Clinical and Angiographic Features of Patients with Moyamoya Disease and the p.R4810K Heterozygous Variant

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■ OBJECTIVE: **To elucidate the clinical and angiographic features in patients with moyamoya disease (MMD) and the p.R4810K heterozygous variant and present an angiographic grading system to evaluate disease severity.**

■ METHODS: **We retrospectively reviewed 87 patients with MMD and the p.R4810K variant treated at Beijing Tiantan Hospital. Clinical features, stroke subtype, and angiographic characteristics were analyzed.**

■ RESULTS: **The median age at diagnosis was 25 years (range, 3–59). The ratio of women to men was 1.2:1. The familial occurrence of MMD was 14.9%. The primary symptom at diagnosis was ischemia, hemorrhage, or other in 67, 16, and 4 patients, respectively. Angiographic features correlating with ischemic stroke or stroke, including Suzuki grade, external carotid artery collaterals, leptomeningeal collaterals, and Mugikura grade, were identified. A binary logistic regression model demonstrated a significant correlation of Suzuki grade ($P = 0.008$) and posterior cerebral artery grade ($P = 0.029$) with ischemic stroke (142 hemispheres). A modified Suzuki-Mugikura grading system was developed. The areas under the receiver operating characteristic curves used to predict ischemic stroke based on the Suzuki grading, Mugikura grading, and modified Suzuki-Mugikura grading systems were 0.736, 0.69, and 0.741, respectively. Furthermore, the modified Suzuki-Mugikura grades were significantly correlated with infarction in posterior circulation and the number of infarcted regions.**

■ CONCLUSIONS: **The clinical and angiographic features of a Chinese MMD population with the p.R4810K variant were similar to those of a Japanese MMD population; they might be a distinct cerebrovascular disease entity and represent a separate subgroup. A modified Suzuki-Mugikura grading system was valuable for predicting stroke and evaluating disease severity.**

INTRODUCTION

Moyamoya disease (MMD) is characterized by a progressive stenosis of the terminal portion of the internal carotid arteries (ICAs) and the development of a network of abnormal collateral vessels.[1,2] It mainly leads to ischemic and hemorrhagic stroke. MMD occurs worldwide, but its prevalence is greatest in East Asian countries, including Japan (6.03/100,000), Korea (6.3/100,000), and China (3.92/100,000).[3-9] The epidemiologic and clinical characteristics of MMD differ between different ethnicities.[1] Despite substantial investigation,

Key words
- Angiographic characteristics
- Clinical features
- moyamoya disease
- p.R4810K variant

Abbreviations and Acronyms
ACA: Anterior cerebral artery
AchoA: Anterior choroidal artery
CT: Computed tomography
ECA: External carotid artery
ICA: Internal carotid artery
LMC: Leptomeningeal collaterals
MCA: Middle cerebral artery
MMD: moyamoya disease
MR: Magnetic resonance
PCA: Posterior cerebral artery
PcomA: Posterior communicating artery
RNF213: Ring finger protein 213
ROC: Receiver operating characteristic

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the molecular etiology of moyamoya angiopathy remains unclear. Ring finger protein 213 (RNF213, NM_001256071), located on chromosome 17q25.3, was identified as the first MMD susceptibility gene.[10,11] The p.R4810K variant (rs112735431) in RNF213 was highly recurrent in Asian patients with MMD but was not found in Caucasian cases.[10-12] The knockdown of RNF213 in zebrafish caused irregular wall formation in trunk arteries and abnormal sprouting vessels.[11] RNF213 knockout mice exhibit abnormal vascular remodeling after carotid artery ligation[13]; however, clinical and angiographic features in patients with MMD and the p.R4810K heterozygous variant have remained poorly understood.

The Suzuki grading system has been applied widely to evaluate the severity of disease[2,14,15]; however, it only exhibits "moyamoya progression" in the ICA. Moreover, steno-occlusive lesions in the posterior cerebral artery (PCA) were observed in 30%–58% of patients.[6,14,16-18] The steno-occlusive lesions in the PCA and the PCA moyamoya vessels were classified into 4 grades as proposed by Mugikura et al.[14] To date, there is no angiographic grading system that simultaneously includes moyamoya progression on anterior and posterior circulation. The purpose of this study was to review the clinical and angiographic features of patients with MMD and the p.R4810K heterozygous variant and to present an angiographic grading system to evaluate disease severity.

MATERIALS AND METHODS

Study Population and Sample Collection

There were 472 patients with MMD or probable MMD from inpatient and outpatient departments of Beijing Tiantan Hospital from January 2013 to May 2015, including those who underwent revascularization surgery and those who did not. The inclusion criteria were as follows: 1) patients who were diagnosed in accordance with the Japanese MMD diagnosis guidelines (probable MMD was included)[19]; 2) patients who carried the p.R4810K heterozygous variant of RNF213; 3) Complete clinical and radiologic data were available; and 4) for postoperative patients, only the angiography and magnetic resonance (MR) imaging and/or computed tomography (CT) studies performed before surgery were reviewed.

Blood samples were collected from 388 of the 472 patients mentioned previously after written informed consent had been obtained. Genomic DNA from the 388 patients was extracted from blood leukocytes with a QIA amp blood kit (QIAGEN, Hilden, Germany). The primers were designed as follows: RNF213-4810F (rs112735431): 5′-GCCCTCCATTTCTAGCACAC-3′; and RNF213-4810R: 5′-AGCTGTGGCGAAAGCTTCTA-3′. Among the 388 sequenced patients, 286 wild-type patients, 2 homozygotes, and 13 heterozygous patients without complete radiologic data were excluded. Finally, 87 patients with p.R4810k heterozygous variants were included. The Ethics Committee of Beijing Tiantan Hospital, Capital Medical University, Beijing, China, approved the study.

Clinical and Radiologic Characteristics

Clinical information on sex, age at diagnosis, family history, primary symptoms at diagnosis, familial occurrence, cerebral aneurysm, intracranial lesions, hypertension, hyperlipidemia, and diabetes mellitus was obtained by clinical chart review. Radiologic profiles, including CT, MR imaging, and angiography, were classified by 2 senior neurovascular surgeons.

An ischemic stroke was confirmed by MR imaging, and a hemorrhagic stroke was identified by CT scan. Ischemic strokes were categorized into the following 7 groups, as suggested by Mugikura et al. and Jang et al.[14,20]: anterior cerebral artery (ACA) infarct; anterior watershed infarct between the ACA and middle cerebral artery (MCA) territories; anterior half of the MCA territory infarct; posterior half of the MCA territory infarct; posterior watershed infarct between the MCA and PCA territories; PCA infarct; and the basal ganglia and thalamus infarct. The number of infarctions was counted according to the regions involved, as described. Hemorrhagic stroke was classified as follows: intracerebral hematoma, intraventricular hemorrhage, intracerebral and intraventricular hemorrhage, and subarachnoid hemorrhage.

Angiographic details of all the hemispheres included the following: ICA, 6 grades as suggested by Suzuki and Takaku[2]; PCA, 4 grades; and leptomeningeal collaterals (LMC), 4 grades as suggested by Mugikura et al.[14] Every angiographic feature, including the posterior communicating artery (PcomA) collaterals (flow from the PCA to the ICA), external carotid artery (ECA) collaterals (transdural anastomosis from the ECA to the ICA and PCA), ophthalmic artery collaterals, fetal PCA development, and dilation of the anterior choroidal artery (AchoA), was classified into 2 grades as follows: grade 0, not found on angiography; grade 1, found on imaging. Angiographic grade and collateral vessels were evaluated in each hemisphere as ordinal variables in this study.

Statistical Analysis

Descriptive statistics were used for the statistical analysis of patient characteristics. To determine which factors predicted a certain pattern of stroke, the χ^2 test or Fisher exact test (when at least 1 cell had an expected value of less than 5) was used. Non-normally distributed continuous variables, such as angiographic grade, were compared with the Wilcoxon rank sum test and the Spearman rank correlation test. Predictors with significance or trend toward significance on univariate analysis ($P < 0.05$) were retested with multivariate analysis (binary logistic regression). To assess the optimal grading system to predict stroke, receiver operating characteristic (ROC) analyses with areas under the ROC curve were used. The comparison of ROC curves was performed with the method of Delong. A probability value of <0.05 was considered significant. The analyses were performed using SPSS 19.0 IBM statistical software package (Armonk, New York, USA) and MedCalc 12.4.0 software (MedCalc Software, Mariakerke, Belgium).

RESULTS

Demographic Data

The median age at diagnosis was 25.4 ± 14.3 years (range, 3–59 years) (Table 1). The ratio of female to male patients was 1.2:1. There were 33 patients younger than 18 years of age (37.9%). Two peaks in age distribution were found in patients. The distribution of age revealed a biphasic age distribution with a pediatric peak (6–10 years) and an adult peak (36–40 years)