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Clinical Study

Clinical characteristics and long-term outcomes of moyamoya syndrome associated with neurofibromatosis type 1

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ABSTRACT

Moyamoya syndrome (MMS) associated with neurofibromatosis type 1 (NF1) has rarely been reported anywhere in the world, particularly in Asia. Because of the rarity of this disorder, its natural history, clinical symptoms, management, and follow-up findings remain unclear. The objective of this study was to evaluate the clinical presentation, neurological imaging, and long-term outcomes of patients with this disease by reviewing Chinese patients with MMS associated with NF1. A retrospective review was conducted from the moyamoya disease (MMD) and MMS patient database of our hospital. Six patients who were diagnosed with MMS associated with NF1 between January 2003 and October 2013 were identified. The clinical symptoms were transient ischemic attack (TIA, three patients), headache (one patient), intracerebral hemorrhage (one patient), and cerebral infarction (one patient). The mean age of diagnosis for NF1 and MMS was 2.7 ± 2.1 years (range, 1–6 years) and 11.4 ± 8.3 years (range, 3.5–23 years), respectively. Five of six patients (nine hemispheres) underwent revascularization surgery, and their clinical symptoms were stable during a 46.3 ± 36.1 month (range, 18–108 month) follow-up. One non-surgical patient had a new infarct that resulted in visual field deficits during follow-up. Three patients had radiographic follow-up, and the postoperative angiograms showed successful revascularizations in the operated hemispheres. To conclude, the clinical and radiographic features for MMS-NF1 are similar to those of typical MMD. Routine vascular screening for NF1 patients is necessary for the early identification of MMS and other cerebral arteriopathies. Revascularization surgery may prevent the progression of clinical symptoms and reduce the risk of subsequent strokes.

1. Introduction

Moyamoya disease (MMD) is a chronic cerebrovascular disorder characterized by progressive stenosis or occlusion of the intracranial internal carotid artery (ICA) that gradually progresses to the proximal branches of the anterior, middle, and posterior cerebral arteries. Due to the gradual stenosis of these arteries, a collateral network of vessels forms at the base of the brain. The etiology of MMD is unknown; therefore, the association of MMD-type angiographic findings with another systemic disease, such as neurofibromatosis type 1 (NF1), is usually called moyamoya syndrome (MMS).

NF1 is a common, inherited, autosomal-dominant multisystem genetic disorder with multiple clinical manifestations, including café au lait spots, neurofibromas, freckling, optic nerve gliomas, Lisch nodules, and distinct bone lesions.

The occurrence of MMS associated with NF1 (MMS-NF1) is rare. Fewer than 100 patients with MMS-NF1 have been reported in the literature at the time of writing [1–2]. Although MMD occurs frequently in Asian countries, most MMS-NF1 patients have been reported in Europe and USA. In addition, there is a scarcity of reports on the treatment and long-term follow-up of these patients. The objective of this study was to report the clinical presentation, neurological imaging, management, and long-term follow-up of several Chinese MMS-NF1 patients.

2. Methods

2.1. Patient selection

We reviewed the patient database of our hospital and selected the MMS patients who were also diagnosed with NF1 between July 2003 and October 2013. All of the patients included met the USA National Institutes of Health diagnostic criteria for NF1 [3]. The diagnosis of MMS was established in accordance with the criteria

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developed by the Research Committee on the Pathology and Treatment of Spontaneous Occlusion of the Circle of Willis in 2012 [4].

2.2. Clinical data and neuroimaging

The clinical information collected included sex, age at NF1 diagnosis, age at MMS diagnosis, clinical manifestations of vasculopathy, neurological imaging findings, treatment, and follow-up outcome. All of the patients underwent MRI of the brain with magnetic resonance angiography (MRA). Conventional digital subtraction angiography (DSA) was also conducted to confirm the diagnosis and to plan treatment. The severity of MMS was measured using Suzuki stages [5]. Brain perfusion single-photon emission computerised tomography (SPECT) was performed to evaluate the hemodynamic status. Based on the SPECT findings, the severity of the cerebral perfusion abnormality was classified as defective (with perfusion being the same as or less than that of white matter) or decreased (compared with contralateral grey matter). DSA, MRI with MRA, and SPECT were conducted during the follow-up. The preoperative and postoperative neurological imaging results were reviewed by an independent neuroradiologist.

2.3. Treatment

Most of the patients with cerebral vasculopathy were advised to undergo revascularization surgery on the side containing the lesion. Before the operation, a carefully designed preoperative evaluation was performed to identify indications and surgical goals. The postsurgical collateral vessels were graded according to the method described by Matsushima et al. [6], where "good" indicates that the postsurgical collateral vessels achieved revascularization of two-thirds of the middle cerebral artery (MCA) distribution, "fair" indicates that the postsurgical collateral vessels achieved revascularization of one-third to two-thirds of the MCA distribution, and "poor" indicates that the postsurgical collateral vessels achieved very little or no revascularization. The functional status of each patient was graded according to the modified Rankin Scale (mRS).

2.4. Statistical analyses

Descriptive statistics only were used in this study.

3. Results

3.1. Clinical features

A total of six patients, two boys and four girls, were enrolled in the study. During this period, 2008 MMD and MMS patients were managed in our hospital. As a result, the proportion of MMS-NF1 patients was 0.3% (6/2008) in this period. The clinical features of all of the patients are summarised in Table 1. The age at diagnosis of NF1 ranged from 1 to 6 years, with a median age of 2.7 ± 2.1 years. The mean age of diagnosis for MMS was 11.4 ± 8.3 years (range, 3.5–23 years). The interval from diagnosis of NF1 to MMS was 8.8 ± 7.0 years (range, 1–17 years). Indications for neurological imaging at the time of treatment included transient ischemic attack (three patients), headache (one patient), intracerebral hemorrhage (one patient), and cerebral infarction (one patient). Four patients were neurologically intact (mRS score 0), and two patients had minimal neurological deficit (mRS score 1). The NF1 clinical features in the other systems are also shown in Table 1.

3.2. Neurological imaging findings

Preoperative imaging and data were available for all patients. Most of the hemispheres (5/10) were in Suzuki stage 4, and the others were in stage 1 (two hemispheres), stage 2 (two hemispheres), or stage 6 (one hemisphere). Defective or decreased perfusion was revealed by SPECT in all six patients (Table 2). Three patients had radiographic follow-up after surgery, and all three presented radiographic progression (Fig. 1).

3.3. Treatment and follow-up outcome

Five patients (nine hemispheres) underwent revascularization surgery, and eight hemispheres were subjected to encephaloduroarteriosynangiosis (EDAS), which is a standard indirect revascularization procedure. One hemisphere was subjected to a superficial temporal artery (STA)–MCA bypass, and one patient was treated with aspirin (Table 2).

All six patients underwent clinical follow-up, and three underwent radiographic follow-up. The average duration of follow-up was 46.3 ± 36.1 months (range, 18–108 months). At the time of the most recent follow-up, the clinical symptoms of the five patients who underwent revascularization surgery were stable, and the degree, frequency, and durations of transient ischemic attacks and headaches were decreased. The patient who presented with hemorrhage did not suffer from rebleeding. The patient who had been treated with aspirin suffered a new infarct that resulted in new visual field deficits, and the mRS score deteriorated during follow-up (2 *versus* 1). During radiographic follow-up, the postoperative angiogram showed good collaterals in one hemisphere and fair collaterals in the other five hemispheres (Table 2).

4. Discussion

According to some recent studies, the incidence of cerebrovascular diseases in NF1 is 2.5–6% [7–9]. MMD-type changes were a significant proportion of the neurological imaging findings, at 47% (7/15 patients), in the study by Ghosh et al. [9] and 76% (13/17 patients) in the study by Rea et al. [8]. There are also several case reports indicating an association of MMS and NF1 [10–11].

Table 1
Clinical features of patients with moyamoya syndrome associated with neurofibromatosis type 1

Patient	Sex	Age at diagnosis of NF1, y	Age at diagnosis of MMS, y	Clinical features of NF1	Neurological symptoms	mRS
1	F	4	17	Café au lait spots, skin-fold freckling, neurofibromas	TIA	0
2	F	1	3.5	Café au lait spots, skin-fold freckling	TIA	0
3	F	6	23	Café au lait spots, skin-fold freckling	Infarction	1
4	F	1	16	Café au lait spots, skin-fold freckling	Hemorrhage	0
5	M	1	5	Café au lait spots, plexiform neurofibroma, skin-fold freckling, bone lesion	Headache	1
6	M	3	4	café au lait spots, neurofibromas	TIA	0

F = female, M = male, MMS = moyamoya syndrome, mRS = modified Rankin Scale, NF1 = neurofibromatosis type 1, TIA = transient ischemic attack, y = years.