Moyamoya Disease – Diagnosis and Treatment: Indirect Cerebral Revascularization at the Sheba Medical Center

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Abstract

Moyamoya disease is a cerebral vasculopathy characterized mainly by progressive narrowing of the major intracranial vessels. While more common and having a familial predilection in the Far East, it can also develop in association with some common hereditary diseases and can be acquired after environmental exposure. In the young its manifestations are the result of cerebral ischemia. Adults usually suffer from repeated incidents of intracerebral hemorrhage. Surgical revascularization of ischemic cerebral territories plays a major role in their treatment. We review the literature and present our series of three adult and five pediatric patients; these patients were diagnosed at our institution and treated with indirect revascularization techniques.

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Moyamoya is a vascular disease characterized by progressive narrowing, leading to occlusion of the major vessels in the circle of Willis and concomitant development of a prominent collateral vascularity in the basal regions of the brain and on the cortex. Especially involved are both distal intracranial internal carotid arteries and their major branches – the anterior cerebral artery or the middle cerebral artery. The posterior cerebral artery and posterior communicating artery can also be affected in advanced stages [1]. The first description of Moyamoya appeared in Japan in the late 1950s and was presented in the English-language medical literature by Kudo [2] in 1968 under the title "Spontaneous occlusion of the circle of Willis. A disease apparently confined to Japanese." The name Moyamoya, meaning "a wavering puff of smoke" in Japanese, describes the typical angiographic appearance of vascularity at the basal regions of the brain [3]. These so-called Moyamoya vessels are a network of preexisting normal collaterals that have dilated in parallel to the occlusion of the circle of Willis.

The etiology of the disease is unknown. The highest incidence is found in the Far East (0.35–2.0 cases per 100,000; prevalence 3.16), but it is a rare disease elsewhere [4]. A genetic predisposition exists in endemic areas, with a familial predilection in about 10%. Linkage was found with loci on chromosomes $3_p24.2$-26 [5], 17_q25 [6] and on chromosome 6 with human leukocyte antigen B51 in the adult (late onset) and HLA B40 in the juvenile form [7].

Moyamoya syndrome refers to findings of Moyamoya vasculopathy in the context of a known systemic disease. It has been described in systemic lupus erythematosus [8], CREST syndrome [9], neurofibromatosis type I [10] and Down syndrome [11], in hypercoagulable states like protein S deficiency and antiphospholipid antibody syndrome [12], after exposure to radiation [13], and in association with cocaine abuse [14].

Clinical manifestations and course of the disease

There are two age peaks for disease presentation: between 6 and 15 years old and around the fourth decade, and a higher incidence among females. Progressive vascular stenosis causes cerebral hypoperfusion and a reduced hemodynamic reserve. These are clinically expressed through ischemic phenomena. Children, more than adults, usually present with cerebral ischemic events, causing transient (or less often, permanent) motor, sensory, cognitive-behavioral deficits or endocrine dysfunction, incontinence, migraine-like symptoms and seizures. Transient ischemic attacks are induced by activities associated with hyperventilation, such as crying, running, eating hot dishes, and singing, or by hyperpyrexia. Ischemic events in adults usually manifest more as an infarction than a TIA [15,16].

A hemorrhagic event is a presentation believed to be more common in adults. The "Moyamoya" collaterals, under hemodynamic overload due to compensatory increase in blood flow, are congested and tend to develop aneurysms and pseudo-aneurysms. Some patients thus tend to suffer from intracerebral (thalamic, basal ganglia), intraventricular or subarachnoid hemorrhage. Rebleeding is associated with higher morbidity and mortality [17].

These relatively different modes of presentation in adults and children are attributed to more stable cerebral hemodynamics on one hand and increased vascular rigidity on the other in adults. The possibility that there are two distinct disease entities has also been raised [18].

HLA = human leukocyte antigen
TIA = transient ischemic attack

Pathology and pathogenesis

The histopathologic changes in the narrowed vessels are non-specific. They include hyperplasia and thickening of the intima due to smooth muscle cell proliferation, accompanied by irregularity and duplication of the internal elastic lamina (without evidence of an inflammatory process). Changes in the collateral Moyamoya vessels probably result from hemodynamic stress on normal vessels [19]. If the disease progresses to occlusion of the stenotic arteries the Moyamoya vessels disappear [3]. Extracerebral vasculature can also be affected by the disease [20].

Basic fibroblast growth factor, an angiogenic factor capable also of inducing smooth muscle cell proliferation through suppressed apoptosis, has been shown to be selectively present (for unknown reasons) in the intima of the stenotic vessels and is implicated to underlie the pathologic process [21].The cerebrospinal fluid of Moyamoya patients contains high levels of inflammatory mediators and the narrowed vessels have an altered reactivity and vessel wall permeability to these substances [22].

Diagnosis and evaluation

Angiography

Considered the gold standard for diagnosis and follow-up, the classical angiographic changes were first described by Suzuki and Takaku [3] in 1969. These include:

- Progressive stenosis leading to occlusion of the supraclinoidal internal carotid arteries (usually bilateral) involving also the proximal MCA/ACA
- Numerous dilated perforating vessels in the base of the brain – giving rise to the typical "Moyamoya" appearance
- Development of leptomeningeal collaterals (and also – transdural "rete mirabile")
- Possible progression of occlusion to the posterior communicating artery and posterior cerebral artery with additional collateral supply from branches of the external carotid artery and the ophthalmic system
- In final stages, the "Moyamoya vessels" can completely disappear with cerebral blood supply becoming totally dependent on external carotid artery and vertebro-basilar blood supply.

Non-invasive evaluation

Angiography has the disadvantage of being an invasive procedure with potential complications. Magnetic resonance angiography techniques, reaching almost 95% sensitivity in diagnosis, are useful in assessing treatment efficacy [23]. Perfusion MRI may be used to detect abnormal tissue perfusion [24]. Since the angiographic findings do not necessarily reflect the true hemodynamic effect of the disease, brain scans with technetium 99m-hexamethyl propylene amine oxime (^{99m}Tc HMPAO) single photon emission computed tomography are used to demonstrate dynamic ischemic low flow states under "hemodynamic stress" situations evoked by an acetazolamide challenge [25]. Acetazolamide, a carbonic anhydrase inhibitor, causes cerebral vasodilation and increased cerebral blood flow in normal cerebral tissue by increasing intracellular CO_2 tension and acidosis. In an ischemic region, where maximal compensatory vasodilatation of stenotic vessels has already occurred, no further vasodilatation or increase in CBF is possible. Moreover, further reduction in CBF to ischemic areas could be observed, due to a steal effect resulting from vasodilatation in normal regions.

Positron emission tomography or Xenon computed tomography with a hyperventilation challenge is similarly used for this purpose. These functional imaging findings are considered important indications for treatment [25,26]. Transcranial Doppler has been suggested as a less elaborate screening tool for Moyamoya disease [27]. One caveat with these methods is that there are indications that deranged cerebral perfusion does not necessarily correlate with jeopardized neuronal function (as reflected in N-acetyl aspartate levels). MR spectroscopy has recently been introduced to investigate the functional implications of these hypoperfusion states [28].

Treatment

Early diagnosis and treatment are important during childhood as the disease can cause progressive disability, including deterioration in cognitive abilities [25,29], and because viable cerebral tissue is necessary for reperfusion procedures to succeed. In adults, treatment is aimed at improving cerebral ischemia and, mainly, preventing repeated intracerebral hemorrhage by reducing the overload on Moyamoya collaterals [4,19]. In children the first line of treatment is pharmacological with antiplatelet therapy or calcium channel blockers, which can ameliorate symptoms but does not halt disease progression.

Demonstrating cerebral hypoperfusion or a reduced perfusion reserve are indications for surgical reperfusion procedures, which are eventually performed in about 80% of patients [25,30–32]. Prior to surgical intervention an assessment of cognitive function is usually performed [29]. The affected cerebral territories lie mainly in the bilateral distribution of the ACA or the MCA. Two basic revascularization procedures are used (separately or in combination):

- D*irect bypass*: mainly superficial temporal artery to MCA. Sometimes combined with STA to ACA bypass. It provides immediate high flow but is difficult to perform in small children due to the small size of the donor and recipient arteries. It is considered less safe than the indirect methods because manipulation of the vessels and the required temporary occlusion of an MCA branch are potentially capable of causing a stroke or reversible ischemic events (reported in about 4.4% and 6.1% of surgeries respectively) [30,32–34].
- I*ndirect bypass*: due to the basic tendency of the ischemic brain to induce the development of collaterals, a direct contact is created between the ischemic brain and another

MCA = middle cerebral artery
ACA = anterior cerebral artery
CBF = cerebral blood flow
STA = superficial temporal artery

tissue that is the source for the blood supply. The sources, which can be used in various combinations, are:

- *Dural arterial*: encephalo-duro-synangiosis – direct application of dura with its blood supply (usually the middle meningeal artery) to a pial surface [35,36]. The same principle can be applied in a more localized fashion by a burr hole and dural incision (to create collaterals to ischemic ACA territories which can be ischemic as the disease progresses) [37].
- *Muscle*: encephalo-myo-synangiosis – using a temporalis muscle graft supplied by the deep temporal artery. A relatively large territory can be covered, but not frontal areas (ACA territories are not reachable). Complications include myoelectric activity-induced seizures, generated by muscle contraction and a cosmetic defect in the temporal fossa [38].
- *Superficial arterial*: encephalo-arterio-synangiosis – the STA is carefully dissected and brought in contact with the brain through an opening in the cranial vault and the dura [39]. This can be modified by suturing the STA to the pia – pial synangiosis [36], to improve neovascularization. In encephalo-duro-arterio-synangiosis a scalp artery (usually the STA) with its adjacent strip of galea aponeurotica is transplanted to the margins of a dural incision [35].
- *Galea*: encephalo-galeo-synangiosis – bringing the galea through a burr hole or craniotomy and dural incision in contact with the brain (usually to improve blood supply to ACA territories). It is considered a safe procedure because blood vessels are not manipulated, the site can be chosen so as not to disrupt existing leptomeningeal collaterals, and because of the short operating time, but the territory that can be revascularized is quite limited in size [37].

The disadvantage of indirect revascularization techniques is their delayed efficacy, pending the development of collaterals, a process that can take months. Strokes occurring during this period could be devastating.

Aside from the general surgical risks, when the dura is opened, there is a risk for a subdural (and epidural) hematoma or empyema and for damaging collateral leptomeningeal blood supply. In addition, Moyamoya patients, suffering already from regional cerebral hypoperfusion, are particularly intolerant perioperatively to an additional reduction in CBF, which can lead to cerebral infarction of territories supplied by the stenotic vessels. Attention is thus paid to the choice of anesthetics, to avoiding hypotension (hypovolemia) or hyperventilation, and also to head (relative to body) positioning – all directed to ensure optimal CBF and hemodynamic stability. Still, with direct or indirect procedures, the incidence of perioperative cerebral infarction has reached 13% [30,35,37].

The above procedures result in hemodynamic improvement, which is manifested by:

- *Improved perfusion*: more than a third of the MCA territory being reperfused in about 53–84% of those treated (expected to develop 6–12 months following treatment using the indirect techniques) and appearance of collaterals supplying ischemic brain with reduction in the typical MRI leptomeningeal enhancement. A higher success rate is achieved in direct or combined procedures, with the EDAS procedure alone reported as being less effective (only in about 53%) and more prone to recurrence of symptoms [15,33,37,39]. This was corroborated by a recent extensive review, but there was no significant difference between procedures regarding symptomatic benefit [30].
- *Reduced hemodynamic load*: diminution of Moyamoya vessels [25,37,39] and aneurysm regression [40].
- *Clinical improvement*: reduction or disappearance of TIAs and of new permanent deficit (within weeks in direct procedures and about 6 months after treatment; earlier than the angiographic improvement, in indirect methods). Direct revascularization is more effective in reducing the incidence of hemorrhage in adults [32].

Moyamoya disease – the Sheba Medical Center Experience

In the period 1998–2004, five young patients aged 7.5–12 years and three adults, 22, 24 and 41 years of age, diagnosed with Moyamoya disease, were admitted for treatment. Patient characteristics, treatment outcome and diagnostic imaging performed pre- and post-treatment are summarized in Table 1.

Their presenting symptoms were headaches, seizures, TIAs, cerebral infarcts with permanent neurologic deficit (hemiparesis, disequilibrium, sensory deficit), cognitive impairment and, in two cases, intracranial hemorrhage (intraventricular hemorrhage in an adult patient and intracerebral hemorrhage in an adolescent).

Diagnostic workup was conducted by a multidisciplinary team comprising a neurologist, a neurosurgeon and a neuroradiologist. MRI findings were confirmed by five-vessel cerebral angiography (performed in all but one patient). Tc-99m HMPAO brain SPECT studies were performed with and without acetazolamide for evaluation of hemodynamic reserve and as baseline for correlation with post-surgical outcome.

The patients underwent indirect cerebral revascularization using EDAS combined with a modified dural synangiosis. In this procedure [38] the STA is identified and isolated. The middle meningeal artery with its adjacent dura is then exposed (through a craniotomy). A dural inversion brings the outer periosteal dura, with its rich blood supply, in contact with the pia over the ischemic territory (encephalo-duro-synangiosis). The adventitia of the STA is sutured to the pial surface (EDAS with pial synangiosis). Replacing the bone flap is done without occluding the STA that passes underneath.

In two cases, where low perfusion to the ACA territory was

EDAS = encephalo-duro-arterio-synangiosis
SPECT = single photon emission computed tomography

Table 1. Moyamoya disease – patient characteristics and treatment outcome

Age at diagnosis	Symptom duration	Follow-up after surgery	Signs, symptoms at presentation	Signs, symptoms at last follow-up	Evaluation: pre- and post-treatment with Angio, MRI, and SPECT
24 years (K.M.)	7 years	54 months	Rt. hemiparesis, dysphasia, dyslexia, dyscalculia, dysgraphia, Rt. hemianopsia, cognitive deficit	Improved verbal and cognitive abilities. Independent in daily activities; began working	Pre-Angio: MMD; post-Angio: no. Pre-MRI: MMV, multiple Lt. and Rt. infarcts; post-MRI: *less* MMV, *enlarged Lt.* STA, **but enlarged Lt. infarction.** Pre-SPECT: severe Lt. hemispheric and Rt. parietal hypoperfusion; post-SPECT: no major changes.
11 years (D.B.)	7 years	48 months	Headache, confusion, recurrent paresis of limbs, visual blurring and dysarthria	Reduced frequency and duration of events. Minimal facial paresthesia, asthenia	Pre-Angio: MMD; post-Angio: no. Pre-MRI: MMD; post-MRI: no new lesions. *Reduced* MMV. Pre-SPECT: bilateral parietal and basal ganglia hypoperfusion, reduced Rt. posterior parietal and Lt. fronto-temporal reserve; post-SPECT: *improved Lt. frontal perfusion*, but **still signs of ischemia.**
41 years (D.R.)	1 week	42 months	Severe headache, vomiting, drowsiness. (Intraventricular hemorrhage)	Rebled 4 years after initial episode and died	Pre-Angio: MMD; post-Angio: refused. Pre-MRI: no; post-MRI: *improved* MMV. No new lesions. Pre-SPECT: no; post-SPECT: no perfusion abnormalities.
7.5 years (S.M.)	3 years	30 months.	Headache, transient limb paresis, ataxia, disequilibrium	Relief of headache and alert. Three events of transient Rt. hemiparesis during previous year. (Underwent frontal burr holes)	Pre-Angio: MMD; post-Angio: *improved supply from* STA *and* MMA. Pre-MRI: MMD (also ACAs, bifrontal ischemia); post-MRI: no new lesions. E*nlarged external carotid artery and choroidal arterial supply.* Pre-SPECT; post-SPECT: **no**.
12 years (G.R.)	0 year	24 months	Lt. hemiparesis. (Acute Rt. fronto- temporal hemorrhage)	Functional improvement. No headache	Pre-Angio: MMD; post-Angio: no. Pre-MRI: MMD, also in PCA, minimal signs of ischemia (Lt. corona radiata); post-MRI: *improvement in* LMC, MMV. Pre-SPECT: Rt. parieto-temporal hypoperfusion; post-SECT: *markedly improved perfusion*.
7.5 years (S.E.)	4 years	12 months	Lt. hemiparesis, headache, behavioral and cognitive changes. Lt. temporal epileptic seizures	Mild Lt. hemiparesis. No headache. (Unilateral treatment)	Pre-Angio: Rt. MMD; post-Angio: no. Pre-MRI: MMD, bilateral ACA, Rt. basal ganglia and internal capsule infarcts; post-MRI: no new infarcts. **No new revascularization to posterior MCA area**. Pre-SPECT: Rt. parietal and Lt. occipital defects, hypoperfusion, Rt. parietal, thalamic, basal ganglia and cingulum. Lt. tempo-occipital; post-SPECT: *minimal, focal* (Rt. *frontal*) *ischemia*.
9 years (S.G.)	6 months	9 months	Transient paresthesia, Lt. arm and facial hemiparesis with aphasia	No paresthesia or headache. Fully active, no recurrent paresis. (Underwent frontal burr holes)	Pre-Angio: no; post-Angio: no. Pre-MRI: MMD; post-MRI: similar to pre-operation, **but more enlarged thalamic MMV** Pre-SPECT: reduced Rt. frontal reserve; post-SPECT: *improved* Rt. *frontal perfusion*.
22 years (A.M.)	7 years	2 months	Progressively severe and intense headache	No change	Pre-Angio: MMD with profuse LMC to fronto-parietal cortex; post-Angio: no. Pre-MRI: Lt. frontal infarct, bilateral frontal ischemic changes. MRA: MMV. Pre-SPECT: Lt. frontal defect, frontal and mild subcortical hypoperfusion, more on the right; post-SPECT: not done yet.

Findings in all modalities appearing in *italics* represent favorable changes, and those in **bold letters** represent unfavorable changes.
MMD = Moyamoya disease, MMA = Moyamoya arteries, MMV= Moyamoya vessels, LMC = leptomeningeal collaterals.

suggested on angiography or SPECT, frontally placed burr holes were added to create an encephalo-galeo-synangiosis. The more symptomatic side was treated first and about 2 months later the contralateral hemisphere was treated as well. In total, 15 operations were performed, with bilateral procedures in seven patients and unilateral in one (who had a predominantly unilateral disease). The adult patient presenting with intraventricular hemorrhage was initially treated for increased intracranial pressure with shunt insertion.

Outcome

There were no delayed permanent postoperative complications. Only one patient had minimal transient distal hand and proximal leg paresis, which gradually resolved.

Patients were followed clinically from 2 months to 4.5 years post-surgery with repeated neurologic evaluation. Radiologic follow-up was conducted 9–12 months after treatment. We performed mostly non-invasive MRA and brain SPECT-acetazolamide studies. Postoperative angiography was performed in only two patients.

All patients demonstrated continued neurologic improvement. This included reduction in frequency or cessation of transient neurologic deficits, seizures or headaches, and improved social and scholastic performance. In patients with permanent deficits there was no further deterioration. The adult patient treated with ventriculo-peritoneal shunt became shunt-independent and the shunt was removed. However, 4 years later, he rebled and died from massive intraventricular hemorrhage. Favorable radiologic changes could be demonstrated. In five of the seven patients followed with MR angiography we observed reduction in the Moyamoya vasculature and five of the six patients studied with SPECT had improved cerebral perfusion and hemodynamic reserve. Only in two patients was there radiologic evidence of disease progression. In one it manifested by an enlarged infarction and further narrowing of MCA and ACA vessels but this was not associated with neurologic deterioration. In the second patient enlarged Moyamoya vessels were observed. Figure 1 demonstrates the angiographic images at diagnosis and the improvement in cortical perfusion one year after treatment in one of the patients (S.M.).

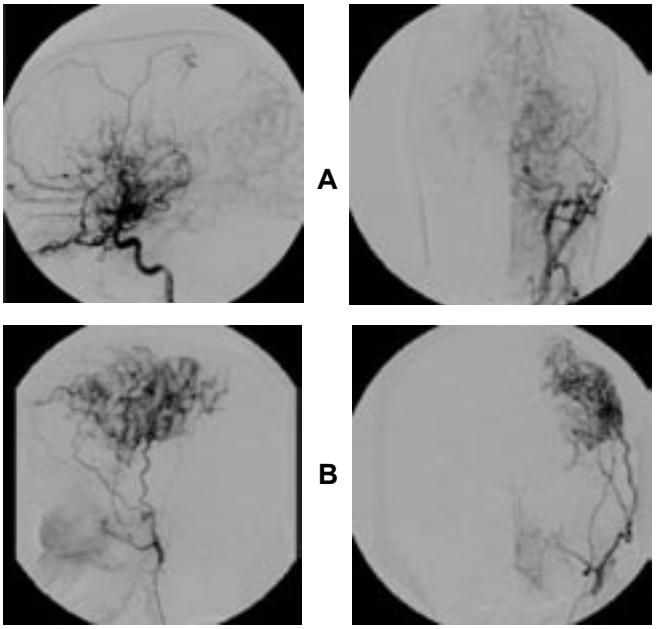

Figure 1. Angiography performed before [A] and after [B] treatment.

[A] Left common carotid angiogram, late arterial phase. Lateral (left) and anteropostero (right) views. Meager cortical supply in the territory of the MCA and ACA together with Moyamoya vessels at the base of the brain.

[B] Left external carotid angiogram. Lateral (left) and anteropostero (right) views. Same patient as above, one year after surgery. Collaterals from superficial temporal artery perfusing MCA territory.

An illustrative case

D.B. had been suffering since the age of 4 from severe headaches. Recurrent episodes of confusion, blurred vision, facial paresthesias accompanied by limb weakness (paraparesis, hemiparesis or quadriparesis) that lasted up to 10 hours, began appearing at age 8. These events were induced by stressful situations and hyperventilation. Between attacks there was no permanent neurologic deficit. At first the diagnosis was complicated migraine, and only at age 11 and after undergoing MR angiography was Moyamoya disease suggested. Initially, treatment with calcium channel blockers and non-steroidal anti-inflammatory drugs ameliorated the symptoms and anticonvulsants were added to treat suspected seizures. Seven years later, at age 18, and due to continued symptoms, a SPECT-acetazolamide study was performed demonstrating right parietal lobe and thalamic hypoperfusion. Two months later a cerebral angiography demonstrated the classic Moyamoya pattern and a modified right EDAS was performed. The outcome of surgery was a reduction in the frequency and duration of attacks.

A second operation was performed 4 months later. After 4 months of postoperative follow-up there were still repeated short events of "heaviness" in the right hand lasting up to 10 minutes, appearing during sleep and awakening the patient. One year postoperatively, there was a distinct abatement of attacks but not of the headaches. At last follow-up, 4 years after treatment, the patient only seldom has tingling sensations in the face with occasional mild headaches, and is leading a normal life.

Summary

Moyamoya disease is associated with severe morbidity in pediatric and adult patients alike. Surgical intervention is indicated when conservative treatment fails to control symptoms or prevent continued neurologic deterioration. While there is an ongoing debate as to the best technique for cerebral revascularization in children, its timing and the means to effectively prevent fatal hemorrhagic stroke in adult patients [39], there is consensus that in children the risk for disease progression and neurologic deterioration mandates early detection and treatment.

Although it is a relatively rare entity, greater awareness of the possible clinical manifestations of the disease and the various conditions predisposing to its development will undoubtedly enable prompt diagnosis and intervention, and thus reduce morbidity.

References

1. Komiyama M, Nishikawa M, Yasui T, Kitao S, Sakamoto H, Fu Y. Steno-occlusive changes in the external carotid system in Moyamoya disease. *Acta Neurochir* (Wien) 2000;142:421–4.
2. Kudo T. Spontaneous occlusion of the circle of Willis. A disease apparently confined to Japanese. *Neurology* 1968;18:485–6.
3. Suzuki J, Takaku A. Cerebrovascular Moyamoya disease: disease showing abnormal net-like vessels in base of brain. *Arch Neurol* 1969;20:288–99.
4. Wetjen NM, Garell C, Stence NV, Loftus C. Moyamoya disease in the midwestern United States. *Neurosurg Focus* 1998;5:5,E1.
5. Ikeda H, Sasaki T, Yoshimoto T, et al. Mapping of a familial Moyamoya disease gene to chromosome 3p24.2-p.26. *Am J Hum Genet* 1999;64:533–7.
6. Ymauchi T, Tada M, Houkin K, et al. Linkage of familial Moyamoya disease (spontaneous occlusion of the circle of Willis) to chromosome 17.25. *Stroke* 2000;31:930–5.
7. Inuoe TK, Ikezaki K, Sasazuki T, Matsushima T, Fufui M. Linkage analysis of Moyamoya disease on chromosome 6. *J Child Neurol* 2000;15:179–82.
8. El Ramahi KM, Al Rayes HM. Systemic lupus erythematosus associated with Moyamoya syndrome. *Lupus* 2000;9:632–6.
9. Terajina K, Shimohata T, Watanabe M, et al. Cerebral vasculopathy showing Moyamoya-like changes in a patient with CREST syndrome. *Eur Neurol* 2001;46:163–5.
10. Rodrigues-Jadraque R, Martinez-Salio A, Garcia de alvaro MT, et al. Arterio venous malformations in neurofibromatosis type 1. A case report and review of the literature. *Rev Neurol* 2000;31:1043–5.
11. Dai AI, Shaikh ZA, Cohen ME. Early-onset Moyamoya syndrome in a patient with Down syndrome: case report and review of the literature. *J Child Neurol* 2000;15:696–9.
12. Bonduel M, Hepner M, Sciuccati G, Torres AF, Tenembaum S. Prothrombotic disorders in children with Moyamoya syndrome. *Stroke* 2001;32:1786–92.
13. Miruyama K, Mishima K, Siato N, Fujimaki T, Sasaki T, Kirino T. Radiation-induced aneurysm and Moyamoya vessels presenting with subarachnoid hemorrhage. *Acta Neurochir* (Wien) 2000;142:139–43.
14. Storen EC, Wejdicks EF, Crum BA, Schultz G. Moyamoya-like vasculopathy from cocaine dependency. *Am J Neuoradiol* 2000;21:1008–10.
15. 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). The Korean Society for Cerebrovascular Disease. *Acta Neurochir* (Wien) 2000;142:1263–74.
16. Mootha SL, Riley WJ, Brosnan PG. Hypothalamic-pituitary dysfunction associated with Moyamoya disease in children. *J Pediatr Endocrinol Metab* 1999;12:449–53.
17. Yoshida Y, Yoshioto T, Shirane R, Sakurai Y. Clinical course, surgical management and long term outcome of Moyamoya patients with rebleeding after an episode of intracerebral hemorrhage: an extensive follow-up study. *Stroke* 1999;30:2272–6.
18. Kobayashi E, Saeki N, Oishi H, Hirai S, Yamaura A. Long term natural history of hemorrhagic Moyamoya disease in 42 patients. *J Neurosurg* 2000;93:976–80.
19. Fukui M, Kono S, Sueishi K, Ikezaki K. Moyamoya disease. *Neuropathology* 2000;20(Suppl):S61–4.
20. Yamada I, Himeno Y, Matsushima Y, Shibuya H. Renal artery lesions in patients with Moyamoya disease: angiographic findings. *Stroke* 2000;31:733–7.
21. Houkin K, Yoshimoto T, Abe H, et al. Role of basic fibroblast growth factor in the pathogenesis of moyamoya disease. *Neurosurg Focus* 1998;5:5E2.
22. 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* 2000;50:544–9.
23. Yoon HK, Shin HJ, Lee M, Byun HS, Na DG, Han BK. MR angiography of Moyamoya disease before and after encephaloduroarteriosynangiosis. *Am J Roentgenol* 2000;174:195–200.
24. Calamante F, Ganesan V, Kirkham FJ, Jan W, Chong WK, Gadian DG, Connely A. MR perfusion studies in Moyamoya syndrome: potential implications for clinical evaluation for clinical evaluation of occlusive cerbrovascular disease. *Stroke* 2001;32:2810–16.
25. Khan N, Shuknecht B, Boltshauser E, et al. Moyamoya disease and Moyamoya syndrome: experience in Europe; choice of revascularization procedures. *Acta Neurochir* (Wien) 2003;145:1061–71.
26. Liu HM, Peng SS, Li YW. The preoperative and postoperative cerebral blood flow and vascularity in childhood Moyamoya disease. *Kieio J Med* 2000;49(Suppl 1):86–9.
27. Ipsiroglu OS, Eichler F, Stockler-Ipsiroglu S, Tratting S. Cerebral blood flow velocities in an infant with Moyamoya disease. *Pediatr Neurol* 1999;21:739–41.
28. Harada M, Mioshi H, Uno M, et al. Neuronal impairment in adult moyamoya disease detected by quantified proton MRS and comparison with cerebral perfusion by SPECT with Tc-99m HM-PAO: a trial of clinical quantification of metabolites. *J Magn Reson Imaging* 1999;10:124–9.
29. Imaizumi C, Imaizumi T, Osawa M, Fukutama Y, Takeshita M. Serial intelligence scores in pediatric Moyamoya disease. *Neuropediatrics* 1999;30:294–9.
30. Fung LW, Thompson D, Ganesan V. Revascularization for pediatric moyamoya; a review of the literature. *Childs Nerv System* 2005;21:358–64.
31. Ikezaki K. Rational approach to treatment of moyamoya disease in childhood. *J Child Neurol* 2000;15:350–6.
32. Kawaguchi S, Okuono S, Skaki 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.
33. Golby AJ, Marks MP, Thompson RC, Steinberg GK. Direct and combined revascularization in pediatric Moyamoya disease. *Neurosurgery* 1999;45:50–8.
34. Houkin K, Kuroda S, Nakayama N. Cerebral revascularization for moyamoya disease in children. *Neurosurg Clin North Am* 2001;12:575–84.
35. Matsuhshima T, Fujiwara S, Nagata S, et al. Surgical treatment of pediatric patients with Moyamoya disease by indirect revascularization procedures (EDAS, EMS, EMAS). *Acta Neurochir* (Wien) 1989;98:135–40.
36. Dauser RC, Tuite GF, McCluggage CW. Dural inversion procedure for Moyamoya disease. Technical note. *J Neurosurg* 1997;86:719–23.
37. Kim SK, Wang KC, Kim IO, Lee DS, Cho BK. Combined encephaloduroarteriosynangiosis and bifrontal encephlogaleo (periosteal) synangiosis in pediatric Moyamoya disease. *Neurosurgery* 2002;50:88–96.
38. Irikura K, Miyasaka Y, Kurata A, et al. The effects of encephalomyo-synangiosis on abnormal collateral vessels in childhood Moyamoya disease. *Neurol Res* 2000;22:341–6.
39. Houkin K, Kuroda S, Ishikawa T, Abe H. Neovascularization (angiogenesis) after revascularization in Moyamoya disease. Which technique is most useful for Moyamoya disease? *Acta Neurochir* (Wien) 2000;142:269–76.
40. Kuroda S, Houkin K, Kimiyama H, Abe H. Effects of surgical revascularization on peripheral artery aneurysms in Moyamoya disease: report of three cases. *Neurosurgery* 2001;49:463–7.

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