Clinical Features and Long-Term Outcomes of Unilateral Moyamoya Disease

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■ OBJECTIVE: **To elucidate the clinical features, risk factors for contralateral progression, and long-term outcomes of patients with unilateral moyamoya disease (MMD).**

■ METHODS: **We retrospectively reviewed 109 patients with unilateral MMD treated at Beijing Tiantan Hospital. Clinical features, radiologic findings, and outcomes were analyzed.**

■ RESULTS: **The mean age at diagnosis was 30.8 ± 14.2 years with a one-peak distribution in the thirties. The ratio of women to men was 1.1:1. Familial occurrence was 5.5%. The primary symptoms at initial presentation were transient ischemic attack (39.4%), infarction (22%), and hemorrhage (26.6%). The distribution of the initial Suzuki stage was as follows: stage 2, $n = 33$; stage 3, $n = 35$; stage 4, $n = 27$; stage 5, $n = 11$, and stage 6, $n = 3$. Contralateral abnormality on initial angiography occurred in 19 adult patients (17.4%). Posterior cerebral artery involvement was observed in 28 (25.7%) patients. During the average follow-up of 43.8 ± 21.3 months, contralateral progression was observed in 18 patients (16.5%). Contralateral abnormalities ($P = 0.033$) on initial angiography and infarction at initial presentation ($P = 0.041$) were significantly associated with contralateral progression in adults and children, respectively. Approximately 91.7% of patients had a modified Rankin Scale score of 0–2 during follow-up.**

■ CONCLUSIONS: **A one-peak pattern in age distribution, lower grade of Suzuki stage, fewer familial cases, and posterior cerebral artery involvement were observed in patients with unilateral MMD. Contralateral abnormalities on initial angiography and infarction at onset were risk factors for contralateral progression in adult and pediatric patients, respectively. Good functional outcomes can be anticipated in the vast majority of surgically treated patients.**

INTRODUCTION

Moyamoya disease (MMD) is characterized by idiopathic steno-occlusion at the terminal portion of the internal carotid artery (ICA) with concomitant abnormal vascular networks.[1,2] If these angiographic findings are present only on one side with an unknown etiology, the diagnosis of unilateral (probable) MMD can be made.[3] In pediatric cases, idiopathic and unilateral moyamoya vasculopathy also is considered to be "definite MMD" and not unilateral MMD if steno-occlusion is identified on another side of the ICA terminal.[3]

Key words
- Clinical features
- Contralateral progression
- Long-term outcomes
- Unilateral moyamoya disease

Abbreviations and Acronyms
ACA: Anterior cerebral artery
CI: Confidence interval
CT: Computed tomography
ICA: Internal carotid artery
IQR: Interquartile range
MCA: Middle cerebral artery
MMD: moyamoya disease
MR: Magnetic resonance
MRA: Magnetic resonance angiography
mRS: Rankin
PCA: Posterior cerebral artery
RNF213: Ring finger protein 213
TIA: Transient ischemic attack

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Citation: World Neurosurg. (2016) 96:474-482.
http://dx.doi.org/10.1016/j.wneu.2016.09.018

*Journal homepage: **www.WORLDNEUROSURGERY.org***

*Available online: **www.sciencedirect.com***

Whether unilateral and bilateral MMD belong to a single entity remains controversial.[4-6] Ring finger protein 213 (RNF213) has been identified as the first susceptibility gene for MMD.[7,8] Moreover, a lower occurrence of a p.R4810K variant (rs112735431) in RNF213 was observed in Japanese patients with unilateral MMD (33.3%, 2/6) than those with bilateral MMD (81.8%, 126/154).[9] An increased prevalence of autoimmune disease in patients with unilateral compared with bilateral MMD was identified.[10] These findings supported that the etiology of some unilateral MMD cases were different from "definite MMD." Furthermore, the natural history, clinical features, and long-term outcomes of unilateral MMD in a general MMD population have not been described fully because of the limited number of published reports.[6,11-15] We reviewed our experiences with patients with unilateral MMD from a larger cohort and focused on the clinical features and risk factors of contralateral progression.

MATERIALS AND METHODS

Study Population and Sample Collection

There were 1137 patients with MMD from the neurosurgical departments of Beijing Tiantan Hospital from January 2002 to May 2014. The diagnostic criteria for definite MMD and unilateral (probable) MMD were in accordance with the published guidelines by the Research Committee on MMD (spontaneous occlusion of the circle of Willis) of Japan in 2012.[3] Patients with a history of cranial irradiation and meningitis, brain tumor, Down syndrome, and neurofibromatosis type 1 were excluded from the analysis. In pediatric cases, "unilateral moyamoya vasculopathy" also was considered to be "definite MMD" if steno-occlusion was identified on another side of the ICA terminal.[3]

Among these patients, 135 patients (11.9%) with unilateral MMD were identified. Seventeen patients with follow-up periods shorter than 24 months and 9 patients without complete radiologic data were excluded. Therefore, a total of 109 patients were included. The blood samples of patients were collected, and the p.R4810K variant was detected. Primers were designed as follows: RNF213-4810F (rs112735431): 5′-GCCCTCCATTTCTAGCACAC-3′; and RNF213-4810R: 5′-AGCTGTGGCGAAAGCTTCTA-3′. The method has been described in our previous studies in detail.[16,17] The Ethics Committee of Beijing Tiantan Hospital, Capital Medical University, Beijing, China, approved the study.

Clinical and Radiologic Characteristics

Clinical information on the sex, age at diagnosis, family history, primary symptoms at onset, including transient ischemic attack (TIA), infarction, hemorrhage, headache, seizure or others, hypertension, hyperlipidemia, diabetes mellitus, tobacco use, thyroid disease, history of infection, initial modified Rankin Scale (mRS) score, and surgical revascularization was obtained by clinical chart review. The genetic backgrounds of the familial cases were collected.

Radiologic data were reviewed blindly by 2 neurosurgeons, including the affected side, Suzuki stage, posterior cerebral artery (PCA) involvement, contralateral abnormalities in the anterior cerebral artery (ACA), middle cerebral artery (MCA), or terminal ICA on initial angiography for adult patients and aneurysm. Any disagreement on the radiologic findings was re-evaluated by a third reader.

Clinical Follow-Up

After discharge, the long-term outcome was ascertained through clinical visits, telephone, or letter interviews. Postoperative stroke was defined as new neurologic deficits and was associated with a new infarct or hemorrhage on magnetic resonance (MR) or computed tomography (CT) imaging in the revascularization hemisphere. Follow-up MR angiography (MRA) or CT angiography was performed at 6 months postoperatively; if the patient remained asymptomatic, this was repeated annually to detect contralateral progression, defined as any noticeable change in the contralateral angiography. If any contralateral progression was suggested by MRA or CT angiography, a follow-up catheter angiography was performed to confirm the presence of the steno-occlusive lesions. The time to disease progression was defined as the duration from the initial angiography to the angiography that showed contralateral disease progression. Second surgical revascularization was considered when angiographic progression and ischemia occurred in the contralateral hemisphere.

Statistical Analysis

Descriptive statistics were used for the statistical analysis of patient characteristics. Progression-free survival was estimated from the Kaplan-Meier method and was tested for statistical significance with the log-rank test. Each variable was dichotomized for the statistical analysis. Clinical data and angiographic findings were analyzed to determine the potential influences of these factors on contralateral progression in pediatric patients, adult patients, and all patients, respectively. Predictors with significance or a trend toward significance on univariate analysis ($P < 0.10$) were retested with multivariate analysis. The estimated hazard ratio and 95% confidence interval (CI) were calculated by the Cox proportional-hazards model. The median time to contralateral progression between the pediatric and adult cases was compared with the Mann-Whitney U test. A probability value <0.05 was considered to indicate statistical significance. The analyses were performed using the SPSS 19.0 IBM statistical software package (Armonk, New York, USA).

RESULTS

Demographic Data

The mean age at diagnosis was 30.8 ± 14.2 years (range, 4–61 years) (Table 1). The ratio of female to male patients was 1.1:1. There were 27 patients younger than 18 years of age (24.8%). One peak in the age distribution was found in patients from 30 to 39 years (Figure 1). Of the 109 patients, 6 (5.5%) had a familial history, 19 (14.9%) had a history of hypertension, 4 (3.7%) had diabetes mellitus, 9 (8.3%) had hyperlipidemia, 18 (16.5%) had a history of tobacco use, and 3 (2.8%) had thyroid disease. A history of infection was identified in 5 (4.6%) patients, including infection of hepatitis B virus in 2 (1.8%) patients, epidemic hemorrhagic fever virus in 2 (1.8%) patients, and syphilis in 1 (0.9%) patient. The genetic background of the 6 familial cases is shown in Figure 2A. Unilateral MMD and bilateral MMD were all coexistent in the 6 families.