Diagnosis of Moyamoya Disease: International Standard and Regional Differences

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Abstract

Moyamoya disease is a chronic, occlusive cerebrovascular disease with unknown etiology characterized by bilateral steno-occlusive changes at the terminal portion of the internal carotid artery (ICA) and an abnormal vascular network at the base of the brain.1,2) These diagnostic criteria of the moyamoya disease, stated by the Research Committee on Spontaneous Occlusion of the Circle of Willis (moyamoya disease) in Japan, are well established and generally accepted as the definition of this rare entity.2–6) On the contrary to the diagnosis of definitive moyamoya disease, there is some confusion in the terminology and understanding of quasi-moyamoya disease; moyamoya disease in association with various disease entities, such as atherosclerosis, autoimmune diseases, Down syndrome, etc.2,7) Although the clinical management is not affected by these semantic distinctions, terminological confusion may interfere with the international collaboration of the clinical investigation of these rare conditions. Thus we sought to review the international standard and regional differences in the diagnosis of moyamoya disease and quasi-moyamoya disease.

Key words: moyamoya disease, moyamoya vasculopathy, quasi-moyamoya disease, diagnosis

Introduction

Moyamoya disease is a chronic, occlusive cerebrovascular disease with an unknown etiology characterized by bilateral steno-occlusive changes at the terminal portion of the internal carotid artery (ICA) and an abnormal vascular network at the base of the brain.1,2) These diagnostic criteria of the moyamoya disease, stated by the Research Committee on Spontaneous Occlusion of the Circle of Willis (moyamoya disease) in Japan, are well established and generally accepted as the definition of this disease in the world.2–6) Moyamoya disease is also known to be associated with various disease entities, such as atherosclerosis, autoimmune diseases, meningitis, von Recklinghausen disease, Down syndrome, cranial irradiation, etc.2,7) Since the definition of moyamoya disease includes idiopathic pathology, the above conditions with associated diseases have been considered to be distinct from the definitive moyamoya disease, which are named as quasi-moyamoya disease.2) On the contrary to the definitive moyamoya disease, there is some confusion in the terminology of quasi-moyamoya disease,8,9) probably due to the epidemiological imbalance of the patient distribution in the world. Although the clinical management is not affected by these semantic distinctions, terminological confusion may interfere with the international collaboration of the clinical investigation of these rare conditions. Thus we sought to review the international standard and regional differences in the diagnosis of moyamoya disease and quasi-moyamoya disease.

Diagnostic Criteria of Moyamoya Disease

I. Current diagnostic criteria by catheter angiography and magnetic resonance (MR) imaging/angiography

Diagnostic criteria of definitive moyamoya disease include all of the following items based on the conventional angiographic findings.8,9) (1) Stenosis or occlusion of the terminal portion of the intracranial ICA or proximal portions of the anterior cerebral artery (ACA) and/or the middle cerebral artery (MCA). (2) Development of abnormal vascular networks near the occlusive or stenotic lesions in the arterial phase. (3) Bilateral lesion (Fig. 1A, B). After the revision of the diagnostic criteria of moyamoya disease in 1995 by the Research Committee on Spontaneous Occlusion of the Circle of Willis (Moyamoya disease) in Japan, definitive diagnosis of moyamoya disease has also been made by satisfying all of the following items by MR imaging/angiography without conventional angiography.
catheter angiography. (1) MR angiography showing stenosis or occlusion of the terminal portion of the intracranial ICA or proximal portions of the ACA and/or the MCA. (2) Presence of the abnormal vascular networks near the occlusive or stenotic lesions by MR angiography, or MR imaging demonstrating two or more flow voids in the basal ganglia on each hemisphere. Regarding the site of the steno-occlusive changes of the intracranial arteries, the involvement of the terminal ICA region has been considered to be one of the most important characteristics of moyamoya disease, together with the visualization of the abnormal vascular networks, so-called moyamoya vessels.\textsuperscript{1,2} Based on the most recent findings on the patients with de novo development of moyamoya disease, however, the initiation of the steno-occlusive changes does not always become evident at the terminal ICA region, but it can also initiate at the M1 portion of MCA.\textsuperscript{10,11} We have reported a young woman with moyamoya disease with unilateral involvement, who initially demonstrated cerebral infarction due to mid-M1 stenosis with unknown etiology.\textsuperscript{11} She developed recurrent cerebral infarction due to progressive moyamoya disease 4 years later when she delivered her child, suggesting that initial stenotic change could occur even at mid-M1 portion of MCA in a rare occasion. Finally, it is essential to rule out the similar cerebrovascular lesions associated with the following underlying diseases; atherosclerosis, autoimmune diseases, meningitis, brain tumors, Down syndrome, neurofibromatosis type-1, traumatic brain injury, cranial irradiation, etc.\textsuperscript{2}

II. Significance of Suzuki’s angiographic staging
Suzuki’s angiographic staging of moyamoya disease is helpful to understand temporal profile of the basic pathology in each patient.\textsuperscript{3} This angiographic staging does not represent the severity of moyamoya disease, but it indicates an intrinsic compensatory reorganization process of moyamoya disease. Initiation of the steno-occlusive changes at terminal ICA region and subsequent development of moyamoya vessels are the characteristic findings of the early stage of moyamoya disease (stages 1–3), while compensatory development of trans-dural/trans-cranial anastomosis from external carotid artery (ECA) system and subsequent disappearance of moyamoya vessels represent the late stage (stages 4–5), finally leading to the disappearance of intracranial ICA (stage 6).\textsuperscript{1} We called this physiological reorganization process as “internal carotid (IC)-external carotid (EC) conversion” as the ideal natural course of the patients with moyamoya disease, either undergoing surgery or conservatively observed.\textsuperscript{12} Thus we consider that Suzuki’s angiographic staging, representing the physiological profile of IC-EC conversion, is still essential to understand the complex pathology of moyamoya disease, even 45 years after the initial proposal of this classic staging.\textsuperscript{1}

III. Supportive findings by histo-pathological analysis and genetic evaluation
Intimal hyperplasia, medial layer thinness, and the waving of internal elastic lamina are the representative histo-pathological characteristics of moyamoya disease.\textsuperscript{2,13} These findings are not only evident at terminal ICA and adjacent structures but also at the peripheral MCA.\textsuperscript{14} Therefore, histological analysis of the surgical specimens as well as the autopsy specimens could support the definitive diagnosis of moyamoya disease. Regarding genetic analysis, the RNF213 gene (RNF213) in the 17q25-ter region

Fig. 1 Representative case of a 28-year-old woman presenting with TIA. Catheter angiography (A, B) demonstrating steno-occlusive changes at the terminal ICA portion bilaterally. MR angiography in the acute stage after left direct/indirect revascularization showed patent STA-MCA bypass (arrow in C). But she suffered crescendo TIA in the late peri-operative period due to newly-diagnosed Graves disease, when MR angiography showed decreased signal intensity of left STA-MCA bypass (arrow) and peripheral MCA (D). ICA: internal carotid artery, MR: magnetic resonance, STA-MCA: superficial temporal artery to middle cerebral artery, TIA: transient ischemic attack.
was recently identified as an important susceptibility gene for moyamoya disease among East Asian population.\textsuperscript{15,16} A polymorphism in c.14576G>A in \textit{RNF213} was identified in 95\% of familial patients with moyamoya disease and 79\% of sporadic cases, and \textit{RNF213} was correlated with the early onset and severe forms of moyamoya disease,\textsuperscript{17} which indicated its value as a good biomarker for predicting prognosis. The mechanism how \textit{RNF213} abnormality leads to moyamoya disease is still unknown, and basic research using genetic engineered animal lacking \textit{RNF213} is now on-going to address this important issue.\textsuperscript{18} It is alternatively important to identify similar susceptibility gene among Caucasian population and others in the future study.

IV. Probable moyamoya disease: moyamoya disease with unilateral involvement

Moyamoya disease with unilateral involvement is defined as “probable moyamoya disease,” when it is not associated with any underlying diseases. The incidence of probable moyamoya disease was reported to be 10.6 among 2,634 patients with moyamoya disease in a primary survey of moyamoya disease conducted in 2,998 Japanese institutions in 2006.\textsuperscript{2} The biological background, clinical presentation, surgical indication, and operative procedures for probable moyamoya disease are basically the same as those of definitive moyamoya disease.\textsuperscript{2} Regarding healthcare benefit for the specified intractable disease in Japan, only definitive moyamoya disease patients are covered by healthcare benefit by the Japanese government, but it is not the case with probable moyamoya disease patients and patients with quasi-moyamoya disease in 2014 (Table 1).

Regional Difference in the Status of Quasi-moyamoya Disease

I. Definition of quasi-moyamoya disease and terminological confusion

Quasi-moyamoya disease represents moyamoya disease, either bilateral or unilateral, in association with an underlying disease (Table 1).\textsuperscript{2} Underlying diseases of quasi-moyamoya disease include atherosclerosis, autoimmune disease, meningitis, von Recklinghausen disease, brain tumors, Down syndrome, traumatic brain injury, cranial irradiation, etc.\textsuperscript{2} Most recent nationwide survey on quasi-moyamoya disease in Japan indicated that the atherosclerosis was the most common associated disease (29\%), which was followed by Down syndrome (15.1\%), von Recklinghausen disease (14\%), and brain tumor (7.5\%).\textsuperscript{7} Atherosclerosis is also reported to be the most common associated illness (32.4\%) in Taiwan, which is followed by thyroid diseases (29.7\%).\textsuperscript{19}

The terminological confusion of quasi-moyamoya disease in the literature could partly be due to large number of the associated diseases,\textsuperscript{2} and also be due to the variety of names of quasi-moyamoya disease itself, such as akin-moyamoya disease, moyamoya syndrome, and secondary moyamoya disease,\textsuperscript{8} and most of the literatures do not describe the exact definition of this condition in each article. In light of the higher proportion of quasi-moyamoya disease than definitive moyamoya disease among Caucasian population, the strict distinction between these two groups may not be essential in most clinical setting because the clinical management is not affected by these semantic distinctions. In fact, the terms “moyamoya vasculopathy” and “moyamoya phenomenon” are likely to be used in universal meaning including both definitive moyamoya disease, quasi-moyamoya disease, and moyamoya disease with unilateral involvement (probable moyamoya disease) in the literatures from Europe and North America.

II. Thyroid diseases as an important associated illness of quasi-moyamoya disease

Thyroid diseases such as Graves disease and Hashimoto disease; autoimmune hypothyroidism are thought to be the common associated conditions that can lead to the diagnosis of quasi-moyamoya disease. Recent evidence indicates that the association of Graves disease with moyamoya disease could be much more common among East Asian population than it was thought previously.\textsuperscript{20,21} Patients with moyamoya disease, also including quasi-moyamoya

| Table 1 | Diagnostic chart of moyamoya disease and current healthcare benefit by the Japanese government in 2014 |
| --- | --- | --- |
| | Affected hemisphere (steno-occlusive side) | Association of underlying disease | Healthcare benefit by the government (Japan) |
| Definitive moyamoya disease | Bilateral | None | Yes |
| Quasi-moyamoya disease | Bilateral or unilateral | Yes* | None |
| Probable moyamoya disease* | Unilateral | None | None |

*: moyamoya disease with unilateral involvement, **: atherosclerosis, autoimmune diseases, meningitis, von Recklinghausen’s disease, brain tumors, Down syndrome, traumatic brain injury, cranial irradiation, hyperthyroidism, etc.
disease with clinical hyperthyroidism, are reported to show elevated thyroid autoantibodies and increased thyroid function more frequently as compared to the non-moyamoya stroke patients among East Asian population.\textsuperscript{20,21} In contrast, association of Hashimoto disease with moyamoya disease is more common among Caucasian patients than Graves disease,\textsuperscript{22} and this association was further reported to be the risk factor of poor outcome of revascularization surgery,\textsuperscript{23} suggesting the importance of the accurate diagnosis of associated thyroid disease in patients with moyamoya disease. We experienced a 28-year old woman initially diagnosed as definitive moyamoya disease presenting with transient ischemic attack (TIA). She underwent successful direct/indirect revascularization surgery on the symptomatic hemisphere (Fig. 1C), but she suffered crescendo TIA postoperatively and subsequently diagnosed as having active hyperthyroidism (Fig. 1D). Introduction of the anti-thyroid therapy significantly relieved her ischemic symptom and she underwent direct/indirect revascularization surgery on the contralateral hemisphere without complication. Thus we consider the accurate diagnosis of the associated illness, especially the thyroid diseases, is essential in patients with moyamoya disease before revascularization surgery.

Diagnosis of Moyamoya Disease: Future Perspective

Definitive diagnosis of moyamoya disease is thoroughly based on the angio-architecture, and the temporal profile of moyamoya disease with dynamic nature is well characterized by Suzuki’s angiographic staging which represents the disease concept of this rare entity. The distinction between definitive moyamoya disease and quasi-moyamoya disease with underlying pathology is also important because the etiology of moyamoya disease remains unknown.\textsuperscript{21} But the recent advance in genetic research and serological examination on moyamoya disease provides new insight not only into the etiology of moyamoya disease but also into the diagnostic concept of moyamoya disease. As described above, RNF213 in the 17q25-ter region is an important susceptibility gene for moyamoya disease among East Asian populations,\textsuperscript{15–17} and this gene is known to be markedly expressed in peripheral white blood cells and spleen.\textsuperscript{15} Taken together with the serological observation that substantial number of the moyamoya patients among East Asian population demonstrate elevated anti-thyroid autoantibody and increased thyroid function,\textsuperscript{20,21} either subclinical or clinically evident condition, autoimmune mechanism could be one of the strong candidates of the underlying pathology of moyamoya disease, as previously hypothesized.\textsuperscript{21} While elucidating the underlying pathology of moyamoya disease, we do not rule out the possibility that the significance of the distinction between definitive moyamoya disease and quasi-moyamoya disease could be alleviated in the future. Alternatively, genetic research for the susceptibility gene such as RNF213 would be more supportive to lead to the definitive diagnosis of moyamoya disease in the future if the genetic analysis of such susceptibility gene becomes generally available in each clinic.

Conclusion

Diagnostic criteria of moyamoya disease are well established and generally accepted as the definition of this rare entity, but the terminology of quasi-moyamoya disease is somewhat confused because of the large number of the associated diseases, and the variety of names of quasi-moyamoya disease itself, such as akin-moyamoya disease, moyamoya syndrome, and secondary moyamoya disease. Recent advance in genetic and serological researches provide new insight into the diagnostic concept of moyamoya disease. Once we obtain the result of the advanced research in genetics and immunity of this entity and clarify the etiology of moyamoya disease in the future, we may be able to simplify the diagnostic concept of moyamoya disease, quasi-moyamoya disease, and moyamoya diseases with unilateral involvement (probable moyamoya disease).

Conflicts of Interest Disclosure

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices in the article. All authors who are members of The Japan Neurosurgical Society (JNS) have registered online Self-reporting COI Disclosure Statement Forms through the website for JNS members.

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