Neurosurgical Treatment of Moyamoya Disease: Bypass Surgery for the Brain

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Abstract

Moyamoya disease leads to disruption of the blood supply to the brain and affects populations around the world; the highest prevalence is reported in the Japanese population. Symptoms of this disease may be due to ischaemia, including transient ischaemic attacks and stroke, or due to haemorrhage from abnormal and weak collateral vessels, leading to loss of consciousness or acute-onset headache. This disease is progressive and cannot be adequately treated medically, requiring neurosurgical intervention for effective treatment. Surgical treatment seeks to increase blood flow to the brain and may be done either by the direct anastomosis of the superficial temporal artery and middle cerebral artery or by a variety of indirect approaches that act to increase collateral blood flow to the brain. Although no standard treatment exists for this disease, many surgical interventions and combinations of interventions have been used with successful outcomes.

Introduction

Moyamoya disease (MMD) is a condition affecting the vasculature supplying the brain, predisposing individuals affected by this disease to stroke. This disease leads to stenosis of the internal carotid arteries (ICA) within the skull, which normally act to supply the brain with the rich blood supply it needs to function[1,2]. The narrowing of the carotid vessels seen in MMD is unlike that seen with atherosclerosis, a more common cause of stroke, and perhaps the most striking difference between these two causes of stroke is the age groups which are affected: while the majority of strokes affect individuals greater than 65 years of age, MMD may lead to stroke in children younger than 3 years old[1,3]. This article will look at how MMD affects both children and adults, how the presentation of this disease differs significantly between children and adults and, lastly, what treatments are available for this disease.

What Causes Moyamoya and Who Does it Affect?

もやもや

Moyamoya is a Japanese word, written above in hiragana, and means puff of smoke. The name originates from the characteristic hazy appearance of angiograms seen in patients with this disease, a result of the growth of collateral vessels that seek to compensate for the limited blood supply provided by the carotid arteries (Figure 1)[1,4,5].

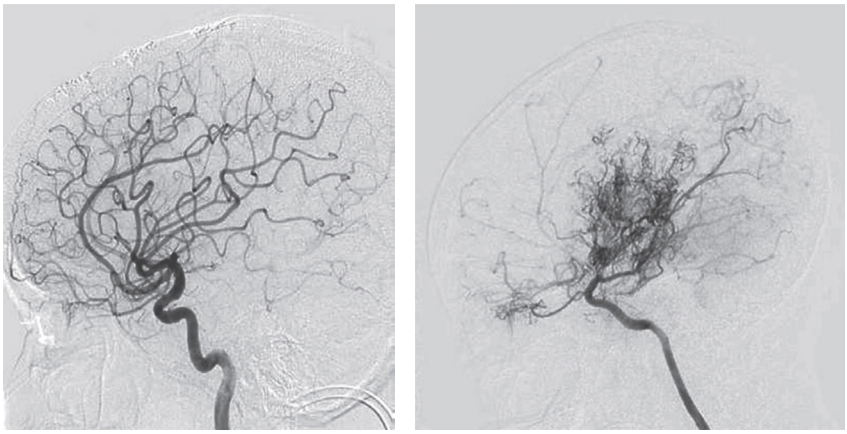

Figure 1. *(Left) Lateral view angiogram of the internal carotid artery (ICA) showing normal perfusion of the brain. (Right) Angiogram of a patient with moyamoya disease showing the "puff-of-smoke" appearance which can be seen in patients with this disease[1].*

First described in Japan in 1957, the cause of MMD remains unclear but it is believed that environmental and genetic factors play a role in its development. Familial cases of MMD have been reported in Asian populations and risk increases to 30 to 40 times that of sporadic cases in first- and second-degree family members of these patients. There also appears to be an association between MMD and genetic disorders such as Down syndrome and neurofibromatosis. However, the majority of presentations of MMD occur sporadically[6-8]. Pathological changes underlying the stenosis of the major vessels supplying the brain do not involve an inflammatory reaction but instead are thought to centre around smooth muscle cell proliferation[9,10]. The brain tissue, in response to the decline in blood supply, stimulates angiogenic cascades, leading to the characteristic collateral vessel growth seen in MMD[2]. Increased blood flow across these weaker collateral vessels leads to high haemodynamic stress, which in turn can cause microaneurysm formation and vessel wall necrosis, changes which are thought to predispose to the haemorrhage seen in this disease[10,11].

Prognosis

MMD is known to be progressive, with rates of morbidity in untreated individuals as high as 65%-70%[2,12,13]. Ischaemia in MMD may result in the loss of the ability to speak, blindness due to cerebral damage and, in long-standing cases, a persistent vegetative state[5]. In cases presenting with haemorrhage, the ability to recover successfully is drastically reduced with each subsequent haemorrhage. After the first episode of haemorrhage, successful recovery is reported at around 45%; after a second bleed, this falls to about 21%. Mortality after the first bleed has been reported at 7%; after a second haemorrhage, this mortality rose to a startling 29%[14]. The high morbidity and mortality associated with both ischaemic and haemorrhagic presentations of MMD highlight the need for effective control of this disease.

Incidence

MMD was originally thought to be a disease solely affecting Japanese and Korean populations; however, the disease has now been described in many other countries, albeit at a much lower incidence[4,10,15]. The prevalence of MMD in Japan is around 3 per 100,000 people, whereas in Europe and the United States, a lower prevalence is observed at about 0.3 and 0.09 per 100,000, respectively[10,16]. Females are more frequently affected by this disease than males, with reported ratios ranging from 1.5 to 2 females for every male affected[10,16]. The disease sees two peaks in incidence, one in children at 5 years of age and again in adults in their mid-40s[1,16]. It is currently the most common cerebrovascular disease affecting the paediatric population in Japan and accounts for 10% to 20% of arterial infarction in children globally[9,16].

Recognising Moyamoya

Presentation

The presentation of moyamoya corresponds with the pathological changes observed. Stenosis causes ischaemia which leads to transient ischaemic attack (TIA), stroke and seizures[1]. In children, episodes of crying and hyperventilation can lead to decreased partial pressure of CO_2 in blood and reflex physiological cerebral vasoconstriction, precipitating symptoms of stenosis. This, in addition to the already diminished blood flow in MMD, can lead to ischaemic events[17]. Patients with MMD may experience persistent headaches, thought to arise from irritation caused by the dilation of collateral vessels within the meninges[1,5]. The cerebral haemorrhage observed in MMD may present with an acute-onset headache but may also lead to loss of consciousness or motor control disturbance[5]. Haemorrhage occurs about 7 times more frequently in adults than in children and presentations due to haemorrhage make up about 66% of MMD cases in adults. Within adults, haemorrhage occurs more commonly in Asian populations than American ones[1,5]. Ischaemic presentations make up about 69% of those seen in children less than 10 years of age[5]. Unfortunately, completed stroke occurs more often in children and is thought to be due to difficulty in reporting symptoms because of limited verbal skills in younger age groups[1]. Children affected by this disease may also experience intellectual disability and reduced IQ[5]. Occasionally, MMD may be identified incidentally in asymptomatic individuals; in such patients, careful monitoring should be undertaken to identify progression of the disease and treatment should be considered[5,18].

Diagnosis

The criteria for diagnosing MMD are defined by the Research Committee on Moyamoya Disease of the Ministry of Health and Welfare in Japan. Based on these guidelines, MMD involves bilateral occlusive change in the terminal ICA and/or proximal portions of the anterior or middle cerebral arteries (MCA), abnormal vascular networks in the region of the occluded vessels and the absence of systemic disorders which might account for these changes[2,10]. The diagnosis of MMD can be carried out using a variety of imaging techniques. Computed tomography (CT) may be used to show haemorrhage in MMD, while magnetic resonance imaging (MRI) may be useful in identifying areas of ischaemia. Traditional angiography and the less invasive magnetic resonance angiography are useful in identifying stenosis across the major vessels supplying the brain[1,19,20]. Cerebral blood flow may be analysed using single-photon emission computed tomography (SPECT) or xenon-enhanced CT scanning, the latter of which could have the potential to be used as a tool for determining stroke risk in patients with MMD as well as the likelihood of ischaemia following revascularization[19,21-23].

Clinical Points

1. Moyamoya disease is a progressive disease and an important cause of stroke in children and young adults.
2. Moyamoya disease most often occurs sporadically.
3. Children with moyamoya disease often present with signs of ischaemia while adults present more commonly with signs of haemorrhage.
4. Neurosurgical intervention by either direct or indirect revascularization techniques is accepted as the primary means of treatment for this disease.
5. Both direct and indirect revascularization techniques halt progression of the disease and effectively reduce morbidity and mortality associated with this disease.
6. No randomised control trials have yet been carried out to determine a standard treatment course.

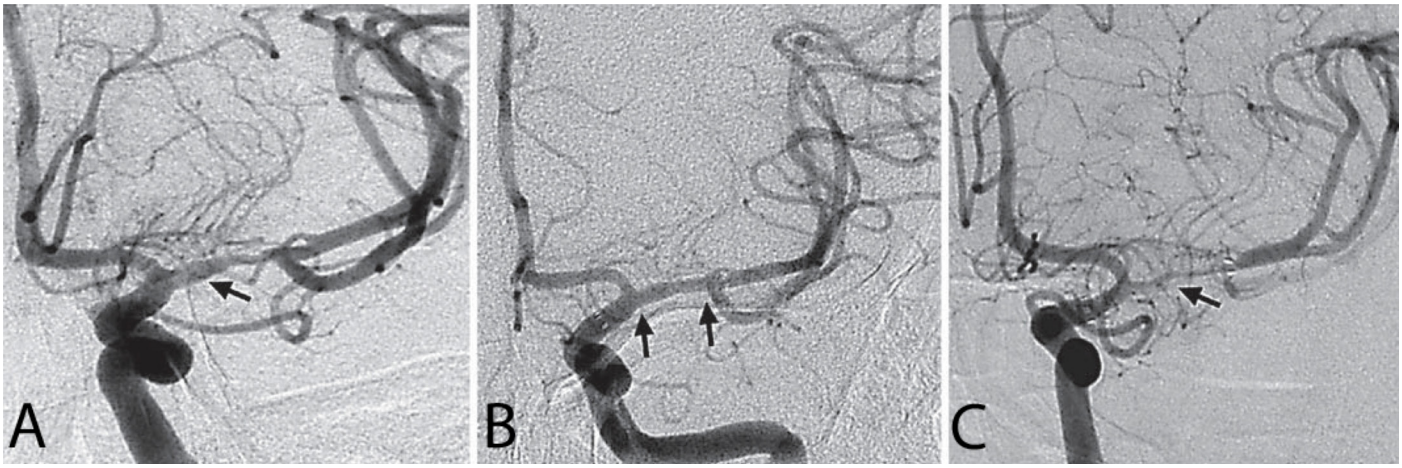

*Figure 2. **(A)** Anteroposterior angiogram of the left ICA showing stenosis of the MCA (arrow). **(B)** Immediately after angioplasty and stenting of the patient's MCA, we see an increased patency of the MCA (arrows). **(C)** 6 months after stenting, re-stenosis of the MCA is noted (arrow)[26]. Reproduced with permission from S. Karger AG Publishers, Basel (Switzerland).*

Treating Moyamoya

Currently, no medical treatment exists to prevent the progression of MMD, and neurosurgical treatment is the accepted means of primary treatment[1,17]. The neurosurgical approach to treatment of this disease aims to increase blood flow in areas of the brain where flow has been compromised, in order to avoid the ischaemia occurring due to vessel stenosis, and also theoretically reduce the strain on collateral vessels in order to reduce haemorrhage and headache. However, whether or not haemorrhagic disease fully responds to revascularization is still up for debate[24,25]. It is interesting to note that accepted treatments for stenosis in atherosclerotic disease, such as balloon angioplasty and stent placement, fail to effectively treat the hypoperfusion seen in MMD (Figure 2)[26]. Most currently accepted surgical interventions for MMD take advantage of the fact that the external branch of the carotid artery is not affected by the disease[1].

There are two general approaches to surgical treatment: direct revascularization and indirect revascularization.

Direct Revascularization

Direct neurosurgical intervention involves joining a branch of the superficial temporal artery (STA), a branch of the unaffected external carotid artery, to the MCA, a major cerebral blood vessel which arises from the now partially occluded ICA[1,2,27]. This procedure was first performed in the 1970s and is similar to a coronary artery bypass graft (CABG) operation where a patent vessel is used to bypass occluded coronary vessels to restore adequate blood flow to the myocardium.

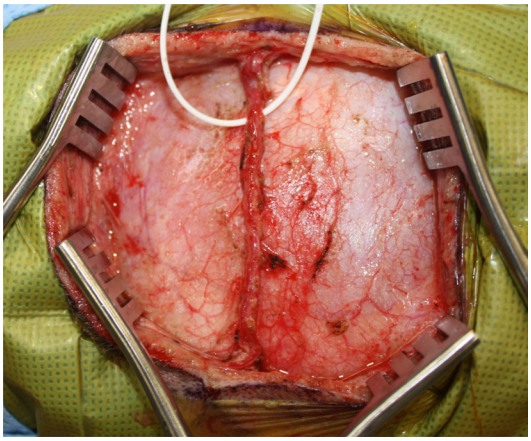

Figure 3. Intraoperative photo showing retraction of the scalp and isolation of the superficial temporal artery (STA). This initial step is similar for STA-MCA anastomosis, encephaloduroarteriosynangiosis and pial synangiosis. Photo provided by Dr Jodi Smith, Associate Professor of Neurological Surgery, Indiana University School of Medicine.

During the neurosurgical approach, the first step involves locating a branch of the STA using Doppler ultrasound followed by careful dissection to expose this vessel (Figure 3). The STA is then moved out of the operative field and a craniotomy delicately performed to avoid damaging the middle meningeal artery: a vessel within the skull that tends to supply important collateral vessels to the brain of patients with MMD. After the craniotomy, the dura (the thick outermost component of the meninges) is opened,

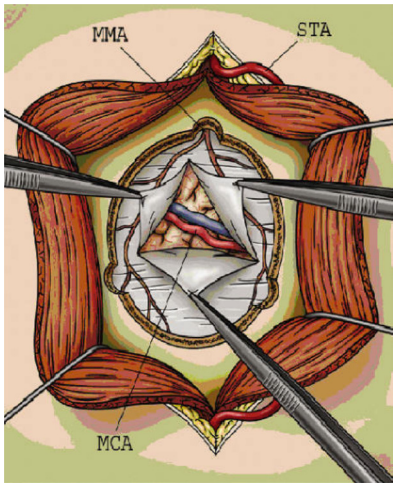

Figure 4. Figure showing the superficial temporal artery (STA) out of the operative field, the preserved middle meningeal artery (MMA) as it courses below the skull, and the middle cerebral artery (MCA) where the dura, pictured here held by forceps, has been removed[10].

exposing the brain's surface and vasculature, now visible through the thinner arachnoid membrane of the meninges. At this point a large-diameter artery is selected for the anastomosis (Figure 4). After identification of an appropriate artery, the arachnoid is opened around the vessel and a segment of the artery is prepared for the anastomosis. Clips are used to prevent bleeding during anastomosis and the previously dissected STA is incised from its distal end and adjoined to the MCA via a longitudinal incision made in the side of this artery (Figure 5)[1,4,10].

Problems arise with this approach in children as their superficial temporal arteries are very small, making the procedure technically difficult to perform[1,10]. Direct techniques are also made more difficult in children due to a higher risk of thrombosis in these smaller vessels. In general, bypass also carries a higher risk of detrimental post-operative haemorrhage[4]. Another complication associated with STA-MCA anastomosis is cerebral hyperperfusion resulting from the sudden increase in blood flow across the MCA. This leads to symptoms such as severe headache or focal neurologic deficits. Fortunately, however, though these patients may appear to show signs of ischaemia, they often make a full recovery from this complication, and it may be avoided altogether with careful management perioperatively[28,29]. Direct STA-MCA anastomosis currently remains a valuable means of treatment for MMD1.

Indirect Revascularization

Indirect treatment options also act to bypass the occluded internal carotid artery supply via the external carotid blood supply, but these approaches do not directly join vessels. Instead, indirect approaches depend on new vessel growth by either tissue or vasculature supplied by the external carotid artery to areas of ischaemia within the brain. These approaches include encephalomyosynangiosis (EMS), encephaloduroarteriosynangiosis (EDAS), pial synangiosis and multiple cranial burr holes, to name a few[1,4,10].

Encephalomyosynangiosis, like direct STA-MCA anastomosis, was first used in the 1970s for the treatment of MMD. This procedure involves suturing the well-vascularised temporalis muscle to the surface of the dura. This may lead to collateral vessel formation should angiogenesis be successful. Disadvantages of this procedure include pressure on the brain because of the additional tissue within the skull, as well as an increased incidence of seizures[10].

During encephaloduroarteriosynangiosis, instead of transecting the STA as in the STA-MCA

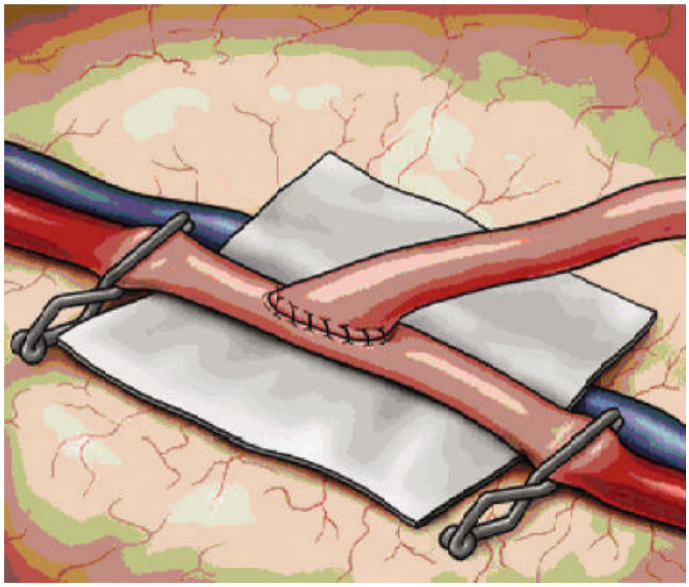

Figure 5. The MCA is represented here in this diagram in red with clips attached, coursing parallel to an adjacent vein in blue. In the centre of the diagram we see the STA anastomosed to the MCA[10].

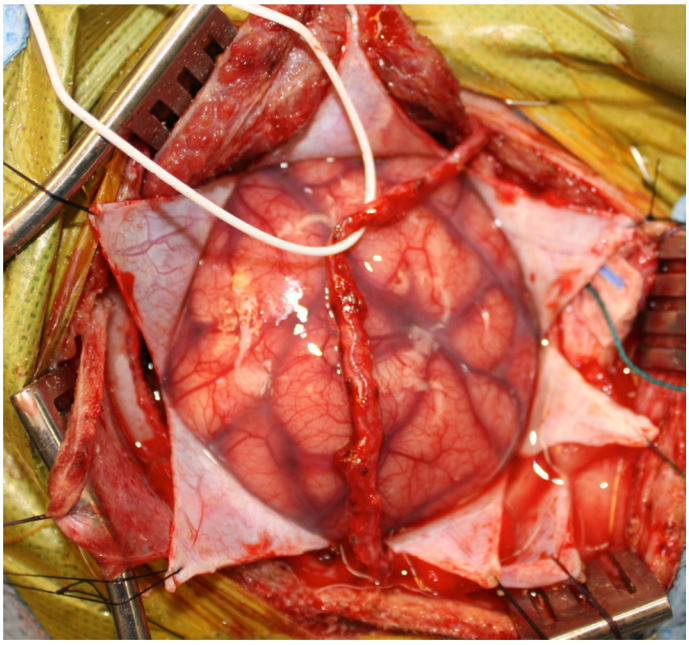

Figure 6. *Intraoperative photo demonstrating a pial synangiosis being performed. The scalp is retracted, bone flap removed and dura opened in a stellate fashion exposing the brain. The branch of the STA to be sewn to the pia can be seen running across the operative field. Photo provided by Dr Jodi Smith, Associate Professor of Neurological Surgery, Indiana University School of Medicine.*

anastomosis, both its attachments are preserved. A craniotomy is performed and the identified vessel is sewn to the dura, then the bone flap is carefully replaced so as to allow patency of the vessel as it passes from scalp to below the skull[4,10]. A pial synangiosis takes this one step further and instead of attaching the artery to the dura, the dura and arachnoid are opened and the vessel sutured directly to the brain surface (Figure 6) before the bone flap is replaced (Figure 7)[10,30]. A follow-up study of 143 patients receiving pial synangiosis for the treatment of MMD found this procedure to be effective in reducing stroke and transient ischaemic attacks and effectively halting the normal course of clinical deterioration[30].

The placement of multiple burr holes is the least technical of these procedures but can provide effective blood vessel growth into targeted localised areas by creating a conduit along which collateral vessel growth may occur[4]. Additional procedures are available for indirect revascularization involving various modifications to these techniques and combinations chosen to target an individual's specific needs[4,10].

Because connections between vessels are not directly made during indirect techniques, increases in blood flow are not seen immediately after surgery. Long-term, however, there appears to be no advantage in using direct techniques over indirect techniques[1,2]. There is conflicting evidence regarding the efficacy of indirect techniques in older patients, with some reporting slightly less benefit from indirect techniques in these patients as compared to paediatric populations[2,10,31,32]. It is proposed that this may be a function of a decline in angiogenic potential with age[10]. Direct arterial bypass to regions other than those supplied by the MCA is often not technically feasible and in these situations, indirect procedures are often favored. Indirect techniques can also be performed faster, reducing complications associated with general anaesthetic[10].

Retrospective analysis of 410 paediatric patients treated for MMD at a single institution supported the early identification and neurosurgical treatment of MMD in order to achieve favourable outcomes[33]. However, there is no standardised approach to MMD

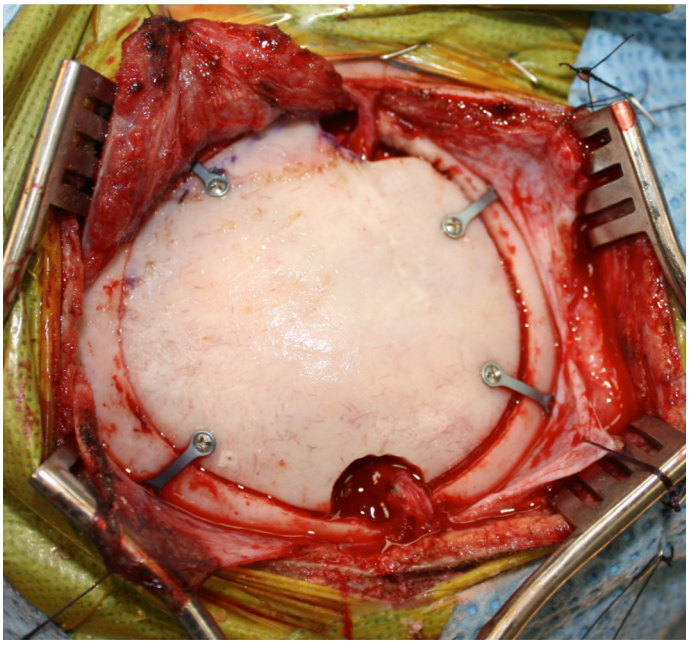

Figure 7. *Intraoperative photo demonstrating the replacement of the bone flap after a pial synangiosis has been carried out. Notice the bone flap has been altered to allow the STA to flow freely beneath the skull and out again. Photo provided by Dr Jodi Smith, Associate Professor of Neurological Surgery, Indiana University School of Medicine.*

and randomised control studies comparing the various surgical techniques do not yet exist[17].

Conclusion

Moyamoya disease is an important cause of stroke in children and young adults and should be suspected in any individual presenting with symptoms of stroke or TIA at a young age. A standardised approach to the treatment of MMD does not exist but direct and indirect revascularization techniques appear to have comparable efficacy in treating this disease. Research is still needed to address whether the haemorrhage seen in MMD can be effectively treated with current revascularization techniques and whether indirect revascularization is as valuable as direct revascularization techniques in adult populations.

References

1. Scott, R. M. & Smith, E. R. Moyamoya disease and moyamoya syndrome. New England Journal of Medicine 360, 1226–1237 (2009).

2. Veeravagu, A. et al. Moyamoya disease in pediatric patients: outcomes of neurosurgical interventions. Neurosurgical Focus 24, E16, doi:10.3171/foc/2008/24/2/e16 (2008).

3. Donnan, G. A., Fisher, M., Macleod, M. & Davis, S. M. Stroke. The Lancet 371, 1612–1623, doi:10.1016/s0140-6736(08)60694-7 (2008).

4. Baaj, A. A. et al. Surgical management of moyamoya disease. Neurosurgical Focus 26, 1–7 (2009).

5. Burke, M. G. et al. Moyamoya disease: a summary Neurosurgical Focus 26, 1–10 (2009).

6. Pandey, P. & Steinberg, G. K. Neurosurgical Advances in the Treatment of Moyamoya Disease. Stroke 42, 3304-3310, doi:10.1161/strokeaha.110.598565 (2011).

7. Achrol, A., Guzman, R., Lee, M. & Steinberg, G. K. Pathophysiology and genetic factors in moyamoya disease. Neurosurgical Focus 26, 1–6 (2009).

8. Han, H., Kuroda, S., Shimoda, Y. & Houkin, K. Early Diagnosis and Surgical Revascularization for a Predictive Case of Moyamoya Disease in a Boy Born to a Moyamoya Mother. Journal of Child Neurology 27, 408–413, doi:10.1177/0883073811422113 (2011).

9. Lynch, J. K., Hirtz, D. G., DeVeber, G. & Nelson, K. B. Report of the National Institute of Neurological Disorders and Stroke Workshop on Perinatal and Childhood Stroke. Pediatrics 109, 116–123, doi:10.1542/peds.109.1.116 (2002).

10. 10 Zipfel, J. G., Fox, J. D. J. & Rivet, J. D. Moyamoya Disease in Adults: The Role of Cerebral Revascularization. Skull Base 15, 27–41 (2005).

11. Group, T. J. A. M. T. Study Design of Prospective Randomized Trial of Extracranial-Intracranial Bypass Surgery For Adults with Moyamoya and Hemorrhagic Onset. Neurol Med Chir (Tokyo) 44, 218–219 (2004).

12. Tomida, M., Muraki, M. & Yamasaki, K. Angiographically verified progression of moyamoya disease in an adult. Journal of Neurosurgery 93, 1055–1057 (2000).

13. Guzman, R. et al. Clinical outcome after 450 revascularization procedures for moyamoya disease. Journal of Neurosurgery 111, 927–935, doi:10.3171/2009.4.jns081649 (2009).

14. Kobayashi, E., Saeki, N., Oishi, H., Hirai, S. & Yamaura, A. Long term natural history of hemorrhagic moyamoya disease in 42 patients. Journal of Neurosurgery 93, 976–980 (2000).

15. Kleinloog, R., Regli, L., Rinkel, G. J. E. & Klijn, C. J. M. Regional differences in incidence and patient characteristics of moyamoya disease: a systematic review. Journal of Neurology, Neurosurgery & Psychiatry 83, 531–536, doi:10.1136/jnnp-2011-301387 (2012).

16. Smith, E. R. & Scott, R. M. Moyamoya: Epidemiology, Presentation, and Diagnosis. Neurosurgery Clinics of North America 21, 543–551, doi:10.1016/j.nec.2010.03.007 (2010).

17. Smith, L. J. Understanding and treating moyamoya disease in children. Neursurgical Focus 26, 1–11 (2009).

18. Kuroda, S., Hashimoto, N., Yoshimoto, T. & Iwasaki, Y. Radiological Findings, Clinical Course, and Outcome in Asymptomatic Moyamoya Disease: Results of Multicenter Survey in Japan. Stroke 38, 1430–1435, doi:10.1161/strokeaha.106.478297 (2007).

19. Lee, M., Guzman, R., Bell-Stephens, T. & Steinberg, G. K. Intraoperative blood flow analysis of direct revascularization procedures in patients with moyamoya disease. Journal of Cerebral Blood Flow & Metabolism 31, 262–274, doi:10.1038/jcbfm.2010.85 (2010).

20. Kwag, H.-J., Jeong, D.-W., Lee, H. S., Kim, H. D. & Kim, J. Intracranial Hemodynamic Changes During Adult Moyamoya Disease Progression. Journal of Clinical Neurology 4, 67–74 (2008).

21. Ikezaki, K. Rational Approach to Treatment of Moyamoya Disease in Childhood. Journal of Child Neurol-

ogy 15, 350–356, doi:10.1177/088307380001500512 (2000).

22. McAuley, D. J., Poskitt, K. & Steinbok, P. Predicting stroke risk in pediatric moyamoya disease with xenon-enhanced computed tomography. Neurosurgery 55, 327–332 (2004).

23. Lee, M. et al. Quantitative hemodynamic studies in moyamoya disease. Neurosurgical FOCUS 26, E5, doi:10.3171/2009.1.focus08300 (2009).

24. Choi, U. J., Kim, S. D., Kim, Y. E. & Lee, C. K. Natural history of Moyamoya disease: comparison of activity of daily living in surgery and non surgery groups. Clinical Neurology and Neurosurgery 99, S11–S18 (1997).

25. Kikuta, K.-I. et al. Asymptomatic microbleeds in moyamoya disease: T2-weighted gradient-echo magnetic resonance imaging study. Journal of Neurosurgery 102, 470–475 (2005).

26. Khan, N. et al. Failure of Primary Percutaneous Angioplasty and Stenting in the Prevention of Ischemia in Moyamoya Angiopathy. Cerebrovascular Diseases 31, 147–153, doi:10.1159/000320253 (2011).

27. 27 Hoffman, J. H. Moyamoya disease and syndrome. Clinical Neurology and Neurosurgery 99, S39–S44 (1997).

28. 28 Uchino, H. et al. Predictors and Clinical Features of Postoperative Hyperperfusion after Surgical Revascularization for Moyamoya Disease: A Serial Single Photon Emission CT/Positron Emission Tomography Study. Stroke 43, 2610–2616, doi:10.1161/strokeaha.112.654723 (2012).

29. Fujimura, M., Mugikura, S., Kaneta, T., Shimizu, H. & Tominaga, T. Incidence and risk factors for symptomatic cerebral hyperperfusion after superficial temporal artery–middle cerebral artery anastomosis in patients with moyamoya disease. Surgical Neurology 71, 442–447, doi:10.1016/j.surneu.2008.02.031 (2009).

30. Scott, R. M. et al. Long-term outcome in children with moyamoya syndrome after cranial revascularization by pial synangiosis. Journal of Neurosurgery (Pediatrics 2) 100, 142–149 (2004).

31. Starke, R. M. et al. Clinical features, surgical treatment, and long-term outcome in adult patients with moyamoya disease. Journal of Neurosurgery 111, 936–942, doi:10.3171/2009.3.jns08837 (2009).

32. Derex, L. et al. Symptomatic Moyamoya disease: Clinical features and outcome after indirect bypass surgery in four French adults. Journal of the Neurological Sciences 288, 92–95, doi:10.1016/j.jns.2009.09.031 (2010).

33. Kim, S.-K. et al. Pediatric moyamoya disease: An analysis of 410 consecutive cases. Annals of Neurology 68, 92–101, doi:10.1002/ana.21981 (2010).

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