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Review article

Moyamoya disease in children

Jun-ichi Takanashi *

Department of Pediatrics, Kameda Medical Center, Kamogawa-shi, Japan

Abstract

Moyamoya disease is an uncommon cerebrovascular disease characterized by progressive steno-occlusive changes in the terminal internal carotid arteries (ICA) and their main branches, associated with the development of moyamoya vessels. The incidence of the disease is high in east Asia, especially in Japan and Korea. The familial form accounts for 10–15%. Moyamoya disease has two age distribution peaks at around 5 and 40 years. Most pediatric patients exhibit transient ischemic attacks or infarction. Headache and involuntary movements are serious symptoms associated with pediatric moyamoya disease. MRI and MR angiography (MRA) are useful and non-invasive methods for diagnosing or monitoring moyamoya disease. Cerebral angiography is still the gold standard for a diagnosis, however, it is not mandatory when MRI and MRA show typical findings of moyamoya disease; steno-occlusive changes at the ends of ICA and an abnormal vascular network in the basal ganglia. Other MRI findings have been reported, including T2 shortening in the white matter, the ivy sign on fluid-attenuated inversion recovery (FLAIR) images, and medullary streaks on FLAIR or enhanced T1-weighted images.

Keywords: Moyamoya disease; Moyamoya syndrome; MRI; MR angiography

1. Introduction

Moyamoya disease is a cerebrovascular disease characterized by slowly progressive steno-occlusive changes in the terminal portions of the bilateral internal carotid arteries (ICA) and their main branches, which results in the formation of a fine vascular network at the base of the brain (moyamoya vessels) to compensate for the steno-occlusion [1]. The hazy appearance of these hypertrophied collaterals on angiography resembles a puff of smoke (moyamoya in Japanese); thus, Suzuki and Takaku named this novel disorder "moyamoya disease" [2]. The predominant feature of the pathology of moyamoya disease is known to be progressive stenosis of the terminal ICA, and the moyamoya vessels are dilated perforating arteries that function as collateral pathways. Moyamoya disease is rare, but important as a cause of cerebral stroke in children, especially in east Asia. Recent studies have expanded our knowledge of the basic and clinical aspects of moyamoya disease, however, the exact pathomechanism of this disease remains unknown.

2. Definitions and diagnosis

In 1997, the research committee published guidelines for the diagnosis of moyamoya disease in English [3]. According to the guidelines, definite moyamoya disease is diagnosed when conventional angiography shows the following findings; stenosis or occlusion in the terminal ICA and/or proximal portion of anterior cerebral artery (ACA) and/or middle cerebral artery (MCA); abnormal vascular networks (moyamoya vessels) in the basal ganglia; and bilateral lesions. Patients with unilateral lesions are diagnosed as having probable moyamoya

* Address: Department of Pediatrics, Kameda Medical Center, 929 Higashi-cho, Kamogawa-shi, Chiba 296-8602, Japan. Tel.: +81 470 92 2211; fax: +81 470 99 1198.
E-mail addresses: jtaka@kameda.jp, jtaka44@hotmail.co.jp

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disease. When an underlying cause is found, such as Down syndrome, neurofibromatosis type 1, sickle cell disease, and radiation therapy, a diagnosis of moyamoya syndrome is given.

3. Cerebral angiography and angiographic staging of moyamoya disease

Cerebral angiography is still the gold standard for the diagnosis of moyamoya disease. Moyamoya disease is a progressive cerebrovascular disorder whose vascular changes are divided into the six stages described below [1,4].

Stage 1. Narrowing of terminal ICA. Only terminal ICA stenosis is observed.
Stage 2. Initiation of basal moyamoya. Appearance of moyamoya vessels and dilated main cerebral arteries is observed.
Stage 3. Intensification of moyamoya. Remarkable moyamoya vessels at the base of the brain. The defection of the ACA and MCA is observed.
Stage 4. Minimization of moyamoya. Decrease of moyamoya vessels and defection of the PCA are observed.
Stage 5. Reduction of moyamoya. Further decrease of moyamoya vessels and the absence of all the main cerebral arteries are observed.
Stage 6. Disappearance of moyamoya. Moyamoya vessels disappear and the cerebral blood supply is only from the external carotid arteries.

Moyamoya disease is characterized by the extensive development of pathognomonic collateral pathways in response to steno-occlusive changes in the terminal ICA. The first pathway is known as basal moyamoya, and includes abnormal dilatation of the lenticulostriate and thalamoperforating arteries in the basal ganglia and thalamus. The second pathway involves substantial dilatation of the anterior choroidal and posterior pericallosal arteries. The third pathway is known as ethmoidal moyamoya, which includes abnormal dilatation of the anterior and posterior ethmoidal arteries, mainly from the ophthalmic arteries to the ACA branches. The final pathway is a vascular network in the cranial vault that is responsible for the collateral flow from dural arteries to pial arteries (vault moyamoya). Steno-occlusive changes in the proximal posterior cerebral artery (PCA) are also observed in about 25% of patients with moyamoya disease [5].

Cerebral angiography is useful for assessing the development of collateral pathways through direct or indirect bypasses, which cannot be fully observed on MR angiography (MRA). Effective bypass surgery leads to the disappearance or regression of the collaterals because they are no longer required. Postoperative angiography is recommended at least 3 months after surgery, because collateral pathways require 3–4 months to develop after indirect bypass surgery [6].

4. Epidemiology

The incidence of moyamoya disease is high in countries in east Asia, such as Japan and Korea. In Japan, the annual prevalence and incidence have been estimated to be 3.16–10.5 and 0.35–0.94 per 100,000 [7,8]. The annual incidences in the USA and Europe have been reported to be about 10% of that in Japan [9]. The female to male ratio has been shown to be 1.8–2.2 (female predominance) [7,8]. A bimodal age distribution has been reported for moyamoya disease, i.e., a high peak at 5 years and a low peak at about 40 years [7]. A recent report, however, revealed a highest peak between 45 and 49 years followed by a second peak between 5 and 9 years [8]. This suggests that the incidence of pediatric moyamoya disease has started to decrease [1,8].

The incidence of familial occurrence is high, accounting for as many as 15% of moyamoya patients [10]. 172 familial cases have been reported; including 38 parent-offspring pairs in 16 pedigrees, and 128 sibling pairs in 51 pedigrees [11]. The female to male ratio in familial moyamoya disease is 5.0, which is much higher than that in sporadic cases (1.6). The mean age at onset of familial moyamoya disease (11.8 years) is lower than that in sporadic cases (30.0 years). Among parent–offspring pairs, the age at onset of offspring (7.2 years) is lower than that of parents (30.7 years), suggesting strong association with anticipation in familial moyamoya disease [11].

5. Histopathology

The histopathological findings for the carotid terminations include fibrocellular thickening of the intima, irregular undulation of the internal elastic lamina, and attenuation of the media [12]. Moyamoya vessels have fibrin deposits in their walls, fragmented elastic laminae, attenuated media, and microaneurysms. Collapse of the arterial lumen and subsequent thrombosis can be seen in moyamoya vessels [13], which might be closely associated with the onset of ischemic stroke and hemorrhage.

6. Pathogenesis of moyamoya disease

Infectious etiologies have been proposed based on the presence of increased Epstein–Barr virus DNA and antibodies in patients with moyamoya disease [14]. Bacterial infection of the head and neck might also be implicated in the development of moyamoya disease [15]. An epidemiological study of familial moyamoya disease suggested that moyamoya disease is probably inherited in a polygenic or autosomal dominant manner with low