comparison with the OSIRIS program between the direct and indirect revascularization modalities in adult moyamoya disease. Neurosurgery 70: 625-632, 2012.

11. Fujimura M, Inoue T, Shimizu H, Saito A, Mugikura S, Tominaga T. Efficacy of prophylactic blood pressure lowering according to a standardized postoperative management protocol to prevent symptomatic cerebral hyperperfusion after direct revascularization surgery for moyamoya disease. Cerebrovasc Dis 33: 436-445, 2012
12. Kim DS, Huh PW, Kim HS, Kim IS, Choi S, Mok JH, Huh CW. Surgical treatment of moyamoya disease in adults: combined direct and indirect vs. indirect bypass surgery. Neurol Med Chir (Tokyo) 52: 333-338, 2012
13. Matsushima Y, Aoyagi M, Suzuki R, Tabata H, Ohno K. Perioperative complications of encephalo-duro-arterio synangiosis: prevention and treatment. Surg Neurol 36: 343-353, 1991
14. Choi JU, Kim DS, Kim EY, Lee KC. Natural history of moyamoya disease: comparison of activity of daily living in surgery and non surgery group. Clin Neurol Neurosurg 99 Suppl 2: S11-18, 1997
15. Kim SK, Seol HJ, Cho BK, Hwang YS, Lee DS, Wang KC. Moyamoya disease among young patients: its aggressive clinical course and the role of active surgical treatment. Neurosurgery 54: 840-846, 2004
16. Starke RM, Komotar RJ, Hickman ZL, Paz YE, Pugliese AG, Otten ML, Garrett MC, Elkind MS, Marshall RS, Festa JR, Meyers PM, Connolly ES Jr. Clinical features, surgical treatment, and long-term outcome in adult patients with moyamoya disease. Clinical article. J Neurosurg 111: 936-942, 2009
17. Hyun SJ, Kim JS, Hong SC. Prognostic factors associated with perioperative ischemic complications in adult-onset moyamoya disease. Acta Neurochir (Wien) 152: 1181-1188, 2010
18. Kim SK, Cho BK, Phi JH, Lee JY, Chae JH, Kim KJ, Hwang YS, Kim IO, Lee DS, Lee J, Wang KC. Pediatric Moyamoya Disease: An Analysis of 410 Consecutive Cases. Ann Neurol 68: 92-101, 2010
19. 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 68: 34-43, 2011
20. Kim SH, Choi JU, Yang KH, Kim TG, Kim DS. Risk factors for postoperative ischemic complications in patients with moyamoya disease. J Neurosurg 103: 433-438, 2005

21. Duan L, Bao XY, Yang WZ, Shi WC, Li DS, Zhang ZS, Zong R, Han C, Zhao F, Feng J. Moyamoya disease in China: its clinical features and outcomes. Stroke 43: 56-60, 2012
22. Ng J, Thompson D, Lumley JP, Saunders DE, Ganesan V. Surgical revascularisation for childhood moyamoya. Childs Nerv Syst 28: 1041-1048, 2012
23. Bao XY, Duan L, Li DS, Yang WZ, Sun WJ, Zhang ZS, Zong R, Han C. Clinical features, surgical treatment and long-term outcome in adult patients with Moyamoya disease in China. Cerebrovasc Dis 34: 305-313, 2012
24. Iwama T, Hashimoto N, Tsukahara T, Murai B. Peri-operative complications in adult moyamoya disease. Acta Neurochir (Wien) 132: 26-31, 1995
25. Iwama T, Hashimoto N, Yonekawa Y. The relevance of hemodynamic factors to perioperative ischemic complications in childhood moyamoya disease. Neurosurgery 38: 1120-1126, 1996
26. Mesiwala AH, Sviri G, Fatemi N, Britz GW, Newell DW. Long-term outcome of superficial temporal artery-middle cerebral artery bypass for patients with moyamoya disease in the US. Neurosurg Focus 24: E15, 2008
27. Guzman R, Lee M, Achrol A, Bell-Stephens T, Kelly M, Do HM, Marks MP, Steinberg GK. Clinical outcome after 450 revascularization procedures for moyamoya disease. Clinical article. J Neurosurg 111: 927-935, 2009
28. Fujimura M and Tominaga T. Lessons Learned From Moyamoya Disease: Outcome of Direct/Indirect Revascularization Surgery For 150 Affected Hemispheres. Neurol Med Chir (Tokyo) 52: 327-332, 2012
29. Shimoda Y, Fujimura M, Inoue T, Shimizu H, Tominaga T. Temporal Profile of De Novo Development of Moymoya Vasculopathy in an Adult-Case Report. Neurol Med Chir (Tokyo) 52: 339-342, 2012
30. 佐々木貴史、藤村幹、赤松洋祐、木村尚人、江面正幸、上之原広司、明城光三、冨永悌二. 周産期に進行性脳梗塞にて発症し両側頭蓋外内血行再建術を行った もやもや病合併妊娠の1例. 脳神経外科 40: 1095-1099, 2012
31. 藤村幹、冨永悌二. もやもや病術後の過灌流：診断と治療. 脳循環代謝 23: 114-119, 2012
32. 藤村幹、清水宏明、井上敬、斉藤敦志、冨永悌二. 周術期管理指針に基づいたもやもや病に対する血行再建術：急性期脳血流評価と予防的降圧の効果と限界. 脳卒中の外科 40: 83-88, 2012
33. Nakagawara J: Iomazenil SPECT (BZP- Receptor). Moyamoya Disease

Update, Springer, Tokyo, pp. 189-196, 2010

34. Nakagawara J, Osato T, Kamiyama K, et al: Diagnostic imaging of higher brain dysfunction in patients with adult moyamoya disease using statistical imaging analysis for ^{123}I-IMZ SPECT. Neurologia medico-chirurgica 52: 318-326, 2012
35. Kobayashi H, Yamazaki S, Takashima S, Liu W, Okuda H, Yan J, Fujii Y, Hitomi T, Harada KH, Habu T, Koizumi A Ablation of Rnf213 retards progression of diabetes in the Akita mouse. *Biochem Biophys Res Commun.* 432(3):519-525, 2013
36. Koizumi A, Kobayashi H, Liu W, Fujii Y, Senevirathna ST, Nanayakkara S, Okuda H, Hitomi T, Harada KH, Takenaka K, Watanabe T, Shimbo S. P.R4810K, a polymorphism of RNF213, the susceptibility gene for moyamoya disease, is associated with blood pressure. *Environ. Health Prev. Med.* 18(2):121-9, 2013
37. 小林果, 人見敏明, 小泉昭夫 もやもや病感受性遺伝子の特定 *BioClinica.* 28巻1号 87-91, 2013
38. Yan JX, Takahashi T, Ohura T, Adachi A, Takahashi I, Ogawa E, Okuda H, Kobayashi H, Hitomi T, Liu WY, Harada KH, Koizumi A Combined linkage analysis and exome sequencing identifies novel genes for familial goiter. *J Hum Genet.* in press
39. Kuroda S, Hashimoto N, Yoshimoto T, Iwasaki Y: Radiological findings, clinical course and outcome in asymptomatic moyamoya disease: Results of multi-center survey in Japan. Stroke 38:1430-1435, 2007
40. 川合かがり、黒田 敏、川堀真人、中山若樹、寺坂俊介、岩崎喜信：病期が進行した無症候性成人もやもや病に対する脳血行再建術—2例報告。脳外 38:825-830, 2010
41. Kawabori M, Kuroda S, Nakayama N, Hirata K, Shiga T, Houkin K, Tamaki N. Effective Surgical Revascularization Improves Cerebral Hemodynamics and Resolves Headache in Pediatric Moyamoya Disease. World Neurosurg. 2012 Sep 25. [Epub ahead of print]
42. Mikami T, Sugino T, Ohtaki S, Houkin K, Mikuni N. Diagnosis of Moyamoya Disease on Magnetic Resonance Imaging: Are Flow Voids in the Basal Ganglia an Essential Criterion for Definitive Diagnosis? J Stroke Cerebrovasc Dis. 2012 Aug 29. [Epub ahead of print]
43. Houkin K, Ito M, Sugiyama T, Shichinohe H, Nakayama N, Kazumata K, Kuroda S. Review of past research and current concepts on the etiology of moyamoya disease. Neurol Med Chir (Tokyo). 2012;52(5):267-77.

44. Kuroda S, Houkin K. Bypass surgery for moyamoya disease: concept and essence of sugical techniques. Neurol Med Chir (Tokyo). 2012;52(5):287-94.
45. Uchino H, Kuroda S, Hirata K, Shiga T, Houkin K, Tamaki N. Predictors and clinical features of postoperative hyperperfusion after surgical revascularization for moyamoya disease: a serial single photon emission CT/positron emission tomography study. Stroke. 2012 Oct;43(10):2610-6.
46. Kuroda S, Kashiwazaki D, Ishikawa T, Nakayama N, Houkin K. Incidence, locations, and longitudinal course of silent microbleeds in moyamoya disease: a prospective t2*-weighted MRI study. Stroke. 2013 Feb;44(2):516-8.
47. Hokari M, Kuroda S, Simoda Y, Uchino H, Hirata K, Shiga T, Nakayama N, Houkin K, Tamaki N. Transient crossed cerebellar diaschisis due to cerebral hyperperfusion following surgical revascularization for moyamoya disease: case report. Neurol Med Chir (Tokyo). 2012;52(5):350-3.
48. Uchino H, Nakamura T, Houkin K, Murata JI, Saito H, Kuroda S. Semiquantitative analysis of indocyanine green videoangiography for cortical perfusion assessment in superficial temporal artery to middle cerebral artery anastomosis. Acta Neurochir (Wien). 2013 Jan 4. [Epub ahead of print]
49. Kawabori M, Yoshimoto T, Ito M, Fujimoto S, Mikami T, Muraki M, Kaneko S, Nakayama N, Kuroda S, Houkin K. Spontaneous echo contrast and thrombus formation at the carotid bifurcation after carotid endarterectomy. Neurol Med Chir (Tokyo). 2012;52(12):885-91.
50. Small but severe residual hypoperfusion relates to symptomatic hemorrhage even after early perfusion improvement in tissue plasminogen activator therapy. Cerebrovasc Dis. 2012;34(5-6):446-7.
51. Abumiya T, Katoh M, Moriwaki T, Yoshino M, Aoki T, Imamura H, Aida T, Nakayama N, Houkin K. Long-term clinical and radiological results of endovascular internal trapping in vertebral artery dissection. Kashiwazaki D, Ushikoshi S, Asano T, Kuroda S, Houkin K. Neuroradiology. 2013 Feb;55(2):201-6.
52. Kurisu K, Kawabori M, Niiya Y, Ohta Y, Nakayama N, Kuroda S, Mabuchi S, Houkin K. Experience of (123)I-iomazenil SPECT study for crossed cerebellocerebral diaschisis: report of two cases. Clin Neurol Neurosurg. 2012 Nov;114(9):1274-6.
53. Miyamoto M, Kuroda S, Zhao S, Magota K, Shichinohe H, Houkin K, Kuge Y, Tamaki N. Bone marrow

stromal cell transplantation enhances recovery of local glucose metabolism after cerebral infarction in rats: a serial 18F-FDG PET study. J Nucl Med. 2013 Jan;54(1):145-50.

54. Ito M, Kuroda S, Sugiyama T, Maruichi K, Kawabori M, Nakayama N, Houkin K, Iwasaki Y. Transplanted bone marrow stromal cells protect neurovascular units and ameliorate brain damage in stroke-prone spontaneously hypertensive rats. Neuropathology. 2012 Oct;32(5):522-33.
55. Kawabori M, Kuroda S, Ito M, Shichinohe H, Houkin K, Kuge Y, Tamaki N. Timing and cell dose determine therapeutic effects of bone marrow stromal cell transplantation in rat model of cerebral infarct. Neuropathology. 2012 Jun 21. [Epub ahead of print]
56. Kuroda S, Houkin K: Bypass surgery for moyamoya disease – Concept and essence of surgical technique –. Neurol Med Chir (Tokyo) 52:287-294, 2012
57. Houkin K, Ito M, Sugiyama T, Shichinohe H, Nakayama N, Kazumata K, Kuroda S: Review of past research and current concepts on the etiology of moyamoya disease. Neurol Med Chir (Tokyo) 52:267-277, 2012
58. Hokari M, Kuroda S, Shimoda Y, Uchino H, Hirata K, Shiga T, Nakayama N, Houkin K, Tamaki N: Transient crossed cerebellar diaschisis due to cerebral hyperperfusion following surgical revascularization for moyamoya disease. Neurol Med Chir (Tokyo) 52:350-353, 2012
59. Uchino H, Kuroda S, Hirata K, Shiga T, Houkin K, Tamaki N: Predictors and clinical features of postoperative hyperperfusion after surgical revascularization for moyamoya disease – A serial SPECT/PET study. Stroke 43:2610-2616, 2012
60. Kawabori M, Kuroda S, Nakayama N, Hirata K, Shiga T, Houkin K, Tamaki N: Effective surgical revascularization improves cerebral hemodynamics and resolves headache in pediatric moyamoya disease. World Neurosurgery 2012 Sept 25 [Epub ahead of print]
61. Kuroda S, Kashiwazaki D, Ishikawa T, Nakayama N, Houkin K: Incidence, locations, and longitudinal course of silent microbleeds in moyamoya disease – A prospective T2*-weighted MRI study. Stroke 44:516-518, 2013
62. Uchino H, Nakamura T, Houkin K, Murata J, Saito H, Kuroda S: Semi-quantitative analysis of indocyanine green videoangiography for cortical perfusion assessment in superficial temporal artery to middle cerebral artery anastomosis. Acta

Neurochir (Wien) 2013 Jan 4 [Epub ahead of print]

63. 黒田　敏、杉山　拓、川堀真人、笹森徹、栗栖宏多、内野晴登、七戸秀夫、中山若樹、宝金清博：もやもや病の病態、診断と治療—最近の知見と今後の課題。脳卒中の外科40:77-82, 2012
64. 黒田　敏、浜田秀雄、黒崎邦和、柏崎大奈、秋岡直樹、桑山直也：小児もやもや病の外科治療と周術期管理—最近の知見と課題。脳外誌（*in press*）
65. 黒田　敏、宝金清博：小児もやもや病の外科治療—より良好な長期予後のために。小児の脳神経（*in press*）
66. 黒田　敏、AMORE Study Group：無症候性もやもや病の予後と治療法の確立をめざした多施設共同研究—AMORE研究について。脳卒中の外科（*in press*）
67. Nakagawara J, Osato T, Kamiyama K, Honjo K, Sugio H, Hironori Fumoto K, Murahashi T, Takada H, Watanabe T, and Nakamura H: Diagnostic imaging of higher brain dysfunction in patients with adult moyamoya disease using statistical imaging analysis for ^{123}I-IMZ SPECT. Neurologia medico-chirurgica 52: 318-326, 2012
68. 中川原譲二、上山憲司、高橋正昭、森大輔、野呂秀策、中村博彦: 軽症頭部外傷例の高次脳機能障害と123I-Iomazenil SPECTのよる局在診断. 日職災医誌60: 199-205, 2012
69. 中川原譲二: 脳血管障害（JETなど）. 最新脳SPECT/PETの臨床, メジカルビュー社, 東京, pp176-180, 2012
70. 中川原譲二：脳血流測定機器の最新事情（PET、SPECTなど）. 脳神経外科速報22：788-796,2012

IV. 研究班構成員名簿

①研究者名	②分担する研究項目	③最終卒業校・卒業年次・学位及び専攻科目	④所属研究機関及び現在の専門（研究実施場所）	⑤所属研究機関における職名
橋本信夫	総括	京都大学医学部、昭和48年卒、医学博士、脳神経外科学	国立循環器病研究センター	総長
寶金清博	小児もやもや病に対する急性期治療およびもやもや病に対する再生治療の検討	北海道大学医学部、昭和54年卒、医学博士、脳神経外科学	北海道大学医学研究科脳神経外科	教授
冨永悌二	もやもや病ガイドラインの出版と更新	東北大学医学部、昭和57年卒、医学博士、脳神経外科学	東北大学大学院医学系研究科神経外科学神経科学	教授
宮本享	JAM trialおよびもやもや病の妊娠出産管理	京都大学医学部、昭和57年卒、医学博士、脳神経外科学	京都大学医学研究科脳神経外科	教授
鈴木則宏	もやもや病疫学画像データベース作成と更新	慶応義塾大学医学部、昭和52年卒、医学博士、神経内科	慶応義塾大学医学部神経内科学	教授
中川原譲二	もやもや病における高次脳機能診断とIMZ-SPECT	札幌医科大学、昭和53年卒、脳神経外科	中村記念病院脳神経外科	診療本部長
小泉昭夫	家族性もやもや病の遺伝子解析と原因遺伝子解析	東北大学医学部、昭和53年卒、医学博士、公衆衛生学	京都大学医学研究科社会医学系環境衛生学分野	教授
黒田敏	無症候性もやもや病	北海道医学部、昭和61年卒、医学博士、脳神経外科	富山大学医学研究科脳神経外科	教授

Neurol Med Chir (Tokyo) 52, 287～294, 2012

Bypass Surgery for Moyamoya Disease
—Concept and Essence of Surgical Techniques—

Satoshi KURODA[1] and Kiyohiro HOUKIN[1]

[1]Department of Neurosurgery, Hokkaido University Hospital, Sapporo, Hokkaido

Abstract

This review describes the basic concepts of surgical revascularization for moyamoya disease, including direct and indirect bypass surgery. Direct bypass surgery can improve cerebral hemodynamics and reduce further ischemic events immediately after surgery, but may be technically challenging in some pediatric patients. Indirect bypass surgery is simple and has widely been used. However, its beneficial effects can be achieved 3 to 4 months after surgery, and surgical design is quite important to determine the extent of surgical collateral pathways. Combined bypass procedure, especially superficial temporal artery (STA) to middle cerebral artery anastomosis and indirect bypass, encephalo-duro-myo-arterio-pericranial synangiosis, is a safe and effective option to improve the short- and long-term outcome in patients with moyamoya disease. Alternative techniques are also described for specific cases with profound cerebral ischemia in the anterior cerebral artery or posterior cerebral artery territory. Special techniques to safely complete bypass surgery and avoid perioperative complications are presented, including methods to prevent delayed wound healing, to avoid facial nerve palsy after surgery, and to preserve the STA and middle meningeal artery during skin incision and craniotomy. Finally, the importance of careful management of patients is emphasized to reduce the incidence of perioperative complications, including ischemic stroke and hyperperfusion syndrome.

Key words: moyamoya disease, bypass surgery, surgical technique, direct bypass, indirect bypass

Introduction

Moyamoya disease is an uncommon cerebrovascular disorder that is characterized by progressive occlusion of the supraclinoid internal carotid artery (ICA) and its main branches within the circle of Willis. This occlusion results in the formation of a fine vascular network (moyamoya vessels) at the base of the brain.[46] The predominant feature of the pathology of moyamoya disease is now known to be progressive stenosis of the carotid artery terminations, and the moyamoya vessels are the dilated perforating arteries that function as collateral pathways.[2] Recent studies have rapidly expanded our knowledge of the basic and clinical aspects of moyamoya disease, including the etiology, pathophysiology, surgical treatment, and long-term prognosis of the disorder.[49] In particular, various types of bypass surgery have been developed and are known to improve the long-term outcome in patients with moyamoya disease.[3-5,9,13,14,31,33,38,40,44] However, further understanding of the pathophysiology, diagnosis, and treatments of this disease is needed to improve the long-term outcome for these patients.[22]

In this article, we review recent surgical advances in the treatment of moyamoya disease. Special points of surgical techniques are precisely described. Surgical techniques for specific cases are also presented. Finally, the importance of perioperative management of patients with moyamoya disease is emphasized to reduce the incidence of perioperative complications during and after surgical revascularization.

Superficial Temporal Artery to Middle Cerebral Artery (STA-MCA) Anastomosis and Encephalo-duro-myo-arterio-pericranial Synangiosis (EDMAPS)—Standard, Tips, and Tricks

As we recently reported, STA-MCA anastomosis

Received December 8, 2011; Accepted January 11, 2012
Author's present address: S. Kuroda, MD, PhD, Department of Neurosurgery, Faculty of Medicine, University of Toyama, Toyama, Toyama, Japan.

and EDMAPS are safe and feasible surgical procedures for pediatric and adult patients with moyamoya disease. These procedures include direct STA-MCA anastomosis and indirect synangiosis. Combined bypass can provide the advantages of both direct and indirect bypass procedures. Clinical results were described previously. Briefly, overall incidences of mortality and morbidity in 123 operations for 75 patients were 0% and 5.7%, respectively. The annual risk of cerebrovascular events during follow-up periods was very low, at 0% in pediatric patients and 0.4% in adults over about 67 months.[24] Here we discuss the theoretical basis and surgical techniques of direct and indirect bypass procedures separately.

Direct Bypass Procedure

Direct bypass is useful to improve cerebral hemodynamics and to resolve ischemic attacks immediately after surgery. The frequency of perioperative ischemic stroke is lower after direct or combined bypass than after indirect bypass.[9] Surgery can be technically challenging in a certain subgroup of pediatric patients, because their cortical branches have smaller diameters and are more fragile than those of adults. Therefore, thorough surgical training in vessel anastomosis is essential. To safely complete direct bypass procedures, the following techniques are quite important. First, complete hemostasis of the entire surgical route, including the scalp, muscle, cranium, and dura mater, is essential to prevent disturbance of fine manipulations during the procedures. Elimination of cerebrospinal fluid from the operative field also facilitates direct bypass procedures. Second, clear visualization of the orifice of arteriotomy by staining blue with methylrosaniline chloride (pyoctaninum blue) is quite useful. Blue silicone rubber should be placed beneath the recipient artery to clearly visualize the semi-translucent recipient vessel, especially in pediatric patients.[12] Our personal experience suggests that these preparations enable safe STA-MCA anastomosis even in a one-year-old baby (Fig. 1).

Although the incidence of ischemic stroke is lower after direct or combined bypass surgery, recent clinical studies have clarified that careful management of patients is quite important to avoid perioperative complications after bypass surgery because pronounced postoperative changes in cerebral hemodynamics may induce hyperperfusion syndrome, particularly in patients with profound ischemia before surgery.[1] Dramatic postoperative changes in cerebral hemodynamics may also cause rapid diminishment of the basal moyamoya vessels and lead to transient cheiro-oral syndrome or small frontal lobe infarction.[26,42] Therefore, pre- and postoperative blood flow studies can be important to identify and prevent such serious complications after direct or combined bypass surgery.

Moyamoya disease is often associated with altered cerebral hemodynamics in the frontal lobe, including the territory of the anterior cerebral artery (ACA).[26,39,47] However, direct STA-ACA anastomosis is not always essential in all patients with moyamoya disease,[10,11] probably because the surgical collaterals to the MCA territory may also provide blood flow to the ACA territory through the pial anastomosis. Thus, the collateral blood flow may be redistributed after surgery.[25,39] However, direct STA-ACA anastomosis is essential in specific patients with pronounced ischemia in the ACA territory, although the number of such cases may be rather small. The frontal branch of STA should be dissected from the scalp to as great a length as possible, which enables easier handling during STA-ACA anastomosis.[10,17] The frontal branch of STA can be anastomosed to the cortical branch of ACA close to the midline with the usual technique, but the direct bypass procedure should be performed more carefully, because the calibers of both donor and recipient vessels are often smaller than the usual situation in STA-MCA anastomosis (Fig. 2). Postoperative angiography and blood flow studies show improvement or normalization of the cerebral hemodynamics in the involved ACA territory.[10,17]

The posterior cerebral artery (PCA) is also involved in a certain subgroup of patients with moyamoya disease, and PCA lesions can be observed in approximately 25% to 60% of cases.[27,34,35,37,43] These patients are considered at higher risk for subsequent ischemic stroke, because the PCA functions as an important collateral route to the ICA territory in moyamoya disease. Some patients are known to develop cerebral infarction in the occipital lobe or temporo-occipital lobe at initial presentation. Surgical revascularization should be planned for both the ICA and PCA territories in these patients.[27,34,35,37,43] We have developed one-stage bypass surgery that can provide extensive collateral blood flow to the entire hemisphere, as reported elsewhere.[28] Briefly, the technique includes STA-MCA anastomosis targeted to the angular artery and indirect bypass through large craniotomy extended from the frontal to the temporo-parietal area. Follow-up cerebral angiography reveals that surgical collaterals supplied blood flow widely to the operated hemispheres including the posterior temporal and parietal lobes. Postoperative blood flow studies also demonstrated marked improvement of cerebral hemodynamics

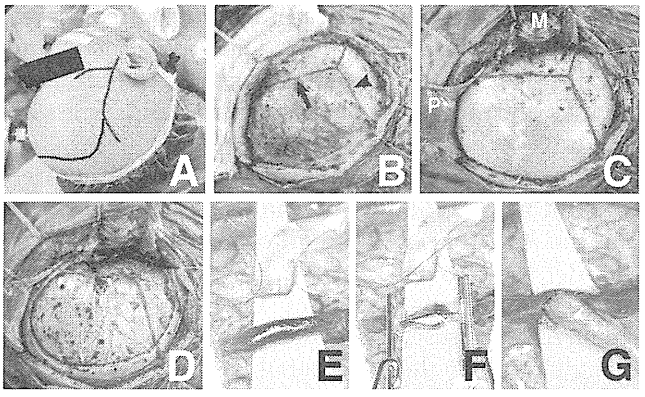

Fig. 1 Intraoperative photographs of superficial temporal artery to middle cerebral artery (STA-MCA) double anastomosis and encephalo-duro-myo-arteriopericranial synangiosis for a one-year-old baby who developed sudden onset of cerebral infarction. A: Skin incision is designed based on the course of the parietal branch of STA. *Red lines* represent the course of the frontal and parietal branches of STA. *Black line* represents the design of skin incision. B: Both the frontal (*arrow*) and parietal branches (*arrowhead*) of STA are carefully dissected under surgical microscope. Note that both branches remain patent even after complete dissection. C: The temporal muscle (M) and frontal pericranial flaps (P) are carefully dissected and the cranium is exposed. D: Fronto-temporal craniotomy is performed, leaving the STA and middle meningeal artery intact. Note the wide extension of craniotomy to the frontal area. E–G: Step-by-step photographs of STA-MCA anastomosis. Note that the orifice of the arteriotomy is clearly visualized by the use of pyoctaninum blue staining and blue silicone rubber.

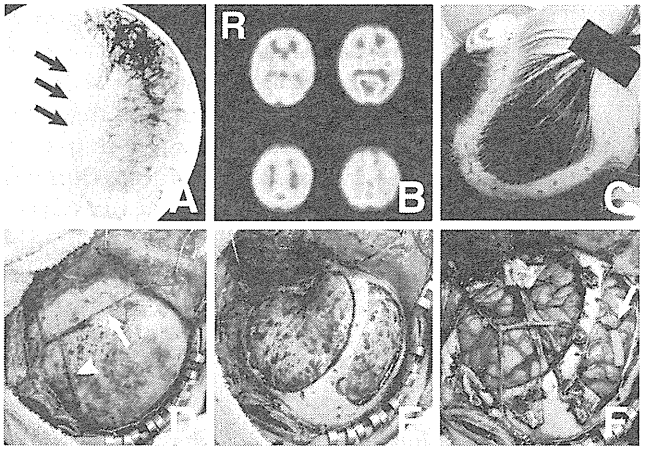

Fig. 2 Radiological and intraoperative findings of a 4-year-old girl who developed transient weakness of the right leg after crying. Her cousin was also diagnosed with moyamoya disease and was surgically treated at our hospital. A: Preoperative left internal carotid angiogram showing almost no filling of contrast material in the left anterior cerebral artery (ACA) territory even at late arterial phase (*arrows*). B: Iodine-123 N-isopropyl-p-iodoamphetamine single photon emission computed tomography scans demonstrating moderate reduction of cerebral blood flow in the left frontal lobe at rest (*left column*) and markedly impaired reactivity to acetazolamide in the bilateral frontal lobes (*right column*). C–F: Intraoperative photographs. Design of skin incision and partial hair shaving (C). The frontal (*arrow*) and parietal branches (*arrowhead*) of superficial temporal artery (STA) are carefully dissected under the surgical microscope (D). Note the very long graft of the frontal STA branch. Two-flap craniotomy is useful to widely expose the medial frontal lobe and perform STA-ACA anastomosis (E). The dura mater is opened, and the main branches of middle meningeal artery are kept intact (F). The frontal STA branch is passed beneath the cranial strip, and anastomosed to the cortical branch of the ACA near the midline.

and metabolism in the operated hemispheres including the occipital lobe (Fig. 3).[28]

Delayed wound healing or scalp necrosis is known as one of the most serious complications after STA-MCA anastomosis in patients with moyamoya disease.[19,29] We have used a modified surgical technique to dissect the STA to avoid this problem for 15 years. No serious complications of wound healing and scalp necrosis have occurred. First, the STA branches are carefully dissected from the surrounding galeal tissue under the surgical microscope. The dissected STA should be "naked," because the surrounding galeal tissue is quite important for wound healing. Next, the galeal "track" is always repaired after STA dissection by suturing the galeal tissue. The small amounts of time and effort contribute to the preservation of scalp blood flow, thus supporting wound healing (Fig. 4). The technique can be applied to STA-MCA anastomosis for patients with atherosclerotic carotid artery diseases (Kuroda et al., unpublished data).

In patients with advanced-stage moyamoya disease, the vault moyamoya vessels are frequently identified through the middle meningeal artery (MMA) and STA.[21] Therefore, the STA branches should be preserved during surgical revascularization if these vessels are involved in the vault moyamoya vessels. A representative case is presented in Fig. 5. This 52-year-old male had spontaneous collaterals to the ACA branches through the frontal branch of STA. Thus, the frontal branch of STA was preserved and used as the donor artery for encephalo-arterio-synangiosis by positioning on the brain surface.

As described above, direct STA-MCA and/or STA-ACA anastomoses are considered to contribute to

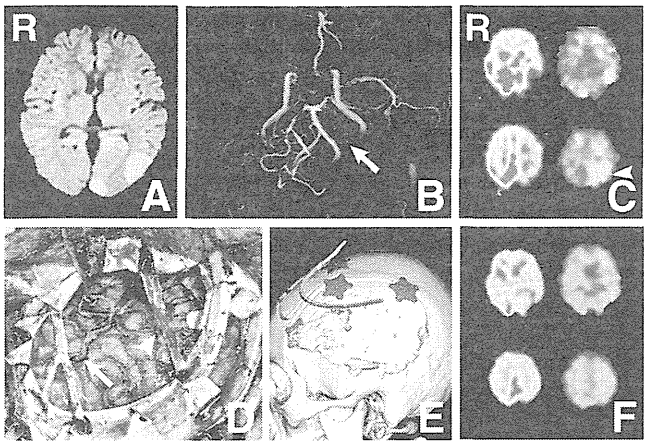

Fig. 3 Radiological and intraoperative findings of a 38-year-old female who developed ischemic stroke. A: Diffusion-weighted magnetic resonance (MR) image demonstrating cerebral infarction in the left posterior temporal and occipital lobes at onset. B: MR angiogram revealing severe stenosis of the left posterior cerebral artery (*arrow*) as well as occlusive lesions in the bilateral internal carotid arteries. C: Preoperative oxygen-15 gas positron emission tomography (^{15}O-gas PET) scans showing marked reduction of cerebral blood flow in the entire left hemisphere (*left column*). Oxygen extraction is elevated in the left parieto-occipital lobe (*right column, arrowhead*). D: Intraoperative photograph showing a wide craniotomy exposing the posterior temporal and parietal lobes. The parietal branch of the superficial temporal artery (STA) is anastomosed to the angular artery to directly supply blood flow to the oxygen extraction-elevated area (*arrow*). The frontal branch of STA is anastomosed to the prefrontal artery (*arrowhead*). E: Postoperative three-dimensional skull computed tomography scan demonstrating the extent of craniotomy. F: Postoperative ^{15}O-gas PET scans showing improvement of the cerebral hemodynamics (*left column*) and oxygen metabolism (*right column*) in the operated hemispheres.

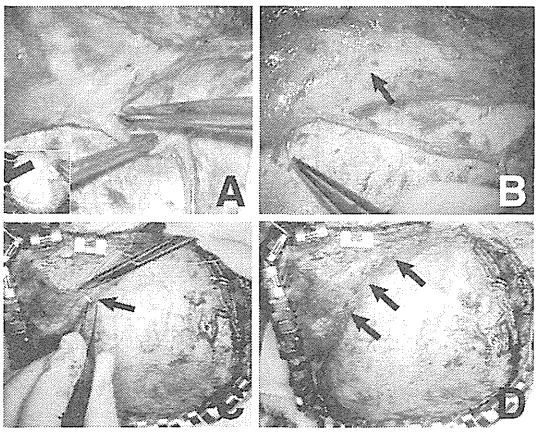

Fig. 4 Intraoperative photographs of left superficial temporal artery (STA) to middle cerebral artery double anastomosis and encephalo-duro-myo-arterio-pericranial synangiosis for a 6-year-old boy who developed transient weakness of the left extremities. A: The main trunk of STA and its two main branches are carefully dissected from the surrounding galeal tissue under surgical microscope. Note that there are no galeal tissues around the dissected STA branches. B: The main trunk of STA and its frontal and parietal branches are still patent after complete dissection. Note that dissection of the STA branch resulted in the track-like galeal injury, where subcutaneous fatty tissue is exposed (*arrow*). C: After STA dissection, the galeal injury should be carefully repaired to preserve blood flow in the scalp, using absorbable surgical sutures (*arrow*). D: The galeal injury after dissection of the frontal STA branch is completely repaired, contributing to good wound healing (*arrows*).

good short- and long-term outcomes of patients with moyamoya disease. However, the course of the frontal STA branch should carefully be checked prior to surgery. As reported before, the frontal branch of STA runs tortuously upward and forward to the forehead, where it supplies the muscles, integument, and pericranium in this region, and anastomoses with the supraorbital and frontal arteries.[18] In a certain subgroup of patients, it runs in an extremely caudal direction. In such cases, full dissection of the frontal STA branch may injure the temporal branch of the facial nerve and cause postoperative palsy of the frontalis muscle.[50] Therefore, only the distal portion of the frontal STA branch should be dissected from the scalp to avoid postoperative frontalis palsy, if the course is extremely caudal. The artery close to the temporal branch of the facial nerve should be left intact (Fig. 6). The dissected length is enough for direct bypass to the frontal branches of the MCA. After STA-MCA anastomosis, the frontal branch of STA can be guided into the intracranial space through the burr hole at the pterion (Fig. 6).

Indirect Bypass Procedure

Surgical procedures for indirect bypass are specific for moyamoya disease. Indirect bypass surgery that induces spontaneous angiogenesis between the brain surface and the vascularized donor tissues is technically simple to do and has been widely used. Donor tissues include the STA, dura mater, temporal muscle, and galeal tissue.[8,13,16,20,32] However, several important issues should be considered when performing indirect bypass procedures. First, the beneficial effects are not immediate because surgical collaterals require 3 to 4 months to develop,[6,7,48]

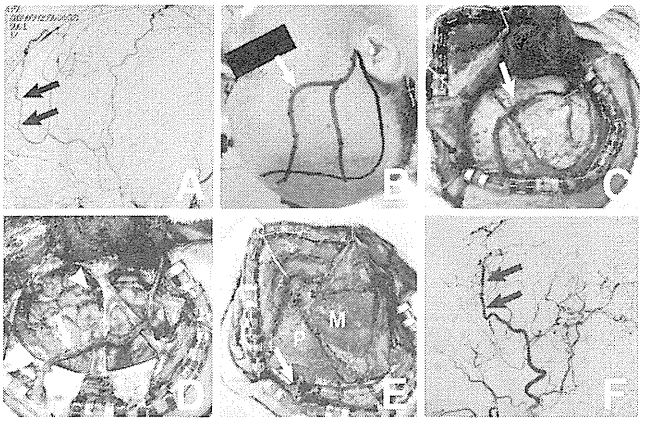

Fig. 5 Intraoperative photographs of superficial temporal artery to middle cerebral artery (STA-MCA) single anastomosis and encephalo-duro-myo-arterio-pericranial synangiosis for a 52-year-old male who developed minor ischemic stroke. A: Preoperative right external carotid angiogram showing the collateral circulation to the anterior cerebral artery branches spontaneously developed through the frontal branch of STA (*arrows*). B: Skin incision (black line) and course of two branches of STA (*red lines*). Note that the frontal branch of STA (*arrow*) is crossing the line of the skin incision. C: The STA branches are carefully dissected, and the scalp flap is reflected. Then, the temporal muscle and frontal pericranial flap are dissected. The frontal branch of STA is still intact (*arrow*). D: The dura mater is opened, leaving the middle meningeal artery branches intact. The parietal branch of STA is anastomosed to the cortical branch of MCA (*arrowhead*). The frontal branch of STA is still intact (*arrow*). E: The dural window is covered by the temporal muscle (M) and frontal pericranium (P). Note that the frontal branch of STA is still intact (*arrow*) and is used as the donor artery for encephalo-arterio-synangiosis. F: Postoperative right external carotid angiogram demonstrating collateral blood flow through the STA-MCA anastomosis and indirect bypass. Note the preserved frontal branch of the STA (*arrows*).

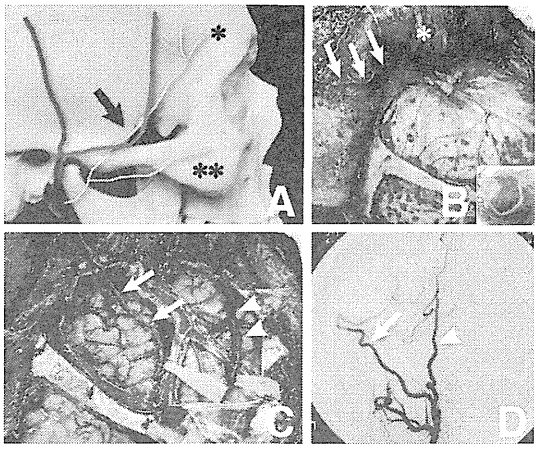

Fig. 6 A: Anatomy of the superficial temporal artery (STA; *red*) and facial nerve (*yellow*). The facial nerve has the temporal branch (*) and zygomatic branch (**). Note that the frontal branch of the STA runs very close to the temporal branch of the facial nerve because of its unusually caudal course in some patients (*arrow*). B: Intraoperative photograph of a 54-year-old female who experienced transient weakness of the left extremities. The frontal branch of STA runs very caudally, and only the distal part is dissected from the scalp (*arrows*). C: Intraoperative photograph showing that STA to middle cerebral artery double anastomosis is completed. Note that the frontal STA branch is guided into the intracranial space through the burr hole made at the pterion (*arrows*). The parietal branch of STA follows the usual course (*arrowheads*). D: Postoperative right external carotid angiogram showing that the frontal branch of the STA (*arrow*) is guided into the subdural space through the burr hole at the pterion. The parietal branch of the STA is guided into the intracranial space with a usual fashion (*arrowhead*).

suggesting that there is a potential risk of perioperative ischemic stroke.[9,41] Second, previous studies have demonstrated that collateral pathways through indirect bypass extensively develop in almost all pediatric patients, but not in about 40% to 50% of adult patients.[36] In fact, combined, but not indirect, bypass surgery could reduce the incidence of rebleeding in adult moyamoya disease.[15] Third, surgical design is quite important because the extent of surgical collateral pathways depends on the size of the craniotomy and the extent of the indirect bypass. Thus, the revascularized area is confined to the craniotomy field after indirect bypass. Recent multivariate analysis has proven that "small craniotomy" surgery can be an independent predictor for poor intellectual outcome in pediatric moyamoya disease, probably because of persistent cerebral ischemia in the frontal lobes even after surgery.[23] Figure 7 shows representative cerebral angiography and three-dimensional skull computed tomography findings after various types of indirect bypass surgery, demonstrating that indirect bypass through a smaller craniotomy develops less extensive surgical collaterals.

Based on these observations, we have recently developed a novel indirect bypass procedure by using the vascularized frontal pericranial flap, named EDMAPS (see above).[24] The frontal pericranial flap is large enough to widely cover the frontal lobe (Figs. 2, 3, and 5). Postoperative cerebral angiography and blood flow studies have shown that the pericranial flap functions well as a donor tissue for indirect bypass, especially in pediatric patients with

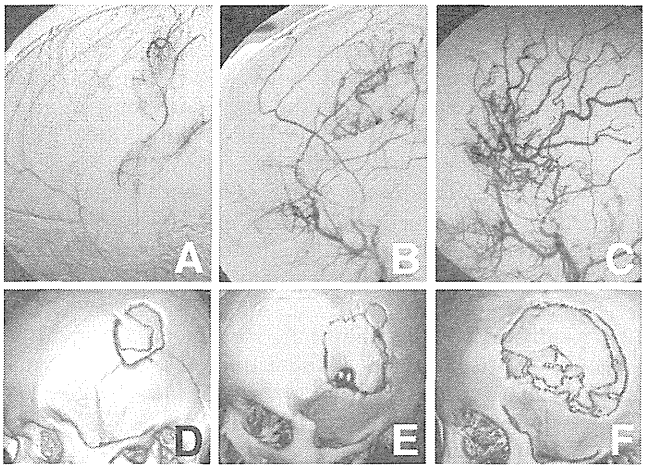

Fig. 7 Postoperative external carotid angiograms (A–C) and three-dimensional skull computed tomography scans (D–F) showing the relationship between craniotomy size and the extent of surgical collaterals through indirect bypass after encephalo-duro-arterio-synangiosis (A, D), encephalo-myo-synangiosis (B, E), and encephalo-duro-arterio-myo-synangiosis (C, F).

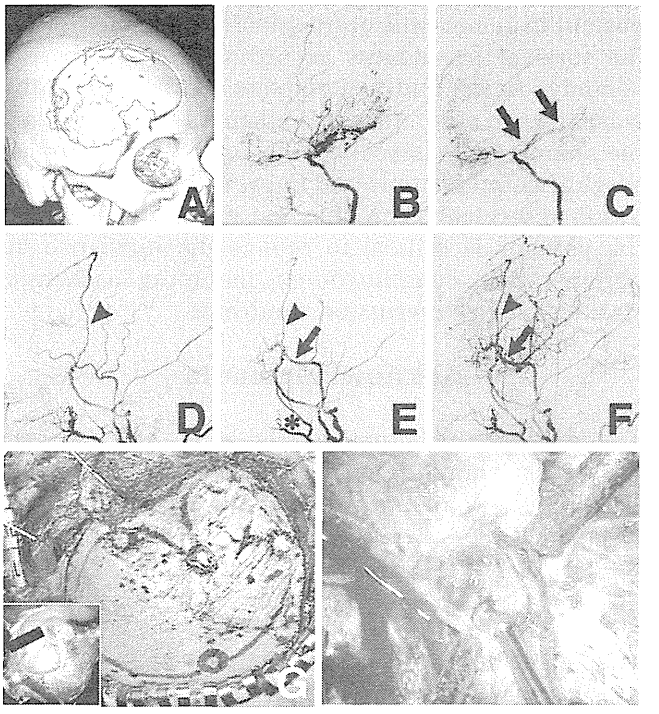

Fig. 8 Radiological findings of a 55-year-old female who developed transient ischemic attacks followed by right thalamic hemorrhage. She underwent right superficial temporal artery to middle cerebral artery (STA-MCA) single anastomosis and encephalo-duro-myo-arterio-pericranial synangiosis (EDMAPS) safely. A: Postoperative three-dimensional skull computed tomography scan showing the extent of craniotomy. B, C: Pre- (B) and postoperative (C) right internal carotid angiograms revealing marked diminishment of the basal moyamoya vessels after surgery (C, *arrows*). D–F: Pre- (D) and postoperative (E, F) right external carotid angiograms showing extensive developments of the surgical collaterals through the STA-MCA anastomosis (E, F; *arrow*) and indirect bypass. Note that the middle meningeal artery (MMA) is preserved even after surgery (D–F, *arrowhead*) and that the deep temporal artery has increased diameter after surgery (E, *asterisk*). G, H: Intraoperative photographs of right STA-MCA single anastomosis and EDMAPS. Fronto-temporal craniotomy is designed to avoid injury of the MMA during craniotomy (G). The MMA can be preserved intact by carefully drilling out the bone surrounding the MMA (H).

moyamoya disease. Figure 8 demonstrates the representative radiological findings before and after STA-MCA single anastomosis and EDMAPS in an adult patient with hemorrhagic onset. Surgical collateral pathways have extensively developed and provide blood flow widely to the operated hemisphere. Finally, the basal moyamoya vessels are markedly diminished.

The MMA can function as one of the important surgical collaterals through the dura mater. Therefore, the MMA should carefully be preserved during craniotomy. However, the course of the anterior (frontal) branch of the MMA in the region of lesser wing of the sphenoid and adjacent parietal bone greatly varies in adults. Generally, the anterior branch of the MMA is believed to run within the groove in the medial surface of bone, but this pattern is observed in less than 30% of adults. Alternatively, the course of the anterior branch of the MMA is completely enclosed within a bony canal in the lesser wing of the sphenoid and parietal bone in about 50% to 75% of adults.[30,45] Therefore, the MMA can easily be damaged during usual fronto-temporal craniotomy. As shown in Fig. 8G and H, we have modified the design of fronto-temporal craniotomy to avoid this problem. The MMA can be kept intact by carefully drilling out the lesser wing of the sphenoid. Figure 8E and F demonstrate that the dilated anterior branch of the MMA remains intact and functions as one of collateral pathways even after surgery.

Conclusions

In this article, we describe the basic concepts of surgical revascularization for moyamoya disease. In particular, STA-MCA anastomosis combined with a novel indirect bypass, EDMAPS, can be a safe and effective procedure for pediatric and adult patients with moyamoya disease. However, it is quite im-

portant to achieve the optimum effects by modifying the surgical procedures according to the cerebral hemodynamics and spontaneous collateral pathways in each case. Also, it is essential to understand the anatomy of the scalp, STA, and MMA to avoid surgical complications and improve outcome. In addition to surgical techniques, careful management of the patients is critical to reduce the incidence of perioperative complications, including ischemic stroke and hyperperfusion syndrome.

Acknowledgments

The authors are supported by a grant from the Research Committee on Moyamoya Disease, sponsored by the Ministry of Health, Labor and Welfare of Japan.

References

1) Fujimura M, Kaneta T, Mugikura S, Shimizu H, Tominaga T: Temporary neurologic deterioration due to cerebral hyperperfusion after superficial temporal artery-middle cerebral artery anastomosis in patients with adult-onset moyamoya disease. *Surg Neurol* 67: 273–282, 2007
2) Fukui M: Current state of study on moyamoya disease in Japan. *Surg Neurol* 47: 138–143, 1997
3) Fung LW, Thompson D, Ganesan V: Revascularisation surgery for paediatric moyamoya: a review of the literature. *Childs Nerv Syst* 21: 358–364, 2005
4) Guzman R, Lee M, Achrol A, Bell-Stephens T, Kelly M, Do HM, Marks MP, Steinberg GK: Clinical outcome after 450 revascularization procedures for moyamoya disease. Clinical article. *J Neurosurg* 111: 927–935, 2009
5) Houkin K, Ishikawa T, Yoshimoto T, Abe H: Direct and indirect revascularization for moyamoya disease surgical techniques and peri-operative complications. *Clin Neurol Neurosurg* 99 Suppl 2: S142–145, 1997
6) 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)* 142: 269–276, 2000
7) Houkin K, Nakayama N, Kuroda S, Ishikawa T, Nonaka T: How does angiogenesis develop in pediatric moyamoya disease after surgery? A prospective study with MR angiography. *Childs Nerv Syst* 20: 734–741, 2004
8) Ishii R: [Surgical treatment of moyamoya disease]. *No Shinkei Geka* 14: 1059–1068, 1986 (Japanese)
9) Ishikawa T, Houkin K, Kamiyama H, Abe H: Effects of surgical revascularization on outcome of patients with pediatric moyamoya disease. *Stroke* 28: 1170–1173, 1997
10) Ishikawa T, Kamiyama H, Kuroda S, Yasuda H, Nakayama N, Takizawa K: Simultaneous superficial temporal artery to middle cerebral or anterior cerebral artery bypass with pan-synangiosis for Moyamoya disease covering both anterior and middle cerebral artery territories. *Neurol Med Chir (Tokyo)* 46: 462–468, 2006
11) Iwama T, Hashimoto N, Miyake H, Yonekawa Y: Direct revascularization to the anterior cerebral artery territory in patients with moyamoya disease: report of five cases. *Neurosurgery* 42: 1157–1162, 1998
12) Kamiyama H, Takahashi A, Houkin K, Mabuchi S, Abe H: Visualization of the ostium of an arteriotomy in bypass surgery. Neurosurgery 33: 1109–1110, 1993
13) Karasawa J, Kikuchi H, Furuse S, Sakaki T, Yoshida Y: A surgical treatment of "moyamoya" disease "encephalo-myo synangiosis". *Neurol Med Chir (Tokyo)* 17(1 Pt 1): 29–37, 1977
14) Karasawa J, Touho H, Ohnishi H, Miyamoto S, Kikuchi H: Long-term follow-up study after extracranial-intracranial bypass surgery for anterior circulation ischemia in childhood moyamoya disease. *J Neurosurg* 77: 84–89, 1992
15) 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* 93: 397–401, 2000
16) Kawaguchi T, Fujita S, Hosoda K, Shose Y, Hamano S, Iwakura M, Tamaki N: Multiple burr-hole operation for adult moyamoya disease. *J Neurosurg* 84: 468–476, 1996
17) Kawashima A, Kawamata T, Yamaguchi K, Hori T, Okada Y: Successful superficial temporal artery-anterior cerebral artery direct bypass using a long graft for moyamoya disease: technical note. *Neurosurgery* 67(3 Suppl Operative): ons145–ons149, 2010
18) Kawashima M, Rhoton AL Jr, Tanriover N, Ulm AJ, Yasuda A, Fujii K: Microsurgical anatomy of cerebral revascularization. Part I: anterior circulation. *J Neurosurg* 102: 116–131, 2005
19) Kim DS, Yoo DS, Huh PW, Kang SG, Cho KS, Kim MC: Combined direct anastomosis and encephaloduroarteriogaleosynangiosis using inverted superficial temporal artery-galeal flap and superficial temporal artery-galeal pedicle in adult moyamoya disease. *Surg Neurol* 66: 389–395, 2006
20) Kinugasa K, Mandai S, Kamata I, Sugiu K, Ohmoto T: Surgical treatment of moyamoya disease: operative technique for encephalo-duro-arterio-myo-synangiosis, its follow-up, clinical results, and angiograms. *Neurosurgery* 32: 527–531, 1993
21) Kodama N, Fujiwara S, Horie Y, Kayama T, Suzuki J: [Transdural anastomosis in moyamoya disease—vault moyamoya (author's transl)]. *No Shinkei Geka* 8: 729–737, 1980 (Japanese)
22) Kuroda S, Houkin K: Moyamoya disease: current concepts and future perspectives. *Lancet Neurol* 7: 1056–1066, 2008
23) Kuroda S, Houkin K, Ishikawa T, Nakayama N, Ikeda J, Ishii N, Kamiyama H, Iwasaki Y: Determinants of intellectual outcome after surgical revascularization

in pediatric moyamoya disease: a multivariate analysis. *Childs Nerv Syst* 20: 302–308, 2004
24) Kuroda S, Houkin K, Ishikawa T, Nakayama N, Iwasaki Y: Novel bypass surgery for moyamoya disease using pericranial flap: its impacts on cerebral hemodynamics and long-term outcome. *Neurosurgery* 66: 1093–1101, 2010
25) Kuroda S, Houkin K, Kamiyama H, Abe H, Mitsumori K: Regional cerebral hemodynamics in childhood moyamoya disease. *Childs Nerv Syst* 11: 584–590, 1995
26) Kuroda S, Houkin K, Nunomura M, Abe H: Frontal lobe infarction due to hemodynamic change after surgical revascularization in moyamoya disease—two case reports. *Neurol Med Chir (Tokyo)* 40: 315–320, 2000
27) Kuroda S, Ishikawa T, Houkin K, Iwasaki Y: [Clinical significance of posterior cerebral artery stenosis/occlusion in moyamoya disease]. *No Shinkei Geka* 30: 1295–1300, 2002 (Japanese)
28) Kuroda S, Kawabori M, Miyamoto M, Sasamori T, Endo S, Nakayama N, Ishikawa T, Houkin K, Iwasaki Y: [Revascularization surgery for moyamoya disease with cerebral ischemia in temporo-occipital lobes]. *Nosotchu No Geka* 37: 345–349, 2009 (Japanese)
29) Kwon H, Kim HJ, Yim YM, Jung SN: Reconstruction of scalp defect after Moyamoya disease surgery using an occipital pedicle V-Y advancement flap. *J Craniofac Surg* 19: 1075–1079, 2008
30) Ma S, Baillie LJ, Stringer MD: Reappraising the surface anatomy of the pterion and its relationship to the middle meningeal artery. *Clin Anat* 25: 330–339, 2012
31) Matsushima T, Fukui M, Kitamura K, Hasuo K, Kuwabara Y, Kurokawa T: Encephalo-duro-arterio-synangiosis in children with moyamoya disease. *Acta Neurochir (Wien)* 104: 96–102, 1990
32) Matsushima Y, Fukai N, Tanaka K, Tsuruoka S, Inaba Y, Aoyagi M, Ohno K: A new surgical treatment of moyamoya disease in children: a preliminary report. *Surg Neurol* 15: 313–320, 1981
33) Miyamoto S, Akiyama Y, Nagata I, Karasawa J, Nozaki K, Hashimoto N, Kikuchi H: Long-term outcome after STA-MCA anastomosis for moyamoya disease. *Neurosurg Focus* 5(5): e5, 1998
34) Miyamoto S, Kikuchi H, Karasawa J, Nagata I, Ihara I, Yamagata S: Study of the posterior circulation in moyamoya disease. Part 2: Visual disturbances and surgical treatment. *J Neurosurg* 65: 454–460, 1986
35) Miyamoto S, Kikuchi H, Karasawa J, Nagata I, Ikota T, Takeuchi S: Study of the posterior circulation in moyamoya disease. Clinical and neuroradiological evaluation. *J Neurosurg* 61: 1032–1037, 1984
36) Mizoi K, Kayama T, Yoshimoto T, Nagamine Y: Indirect revascularization for moyamoya disease: is there a beneficial effect for adult patients? *Surg Neurol* 45: 541–549, 1996
37) Mugikura S, Takahashi S, Higano S, Shirane R, Kurihara N, Furuta S, Ezura M, Takahashi A: The relationship between cerebral infarction and angiographic characteristics in childhood moyamoya disease. *AJNR Am J Neuroradiol* 20: 336–343, 1999
38) Nakagawa Y, Abe H, Sawamura Y, Kamiyama H, Gotoh S, Kashiwaba T: Revascularization surgery for moyamoya disease. *Neurol Res* 10: 32–39, 1988
39) Nakagawara J, Takeda R, Suematsu K, Nakamura J: Quantification of regional cerebral blood flow and vascular reserve in childhood moyamoya disease using [123I]IMP-ARG method. *Clin Neurol Neurosurg* 99 Suppl 2: S96–99, 1997
40) Okada Y, Shima T, Nishida M, Yamane K, Yamada T, Yamanaka C: Effectiveness of superficial temporal artery-middle cerebral artery anastomosis in adult moyamoya disease: cerebral hemodynamics and clinical course in ischemic and hemorrhagic varieties. *Stroke* 29: 625–630, 1998
41) Sakamoto T, Kawaguchi M, Kurehara K, Kitaguchi K, Furuya H, Karasawa J: Risk factors for neurologic deterioration after revascularization surgery in patients with moyamoya disease. *Anesth Analg* 85: 1060–1065, 1997
42) Sasamori T, Kuroda S, Nakayama N, Iwasaki Y: Incidence and pathogenesis of transient cheiro-oral syndrome after surgical revascularization for moyamoya disease. *Neurosurgery* 67: 1054–1060, 2010
43) Satoh S, Shibuya H, Matsushima Y, Suzuki S: Analysis of the angiographic findings in cases of childhood moyamoya disease. *Neuroradiology* 30: 111–119, 1988
44) Scott RM, Smith JL, Robertson RL, Madsen JR, Soriano SG, Rockoff MA: Long-term outcome in children with moyamoya syndrome after cranial revascularization by pial synangiosis. *J Neurosurg* 100: 142–149, 2004
45) Shimizu S, Hagiwara H, Utsuki S, Oka H, Nakayama K, Fujii K: Bony tunnel formation in the middle meningeal groove: an anatomic study for safer pterional craniotomy. *Minim Invasive Neurosurg* 51: 329–332, 2008
46) Suzuki J, Takaku A: Cerebrovascular "moyamoya" disease. Disease showing abnormal net-like vessels in base of brain. *Arch Neurol* 20: 288–299, 1969
47) Touho H, Karasawa J, Ohnishi H: Haemodynamic evaluation of paraparetic transient ischaemic attacks in childhood moyamoya disease. *Neurol Res* 17: 162–168, 1995
48) Veeravagu A, Guzman R, Patil CG, Hou LC, Lee M, Steinberg GK: Moyamoya disease in pediatric patients: outcomes of neurosurgical interventions. *Neurosurg Focus* 24(2): E16, 2008
49) Yonekawa Y, Ogata N: Spontaneous occlusion of the circle of Willis (cerebrovascular moyamoya disease): with special reference to its disease entity and etiological controversy. *Brain Dev* 14: 253–254, 1992
50) Yoon MK, Horton JC, McCulley TJ: Facial nerve injury: a complication of superficial temporal artery biopsy. *Am J Ophthalmol* 152: 251–255.e1, 2011

Address reprint requests to: Satoshi Kuroda, MD, PhD, Department of Neurosurgery, Faculty of Medicine, University of Toyama, 2630 Sugitani, Toyama, Toyama 930–0194, Japan.
e-mail: skuroda@med.hokudai.ac.jp

Neurol Med Chir (Tokyo) 52, 267～277, 2012

Review of Past Research and Current Concepts on the Etiology of Moyamoya Disease

Kiyohiro HOUKIN,[1] Masaki ITO,[1] Taku SUGIYAMA,[1] Hideo SHICHINOHE,[1] Naoki NAKAYAMA,[1] Ken KAZUMATA,[1] and Satoshi KURODA[1]

[1]*Department of Neurosurgery, Hokkaido University Graduate School of Medicine, Sapporo, Hokkaido*

Abstract

Research on moyamoya disease has progressed remarkably in the past several decades. Indeed, many new facts concerning the epidemiology of the disease have been revealed and surgical treatments have been drastically improved. However, despite extensive research, the mechanism of moyamoya disease is still unknown. Consequently, the cardinal treatment of this disease has not yet been developed. For further clarification of its etiology, innovative studies are therefore indispensable. The aim of this paper is to review research on the pathogenesis of moyamoya disease to identify milestones in the direction of its true solution. Many hypotheses of the pathogenesis of moyamoya disease have been proposed in the past half century, including infection (viral and bacterial), autoimmune disorders, proteins abnormality, and gene abnormality. Some of these are now considered to be historical achievements. Others, however, can be still subjected to contemporary research. Currently, several genetic abnormalities are considered to offer the most probable hypothesis. In addition, interesting papers have been presented on the role of the endothelial progenitor cell on the pathogenesis of moyamoya disease. Intuitively, however, it appears that a single theory cannot always explain the pathogenesis of this disease adequately. In other words, the complex mechanism of several factors may comprehensively explain the formation of moyamoya disease. The "double hit hypothesis" is probably the best explanation for the complicated pathology and epidemiology of this disease.

Key words: moyamoya disease, etiology, proteomics, genetics, endothelial progenitor cell

Introduction

Cerebrovascular moyamoya disease is characterized by progressive stenotic change in the terminal portion of the bilateral internal carotid arteries and the formation of an abnormal vascular network at the base of the brain.[35,49,62,63,67] The latter is thought to be a secondary phenomenon that compensates for the cerebral ischemia due to the primary internal carotid artery stenosis. The abnormally developed vascular network is defined as "moyamoya vessels."[63]

The pathological entity of moyamoya disease was established in the 1960s.[35,49,63,67] Since then, particularly enthusiastic research has been conducted in Japan and progress has been remarkable in the past several decades. So far, many new aspects of the epidemiology have been uncovered and innovations in surgical treatment have been developed, including direct bypass surgery and other combined revascularization treatments.[6,36,37,71]

Despite these many and extensive studies, however, the mechanism of moyamoya disease is still unknown. From a historical point of view, some of the hypotheses are now considered to be historical achievements. Thus, cerebrovascular disease with certain basic diseases or conditions, including infection and autoimmune disease are currently distinguished from definitive or probable moyamoya disease.[11] However, these hypotheses have been occasionally proposed in the history of the investigation of moyamoya disease. Innovative research is indispensable for further clarification of the pathogenesis. In a sense, moyamoya disease is shrouded still in mystery, literally as a "puff of smoke" (Table 1). Consequently, the cardinal treatment to block the pathogenesis of the disease has not yet been developed. The aim of this paper is, therefore, to review the past clinical and basic research on the pathogen-

Received January 30, 2012; Accepted April 16, 2012

Table 1 Summary of unknown issues in moyamoya disease

1 Geographical distribution	Japanese, Korean
2 Sex specificity	woman 2 times
3 Heredity	10–20%, low penetration
4 Pathological specificity	different from atherosclerosis
5 Vasculogenesis (angiogenesis?)	
6 Etiology	unknown

esis of moyamoya disease in order to find a guide to the true solution of this disease.[1,58]

There are many ways to uncover the etiology of a disease. Conventional methods include the epidemiological approach, basic research including the animal model approach, and the clinical approach. As is well known, however, the animal model of this disease has not been established.[9,10,23,40] In this paper, therefore, research on moyamoya disease and moyamoya syndrome using conventional pathological methods as well as research on proteomics, relationship between immune system and moyamoya disease or syndrome, gene abnormality, and cell abnormality will be reviewed. Finally, the authors will propose a comprehensive idea to explain the many aspects revealed by many approaches.

Materials and Methods

In this paper, studies published in English and the main studies in Japan on moyamoya disease are reviewed as comprehensively as possible. The main studies are summarized according to the following five viewpoints: i) Pathological study and abnormal thrombogenesis, ii) proteomics, iii) infection and autoimmune abnormality and human leucocytes antigen (HLA) abnormality, iv) genetics, and v) endothelial progenitor cell (EPC). These particular viewpoints are discussed in each part.

Results

I. Pathological study and abnormal thrombogenesis

Needless to say, pathological study offers essential information about the pathogenesis of moyamoya disease. However, the difficulty of the pathological approach is that specimens of the terminal portion of the internal carotid artery are difficult to obtain since autopsies conducted in patients with moyamoya disease have decreased recently. For this reason, pathological study has to be traced back to the 1990s.

Firstly, the inflammatory process hypothesis has been proposed by Masuda et al.[41] However, as is well known, the characteristics of the stenotic change seen in moyamoya disease are quite different from those of the atherosclerotic process seen in adults. There is no lipid pool or inflammatory cell or macrophage invasion to the sub-intimal layer as typically seen in atherosclerosis.[20] The typical pathological finding seen in the terminal of the internal carotid artery is a concentric and eccentric fibrocellular thickening of the intima that induces the stenosis of the vascular lumen. The intimal elastic lamina shows an abnormal waving form without the rupture, although it is basically maintained. Masuda et al. have demonstrated that the thickening of the intimal layer includes migration of the smooth muscle cell of media that resembles atherosclerosis but no inflammatory cells are observed. From these classic studies, we can learn that the mechanism of stenotic change seen in moyamoya disease is quite different from that of atherosclerosis. However, unfortunately, no clear hints are obtained to connect with the true pathogenesis of moyamoya disease.

On the other hand, a hypothesis of abnormal thrombogenesis has been advanced by Hosoda et al.,[17] who reported that thromboemboli are occasionally (around 50% in their autopsy cases) seen in the internal wall of the moyamoya artery and its distribution correlates well with the character of moyamoya disease. They have suggested that abnormal thrombogenesis plays an important role in the etiology of this disease. However, another study by Ikeda and Hosoda has failed to demonstrate any difference in expression of the thrombomodulin (anticoagulant protein expressed in the endothelial cells) between normal controls and moyamoya patients.[21] Subsequently, few papers have been published to demonstrate the relationship between the etiology of moyamoya disease and abnormal thrombogenesis. Clinically sickle cell anemia is well known to cause moyamoya syndrome and abnormality in thrombogenesis is suspected in its etiology. Other research has pointed out that prothrombotic abnormality, antiphospholipid syndrome, and protein-S abnormality are commonly reported in moyamoya disease and moyamoya syndrome.[2,7,27,57,60]

In conclusion, morphological study using classical techniques has successfully demonstrated the typical change in internal thickening of the intima in moyamoya disease. However, it has not necessarily offered insight into the essential pathogenesis of this disease.

II. Proteomics

There are many successful studies on the detec-

Table 2 Change in cytokines

	Elevation	No change
CSF	b-FGF	TGF-β
	HGF	VEGF, IL-8
	CRABP-I	PDGF
	ICAM-I	
	E-selectin	
Cerebral artery, STA, cultured SMCs	b-FGF	
	TGF-β	
	PDGF	
	HGF	
	HIF-1α	

b-FGF: basic fibroblast growth factor, CRABP-I: cellular retinoic acid-binding protein type I, HGF: hepatocyte growth factor, HIF-1α: hypoxia-inducible factor 1α, ICAM-1: intercellular adhesion molecule type 1, IL-8: interleukin-8, PDGF: platelet-derived growth factor, SMCs: smooth muscle cells, STA: superficial temporal artery, TGF-β: transforming growth factor β, VEGF: vascular endothelial growth factor.

tion of cytokine increase in specimens obtained from patients with moyamoya disease. Indeed, in the last 15 years, many investigations have been conducted in this field.[3,15,18,30,33,46,65,69,75] The results are summarized in Table 2. Most studies are based on the examination of cerebrospinal fluid (CSF) obtained from the surface subarachnoid space during surgery on moyamoya disease patients. Angiogenetic cytokines such as basic fibroblast growth factor (b-FGF), hepatocyte growth factor, and transforming growth factor (TGF) are mainly shown to have increased in CSF and other surgical specimens such as artery walls and the dura mater. These proteins may relate to the pathogenesis of moyamoya disease.

Among the angiogenetic cytokines, the b-FGF has attracted most attention since it can rationally explain the apparently inconsistent phenomena seen in moyamoya disease, namely, steno-occlusive lesion in the Willis ring and the development of moyamoya vessels and dilation of the cortical small arterioles and angiogenesis/vasculogenesis after indirect synangiosis. It is well known that b-FGF induces the proliferation of endothelial cells which may produce the stenotic change of the major arteries in moyamoya disease. On the other hand, b-FGF has an angiogenetic and vasodilative effect on the small pial arteries that can rationally explain the development of abnormally dilated vasculature and the dilated superficial pial arterioles on the cortex in moyamoya disease. In addition, it has been demonstrated that the level of b-FGF in the CSF is closely related to the level of neo-vascularization after an indirect bypass. It is noteworthy, however, that strong angiogenetic factors such as vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) are not always increased in moyamoya disease.[18]

Table 3 Correlation between moyamoya disease and infection/autoimmune disease

Infection	
bacterial Infection	pneumococcus
	tuberous infection
	Propionibacterium acnes
	Leptospira
	Streptococcus
viral infection	Epstein-Barr virus
	varicella-zoster virus
	measles virus
	human immunodeficiency virus
	cytomegalovirus
Auto-immune disease	antiphospholipid antibodies syndrome
	systemic lupus erythematosus
	Graves' disease

Nevertheless, there is some skepticism regarding the role of abnormality of proteins seen in moyamoya disease. We do not have reliable control data of the cytokine level that may differ according to location and age. In addition, under some hypoxic and ischemic conditions, it is well known that these cytokines significantly fluctuate. In other words, the data might simply reflect the response of cytokines to hypoxic and ischemic processes in moyamoya disease. It is thus conceivable that cytokine abnormalities may be the result of ischemia but not the cause of moyamoya disease.[18]

III. Infection and autoimmune abnormality and HLA abnormality

These three hypotheses have been occasionally proposed in the history of the investigation of moyamoya disease (Table 3). As mentioned above, the moyamoya phenomenon observed in patients with infection or autoimmune diseases is now eliminated from moyamoya disease. However, all three are considered to correlate with each other through the common pathway of abnormality in the immune system in moyamoya disease. It is important, therefore, to review and know past research on the relationships between moyamoya disease or moyamoya syndrome and infection or immune system disorder, including autoimmune abnormality and HLA abnormality. Many infections have been reported to be related to the moyamoya phenomenon, including bacterial meningitis due to pneumococcus, tuberous infection, viral infection by varicella-zoster virus, measles virus, human immunodeficiency virus, cytomegalovirus, Epstein-Barr virus, and *Leptospira* infection.[8,19,42,45,66,68,70]

Among these sporadic case reports, Yamada et al. have systematically studied the serum of 85 patients suffering moyamoya disease, and revealed that *Propionibacterium acnes* antibody and immunoglobulin M, transferrin, and α2-macroglobulin levels are significantly higher in cases of moyamoya disease.[74] However, there are few systemic studies on subsequent infection and moyamoya disease.

Many autoimmune diseases have been reported to be related to the moyamoya phenomenon, including antiphospholipid antibodies syndrome, systemic lupus erythematosus, Graves' disease, and HLA class I or II alleles abnormality.[13,56,64,72] However, these studies have indirectly proved the correlation between abnormalities of the immune system and moyamoya disease. Indeed, it is conceivable that the true genetic triggers of moyamoya disease are close to the abnormalities seen in HLA alleles disclosed.

IV. Genetics

Some genetic factors are believed to contribute to the etiology and development of moyamoya disease.[1,14,37,52,73] Evidence for a genetic contribution to moyamoya disease is suggested by strong regional differences with a high occurrence in Asian countries (primarily Japan and Korea) and much smaller rates in Western countries, as well as with many familial occurrences and high incidence in concordant monozygotic twins.[12,37,50,52] Further evidence shows that the female to male ratio rises from 1.6:1 in sporadic cases to 5.0:1 in familial cases; and the mean age of onset drops from 30.0 years in sporadic cases to 11.8 years in familial cases. Moreover, while the onset of symptoms in parents of affected families shows an average of 30.7 years, their offspring show the first signs of moyamoya disease at an average age of 7.2 years.[37] Moyamoya syndrome has also been reported in patients with other diseases of known genetic origin, such as neurofibromatosis type I and Down syndrome, among others, highlighting the evidence for a possible genetic etiology for this severe disease.[37] Additionally, the following facts suggest a multifactorial etiology of moyamoya disease: the predisposition of familial occurrence,[6,71,76] the non-Mendelian pattern of inheritance in familial cases.[44,50] Based on these considerations, some researchers believe that moyamoya disease is inherited in a polygenic or autosomal dominant mode with a low penetrance.[44,50] For decades, studies have implicated certain genetic loci or susceptibility genes in harboring a risk for developing moyamoya disease, as shown in Tables 4, 5, and 6.

To specify the locus or the causative gene for moyamoya disease, linkage analysis (family-based studies such as parametric linkage analysis and affected sibling pair analysis) and association studies (case-control studies) have been performed. As shown in Table 4, four reports from Japan have conducted linkage analysis by using microsatellite markers to specify the susceptible genetic loci on familial moyamoya disease.[22,25,54,77] These reports have specified the susceptible linkage at 3p24.2-p26, 6q25, 17q25, and 8q23 for familial moyamoya disease. A suggestive linkage at 12p12 has also been demonstrated. As shown in Table 5, several association stu-

Table 4 Summary of linkage analysis to specify the susceptible genetic loci for familial moyamoya disease (MMD)

Author (Year)	Method	Subject	Ethnicity	DNA marker	Coverage	Result
Ikeda et al. (1999)[22]	non-parametric linkage analysis	77 individuals in 16 families, including 37 MMD patients	Japanese	371 microsatellite markers	22 autosomes	linkage at 3p24.2-p26 (maximal NPL score 3.46 on D3S3050)
Inoue et al. (2000)[25]	non-parametric linkage analysis; affected sibling pair analysis	20 affected sibling pairs in 19 families	Japanese	15 microsatellite markers	chromosome 6	linkage at 6q25 (linkage disequilibrium at D6S441; IBD [0:12:8])
Yamauchi et al. (2000)[77]	a combination of parametric and non-parametric linkage analysis	103 individuals in 24 families, including 56 MMD patients	Japanese	22 microsatellite markers	chromosome 17	linkage at 17q25 (maximal LOD score 4.58) within the 9-cM region of D17S785 to D17S836
Sakurai et al. (2004)[54]	non-parametric linkage analysis followed by TDT method	46 individuals in 12 families, including 12 affected sibling pairs	Japanese	428 microsatellite markers	genome-wide linkage analysis	linkage at 8q23 (MLS 3.6 and NPL 3.3 on D8S546) and suggestive linkage at 12p12 (MLS 2.3, NPL 2.5 on D12S1690), no linkage disequilibrium at markers in these loci

DNA: deoxyribonucleic acid, IBD: identical by descent, LOD: logarithm of odds, MLS: maximal LOD score, NPL: non-parametric LOD, TDT: transmission disequilibrium test.

Table 5 Summary of case-control association studies to specify the candidate gene or polymorphism for moyamoya disease (MMD)

Author (Year)	Subjects	Control	Ethnicity	Candidate genotype	Significantly associated allele for MMD
Kitahara et al. (1982)[34]	18 patients and 31 reviewed cases with MMD	106 normal controls	Japanese	HLA class I genotype	HLA-AW24(RR 3.83), BW46(RR6.50), BW54(RR3.58)
Aoyagi et al. (1995)[4]	32 unrelated patients with MMD	178 unrelated normal controls without history of CVD	Japanese	HLA class I and II genotype	HLA-B51(RR 3.7), the combination of the HLA-B51 and -DR4
Inoue et al. (1997)[24,26]	71 unrelated patients with MMD	525 normal controls	Japanese	HLA class I and II genotype	HLA-DQB1*0502 (positive association), HLA-DRB1*0405 and -DQB1*0401 (negative association)
Han et al. (2003)[13]	28 patients with MMD	198 normal controls	Korean	HLA-B and HLA class II genotype	HLA-B35 (RR4.2)
Kang et al. (2006)[31]	11 patients with familial MMD	50 patients with non-familial MMD and 50 normal controls	Korean	SNPs of TIMP4 and TIMP2 gene on chromosomes 3p24.2-p26 and 17q25	G/C heterozygous genotype at position -418 in TIMP2 promoter (OR9.56: familial vs non-familial MMD, OR10.5: familial MMD vs non-MMD)
Hong et al. (2009)[16]	10 children with familial MMD	54 children with non-familial MMD and 207 normal controls	Korean	high resolution HLA-DRB1 and DQB1 genotypes	HLA-DRB1*1302 (OR12.76: familial MMD vs non MMD, OR13.42: familial vs non-familial MMD), HLA-DQB1*0609 (OR14.67: familial MMD vs non-MMD, OR35.33: familial vs non-familial MMD)
Roder et al. (2010)[53]	40 patients with MMD	68 normal controls	central European	13 SNPs in and upstream of b-FGF, CRABP1, PDGFRβ and TGF β1 gene	rs382861(A/C) in the promotor region of PDGFRβ (OR1.81) and rs1800471(C/G) in the first exon of TGF β1 (OR7.65)

b-FGF: basic fibroblast growth factor, CRABP1: cellular retinoic acid-binding protein 1, CVD: cerebrovascular disease, HLA: human leukocyte antigen, OR: odds ratio, PDGFRβ: platelet derived-growth factor receptor β, RR: relative risk, SNP: single nucleotide polymorphism, TIMP: tissue inhibitor of metalloproteinase, TGF β1: transforming growth factor β1.

dies have been reported by using HLA genotype and single nucleotide polymorphisms (SNPs) of several cytokines or growth factors.[4,13,16,24,26,31,34,53] Thus, the association has been investigated between moyamoya disease and several markers involved in cell proliferation, constituting vessel strictures or expressing in the brain and/or vessels. As a result, several HLA alleles, SNPs of tissue inhibitor of metalloproteinase 2 promoter, PDGF receptor β and TGF β1 have been revealed to be candidate genes or polymorphism. However, these studies have not elucidated the susceptibility gene for moyamoya disease. As Mineharu et al. have pointed out, there seem to be three main explanations as follow.[44] First, moyamoya disease may be caused by several different mechanisms (disease heterogeneity). Second, moyamoya disease exhibits different modes of inheritance (genetic heterogeneity). Finally, several genetic factors in different loci can cause the same disease (locus heterogeneity). From these view points, several studies have been conducted by using a combination of several methods to specify the susceptibility gene for moyamoya disease (Table 6).[29,38,39,43,47] Of these, two independent groups from Japan have identified, very recently, the susceptibility gene for moyamoya disease by employing a combination of several methods, including linkage analysis, case-control association studies, and gene annotation studies. Thus, Kamada and colleagues from Tohoku University employed a genome-wide association study and identified ring finger protein (RNF) 213 (*613768; http://omim.org/entry/613768) as the first moyamoya disease gene.[29] Around the same time, Liu and colleagues from Kyoto University, the University of Tubingen, Palacky University, the Chinese People's Liberation Army General Hospital, and Seoul National University employed genome-wide linkage analysis by assuming the inheritance pattern of moyamoya disease as autosomal dominant mode with incomplete penetrance and whole genome-exome analysis. As a result, they provided evidence suggesting the involvement of RNF213 in genetic susceptibility to moyamoya disease.[39] As Liu et al. noted, the discoveries of the susceptibility gene, its association with moyamoya disease, and its unique roles in angiogenesis may yield a way to early diagnosis and prevention of the disease. It should be noted, however, that further studies are necessary to clarify the biochemical function and pathological role of RNF213 in moyamoya disease.