60 Moyamoya Disease

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Overview

Moyamoya disease is a rare chronic cerebral vasculopathy characterized by progressive stenosis and occlusion of the terminal portions of the internal carotid arteries, as well as the circle of Willis and its major branches. The term "moyamoya" stems from Japanese and translates to vague or hazy puff of smoke, and was coined by Suzuki and Takaku to refer to the vascular collaterals seen at the base of the skull in individuals with moyamoya disease.[1] Initially described by Takeuchi and Shimizu as bilateral hypoplasia of the internal carotid arteries, moyamoya disease has also been referred to as cerebral juxtabasal telangiectasia, cerebral arterial rete, rete mirabele, or spontaneous occlusion of the circle of Willis.[2–6] Since its initial description over 30 years ago the majority of cases have been described in the Pacific Rim, predominantly in Japan and Korea. The majority of data stem from this region and strict diagnostic guidelines have been established by the research committee on spontaneous occlusion of the circle of Willis (moyamoya disease) sponsored by the Ministry of Health and Welfare of Japan.

Epidemiology

In a nationwide survey of randomly selected hospitals in Japan conducted in 1995, 3900 patients were identified that had been treated for moyamoya disease.[7] These findings yield prevalence and incidence rates of 3.16 and 0.35 respectively per 100 000 population. A bimodal age distribution was observed, with 48% of cases having a clinical onset before age 10 (childhood moyamoya), and an additional peak in individuals aged 25–59 years (adult moyamoya). The female to male ratio was 1.8 and a family history of moyamoya was found in 10% of cases. Three-quarters of patients were noted to have normal activity of daily living scores prior to any treatment. While a similar bimodal distribution of disease onset was seen in a Korean study, the age of onset was 20% higher, the female : male ratio was 1.3 and only 1.8% of cases were familial.[8] Regional differences do exist, for example China has a male to female ratio of 1 : 0.35–0.75 and Taiwan has an annual incidence rate of 0.048 per 100 000 population, but has a similar age and gender distribution as in Korea.[9,10] There is a relative paucity on epidemiological information on moyamoya disease in the USA.[11–15]

Etiology, pathophysiology and pathogenesis

The etiology of the progressive stenosis and subsequent occlusion of the distal internal carotid arteries and the circle of Willis and its major branches characteristic of moyamoya disease is unclear. Autopsy studies have demonstrated fibro-intimal thickening of the intima and thinning of the media associated with a multi-layered elastic laminae without evidence of an active inflammatory process or atherosclerosis.[16,17] It has been hypothesized that smooth muscle cells are stimulated to undergo proliferation and migration, subsequently leading to intimal thickening in conjunction with intrinsic changes to elastin, collagen and other proteoglycans. Recently, antibodies for proliferating nuclear antigen have been identified as a proposed mechanism to induce smooth muscle cell moyamoya disease.[17,18] Other potential etiologies to the genesis of moyamoya vessels may be related to various abnormalities noted in a variety of angiogenic factors, cytokines and growth factors, such as basic fibroblast growth factor, platelet derived growth factor, interleukin (IL)-1, IL-6, IL-8, and transforming growth factor-beta-1.[19–22]

Intracerebral hemorrhage occurs in approximately 18% of cases and is related to two types of intracranial aneurysms identified in moyamoya patients; (1) major artery aneurysm stemming from the circle of Willis and (2) peripheral artery aneurysms located on moyamoya vessels, arteries serving as collaterals and the choroidal arteries.[23] Major arterial aneurysms are found more frequently in the anterior cerebral or anterior communicating artery in individuals with unilateral moyamoya disease and in the posterior circulation in cases with bilateral moyamoya. Aneurysms are four times more common in patients with unilateral than bilateral moyamoya.[23,24] In approximately 16% of cases multiple aneurysms are present. The proposed mechanism for the higher aneurysm rate in unilateral cases is thought to stem from the increased blood flow in a partially stenotic circle of Willis. Histologically, there is a disappearance of the internal elastic lamina and media (similar to the histology found in non-moyamoya aneurysm patients) in major artery aneurysms. Peripheral artery aneurysms are thought to be the etiology for parenchymatous hemorrhage. These aneurysms tend to be smaller than the major artery aneurysms and are frequently not visualized angiographically; up to 33% of them have been reported to vanish on repeat neuroimaging.[25]

Genetics

In Japan and Korea 2% to 10% of moyamoya cases are reported to be familial, and the association of this disorder with sickle cell anemia, neurofibromatosis and Down syndrome have prompted a number of genetic

investigations.[7,8,26] An association between human leukocyte antigens (HLA) class I and II as well as the Aw24, Bw46 and Bw 54 and B51-DR4 and DQB1 0502 antigens have been reported in patients with moyamoya disease.[27–29] Recently, two chromosomes have been linked to moyamoya disease. Chromosome 17q25, which is adjacent to the triplicate repeat found in neurofibromatosis, was found to be linked to 56 patients' from 24 families with moyamoya disease, while a simultaneous publication reported linkage with chromosome 6, which was found in 82% of subjects in 19 families.[30,31] These findings leave some to argue that a multifactorial etiology may exist.

Clinical features and natural history

Signs and symptoms of moyamoya disease are related to either the ischemic or the hemorrhagic cerebrovascular complications of this vasculopathy. At initial presentation (combined childhood and pediatric moyamoya), cerebral ischemic events account for 63% of cases, intracerebral hemorrhage (ICH) for 22% of cases, seizures occur in 8% and other events in 7.5% of cases.[32,33]

Ischemic events are predominant in childhood moyamoya disease, occurring in 69% of cases less than age 10 years, with 70% to 80% of events accounted for by transient ischemic attacks and the remaining being cerebral infarction.[32,33] Ischemic events may be precipitated by maneuvers that alter cerebral blood flow, such as hyperventilation.[34] In one study, approximately 44% of patients with known childhood moyamoya suffered an ICH as an adult.[35] There are no predictors either for rate of progression or of recurrent events in childhood moyamoya disease, although early onset (<4 years) is associated with mental retardation and epilepsy in the first year of life and is associated with a poor outcome. Frequent ischemic events are associated with low intelligence quotients and impaired activities of daily living.[36,37] The majority of childhood moyamoya cases have a relatively benign course, with approximately 80% being independent in their activities of daily living and having a normal life expectancy.[33]

ICH is the most common cause of death in moyamoya disease and is much more common in the Japanese and Asian adult variant, occurring in approximately 66% of adult cases, with a preponderance of females.[33] There are no predictors of ICH, although age and hypertension are thought to be contributing factors. ICHs may be multiple and recur from days to years after the initial event. The majority of hemorrhages are intraventricular or intracerebral,

Table 60.1 Guidelines for the diagnosis of moyamoya disease

(1) Angiographic requirements:
  a. Stenosis or occlusion of the terminal internal carotid artery (ICA) and/or of the proximal portion of the anterior cerebral arteries (ACA) and/or middle cerebral arteries (MCA)
  b. Abnormal vascular networks in the region of the occlusive or stenotic lesions in the arterial phase of angiography
  c. Findings A and B present bilaterally.
(2) If magnetic resonance angiography (MRA) is employed, all of the following criteria must be met:
  a. Stenosis or occlusion of the terminal ICA and/or of the proximal portion of the ACA and MCA on MRA.
  b. Abnormal vascular networks in the basal ganglia on MRA (more than two flow voids in the basal ganglia on either side)
  c. Findings a and b present bilaterally.
(3) Exclusion of the following disease processes:
  a. Arteriosclerosis
  b. Autoimmune disease
  c. Brain tumor
  d. Down syndrome
  e. Head trauma
  f. Irradiation of the head
  g. Meningitis
  h. Neurofibromatosis
  i. Other.
(4) Pathological findings:
  a. Thickening of the intima with resultant stenosis or occlusion in the terminal portion of the ICA, usually bilaterally; lipid deposits may be seen in the intima
  b. Fibrocellular thickening of the intima, waving of the internal elastic lamina, thinning of the tunica media, and varying degrees of stenosis are seen in the main arteries of the circle of Willis (ACA, MCA, posterior communicating artery)
  c. Numerous perforating and anastomotic branches around the circle of Willis
  d. Networks of small vessels are found in the pia matter.
(5). Diagnostic certainty:
  a. Definite moyamoya: cases that fulfill criteria 1 or 2, and 3. Childhood cases, however, need only fulfill criteria 1 a and b or 2 a or b on one side, and also must have stenosis of the terminal ICA on the opposite side.
  b. Probable moyamoya: cases that fulfill criteria 1 a and b or 2 a and b, and criterion 3; however, findings are only unilateral.

Modified from Fukui et al.[41]

and recur in up to one-third of patients.[38] Acute stroke mortality has been reported as 2.4% in ischemic stroke and 16.4% in hemorrhagic stroke.[33]

In contrast to these findings, adult moyamoya disease in the USA tends to have a predominance of ischemic and not hemorrhagic strokes. Furthermore, North American studies have not found an age peak in childhood.[13,39]

Classification

Currently, the Suzuki grading scale is use to stage the progression of moyamoya disease. There are six stages, defined as:

Stage 1 Narrowing of the carotid fork
Stage 2 Initial appearance of moyamoya vessels
Stage 3 Intensification of moyamoya vessels
Stage 4 Minimization of moyamoya vessels
Stage 5 Reduction of moyamoya vessels
Stage 6 Disappearance of moyamoya vessels (collateral circulation only from the external carotid arteries).[1,40]

Diagnosis

Strict criteria for the diagnosis of moyamoya disease have been established by the research committee on spontaneous occlusion of the circle of Willis of the Ministry of Health and Welfare, Japan, and are summarized in Table 60.1.[41] As stated in this table, patient's may be classified as either definite or probable moyamoya patients, with unilateral findings found in the probable cases. In unilateral cases repeat neuroimaging is recommended, as 7% to 27% of cases will have subsequent bilateral findings, particularly children aged under 10.[42] Unilateral cases associated with other systemic or underlying diseases (see Table 60.2) should be called unilateral moyamoya.

Differential diagnosis

Quasi moyamoya disease, or *rui* in Japanese, was initially described by Watanabe and Suzuki and refers to:

1. unilateral moyamoya
2. moyamoya vessels associated with stenosis or occlusion of the proximal portion of the MCA
3. an association with vascular malformations
4. known causes as defined in Table 60.1.
5. other causes.[45]

Other causes encompass a broad array of disorders that have been reported in the medical literature as having similar angiographic findings as moyamoya disease, and are listed in Table 60.2.

Treatment

Indications for surgical or medical treatment are unclear, and the tendency is for conservative medical management in mildly affected patients with transient symptoms and for surgical intervention in the more severely affected cases, particularly when regional deficits are seen on blood-flow studies.[26,46] There is a paucity of data on the role of vasodilators and antiplatelet agents in preventing recurrent ischemic

Table 60.2 Conditions that may mimic moyamoya disease angiographically

1. Autoimmune disorders
   - Graves disease
   - Sjögren syndrome
   - Vasculitis
   - Sarcoidosis
2. Congenital/genetic disorders
   - Alagille syndrome
   - Apert syndrome
   - Down syndrome
   - Hirschsprung disease
   - Homocystinuria
   - Marfan syndrome
   - Neurofibromatosis
   - Osteogenesis imperfecta
   - Retinitis pigmentosa
   - Tuberous sclerosis
   - Turner syndrome
3. Drug
   - Oral contraceptives
   - Phenobarbital
4. Infectious disorders
   - Leptospirosis
   - Propionibacterium
   - Tuberculosis
   - EBV
5. Hematological disorders
   - Aplastic anemia
   - Fanconi's anemia
   - Factor XII deficiency
   - Sickle cell anemia
   - Thalassemia
   - Thrombotic thrombocytopenic purpura
6. Metabolic disorders
   - Altered NADH-CoQ reductase activity
   - Glycogen storage disease type 1
   - Hyperlipoproteinemia type 2A
   - Hyperthyroidism
   - Lipohyalinosis
   - Pseudoxanthoma elasticum
7. Other
   - Cardiomyopathy
   - Cranial trauma
   - Cranial irradiation
   - Eosinophilic granuloma
   - Harlequin syndrome
   - Hydrocephalus
   - Hypertension
   - Neonatal anoxia
   - Polycystic kidney disease
   - Myopathy
   - Neonatal anoxia
8. Serologies
   - Anti-DNA antibody
   - Anti-nuclear antibody
   - Anti-ssA antibody
   - Anti-ssB antibody
   - Lupus anticoagulants
9. Tumors
   - Sellar and parasellar tumors
   - Wilms tumor
10. Vascular
    - Aneurysms
    - Arterial venous malformation
    - Atherosclerotic disease
    - Cerebral arterial dolioectasia
    - Coarctation of the aorta
    - Fibromuscular dysplasia
    - Radiation-induced arteritis

Modified from Garg et al., Natori et al. and Yonekawa and Taub[40,43,44]

events in moyamoya disease. Nicardipine has been reported to alleviate transient ischemic attacks. Current management attempts to maintain individuals euvolemic, normotensive, normocapnic and on nimodipine to prevent cerebrovascular events.[47]

Surgical intervention has been the accepted norm for individuals with recurrent ischemia and/or moderate to severe disease. Revascularization procedures have focused on the following three methods:

1. Direct revascularization procedures such as superficial temporal artery to middle cerebral artery bypass (STA–MCA) or extracranial to intracranial (EC-IC) bypass
2. Indirect revascularization with or without anastomosis, which brings external carotid artery flow to the internal carotid artery system (such procedures are encephaloduroarteriosynangiosis (EDAS), enencephalomyosynangiosis (EMS), encephalomyosynangiosis (EMS), encephaloarteriosynangiosis (EAS) and omentum transplantation
3. Combination of direct and indirect revascularization procedures.

STA–MCA bypass has been documented, in a number of studies, to increase cerebral blood flow and improve prognosis when compared to conservative medical therapy in select patients. Initially performed by Karasawa et al., 23 STA–MCA anastomoses were performed in addition to 7 EMS on 17 cases with typical and atypical moyamoya disease. With a follow-up ranging from 16 months to 49 months, 9/17 patients had an excellent outcome, 5/17 had a good outcome and 1/17 a fair outcome. Two patients remained unchanged. The greatest benefit was noted in subjects with recurrent transient ischemic attacks.[48] Improvement of cerebral blood flow has also been documented, but the procedure does not prevent rebleeding.[49,50] This procedure, however, is limited by the availability of adequate cortical vessels for anastomosis, and may only improve regional cerebral blood flow. As a result of this difficulty, indirect revascularization procedures were developed.

EMS and EDAS are the commonest indirect revascularization procedures performed, while EAS, duraplexy and omental transplantation remain alternative therapeutic options.[51–53] A Korean study reported results on 17 carefully selected patients who had undergone SPECT scanning and received EDAS compared to nine non-surgical moyamoya patients. In follow-up, ten surgical patients had an excellent to good outcome at 1 year, two had a fair outcome and three remained unchanged (two patients were lost to follow-up). In the non-surgical group, six remain unchanged, one had a fair outcome and two were lost to follow-up.[54] Chiu et al., in an American study, reported perioperative stroke in 1/24 cases undergoing EDAS, 0/2 receiving EDAMS, 1/2 EC–IC bypass, and 2/3 omental transpositions of which one was fatal. Kaplan–Meier estimate for the 5-year risk for ipsilateral stroke after EDAS or EDAMS was 15% compared to 20% in the medically treated arm.[15] Indirect procedures are preferable to the STA–MCA procedure, particularly when there is decreased blood flow in the occipital region. Indirect procedures alone, however, are not always able to provide adequate collateral flow to prevent recurrent ischemia. For this reason, a combined surgical approach is often performed when anatomically feasible.

Ishikawa et al. compared the effectiveness of a combined STA–MCA with EDAMS ($n = 48$ hemispheres) to EDAMS alone ($n = 16$ hemispheres). While there was no difference in perioperative ischemic events, postoperatively, ischemic events occurred in 10% of cases undergoing a combined procedure compared to 56% of cases in the indirect group ($P < 0.01$). In a study from Osaka, Japan, of 19 hemispheres undergoing combined procedures, no recurrent cerebrovascular events occurred within the 4-year follow-up.[55] Further support for the favorability of a combined procedure stems from data from a study by Matsushima et al., who compared a combined procedure to EDAS alone.[56] Complete resolution of symptoms was clearly superior in the combined group than in individuals undergoing EDAS (56% to 41%).

Controversy still remains regarding the optimal surgical procedure for moyamoya disease. Nakashima et al., in a retrospective study, reviewed 71 cases of moyamoya who had undergone either STA–MCA bypass, a combined procedure, EDAS, EDAMS or ribbon EDAMS.[57] Follow-up arteriography revealed collateral formation to be optimal in the ribbon EDAMS procedure and EDAMS, with much poorer collateral formation in the direct and combined procedure groups. All patients in this study had resolution of either transient ischemic symptoms or seizures by 1 year. Interestingly, the surgical group that benefited most from their procedure was the EDAS group followed by EDAMS, ribbon EDAMS, STA–MCA bypass, and finally the combined procedure. Thus in this study, the extent of collateral did not completely correlate to clinical resolution of symptoms.

While surgical intervention shows promise in preventing recurrent ischemic, controversy exists as to whether revascularization surgery can prevent and/or reduce ICH or rebleeding rates. In a retrospective study, 282 hemispheres with ICH were reviewed for their management and outcome.[58] Conservative management was employed in 13% of cases, medical management of their ICH in 32% of cases, ventricular drain and/or hematoma removal was performed in 16% of cases, and a revascularization procedure in 38% of patients. Of those undergoing surgical revascularization, 46% underwent indirect revascularization procedures, 22% received a direct procedure and 32% underwent a combined direct and indirect procedure. Approximately 18% of patients experienced rebleeding, and no differences were found between any of the treatment arms. In a study of 28 patients presenting with ICH and a mean follow-up of 14 years, Yoshida et al. reported their experience on rebleeding following revascularization. Five (18%)

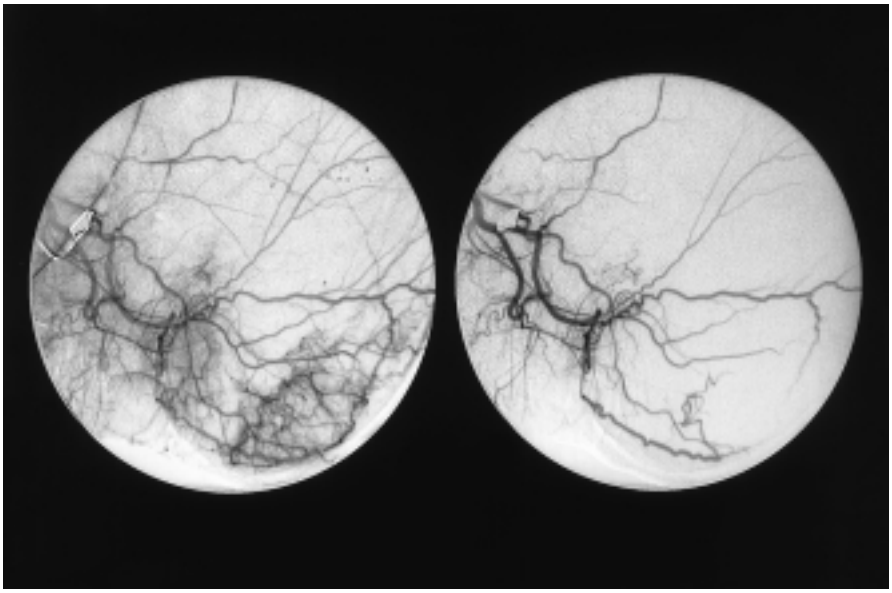

Figure 60.1 External carotid injection displaying hypertrophied middle meningeal artery (right) and the presence of numerous transdural anastomosis (left) providing collateral circulation in an individual with moyamoya disease.

patients died as a result of the initial ICH and two more died from other causes. Rebleeding occurred in 6/21 (18%) and occurred anywhere from 2–20 years following the initial ICH. No significant difference in rebleeding rates was found between the surgical revascularization group and the conservatively managed group.[59] In a study of 35 cases, 24 presenting with an ICH and 11 with an ischemic event, in which all had undergone combined STA–MCA and EDAS, Houkin and colleagues found similar bleeding rates between the two groups (3/24 vs. 2/11).[60] While revascularization did not decrease the rebleeding rate, they were able to document a 25% decrease in moyamoya vessels. While the results presented above show no benefit to surgery, others argue surgery may be detrimental and actually increase the risk of hemorrhage.[61]

Irrespective of the type of the revascularization procedure to be performed, or an ischemic or hemorrhagic indication, intraoperative, perioperative and postoperative meticulous medical management is necessary to optimize a favorable outcome. Normocapnea, a euvolemic state, the use of nimodipine and the selection of appropriate anesthetic agents are all necessary to reduce the risk of potential perioperative ischemia or hemorrhage.[62,63]

At the University of Texas, Houston, surgical revascularization is performed on moyamoya patients with moderate to severe disease and/or those who have failed maximal medical management. Direct, indirect or combined surgical revascularization procedures are tailored on an individual basis, and decision-making is based on arteriographic findings as well as the location of hypoperfusion based either on blood flow or perfusion studies. Individuals with spontaneous transdural collateral vessels are generally not considered for synangiosis. We avoid long-term use of anticoagulation because of the concern for hemorrhagic stroke.

References

1. Suzuki J, Takaku A. Cerebrovascular "moyamoya" disease: disease showing abnormal net-like vessels in base of brain. Arch Neurol 1969;20:288–299
2. Sano K. Cerebral juxta-basal telangectasie. No To Shinkei 1965;17:748–750
3. Handa H, Tani K, Kajikawa H, et al. Autopsy case of the so called cerebral arterial rete in an adult. No To Shinkei 1969;21(2):181–191
4. Weidner W, Hanafee W, Markham C. Intracranial collateral circulation via leptomeningeal and rete mirabile anastomosis. Neurology 1965;15:39–48
5. Nishimoto A, Takeuchi S. Abnormal cerebrovascular network related to the internal carotid arteries. J Neurosurg 1968;29:255–260
6. Kudo T. Spontaneous occlusion of the circle of Willis, a disease apparently confined to Japanese. Neurology 1968;18:485–496
7. Wakai K, Tamakoshi A, Ikezaki K, et al. Epidemiological features of moyamoya disease in Japan: findings from a nationwide survey. Clin Neurol Neurosurg 1997;99(Suppl 2):S1–S5
8. Ikezaki K, Han D, Kawano T, et al. Epidemiological survey of moyamoya disease in Korea. Clin Neurol Neurosurg 1997;99(Suppl 2):S6–S10
9. Matsushima Y, Qian L, Aoyagi M. Comparison of moyamoya disease in Japan and moyamoya disease (or syndrome) in the People's Republic of China. Clin Neurol Neurosurg 1997;99(Suppl 2):S19–S22
10. Hung C, Tu Y, Su C, et al. Epidemiological study of moyamoya disease in Taiwan. Clin Neurol Neurosurg 1997;99(Suppl 2):S23–S25
11. Bruno A, Adams H, Biller J, et al. Cerebral infraction due to moyamoya disease in young adults. Stroke 1988;19:826–833
12. Bruno A, Yuh W, Biller J, et al. Magnetic resonance imaging in young adults with cerebral infraction due to moyamoya. Arch Neurol 1988;45:303–306
13. Numaguchi Y, Gonzalez C, Davis P, et al. Moyamoya disease in the United States. Clin Neurol Neurosurg 1997;99(Suppl 2):S26–S30
14. Brown M, Quets J. Midwest experience with moya-

moya disease. Clin Neurol Neurosurg 1997;99(Suppl 2):S36–S38
15. Chiu D, Sheddon P, Batina P, et al. Clinical features of moyamoya disease in the United States. Stroke 1998;29: 1347–1351
16. Fukushima Y, Kondo Y, Kuroki Y, et al. Are Down syndrome patients predisposed to moyamoya disease? (letter). Eur J Pediatr 1986;144:516–517
17. Yamashita M, Oka K, Tanaka K. Histopathology of the brain vascular network in moyamoya disease. Stroke 1983;14:50–58
18. Masuda J, Ogata J, Utani C. Smooth muscle cell proliferation and localization of macrophages and T-cell in the occlusive intra-cranial major arteries in moyamoya disease. Stroke 1993;24:1960–1967
19. Yoshimoto T, Houkin K, Takahashi A, Abe H. Angiogenic factors in moyamoya disease. Stroke 1996;27: 2160–2165
20. Yamamoto M, Aoyagi M, Fukai N, et al. Differences in cellular responses to mitogens in arterial smooth muscle cells derived from patients with moyamoya disease. Stroke 1998;29:1188–1193
21. Yamamoto M, Aoyagi M, Tajima S, et al. Increase in elastin gene expression and protein synthesis in arterial smooth muscle cells derived from patients with moyamoya disease. Stroke 1997;28:1833–1738
22. Takahashi A, Sawamura Y, Houkin K, et al. The cerebrospinal fluid in patients with moyamoya disease (spontaneous occlusion of the circle of Willis) contains high level of basic fibroblast growth factor. Neurosci Lett 1993;160:214–216
23. Kawaguchi S, Sakaki T, Morimoto T, et al. Characteristics of intracranial aneurysms associated with moyamoya disease: a review of 111 cases. Acta Neurochir (Wien) 1996;138:1287–1294
24. Herreman F, Nathal E, Yasui N, Yonekawa Y. Intracranial aneurysms in moyamoya disease: report of ten cases and review of the literature. Cerebrovasc Dis 1994;4:329–336
25. Ogata J, Masuda J, Nishikawa M, Yokota T. Sclerosed peripheral-artery aneurysm in moyamoya disease. Cerebrovasc Dis 1996:6:248–249
26. Masuda J, Ogata J, Yamaguchi T. Moyamoya disease: *In:* Barnett HJM, Mohr JP, Stein BM, Yatsu FM, eds. Stroke: Pathophysiology, Diagnosis and Management. New York: Livingstone, 1998:815–832
27. Aoyagi M, Ogami K, Matsushima Y, et al. Human leukocyte antigen in patients with moyamoya disease. Stroke 1995;26:415–417
28. Kitahara T, Okumura K, Semba A, et al. Genetic and immunologic analysis on moyamoya. J Neurol Neurosurg Psychiatry 1983;45:1048–1052
29. Inoue T, Ikezaki K, Sasazuki T, et al. Analysis of class II genes of human leukocyte antigen in patients with moyamoya disease. Clin Neurol Neurosurg 1997; 99(Suppl 2):S234–S237
30. Yamauchi T, Tada M, Houkin K, et al. Linkage of familial moyamoya disease (spontaneous occlusion of the circle of Willis) to chromosome 17q25. Stroke 2000; 31:930–935
31. Inoue T, Ikezaki K, Sasazuki T, et al. Linkage analysis of moyamoya disease on chromosome 6. J Child Neurol 2000;15:179–182
32. Fukui M, Kawano T. Follow-up study of registered cases in 1995. *In:* Fukui M, ed. Annual Report by Research Committee on Spontaneous Occlusion of the Circle of Willis (Moyamoya Disease) 1995. Japan: Ministry of Health and Welfare, 1996:12
33. Handa H, Yonekawwa Y. Analysis of the filing data bank of 1500 cases of spontaneous occlusion of the circle of Willis and follow-up study of 200 cases for more than 5 years. Stroke (Tokyo) 1985;7:477–480
34. Ogawa A, Nakamura N, Yoshimoto T, Sakurai Y. Cerebral blood flow in moyamoya disease. Part 1: Correlation with age and regional distribution. Acta Neurochir (Wein) 1990;105:30–34
35. Hashimoto N, Iwama T, Tsukahara T, Goto Y. Potential hazard of intracranial bleeding and cerebral ischemia in patients with moyamoya disease. *In:* Gukui M, ed. Annual Report of the Research Committee on Spontaneous Occlusion of the Circle of Willis (Moyamoya Disease) 1995. Japan: Ministry of Health and Welfare, 1996:55–60
36. Moritake K, Handa H, Yonekawa Y, et al. Follow-up study on the relationship between age at onset of illness and outcome in patients with "moyamoya disease." Neurol Surg 1986;14:957–963
37. Nakase H, Ohnishi H, Touho H, et al. Long-term follow-up of epileptic moyamoya disease in children. Neurol Med Chir (Tokyo) 1993;33:621–624
38. Yonekawa Y, Goto Y, Ogata N. Moyamoya disease: Diagnosis treatment and recent achievement. Part IV. Specific medical diseases and stroke. *In:* Barnett HJM, Mohr JP, Stein BM, Yatsu FM, eds. Stroke: Pathophysiology, Diagnosis and Management. New York: Livingstone, 1992:721–747
39. Numaguchi Y, Gonzalez C, Davis P, et al. Moyamoya disease in the United States. Clin Neurol Neurosurg. 1997;99(Suppl 2):S26–S30
40. Garg B, Bruno A, Biller J. Moyamoya disease and cerebral ischemia. *In:* Batjer HH, ed. Cerebrovascular Disease. Philadelphia: Lippincott–Raven Publishers, 1997:489–499
41. Fukui M, for Members of the Research Committee on Spontaneous Occlusion of the Circle of Willis. Moyamoya disease. Clin Neurol Neurosurg 1997;99(Suppl 2):S238–S240
42. Ikezaki K, Inamura T, Kawano T, Fukui M. Clinical features of probable moyamoya disease in Japan. Clin Neurol Neurosurg 1997;99(Suppl 2):172–177
43. Natori Y, Kiyonobu I, Matsushima T, Fukui M. Angiographic moyamoya: its definition, classification and therapy. Clin Neurol Neurosurg 1997;2(Suppl 2): 168–172
44. Yonekawa Y, Taub E. Moyamoya disease: status 1998. Neurologist 1999;5:13–23
45. Watanabe T, Suzuki N. Quasi-moyamoya disease. *In:* Suzuki J, ed. Moyamoya Disease. New York: Springer-Verlag, 1986:145–168
46. Ikezaki K, Matsushima T, Kuwabara Y. Cerebral circulation and oxygen metabolism in childhood moyamoya disease: a perioperative positron emission tomography study. J Neurosurg 1994.81:843–850
47. Hosain S, Hughes J, Forem S, et al. Use of a calcium channel blocker (nincardipine HCL) in the treatment of childhood moyamoya disease. J Child Neurol 1994;9:378–380
48. Karasawa J, Kikuchi H, Furuse S, et al. Treatment of moyamoya disease with STA–MCA anastomosis. J Neurosurg 1978;49:679–688
49. Ikezake K, Matsushima T, Kuwabara Y, et al. Cerebral circulation and oxygen metabolism in childhood moyamoya disease. A perioperative positron emission tomography study. J Neurosurg 1994;81:843–850
50. Okada Y, Shima T, Nishida M, et al. Effectiveness of superficial temporal artery–middle cerebral artery

anastomosis in adult moyamoya disease. Cerebral hemodynamics and clinical course in ischemic and hemorrhagic varieties. Stroke 1998;29:625–630
51. Karasawa J, Kikuchi H, Furuse S, et al. A surgical treatment of moyamoya disease. Encephalomyosynangiosis. Neurol Med Chir (Tokyo) 1977;17:29–37
52. Karasawa J, Touhou H, Ohnishi H, et al. Cerebral revascularization using omental transplantation for childhood moyamoya disease. J Neurosurg 1993;79: 192–196
53. Matsushima Y, Inaba Y. Moyamoya disease in children and its surgical treatment. Introduction of a new surgical procedure and its follow-up angiogram. Childs Brain 1984;11:155–170
54. Han D, Nam D, Oh C. Moyamoya disease in adults: characteristics of clinical presentation and outcome after encephaloduro-arteriosynangiosis. Clin Neurol Neurosurg 1997;99(Suppl 2):151–155
55. Sakamoto H, Kitano S, Yaui T, et al. Direct extracranial–intracranial bypass for children with moyamoya disease. Clin Neurol Neurosurg 1997;99(Suppl 2): 128–133
56. Matsushima T, Inoue T, Suzuki S, et al. Surgical techniques and the results of a fronto-temporo-parietal combined indirect bypass procedure for children with moyamoya disease: a comparison with the results of encephaloduro-arteriosynangiosis. Clin Neurol Neurosurg 1997;99(Suppl 2):S123–S127
57. Nakashima H, Meguro T, Kawada S, et al. Long-term results of surgically treated moyamoya disease. Clin Neurol Neurosurg 1997;99(Suppl 2):S156–S161
58. Ikezaki K, Fukui M, Inamura T, et al. The current status of treatment for hemorrhagic type moyamoya disease based on a 1995 nationwide survey in Japan. Clin Neurol Neurosurg 1997;99(Suppl 2):S183–S186
59. Yoshida Y, Yoshimoto T, Shirane R, Sakurai Y. Clinical course, surgical management, and long term outcome of moyamoya patients with rebleeding after an episode of intracerebral hemorrhage. An extensive follow-up study. Stroke 199;30:2272–2276
60. Houkin K, Kamiyama H, Hiroshi A, et al. Surgical therapy for adult moyamoya disease. Can surgical revascularization prevent the recurrence of intracerebral hemorrhage? Stroke 1996;27:1342–1346
61. Aoki N. Cerebrovascular bypass surgery for the treatment of moyamoya disease: unsatisfactory outcome in the patients presenting with intracranial hemorrhage. Surg Neurol 1993:40;372–377
62. Iwama T, Hashimoto N, Yonekawa Y. The relevance of hemodynamic factors to perioperative ischemic complications in childhood moyamoya disease: Clinical studies. Neurosurgery 1996;38:1120–1126
63. Sato K, Shirane R, Yoshimoto T. Perioperative factors related to the development of ischemic complications in patients with moyamoya disease. Childs Nerv Syst 1997;13:68–72