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MOYAMOYA: AN OVERVIEW OF THE DISEASE WITH SPECIFIC REFERENCE TO DIAGNOSIS AND TREATMENT

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ABSTRACT

Moyamoya is a chronic and progressive cerebrovascular disease, which is characterized by formation of occlusive lesions and stenosis in bilateral internal carotid arteries of brain. In such special cases aberrant vascular network is formed in close proximity to arterial occlusion. The process of narrowing down of arteries is followed, leading to repeated transient ischemic attacks, headaches etc. The ischemic attacks occur occasionally for short span of time and that may resolve in few minutes. This also causes involuntary movements of body parts such as legs, hands and even tongue. Revascularization method for symptomatic MMD is considered the standard treatment for preventing further stroke.

KEYWORDS: Moyamoya disease; chronic and progressive neurological disorder; pathophysiology; angiography; surgical revascularization.

INTRODUCTION

Though rare, moyamoya disease (MMD) is a potentially severe illness. MMD is a retrogression of intracranial arteriopathy. The progressive stenosis of the distal portion of the internal carotid artery and the proximal anterior and middle cerebral arteries is an attribute of moyamoya disease which consequently causes transient ischemic attacks or thrombotic strokes with frequent recurrences. The pathogenesis of MMD is still uncertain, but thickened intima of the major branches of the circle of Willis, and moyamoya vessels has been noted. Japan's Ministry of Health and Welfare, has defined four types of MMD, namely, ischemic, hemorrhagic, epileptic, and "other." It has been observed that clinical manifestation of MMD is ischemic attacks in pediatric patients and either ischemic or hemorrhagic events in adults. Another clinical feature of MMD is the higher prevalence of moyamoya disease in female patients than male patients with an approximate female predominance of 2:1.[1] Due to a low incidence and the clinical course changes with age and race, at present the natural history of MMD is unclear, thus treatment mainly depends on a doctor's experience.

BACKGROUND AND EPIDEMIOLOGY OF MMD

In 1957 Takeuchi and Shimizu were the first to report moyamoya and described it as hypoplasia of the bilateral internal carotid arteries.[2] "Spontaneous occlusion of circle of Willis" was the first official Japanese name of the disease, which was given the nick name moyamoya by Suzuki and Takaku in 1967.[3] In Japanese moyamoya means a "hazy puff of smoke" which appears similar to the fragile collateral blood vessels that forms in response to the blockage at basal ganglia.[4] Collateral blood vessels are created by brain to compensate for the narrowing arteries and deliver oxygen-rich blood to deprived areas of the brain. The activities leading to hyperventilation may cause ischemic attacks and also results in condensation of carotid arteries. Excessive constriction may lead to intracerebral hemorrhage. A significant rise in diagnosis of moyamoya disease in adults was observed according Korean National Health Insurance Service (NHIS) data (2008-2016), while a decrement was seen in pediatric patients at the same time by 18.0%. In 2016 the age-standardized incidences were found to be 2.4 and 3.4 per hundred thousand persons-years in pediatric and adult patients respectively.[5] Globally, the distribution of the onset age of MMD is significantly bimodal, with a major peak in the first decade of life and a moderate peak in the third decade.

In pregnant women with MMD it has been found that stroke susceptibility exist till gestational age but they can safely give birth when the cerebral blood flow (CBF) is stable. Therefore, before conception, an evaluation of cerebral circulation is important.[6] The moyamoya disease affects CNS, consequently influencing an individual's skills of analysis, integration, and interpretation of essential visual and auditory information. This results in learning difficulties and acquired language alterations.[7] Though there has been no treatment available genetic analysis and high throughput proteome-wide approaches aid in discovering the pathogenic mechanisms of MMD which could enhance the understanding of this vascular disease and novel target identification for development of therapeutic techniques.[8]

ETIOLOGY

Regardless of very vast and immense studies from many past years of research on moyamoya the exact etiology of moyamoya cannot be well stated. The pathophysiology of MMD thus far is poorly understood and remains controversial.[9] But the ultimate pathway involves proliferation of smooth muscle cells and their movement

from the media to the intima. Moyamoya disease (MMD) also known as spontaneous occlusion of the circle of Willis, is a chronic, occlusive cerebrovascular disease distinguished by progressive stenosis at the terminal portion of the internal carotid artery (ICA) and an abnormal vascular network at the base of the brain, for unknown reasons. Studies in Asian population show slight genetic correlation with RNF213 (MIM no.613768) being identified as a susceptibility gene for moyamoya.[7] The genome wide linkage analysis of many individuals unveiled linkage of chromosomal location 17q25.3 to moyamoya disease, the gene at this specific location RNF213 may also have its possible role in vascular development along with the susceptibility to moyamoya.[10] Mutation in smooth muscles (ACTA2 gene) may also make the individual prone to occlusive diseases like moyamoya. ACTA 2 is an α-actin isoform, which is a major component in smooth muscle cells located all over in the arterial system.[11] Although, the pathogenesis of MMD has not been completely understood, in current genetic studies, the RNF213 in the 17q25-ter region has been identified as the chief susceptibility gene of MMD amid East Asian populations.[12] Due to genetic differences, MMD is found to be common in people of East Asian countries like Korea and Japan, as compared with the Western Hemisphere.

CLASSIFICATION

According to analysis several cases of moyamoya, it has been generally classified into two: Probable moyamoya and definite moyamoya. The conditions which manifest unilateral involvement and also may have some other causes is classified as probable moyamoya. These have certain correlation with systemic disease or disorders having angiographic features are indistinguishable to moyamoya disease. Thus Wanatbe and Suzuki proposed the term 'quasi-moyamoya' in 1986.[13]

Table 1: Disorders having angiographic correlation to moyamoya.[6]

Infectious disease
Leptospirosis
Tuberculosis
Hematological disorders
Aplastic anemia
Fanconi's anemia
Sickle cell anemia
Congenital disorders
Apert syndrome
Down's syndrome
Marfan syndrome
Tuberous sclerosis
Turner's syndrome
von Recklinghausen disease
Vascular disorders
Atherosclerotic disease
Coarctation of aorta
Fibromuscular dysplasia
Others
Cranial trauma
Cranial irradiation
Parasellar tumors
Hypertension

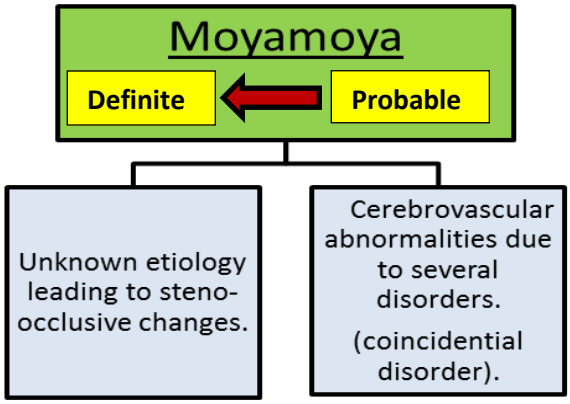

Fig. 1: Classification of moyamoya disease showing definite and probable moyamoya.

DIAGNOSIS

In 1979 research committee on spontaneous occlusion of the circle of Willis of ministry of health and welfare, Japan, proposed the guidelines for the diagnosis of moyamoya disease. The guidelines were further revised twice in 1988 and 1995. Only some of the guidelines are present in English text as all rest guidelines are originally written in Japanese.

For diagnosis, careful interpretations of predicting factors of MMD like disease severity, future hemorrhage, prognosis, and treatment outcome as well as excluding quasi-MMD are required. Catheter angiography is the preferred diagnostic method for MMD. Other noninvasive diagnostic methods are magnetic resonance (MR) angiography and computed tomographic angiography. High-resolution vessel wall MR imaging also helps diagnose MMD by revealing concentric vessel wall narrowing with basal collaterals.[14] The diagnosis by angiographic or arteriographic examination helps to confirm typical characteristics of MMD, such as stenosis or occlusion at the main branch of the ICA, and an abnormal vascular network at the skull base.[15] Angiograms produced by cerebral angiography aids in detection of smoky appearance of arteries at basal ganglia in brain. The cerebral angiography for moyamoya depicts stenosis or occlusion of arteries at circle of Willis or terminal portions of internal carotid arteries, bilateral involvement and aberrant vascular networks of cerebral arteries.

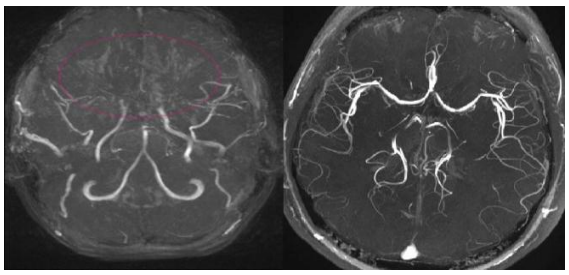

Fig 2: (left) Maximum intensity projection (MIP) reconstructed MR angiography of a 11 year old girl with Moyamoya disease. On (right) healthy patient, for comparison.

TREATMENT

At present, there is no treatment for halting the progression or reversal of intracranial arteriopathy of MMD. Treatment strategies mostly aim to alleviate symptoms and prevent occurrence of strokes.[16] Recurrent ischemic attacks and cerebral hemodynamic impairment have been till date the main symptoms for treatment.

MMD patients with acute infarction and relative mild MMD, nonsurgical treatment is recommended to prevent further stroke. Nonsurgical treatment for MMD uses aspirin, mannitol, steroids, and vasodilators, outcomes of which are unclear and are ergo unsuccessful.[17] Largely the treatment of moyamoya disease is surgical revascularization using revascularization method that include -- direct, indirect, and combined strategies.[4] Surgical revascularization has been observed to prevent ischemic attacks by improving the cerebral blood flow. In symptomatic MMD patients, direct bypass surgery is recommended as it is known to reduce risk of recurrent stroke, especially in hemorrhagic MMD patients.[18] However, obstacles which need to be considered for the treatment of MMD are the perioperative complications and the demanding nature of surgical techniques. Predominantly, the standard surgical treatment performed for adult moyamoya disease is superficial temporal artery (STA)-middle cerebral artery (MCA) anastomosis.[19] Notably, most studies have involved the East Asian population and emerging evidence in one such study suggests that non-Asian patients with MMD have higher probability of recovering from postsurgical complications.[20]

CONCLUSION

Blocked arteries at basal ganglia causes rare, chronic and progressive neurological disorder called moyamoya. The process of narrowing down of arteries is followed, leading to repeated transient ischemic attacks, headache, disturbed consciousness, involuntary movements, vision problems and sensory impairment. The etiology of MMD remains obscure but available studies supports the idea that one single mechanism cannot explain the complex disease pathogenesis. MMD could be a multigene and multifactor disease, resulting from events in which environmental and epigenetic factors may influence the development of arteriopathy in genetically susceptible individuals.

RNF213 is identified as a susceptibility gene for moyamoya and mutation in smooth muscles (ACTA2 gene) may also make the individual prone to MMD. It has been generally classified into two types: probable moyamoya and definite moyamoya. For diagnosis of MMD angiography is preferred. Angiograms show a network of abundant fragile collateral blood vessels imparting a “puff of smoke” aspect at basal ganglia. The treatment of moyamoya disease is subjected to its aggressiveness. Patients having milder symptoms are treated with vasodilators, antiplatelet agents, antifibrolytic agents and fibrinolytic agents. Patients with more severe symptoms are treated via revascularization procedures. Since surgical treatment has been observed to be more effective than nonsurgical treatment, most of the cases (approx. 77%) are surgically treated.[21] Although currently, there is still no consensus about the best type of revascularization surgery.

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