Asymptomatic Moyamoya Disease: Literature Review and Ongoing AMORE Study

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Abstract

Recent development of a non-invasive magnetic resonance examination has increased the opportunity to identify asymptomatic patients with moyamoya disease who have experienced no cerebrovascular events. However, their clinical features, prognosis, and treatment strategy are still unclear because of small number of subjects and short follow-up periods. Therefore, we have designed Asymptomatic Moyamoya Registry (AMORE) study in Japan. The objectives of this nation-wide, multi-center prospective study are to clarify long-term prognosis of asymptomatic patients with moyamoya disease and to determine the risk factors that cause ischemic and hemorrhagic stroke in them. In this article, we review the published data on asymptomatic moyamoya disease and report the on-going multi-center prospective cohort study, AMORE study. We would like to emphasize the importance to determine the clinical features, prognosis, and treatment strategies of asymptomatic moyamoya disease in very near future.

Key words: asymptomatic moyamoya disease, AMORE study, prognosis

Introduction

Moyamoya disease is a unique cerebrovascular disorder characterized by progressive stenosis of the terminal portion of the internal carotid artery (ICA). The perforating arteries in the basal ganglia and thalamus markedly dilate and function as an important collateral circulation, called as “moyamoya” vessels. The posterior cerebral arteries are also involved in a certain subgroup of patients. Therefore, cerebral hemodynamics is often impaired especially in the frontal lobe, leading to transient ischemic attack (TIA) and cerebral infarction. Furthermore, the dilated, fragile moyamoya vessels often rupture and cause intracranial hemorrhage.1,2) The etiology of the disease is still unknown; however, recent studies have strongly suggested the involvement of some genetic factors in its pathogenesis.3) The potential contribution of infections has also been pointed out, although specific pathogens have not been identified. Superficial temporal artery to middle cerebral artery (STA-MCA) anastomosis and indirect synangiosis are well known to improve cerebral hemodynamics and reduce the risk of subsequent cerebrovascular events, including both ischemic and hemorrhagic stroke, and improve long-term outcome in patients with moyamoya disease.4–11)

On the other hand, the recent development of noninvasive diagnostic modalities, including magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA), has shown that the incidence of asymptomatic moyamoya disease may be much higher than previously believed (see below). Even in Japan, however, the epidemiology of asymptomatic moyamoya disease is still obscure, and the guidelines for the management of asymptomatic moyamoya disease have not yet been established. In this article, we review the published data on asymptomatic moyamoya disease and report the on-going multi-center prospective cohort study, Asymptomatic Moyamoya Registry (AMORE) study.

Definition

All patients should meet the guidelines for the diagnosis of moyamoya disease set by the Research Committee on Moyamoya Disease of the Ministry of Health, Labor, and Welfare of Japan. All patients should previously have no ischemic or hemorrhagic episode and be neurologically free. Patients who had previously experienced any episode suggestive
of TIA, cerebral infarction, intracranial hemorrhage, seizure, or involuntary movement caused by moyamoya disease should be excluded. Careful medical interview should be performed to distinguish moyamoya disease-related headache from non-specific headache such as tension-type headache. \(12\)

**Epidemiology**

The incidence of moyamoya disease is high in countries in East Asia such as Japan and Korea. In Japan, the annual prevalence has been estimated to be 3.16–10.5 per 100,000. The female to male ratio was shown to be 1.8. \(2\) However, both the prevalence and incidence of asymptomatic moyamoya disease are still unclear. Previously, asymptomatic patients with moyamoya disease have rarely been sporadically reported. Screening of family members with moyamoya disease has also identified small number of asymptomatic patients. Therefore, the incidence of asymptomatic moyamoya disease had been believed very low. In fact, Yamada et al. (2005) reported the results of a nation-wide questionnaire conducted in 1994 and identified 33 asymptomatic patients (1.5%) out of a total of 2,193 patients. \(13\) Nanba et al. (2003) reviewed their single-center experiences and precisely reported the clinical features of 10 asymptomatic patients with moyamoya disease. \(14\) Furthermore, an all-inclusive survey of moyamoya disease in Hokkaido, one of the major islands in Japan, revealed that 47 (17.8%) of 267 newly enrolled patients between 2002 and 2006 were asymptomatic. \(15\)

The first multi-center, nation-wide survey focused on asymptomatic patients with moyamoya disease was conducted between 2003 and 2006 in Japan. As a result, totally 40 patients were enrolled from 12 hospitals. Their mean age was 41.4 years ranging from 13 years to 67 years. The female-to-male ratio was 2.1. Clues to the diagnosis were tension-type headache in 14 patients, dizziness in 5, and head trauma in 4. Five patients were incidentally diagnosed on MRI and MRA performed for a brain health check-up. Five diagnoses were made on MRI and MRA performed for screening, because a member of their family had moyamoya disease diagnosed. They were siblings in two and offspring in three. The remaining seven cases were diagnosed on MRI and MRA performed because of an unrelated disease in other organs. Therefore, the prevalence and incidence may be much higher than considered before. The female-to-male ratio and mean age of the patients in these studies were very similar to those of moyamoya disease as a whole. \(12\)

**Radiological Findings**

On cerebral angiography, the bilateral carotid forks were involved in a majority of asymptomatic patients with moyamoya disease. Thus, Nanba et al. (2003) reported that all 10 patients were classified into bilateral type. \(14\) Subsequently multi-center, nation-wide survey in Japan also reported that 37 of 40 asymptomatic patients were judged as bilateral type. Of 72 involved hemispheres, 33 (45.8%) and 21 (29.2%) were graded as stage 3 and stage 4, respectively. More importantly, older patients had significantly more advanced disease stage \((P = 0.0134)\). \(12\)

Cerebral infarction was identified in a certain subgroup of asymptomatic patients with moyamoya disease, although they experienced no cerebrovascular events. Nanba et al. (2003) reported that 3 (30%) of 10 asymptomatic patients had cerebral infarction in the watershed zone. \(14\) Multi-center, nation-wide survey in Japan also reported that cerebral infarction was identified in 16 (20.8%) of 77 involved hemispheres. \(12\) According to a population-based autopsy study in Japan, the incidence of silent cerebral infarction was 4.4% in 40–59-year-old people. \(16\)

Therefore, the incidence of silent cerebral infarction is much higher in asymptomatic moyamoya disease than in normal population.

None of these studies detected intracranial hemorrhage in asymptomatic moyamoya disease. However, recent studies have demonstrated that \(T_2^*\)- or susceptibility-weighted MRI can more sensitively detect silent microbleeds in moyamoya disease than conventional MRI. Thus, 15–44% of adult patients with moyamoya disease have silent microbleeds in the basal ganglia, thalamus, and periventricular white matter, where they are prone to intracranial hemorrhage. Silent microbleeds may also be an independent predictor for subsequent hemorrhagic stroke. \(17–21\) More notably, Kuroda et al. (2013) reported that silent microbleeds were even found in 5 (25%) of 20 asymptomatic patients. \(21\) Therefore, further study would be warranted to evaluate the incidence of silent microbleeds in larger cohort of asymptomatic moyamoya disease.

The data on cerebral hemodynamics is limited in asymptomatic patients with moyamoya disease. Thus, Nanba et al. (2003) quantified cerebral blood flow (CBF) and cerebrovascular reactivity (CVR) to acetazolamide in 10 asymptomatic patients and found that 2 patients had normal CBF but reduced CVR and other two had reduced CBF and CVR in the involved middle cerebral artery (MCA) territory. \(14\) Multi-center, nation-wide survey in Japan...
also reported that 24 (34.3%) of 70 involved hemispheres had normal CBF but reduced CVR and other 7 (10%) had reduced CBF and CVR. Therefore, cerebral hemodynamics may be disturbed even in about 40% of asymptomatic patients. The findings are quite important to further consider the prognosis and treatment strategy in asymptomatic moyamoya disease, because the patients with reduced CBF and CVR due to occlusive carotid artery diseases are known to be at higher risk for subsequent ischemic stroke.

**Prognosis**

As aforementioned, the long-term prognosis in asymptomatic patients with moyamoya disease is not fully understood. Based on a nation-wide questionnaire study conducted in 1994, Yamada et al. (2005) retrospectively analyzed the prognosis in 33 asymptomatic patients and found that 4 patients developed TIA and other two died of intracranial hemorrhage. Nanba et al. (2003) followed up 10 asymptomatic patients during a mean period of 4.1 years. As a result, one patient (10%) developed ischemic stroke due to the progression of disease stage.

Multi-center, nation-wide survey in Japan was the first historical prospective cohort study to evaluate the prognosis in asymptomatic patients. Of totally 40 patients enrolled in this study, 6 underwent surgical revascularization including STA-MCA anastomosis, and other 34 were conservatively followed up. Of these, antiplatelets and/or anticonvulsants were prescribed in 11 asymptomatic patients. During a mean period of 43.7 months, 6 surgically treated patients experienced no cerebrovascular events. On the other hand, 7 of 34 conservatively treated patients developed any cerebrovascular events, including TIA in three patients, ischemic stroke in one, and hemorrhagic stroke in three. As a result, the annual risk of any cerebrovascular events and stroke was 5.7% and 3.2%, respectively. Disturbed cerebral hemodynamics at initial diagnosis was significantly linked to ischemic episodes (P < 0.05). Disease progression during follow-up periods also highly caused ischemic episodes. Follow-up MRI and MRA revealed silent radiological changes in other three patients, including cerebral infarction, microbleed, and disease progression. As previously reported, disease progression occurs in about 20% of patients during a mean follow-up period of 6 years. Occlusive arterial lesions progress in both anterior and posterior circulation, in both bilateral and unilateral types, and in both symptomatic and asymptomatic patients. Multivariate analysis has revealed that female gender is an independent risk factor for disease progression. Therefore, it would be natural that disease progression occurs and causes ischemic or hemorrhagic stroke even in asymptomatic patients.

Based on these observations, asymptomatic moyamoya disease is not a “silent” disorder and readily progress to cause ischemic and hemorrhagic stroke. It would also be essential to repeat MRI and MRA at regular intervals when asymptomatic patients are conservatively followed up to detect disease progression before any cerebrovascular events occur.

**Management**

Surgical revascularization has widely been accepted to reduce the risk of subsequent ischemic and hemorrhagic stroke in symptomatic patients with moyamoya disease. However, management strategies for asymptomatic moyamoya disease have not been established yet because of limited information on its clinical features.

The Research Committee on Moyamoya Disease in Japan recommends the management of risk factors and lifestyle guidance. Antiplatelet agents are not recommended for asymptomatic patients, because they may suffer hemorrhagic stroke. Surgical revascularization may be indicated, at least, in asymptomatic patients with disturbed cerebral hemodynamics, if surgical morbidity is low enough. As aforementioned, precise and regular MRI/MRA examinations should be repeated to improve their long-term outcome by predicting ischemic and hemorrhagic stroke before the onset. However, the first multi-center, nation-wide survey in Japan was a historical prospective cohort study and not a prospective study. Therefore, a prospective cohort or randomized study is warranted on the basis of a larger population of asymptomatic patients to build accurate evidence on the clinical features and outcome of asymptomatic moyamoya disease.

**AMORE Study**

Based on these observations, the Research Committee on Moyamoya Disease in Japan conducted a prospective multi-center, nation-wide observational study, AMORE study, in January 2012 to further clarify the epidemiology, pathophysiology, and prognosis in asymptomatic moyamoya disease. This study is done at 20 centers in Japan (see Appendix). The study confirmed to the Helsinki Declaration, and Good Clinical Practice Guideline, and was approved by the ethics committees at participating centers.
I. Patient eligibility

Patients are eligible if they meet the following criteria: age 20–70 years; bilateral or unilateral moyamoya disease on cerebral angiography or MRA; no episodes suggestive of TIA, ischemic stroke, and hemorrhagic stroke; possible to conservatively follow-up; and independent in daily life (modified Rankin scale 0 or 1). Exclusion criteria are previous episodes suggestive of TIA, ischemic stroke, and hemorrhagic stroke, and quasi-moyamoya disease. The patients are registered for 4 years between January 2012 and December 2015. All patients provide written informed consent when included in this study. Clinical information at enrollment includes patient’s age, gender, clue of diagnosis, past history, family history of moyamoya disease, modified Rankin scale, medicine, the frequency, location, and severity of headache, laboratory data, blood pressure, MRI (T1-weighted images, T2*-weighted images, and fluid-attenuated inversion recovery [FLAIR] images), MRA (3-dimensional time-of-flight) or cerebral angiography, and single photon emission computed tomography/positron emission tomography (SPECT/PET) data.

II. Follow-up

All enrolled patients are followed up for 5 years. A follow-up assessment is scheduled at 12 months, including any cerebrovascular event, blood pressure, MRI (T1-weighted images, T2*-weighted images, and FLAIR images), and MRA (3-dimensional time-of-flight). Primary endpoint is any ischemic and hemorrhagic stroke during a follow-up period of 5 years. Any ischemic stroke includes fresh cerebral infarction on diffusion-weighted MRI in spite of clinically transient neurological deficits that resolve within 24 hours after the onset. Secondary outcomes are TIA, newly developed ischemic and hemorrhagic lesions, and disease progression during a follow-up period of 5 years.

Conclusion

Clinical features and outcomes of asymptomatic moyamoya disease should be clarified by conducting further studies, including ongoing AMORE study. Treatment strategies would be established through these efforts.

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Conflicts of Interest Disclosure

None.

References


**Appendix**

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