Clinical features of familial juvenile cases of moyamoya disease: analysis of patients treated in a single institute over a 28-year period

Clinical article

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Object. The authors compared the clinical features between familial and sporadic cases of moyamoya disease (MMD) by retrospectively analyzing data on patients with MMD registered in the database of Tokyo Medical and Dental University over a period of 28 years.

Methods. In total, 383 patients with hospital records at Tokyo Medical and Dental University from 1980 to 2007 were registered into the database. The data on all of these patients were retrospectively reviewed to clarify the occurrence of familial cases. Clinical features of child or adolescent patients (<20 years of age) with MMD were compared between familial and sporadic cases in a subgroup of patients who were registered after 1995, initially diagnosed using MR angiography, and assessed using an intelligence scale.

Results. Familial occurrence was observed in 59 patients (15.4%) in 40 pedigrees. The clinical features of juvenile patients were analyzed in 124 patients, 22 (17.7%) of whom had familial histories. In comparison with the sporadic cases, patients with familial histories were significantly younger at onset (4.7 vs 6.6 years old), had significantly more cortical infarction (59.1% vs 25.5%), and had significantly more stenoocclusive lesions in the posterior cerebral artery (45.4% vs 24.5%). The rate of patients with intellectual disturbance (intelligence quotient < 75) was significantly larger in the familial cases (47.4%) than in the sporadic cases (17.8%).

Conclusions. This survey of the clinical features of familial MMD suggests that patients with familial MMD had a more serious clinical course in childhood than the sporadic MMD cases.

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Key Words • moyamoya disease • intelligence • vascular disorders

MOYAMOYA disease is diagnosed solely on the characteristic morphology of the terminal portion of the bilateral internal carotid arteries and the accompanying formation of extensive collateral vessels at the base of the brain. There have been no genetic or serum markers to support the diagnosis of MMD. Without these markers, it can be extremely difficult to understand the pathological features of this syndrome. One of the research targets should be to clarify the contribution of genetic factors and environmental factors. Although RNF213 was recognized as a susceptibility gene for MMD in an East Asian population, the necessity of investigating other compounding factors to explain the disease presentation was also indicated. Therefore, it should be important to compare the clinical features of MMD between sporadic and familial cases using objective parameters such as MRI and an intelligence scale.

While most cases of MMD appear to be sporadic, genetic factors of MMD appear to be involved in the pathogenesis of the disease. Familial MMD is estimated to comprise approximately 10%–15% of all reported MMD cases. A higher proportion of cases are identified as familial now that MR angiography is widely applied. Only a few large patient series, however, have investigated the detailed clinical features of familial MMD. In the present analysis we searched for differences between the familial and sporadic cases by retrospectively surveying all of the MMD cases treated at our institute over a 28-year period. We were able to perform this analysis because our department has been mainly applying its own indirect-bypass technique for the treatment of both juvenile and adult patients with MMD since 1980, and we obtained the present clinical status of a large number of those patients and surveyed the long-term surgical outcome. We also have detailed clinical records on IQs and morphological and functional neuroimaging for analysis. This type of single-institute study should be useful in considering the genetic characteristics of MMD and in finding clues on the pathognomonic features of this syndrome.

Methods

Study Population

A total of 383 MMD patients who were diagnosed by conventional angiography or MR angiography at our in-
stitute between January 1980 and December 2007 were registered in our database. For the epidemiological analysis, data on all of these patients were retrospectively reviewed to clarify the frequency of familial cases. When familial history was unclear, an additional interview was conducted.

Data Collection

To compare the clinical features of child and adolescent patients with MMD (< 20 years of age) between familial and sporadic cases, the data on patients registered after 1995 were surveyed. We selected this strategy because our institute adopted MRI and MR angiography with a 1.5-T machine for the initial diagnosis of MMD since 1995 and thus has images of cerebral vasculature and brain parenchyma that can be retrospectively analyzed for most patients. Many of the patients registered after 1995 were also assessed on the Wechsler Intelligence Scale for Children-Revised to analyze higher brain function for the Wechsler Adult Intelligence Scale-Revised, if > 15 years old. In total, 147 patients were treated between 1995 and 2007, but 23 were excluded from the analysis for the following reasons: 14 patients underwent operations at other hospitals and lacked appropriate preoperative data; intracranial hemorrhage was the presentation in 3 patients (cerebral ischemia was not the cause of neurological deterioration); and 6 patients were not examined using MRI at their initial visits. The clinical data on the remaining 124 patients were analyzed as follows.

Magnetic resonance angiographic images before treatment were analyzed in 2 surveys to clarify 2 points. In the first survey, T2-weighted MR images obtained before the treatments were examined to identify detectable cerebral cortical infarctions. In the second survey, the severity of major cerebral arterial occlusion was assessed by examining whether the lesions in the main arterial trunk had spread out in the vicinity of not only the anterior cerebral circulation, but also the posterior cerebral circulation. Ninety-two (74.2%) of 124 patients underwent intelligence tests. The final Wechsler Intelligence Scale for Children-Revised to analyze higher brain function for the Wechsler Adult Intelligence Scale-Revised, if > 15 years old. In total, 147 patients were treated between 1995 and 2007, but 23 were excluded from the analysis for the following reasons: 14 patients underwent operations at other hospitals and lacked appropriate preoperative data; intracranial hemorrhage was the presentation in 3 patients (cerebral ischemia was not the cause of neurological deterioration); and 6 patients were not examined using MRI at their initial visits. The clinical data on the remaining 124 patients were analyzed as follows.

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Statistical Analysis

Statistical comparisons were performed using the Student t-test, chi-square test, and logistic regression analysis. The Institutional Review Board of Tokyo Medical and Dental University approved the study protocol.

Results

Familial occurrence was observed in 59 (15.4%) of 383 patients and in 40 of 364 pedigrees (11.0%). There were 24 males and 35 females in the familial group (male/female ratio of 1.15). No significant differences between familial and sporadic cases were observed.

Among the 40 pedigrees in the familial cases, 17 pedigrees were siblings, 11 pedigrees were parent-and-offspring, 2 pedigrees were cousins, 8 pedigrees were other relations, and 2 were unknown (Fig. 1). The patterns of MMD inheritance were mother-daughter in 6 pairs, mother-son in 5 pairs, father-daughter in 4 pairs, father-son in no pairs, and both parents—daughter in 1 family. In 1 pedigree, both of a pair of identical twins were diagnosed with MMD and treated as patients. In another pedigree, 1 identical twin was diagnosed with MMD while her twin was not diagnosed and appeared normal on MR angiography 11 years after the diagnosis (Fig. 2). The incidence of familial cases is increasing (12.0% in 1980–1994 vs 16.0% in 1995–2007), but not significantly.

To compare the clinical features between sporadic and familial MMD, we conducted a subgroup analysis by selecting 124 patients who had been examined preoperatively by 1.5-T MRI and MR angiography and at their initial visits in childhood (< 20 years old). This was determined to be the best strategy because data on the whole-brain vessels (including posterior circulation) have only been uniformly obtained for patients undergoing operations or in conservative follow-up since the widespread adoption of MR angiography. In this subgroup, 102 patients had sporadic MMD and 22 patients had familial MMD (Table 1). The male/female ratio in the familial group was 1:1.2, which was not significantly different from the ratio obtained in the whole group analysis. Eighty-nine patients (87%) in the sporadic group and 21 patients (95%) in the familial group were surgically treated by the indirect bypass procedure. In this subgroup from the MR angiography era, the age at onset was 6.6 ± 3.8 years in the sporadic group and 4.7 ± 2.4 years in the familial group. There was a statistically significant difference between these 2 groups (p = 0.034); the disease onset in the familial group was significantly earlier. However, there was no significant difference in age at the initial diagnosis between the 2 groups. A comparison of several factors between sporadic and familial groups is summarized in Table 1. At the preoperative initial examination, cerebral cortical infarction was observed in 26 (25.5%) of 102 cases in the sporadic group compared with 13 (59.1%) of 22 cases in the familial group. The stenotic or obstructive lesions of the PCAs were observed in 25 cases (24.5%) in the sporadic group compared with 10 cases (45.4%) in the familial group. In the final intelligence test after treatment, intellectual disturbance (IQ < 75) was observed in 13 cases (17.8%) in the sporadic group compared with 9 cases (47.4%) in the familial group. Significant differences were observed in these 3 factors.

We examined how these 4 factors (age at onset, cortical infarction, PCA lesion, and intellectual disturbance) correlated among familial and sporadic cases (Table 2). In familial cases, all these factors were well-correlated (but not all statistically significant) and the presence of PCA lesion had significant correlation with the other 3 factors; in sporadic cases, cortical infarction correlated with low IQ, but there were no correlations among other pairs.

Case Illustrations

Case 1: Two Sister Siblings

An 8-year-old girl who had presented with transient
ischemic attacks from the age of 4 had a large cerebral infarction of the right temporooccipital lobe and cerebellum (Fig. 3A). Stenooocclusive changes of the major arterial trunk were observed not only in the anterior cerebral circulation, but also in the posterior circulation, including obstructions of bilateral vertebral arteries (Fig. 3B). Fortunately, the brainstem flow was supplied through collaterals, mainly from the cervical muscular branches. Indirect bypass surgery into the noninfarcted area was successfully applied and no additional infarction appeared in 8 years of follow-up after the operation (Fig. 3C). She has no physical deficits such as paresis or ataxia, but her final IQ was 52. Although she managed to graduate from senior high school and can now live without any special assistance, she is having difficulty in finding a job.

Soon after her diagnosis, her 5-year-old sister (3 years younger) also presented with a cerebral cortical infarction. A vascular lesion of the left PCA was detected (Fig. 3D). Bilateral indirect bypass procedures were applied to the 2 hemispheres and no additional infarctions have appeared in the 8 years since; her final IQ was 78.

**Case 2: Brother-Sister Siblings**

A 4-year-old boy presented with a large cortical infarction in the left cerebral hemisphere (Fig. 4A). Although he received successful bilateral indirect bypass surgery, his final IQ was 45 and he has had to attend a special school for the handicapped.

A younger sister (by 2 years) visited our hospital at 6 years of age presenting with a transient ischemic attack. Her initial MRI and cerebral angiography revealed MMD, and an occlusion of her right PCA was detected at the initial diagnosis (Fig. 4B left). Bilateral indirect surgery achieved marked revascularization (Fig. 4C) without any infarction. Her IQ (104) has been normal since, and her final angiogram revealed rapid worsening of the obstruction of bilateral PCAs (Fig. 4B right).

**Discussion**

The current study demonstrated the epidemiological features of familial MMD using a database collected by a single institute over the course of 28 years. We statistically

**TABLE 1: Summary of clinical characteristics in pediatric patients with familial and sporadic MMD**

<table>
<thead>
<tr>
<th>Variable</th>
<th>All</th>
<th>Sporadic</th>
<th>Familial</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of patients (%)</td>
<td>124</td>
<td>102 (82.3)</td>
<td>22 (17.7)</td>
<td></td>
</tr>
<tr>
<td>pedigrees (%)</td>
<td>118</td>
<td>102 (86.4)</td>
<td>16 (13.6)</td>
<td></td>
</tr>
<tr>
<td>M/F ratio</td>
<td>1:1.5</td>
<td>1:1.6</td>
<td>1:1.2</td>
<td>0.530</td>
</tr>
<tr>
<td>males</td>
<td>49</td>
<td>39</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>females</td>
<td>75</td>
<td>63</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>mean age at onset ± SD (yrs)</td>
<td>6.2 ± 3.7</td>
<td>6.6 ± 3.8</td>
<td>4.7 ± 2.4</td>
<td>0.034</td>
</tr>
<tr>
<td>mean age at initial diagnosis ± SD (yrs)</td>
<td>8.3 ± 4.1</td>
<td>8.6 ± 4.2</td>
<td>7.0 ± 3.5</td>
<td>0.089</td>
</tr>
<tr>
<td>cerebral infarction (%)</td>
<td>39</td>
<td>26 (25.5)</td>
<td>13 (59.1)</td>
<td>0.002</td>
</tr>
<tr>
<td>stenosis of posterior circulation (%)</td>
<td>35</td>
<td>25 (24.5)</td>
<td>10 (45.4)</td>
<td>0.048</td>
</tr>
<tr>
<td>intellectual disturbance† (%)</td>
<td>25/92</td>
<td>13/73 (17.8)</td>
<td>9/19 (47.4)</td>
<td>0.007</td>
</tr>
</tbody>
</table>

* Values in boldface are statistically significant.
† IQ < 75.

**Fig. 1.** Patterns of inheritance in familial MMD. There were 40 pedigrees (59 patients) in total.

**Fig. 2.** Magnetic resonance angiograms of 2 pairs of identical twins. Two of the patients (A and B) were sisters with MMD, both of whom underwent surgical treatment over a 5-year interval; the other 2 patients (C and D) were also twin sisters. Their identity was confirmed from the birth record of a single placenta. One of the patients (C) presented with severe cerebral infarction at the age of 2 years and was diagnosed with MMD. Meanwhile, her twin sister appeared normal on MR angiography. Thus, the A-B pair were both patients with MMD, while the C-D pair were 1 patient with MMD (C) and 1 normal individual (D).
compared the various clinical factors between familial and sporadic cases of MMD. Such a large and detailed retrospective analysis of clinical features can only be achieved on a single-institute basis.

The frequency of current familial cases from 1995 to 2007 was 16.0%. This exceeds the rate from 1980 to 1994 (12%) and the rate reported in 2 previous studies in 19797 and 19862 (7%–10%), presumably because MRI and MR angiography have been introduced and MMD has been publicly recognized recently.

The pattern of heredity in the familial group was similar to previous reports.2 Most of the familial patients were related as siblings or as parents-offspring. Several other authors have reported that the disease commonly affects pairs of identical twins.5,6 We report 2 pairs of identical twins in our study. In one pair, both of the twins were patients with MMD; in the other pair, one twin was a patient with MMD but the other was not. We surmise, on this basis, that the genetic factor is only one of several factors involved in the origin of MMD.

The current series suggests that familial MMD follows a more serious clinical course than sporadic MMD and has characteristics commonly shared by other familial diseases. In the current series, for example, familial MMD tended to manifest arterial stenosis in the posterior circulation and cerebral cortical infarction at the initial presentation, compared with the sporadic cases; and an analysis of the final IQs indicated that the intellect was more frequently impaired in familial MMD than in sporadic MMD. In a review of previous reports, Seol et al. found no significant differences in clinical characteristics such as angiographic stages, SPECT findings, overall clinical outcome, or infarctions and hemorrhages observed by MRI and CT.24 We can identify 3 points that may explain the discrepancy between our results and those of Seol et al. First, our series included patients who received no operations, as the perfusion deficits were minor, whereas Seol et al. included only patients who had received indirect bypass surgery. According to our study, the patients who were conservatively followed were more frequently cases of sporadic MMD. The frequency of infarctions in sporadic MMD therefore differed between the current series (25.5%) and the series of Seol et al. (54%), while the frequency in familial MMD was

<table>
<thead>
<tr>
<th>Variable</th>
<th>Age at Onset</th>
<th>Infarction</th>
<th>PCA Lesion</th>
<th>Low IQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>age at onset</td>
<td>—</td>
<td>0.11</td>
<td>0.02</td>
<td>0.004</td>
</tr>
<tr>
<td>infarction</td>
<td>0.37</td>
<td>—</td>
<td>0.04</td>
<td>0.09</td>
</tr>
<tr>
<td>PCA lesion</td>
<td>0.52</td>
<td>0.07</td>
<td>—</td>
<td>0.03</td>
</tr>
<tr>
<td>low IQ</td>
<td>0.10</td>
<td>0.04</td>
<td>0.64</td>
<td>—</td>
</tr>
</tbody>
</table>

* All values in the table are p values (rate of Type 1 error) among 6 correlations for familial (shaded) and sporadic MMD. The statistical comparison was performed using the chi-square test or logistic regression analysis. Values in boldface are statistically significant (p < 0.05).

The various clinical factors between familial and sporadic cases of MMD were compared.
Clinical features of familial moyamoya disease

similar between the 2 series (59.1% and 50%, respectively). Second, previous studies defined the criterion of favorable or unfavorable outcome based only on the disappearance of preoperative transient ischemic attacks. Instead, in the present study, we clearly determined favorability of outcome using IQs. Third, our survey included more patients with familial MMD than the previous survey (n = 10). Namba et al. reported a significantly younger mean age of onset in the familial group than in the sporadic group, as well as a significantly younger mean age of onset in the second generation than in the first generation. Our series also had a significantly younger mean age of onset in the familial group than in the sporadic group.

The RNF213 gene was recognized as a susceptibility gene for MMD, in an East Asian population, but at the same time, the necessity of investigating other compounding factors to explain the disease presentation was also noted. Our report on 2 monozygotic twins, as demonstrated in Fig. 2, also suggested contribution of both genetic and nongenetic factors for the appearance of MMD. However, Miyatake et al. reported that a homozygous variant of RNF213 was associated with a more severe clinical presentation such as earlier onset, presence of infarction at initial presentation, and presence of PCA lesions than the heterozygous or wild type. The clinical features of familial MMD cases in this study may also depend on the degree of RNF213 variation.

Our result, therefore, may not be applicable for non-East Asian MMD. Scott et al. reported a retrospective analysis on MMD and moyamoya syndrome at their institute in the US. In this series, there were 8 familial patients (5.6%) among 143. Kossorotoff et al. also reported that 4 children (7.5%) among 53 children with MMD/moyamoya syndrome in France had an affected family member. Both of these rates were lower than the rate of familial cases in Japan. One of the possible reasons of this difference is that these data included cases of moyamoya syndrome. If we include moyamoya syndrome, diseases with an already known other genetic background—such as Down syndrome, sickle cell disease, or neurofibromatosis—will be included and should lead to a more complicated result.

In the diagnostic criteria of MMD in Japan, exclusion of syndrome, sickle cell disease, or neurofibromatosis—will be included and should lead to a more complicated result. In the diagnostic criteria of MMD in Japan, exclusion of moyamoya syndrome is mandatory. Another reason for these differences may be attributable to characteristics of a susceptible gene. As Liu et al. reported, the association of a susceptibility polymorphism in RNF213 with MMD is different even among Asian populations. There may be a larger difference in the contribution of genetic factors to clinical features between Asian and Caucasian MMD.

By understanding information on more severe clinical features of familial MMD, physicians face a dilemma in deciding, in the daily clinical setting, whether to screen the family members of MMD patients using imaging modalities such as MRI or MR angiography. A family member with symptoms such as headache or transient ischemic attack should, of course, be examined. We concur with the recommendation of the American Heart Association, namely that it may not be justified (at present) to screen asymptomatic cases or the relatives of patients. Magnetic resonance angiography screening for small children may not be safe, as sedation is required. This point will require attention, however, if familial MMD tends to show a more serious clinical course than sporadic MMD, as our study indicates. We believe that an analysis of both a genetic marker, such as RNF213, and clinical features of familial and sporadic MMD cases, together with a survey of disease-free relatives of patients with MMD, may be the next step to be performed. We have begun such a screening study based on our present database. It may be useful to clarify how genetic and environmental factors correlate with severity of MMD.

Conclusions

The authors of this study surveyed the clinical features of familial MMD. The results suggest that patients with familial MMD follow a more serious clinical course in childhood than patients with sporadic MMD.
Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Concept and design: Nariai, Matsushima, Ohno. Acquisition of data: Mukawa. Analysis and interpretation of data: Nariai, Mukawa. Drafting the article: Mukawa. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Nariai. Statistical analysis: Mukawa. Study supervision: Matsushima, Ohno.

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