EXPERT OPINION

Moyamoya: An Update for the Practicing Neurologist

Distinguishing between definite MMD, probable MMD, and MMS may not have significant practical implications.

By Timothy G. White, MD; Julia R. Schneider, BS; Kay O. Kulason, BA; Ralph Rahme, MD; Kevin Kwan, MD; Rafael A. Ortiz, MD; and David J. Langer, MD
Section Editor: Steven Mandel, MD

Moyamoya disease (MMD) is a rare idiopathic disorder characterized by progressive narrowing of the bilateral supraclinoid internal carotid arteries (ICAs) and/or proximal anterior and middle cerebral arteries (ACAs, MCAs). The term "moyamoya," Japanese for "something hazy, like a puff of smoke," serves to describe the abnormal network of fine collateral vessels that develops at the base of the brain and is often seen angiographically in patients with MMD.[1-3] Over time, additional collaterals may develop, including leptomeningeal collaterals on the surface of the brain from the posterior cerebral artery and transdural collaterals from the external carotid artery.[4]

Similar angiographic findings resembling MMD have also been observed in a variety of pathologic conditions, including atherosclerosis, radiation toxicity, traumatic brain injury, meningitis, Down syndrome, neurofibromatosis type 1, microcephalic primordial dwarfism, sickle cell disease, thyroid disease, autoimmune diseases, and brain tumors.[5,6] Those cases, which can involve a single or both ICAs, are generally referred to as *moyamoya syndrome* (MMΣ).

Although the diagnosis of "definite" MMD requires bilateral presentation, patients with unilateral ICA involvement and no associated predisposing pathology are considered to have "probable" MMD, given that many such patients (i.e., up to 70%) will ultimately develop contralateral disease over time.[7-9] Similarly, in some cases, MMD may start in the proximal MCA (M1 segment) before spreading to the ICA terminus.[6] MMD is more common in Asia, whereas MMS tends to be more prevalent in North America and Europe. However, given that clinical features, pathophysiology, and treatment are essentially the same for both entities, distinguishing between definite MMD, probable MMD, and MMS may not have significant practical implications. Thus, the term *moyamoya phenomenon* or simply *moyamoya* can be used to refer to either of these pathologic entities.[6]

Epidemiology and Pathogenesis

Although it has been reported worldwide, MMD is most commonly seen in Asian countries and among people of Asian descent.[10,11] In Japan and Korea, the annual incidence of MMD varies from 0.4 to two per 100,000, and its prevalence varies from three to 10 per 100,000.[12-16] In contrast, the incidence in the US is less than 0.1 per 100,000 and is highest among Asian Americans.[11] Likewise, the incidence in Europe has been estimated at one-tenth of that in Japan.[17] Interestingly, in recent years, there has been a dramatic increase in hospital admissions for moyamoya in the US, as well as a rising trend in surgical revascularization for moyamoya, despite an overall decline in cerebrovascular bypass surgery.[18,19]

When it comes to age, moyamoya has a bimodal distribution, with a first peak in the first decade of life and a second peak in the fifth decade.[12,13,20,21] There is also clear female predominance, with a female-to-male ratio close to 2:1.[12,22,23] A family history of MMD increases the risk of developing the disease 30-to-40-fold. Roughly 10-15% of patients with MMD have a positive family history, the mode of inheritance appearing to be either polygenic or autosomal dominant with incomplete penetrance.[4,12,14]

Pathologic examination of stenotic vessels in MMD reveals hyperplasia of smooth muscle cells causing eccentric fibrocellular thickening of the intima with intraluminal thrombosis. In contrast, there is attenuation of the media with an irregular

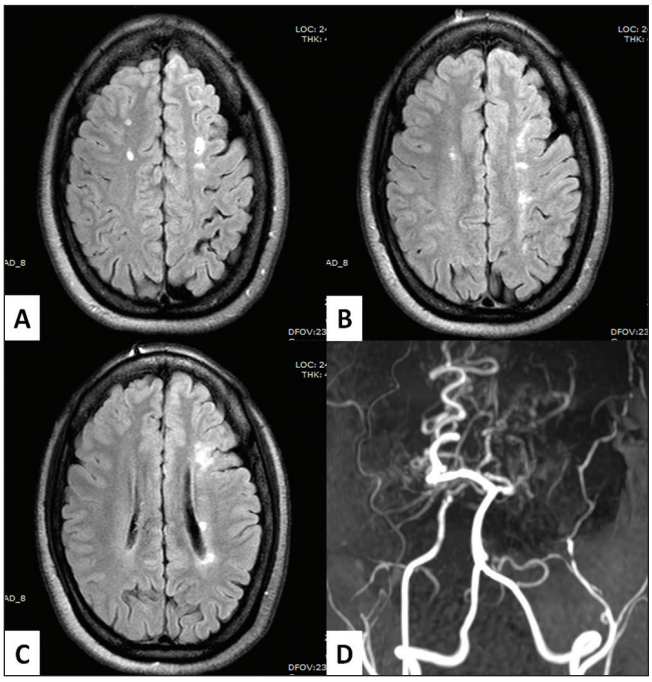

Figure 1. A 30-year-old woman presented with recurrent TIAs consisting of transient expressive aphasia. Brain MRI FLAIR reveals multiple chronic bihemispheric watershed infarcts, worse on the left side (A-C). MRA shows complete occlusion of the left ICA and severe stenosis of the intracranial right ICA (D).

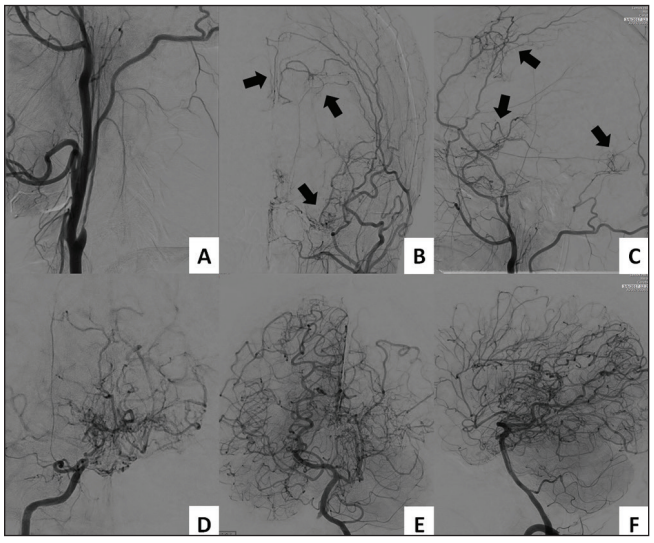

Figure 2. Same patient as in Figure 1. Lateral projection, cervical view DSA of the left common carotid artery (CCA) demonstrates adaptive narrowing of the cervical portion of the distally occluded left ICA (A). Anteroposterior (B) and lateral (C) projection DSA of the left CCA shows transdural anastomoses (arrows) from the inferolateral trunk and the transmastoid branch of the left occipital artery to the left MCA territory, and from the left middle meningeal artery to the bilateral ACA territories. No moyamoya vessels are seen. This is Suzuki stage VI disease. Anteroposterior projection DSA of the right ICA reveals occlusion of the supraclinoid right ICA, with distal reconstitution through prominent moyamoya collaterals (D). This is Suzuki stage III disease. Anteroposterior (E) and lateral (F) projection DSA of the left vertebral artery demonstrates asymmetric caudal regression of the basilar artery, retrograde opacification of the right ACA, leptomeningeal collaterals from the right PCA to the right MCA territory, and prominent moyamoya collaterals off the left PCA.

elastic lamina.[2,23,24] There are multiple genetic associations between MMD and specific chromosomal loci, the most promising of which (RNF 213 and TIMP-2) are located on chromosome 17.[4,25,26] Specifically, the TIMP-2 gene (tissue inhibitor of matrix metalloproteinase type 2) on chromosome 17q25 is a known regulator of vascular remodeling and angiogenesis.[26]

In fact, MMD is characterized by a heavily proangiogenic environment that contains high levels of growth factors and extracellular matrix peptides, including hypoxia-inducing factor 1α, vascular endothelial growth factor, basic fibroblast growth factor (bFGF), transforming growth factor-β1, hepatocyte growth factor, and matrix metalloproteinases (MMPs).[4,27-30]

Clinical Features

The two classic modes of moyamoya presentation are cerebral ischemia and intracranial hemorrhage (ICH).[5] As stenosis progresses in the distal ICA, cerebral perfusion pressure (CPP) drops, ultimately reaching values below the physiologic limits of cerebrovascular autoregulation. This results in reduced cerebral blood flow (CBF) and increased hemodynamic stress on circle of Willis and leptomeningeal collaterals. The ensuing cerebral ischemia induces a proangiogenic environment promoting the development of fragile moyamoya collaterals, which are prone to hemorrhage and hemodynamic failure.[5,31]

Ischemic stroke and TIA are the most common mode of presentation in both children and adults, representing 50-75% of cases.[4]

Given their frail cerebrovascular reserve (CVR), patients with moyamoya have very low tolerance for any sort of physiologic stress. Thus, cerebral ischemia can often be precipitated by such events, including dehydration, blood pressure fluctuations (e.g., general anesthesia for minor procedures), and excessive crying in children, which may lead to hyperventilation and hypocapnia.[4,22,32-34] ICH is a common presentation in adults, representing 20-50% of cases, but it only rarely affects children (2-3% of cases).[4,35] Intraparenchymal, intraventricular, and subarachnoid hemorrhage have all been reported. They are thought to result from rupture of the fragile moyamoya vessels, although hemodynamic stress-induced aneurysms may also develop in circle of Willis collaterals and eventually rupture.[4,5] In addition to ischemia and hemorrhage, individuals

with moyamoya may also present with seizures (probably ischemia-related) and headaches. The latter are thought to result from stimulation of dural nociceptors by pathologic transdural collaterals. Finally, movement disorders (chorea) and cognitive decline have been reported in children. Rather than ischemia, direct pressure on the basal ganglia by moyamoya vessels is believed to underlie choreiform movements in children.[4]

Radiologic Features

Although cerebral catheter angiography is considered the gold standard imaging modality for moyamoya, diagnosis can often be made solely on noninvasive imaging, such as magnetic resonance imaging and angiography (MRI and MRA) and computerized tomography angiography. To avoid radiation exposure, MRI and MRA are generally preferred in children. Cerebrovascular imaging, particularly catheter angiography, also provides an assessment of disease severity, associated intracranial aneurysms, and external carotid artery anatomy (transdural collaterals, surgical planning).[36,37]

While required for the diagnosis of "definite" MMD, moyamoya collaterals are not always angiographically visible. In fact, angiographic findings in moyamoya progress through six stages (I–VI) described by Suzuki and Takaku (Table 1).[1] Moyamoya vessels are not visible in stage I, start developing in stage II, become prominent in stages III and IV, then start regressing in stage V, before disappearing completely in stage VI. In addition to vascular imaging, CBF assessment is another essential component of moyamoya workup. Some of the available hemodynamic imaging modalities include single-photon emission computed tomography, positron emission tomography, CT perfusion, MR perfusion, and noninvasive optimal vessel analysis quantitative MRA (NOVA qMRA).

Hemodynamic imaging can also be performed after acetazolamide or carbon dioxide (CO_2) challenge. In patients with poor or no CVR, this will result in a steal phenomenon, given that cerebral arteries are already maximally dilated on the affected side. Patients with impaired CVR are generally those most likely to benefit from surgical revascularization.[32] In our practice, the standard workup for individuals with moyamoya includes cerebral angiography (or MRI/A in children), SPECT without and with acetazolamide challenge, and NOVA qMRA.

Treatment

Medical therapy has been used with some success in patients with mild and asymptomatic forms of moyamoya.[5] In the absence of ICH, antiplatelet therapy, particularly aspirin, is typically used for secondary stroke prevention. Likewise, factors that can precipitate cerebral infarction, such as hypotension, dehydration, hyperthermia, hypoxia, hypercapnia, hypocapnia, or anemia, should be strictly avoided in patients with impaired CVR.[4,22,33,34] This becomes particularly important in the setting of physiologic stress, such as after acute stroke or during and after surgery. Perioperative cerebral ischemia may complicate moyamoya-unrelated elective procedures and has been reported in up to 12% (mean, 4-5%) of patients after revascularization surgery.[38] In young children, it is essential to ensure excellent postoperative pain control, so that excessive crying, hyperventilation, and hypocapnia are avoided. Hypocapnia can induce cerebral vasoconstriction and precipitate infarction in patients with moyamoya.[4,31,33,34] Finally, calcium channel blockers (e.g., verapamil) can be used to relieve intractable headaches and reduce the frequency and severity of TIAs in well-selected individuals with moyamoya.[4,5,33]

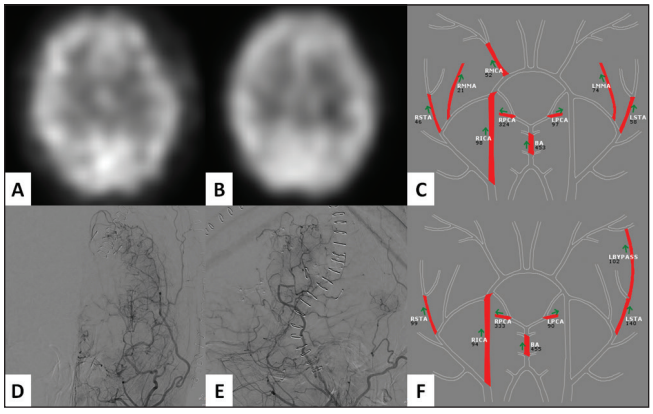

Figure 3. Same patient as in Figures 1 and 2. Brain SPECT at baseline (A) and after acetazolamide challenge (B) demonstrate perfusion asymmetry favoring the right hemisphere, significantly worse after acetazolamide challenge. This is indicative of poor CVR in the left hemisphere. Baseline NOVA Qmra (C). Arrows depict direction of blood flow, while numbers indicate corresponding flow rate in mL/min. Anteroposterior (D) and lateral (E) projection DSA of the left CCA, following combined direct-indirect surgical revascularization, reveals a patent STA-MCA bypass graft providing robust opacification of the MCA territory. Postoperative NOVA qMRA shows a very high flow rate of 102 mL/min in the bypass graft (F).

However, in more advanced forms of the disease, medical therapy becomes less effective. In one study, patients with symptomatic moyamoya had a 65% ipsilateral stroke risk at five years when treated medically, compared with only 17% in the surgically revascularized group.[39] Although a less aggressive natural history has been suggested by others,[40,42] and despite the lack of a conclusive randomized controlled trial it is generally well accepted that, for patients with ischemic symptoms, surgical revascularization is more beneficial than conservative management in terms of secondary stroke prevention.[39,42-45]

Conversely, in adult patients with hemorrhagic moyamoya, the role of surgical revascularization has long remained a matter of controversy.[35,46-49] Recently, however, the effectiveness of surgery in this patient population was established by the Japan Adult Moyamoya Trial. In fact, in this multicenter RCT, an

TABLE 1. THE SUZUKI STAGING SYSTEM[1,36]

Stage	Angiographic Findings
I	Narrowing of the carotid fork (i.e., ICA bifurcation)
II	Initiation of the moyamoya: continued narrowing of the ICA; dilation of the ACA and MCA; initial moyamoya blush
III	Intensification of the moyamoya: loss of proximal ACA and MCA; leptomeningeal collateralization from the PCA; increase in moyamoya blush
IV	Minimization of the moyamoya: progressive occlusion of ICA reaching origin of PCA; reduction in moyamoya blush
V	Reduction of the moyamoya: complete loss of ICA, ACA, and MCA; increased collateral supply from ECA; further reduction in moyamoya blush
VI	Disappearance of the moyamoya: disappearance of blood supply from ICA; blood supply exclusively from ECA; disappearance of moyamoya vessels

Abbreviations: ACA, anterior cerebral artery; ECA, external carotid artery; ICA, internal carotid artery, MCA, middle cerebral artery; PCA, posterior cerebral artery.

8.2% per year recurrent hemorrhage rate was observed in the medical arm, compared with only 3.2% per year in the surgical arm, a statistically significant difference.[35] In terms of surgical technique, there are three types of revascularization procedures: direct bypass, indirect revascularization, and combined techniques.

In the direct bypass, a donor vessel, most typically the superficial temporal artery (STA), is harvested, brought into direct contact, and anastomosed with a distal branch of the MCA (M3 or M4 segment), via a small frontotemporal craniotomy. In indirect revascularization, a vascularized extracranial or extradural tissue is brought into direct contact with the cerebral cortex and allowed to slowly form collaterals to the ischemic brain, over a period of weeks to months, driven by the proangiogenic moyamoya environment.[50,52]

Multiple variations of this procedure exist, depending on which exact tissue is being laid onto the brain. For instance, encephalo-duro-synangiosis, encephalo-myo-synangiosis, and encephalo-duro-arterio-synangiosis (EDAS) involve using the dura, temporalis muscle, and both dura and STA, respectively.[50] EDAS is probably the most commonly performed indirect procedure today.[50,52] Another technical variation, multiple burr hole placement, is also being increasingly used, given its versatility and high efficacy.[50,53-55] Indirect revascularization techniques are generally less technically challenging and less time-consuming than direct bypass, because they often do not involve temporary occlusion of a cerebral artery or direct microanastomosis.[45,50,52] In combined techniques, both direct bypass and indirect revascularization are performed concomitantly.

The main advantage of direct bypass is that it provides immediate flow augmentation and, thus, may provide protection against perioperative cerebral ischemia.[38,52,54,56,57] In contrast, indirect revascularization can be particularly valuable in patients with tiny cerebral arteries who are unsuitable for a direct anastomosis, particularly young children, and those without adequate donor vessels.[22,51,52,58]

Additionally, indirect revascularization is not associated with a postoperative risk of cerebral hyperperfusion, which has been reported in as many as 45% of patients undergoing direct bypass.[59-61] Combined techniques tend to offer the best of both worlds and, compared with STA-MCA bypass alone, provide improved ACA territory coverage.[38,57,59,62,63] Both direct and indirect techniques have been associated with excellent angiographic and clinical outcomes and minimal morbidity.[22,38,50-52,54,58,63]

In general, it is well accepted that both techniques are equally effective in children, possibly as a result of their high angiogenic activity after indirect revascularization.[50,64] For this reason, indirect procedures are often preferred in the pediatric population.[33,50,52] In contrast, direct or combined procedures usually lead to earlier and more robust angiographic collateralization and overall better clinical outcomes in adults.[38,45,52,65,66] In a recent meta-analysis, adults with moyamoya undergoing direct bypass had significantly higher rates of good angiographic outcome (89.6% vs. 52.8%) and lower rates of future stroke events (7.7% vs. 16.5%) compared with indirect revascularization, despite a trend toward more complications in this group (30.2% vs. 18.8%).[45]

In our practice, we favor the use of combined revascularization for all patients with moyamoya, whenever possible. We generally use both frontal and parietal branches of the STA to perform direct STA-MCA bypass and EDAS, respectively.[37] If a direct bypass is not feasible (e.g., young children, inadequately small vessels), we then perform an indirect EDAS procedure. We frequently add medial frontal and parietal burr holes whenever ACA territory coverage is a concern. ■

Timothy G. White, MD is a resident in the department of Neurosurgery at Lenox Hill Hospital and Hofstra Northwell School of Medicine in New York.

Julia R. Schneider, BS is a medical student at Lenox Hill Hospital and Hofstra Northwell School of Medicine.

Kay O. Kulason, BA is a medical student at Lenox Hill Hospital and Hofstra Northwell School of Medicine.

Ralph Rahme, MD is a neurosurgeon at Lenox Hill Hospital and Hofstra Northwell School of Medicine.

Kevin Kwan, MD is a resident in the Department of Neurosurgery at Lenox Hill Hospital and Hofstra Northwell School of Medicine.

Rafael A. Ortiz, MD is the Chief of Neuroendovascular Surgery and Interventional Neuroradiology at Lenox Hill Hospital and is an Associate Professor of Neurosurgery, Neurology, and Radiology at Hofstra Northwell School of Medicine.

David J. Langer, MD is Chairman of the Department of Neurosurgery at Lenox Hill Hospital and Hofstra Northwell School of Medicine.

1. Suzuki J, Takaku A. Cerebrovascular "moyamoya" disease. Disease showing abnormal net-like vessels in base of brain. Arch Neurol. 1969 Mar;20(3):288-299.
2. Kuroda S, Houkin K. Moyamoya disease: current concepts and future perspectives. Lancet Neurol. 2008 Nov;7(11):1056-1066.
3. Hayashi K, Horie N, Izumo T, Nagata I. A nationwide survey on unilateral moyamoya disease in Japan. Clin Neurol Neurosurg. 2014 Sep;124:1-5.
4. Scott RM, Smith ER. Moyamoya disease and moyamoya syndrome. N Engl J Med. 2009 Mar 19;360(12):1226-1237.
5. Rahme R, Crevier L, Dubois J, Mercier C. Moyamoya-like vasculopathy and Seckel syndrome: just a coincidence? Childs Nerv Syst. 2010 Jul;26(7):983-986.
6. Fujimura M, Tominaga T. Diagnosis of moyamoya disease: international standard and regional differences. Neurol Med Chir (Tokyo). 2015;55(3):189-193.
7. Lee SC, Jeon JS, Kim JE, et al. Contralateral progression and its risk factor in surgically treated unilateral adult moyamoya disease with a review of pertinent literature. Acta Neurochir (Wien). 2014 Jan;156(1):103-111.
8. Yeon JY, Shin HJ, Kong DS, et al. The prediction of contralateral progression in children and adolescents with unilateral moyamoya disease. Stroke. 2011 Oct;42(10):2973-2976.
9. Zhang Q, Wang R, Liu Y, et al. Clinical features and long-term outcomes of unilateral moyamoya disease. World Neurosurg. 2016 Dec;96:474-482.
10. Suzuki J, Kodama N. Moyamoya disease--a review. Stroke. 1983 Jan-Feb;14(1):104-109.
11. Uchino K, Johnston SC, Becker KJ, Tirschwell DL. Moyamoya disease in Washington State and California. Neurology. 2005 Sep 27;65(6):956-958.
12. Wakai K, Tamakoshi A, Ikezaki K, et al. Epidemiological features of moyamoya disease in Japan: findings from a nationwide survey. Clin Neurol Neurosurg. 1997 Oct;99(suppl 2):S1-5.
13. Baba T, Houkin K, Kuroda S. Novel epidemiological features of moyamoya disease. J Neurol Neurosurg Psychiatry. 2008 Aug;79(8):900-904.
14. Kuriyama S, Kusaka Y, Fujimura M, et al. Prevalence and clinicoepidemiological features of moyamoya disease in Japan: findings from a nationwide epidemiological survey. Stroke. 2008 Jan;39(1):42-47.
15. Im SH, Cho CB, Joo WI, et al. Prevalence and epidemiological features of moyamoya disease in Korea. J Cerebrovasc Endovasc Neurosurg. 2012 Jun;14(2):75-78.
16. Ahn IM, Park DH, Hann HJ, et al. Incidence, prevalence, and survival of moyamoya disease in Korea: a nationwide, population-based study. Stroke. 2014 Apr;45(4):1090-1095.
17. Yonekawa Y, Ogata N, Kaku Y, et al. Moyamoya disease in Europe, past and present status. Clin Neurol Neurosurg. 1997 Oct;99(suppl 2):S58-60.
18. Rahme R, Jimenez L, Ringer AJ, et al. Hospital admissions for moyamoya disease are dramatically increasing: survey of nationwide inpatient sample database 1994-2009. 2012 American Association of Neurological Surgeons Annual Meeting, Miami, FL, USA, April 2012.
19. White TG, O'Donnell D, Rosenthal J, et al. Trends in cerebral revascularization in the era of pipeline and carotid occlusion surgery study. World Neurosurg. 2016 Jul;91:285-296.
20. Han DH, Nam DH, Oh CW. Moyamoya disease in adults: characteristics of clinical presentation and outcome after encephalo-duro-arterio-synangiosis. Clin Neurol Neurosurg. 1997 Oct;99(suppl 2):S151-5.
21. Han DH, Kwon OK, Byun BJ, et al. Korean society for cerebrovascular disease. 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(11):1263-1274.
22. Scott RM, Smith JL, Robertson RL, et al. Long-term outcome in children with moyamoya syndrome after cranial revascularization by pial synangiosis. J Neurosurg. 2004 Feb;100(2 Suppl Pediatrics):142-149.
23. Takagi Y, Kikuta K, Sadamasa N, et al. Caspase-3-dependent apoptosis in middle cerebral arteries in patients with moyamoya disease. Neurosurgery. 2006 Oct;59(4):894-900; discussion 900-901.
24. 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 Jan;47(1):1-4.
25. Kamada F, Aoki Y, Narisawa A, et al. A genome-wide association study identifies RNF213 as the first Moyamoya disease gene. J Hum Genet. 2011 Jan;56(1):34-40.
26. 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 Aug;3(3):237-245.
27. Yoshimoto T, Houkin K, Takahashi A, Abe H. Angiogenic factors in moyamoya disease. Stroke. 1996 Dec;27(12):2160-2165.
28. Malek AM, Connors S, Robertson RL, et al. Elevation of cerebrospinal fluid levels of basic fibroblast growth factor in moyamoya and central nervous system disorders. Pediatr Neurosurg. 1997 Oct;27(4):182-189.
29. Nanba R, Kuroda S, Ishikawa T, et al. Increased expression of hepatocyte growth factor in cerebrospinal fluid and intracranial artery in moyamoya disease. Stroke. 2004 Dec;35(12):2837-2842.
30. 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 Feb;60(2):338-345.
31. Lee M, Zaharchuk G, Guzman R, et al. Quantitative hemodynamic studies in moyamoya disease: a review. Neurosurg Focus. 2009 Apr;26(4):E5.
32. Nomura S, Kashiwagi S, Uetsuka S, et al. Perioperative management protocols for children with moyamoya disease. Childs Nerv Syst. 2001 Apr;17(4-5):270-274.
33. Roach ES, Golomb MR, Adams R, et al. American Heart Association Stroke Council; Council on Cardiovascular Disease in the Young. Management of stroke in infants and children: a scientific statement from a special writing group of the American Heart Association Stroke Council and the Council on Cardiovascular Disease in the Young. Stroke. 2008 Sep;39(9):2644-2691.
34. Parray T, Martin TW, Siddiqui S. Moyamoya disease: a review of the disease and anesthetic management. J Neurosurg Anesthesiol. 2011 Apr;23(2):100-109.
35. Miyamoto S, Yoshimoto T, Hashimoto N, et al. Effects of extracranial-intracranial bypass for patients with hemorrhagic moyamoya disease: results of the Japan Adult Moyamoya Trial. Stroke. 2014 May;45(5):1415-1421.
36. Bacigaluppi S, Dehdashti AR, Agid R, et al. The contribution of imaging in diagnosis, preoperative assessment, and follow-up of moyamoya disease: a review. Neurosurg Focus. 2009 Apr;26(4):E3.
37. Nossek E, Langer DJ. How I do it: combined direct (STA-MCA) and indirect (EDAS) EC-IC bypass. Acta Neurochir (Wien). 2014 Nov;156(11):2079-2084.
38. Kazumata K, Ito M, Tokairin K, et al. The frequency of postoperative stroke in moyamoya disease following combined revascularization: a single-university series and systematic review. J Neurosurg. 2014 Aug;121(2):432-440.
39. Hallemeier CL, Rich KM, Grubb RL Jr, et al. Clinical features and outcome in North American adults with moyamoya phenomenon. Stroke. 2006 Jun;37(6):1490-1496.
40. Chiu D, Shedden P, Bratina P, Grotta JC. Clinical features of moyamoya disease in the United States. Stroke. 1998 Jul;29(7):1347-1351.
41. Derdeyn CP, Zipfel GJ, Zazulia AR, et al. Baseline hemodynamic impairment and future stroke risk in adult idiopathic moyamoya phenomenon: results of a prospective natural history study. Stroke. 2017 Apr;48(4):894-899.
42. Fung LW, Thompson D, Ganesan V. Revascularisation surgery for paediatric moyamoya: a review of the literature. Childs Nerv Syst. 2005 May;21(5):358-364.
43. Lee SB, Kim DS, Huh PW, et al. Long-term follow-up results in 142 adult patients with moyamoya disease according to management modality. Acta Neurochir (Wien). 2012 Jul;154(7):1179-1187.
44. Kim T, Oh CW, Kwon OK, et al. Stroke prevention by direct revascularization for patients with adult-onset moyamoya disease presenting with ischemia. J Neurosurg. 2016 Jun;124(6):1788-1793.
45. Jeon JP, Kim JE, Cho WS, et al. Meta-analysis of the surgical outcomes of symptomatic moyamoya disease in adults. J Neurosurg. 2017 May 5:1-7.
46. Aoki N. Cerebrovascular bypass surgery for the treatment of moyamoya disease: unsatisfactory outcome in the patients presenting with intracranial hemorrhage. Surg Neurol. 1993 Nov;40(5):372-377.
47. 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 Sep;93(3):397-401.
48. Liu X, Zhang D, Shuo W, et al. Long-term outcome after conservative and surgical treatment of haemorrhagic moyamoya disease. J Neurol Neurosurg Psychiatry. 2013 Mar;84(3):258-265.
49. Derdeyn CP. Direct bypass reduces the risk of recurrent hemorrhage in moyamoya syndrome, but effect on functional outcome is less certain. Stroke. 2014 May;45(5):1245-1246.
50. Patel NN, Mangano FT, Klimo P Jr. Indirect revascularization techniques for treating moyamoya disease. Neurosurg Clin N Am. 2010 Jul;21(3):553-563.
51. Dusick JR, Gonzalez NR, Martin NA. Clinical and angiographic outcomes from indirect revascularization surgery for moyamoya disease in adults and children: a review of 63 procedures. Neurosurgery. 2011 Jan;68(1):34-43.
52. Liu J, Steinberg G. Direct versus indirect bypass for moyamoya disease. Neurosurg Clin N Am. 2017 Jul;28(3):361-374.
53. Sainte-Rose C, Oliveira R, Puget S, et al. Multiple bur hole surgery for the treatment of moyamoya disease in children. J Neurosurg. 2006 Dec;105(6 suppl):437-443.
54. McLaughlin N, Martin NA. Effectiveness of burr holes for indirect revascularization in patients with moyamoya disease—a review of the literature. World Neurosurg. 2014 Jan;81(1):91-98.
55. Blauwblomme T, Mathon B, Naggara O, et al. Long-term outcome after multiple burr hole surgery in children with moyamoya angiopathy: a single-center experience in 108 hemispheres. Neurosurgery. 2017 Jun 1;80(6):950-956.
56. Czabanka M, Peña-Tapia P, Scharf J, et al. Characterization of direct and indirect cerebral revascularization for the treatment of European patients with moyamoya disease. Cerebrovasc Dis. 2011;32(4):361-369.
57. Teo MK, Madhugiri VS, Steinberg GK. Editorial: direct versus indirect bypass for moyamoya disease: ongoing controversy. J Neurosurg. 2017 May;126(5):1520-1522.
58. Guzman R, Lee M, Achrol A, et al. Clinical outcome after 450 revascularization procedures for moyamoya disease. Clinical article. J Neurosurg. 2009 Nov;111(5):927-935.
59. Fujimura M, Niizuma K, Inoue T, et al. Minocycline prevents focal neurological deterioration due to cerebral hyperperfusion after extracranial-intracranial bypass for moyamoya disease. Neurosurgery. 2014 Feb;74(2):163-170.
60. Seo H, Ryu HG, Son JD, et al. Intraoperative dexmedetomidine and postoperative cerebral hyperperfusion syndrome in patients who underwent superficial temporal artery-middle cerebral artery anastomosis for moyamoya disease: A retrospective observational study. Medicine (Baltimore). 2016 Dec;95(52):e5712.
61. Uchino H, Nakayama N, Kazumata K, et al. Edaravone reduces hyperperfusion-related neurological deficits in adult moyamoya disease: historical control study. Stroke. 2016 Jul;47(7):1930-1932.
62. Kuroda S. Cerebrovascular disease: New data on surgical therapy for pediatric moyamoya disease. Nat Rev Neurol. 2010 May;6(5):242-243.
63. Cho WS, Kim JE, Paeng JC, et al. Can combined bypass surgery at middle cerebral artery territory save anterior cerebral artery territory in adult moyamoya disease? Neurosurgery. 2017 Mar 1;80(3):431-438.
64. Veeravagu A, Guzman R, Patil CG, et al. Moyamoya disease in pediatric patients: outcomes of neurosurgical interventions. Neurosurg Focus. 2008;24(2):E16.
65. Starke RM, Komotar RJ, Connolly ES. Optimal surgical treatment for moyamoya disease in adults: direct versus indirect bypass. Neurosurg Focus. 2009 Apr;26(4):E8.
66. Macyszyn L, Attiah M, Ma TS, et al. Direct versus indirect revascularization procedures for moyamoya disease: a comparative effectiveness study. J Neurosurg. 2017 May;126(5):1523-1529.