

REVIEW ARTICLE

Moyamoya Disease in Asia

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Abstract

Moyamoya disease is a rare cerebrovascular disorder, characterised by progressive stenosis and/or occlusion of the intracranial internal carotid artery and its proximal branches with the development of a basal collateral network. Moyamoya disease has a high prevalence in Asia, particularly in Japan, Korea and China. Ischemic events and intracranial bleeding are the most common clinical manifestation of moyamoya disease. Although the beneficial effect on hemorrhage is still not clear, revascularisation surgery remains the most effective way to prevent the progression of ischemic symptoms. Moyamoya disease has been investigated by numerous studies since it was first described 50 years ago, many conundrums remain to be solved. In this article, we review the history, epidemiology, aetiology, clinical manifestation, diagnosis and treatment of moyamoya disease. Recent advances and future challenges of moyamoya disease are also discussed.

INTRODUCTION AND HISTORICAL REVIEW

Moyamoya disease is a chronic cerebrovascular disorder, defined as the progressive stenosis or occlusion of the intracranial vessels. The stenosis begins from the terminal bifurcation of internal carotid arteries and gradually progresses to the anterior, middle, and posterior cerebral arteries. The gradual stenosis of these arteries is accompanied by a collateral network of vessels formed at the base of the brain, which produces the characteristic reticulate appearance “puff of smoke” on angiography.

In 1957, Takeuchi and Shimizu in Japan published the first description of moyamoya disease in the medical literature.¹ In 1963, Suzuki *et al.* proposed this cerebrovascular condition as a new disease to the Japanese medical community.² In 1969, Suzuki and Takaku described 21 cases and suggested the term “moyamoya disease”. This name later became well known internationally³, and a number of typical cases had been reported all over the world.^{4,5} The medical community initially thought that moyamoya disease was a regional disease of East Asia, especially in Japan, China and Korea, based on the reports from Asia in 1970s and 1980s.⁶⁻¹⁰ With the development of the noninvasive diagnostic tools such as

magnetic resonance angiography (MRA) and other investigations, moyamoya disease has been increasingly reported from many other regions of the world.

The clinical features and histopathological characteristics of moyamoya disease were established in the 1970s. Surgical procedures for the ischemic form of moyamoya disease were performed from the late 1970s to the 1980s. In the 1990s, the rapid development of investigations facilitated the search for the causative gene of moyamoya disease. In the last decade, there was more research to determine the pathogenesis of moyamoya disease. However, despite the many advances in the past 50 years, moyamoya disease remains an enigma with many aspects of the disease remaining unsolved.

EPIDEMIOLOGY

Japan is the country where moyamoya disease was first reported, and it continues to report the highest incidence rate of the disease. A nationwide

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epidemiological survey of moyamoya disease has been conducted 4 times in Japan: 1986, 1990, 1995, and 2003.^{11,12} The survey in 2003¹² showed that the prevalence and incidence was 6.03 and 0.54 per 100 000 respectively. This is in contrast to lower rates reported in the survey of 1995¹¹ at 3.16 and 0.35 per 100 000 respectively. A regional epidemiological survey in Hokkaido (island of Northern Japan) revealed a further increase in the prevalence and incidence at 10.5 and 0.94 per 100 000 population from 2002 to 2006.¹³ This increase in prevalence and incidence may be partly explained by better ascertainment of the cases, with the development of non-invasive diagnostic technologies.

There has been no nationwide epidemiological survey of the prevalence and incidence of moyamoya disease in other Asian countries. In China, a regional epidemiological survey in Nanjing, the capital city of Jiangsu province¹⁴ has reported the prevalence and incidence as 3.92 and 0.43 per 100 000 respectively from 2000 to 2007. In Taiwan, the annual incidence has been estimated to be 0.48 per 100 000 population in 1978 to 1995, a rate close to that of Nanjing.¹⁵ Taking into account the differences in methodologies and years of study, the prevalence of moyamoya disease among the Chinese may be similar to that of Japan.

As for gender and age distribution, the patterns appear to vary in different countries. According to the survey in 2003¹² in Japan, there was a high female to male ratio at 1.8:1. In men, there was a major peak at age 10 to 14 years, and two smaller peaks at 35 to 39 years and 55 to 59 years. In women, two peaks were seen at 20 to 24 years and 50 to 54 years. In the report from Hokkaido¹³, the ratio of female to male patients was even higher at 2.18:1, and the highest peak was observed at 45 to 49 years, and a smaller peak at 5 to 9 years. In Korea, two peaks of age distribution was reported, at 0 to 10 years and 20 to 39 years.¹⁶ The study in Nanjing, China reported a lower female to male ratio of 1.15:1.¹⁴ The age peaks observed were 5 to 9 years and 35 to 39 years. Thus, it appears that all the three countries reported a similar age distributions of peaks in childhood and adulthood, but the female preponderance seen in Japan was not observed among the Chinese. These differences among patients of different nationalities may be related to genetic, environmental and other unknown factors.

PATHOGENESIS

In the 1970s and early 80s, moyamoya disease has been observed to be associated with neurofibromatosis¹⁷, radiation therapy¹⁸, cranial trauma⁹, as well as tuberculous meningitis²⁰, leptospirosis²¹, atherosclerosis²² and sickle cell anemia.²³ In 1997 however, the Research Committee on Spontaneous Occlusion of the Circle of Willis published guidelines for the diagnosis of moyamoya disease (Table 1).²⁴ According to the guidelines, moyamoya disease can only be diagnosed after the exclusion of other underlying or "basic" diseases and conditions, such as arteriosclerosis and autoimmune disease as listed in Table 1. The term is thus restricted to patients where the etiology is unknown.

According to the Japanese epidemiological survey in 2003¹², 12.1% of the patients had family history of moyamoya disease. Furthermore, in the identical twin study, concordance of disease involvement was observed to be 80%, again suggesting the importance of genetic factor in the pathogenesis.²⁵ In 1995, Aoyagi²⁶ studied 32 Japanese patients and found a significant association between human leukocyte antigen (HLA) B51 and moyamoya disease, with the frequency of the B51-DR4 combination to be significantly higher as compared to controls. Subsequently, HLA- DRB1, HLA- DQB1²⁷ and HLA- B35²⁸ were also found to be associated with moyamoya disease, confirming the role of HLA alleles in the pathogenesis. A linkage study of moyamoya disease using markers on chromosome 6, where the HLA gene is located, showed that the marker D6S441 was likely to be linked to moyamoya disease.²⁹ As for neurofibromatosis type 1, where the causative gene is reported to be located on chromosome 17q11.2.6³⁰, the locus of moyamoya disease has also been suggested to be on chromosome 17 (17q25 region).³¹ Other candidate genes that have been reported were on 3p24.2-26³², 8q23³³ and 17q25.3.³⁴

The pathological studies indicated that progressive stenosis or occlusion of moyamoya disease were principally associated with fibrocellular thickening of the intima, irregular undulation of the internal elastic laminae and attenuation of the media.^{35,36} During the development of moyamoya disease, excessive accumulation of the smooth muscle cells and abnormal production of extracellular matrix played important roles in the pathogenesis.³⁷ It has been suggested that matrix metalloproteinases (MMPs) and their tissue inhibitors (TIMPs), which regulate

the interaction between smooth muscle cells and the extracellular matrix, may be responsible for the development of moyamoya disease. A potentially functional polymorphism G-418C in the TIMP2 promoter was suggested to be a genetic predisposing factor for Korean familial moyamoya disease from a single nucleotide polymorphisms (SNPs) scan.³⁸ Moreover, several studies demonstrated an over-expression of MMP-9 and under-expression of MMP-3, TIMP1 and TIMP2 were related to moyamoya disease.^{39,40} Recently, we found an association of the MMP-3 functional polymorphism at position-1171 with both moyamoya disease and familial moyamoya disease in the Han Chinese population, which indicated the important role of the balance between MMPs and TIMPs in the pathogenesis of moyamoya disease.⁴¹

Thus, although there has been some important recent progress in the understanding of moyamoya disease, the pathogenesis remains an enigma. There are various evidences pointing to genetic factors playing a major role in the pathogenesis, the epidemiological studies indicate that environmental and other factors, such as cytokines parasecretion⁴² and infection⁴³ may also be important in the development of the disease.

CLINICAL PRESENTATION

Moyamoya disease usually causes two major categories of symptoms, transient ischaemic attack or cerebral infarction due to the occlusion or stenosis of the internal carotid artery; and intracranial bleeding due to dilated, fragile collateral vessels as compensatory response to ischemia.

The clinical manifestations of moyamoya disease has strong age-related and geographic differences.¹¹⁻¹⁶ In Hokkaido Japan, 57.4% of patients inclusive of adults and children presented with ischemic symptoms, with 78.4% of the patients below 10 years of age having ischemia.¹³ However in Korea, the incidence of hemorrhage is higher at 42.4% overall, and 69% in adults.¹⁶ In Nanjing China, hemorrhage is again more common, at 56% overall and 62% in the adult.¹⁴ In United States, most adults and children presented with ischemic symptoms, but the rate of hemorrhage was also higher in adults as compared to children (20% vs 2.8%).^{44,45}

Overall, the main symptoms in pediatric patients with moyamoya disease were cerebral ischemia. Intracranial bleeding was more commonly seen among the adults.

DIAGNOSIS

The Japanese Research Committee of the Ministry of Health and Welfare concerning Spontaneous Occlusion of the Circle of Willis proposed diagnostic criteria for moyamoya disease in 1997 (Table 1), which has been used worldwide, helped to improve the knowledge and facilitate the investigations of the disease.²⁴ However, there remains a number of practical issues related to the diagnosis.

The first is regarding the definition between the terms “moyamoya disease” and “moyamoya syndrome”. The term “moyamoya syndrome” has been commonly used when there are similar findings to moyamoya disease in a patient with underlying or “basic disease”, which is thus excluded by the diagnostic criteria for moyamoya disease. However, the absence of so-called “basic diseases” only meant this was not found during the time of presentation. Particularly for adult patients, the natural history of moyamoya disease is variable and disease progression can be slow, so the preceding “basic disease” could have been missed and the patient misdiagnosed as having “moyamoya disease” when they should be classified as “moyamoya syndrome”. On the other hand, it is also possible to have patients diagnosed to have “moyamoya syndrome”, when they in fact initially had “moyamoya disease”, and the “basic disease” such as atherosclerosis develop later.

Secondly, the diagnostic criteria classically describe the stenosis or occlusion observed “at the terminal portion of the internal carotid artery and/or at the proximal portion of the anterior and/or the middle cerebral arteries.” However, the stenosis or occlusion of the posterior cerebral artery can also be observed in about 30-58% of the patients.^{46,47}

Thirdly, the question of formation of moyamoya vessels is confusing for many non-neurologists. Conventional cerebral angiography is still the golden standard for the diagnosis of moyamoya disease, and the six-stage classification for cerebral angiography originally introduced by Suzuki and Takaku³ is still widely used. However, the classic extensive collateral network at the base of the brain on angiography can only be seen during the intermediate stages. The clinicians should thus be aware of the full spectrum of the imaging changes so as not to miss the diagnosis.

Table 1: Diagnostic criteria for moyamoya disease²⁴

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- (1) Cerebral angiography is indispensable for the diagnosis and should present at least the following findings:
 - 1) Stenosis or occlusion at the terminal portion of the internal carotid artery and/or at the proximal portion of the anterior and/or the middle cerebral arteries.
 - 2) Abnormal vascular networks in the vicinity of the occlusive or stenotic lesions in the arterial phase.
 - 3) These findings should present bilaterally.
 - (2) When MRI and MRA clearly demonstrate all the findings described below, conventional cerebral angiography is not mandatory.
 - 1) Stenosis or occlusion at the terminal portion of the internal carotid artery and at the proximal portion of the anterior and middle cerebral arteries on MRA.
 - 2) An abnormal vascular network in the basal ganglia on MRA. Note: an abnormal vascular network can be diagnosed when more than two apparent flow voids are seen in one side of the basal ganglia on MRI.
 - 3) 1) and 2) are seen bilaterally. (Refer to the Image Diagnostic Guidelines by MRI and MRA.)
 - (3) Because the etiology of this disease is unknown, cerebrovascular disease with the following basic diseases or conditions should thus be eliminated:
 - 1) Arteriosclerosis; 2) autoimmune disease; 3) meningitis; 4) brain neoplasm; 5) Down syndrome; 6) Recklinghausen's disease; 7) head trauma; 8) irradiation to the head; 9) others.
 - (4) Instructive pathological findings:
 - 1) Intimal thickening and the resulting stenosis or occlusion of the lumen are observed in and around the terminal portion of the internal carotid artery usually on both sides. Lipid deposits are occasionally seen in the proliferating intima.
 - 2) Arteries constituting the circle of Willis such as the anterior and the middle cerebral and the posterior communicating arteries often show stenosis of various degrees or occlusion associated with fibrocellular thickening of the intima, a waving of the internal elastic lamina, and an attenuation of the media.
 - 3) Numerous small vascular channels (perforators and anastomotic branches) are observed around the circle of Willis.
 - 4) Reticular conglomerates of small vessels are often seen in the pia mater.
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TREATMENTS

Till to date, there is no proven effective medical therapy for moyamoya disease. Among all the treatment options, revascularisation surgery is the most successful therapy in preventing stroke for moyamoya disease patients.³⁶ Surgical revascularisation techniques for moyamoya disease can be classified into direct, indirect, and combined bypass.

Direct bypass is a procedure for directly anastomosing a branch of the extracranial artery to an intracranial cortical artery. Superficial temporal artery-to-middle cerebral artery (STA-MCA) anastomosis is the most widely used. Under special conditions, an occipital artery to middle cerebral artery (OA-MCA) anastomosis⁴⁸ or a superficial temporal artery to anterior cerebral artery (STA-ACA) anastomosis⁴⁹ can be used as an alternative. The first superficial temporal artery-to-middle cerebral artery bypass for moyamoya disease was performed in 1972⁵⁰, and it has become the

most common surgical procedure for patients with moyamoya disease. Direct bypass surgery can improve cerebral blood perfusion immediately and thus reduce the risk of perioperative ischaemic stroke.⁵¹ However, it is difficult to perform when the cortical branches have a small diameter and/or a fragile wall especially in some paediatric patients. Another disadvantage of direct techniques is that immediate pronounced changes in cerebral haemodynamics may induce serious complications due to hyperperfusion and increased risk of stroke.

There are various methods for *indirect bypass* procedures, including:

- Cervical sympathectomy (CS)
- Omental transplantation (OT)
- Multiple burr holes (MBH)
- Encephalo-myio-synangiosis (EMS)
- Encephalo-arterio-synangiosis (EAS)
- Encephalo-duro-synangiosis (EDS)
- Encephalo-myio-arterio-synangiosis (EMAS)

- Encephalo-duro-arterio-synangiosis (EDAS)
- Encephalo-duro-arterio-myo-synangiosis (EDAMS)
- Encephalo-duro-galeo (periosteal)-synangiosis (EDGS)
- Multiple combined indirect procedures (MCI)

In 1980, encephalo-duro-arterio-synangiosis (EDAS)⁵² was reported. The results of this procedure surprised many moyamoya disease neurosurgeons for its remarkable effect and since then many other indirect operations of the same principal have been reported as listed above. The mechanism of indirect methods is the spontaneous revascularisation between the brain surface and the vascularised donor tissues. One of the advantages of indirect techniques is that it is easy to perform, but the efficacy of the surgery is not immediate because the formation of collateral vessels requires approximate 2 weeks⁵³ to 3 months⁵⁴ to develop. Among the indirect methods, encephalo-duro-arterio-synangiosis (EDAS) is the most commonly performed. Encephalo-duro-arterio-synangiosis (EDAS) requires less operation time and thus lessens the perioperative risks.

To date, the debate over the superiority between direct and indirect methods continues. Some researchers attempted to combine these two bypass procedures, and hope that the two procedures could complementing each other.^{51,55} The combined bypass can be used particularly when it is difficult to obtain adequate collateral vessels as a result of revascularisation, especially in adult patients.

Presently, most researchers generally accept that surgical interventions can improve cerebral haemodynamics and reduce the risk of subsequent strokes in patients with ischemic moyamoya disease. Both direct⁵⁶ and indirect⁴⁴ bypasses are effective especially on pediatric patients. For adult, a number of studies indicated better collateral vessels formation by direct⁵⁷ or combined⁵⁸ bypass in comparison with indirect approach. So far evidences from randomised clinical trials to assess and compare the efficacy of two surgical methods are lacking.

In our own experience, we do not find the adults to have less collateral vessels formation with indirect bypass. We believe that a carefully designed preoperative evaluation is the most important factor in achieving satisfactory treatment results. This evaluation includes: 1) Detailed clinical assessment of vascular risk

factors, such as hypertension, hyperlipidemia, and evidence of atherosclerosis; 2) Transcranial Doppler sonography (TCD), perfusion magnetic resonance (MR), single-photon emission computed tomography (SPECT) or positron emission tomography (PET) to determine the hemodynamic status and metabolism; 3) Cerebral angiography; 4) Special protocol during anesthesia to avoid hyperventilation and to maintain blood pressure at patient's usual levels.

Recurrent haemorrhage is still one of the most serious complications in the adult patients. The tiny moyamoya vessels were the source of the hemorrhage. For the moyamoya disease patients who present with intracranial hemorrhage, revascularisation surgery is the only possible treatment to prevent future recurrent bleeding. A tendency towards decrease in moyamoya vessels with a reciprocal relation between neovascularisation induced by bypass surgery and moyamoya vessels⁵⁴, is the basis for surgery. In order to study the effectiveness of bypass surgeries for the hemorrhage^{59,60}, Japan initiated a multicentre, randomised clinical trial on adult in 2001⁶¹ and the result of this clinical trial will be available in 2013, which is probably going to be the key evidence to put the controversy of the treatments to an end.

In conclusion, the aetiology and pathogenesis of moyamoya disease remain incompletely understood, and genetic analysis may to unveil the mysteries in the future. However, presently there are challenges in identifying the causative genes of familial moyamoya disease. The natural history of moyamoya disease is another area that requires further study, as it can guide the clinicians to prognosticate more accurately and choosing the timing of surgical intervention. Revascularisation surgery appears to be the most effective way to prevent the progression of clinical symptoms for ischemic moyamoya disease. In general early diagnosis and surgical treatment can reduce the risk stroke complications. Individually tailored surgical plan is also crucial to achieve the optimal treatment effect.

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