The Prediction of Contralateral Progression in Children and Adolescents With Unilateral Moyamoya Disease

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Background and Purpose—To evaluate the factors predictive of contralateral progression in children and adolescents with unilateral moyamoya disease (MMD), the authors retrospectively analyzed clinicoradiological findings.

Methods—The records of 394 consecutive patients with MMD aged 0 to 17 years were reviewed. Unilateral MMD was defined based on the typical angiographic findings of MMD in 1 hemisphere and no abnormality in the contralateral hemisphere. Of the 394 patients with MMD, 45 (11.4%) had unilateral MMD and the prevalence increased with age. Untreated contralateral hemispheres were followed by serial MR angiography. Follow-up angiography was performed if contralateral progression, defined as any noticeable change in the contralateral hemisphere, was suggested by MR angiography.

Results—Eight of the 45 (17.8%) had angiographically documented progression over a mean follow-up of 53.4 months. Mean time to contralateral progression was 27 months (range, 21 to 37 months). An age at diagnosis of <9 years was found to be the only independent predictor of contralateral progression (P = 0.025), which persisted despite adjustment for sex and ipsilateral Suzuki stage (hazard ratio, 8.26; 95% CI, 1.01 to 67.94). Other factors, including abnormalities in the contralateral anterior cerebral artery, were not found to be predictive of progression to bilateral MMD.

Conclusions—The incidence of contralateral progression in our cohort of children and adolescents with unilateral MMD appears to be lower than those previously reported. Furthermore, contralateral progression tended to occur in children aged <9 years within 3 years of initial diagnosis (32%). (Stroke. 2011;42:2973-2976.)

Key Words: adolescents ■ children ■ moyamoya disease ■ pediatric ■ progression ■ unilateral moyamoya disease

Moyamoya disease (MMD) is characterized by idiopathic steno-occlusion at the terminal portion of the internal carotid artery (ICA) and/or at the proximal portion of the anterior cerebral artery (ACA) and/or the middle cerebral artery (MCA) with concomitant abnormal vascular networks.1 If these angiographic findings present on only 1 side in the absence of associated conditions (moyamoya syndromes), a presumptive diagnosis of unilateral (probable) MMD can be made.1 Unilateral and bilateral MMD may reflect different phenotypes caused by the same genetic defects such as the RNF213 mutation.2 The prevalence of unilateral MMD has been reported to be in the range of 9.5% to 17.8% among patients with MMD.3–7

Clinically, the identification of patients likely to progress to bilateral disease would be of substantial clinical benefit, because this would help ensure that patients with unilateral MMD are properly followed and treated before strokes are experienced. However, the natural history of unilateral MMD remains unclear because of its rarity.5,6,8 Although children are known to have a greater risk of developing bilateral disease than adults,5,5 information on patients aged 10 to 17 years has been limited due to the lack of a fixed age range in defining children or adolescents. We reviewed our experiences of children and adolescents with unilateral MMD and placed a focus on contralateral progression.

Methods

Three hundred ninety-four consecutively treated children and adolescents with MMD, who underwent 679 revascularization surgeries between March 1995 and February 2009, were retrospectively reviewed. The Institutional Review Board approved this study and waived the need for consent from patients. The female-to-male ratio was 233:161 (1.4), and mean subject age was 8.2 years (range, 10 months to 17 years). In all patients, a diagnosis of MMD was made based on cerebral angiography findings.

Angiographic findings of the contralateral hemisphere are considered to be normal in unilateral MMD but may include mild abnormalities in the ICA, ACA, or MCA.3–7 In the present study, patients initially showing contralateral ICA or MCA stenosis on angiography, even when it was very mild, were considered to have bilateral disease. However, patients with narrowing or nonvisualization of the contralateral ACA only were considered to have unilateral MMD, because in such cases, it was not clear whether the contralateral ACA was hypoplastic or affected by MMD.6,8

Of the 394 patients with MMD, 45 (11.4%) fulfilled the mentioned criteria of unilateral MMD (Figure 1). Mean age at diagnosis of unilateral MMD was 9.9 years (range, 2 to 17 years) and there was...
no female predominance (24 males and 21 females). The prevalence of unilateral MMD among patients with MMD increased with age, particularly in patients >12 years, and this trend was more evident among males when patients were stratified by gender.

Thirty-eight of the 45 unilateral patients presented with transient ischemic attacks, 5 with strokes, 1 with a headache, and 1 with involuntary arm movement. Six patients had a family history of MMD (13%). The ipsilateral hemisphere was classified as Suzuki Stage 1 in 1 patient, Stage 2 in 5, Stage 3 in 30, Stage 4 in 7, and Stage 5 in 2. Twenty-nine of the 45 initially presented with left-sided moyamoya. Angiographic findings of contralateral hemispheres were completely normal in 17 patients, and the remaining 28 demonstrated a normal ICA and MCA with either narrowing (n=22) or nonvisualization (n=6) of the proximal ACA (A1 segment).

Diamox-enhanced single photon emission computed tomography using 99mTc-ethyl cysteinate dimer revealed that ipsilateral vascular reserve was diminished in 14 with normal perfusion and 18 with hypoperfusion.

All 45 patients with unilateral MMD underwent encephaloduroarteriosynangiosis on the ipsilateral hemisphere only and continued to have follow-ups without antiplatelet medication. No complications related to encephaloduroarteriosynangiosis occurred. Follow-up 3-dimensional time-of-flight MR angiography (MRA) with MRI was performed at 6 months postoperatively, and if the patient remained asymptomatic, this was repeated annually to detect contralateral progression defined as any noticeable change in the contralateral ICA and/or MCA. If any contralateral progression was suggested by MRA,10 follow-up angiography was performed to confirm the presence of the steno-occlusive lesions shown by MRA. Second encephaloduroarteriosynangiosis was considered only when angiographic progression occurred in the contralateral ICA and/or MCA.

Progression-free survival was estimated from the Kaplan-Meier method and tested for statistical significance with the log-rank test. Estimated hazard ratio and 95% CI were calculated by the Cox proportional-hazards model using PASW 17.0 (SPSS Inc).

Results

Serial MRAs suggested contralateral progression in 9 of the 45 patients, but 1 of these patients was found to have no definite contralateral progression by angiography. Thus, 8 of the 45 patients (17.8%) had angiographically documented progression over a mean follow-up of 53.4 months (range, 13 to 157 months). Mean time to contralateral progression was 27 months (range, 21 to 37 months) after initial diagnosis. Three patients showed mild narrowing of the contralateral ICA and/or MCA (Suzuki Stage 1 in 2 or Stage 2 in 1). Concurrent progression of the contralateral ACA leading to occlusion was noted in 2 of these 3 patients. Five patients demonstrated typical contralateral progressions involving the ICA bifurcation area, corresponding to Suzuki Stage 2 in 2 or Stage 3 in 3. Although none of the 8 patients developed a new lesion by MRI in either hemisphere, transient ischemic attacks in the side showing progression occurred in 5. Eventually, all 8 patients that progressed underwent second encephaloduroarteriosynangiosis. Subsequent MRAs performed 6 months after second encephaloduroarteriosynangiosis confirmed typical progressions in the 2 patients with Suzuki Stage 1 progression.

Estimated progression-free survival from initial diagnosis to the last available MRA or the MRA on which progression was noted was 81% at 3 years and 77% at 5 years. Clinical data, angiographic findings, and hemodynamic statuses were analyzed to determine the potential influences of these factors on contralateral progression (Table). Each variable was dichotomized for the statistical analysis. Of the variables analyzed, only age at diagnosis was found to be significantly associated with contralateral progression (P=0.025), whereas of only 1 (4%) of the 23 patients aged ≥9 years, 7 (32%) of the 22 patients aged <9 years progressed to bilateral disease.

Gender, family history, hemisphere sidedness, and visibility of the contralateral A1 segment did not predict contralateral progression. Presentation could not be properly analyzed because none of the 5 patients with strokes progressed. Ipsilateral Suzuki stage did not reach statistical significance despite the fact that only 1 of the 9 patients with Suzuki Stage 4 or 5 progressed. A trend toward contralateral progression was observed in patients with normal perfusion (P=0.097).
However, this seemed to be related to early Suzuki stages (3 in 16 of these 17 patients) and hemodynamic status was available in only 40 patients. The Cox proportional hazards analysis showed that the higher risk of contralateral progression in patients aged $<9$ years persisted despite adjustment for sex and ipsilateral Suzuki stage (hazard ratio, 8.26; 95% CI, 1.01 to 67.94).

### Table. Factors Predicting Contralateral Progression

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All Patients (n=45)</th>
<th>Patients With Contralateral Progression (n=8)</th>
<th>P (Log-Rank Test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, $&lt;9$ y/ $\geq 9$ y</td>
<td>22/23</td>
<td>7/1</td>
<td>0.025</td>
</tr>
<tr>
<td>Gender, male/female</td>
<td>24/21</td>
<td>5/3</td>
<td>0.867</td>
</tr>
<tr>
<td>Presentation, TIA and others*/stroke</td>
<td>40/5</td>
<td>8/0</td>
<td>0.292</td>
</tr>
<tr>
<td>Family history, absence/presence</td>
<td>39/6</td>
<td>7/1</td>
<td>0.959</td>
</tr>
<tr>
<td>Ipsilateral Suzuki Stage, $\leq 3/\geq 4$</td>
<td>36/9</td>
<td>7/1</td>
<td>0.333</td>
</tr>
<tr>
<td>Side of the contralateral hemisphere, right/left</td>
<td>16/29</td>
<td>3/5</td>
<td>0.851</td>
</tr>
<tr>
<td>Contralateral A1 segment, normal/narrow or invisible</td>
<td>17/28</td>
<td>4/4</td>
<td>0.465</td>
</tr>
<tr>
<td>Ipsilateral cerebral perfusion,† normal/hypoperfusion</td>
<td>17/23</td>
<td>5/2</td>
<td>0.097</td>
</tr>
<tr>
<td>Ipsilateral vascular reserve,‡ preserved/diminished</td>
<td>8/32</td>
<td>1/6</td>
<td>0.618</td>
</tr>
</tbody>
</table>

TIA indicates transient ischemic attack.
*Headache and involuntary movement.
†Ipsilateral cerebral perfusion and ‡vascular reserve: available in 40 patients.

### Discussion

In the present study, the incidence of contralateral progression in children and adolescents was only 17.8% over a mean follow-up of 53 months and appears to be lower than previously believed (27.6% to 70.6%).3–5 The inclusion of children with mild contralateral ICA or MCA stenosis might have increased the incidence of contralateral progression observed in prior studies.3–5,7 In addition, unilateral MMD and its progression in older children and adolescents have been rarely reported.7

We classified our patients (<18) into 2 groups depending on age at diagnosis, that is, $<9$ years and $\geq 9$ years of age. We observed that patients aged $\geq 9$ years at diagnosis were less likely to progress (1 of 23) than patients aged $<9$ years (7 of 22). Accordingly, the inclusion of patients with unilateral MMD aged $\geq 9$ years would lower the overall incidence of contralateral progression and a substantial portion of these patients would eventually shift to the adult unilateral MMD population (Figure 2).

Regarding time to progression, it has been reported that times to progression in patients aged $<7$ or $\geq 7$ years (including adults) were 0.9 and 3.1 years, respectively.7 However, in the present study, no significant difference was found between the 2 age groups with respect to progression time. Rather, we observed a relatively constant progression time of 1.8 to 3.1 years regardless of age (Figure 2). Contralateral progression in children and adolescents seems to usually occur within 3 years of initial diagnosis,4–6,8 which may suggest that processes involved in bilateral progression stabilize thereafter.

Recently, the presence of contralateral ACA abnormalities at the time of initial diagnosis was identified as a predictor of contralateral progression.6,7 However, in the present study,
the visibility of the contralateral A1 segment was not found to be associated with contralateral progression, which occurred in 4 of 17 patients with a normal A1, 4 of 22 patients with a narrow A1, and none of 6 patients with an invisible A1 segment. Although we defined contralateral progression as any noticeable change in the contralateral ICA and/or MCA, serial MRAs suggested nonvisualization of the contralateral ACA without ICA/MCA progression in 9 of 22 patients with an initial narrow contralateral A1 segment. Mean time to these ACA changes was 12.6 months (range, 6 to 23 months), which is markedly shorter than time to ICA/MCA progression. Interestingly, had these contralateral ACA changes been counted as true contralateral progression, time to progression would have been shortened to as little as 6 months and the incidence of contralateral progression would have increased to >30%.

However, subsequent MRAs, performed in 8 of the 9 patients, did not demonstrate contralateral ICA/MCA progression over follow-ups of 18 to 145 months. Accordingly, these findings suggest that unlike mild stenotic changes in the contralateral ICA and MCA, isolated changes in the contralateral ACA should not be regarded as early changes before typical progression. Furthermore, preventive surgery targeted at revascularization of the MCA territory appears to be unnecessary in these patients.

We retrospectively analyzed a surgical cohort of children and adolescents with unilateral MMD, and thus, our findings are limited by selection bias and the inherent biases associated with a retrospective study. Moreover, the lack of significance noted for some comparisons could have been due to the small numbers analyzed. Nevertheless, the present study includes a relatively large population of children and adolescents with uniformly managed unilateral MMD. Furthermore, contralateral progression was defined strictly as any noticeable change in the contralateral ICA and/or MCA. Hence, we believe that our results contribute to the understanding of contralateral progression, which tended to occur in children aged <9 years within 3 years of initial diagnosis (32%).

Disclosures

None.

References

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