Clinical Features of Unilateral Moyamoya Disease

Kentaro HAYASHI, Kazuhiko SUYAMA, and Izumi NAGATA

Department of Neurosurgery, Nagasaki University School of Medicine, Nagasaki

Abstract

Moyamoya disease is characterized by progressive occlusion of the internal carotid artery or its terminal branches, associated with formation of extensive collateral vessels (moyamoya vessels) at the base of the brain. Whether unilateral moyamoya disease, confirmed by typical angiographic evidence of moyamoya disease unilaterally and normal or equivocal findings contralaterally, is an early form of definite (bilateral) moyamoya disease remains controversial. The present study investigated the incidence and clinical features of unilateral moyamoya disease in a series of patients treated for moyamoya disease. Fifty-two patients were diagnosed with definite moyamoya disease and nine patients with unilateral moyamoya disease. Sex, age, signs at onset, neuroimaging findings, treatment, course of the disease, and family history of unilateral moyamoya disease were reviewed. Among the nine patients with unilateral moyamoya disease, there were twice as many females as males, and mean age at onset was 39.0 years. The clinical presentation was ischemic in three patients, bleeding in one, and asymptomatic in five. Two had familial moyamoya disease. Progression to bilateral lesions is known to occur in pediatric patients and patients with stenotic changes of the contralateral internal carotid artery bifurcation. Some unilateral cases are caused by the same genetic defects as definite cases, and others seem to be an unusual form of stenoocclusive process of cerebral arteries. Surgical treatment on the symptomatic side followed by close observation for bilateral involvement is recommended.

Key words: unilateral moyamoya disease, clinical feature, surgery

Introduction

Moyamoya disease is characterized by progressive occlusion of the internal carotid artery (ICA) or its terminal branches, associated with formation of extensive collateral vessels (moyamoya vessels) at the base of the brain. Moyamoya disease can occur in both children and adults, but the clinical features often differ. Most pediatric patients present with transient ischemic attack or cerebral infarction, whereas about half of adult patients experience intracranial bleeding.2)

The diagnostic criteria of the Research Committee on Moyamoya Disease (Spontaneous Occlusion of the Circle of Willis) of the Ministry of Health and Welfare of Japan (RCMJ) considers only cases with bilateral lesions as definite moyamoya disease.3) However, some cases with unilateral involvement also show angiographic findings on the affected side similar to those of definite cases, and so are classified as probable moyamoya disease. Whether unilateral moyamoya disease, as confirmed by typical angiographic evidence of moyamoya disease unilaterally and normal or equivocal findings contralaterally, is an early form of definite (bilateral) moyamoya disease remains controversial.7,28,30) Progression of the contralateral side in patients with predominantly unilateral moyamoya disease is reported, especially in young patients.7) Therefore, familial occurrence of unilateral moyamoya disease is known in the development of definite moyamoya disease.19,23)

The present study aimed to clarify the incidence and clinical features of unilateral moyamoya disease.

Clinical Materials and Methods

This study retrospectively reviewed patients with moyamoya disease treated at Nagasaki University Hospital from 1985 to 2005. Fifty-two patients had definite moyamoya disease based on the guidelines for the diagnosis of moyamoya disease set by RCMJ. Unilateral moyamoya disease was defined angiographically as unilateral occlusive lesion of the terminal portion of the ICA, the proximal portion of the anterior cerebral artery (ACA) or middle
cerebral artery (MCA), and the formation of moyamoya vessels, with none or equivocal stenosis on the contralateral side. Moyamoya-like vascular abnormality has been reported in association with various disease entities including atherosclerosis, autoimmune disease, meningitis, brain tumor, neurofibromatosis type 1, Down syndrome, cranial irradiation, and others. Such conditions were distinguished from moyamoya disease according to the diagnostic criteria of the RCMJ, and named quasi-moyamoya disease. These patients were excluded in this study.

Unilateral moyamoya disease was identified in 9 patients. We analyzed the angiographic stage (Suzuki classification), ischemic or hemorrhagic lesions on computed tomography (CT) or magnetic resonance (MR) imaging, and findings of hemodynamic hypoperfusion or decreased vascular reactivity to acetazolamide on single photon emission computed tomography (SPECT). Neuroimaging examinations were interpreted by two neuroradiologists. Surgical treatment was performed only on the symptomatic side. Patients were followed up clinically and with neuroimaging. Angiography was performed to verify any suspected progression of the occlusive lesion in the major intracranial arteries.

**Results**

The baseline patient characteristics of our nine cases of unilateral moyamoya disease are summarized in Table 1. The female-to-male ratio was 2.0, and the mean age at initial diagnosis was 39.0 years (range 10 to 65 years). The clinical presentation was ischemic in three patients, bleeding in one, and asymptomatic in five.

Table 1  Clinical summary of nine cases of unilateral moyamoya disease

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs), Sex</th>
<th>Symptom</th>
<th>CT, MR imaging</th>
<th>Angiography</th>
<th>Treatment</th>
<th>Follow-up period (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>23, M</td>
<td>aphasia</td>
<td>infarction</td>
<td>III, C₁</td>
<td>A₁ occlusion</td>
<td>STA-MCA</td>
</tr>
<tr>
<td>2</td>
<td>36, F</td>
<td>asymptomatic</td>
<td>normal</td>
<td>II, M₁</td>
<td>M₁ stenosis</td>
<td>no</td>
</tr>
<tr>
<td>3</td>
<td>35, F</td>
<td>TIA</td>
<td>lacuna</td>
<td>III, C₁</td>
<td>normal</td>
<td>no</td>
</tr>
<tr>
<td>4</td>
<td>52, F</td>
<td>asymptomatic</td>
<td>leukomalacia</td>
<td>II, M₁</td>
<td>normal</td>
<td>no</td>
</tr>
<tr>
<td>5</td>
<td>61, F</td>
<td>asymptomatic</td>
<td>normal</td>
<td>III, C₁</td>
<td>normal</td>
<td>no</td>
</tr>
<tr>
<td>6</td>
<td>27, F</td>
<td>asymptomatic</td>
<td>normal</td>
<td>III, M₁</td>
<td>normal</td>
<td>no</td>
</tr>
<tr>
<td>7</td>
<td>65, M</td>
<td>asymptomatic</td>
<td>normal</td>
<td>III, C₁</td>
<td>normal</td>
<td>no</td>
</tr>
<tr>
<td>8</td>
<td>42, F</td>
<td>hemiparesis</td>
<td>ICH</td>
<td>III, C₁</td>
<td>A₂ stenosis</td>
<td>no</td>
</tr>
<tr>
<td>9</td>
<td>10, M</td>
<td>TIA</td>
<td>normal</td>
<td>III, C₁</td>
<td>normal</td>
<td>STA-MCA</td>
</tr>
</tbody>
</table>


Two patients with the ischemic type underwent bypass surgery for superficial temporal artery (STA)-MCA anastomosis with encephalo-myo-synangiosis (EMS) on the symptomatic side. Postoperative courses were uneventful and no ischemic attack occurred. The other 7 patients were followed up by noting clinical symptoms and performing SPECT and MR imaging including MR angiography. Mean follow-up duration was 55.7 months, ranging from 14 months to 21 years. Disease progression of the symptomatic side was not observed in this series. No evidence of contralateral involvement was identified during the follow-up period.

Two patients had familial moyamoya disease, as the son of Case 5 and the brother of Case 9 had definite moyamoya disease diagnosed with angiography.

**Illustrative Cases**

**Case 1**: A 23-year-old man was referred to our
Fig. 1  Representative Case 1.  A: Right carotid angiogram showing absence of the anterior cerebral artery. Moyamoya vessels were not identified.  B: Left carotid angiogram showing stenoocclusive changes at the terminal portion of the internal carotid artery and massive formation of moyamoya vessels.  C: Vertebral angiogram showing development of leptomeningeal anastomosis in the right side dominantly.  D: T2-weighted magnetic resonance (MR) image revealing left frontal infarction.  E, F: Single photon emission computed tomography images at rest (E) and after acetazolamide loading (F) showing hypoperfusion with decreased hemodynamic reserve capacity in the left cerebral hemisphere.  G: MR angiogram obtained 36 months after vascular reconstruction showing collateral flow from the left superficial temporal artery. No definite angiographic change was observed on the right side.

Fig. 2  Representative Case 4.  A: Right carotid angiogram showing a normal internal carotid artery terminal.  B: Left carotid angiogram showing stenoocclusive changes at the proximal portion of the middle cerebral artery and development of mild moyamoya vessels.  C: Vertebral angiogram showing development of leptomeningeal anastomosis on the left side.  D: T2-weighted magnetic resonance (MR) image revealing mild ischemic change in the white matter.  E, F: Single photon emission computed tomography images at rest (E) and after acetazolamide loading (F) showing hypoperfusion with decreased hemodynamic reserve capacity in the left cerebral hemisphere.  G: MR angiogram obtained 60 months later showing no definite angiographic change.
hospital for left frontal infarction manifesting as motor aphasia. Angiography did not visualize the right ACA, but no moyamoya vessels were identified (Fig. 1A). Left carotid angiography showed occlusion of the left ICA with massive moyamoya vessels (Fig. 1B). Collateral flow from the external carotid artery was seen. Vertebral angiography showed development of leptomeningeal anastomosis in the left cerebral hemisphere (Fig. 1C). MR imaging showed left frontal infarction (Fig. 1D). SPECT imaging revealed hemodynamic hypoperfusion in the left cerebral hemisphere and impaired response to acetazolamide (Fig. 1E, F). She was treated conservatively because she was asymptomatic and cerebral perfusion was within normal limits. Brain MR imaging and MR angiography were repeated annually at an outpatient clinic. MR angiography 60 months later showed no progression (Fig. 2G).

**Case 9:** A 10-year-old boy referred to our hospital for transient left hemiparesis following hyperventilation. His elder brother had moyamoya disease and underwent bilateral vascular reconstruction. Right carotid angiography revealed marked stenosis at the terminal portion of the ICA and enlarged perforating arteries (Fig. 3A). Left carotid angiography showed no abnormality but left carotid angiography showed marked stenosis at the proximal portion of the MCA associated with moyamoya vessels (Fig. 2A, B). Leptomeningeal anastomosis was seen in the left cerebral hemisphere (Fig. 2C). MR imaging did not show any ischemic lesion (Fig. 2D). SPECT revealed mild reduction of cerebral blood flow and reactivity to acetazolamide (Fig. 2E, F). She was treated conservatively because she was asymptomatic and cerebral perfusion was within normal limits. Brain MR imaging and MR angiography were repeated annually at an outpatient clinic. MR angiography 60 months later showed no progression (Fig. 2G).
Table 2 Summary of characteristics of unilateral moyamoya disease

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>No. of patients</th>
<th>Female to male ratio</th>
<th>Mean age (yrs)</th>
<th>Mean follow-up period (mos)</th>
<th>Disease type (CI/TIA/CH/others/asymptomatic)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kawano et al. (1994)</td>
<td>32</td>
<td>2.6</td>
<td>19.7</td>
<td>32</td>
<td>5/17/7/3/0</td>
</tr>
<tr>
<td>Matsushima et al. (1994)</td>
<td>6</td>
<td>1.0</td>
<td>7.2</td>
<td>54</td>
<td>1/5/0/0/0</td>
</tr>
<tr>
<td>Houkin et al. (1996)</td>
<td>10</td>
<td>1.0</td>
<td>26.9</td>
<td>42</td>
<td>1/5/4/0/0</td>
</tr>
<tr>
<td>Hirotsume et al. (1997)</td>
<td>17</td>
<td>1.4</td>
<td>13.5</td>
<td>20</td>
<td>0/12/3/2/0</td>
</tr>
<tr>
<td>Ikezaki et al. (1997)</td>
<td>180</td>
<td>1.7</td>
<td>(2 peaks)</td>
<td>78</td>
<td>25/61/68/26/0</td>
</tr>
<tr>
<td>Kuroda et al. (2005)</td>
<td>11</td>
<td>—</td>
<td>(adult study)</td>
<td>74</td>
<td>—</td>
</tr>
<tr>
<td>Kelley et al. (2006)</td>
<td>18</td>
<td>2.6</td>
<td>29.8</td>
<td>25</td>
<td>6/7/1/3/0</td>
</tr>
<tr>
<td>Seol et al. (2006)</td>
<td>7</td>
<td>2.5</td>
<td>5.1</td>
<td>65</td>
<td>3/4/0/0/0</td>
</tr>
<tr>
<td>Present series</td>
<td>9</td>
<td>2.0</td>
<td>39.0</td>
<td>56</td>
<td>1/2/1/0/5</td>
</tr>
</tbody>
</table>

CH: cerebral hemorrhage, CI: cerebral infarction, TIA: transient ischemic attack.

with EMS was performed. Postoperative course was uneventful. Hypoperfusion of the right cerebral hemisphere was improved 6 months after surgery (Fig. 3F).

Discussion

The clinical characteristics of our 9 patients with unilateral moyamoya disease are summarized in Table 1. The incidence of unilateral moyamoya disease (9/61 = 14.8%) in our series was consistent with previous series, which demonstrated an incidence of approximately 15%.12,14) Six of the nine patients were female, and the mean age was 39 years. Previous cases of unilateral moyamoya disease are summarized in Table 2. Female predominance with the female to male ratio of approximately double that found in definite cases were observed.16,27,29) Patient age distribution seems to show two peaks in both unilateral and definite, and the adult onset rate is higher in unilateral than in definite moyamoya disease.7,8,12,13)

Moyamoya disease is associated with various disease entities and occasionally accompanies unilateral moyamoya lesion, for example induced by irradiation.10) Moyamoya-like vasculopathy more often tends to occur unilaterally in patients with Down syndrome.9) Therefore, the steno-occlusive changes occur unilaterally in up to 30% of patients with neurofibromatosis type 1-associated cerebral vascular lesion.6)

The clinical presentation was ischemia in 3 of 9 patients, manifesting as transient ischemic attack (n = 2) or cerebral infarction (n = 1). Only one patient presented with intracranial hemorrhage, and five patients were identified incidentally. Pediatric patients are well known to present with ischemic attack whereas adults tend to suffer from intracranial bleeding among patients with definite moyamoya disease.16,27) Similarly, pediatric patients commonly have ischemic attack and adults suffer bleeding among patients with unilateral moyamoya disease.1,5,8) Recently, moyamoya disease has been identified by MR imaging and MR angiography, which can detect asymptomatic moyamoya disease.15) Consequently, half of our unilateral cases were found incidentally.

Neuroimaging found initial cerebral artery steno-occlusion with ipsilateral formation of moyamoya vessels in all 9 patients. Occlusive lesions were identified in two locations, the terminal portion of the ICA and the proximal portion of the MCA. The development of moyamoya vessels was mild except for one case. Unilateral cases showed earlier angiographical stage compared with definite cases. Only our Case 1 had typical moyamoya vessels and the clinical course was consistent with definite moyamoya disease. No contralateral moyamoya vessels were found but steno-occlusion at the ACA or MCA was identified. One previous case of unilateral moyamoya disease had involvement of the posterior cerebral artery.20) The posterior circulation was not involved in this series.

No progression from unilateral to bilateral moyamoya disease was observed in our nine patients. However, unilateral lesions often progress
Table 3 Summary of progression of unilateral moyamoya disease

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Progression (%)</th>
<th>Duration (mos)</th>
<th>Indicative factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kawano et al. (1994)</td>
<td>53.1</td>
<td>—</td>
<td>young children, frequent ischemic attacks</td>
</tr>
<tr>
<td>Matsushima et al. (1994)</td>
<td>33.3</td>
<td>26</td>
<td>—</td>
</tr>
<tr>
<td>Houkin et al. (1996)</td>
<td>10.0</td>
<td>6</td>
<td>pediatric patient</td>
</tr>
<tr>
<td>Hirotsune et al. (1997)</td>
<td>35.3</td>
<td>—</td>
<td>pediatric patient</td>
</tr>
<tr>
<td>Ikezaki et al. (1997)</td>
<td>6.7</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Kuroda et al. (2005)</td>
<td>36.4</td>
<td>—</td>
<td>female</td>
</tr>
<tr>
<td>Kelley et al. (2006)</td>
<td>38.9</td>
<td>12.7</td>
<td>stenotic change in contralateral ICA bifurcation</td>
</tr>
<tr>
<td>Seol et al. (2006)</td>
<td>28.6</td>
<td>25.5</td>
<td>—</td>
</tr>
<tr>
<td>Present series</td>
<td>0</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

ICA: internal carotid artery.

to typical bilateral lesions during follow up, particularly in children, as shown in Table 3. Moreover, it is reasonable to assume that this disease does not necessarily develop bilaterally in synchronized fashion and that unilateral involvement at the initial presentation is likely. In fact, asymmetrical involvement of the bilateral ICAs and posterior cerebral arteries is common in pediatric-onset moyamoya disease. Angiographic findings in 32 cases of unilateral moyamoya disease suggested that bilateral lesions are likely to develop within 1–2 years in young children with unilateral evidence of moyamoya disease, whereas lesions in adults tend to remain unilateral. Furthermore, patients with unilateral disease and contralateral equivocal arterial stenotic changes have increased risk of progression. Based on these findings, the diagnosis criteria of RCMJ were modified in 1988 so that unilateral lesion with contralateral stenosis is sufficient to diagnose definite disease in the pediatric age group.

Two of our 9 patients with unilateral moyamoya disease underwent STA-MCA direct bypass procedure on the symptomatic side. Vascular reconstruction is effective for both definite and unilateral moyamoya disease to prevent disease progression and improve cerebral hypoperfusion postoperatively. Vascular reconstruction for the asymptomatic side has been controversial. Initial bypass surgery performed only on the symptomatic side and observation of the untreated side concluded that bypass surgery to the asymptomatic side can be delayed until the development of ischemic symptoms. Our present series also suggests that surgical indications are less aggressive for asymptomatic moyamoya disease, even in the pediatric age group.

Familial occurrence was found in approximately 10% of patients with moyamoya disease. Family history was confirmed in two of our nine patients with unilateral series. No familial occurrence was found in 7 unilateral cases and 10 unilateral cases. On the other hand, adult unilateral moyamoya disease with familial occurrence was reported in two definite cases. Previous large series of unilateral moyamoya disease demonstrated family occurrence rate of 6.7%. The coincidence of unilateral and definite moyamoya disease within a single family indicates that different phenotypes caused by the same genetic defects. Analysis of six cases of familial occurrence of unilateral moyamoya disease suggested that the mode of inheritance of familial moyamoya disease is autosomal dominant with incomplete penetrance. Various explanations for this phenomenon were suggested such as disease heterogeneity, genetic heterogeneity, and locus heterogeneity. Such heterogeneity may be related to the unilateral expression of the disease.

Definite moyamoya disease is defined as bilateral lesions, but unilateral involvement also occurs. Pediatric patients and the presence of stenotic change in the contralateral ICA are important factors in symptomatic occurrence. Some cases of unilateral moyamoya disease reflect different phenotypes caused by the same genetic defects. Others seem to be an unusual form of stenoocclusive process of the proximal intracranial arteries, thus
distinguished from definite moyamoya disease. Surgical treatment on the symptomatic side followed by close observation for bilateral involvement is recommended.

References

Unilateral Moyamoya Disease

It is still controversial whether moyamoya disease with unilateral involvement is an early stage of definite bilateral moyamoya disease or a distinct pathological entity. The authors reported a series of unilateral moyamoya disease patients within a relatively restricted area of Japan, and studied their sex, age, initial symptoms, neuroradiological findings, treatments, follow-up results and family history. This series is distinct from other series listed in Table 2 because of the older age and the involvement of asymptomatic patients. The female to male ratio was 2.0 and the mean age at diagnosis was 39.0 years. The initial clinical symptoms were ischemic in three, hemorrhagic in one, and asymptomatic in five. There were two familial involvement with definite bilateral moyamoya disease. Angiographically, all 9 patients showed only early changes and no involvement of the posterior circulation. The development of the moyamoya vessels was mild except for one case. The important information in this series is that there was no progression of the disease on the contralateral side during the follow-up periods (mean duration, 55.7 months) even with four symptomatic cases, initial observations of contralateral steno-occlusive vessels in three cases, and with familial involvement in two cases. We congratulate the authors for this well-documented report, as the accumulation of detailed data, especially in local populations, should be essential for further understanding this disease entity. Although the authors concluded that surgical treatment on the symptomatic side followed by close observation for bilateral involvement is recommended, only half of the symptomatic cases in this series were surgically treated. As the authors described clearly in their illustrative cases, tailored management should be considered with reference to the patient’s profile such as age, type of symptom, and compromised cerebral hemodynamics. Obviously there have been reports describing familial occurrence of moyamoya disease, but no clinical molecular evidence so far has shown that any specific genetic factor causes moyamoya disease.

Toshio HIGASHI, M.D., Ph.D.
and Tooru INOUE, M.D., Ph.D.
Department of Neurosurgery
Faculty of Medicine, Fukuoka University
Fukuoka, Japan

Address reprint requests to: Kentaro Hayashi, M.D.,
Department of Neurosurgery, Nagasaki University
School of Medicine, 1–7–1 Sakamoto, Nagasaki
852–8501, Japan.
e-mail: kenkuni@net.nagasaki-u.ac.jp

Commentary

Neurol Med Chir (Tokyo) 50, May, 2010