Moyamoya Disease: Recent Progress and Outlook

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Abstract

Moyamoya disease as a clinical entity has been known for more than 40 years. Constant efforts have been directed at clarifying the pathogenesis of this disorder and improving therapeutic methods for the ischemic and hemorrhagic stroke caused by the characteristic vasculopathy of this disease. Although much knowledge has been gained, unresolved problems remain, such as the true epidemiology of this disease, elucidation of the genetic mechanism, and prevention of repeated hemorrhagic events. In this paper, we review recent progress and discuss the outlook for this disorder.

Key words: moyamoya disease, epidemiology, genetic analysis, hemorrhage, pregnancy and delivery

Introduction and Historical Review

Moyamoya disease is a unique cerebrovascular disease characterized by progressive stenosis or occlusion of the bilateral terminal internal carotid arteries (ICAs) and secondary formation of unusual vascular networks that act as collateral pathways. These occlusive changes probably occur in the primitive internal carotid artery system, so the posterior cerebral artery, which originates in the embryologic primitive internal carotid artery, can be involved. This disorder was initially reported in Japan in 1957, and its clinical features were investigated in detail in the 1960s. Various names had been given to this clinical entity in the early years, such as Nishimoto disease and cerebral arterial rete, but the name spontaneous occlusion of the circle of Willis was proposed in 1968, and has been used ever since by the research committee for this disease established in 1977 by the Japanese Ministry of Health and Welfare. However, this disease was first described with the notable term moyamoya (a Japanese word meaning “puff of smoke”) in 1969, and this name became popular internationally. During the early period, this vasculopathy was considered a regional disease of East Asia, particularly Japan and the Republic of Korea. However, several Western countries began to report cases after publication of the literature in English.

The histopathology of moyamoya disease was studied in detail in the 1970s and 1980s, and revealed that the affected vessels had a fibrous intimal thickening with laminated elastic fibers but without atherosclerotic or inflammatory changes. Many patients, especially those in early childhood, suffered ischemic attacks, and no specific medical treatment was found. Surgical treatments were adopted for the ischemic form of moyamoya disease in the 1970s. The first procedure proposed was superficial temporal artery-middle cerebral artery (STA-MCA) anastomosis, and many kinds of indirect procedures have been proposed since, such as encephalo-myo-synangiosis (EMS) and encephalduro-arterio-synangiosis (EDAS). A number of neurosurgeons engaged in a heated debate over the relative merits of direct and indirect bypass procedures in the 1980s, but such arguments are rarely heard today. The consensus, at least in Japan, seems to be that the direct bypass is preferable for adults while either the direct or indirect procedure is effective for pediatric patients.

Noninvasive magnetic resonance (MR) angiography became common in the 1990s, so the number of asymptomatic or minimally symptomatic patients diagnosed with MR angiography increased rapidly. Research also began on the genetic factors in moyamoya disease during this decade. The causative genes for moyamoya disease have not yet been completely identified, but are likely to be revealed in the near future. While much progress has been achieved in research on this disease, many problems remained unsolved. In this paper, the authors review the recent progress in research and discuss the outlook for moyamoya disease.
Current Knowledge of the Epidemiology of Moyamoya Disease

I. Epidemiological features in Japan

In Japan, four nationwide surveys were conducted in 1984, 1989, 1994, and 2003. The 1994 study estimated the total annual number of patients treated for moyamoya disease at 3,900, with the prevalence and the annual incidence rates being 3.16 and 0.35 per 100,000 population, respectively.55) The female-to-male ratio was 1.8 and 10% of the patients had a family history of the disease. The distribution of the age at onset had two peaks: a large peak at 5 years of age and a smaller peak around the late 20s to 30 years of age. The age at onset was under 10 years in 47.8% of the patients.

The more recent survey shows a dramatic increase in the number of patients.32) In 2003, the total number of patients treated in Japan was estimated at 7,700. The female-to-male ratio was 1.8, and a family history was found in 12.1% of patients. The prevalence rate was calculated at 6.03 per 100,000 population, and the annual rate of newly diagnosed cases in 2003 was 0.54 per 100,000 population. Furthermore, in 2009, an analysis of the regional all-inclusive epidemiological data obtained in Hokkaido, a major island of Japan with a population of 5.63 million,2) reported the prevalence as 10.5 patients per 100,000 population and the annual incidence as 0.94 per 100,000 population, both of which greatly exceeded the results of previous surveys. The female-to-male ratio was 2.18. Age of onset occurred in two peaks: the highest was observed between 45 and 49 years, and the second occurred between 5 and 9 years. A familial history was observed in 15.4% of patients. These epidemiological features differed significantly from the data obtained in the previous studies. The higher detection and prevalence rates do not seem to indicate an actual rapid increase in the incidence of moyamoya disease; as this survey probably reflects the recently increased access to noninvasive diagnostic tools, such as MR angiography.

II. Moyamoya disease worldwide

Moyamoya disease occurs predominantly in Asians, but has also been reported among Caucasians, African-Americans, and Hispanics. A survey of the literature published between 1972 and 1989 found 1,063 cases reported outside Japan,7) including 625 cases in Asia (289 in Korea and 245 in China), 201 in Europe, 176 in North and South America, 52 in Africa, and 9 in Oceania. Regrettably, cases of "moyamoya syndrome" associated with other disorders (e.g., sickle cell anemia) were included in this series and were not differentiated from true moyamoya disease.

To the authors' knowledge, only Japan and the Republic of Korea have conducted large-scale nationwide epidemiological surveys of moyamoya disease. The cooperative survey in Korea, which was published in 2000, evaluated 334 patients with definite moyamoya disease who were diagnosed before 1995. The clinical features seem to resemble those of Japanese patients.9) Analysis of the characteristics of the patients in these two countries in detail compared 296 definite cases in Korea with 731 definite cases in Japan, and concluded that the clinical background of moyamoya disease in Korea is essentially similar to that of Japan.14) In China, there have been few systematic epidemiological investigations into moyamoya disease. According to a clinical review, the clinical features of moyamoya disease in China differ somewhat from those in other countries.33) Although the age distribution among Chinese patients is similar to that among Japanese and Korean patients, the Chinese exhibit a male prevalence over females (1.16:1) and the incidence of adult moyamoya disease is higher than that of children (3.5:1). Addressing these differences, cases of moyamoya syndrome were included in the study and pediatric cases might have been ignored because neurological pediatrics is not a common area of practice in China.

Moyamoya disease is extremely uncommon in non-Asian populations. Limited data about Caucasian patients suggest notable differences in clinical presentation of the disease. A survey in the western U.S. states of Washington and California found the annual incidence was 0.086 per 100,000 population.54) Ethnicity-specific incidences were highest among Asian-Americans (0.28), followed by African-Americans (0.13), whites (0.06), and Hispanics (0.03), which indicates that ethnic differences in moyamoya incidence appear to remain after immigration to the U.S.A. At present, several differences between moyamoya disease in the U.S.A. and east Asian countries have been pointed out, with cases in the U.S.A. showing predominance of ischemic over hemorrhagic stroke in adult cases3,8,43); absence of an age peak in childhood35); extreme female predominance9); and remarkably high rate of recurrent stroke in the first few years after presentation3,8) For example, a female-to-male ratio of 2.7:1 was reported and only 20.5% of the adult patients presented with hemorrhage. In medically treated symptomatic hemispheres, the 5-year risk of recurrent ipsilateral stroke reached 65% after the initial symptoms and 27% after angiographic diagnosis. The North American and Asian forms of moyamoya disease might differ because their clinical manifesta-
tions exhibit no coincidence at all.

The situation in Europe has proved to be similar to that of the U.S.A. In 2008, detailed demographic and clinical data about white European patients with moyamoya disease presented the following notable findings: older age at onset (median age 34 years) and absence of an age peak in childhood; extreme female predominance (4.25:1); rarity of hemorrhagic attack (5%); high risk of recurrent ischemic events following the onset of symptoms (61.9% in the first year); and high risk of perioperative stroke (27.3%). The difference between white and Asian patients may be related to the timing of onset of occlusive vasculopathy. In Asia, arterial occlusion occurs most frequently in childhood and the frequency of ischemic attack peaks at that time. The increased risk of intracranial bleeding in Asian adults might be a consequence of an extensive network of fragile moyamoya collaterals developing for decades since childhood. On the other hand, occlusive vasculopathy in white patients may occur in adulthood and induce ischemic attacks soon after the onset of the arterial occlusion. At present, it is not clear whether Asians and Caucasians develop an identical form of moyamoya disease. Further research is needed to identify the clinical, pathological, and genetic differences to demonstrate whether treatments established in Asia are effective for Caucasians and vice versa.

Diagnostic Criteria for Moyamoya Disease: Time to Reconsider?

In 1977, a research committee was organized with the support of the Japanese Ministry of Health and Welfare to initiate systematic research on moyamoya disease. The committee proposed diagnostic criteria for moyamoya disease in 1995 (published in English in 1997) that have been in wide use worldwide (Table 1). While these diagnostic criteria have contributed to appropriate diagnosis of this disease, the research committee has recently pointed out several problems.

First, occlusive changes at the proximal middle cerebral artery (MCA) or at the anterior cerebral artery (ACA) without involvement of the terminal portion of the ICA can be misdiagnosed as moyamoya disease. This may be because the Japanese-language version of the diagnostic criteria describes lesions of the ICA, MCA and ACA equally and does not stipulate the absolute inclusion of the ICA lesion. In the English-language version, as shown in Table 1, the requirement of an ICA lesion is also ambiguous because of the usage of the term “and/or.” It is possible that vasculopathy with proximal MCA/ACA stenosis is identical to moyamoya disease; however, moyamoya disease has been defined historically as an occlusive disorder that affects the terminal portion of the ICA. Therefore, a line should be clearly drawn between these variants and “true” moyamoya disease.

Second, the use of the Japanese term utagai (“probable”), which refers to unilateral involvement of occlusive disease, is confusing. Originally, the word utagai in the criteria for moyamoya disease meant “doubtful” or “less certain” rather than “likely.” According to the Collins COBUILD Advanced Learner’s English Dictionary, the word probable means “likely to be true” or “likely to happen.” Therefore, the English-language version of the criteria is not appropriate; moreover, even the Japanese-language edition is ambiguous, as utagai

Table 1  Diagnostic criteria for moyamoya disease

<table>
<thead>
<tr>
<th>Requirement</th>
<th>Example</th>
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<tbody>
<tr>
<td>(A) Cerebral angiography is indispensable for the diagnosis, and should</td>
<td>(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.</td>
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<td>present at least the following findings:</td>
<td>(2) Abnormal vascular networks in the vicinity of the occlusive or stenotic lesions in the arterial phase.</td>
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<td>older age at onset (median age 34 years) and absence of an age peak in</td>
<td>(3) These findings should present bilaterally.</td>
</tr>
<tr>
<td>childhood; extreme female predominance (4.25:1); rarity of hemorrhagic</td>
<td>(B) When magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) clearly demonstrate all the below described findings, conventional cerebral angiography is not mandatory.</td>
</tr>
<tr>
<td>attack (5%); high risk of recurrent ischemic events following the onset of</td>
<td>(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.</td>
</tr>
<tr>
<td>symptoms (61.9% in the first year); and high risk of perioperative stroke</td>
<td>(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.</td>
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<td>(27.3%).</td>
<td>(3) (1) and (2) are seen bilaterally. (Refer to the Image Diagnostic Guidelines by MRI and MRA).</td>
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<td>The difference between white and Asian patients may be related to the</td>
<td>(C) Because the etiology of this disease is unknown, cerebrovascular disease with the following basic diseases or conditions should thus be eliminated:</td>
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<td>timing of onset of occlusive vasculopathy.</td>
<td>(1) Arteriosclerosis.</td>
</tr>
<tr>
<td>In Asia, arterial occlusion occurs most frequently in childhood and the</td>
<td>(2) Autoimmune disease.</td>
</tr>
<tr>
<td>frequency of ischemic attack peaks at that time.</td>
<td>(3) Meningitis.</td>
</tr>
<tr>
<td>The increased risk of intracranial bleeding in Asian adults might be a</td>
<td>(4) Brain neoplasm.</td>
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<td>consequence of an extensive network of fragile moyamoya collaterals</td>
<td>(5) Down syndrome.</td>
</tr>
<tr>
<td>developing for decades since childhood. On the other hand, occlusive</td>
<td>(6) Recklinghausen’s disease.</td>
</tr>
<tr>
<td>vasculopathy in white patients may occur in adulthood and induce</td>
<td>(7) Head trauma.</td>
</tr>
<tr>
<td>ischemic attacks soon after the onset of the arterial occlusion.</td>
<td>(8) Irradiation to the head.</td>
</tr>
<tr>
<td>At present, it is not clear whether Asians and Caucasians develop an</td>
<td>(9) Others.</td>
</tr>
<tr>
<td>identical form of moyamoya disease. Further research is needed to</td>
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<td>identify the clinical, pathological, and genetic differences to</td>
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<td>demonstrate whether treatments established in Asia are effective for</td>
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<td>Caucasians and vice versa.</td>
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Definite case: Satisfies criteria (A) or (B) and (C). However, a pediatric case which fulfills (A) (1) and (2) or (B) (1) and (2) on one side, with remarkable stenosis at the terminal portion of the internal carotid artery on the opposite side, is also defined as definite. Probable case: Satisfies (A) (1) and (2) or (B) (1) and (2) and (C) (unilateral involvement).
can be taken to mean either “likely” or “doubtful.” The research committee is engaged in ongoing discussion about this point. Accordingly, the phrase “unilateral moyamoya disease” might be preferable.

Third, a question has arisen regarding the stereotypical exclusion of cases involving basic disorders such as autoimmune disease and arteriosclerosis. At present, such cases are referred to as “akin-moyamoya disease,” “quasi-moyamoya disease,” and particularly in western countries, “moyamoya syndrome.” It is true that some disorders, such as neurofibromatosis type 1, cause moyamoya-like vasculopathy, and vascular occlusion following radiation therapy for intracranial tumors must be attributed to the irradiation itself. However, the incidental coexistence of moyamoya disease and other disorders cannot be denied, especially in cases of arteriosclerosis or common autoimmune disease (e.g., Graves disease) when the angiographic findings and clinical features are fully compatible with those of moyamoya disease. The committee is now addressing this issue. Therefore, the description of the basic disease might undergo revision.

Progress and Recent Findings on the Genetic Analysis of Moyamoya Disease

A family history is present in 12.1% of patients with moyamoya disease.32) Furthermore, the incidence of the disease in both monozygotic twins is estimated to be 80%.10) Although the pathogenesis of moyamoya disease remains unclear, these data strongly indicate that moyamoya disease is related to genetic factors. Several research groups began to search for the causative gene of moyamoya disease in the late 1990s, and some candidates have been found.

The first report on the genetic locus of familial moyamoya disease was presented in 1999.13) This genome-wide linkage study on 16 Japanese families with moyamoya disease found a significant linkage between the disease and markers located at 3p24.2–26. Some other groups focused on specific chromosomes instead of a genome-wide study; for example, chromosome 6, where the genes of human leukocyte antigen (HLA) are located, was examined closely. HLA plays an important role in controlling the immune system and is known to be associated with various diseases such as autoimmune diseases.51) First, a significant association of HLA-B51 was reported in 32 unrelated Japanese patients with moyamoya disease in 1995.17) This result was obtained by serological typing and subsequent DNA-typing of HLA in 71 unrelated Japanese patients86) revealed that several HLA alleles had a significant association with moyamoya disease. Using these results, an additional linkage study using markers on chromosome 6 in 19 families reported that D6S441(6q) might be linked to moyamoya disease.15) Moyamoya syndrome is occasionally seen in neurofibromatosis type 1 and its causative gene NF1 is located on chromosome 17q11.2. Therefore, linkage analyses on chromosome 17 in 24 families identified the locus of the disease in 17q25.37) A genome-wide linkage analysis in 12 families with affected sibling pairs reported significant evidence of linkage to 8q23 (maximum logarithm of odds [LOD] score of 3.6) and suggestive evidence of linkage to 12q12 (maximum LOD score of 2.3).47) Each of these results indicated a different location for the causative genes of moyamoya disease; moreover, the mode of genetic inheritance was not determined. For example, pedigree analysis of familial moyamoya disease found no specific pattern of genetic inheritance.49)

Recently, novel findings have been presented from surveys of highly aggregated families. Fifteen Japanese families with three or more affected members (52 patients and 14 obligatory carriers) were examined.30) Twelve families were three-generation, two were four-generation and one was five-generation. A total of 43.7% of the 135 offspring of the affected people were patients with moyamoya disease or obligatory carriers, and the mode of inheritance of familial moyamoya disease was concluded to be autosomal dominant with incomplete penetrance. Genome-wide parametric linkage analysis in 15 highly aggregated families35) used two diagnostic classifications: narrow (definite moyamoya disease) and broad (any steno-occlusive lesions around the terminal portions of the internal carotid arteries). Under both classifications, significant evidence of linkage was observed only on chromosome 17q25.3 with maximum LOD scores of 6.57 (under the narrow classification) and 8.07 (under the broad classification). The moyamoya disease locus was mapped to a 3.5 Mb region between D17S1806 and the telomere of 17q, close to the previously reported loci at 17q25.57) but the two loci did not overlap. This study had three unique concepts: only highly aggregated families with more than three affected generations were recruited; parametric linkage analysis assuming an autosomal dominant model could be adopted; and obligatory carriers were regarded as being affected.24) Four candidate genes have been selected on the basis of the biological functions and further analysis is now under way.

Neurol Med Chir (Tokyo) 50, September, 2010
Surgical Treatment for Ischemic Moyamoya Disease

Surgical revascularization improves hemodynamic impairment and reduces ischemic attacks in patients with ischemic moyamoya disease.38) Since the 1970s, many kinds of bypass procedures have been proposed, which can be roughly divided into three categories: direct anastomotic bypass, indirect bypass, and combinations. Active debates on the superiority and inferiority of direct and indirect bypass procedures were once common, with each procedure being proposed according to its clinical effectiveness. A consensus on this issue has since emerged, as clearly stated in the new guidelines published in 2009 (in Japanese).45)

(1) Pediatric cases: Either one of the following approaches is effective at improving hemodynamic impairment: direct bypass procedures or indirect bypass procedures.
(2) Adult cases: Either one of the following approaches is effective: direct bypass procedures or a combination of procedures including direct bypass. Indirect bypass procedures only are not recommended because of inferior effectiveness.

A number of papers and review articles explain these surgical procedures, so they are not discussed here in detail. It should be emphasized that perioperative management is extremely important in bypass surgery for moyamoya disease. Nonsurgical intraoperative factors such as hypercapnia, hypocapnia, and hypotension can increase the risk of postoperative ischemic complications.17,42,46,48)

Recent progress in postoperative management has included detection of local hyperperfusion. It is widely known that transient neurological deficits are frequently observed after direct bypass procedures with no evidence of infarction apparent in MR imaging. Although these phenomena mimic transient ischemic attacks, their pathophysiology has long remained a mystery. Recently, a postoperative study with single photon emission computed tomography has revealed that these events can be caused by local hyperperfusion after direct anastomosis.5) Because the approach to managing ischemia is completely different from that of hyperperfusion, the postoperative routine study of cerebral blood flow is essential.

Prevention of Intracranial Hemorrhage

More than one-half of all adult-onset patients with moyamoya disease suffer intracranial hemorrhage.39) Such bleeding attacks, which are potentially fatal, seriously affect the patient’s prognosis.58) Typically, the hemorrhage occurs in the thalamus and basal ganglia, and frequently involves perforation to the lateral and third ventricles. In rare instances, subcortical or subarachnoid hemorrhage can also be observed. Chronic hemodynamic stress may induce pathological change in the collateral moyamoya vessels and the following phenomena cause bleeding attacks:
(1) rupture of fragile and maximally dilated moyamoya vessels;
(2) rupture of microaneurysms formed in the moyamoya vessels (Fig. 1A); and
(3) rupture of saccular aneurysms located on the circle of Willis, especially on the basilar bifurcation and the posterior cerebral arteries (Fig. 1B).

In addition to the various neurological deficits that can result from the initial hemorrhagic attacks, patients also face frequent rebleeding attacks that seriously affect the patients’ prognosis.23,41) A survey revealed that 33% of 175 patients with hemorrhagic moyamoya disease experienced a rebleeding attack.41) Moreover, the annual rebleeding rate was reported as 7.09%.23) Therefore, management of hemorrhagic moyamoya disease presents a serious and urgent challenge. Although typical saccular aneurysms in the posterior circulation can be treated mainly by endovascular embolization, direct treatment of most of the bleeding sources in moyamoya vessels is not possible. No therapeutic method of preventing rebleeding attacks has yet been established.

At present, bypass surgery is the only promising strategy. Reductions in moyamoya vessels can often be detected by angiography after direct bypass surgery for ischemic moyamoya disease (Fig. 2).12) Because tiny moyamoya vessels are the source of the bleeding, the rate of hemorrhagic attacks can possi-
Moyamoya Disease: Recent Progress and Outlook

Fig. 2  Reduction of moyamoya vessels after superficial temporal artery-middle cerebral artery (STA-MCA) bypass in adult patients. A: Left internal carotid angiograms obtained before surgery showing the moyamoya vessels are remarkably well developed. B: Left external carotid angiogram obtained after STA-MCA anastomosis showing the collateral blood flow via the direct bypass covers approximately two-thirds of the outer surface of the left hemisphere. C: A left internal carotid angiogram obtained after surgery showing the reduced size of the moyamoya vessels.

possibly be decreased by reducing this hemodynamic stress, and consequently reducing the size and number of moyamoya vessels. As a result, a hypothesis has emerged that direct anastomotic bypass surgery prevents future rebleeding; in fact, some authors have reported the effectiveness of direct bypass for hemorrhagic moyamoya disease. On the other hand, some reports indicate no significant reduction in the rebleeding rate, therefore, surgical treatment of adult hemorrhagic moyamoya disease remains controversial.

To resolve these issues, the Japan Adult Moyamoya (JAM) Trial was undertaken in Japan in 2001. This randomized controlled trial seeks to determine whether direct bypass surgery such as STA-MCA anastomosis reduces the rate of recurrent bleeding attacks. After giving informed consent, patients who fulfilled all the clinical and radiological requirements underwent a computer-generated randomization scheme and were assigned to receive either the best medical care to modify risk factors or the best medical care plus extracranial-intracranial (EC-IC) bypass. Eighty patients were enrolled in the trial and registration was closed in June 2008. These patients are now under close follow up. The results of the trial will be disclosed in 2013, and expectations are high that this trial will reveal the key to solving the problem of rebleeding.

Pregnancy, Childbirth, and Moyamoya Disease

Moyamoya disease is more prevalent in females and occurs most frequently in childhood and early adulthood, so it is not uncommon for such patients to become pregnant and give birth. In general, pregnancy is known to increase the risk of cerebrovascular disease. No evidence exists that the risk of stroke increases during pregnancy in patients with moyamoya disease; however, there have been sporadic case reports of pregnant moyamoya patients presenting with stroke. In 1998, these case reports were analyzed in an extensive review of the management of pregnancy and delivery in patients with moyamoya disease. In summary, the prognosis for pregnant patients known to have moyamoya disease is generally good, whereas the prognosis for women who were first diagnosed with moyamoya disease following the occurrence of a stroke during the period of pregnancy and delivery is poor. With one exception, all maternal deaths and cases of poor prognosis were the result of cerebral hemorrhage.

At present, no guidelines have been issued for managing pregnancy in patients diagnosed with moyamoya disease, and even recommendations regarding delivery method (natural labor, painless labor with spinal epidural anesthesia, or caesarian section) seem to differ from one hospital to the next. In 2008, the present authors conducted a nationwide survey on the management of pregnancy and delivery in women with moyamoya disease in Japan. This survey targeted the experiences of 270 perinatal medical centers in Japan during the preceding 5 years. The survey cited 64 deliveries comprising 59 cases of previously diagnosed moyamoya disease and 5 cases of moyamoya disease newly diagnosed as a result of perinatal stroke.

The results of this survey indicate that the incidence of perinatal stroke is low in pregnant women previously diagnosed with moyamoya disease. Only one case of cerebral hemorrhage during pregnancy was reported in which the maternal prognosis was poor (modified Rankin scale score 4). Although caesarian section was mainly employed for women previously diagnosed with moyamoya disease (76%), no attacks were observed during either caesarian sections or vaginal deliveries; therefore, no evidence

Neurol Med Chir (Tokyo) 50, September, 2010
exists that vaginal delivery should be avoided. Extracranial-intracranial bypass surgery had been performed on 58% of the patients before pregnancy, and the experience of previous bypasses had no significant influence on the choice of delivery method. On the other hand, serious cerebrovascular events (3 cases of cerebral hemorrhage and 2 cases of cerebral ischemia) occurred in patients who had not been diagnosed with moyamoya disease before pregnancy, and one patient with intracerebral hemorrhage died. The modified Rankin scale scores of these all patients at discharge were 6 (death), 2, 1, 0, and 0.

Most pregnant patients known to have moyamoya disease can deliver safely. This could be attributable to the adequate management provided by obstetricians or previous bypass surgery. However, serious cerebrovascular events occur in patients with moyamoya disease undiagnosed before pregnancy, indicating that the risk of pregnancy and delivery in women with moyamoya disease should not be underestimated. Patients known to have moyamoya disease should be made aware of the risks of pregnancy. Moreover, it should be emphasized that a poor prognosis is mostly likely to result from cerebral hemorrhage and not cerebral ischemia. All physicians have an obligation to provide accurate information and ensure appropriate management of patients with moyamoya disease. We anticipate the rapid formulation of guidelines on management of pregnancy and delivery in women with moyamoya disease.

**Outlook**

How will moyamoya disease be treated in 30 years? Will most of the current problems be solved? The most serious and urgent problem seems to be the prevention of potentially fatal intracranial hemorrhage. As mentioned above, the JAM Trial is expected to provide some answers regarding the effectiveness of direct bypass surgery; however, while some risk-reduction effect can be expected, it may be impossible to stop recurrent bleeding attacks completely through surgical intervention. Innovative therapeutic approaches will be needed to overcome fatal rebleeding. On the other hand, the treatment of cerebral ischemia from moyamoya disease requires a greater focus on higher cognitive function, which must be maintained at least and improved if possible. Furthermore, the most fundamental issue is to clarify the entire pathogenesis of this disease. Recent genetic studies have made great strides toward identifying the causative genes in patients with familial moyamoya disease. If these genes are identified in the near future, the next step will be to clarify how these genes act to cause and contribute to the vasculopathy, which could lead to a basic treatment and possible prevention of moyamoya disease.

**Conclusion**

Current progress in research on moyamoya disease has been reviewed. Although much knowledge about this disease has been gained during the past 40 years, many issues remain unresolved. A continuous effort is required to address this disease.

**References**


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