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

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Key words: Moyamoya, cerebral ischemia, subarachnoid hemorrhage, angiography, cerebral revascularization

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.

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 1 [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 (99mTc 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 CO₂ 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):

- **Direct 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].
- **Indirect 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

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MCA = middle cerebral artery
ACA = anterior cerebral artery

CBF = cerebral blood flow
STA = superficial temporal artery

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which is manifested by:

1. Incidence of perioperative cerebral infarction has reached 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 from regional cerebral hypoperfusion, are particularly intolerant peripherally 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

<table>
<thead>
<tr>
<th>Age at diagnosis</th>
<th>Symptom duration</th>
<th>Follow-up after surgery</th>
<th>Signs, symptoms at presentation</th>
<th>Signs, symptoms at last follow-up</th>
<th>Evaluation: pre- and post-treatment with Angio, MRI, and SPECT</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 years (K.M.)</td>
<td>7 years</td>
<td>54 months</td>
<td>Rt. hemiparesis, dysphasia, dyslexia, dyscalculia, dysgraphia, Rt. hemianopsia, cognitive deficit</td>
<td>Improved verbal and cognitive abilities, Independent in daily activities, began working</td>
<td>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.</td>
</tr>
<tr>
<td>11 years (D.B.)</td>
<td>7 years</td>
<td>48 months</td>
<td>Headache, confusion, recurrent paresis of limbs, visual blurring and dysarthria</td>
<td>Reduced frequency and duration of events: Minimal facial paresthesia, asthenia</td>
<td>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.</td>
</tr>
<tr>
<td>41 years (D.R.)</td>
<td>1 week</td>
<td>42 months</td>
<td>Severe headache, vomiting, drowsiness (Intraventricular hemorrhage)</td>
<td>Rebled 4 years after initial episode and died</td>
<td>Pre-Angio: MMD; post-Angio: refused. Pre-MRI: no; post-MRI: improved MMV. No new lesions. Pre-SPECT: no; post-SPECT: no perfusion abnormalities.</td>
</tr>
<tr>
<td>7.5 years (S.M.)</td>
<td>3 years</td>
<td>30 months</td>
<td>Headache, transient limb paresis, ataxia, disequilibrium</td>
<td>Relief of headache and alert. Three events of transient Rt. hemiparesis during previous year (Underwent frontal burr holes)</td>
<td>Pre-Angio: MMD; post-Angio: improved supply from STA and MMA. Pre-MRI: MMD (also ACAs, bifrontal ischemia); post-MRI: no new lesions. Enlarged external carotid artery and choroidal arterial supply. Pre-SPECT: post-SPECT: no.</td>
</tr>
<tr>
<td>12 years (G.R.)</td>
<td>0 year</td>
<td>24 months</td>
<td>Lt. hemiparesis (Acute Rt. fronto-temporal hemorrhage)</td>
<td>Functional improvement. No headache</td>
<td>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-SPECT: markedly improved perfusion.</td>
</tr>
<tr>
<td>7.5 years (S.E.)</td>
<td>4 years</td>
<td>12 months</td>
<td>Lt. hemiparesis, headache, behavioral and cognitive changes, Lt. temporal epileptic seizures</td>
<td>Mild Lt. hemiparesis. No headache. (Unilateral treatment)</td>
<td>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.</td>
</tr>
<tr>
<td>9 years (S.G.)</td>
<td>6 months</td>
<td>9 months</td>
<td>Transient paresthesia, Lt. arm and facial hemiparesis with aphasia</td>
<td>No paresthesia or headache. Fully active, no recurrent paresis. (Underwent frontal burr holes)</td>
<td>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.</td>
</tr>
<tr>
<td>22 years (A.M.)</td>
<td>7 years</td>
<td>2 months</td>
<td>Progressively severe and intense headache</td>
<td>No change</td>
<td>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.</td>
</tr>
</tbody>
</table>

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.).

**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


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