Asymptomatic Moyamoya Disease

12

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Abstract

The pathogenesis, prognosis, and treatment strategy of asymptomatic moyamoya disease is still obscure. In this chapter, our knowledge is summarized by reviewing previous articles on asymptomatic moyamoya disease. Then, the results of previous small-volume cohort studies on asymptomatic moyamoya disease are reviewed, and the on-going multicenter observational study in Japan (AMORE Study) is also described.

Keywords

Asymptomatic moyamoya disease · Cerebral infarct · Microbleed · Cerebral blood flow · Outcome · Stroke · Risk · Multicenter observational study

12.1 Introduction

Moyamoya disease (spontaneous occlusion of the circle of Willis) is a disease of unknown etiology that occurs frequently in East Asia, especially in Japan, Korea, and China. This disease was first named as moyamoya disease by Suzuki and Takaku [1]. Recent studies have gradually elucidated the genes involved in the development of moyamoya disease. In addition, advances and widespread use of non-invasive imaging techniques such as MRI have contributed enormously to early diagnosis, understanding of the pathophysiology, prognosis, determination of

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treatment strategy, and improved perioperative management [2]. It is widely known that surgical revascularization is effective in preventing future TIAs and cerebral infarctions, and improved surgical techniques and perioperative management have reduced complications and improved long-term outcomes [2]. Recently, the Japan Adult Moyamoya (JAM) Trial, a randomized multicenter trial conducted in Japan, found that surgical revascularization, including direct bypass, significantly reduced rebleeding attacks in adult hemorrhagic moyamoya disease [3, 4].

However, the significance of medical and surgical treatment for incidentally discovered asymptomatic moyamoya disease remains unclear to this day [5]. This section summarizes our knowledge to date on the pathogenesis, prognosis, and treatment strategy of asymptomatic moyamoya disease and reviews the multicenter observational study initiated in January 2012 by the Research Committee on Moyamoya Disease in Japan.

12.2 Definition and Epidemiology

As mentioned above, it is a well-known fact that moyamoya disease can cause cerebral ischemic attacks such as TIA and cerebral infarction or intracranial hemorrhage. In addition, epilepsy, headache, and involuntary movements have also been reported to occur in some patients. Conversely, asymptomatic moyamoya disease is defined as an absence of previous episodes specific to moyamoya disease, such as transient ischemic attack (TIA), cerebral infarction, intracranial hemorrhage (cerebral hemorrhage, intraventricular hemorrhage, or subarachnoid hemorrhage), or involuntary movements [5].

The prevalence of moyamoya disease is reported to range from 3.16 to 10.5 per 100,000 people and has been increasing in recent years due to widespread acceptance of the disease concept and the development of non-invasive diagnostic imaging. However, the prevalence and incidence of asymptomatic moyamoya disease are not known at present. Previously, it was thought that the frequency of asymptomatic moyamoya disease was extremely low because it was mostly detected only in family members of patients with moyamoya disease when they were screened for the disease. However, with the widespread use of non-invasive diagnostic equipment such as MRI and MRA as described above, the detectability of asymptomatic moyamoya disease is increasing. Asymptomatic cases accounted for 1.5% of all cases of moyamoya disease in a nationwide survey conducted by Yamada et al. in 1994 [6], but this figure increased to 17.8% in a 2008 exhaustive survey conducted by Baba et al. in Hokkaido, the most northern island in Japan [7]. Thus, the frequency of asymptomatic moyamoya disease with no prior cerebrovascular events is now considered to be potentially higher than previously thought.

In 2007, the Research Committee on Moyamoya disease in Japan published the results of the first nationwide survey of asymptomatic moyamoya disease in Japan. Totally 40 cases of asymptomatic moyamoya disease were registered in the survey, of which one was in children and 39 in adults. Their age ranged from 13 to 67 years (mean 41.4 years), with a male-to-female ratio of 2.1, and they were found not to be significantly different from the adult symptomatic moyamoya disease. The clue of

diagnosis included 14 cases of tension-type headache, 5 cases of non-specific dizziness, 4 cases of head injury, 5 brain check-up, 5 screenings for intra-familial onset, and 7 close examinations for other organ diseases [8].

12.3 Radiological Findings

As mentioned above, the widespread use of MRI and MRA has contributed significantly to the detection of asymptomatic moyamoya disease [5, 7]. There are not so many reports that investigate cerebral angiography in asymptomatic moyamoya disease. Nanba et al. (2003) reported that all 10 cases were bilateral [9], and the first nationwide survey in Japan found that 37 of the 40 cases were bilateral and the other 3 were unilateral [8]. Thus, most moyamoya disease may have already progressed to bilateral form before its onset (Figs. 12.1, 12.2, and 12.3). The former found a tendency for Stage 1–3 to be more common in cases in the

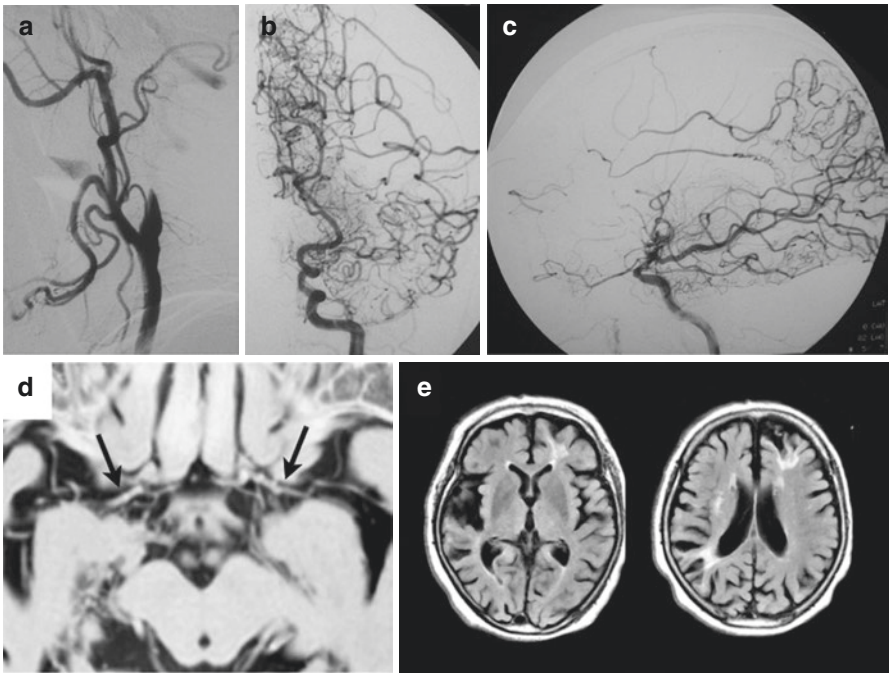

Fig. 12.1 Radiological findings of a 65-year-old female with asymptomatic moyamoya disease. Right carotid angiography (**a**) shows complete occlusion of the internal carotid artery. The Towne's (**b**) and lateral views (**c**) of left internal carotid angiography show an occlusion of supraclinoid portion of the internal carotid artery associated with dilated moyamoya vessels. Inverted image of heavy T2-weighted image (**d**) demonstrates a marked decrease of outer diameter of the middle cerebral artery on both sides (arrows), which is known specific for moyamoya disease (*see Chap.* 14). FLAIR images (**e**) reveal old cerebral infarction in the right deep white matter and parietal lobe and left frontal lobe. All of them correspond to the borderzone areas, suggesting the presence of hemodynamic insufficiency

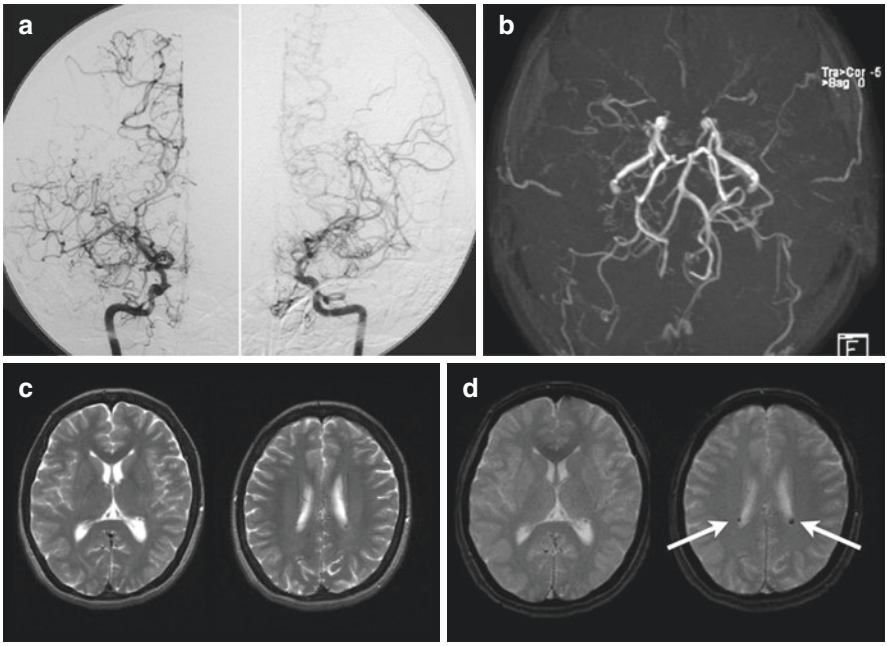

Fig. 12.2 Radiological findings of a 38-year-old female with asymptomatic moyamoya disease. No parenchymal lesions are noted on both T2- (**a**) and T2*-weighted images (**b**). MR angiography (**c**) demonstrated severe stenosis of the supraclinoid portion of the internal carotid artery and its main branches on both sides. On 15O-gas PET (**d**), cerebral blood flow (CBF) is decreased in the right frontal and temporal lobe and left frontal lobe (arrows). Cerebrovascular reactivity to acetazolamide (ACZ) is impaired in the same areas. Cerebral blood volume (CBV) is markedly elevated due to autoregulatory vasodilation in response to prolonged ischemia. Cerebral metabolic rate for oxygen (CMRO2) is also decreased. As a result, there is no definite abnormality in oxygen extraction fraction (OEF)

30s, whereas Stage 4–6 was more common in cases in the 40s and beyond [9]. Conversely, the latter report including a larger cohort showed that of the 72 affected hemispheres, angiographical stage was classified into Stage 1 on the 4 sides (5.6%), Stage 2 on the 10 sides (13.9%), Stage 3 on 33 sides (45.8%), Stage 4 on 21 sides (29.2%), Stage 5 on two sides (2.8%), and Stage 6 on two sides (2.8%). Thus, about 75% of the affected hemispheres presented Stage 3 to 4, with a significant stage progression with age [8].

Not a few cases of asymptomatic moyamoya disease show some abnormalities on brain MRI. According to a report by Nanba et al. (2003), 3 out of 10 cases (30%) had a brain infarction centered in the borderzone area [9]. In a nationwide survey in Japan, cerebral infarction was also found in 16 of 77 affected hemispheres (20.8%) [8]. Thus, cerebral infarction may have already occurred in about 20–30% of cases before the onset of the disease in asymptomatic moyamoya disease (Fig. 12.1). In these two reports, no hemorrhagic lesions have been identified in asymptomatic moyamoya disease, suggesting that a majority of intracranial hemorrhage are symptomatic. However, later, since T2*-weighted images were routinely performed, it

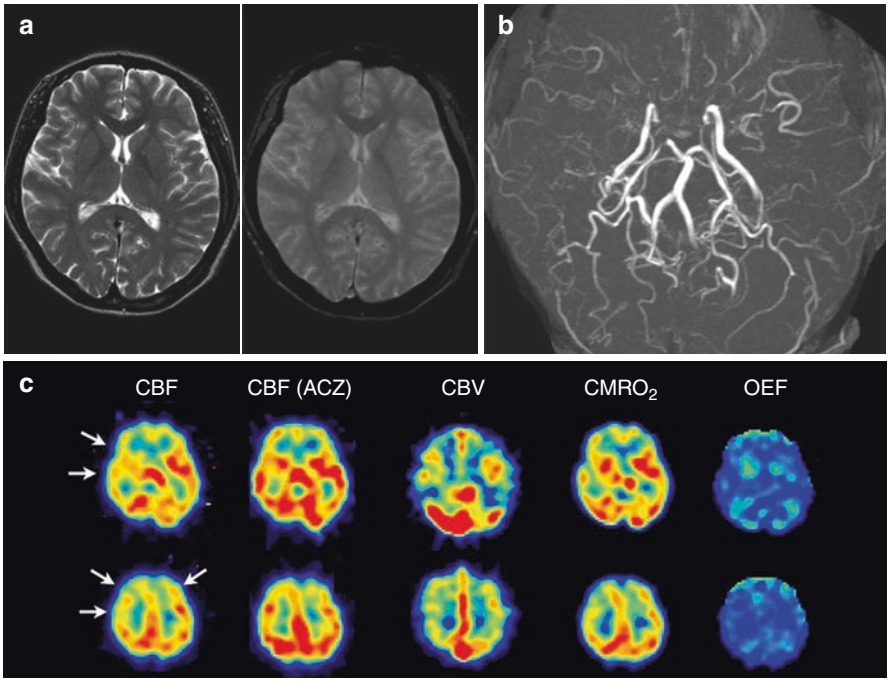

Fig. 12.3 Radiological findings of a 40-year-old female with asymptomatic moyamoya disease. On cerebral angiography (**a**), the supraclinoid portion of the internal carotid artery and its main branches are severely stenotic on both sides, which is associated with typical moyamoya vessels. MR angiography (**b**) demonstrates very similar findings. T2-weighted images (**c**) show no parenchymal lesions, but T2*-weighted images clearly demonstrate the microbleed in the subependymal area of the lateral ventricle on both sides (arrows)

became clear that a certain subgroup of patients with moyamoya disease had microbleeds. Microbleeds in moyamoya disease have been shown to be a risk factor for hemorrhagic stroke [10–12]. Therefore, it remains to be clarified how often patients with asymptomatic moyamoya disease have microbleeds (Fig. 12.2).

Previous reports have shown normal cerebral blood flow (CBF) but reduced cerebrovascular reactivity (CVR) to acetazolamide in 2 of 10 asymptomatic moyamoya disease cases (Type 2), and CBF and CVR were both reduced in a further 2 cases (Type 3) [9]. In a subsequent nationwide survey conducted in 70 hemispheres of asymptomatic moyamoya disease, both CBF and CVR were normal in 39 hemispheres (55.7%), while 24 hemispheres (34.3%) had normal CBF, but decreased CVR, suggesting moderate reduction of cerebral perfusion pressure (CPP). Other 7 hemispheres (10%) showed a decrease in both CBF and CVR, which indicates a marked reduction of CCP because of poorly developed collateral circulation (Fig. 12.3) [8]. Therefore, it is important to keep in mind that the number of cases with potential hemodynamic ischemia is not small even in asymptomatic moyamoya disease. These findings are crucial to addressing the problem of asymptomatic moyamoya disease.

12.4 Natural Course

The natural course of asymptomatic moyamoya disease is also poorly understood. Yamada et al. (2005) reported the outcome in 33 cases of asymptomatic moyamoya disease, of which TIAs occurred in 4 cases and fatal intracranial hemorrhage in two [6]. Nanba et al. (2003) conservatively followed up 10 cases of asymptomatic moyamoya disease for an average of 4.1 years and found that ischemic stroke associated with disease progression occurred in one case. This means that despite the small number of cases, the annual stroke rate was 2.4% [9].

In a subsequent nationwide survey in Japan, of the 40 enrolled cases of asymptomatic moyamoya disease, 6 patients underwent superficial temporal artery to middle cerebral artery anastomosis (STA-MCA) anastomosis and 34 patients were conservatively treated; 11 patients received some kinds of drug therapies, such as anticonvulsants or antiplatelet agents, and 24 patients received no drug therapy. During an average of 43.7 months of follow-up, there were no cerebrovascular events in the 6 patients who underwent surgical revascularization. In contrast, cerebrovascular events occurred in 7 of the 34 patients who were conservatively followed up. This included 3 TIAs, 1 ischemic stroke, and 3 intracranial hemorrhages. That means the annual incidence of stroke was 3.2% and the annual incidence of cerebrovascular events, including TIAs, was 5.7% (Fig. 12.4) [8]. More importantly, hemorrhagic stroke may more readily occur than ischemic stroke in asymptomatic moyamoya disease. The speculation correlates very well with the findings on cerebral angiography in a recent comparative study. In this study, the data set of cerebral angiography were compared between Asymptomatic Moyamoya Registry (AMORE) Study and Japan Adult Moyamoya (JAM) Trial at enrollment. The development of 3 subtypes of collateral vessels, including lenticulostriate, thalamic, and choroidal anastomosis, was evaluated on cerebral angiography. As a result, there were no significant differences in the development of choroidal anastomosis between asymptomatic and hemorrhagic-onset moyamoya disease. Considering an increasing evidence that choroidal channel plays an important role in the occurrence of hemorrhagic stroke, a certain subgroup of cases of asymptomatic moyamoya disease may be at potential risk for hemorrhagic stroke [13].

In addition, there was an association between SPECT/PET findings and prognosis at diagnosis, with a higher rate of ischemic events in patients with reduced cerebral perfusion pressure at diagnosis. On MR imaging and MR angiography, an even higher frequency of imaging changes is identified. That is, various kinds of *de novo* abnormalities were identified in 9 (26.5%) of the 34 patients who did not undergo surgical revascularization. Of these, 3 patients had advanced disease progression and cerebral infarction (2 symptomatic and 1 asymptomatic), 2 had only advanced disease progression (2 asymptomatic), 3 had hemorrhagic attacks, and 1 had new microbleeds (asymptomatic) [8].

These findings strongly suggest that asymptomatic moyamoya disease is not a stable disease, but should be recognized as a preliminary stage to a cerebrovascular event such as TIA, ischemic stroke, or hemorrhagic stroke, with a minor frequency of subclinical progression of the disease or microbleeds or cerebral infarction.

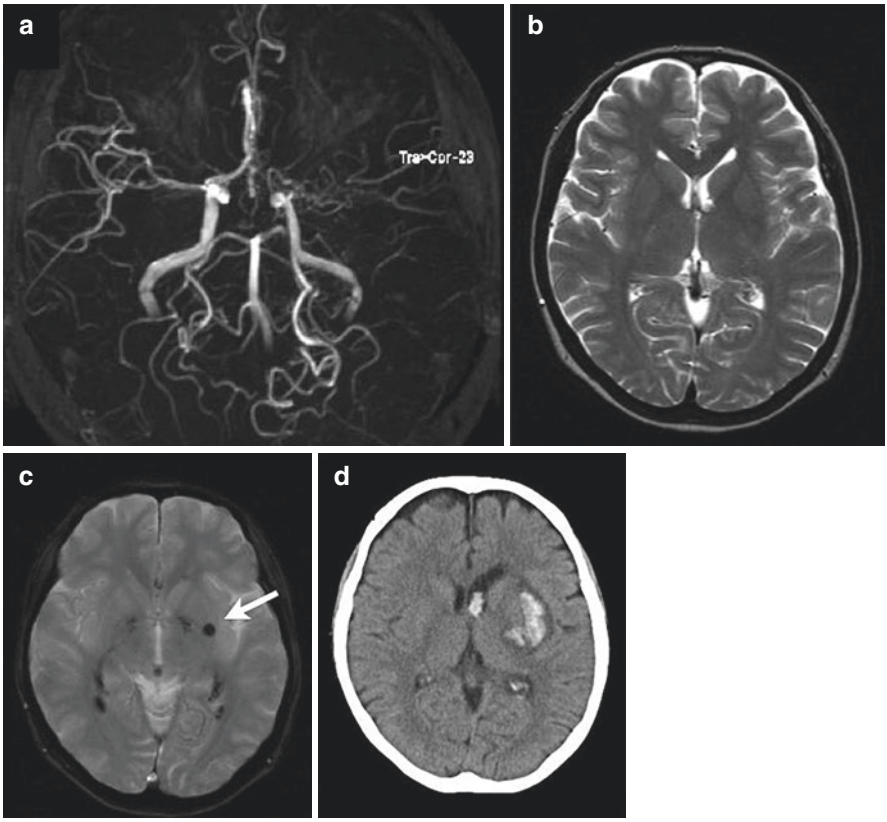

Fig. 12.4 Radiological findings of a 26-year-old female with asymptomatic moyamoya disease. On MR angiography (**a**), the supraclinoid portion of the internal carotid artery and its main branches are severely stenotic on the left sides, which is associated with typical moyamoya vessels. T2-weighted images (**b**) show no parenchymal lesions, but T2*-weighted images (**c**) clearly demonstrate the microbleed in the left putamen (arrow). Plain CT scan (**d**) taken 4 years later shows intracerebral hemorrhage in the left putamen

Therefore, when asymptomatic moyamoya disease is diagnosed, care must be taken to avoid overlooking potential changes, at least through regular MR examinations and imaging checks.

Appropriate surgical revascularization has been widely accepted as a treatment to prevent future TIA, ischemic stroke, and hemorrhagic stroke, but there is very limited information on the efficacy of surgical revascularization for asymptomatic moyamoya disease and no definitive guideline has been established. The "Guidelines for the Diagnosis and Treatment of Moyamoya Disease" published by Japanese group just focuses on the appropriate management of risk factors and lifestyle guidance from a medical perspective. Asymptomatic moyamoya disease does not have a low risk of developing hemorrhagic stroke and therefore the use of antiplatelet agents is not recommended [14]. Recently, Kawai et al. (2010) reported 2 cases of

asymptomatic moyamoya disease that presented with a worsening of cerebral hemodynamics due to disease progression during follow-up. Although they had yet experienced no cerebrovascular events, they underwent surgical revascularization, including STA-MCA anastomosis and indirect bypass, and had a good postoperative course [15]. Furthermore, Yamamoto et al. reported a 61-year-old female with asymptomatic moyamoya disease. She had silent microbleeds in the corpus callosum at initial presentation and was conservatively followed up. However, *de novo* microbleeds developed in the right frontal and temporal lobe 6 months later, although she had no cerebrovascular events yet. She underwent STA-MCA anastomosis and indirect bypass on the right side to reduce hemodynamic stress onto the dilated, fragile moyamoya vessels. Postoperative course was uneventful. She is completely free from any cerebrovascular events and repeated MR examinations revealed no further development of *de novo* microbleeds for 7 years after surgery [16]. These data would be important to consider the treatment strategy in the future.

12.5 Asymptomatic Moyamoya Registry (AMORE) Study

Based on these observations, the Research Committee on Moyamoya Disease in Japan have started a prospective multicenter, nation-wide observational study, Asymptomatic Moyamoya Registry (AMORE) study, in January 2012 to further evaluate the epidemiology and outcome in asymptomatic moyamoya disease with a larger cohort [5]. They planned to enroll the eligible cases of asymptomatic moyamoya disease between January 2012 and December 2015 and to follow-up them conservatively for at least 5 years after the enrollment. Totally 20 centers in Japan joined this study.

In this study, the inclusion criteria include age 20–70 years; bilateral or unilateral form of moyamoya disease on cerebral angiography and/or MRA; no episodes that suggest TIA, ischemic stroke, and hemorrhagic stroke; possible to conservatively follow-up; independent in daily life (modified Rankin scale 0 or 1); and written informed consent. Exclusion criteria are previous episodes suggestive of TIA, ischemic stroke, and hemorrhagic stroke, quasi-moyamoya disease (moyamoya syndrome), and non-moyamoya disease. Following data are provided at the enrollment: demographic data, past history, family history, blood pressure, medicine, MRI (FLAIR image, T2-weighted image, and T2*-weighted image), MR angiography or cerebral angiography, and cerebral blood flow data on SPECT or PET.

A follow-up assessment is scheduled every 12 months, including any cerebrovascular event, blood pressure, MRI (T2-weighted images, T2*-weighted images, and FLAIR images), and MR angiography. Primary endpoint is any ischemic and hemorrhagic stroke during a follow-up period of 5 years. In AMORE Study, 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 without newly developed cerebral infarction, *de novo* development of silent cerebral infarction and bleeding, disease progression, and any death during a follow-up period of 5 years [5].

The AMORE study is expected to be a clinical study that will provide definitive information for future treatment guidelines for asymptomatic moyamoya disease; by December 2015, 109 cases had been enrolled from participating centers across the country, and a five-year follow-up of all cases will be completed in December 2020. The results are expected to be announced in early 2021.

12.6 Conclusion

The epidemiology, clinical profile, prognosis, and new clinical trial of asymptomatic moyamoya disease are described. As the frequency of asymptomatic moyamoya disease constantly increases, we will face more opportunities to determine a treatment strategy in daily clinical practice in the future; however, the evidence for the outcome and treatment of asymptomatic moyamoya disease has not yet been sufficiently accumulated, and the results of AMORE Study are greatly anticipated.

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