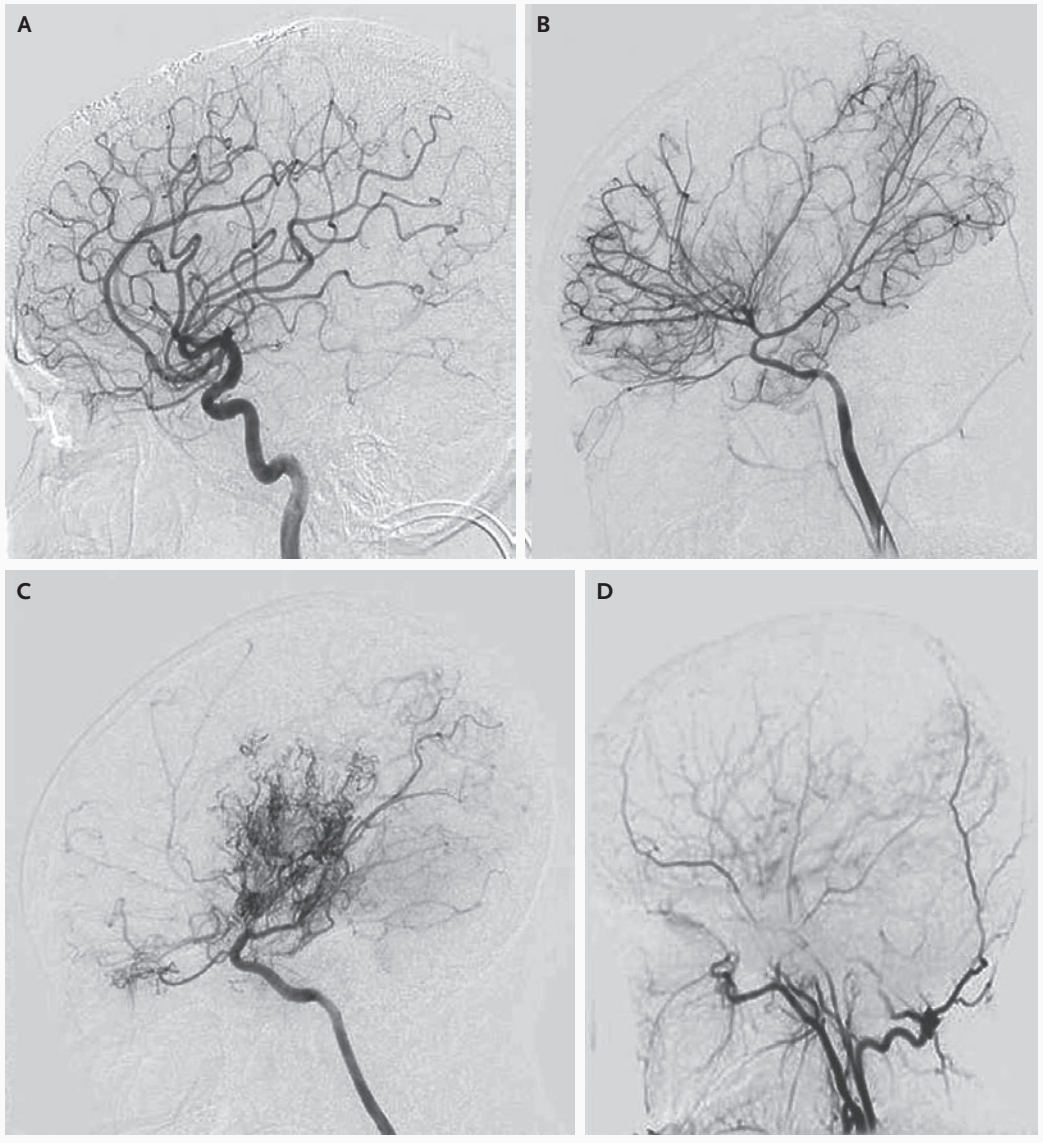

Figure 1. Angiographic Findings in Moyamoya.

Angiograms show the progression from normal findings through progressive stages of moyamoya. Panel A shows a normal lateral-projection angiogram with injection of the internal carotid artery. Panel B shows Suzuki grades I to II (on a scale of I to VI, with higher scores indicating more occlusion), with narrowing of the internal carotid artery before the development of extensive collateral vessels. Panel C shows Suzuki grades III to IV, with significant narrowing of the internal carotid artery and characteristic "puff-of-smoke" collaterals. There is diminished cortical perfusion as compared with the findings shown in Panels A and B. Panel D shows Suzuki grades V to VI, with obliteration of the internal-carotid-artery flow. This occlusion of the internal carotid artery results in concomitant disappearance of the puff-of-smoke collaterals, since they are supplied by the internal carotid artery. Cortical perfusion is markedly reduced, with supply derived from the posterior (basilar) circulation (which is not visible without a vertebral-artery injection) and collateral vessels of the external carotid artery.

PRESENTATION

Symptoms and signs of moyamoya can be attributed to changes in flow resulting from stenosis of the internal carotid artery. Broadly speaking, there are two major etiologic categories of symptoms: those due to brain ischemia (i.e., stroke, transient ischemic attacks [TIAs], and seizures)

Table 1. Symptoms of Moyamoya and Associated Characteristics and Conditions.

Variable	Prevalence*
	%
Symptoms at presentation	
Common	
Ischemic stroke	50–75
Transient ischemic attack (including drop attacks)	50–75
Hemorrhage (in adults)	10–40
Less common	
Seizures	
Headache	
Rare	
Choreiform movements	
Cognitive or psychiatric changes	
Associated characteristics and conditions	
Common	50–75
Angiographic findings of moyamoya without other disease	
Asian heritage	
Less common (moyamoya syndrome)	10–20
Sickle cell disease	
Neurofibromatosis type 1	
Cranial therapeutic irradiation	
Down's syndrome	
Rare (moyamoya syndrome)	<10
Congenital cardiac anomaly	
Renal-artery stenosis	
Giant cervicofacial hemangiomas	
Hyperthyroidism	

* The prevalence is among persons with diagnosed moyamoya disease or syndrome.

and those due to the deleterious consequences of the compensatory mechanisms responding to the ischemia (i.e., hemorrhage from fragile collateral vessels and headache from dilated transdural collaterals). Individual variations in the degree of arterial involvement, progression of stenosis, regions of ischemic cortex, and response to the reduction in blood supply help to explain the wide range of clinical presentations.

AGE-RELATED AND GEOGRAPHIC DIFFERENCES IN PRESENTATION

In the United States, the majority of affected adults and children present with ischemic symptoms, although the rate of hemorrhage among adults is approximately seven times as high as the rate among children (20.0% vs. 2.8%).[12,16] Manifestations vary among geographic regions. Studies involving Asian populations indicate that adults have much higher rates of hemorrhage as a presenting symptom (42%) than adults in the United States.[10,11,17,18] In contrast, only 2.8% of children in Asian populations present with hemorrhage, and 68% present with TIAs or ischemic strokes (Table 1).[12] Children have a higher rate of completed strokes; it is thought that because of their immature verbal and reporting skills, they simply may not be able to communicate TIA symptoms clearly, delaying diagnosis and increasing the likelihood of a completed stroke.[19]

ISCHEMIC SYMPTOMS

Symptoms of cerebral ischemia in moyamoya are typically associated with the regions of the brain supplied by the internal carotid arteries and middle cerebral arteries; these regions include the frontal, parietal, and temporal lobes. Hemiparesis, dysarthria, aphasia, and cognitive impairment are common.[12] Patients may also have seizures, visual deficits, syncope, or personality changes that can be mistaken for psychiatric illness.[20]

Ischemic symptoms may be transient or fixed. A TIA or stroke may be precipitated by common childhood events such as hyperventilation with crying. Signs and symptoms of cerebral ischemia can result from exertion or even from induction of anesthesia for a minor surgical procedure. The presumed mechanism of these events is that normal cortical vessels, already maximally dilated in patients with chronic ischemia, constrict in response to the decrease in the partial pressure of carbon dioxide due to hyperventilation, resulting in reduced cerebral perfusion.[21] Dehydration may also precipitate ischemic symptoms.

HEMORRHAGE

Intracranial hemorrhage is common in adults with moyamoya, but it has also been described in children.[10,12] The location of the hemorrhage can be intraventricular, intraparenchymal (frequently in the region of the basal ganglia), or subarachnoid. Historically, bleeding has been attributed to rupture of fragile collateral vessels associated with moyamoya as progressive stenosis of the internal carotid artery occurs.[22,23] Shifting circulatory patterns at the base of the brain have been impli-

cated in the development of cerebral aneurysms (usually at the apex of the basilar artery and posterior communicating artery, areas of increased shear stress in moyamoya); this may be another cause of hemorrhage in moyamoya.[24,25]

HEADACHE AND OTHER SYMPTOMS

Headache is a frequent presenting symptom in patients with moyamoya. A review suggested that dilatation of meningeal and leptomeningeal collateral vessels may stimulate dural nociceptors.[26] Typically, headache is migrainelike in quality and refractory to medical therapies; it persists in up to 63% of patients, even after successful surgical revascularization.[26] In some patients, however, headache subsides within 1 year after surgical treatment of moyamoya, possibly reflecting the regression of pbasal collateral vessels.

Dilated moyamoya-associated collateral vessels in the basal ganglia have also been implicated in the development of choreiform movements, another presentation of this condition in children.[12,27] To our knowledge, there are no published series documenting the clinical course of this movement disorder in moyamoya, but in our series of children presenting with choreiform movements, 8 of 10 had resolution 1 year after revascularization surgery, a finding that was concomitant with reduction in moyamoya-associated collaterals in the basal ganglia.

An ophthalmologic finding occasionally seen in association with moyamoya is the "morning glory disk," an enlargement of the optic disk with concomitant retinovascular anomalies.[28] If this finding is observed, the diagnosis of moyamoya should be considered, and cerebrovascular imaging may be helpful in the evaluation.

ASSOCIATED CONDITIONS

Moyamoya is strongly associated with radiotherapy to the head or neck (particularly radiotherapy for optic gliomas, craniopharyngiomas, and pituitary tumors), although the dose of radiation that is capable of causing this effect is unknown and the time between treatment and the onset of disease can range from months to decades. Down's syndrome, neurofibromatosis type 1 (with or without tumors of the hypothalamic–optic pathway), and sickle cell disease have also been reported in association with moyamoya.[12,19,29,30] There are numerous reported links between moyamoya and a wide variety of other disorders (Table 1).[12]

PATHOPHYSIOLOGICAL FEATURES

Angiographic changes associated with moyamoya are shared by a diverse collection of genetic and acquired conditions. The heterogeneity of the pathophysiological processes underlying these radiographic findings reflects distinct clinical presentations and responses to therapeutic interventions. Three types of research have aimed at explaining the pathogenesis of moyamoya: pathological analysis of affected tissue, genetic-linkage studies, and studies of the role of angiogenesis and extracellular matrix–related peptides in disease development and progression.

ANALYSIS OF PATHOLOGICAL FINDINGS

In patients with moyamoya, stenosis occurs in the distal internal carotid artery and often involves the proximal anterior and middle cerebral arteries (Fig. 2A). Pathological analysis has revealed that affected vessels do not show arteriosclerotic or inflammatory changes leading to occlusion.[31] Rather, vessel occlusion results from a combination of hyperplasia of smooth-muscle cells and luminal thrombosis (Fig. 2C through 2F). The media is often attenuated, with irregular elastic lamina.[32] Caspase-dependent apoptosis has been implicated as a contributory mechanism in the associated degradation of the arterial wall.[33]

Moyamoya-associated collaterals are generally dilated perforating arteries that are believed to be a combination of preexisting and newly developed vessels.[34,35] These collaterals show evidence of stress related to increased flow, including the combination of fragmented elastic lamina, thinned media in the vessel wall, and the presence of microaneurysms; these findings help to explain why some patients present with hemorrhage.[36] Other moyamoya-related vessels are collapsed and their lumens thrombosed, findings that may account for the cause of ischemic symptoms.[37]

GENETIC STUDIES

Genetic factors appear to play a major role in moyamoya. The proportion of patients who have affected first-degree relatives is 10% in Japan, and a rate of 6% was reported in a U.S. series.[12,31] Associations with loci on chromosomes 3, 6, 8, and 17, as well as specific HLA haplotypes, have been described.[38-42]

Most familial cases appear to be polygenic or inherited in an autosomal dominant fashion with

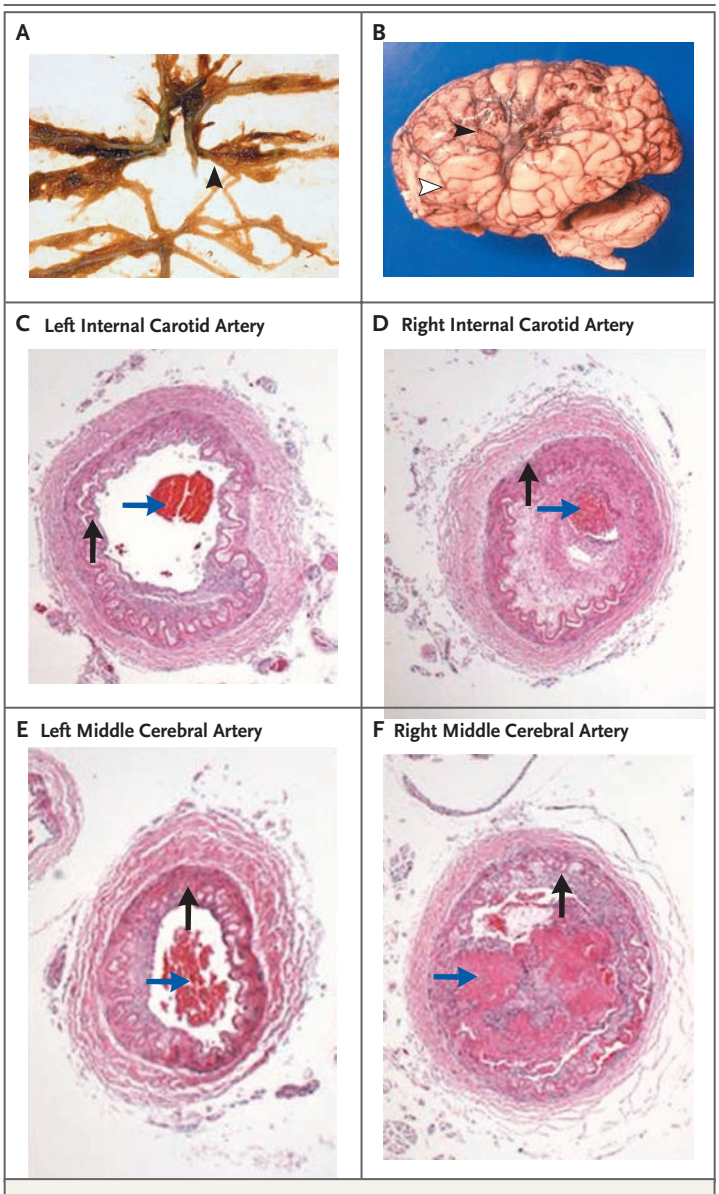

Figure 2. Pathological and Histopathological Findings in Moyamoya.

A gross pathological specimen of the circle of Willis obtained from a patient with moyamoya (Panel A) shows the narrowing of both middle cerebral arteries, particularly on the right (arrowhead). An autopsy specimen of the brain (Panel B) shows both an acute infarct (white arrowhead) and a chronic infarct (black arrowhead) resulting from moyamoya. Panels C through F (hematoxylin and eosin) show vessels in the internal-carotid-artery distribution with hyperproliferation (black arrows) of the vessel-wall components and abundant intraluminal thrombi (blue arrows), leading to narrowing and occlusion of the lumen. The right middle cerebral artery is particularly narrow, as shown in both the gross specimen (Panel A) and the microscopical analysis. The images show that the vessel occlusion is a combination of hyperplasia of smooth-muscle cells and luminal thrombosis. (Pathological images courtesy of Elizabeth A. Bundock, M.D., Ph.D., Office of the Chief Medical Examiner, Burlington, VT.)

incomplete penetrance. A 2008 study reported a major gene locus for autosomal dominant moyamoya disease on chromosome 17q25; this finding requires replication.[43] The recent discovery of a moyamoya-associated mutation in this region affecting TIMP-2 (tissue inhibitor of matrix metalloproteinase type 2) is of particular interest, given the important role of extracellular-matrix remodeling and angiogenesis in both the primary arteriopathy and subsequent response of the ischemic brain.[35,44]

However, despite evidence of a genetic basis of moyamoya, important caveats remain. For example, reports of identical twins with only one affected sibling[12,45] provide support for the premise that environmental factors precipitate the clinical emergence of the condition in susceptible persons.

ANGIOGENESIS AND EXTRACELLULAR-MATRIX–RELATED PEPTIDES

Levels of many growth factors, enzymes, and other peptides have been reported to be increased in association with moyamoya, including basic fibroblast growth factor, transforming growth factor β-1, hepatocyte growth factor, vascular endothelial growth factor, matrix metalloproteinases, intracellular adhesion molecules, and hypoxia-inducing factor 1α.[35,46-52] Levels of individual peptides have been studied in cultured smooth-muscle cells, dura, cerebrospinal fluid, and vessels. However, to our knowledge, no comprehensive investigations have surveyed groups of mechanistically related proteins. An example highlighting the potential usefulness of such a strategy may be relevant to the possible mutation of TIMP-2, which is a regulator of matrix metalloproteinases (enzymes that are an integral part of extracellular-matrix remodeling and angiogenesis). If studies were to link this given pathway to moyamoya, it might be possible to uncover a mechanism capable of explaining both the primary arteriopathy and the pronounced response to ischemia.

Investigations into the pathogenesis of moyamoya to date suggest that the clinical presentation of affected patients may be the result of disparate underlying genetic and environmental cues. Of particular interest is the genetic link between enzyme regulation and the abnormal levels and activity of related proteins in the aforementioned studies, which may suggest that underly-

ing defects in regulation of specific extracellular proteins have effects on cerebral vessels in susceptible persons, resulting in the moyamoya phenotype when particular environmental triggers, such as radiation, are present.

NATURAL HISTORY AND PROGNOSIS

The natural history of moyamoya is variable. Disease progression can be slow, with rare, intermittent events, or fulminant, with rapid neurologic decline.[12] However, regardless of the course, moyamoya inevitably progresses in the majority of patients.[2,53] A 2005 report indicated that the rate of disease progression is high, even among asymptomatic patients, and that medical therapy alone does not halt disease progression.[54] It has been estimated that up to two thirds of patients with moyamoya have symptomatic progression over a 5-year period; the outcome is poor without treatment.[55-57] In contrast, the estimated rate of symptomatic progression is only 2.6% after surgery, according to a meta-analysis involving 1156 patients.[58]

In general, neurologic status at the time of treatment, more than the patient's age, predicts the long-term outcome.[12] Thus, early diagnosis of moyamoya coupled with the expeditious institution of therapy is of paramount importance.

DIAGNOSIS

Moyamoya should be considered — and diagnostic evaluation initiated — in patients, particularly children, presenting with acute neurologic deficits or unexplained symptoms referable to cerebral ischemia. A delay in diagnosis results in a delay in treatment, increasing the risk of permanent disability from stroke. It is critically important to refer patients with moyamoya, or suspected moyamoya, to centers experienced in the care of such patients. Any patient with unexplained symptoms suggestive of cerebral ischemia should be considered as possibly being at risk for moyamoya. Although the differential diagnosis for these symptoms is broad, the presence of moyamoya can be readily confirmed by means of radiographic studies. Radiographic evaluation of a patient suspected of having moyamoya usually requires several studies.

COMPUTED TOMOGRAPHY

Computed tomography (CT) in a patient with moyamoya disease may show small areas of hypodensity suggestive of hemorrhage or of a stroke in the cortical watershed zones, basal ganglia, deep white matter, or periventricular regions.[12] However, the CT scan can be normal, particularly in patients presenting solely with TIAs.

CT angiography can show the intracranial stenoses seen in moyamoya. Thus, CT angiography should be considered when magnetic resonance imaging (MRI) is not readily available and a diagnosis of cerebral occlusive vasculopathy is being considered.

MAGNETIC RESONANCE IMAGING

The widespread availability of MRI and magnetic resonance angiography has led to the increasing use of these methods for primary imaging in patients with symptoms suggestive of moyamoya.[59-61] An acute infarct is more likely to be detected with the use of diffusion-weighted imaging, whereas a chronic infarct is more likely to be seen with T_1- and T_2-weighted imaging (Fig. 3A through 3D). Diminished cortical blood flow due to moyamoya can be inferred from fluid-attenuated inversion recovery (FLAIR) sequences showing linear high signals that follow a sulcal pattern, which is called the "ivy sign"[62] (Fig. 3E and 3F). The finding most suggestive of moyamoya on MRI is reduced flow voids in the internal, middle, and anterior cerebral arteries coupled with prominent flow voids through the basal ganglia and thalamus from moyamoya-associated collateral vessels (Fig. 3G and Fig. 3H). These findings are virtually diagnostic of moyamoya.[63]

ANGIOGRAPHY

Formal angiography should consist of a full five-vessel or six-vessel study that includes both external carotid arteries, both internal carotid arteries, and one or both vertebral arteries, depending on the collateral patterns seen. In a study of 190 patients undergoing diagnostic angiography, complication rates among patients with moyamoya were no higher than those among patients with other forms of cerebrovascular disease. The definitive diagnosis is based on a distinct arteriographic appearance characterized by stenosis of the distal intracranial internal carotid artery, extend-

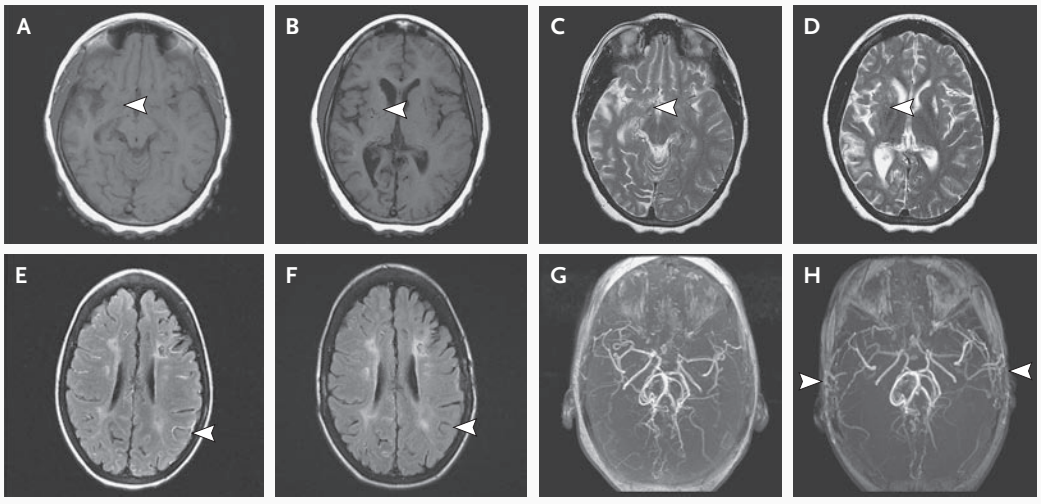

Figure 3. MRI Findings in Moyamoya.

T_1-weighted images (Panels A and B) and T_2-weighted images (Panels C and D) reveal cortical atrophy, old infarcts, and flow-void signals resulting from basal collaterals (white arrowheads). Noncontrast fluid-attenuated inversion recovery (FLAIR) images obtained before surgery (Panel E) and 1 year after surgery (Panel F) show the "ivy sign" (arrowheads), which is consistent with bilateral ischemia in the preoperative scan and marked improvement in the postoperative scan. Magnetic resonance angiograms obtained before surgery (Panel G) and 1 year after surgery (Panel H) reveal the diminished internal-carotid-artery flow that is typical of moyamoya. This type of imaging can be used as an alternative to conventional angiography for evaluating cerebral vessels. The sites of pial synangiosis with hypertrophied superficial temporal arteries and abundant collateral-vessel development postoperatively (Panel H, arrowheads) are shown.

ing to the proximal anterior and middle arteries (Fig. 1). Disease severity is frequently classified into one of six progressive stages that were originally defined in 1969.[2] Development of an extensive collateral network at the base of the brain along with the classic "puff of smoke" appearance on angiography is seen in the intermediate stages of the Suzuki grading system (Table 2). Imaging of the external carotid arteries is essential to identify any preexisting collateral vessels so that surgery, if performed, will not disrupt them. Aneurysms, as well as the rare arteriovenous malformation known to be associated with certain cases of moyamoya, are also best detected by means of conventional angiography.

OTHER DIAGNOSTIC TECHNIQUES

Other diagnostic evaluations that may be useful in evaluating patients with moyamoya include electroencephalography (EEG) and cerebral blood-flow studies. Specific alterations of EEG recordings, which are usually observed only in children, include posterior or centrotemporal slowing, a hyperventilation-induced diffuse pattern of monophasic slow waves (called "build-up"), and a characteristic "rebuild-up" phenomenon,[64] which looks identical to the build-up slow waves seen in patients without moyamoya, but differs in the timing of its presentation. Build-up occurs during hyperventilation, whereas rebuild-up occurs after hyperventilation and indicates a diminished cerebral perfusion reserve.

Techniques such as transcranial Doppler, perfusion CT, xenon-enhanced CT, positron-emission tomography, magnetic resonance perfusion imaging, and single-photon-emission CT with acetazolamide challenge have all been used in the evaluation of patients with moyamoya. These imaging studies may help to quantify blood flow, serve as a baseline before the institution of treatment, and occasionally aid in treatment decisions.

SCREENING

There are no data to support indiscriminate screening for moyamoya, and there is little evidence to warrant the screening of first-degree relatives of patients with moyamoya when only a single family member is affected. However, a 2008 article concerning patients with unilateral

moyamoya showed a decreased stroke burden and better clinical outcome when this specific population underwent imaging at intervals, providing evidence in support of selective screening.[5] Although widespread screening for moyamoya is not yet standard for any specific group, the diagnosis should be considered when patients with certain high-risk disorders such as neurofibromatosis 1, Down's syndrome, and sickle cell disease are undergoing routine examinations in order to identify symptomatic patients and refer them for imaging.[19,65-67]

Table 2. Suzuki Grading System.*

Grade	Definition
I	Narrowing of ICA apex
II	Initiation of moyamoya collaterals
III	Progressive ICA stenosis with intensification of moyamoya-associated collaterals
IV	Development of ECA collaterals
V	Intensification of ECA collaterals and reduction of moyamoya-associated vessels
VI	Total occlusion of ICA and disappearance of moyamoya-associated collaterals

*Data are from Suzuki and Takaku.[2] ECA denotes external carotid artery, and ICA internal carotid artery.

TREATMENT

No known treatment will reverse the primary disease process, and current treatments are designed to prevent strokes by improving blood flow to the affected cerebral hemisphere. Improvement in cerebral blood flow may provide protection against future strokes, effect a concurrent reduction in moyamoya-associated collaterals, and reduce the frequency of symptoms.

MEDICAL THERAPY

Medical therapy has been used in patients with moyamoya, particularly when surgery has been considered to present a high risk or the patient has had relatively mild disease, but there are few data showing either its short-term or long-term efficacy. A large survey from Japan showed no significant differences in outcome between medically and surgically treated patients with moyamoya, although a more recent review revealed that 38% of 651 patients with moyamoya who were initially treated medically ultimately underwent surgery because of progressive symptoms.[3,68] Antiplatelet agents have been used to prevent emboli from microthrombi formed at sites of arterial stenosis — a possible cause of ischemic symptoms in patients with moyamoya — and these agents, although not used universally, are used routinely in patients in many operative series.[12] Anticoagulants such as warfarin are rarely used, although there has been some experience with low-molecular-weight heparin.[69,70] Calcium-channel blockers may be useful in ameliorating intractable headaches or migraines, which are commonly seen in patients with moyamoya, and these agents may be effective in reducing both the frequency and the severity of refractory TIA. Because calcium-channel blockers may cause hypotension, they must be used with caution in this patient population.

SURGERY

The arteriopathy of moyamoya affects the internal carotid artery while sparing the external carotid artery. Surgical treatment of patients with moyamoya typically uses the external carotid artery as a source of new blood flow to the ischemic hemisphere. Two general methods of revascularization are used: direct and indirect. In direct revascularization, a branch of the external carotid artery (usually the superficial temporal artery) is directly anastomosed to a cortical artery. Indirect techniques involve the placement of vascularized tissue supplied by the external carotid artery (e.g., dura, temporalis muscle, or the superficial temporal artery itself) in direct contact with the brain, leading to an ingrowth of new blood vessels to the underlying cerebral cortex.

Historically, direct procedures have been used in adults for whom an immediate increase of blood flow to the ischemic brain is a major benefit. Augmentation of cerebral blood flow usually does not occur for several weeks with indirect techniques. However, direct bypass is often technically difficult to perform in children because of the small size of both donor and recipient vessels, making indirect techniques appealing. Nonetheless, direct operations have been successful in some children, and indirect procedures have been successful in some adults.[71-73] There is considerable debate about the relative merits and shortcomings of the two approaches; in fact, some centers advocate a combination of direct and indirect approaches.[68,73,74]

Indirect revascularization procedures include encephaloduroarteriosynangiosis, encephalomyoarteriosynangiosis, pial synangiosis (Fig. 4), and the drilling of burr holes without vessel synangiosis.[12,75-80] A review of 143 patients treated with pial synangiosis showed marked reductions in the frequency of stroke after surgery; 67% of the patients had strokes before treatment, whereas 7.7% had strokes in the perioperative period, and only 3.2% had strokes after at least 1 year of follow-up. Among patients who had a minimum of 5 years of follow-up, the long-term rate of stroke was 4% (2 of 46 patients).[12]

Increasingly, surgical revascularization is gaining acceptance as a primary treatment for moyamoya, given the contrast between the poor response to medical therapy and the documented success of surgery.[58] Two large studies with long-term follow-up showed a good safety profile for surgical treatment. The risk of stroke is highest within the first 30 days after surgery (approximately 4% per hemisphere); after the first month, the risk decreases considerably. Patients reportedly have a 96% probability of remaining stroke-free over the subsequent 5 years.[12,55] A meta-analysis concluded that 1003 of 1156 patients (87%) derived symptomatic benefit from surgical revascularization, with indirect, direct, and combined techniques showing equal effectiveness.[58]

Patients with moyamoya have an additional risk of ischemic events during the perioperative period. Potential complications of surgery for moyamoya include stroke, infection, and intracranial hemorrhage. As previously noted, crying and hyperventilation can lower the partial pressure of carbon dioxide and induce ischemia due to cerebral vasoconstriction. Effective pain control, including the use of perioperative sedation, painless wound-dressing techniques, and closure of the wound with absorbable sutures to prevent the pain of suture removal may reduce the likelihood of postoperative stroke and shorten the duration of hospitalization.[81] During surgery, it is important to avoid hypotension, hypovolemia, hyperthermia, and both hypocarbia and hypercarbia.[12,82] Postoperatively, patients should be given intravenous fluids at 1.25 to 1.50 times the normal maintenance rate for 48 to 72 hours.[81]

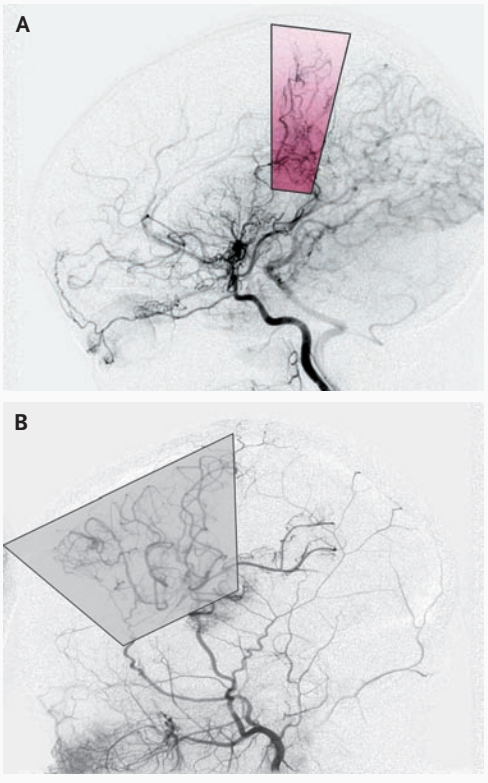

Figure 4. Effects of Surgical Revascularization in Moyamoya.

Angiographic images obtained 1 year after surgical treatment of moyamoya with pial synangiosis show internal (Panel A) and external (Panel B) carotid injections. There is abundant filling of the middle-cerebral-artery region as a result of surgical treatment (gray area in Panel B), whereas a small region of cortex is perfused by the internal carotid (red area in Panel A).

TREATMENT OF ACUTE SYMPTOMS

When patients present with cerebral ischemia, oxygenation and the rapid institution of measures to increase cerebral blood flow may reduce the likelihood that a TIA will progress to a completed stroke. Initial treatment steps are similar to perioperative management and should include intravenous hydration with isotonic fluids (usually at a daily dose of 1.25 to 1.50 times the normal maintenance rate), avoidance of hypotension, and administration of supplemental oxygen.[12,81,83] Hyperventilation is to be avoided. Serum electrolyte and glucose levels should be normalized. Seizure activity, if present, should be treated with appropriate pharmacologic agents.

Imaging can be performed on an emergency basis to ascertain whether a hemorrhage has occurred. Although patients are often evaluated initially with the use of CT, which will readily detect hemorrhage, MRI with diffusion-weighted images will confirm the presence of a completed stroke. In the absence of hemorrhage, antiplatelet agents

can be used, as noted above, to lessen the likelihood that microthrombi will form at sites of arterial stenosis.[12,84] Aspirin is used at many institutions (at a daily dose of 325 mg for adults and 81 mg [or less] for preteen children), and treatment is instituted even when surgical revascularization is planned.

CONCLUSIONS

Moyamoya is an increasingly recognized cause of stroke in both children and adults. Patients with certain conditions such as Down's syndrome[19] and sickle cell disease[29,85-88] may be particularly at risk for moyamoya. Characteristic radiographic findings confirm the diagnosis, and recognition of the disease early in its course, with prompt institution of therapy, is critical in order to achieve the best outcome in patients. Revascularization surgery appears to be effective in preventing stroke in patients with moyamoya.

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. Takeuchi K, Shimizu K. Hypoplasia of the bilateral internal carotid arteries. Brain Nerve 1957;9:37-43.
2. Suzuki J, Takaku A. Cerebrovascular "moyamoya" disease: disease showing abnormal net-like vessels in base of brain. Arch Neurol 1969;20:288-99.
3. Fukui M. Guidelines for the diagnosis and treatment of spontaneous occlusion of the circle of Willis ('moyamoya' disease). Clin Neurol Neurosurg 1997;99:Suppl 2: S238-S240.
4. Kelly ME, Bell-Stephens TE, Marks MP, Do HM, Steinberg GK. Progression of unilateral moyamoya disease: a clinical series. Cerebrovasc Dis 2006;22:109-15.
5. Smith ER, Scott RM. Progression of disease in unilateral moyamoya syndrome. Neurosurg Focus 2008;24(2):E17.
6. Caldarelli M, Di Rocco C, Gaglini P. Surgical treatment of moyamoya disease in pediatric age. J Neurosurg Sci 2001;45: 83-91.
7. Suzuki J, Kodama N. Moyamoya disease — a review. Stroke 1983;14:104-9.
8. Baba T, Houkin K, Kuroda S. Novel epidemiological features of moyamoya disease. J Neurol Neurosurg Psychiatry 2008; 79:900-4.
9. Wakai K, Tamakoshi A, Ikezaki K, et al. Epidemiological features of moyamoya disease in Japan: findings from a nationwide survey. Clin Neurol Neurosurg 1997; 99:Suppl 2:S1-S5.
10. Han DH, Nam DH, Oh CW. Moyamoya disease in adults: characteristics of clinical presentation and outcome after encephaloduro-arterio-synangiosis. Clin Neurol Neurosurg 1997;99:Suppl 2:S151-S155.
11. Han DH, Kwon OK, Byun BJ, et al. A co-operative study: clinical characteristics of 334 Korean patients with moyamoya disease treated at neurosurgical institutes (1976-1994). Acta Neurochir (Wien) 2000; 142:1263-73.
12. Scott RM, Smith JL, Robertson RL, Madsen JR, Soriano SG, Rockoff MA. Long-term outcome in children with moyamoya syndrome after cranial revascularization by pial synangiosis. J Neurosurg 2004;100:Suppl:142-9.
13. Nagaraja D, Verma A, Taly AB, Kumar MV, Jayakumar PN. Cerebrovascular disease in children. Acta Neurol Scand 1994; 90:251-5.
14. Yonekawa Y, Ogata N, Kaku Y, Taub E, Imhof HG. Moyamoya disease in Europe, past and present status. Clin Neurol Neurosurg 1997;99:Suppl 2:S58-S60.
15. Uchino K, Johnston SC, Becker KJ, Tirschwell DL. Moyamoya disease in Washington State and California. Neurology 2005;65:956-8.
16. Hallemeier CL, Rich KM, Grubb RL Jr, et al. Clinical features and outcome in North American adults with moyamoya phenomenon. Stroke 2006;37:1490-6.
17. Yilmaz EY, Pritz MB, Bruno A, Lopez-Yunez A, Biller J. Moyamoya: Indiana University Medical Center experience. Arch Neurol 2001;58:1274-8.
18. Ikezaki K, Han DH, Kawano T, Kinukawa N, Fukui M. A clinical comparison of definite moyamoya disease between South Korea and Japan. Stroke 1997;28: 2513-7.
19. Jea A, Smith ER, Robertson R, Scott RM. Moyamoya syndrome associated with Down syndrome: outcome after surgical revascularization. Pediatrics 2005;116(5): e694-e701.
20. Lubman DI, Pantelis C, Desmond P, Proffitt TM, Velakoulis D. Moyamoya disease in a patient with schizophrenia. J Int Neuropsychol Soc 2003;9:806-10.
21. Tagawa T, Naritomi H, Mimaki T, Yabuuchi H, Sawada T. Regional cerebral blood flow, clinical manifestations, and age in children with moyamoya disease. Stroke 1987;18:906-10.
22. Iwama T, Morimoto M, Hashimoto N, Goto Y, Todaka T, Sawada M. Mechanism of intracranial rebleeding in moyamoya disease. Clin Neurol Neurosurg 1997;99: Suppl 2:S187-S190.
23. Irikura K, Miyasaka Y, Kurata A, et al. A source of haemorrhage in adult patients with moyamoya disease: the significance of tributaries from the choroidal artery. Acta Neurochir (Wien) 1996;138:1282-6.
24. Kawaguchi S, Sakaki T, Morimoto T, Kakizaki T, Kamada K. Characteristics of intracranial aneurysms associated with moyamoya disease: a review of 111 cases. Acta Neurochir (Wien) 1996;138:1287-94.
25. Kuroda S, Houkin K, Kamiyama H, Abe H. Effects of surgical revascularization on peripheral artery aneurysms in moyamoya disease: report of three cases. Neurosurgery 2001;49:463-7.
26. Seol HJ, Wang KC, Kim SK, Hwang YS, Kim KJ, Cho BK. Headache in pediatric moyamoya disease: review of 204 consecutive cases. J Neurosurg 2005;103:Suppl: 439-42.
27. Parmar RC, Bavdekar SB, Muranjan MN, Limaye U. Chorea: an unusual presenting feature in pediatric Moyamoya disease. Indian Pediatr 2000;37:1005-9.
28. Massaro M, Thorarensen O, Liu GT, Maguire AM, Zimmerman RA, Brodsky MC. Morning glory disc anomaly and moyamoya vessels. Arch Ophthalmol 1998;116: 253-4.
29. Hankinson TC, Bohman LE, Heyer G, et al. Surgical treatment of moyamoya syndrome in patients with sickle cell anemia: outcome following encephaloduroarteriosynangiosis. J Neurosurg Pediatrics 2008;1:211-6.
30. Ullrich NJ, Robertson R, Kinnamon DD, et al. Moyamoya following cranial irradiation for primary brain tumors in children. Neurology 2007;68:932-8.
31. Fukui M, Kono S, Sueishi K, Ikezaki K. Moyamoya disease. Neuropathology 2000;20:Suppl:S61-S64.
32. Takagi Y, Kikuta K, Nozaki K, Hashimoto N. Histological features of middle cerebral arteries from patients treated for Moyamoya disease. Neurol Med Chir (Tokyo) 2007;47:1-4.
33. Takagi Y, Kikuta K, Sadamasa N, Nozaki K, Hashimoto N. Proliferative activity through extracellular signal-regulated kinase of smooth muscle cells in vascular walls of cerebral arteriovenous malformations. Neurosurgery 2006;58:740-8.
34. Kono S, Oka K, Sueishi K. Histopathologic and morphometric studies of leptomeningeal vessels in moyamoya disease. Stroke 1990;21:1044-50.
35. Lim M, Cheshier S, Steinberg GK.

New vessel formation in the central nervous system during tumor growth, vascular malformations, and Moyamoya. Curr Neurovasc Res 2006;3:237-45.
36. Yamashita M, Tanaka K, Matsuo T, Yokoyama K, Fujii T, Sakamoto H. Cerebral dissecting aneurysms in patients with moyamoya disease: report of two cases. J Neurosurg 1983;58:120-5.
37. Oka K, Yamashita M, Sadoshima S, Tanaka K. Cerebral haemorrhage in Moyamoya disease at autopsy. Virchows Arch A Pathol Anat Histol 1981;392:247-61.
38. Ikeda H, Sasaki T, Yoshimoto T, Fukui M, Arinami T. Mapping of a familial moyamoya disease gene to chromosome 3p24.2-p26. Am J Hum Genet 1999;64:533-7.
39. Nanba R, Tada M, Kuroda S, Houkin K, Iwasaki Y. Sequence analysis and bioinformatics analysis of chromosome 17q25 in familial moyamoya disease. Childs Nerv Syst 2005;21:62-8.
40. Inoue TK, Ikezaki K, Sasazuki T, Matsushima T, Fukui M. Linkage analysis of moyamoya disease on chromosome 6. J Child Neurol 2000;15:179-82.
41. Han H, Pyo CW, Yoo DS, Huh PW, Cho KS, Kim DS. Associations of Moyamoya patients with HLA class I and class II alleles in the Korean population. J Korean Med Sci 2003;18:876-80.
42. Sakurai K, Horiuchi Y, Ikeda H, et al. A novel susceptibility locus for moyamoya disease on chromosome 8q23. J Hum Genet 2004;49:278-81.
43. Mineharu Y, Liu W, Inoue K, et al. Autosomal dominant moyamoya disease maps to chromosome 17q25.3. Neurology 2008;70:2357-63.
44. Kang HS, Kim SK, Cho BK, Kim YY, Hwang YS, Wang KC. Single nucleotide polymorphisms of tissue inhibitor of metalloproteinase genes in familial moyamoya disease. Neurosurgery 2006;58:1074-80.
45. Tanghetti B, Capra R, Giunta F, Marini G, Orlandini A. Moyamoya syndrome in only one of two identical twins: case report. J Neurosurg 1983;59:1092-4.
46. Takagi Y, Kikuta K, Nozaki K, et al. Expression of hypoxia-inducing factor-1 alpha and endoglin in intimal hyperplasia of the middle cerebral artery of patients with Moyamoya disease. Neurosurgery 2007;60:338-45.
47. Malek AM, Connors S, Robertson RL, Folkman J, Scott RM. Elevation of cerebrospinal fluid levels of basic fibroblast growth factor in moyamoya and central nervous system disorders. Pediatr Neurosurg 1997;27:182-9.
48. Nanba R, Kuroda S, Ishikawa T, Houkin K, Iwasaki Y. Increased expression of hepatocyte growth factor in cerebrospinal fluid and intracranial artery in moyamoya disease. Stroke 2004;35:2837-42.
49. Soriano SG, Cowan DB, Proctor MR, Scott RM. Levels of soluble adhesion molecules are elevated in the cerebrospinal fluid of children with moyamoya syndrome. Neurosurgery 2002;50:544-9.
50. Ueno M, Kira R, Matsushima T, et al. Moyamoya disease and transforming growth factor-beta1. J Neurosurg 2000;92:907-8.
51. Hojo M, Hoshimaru M, Miyamoto S, et al. Role of transforming growth factor-beta1 in the pathogenesis of moyamoya disease. J Neurosurg 1998;89:623-9.
52. Yoshimoto T, Houkin K, Takahashi A, Abe H. Angiogenic factors in moyamoya disease. Stroke 1996;27:2160-5.
53. Imaizumi T, Hayashi K, Saito K, Osawa M, Fukuyama Y. Long-term outcomes of pediatric moyamoya disease monitored to adulthood. Pediatr Neurol 1998;18:321-5.
54. Kuroda S, Ishikawa T, Houkin K, Nanba R, Hokari M, Iwasaki Y. Incidence and clinical features of disease progression in adult moyamoya disease. Stroke 2005;36:2148-53.
55. Choi JU, Kim DS, Kim EY, Lee KC. Natural history of moyamoya disease: comparison of activity of daily living in surgery and non surgery groups. Clin Neurol Neurosurg 1997;99:Suppl 2:S11-S18.
56. Kurokawa T, Chen YJ, Tomita S, Kishikawa T, Kitamura K. Cerebrovascular occlusive disease with and without the moyamoya vascular network in children. Neuropediatrics 1985;16:29-32.
57. Ezura M, Takahashi A, Yoshimoto T. Successful treatment of an arteriovenous malformation by chemical embolization with estrogen followed by conventional radiotherapy. Neurosurgery 1992;31:1105-7.
58. Fung LW, Thompson D, Ganesan V. Revascularisation surgery for paediatric moyamoya: a review of the literature. Childs Nerv Syst 2005;21:358-64.
59. Yamada I, Suzuki S, Matsushima Y. Moyamoya disease: comparison of assessment with MR angiography and MR imaging versus conventional angiography. Radiology 1995;196:211-8.
60. Katz DA, Marks MP, Napel SA, Bracci PM, Roberts SL. Circle of Willis: evaluation with spiral CT angiography, MR angiography, and conventional angiography. Radiology 1995;195:445-9.
61. Takanashi JI, Sugita K, Niimi H. Evaluation of magnetic resonance angiography with selective maximum intensity projection in patients with childhood moyamoya disease. Eur J Paediatr Neurol 1998;2:83-9.
62. Fujiwara H, Momoshima S, Kuribayashi S. Leptomeningeal high signal intensity (ivy sign) on fluid-attenuated inversion-recovery (FLAIR) MR images in moyamoya disease. Eur J Radiol 2005;55:224-30.
63. Yamada I, Matsushima Y, Suzuki S. Moyamoya disease: diagnosis with three-dimensional time-of-flight MR angiography. Radiology 1992;184:773-8.
64. Kodama N, Aoki Y, Hiraga H, Wada T, Suzuki J. Electroencephalographic findings in children with moyamoya disease. Arch Neurol 1979;36:16-9.
65. Kirkham FJ, DeBaun MR. Stroke in children with sickle cell disease. Curr Treat Options Neurol 2004;6:357-75.
66. Roach ES. Etiology of stroke in children. Semin Pediatr Neurol 2000;7:244-60.
67. Rosser TL, Vezina G, Packer RJ. Cerebrovascular abnormalities in a population of children with neurofibromatosis type 1. Neurology 2005;64:553-5.
68. Ikezaki K. Rational approach to treatment of moyamoya disease in childhood. J Child Neurol 2000;15:350-6.
69. Bowen MD, Burak CR, Barron TF. Childhood ischemic stroke in a nonurban population. J Child Neurol 2005;20:194-7.
70. Scott RM. Moyamoya syndrome: a surgically treatable cause of stroke in the pediatric patient. Clin Neurosurg 2000;47:378-84.
71. Isono M, Ishii K, Kobayashi H, Kaga A, Kamida T, Fujiki M. Effects of indirect bypass surgery for occlusive cerebrovascular diseases in adults. J Clin Neurosci 2002;9:644-7.
72. Smith ER, Scott RM. Surgical management of moyamoya syndrome. Skull Base 2005;15:15-26.
73. Veeravagu A, Guzman R, Patil CG, Hou LC, Lee M, Steinberg GK. Moyamoya disease in pediatric patients: outcomes of neurosurgical interventions. Neurosurg Focus 2008;24(2):E16.
74. Matsushima T, Inoue T, Ikezaki K, et al. Multiple combined indirect procedure for the surgical treatment of children with moyamoya disease: a comparison with single indirect anastomosis with direct anastomosis. Neurosurg Focus 1998;5(5):e4.
75. Matsushima T, Inoue T, Katsuta T, et al. An indirect revascularization method in the surgical treatment of moyamoya disease — various kinds of indirect procedures and a multiple combined indirect procedure. Neurol Med Chir (Tokyo) 1998;38:Suppl:297-302.
76. Kawaguchi S, Okuno S, Sakaki T. Effect of direct arterial bypass on the prevention of future stroke in patients with the hemorrhagic variety of moyamoya disease. J Neurosurg 2000;93:397-401.
77. Houkin K, Kamiyama H, Abe H, Takahashi A, Kuroda S. Surgical therapy for adult moyamoya disease: can surgical revascularization prevent the recurrence of intracerebral hemorrhage? Stroke 1996;27:1342-6.
78. Sencer S, Poyanli A, Kiris T, Sencer A, Minareci O. Recent experience with Moyamoya disease in Turkey. Eur Radiol 2000;10:569-72.
79. Houkin K, Kuroda S, Nakayama N. Cerebral revascularization for moyamoya disease in children. Neurosurg Clin N Am 2001;12:575-84.
80. Dauser RC, Tuite GF, McCluggage

CW. Dural inversion procedure for moyamoya disease: technical note. J Neurosurg 1997;86:719-23.
81. Nomura S, Kashiwagi S, Uetsuka S, Uchida T, Kubota H, Ito H. Perioperative management protocols for children with moyamoya disease. Childs Nerv Syst 2001; 17:270-4.
82. Iwama T, Hashimoto N, Yonekawa Y. The relevance of hemodynamic factors to perioperative ischemic complications in childhood moyamoya disease. Neurosurgery 1996;38:1120-5.
83. Fujiwara J, Nakahara S, Enomoto T, Nakata Y, Takita H. The effectiveness of O2 administration for transient ischemic attacks in moyamoya disease in children. Childs Nerv Syst 1996;12:69-75.
84. Ohaegbulam CMS, Scott RM. Moyamoya syndrome. In: McLone D, ed. Pediatric neurosurgery. Philadelphia: W.B. Saunders, 2001:1077-92.
85. Pegelow CH. Stroke in children with sickle cell anaemia: aetiology and treatment. Paediatr Drugs 2001;3:421-32.
86. Gebreyohanns M, Adams RJ. Sickle cell disease: primary stroke prevention. CNS Spectr 2004;9:445-9.
87. Dobson SR, Holden KR, Nietert PJ, et al. Moyamoya syndrome in childhood sickle cell disease: a predictive factor for recurrent cerebrovascular events. Blood 2002;99: 3144-50.
88. Riebel T, Kebelmann-Betzing C, Götze R, Overberg US. Transcranial Doppler ultrasonography in neurologically asymptomatic children and young adults with sickle cell disease. Eur Radiol 2003;13:563-70.