Regional Cerebral Blood Flow, Clinical Manifestations, and Age in Children With Moyamoya Disease

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In children with Moyamoya disease, transient ischemic attacks often occur during hyperventilation, and the frequency of attacks usually decreases with advancing age. To elucidate the mechanism of the attacks, the regional cerebral blood flow was measured during rest and/or hyperventilation in children aged 3–16 with Moyamoya disease. Regional cerebral blood flow during rest was significantly higher in younger children with Moyamoya disease, and it progressively decreased with advancing age through childhood. During hyperventilation, regional cerebral blood flow decreased in all the children, although blood flow in younger children was still higher than that in the older children. Nevertheless, transient ischemic attacks were more readily precipitated by hyperventilation in the younger than in the older children. Cerebral metabolic demand is much higher in the first decade of life than in later decades. Therefore, it seems likely that even a moderate reduction in cerebral blood flow can cause metabolic impairment in young children. Such high cerebral metabolic demand may play an important role in the frequent occurrence of transient ischemic attacks in young children with Moyamoya disease. (Stroke 1987;18:906–910)

Moyamoya disease (MMD) is a peculiar cerebrovascular disease characterized by spontaneous occlusion of the circle of Willis associated with the development of abnormal vascular networks at the base of the brain. The clinical manifestations of MMD differ depending on the patient’s age. The most common symptom in children with MMD is transient ischemic attack (TIA), while in adults intracranial hemorrhage occurs more frequently. The incidence of TIA is highest in the first decade of life and decreases rapidly thereafter. The question thus arises as to why TIAs occur more frequently in younger children with MMD and why the frequency of TIAs decreases rapidly with advancing age. In an attempt to resolve these problems, the regional cerebral blood flow (rCBF) was measured in children with MMD, and the relations between their ages, rCBF, and clinical manifestations were examined.

Subjects and Methods

Twenty children with MMD were studied, 9 boys and 11 girls aged 3–16 years. In accordance with the occlusive and intermediate stages of Kudo and Fukuda, these children were divided into 2 groups: a younger group, aged < 10 years, and an older group, aged > 10 years. These children had suffered only recurrent TIAs since ages 2–10 and had no permanent neurologic deficit at the time of study. The frequency of recent TIAs is shown in Table 1, and the most common precipitating factor was assessed based on the detailed history.

The diagnosis of MMD was confirmed by cerebral angiography in all children (Figure 1). In 18 of the 20 children, angiography revealed typical findings of MMD, occlusion or stenosis at the distal portion of the internal carotid arteries and characteristic Moyamoya vessels at the base of the brain bilaterally. In the remaining 2 children (Cases 4 and 5), occlusion of the internal carotid artery and the abnormal vascular networks were seen only unilaterally. These 2 children had typical clinical manifestations of MMD, i.e., TIAs while eating hot soup and “rebuild up” on their electroencephalogram (EEG). They were included in the present study since they were at the initial stage of MMD.

rCBF was measured using the 133Xe inhalation method described by Obrist et al, the validity of which in children has been reported previously. rCBF was calculated according to Risberg et al as the initial slope index (ISI). Using a 32-channel detector system (Novo Cerebrograph, Wilton, Conn.) to measure rCBF, data from the 9 detectors on each hemisphere, which had been confirmed by x-ray examination to be placed exactly over the hemisphere, were analyzed. In this paper, since no significant regional difference was observed, rCBF indicates the mean hemispheric blood flow. In each child, rCBF of the hypoperfused hemisphere was studied as the symptomatic side of the brain. rCBF was measured during both rest and voluntary hyperventilation in 9 children with MMD. The first measurement was performed in a dark quiet laboratory with the child lying comfortably and at rest. The second measurement was performed after an interval of about 30 minutes. One minute before the second
measurement, the child was instructed to start hyper-
ventilating and to continue for 4–5 minutes. Two of the
20 children (Cases 1 and 3) cried throughout the rest
and hyperventilation measurements, and Cases 2 and
12 spontaneously hyperventilated during the at rest
measurement. In these 4 children, therefore, rCBF was
measured only during hyperventilation. In another 7
children, rCBF was measured only during rest. Arteri-
al blood was sampled from the brachial artery between
the second and the third minute after initiation of the
rCBF measurement. Blood pressure was repeatedly
measured by auscultation. Informed consent was ob-
tained in all children.

Results

Age and Clinical Manifestations

All 20 children with MMD in the present study had
only recurrent TIAs, with no permanent neurologic
deficit. Most of the younger group suffered frequent
TIAs more than several times per month. On the other
hand, 4 children in the older group had experienced no
TIA for the past 6 months or more. In 17 children,
precipitating factors were found, including crying, eat-
ing hot noodles, or blowing up a balloon (Table 1).
TIAs were most frequently precipitated by crying, par-
ticularly in the younger children. Cases 3 and 10 cried
at the end of the rCBF measurement, and transient
hemiparesis developed in both children after comple-
tion of the measurement.

A characteristic EEG abnormality caused by hyper-
ventilation in MMD was found in 17 children. Irreg-
ular slow waves were activated by 2 or 3 minutes of
hyperventilation; after hyperventilation, the slow
waves quieted down. Then, after intervals of about 1
minute, irregular high-voltage slow waves appeared
again and persisted for several minutes. This EEG
abnormality is usually termed "rebuild up" and is often
associated with clinical cerebral ischemic symptoms.
The 3 oldest children (Cases 18, 19, and 20) showed
no rebuild up on their EEG. In 5 children (Cases 1, 3,
4, 9, and 13), clinical ischemic symptoms were ob-
served after hyperventilation when the EEG showed
rebuild up.

rCBF During Rest and Hyperventilation

Table 2 shows the mean rCBF in the 20 children
with MMD. Mean Paco2 during the rCBF measure-
ments during rest was 39.0 ± 2.7 mm Hg in the youn-
ger group and 41.1 ± 1.7 mm Hg in the older group.
Mean arterial blood pressure (MABP) in the younger
and older groups was 84.8 ± 5.7 and 82.9 ± 15.2 mm
Hg, respectively. There was no significant difference
in Paco2 or MABP between the groups; however,
mean rCBF in the younger group was 68.8 ± 9.0 and
that in the older group was 55.8 ± 6.8. In the children
with MMD, the mean rCBF of the younger group was
significantly higher than that of the older group
(p < 0.005).

During hyperventilation, a marked decrease in
rCBF was observed in all children. Mean Paco2 during
hyperventilation or crying was 29.0 ± 3.5 mm Hg in
the younger and 28.0 ± 2.2 mm Hg in the older group;

### Table 1. Clinical Profiles of 20 Children With Moyamoya Disease

<table>
<thead>
<tr>
<th>Case</th>
<th>Age/Sex</th>
<th>Symptoms</th>
<th>Frequency of ischemic attacks</th>
<th>Precipitating factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3/F</td>
<td>Alternating hemiparesis</td>
<td>+ + +</td>
<td>Crying</td>
</tr>
<tr>
<td>2</td>
<td>4/M</td>
<td>Left hemiparesis</td>
<td>+ + +</td>
<td>Crying</td>
</tr>
<tr>
<td>3</td>
<td>5/F</td>
<td>Alternating hemiparesis</td>
<td>+ + +</td>
<td>Crying</td>
</tr>
<tr>
<td>4</td>
<td>6/F</td>
<td>Left hemiparesis</td>
<td>+ +</td>
<td>Riding a bicycle</td>
</tr>
<tr>
<td>5</td>
<td>6/F</td>
<td>Right hemiparesis, aphasia</td>
<td>+ + +</td>
<td>Eating hot soup</td>
</tr>
<tr>
<td>6</td>
<td>7/F</td>
<td>Weakness, aphasia</td>
<td>+ +</td>
<td>Crying</td>
</tr>
<tr>
<td>7</td>
<td>7/F</td>
<td>Numbness</td>
<td>+ + +</td>
<td>Blowing up a balloon</td>
</tr>
<tr>
<td>8</td>
<td>8/M</td>
<td>Weakness</td>
<td>+ +</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>8/F</td>
<td>Right hemiparesis, aphasia</td>
<td>+</td>
<td>Crying</td>
</tr>
<tr>
<td>10</td>
<td>8/M</td>
<td>Numbness</td>
<td>+ +</td>
<td>Running</td>
</tr>
<tr>
<td>11</td>
<td>8/F</td>
<td>Alternating hemiparesis</td>
<td>+</td>
<td>Crying</td>
</tr>
<tr>
<td>12</td>
<td>10/F</td>
<td>Left weakness</td>
<td>No attack for 6 months</td>
<td>Eating hot noodles</td>
</tr>
<tr>
<td>13</td>
<td>10/M</td>
<td>Weakness</td>
<td>+ +</td>
<td>Running</td>
</tr>
<tr>
<td>14</td>
<td>10/M</td>
<td>Weakness</td>
<td>+</td>
<td>Eating hot noodles</td>
</tr>
<tr>
<td>15</td>
<td>11/M</td>
<td>Right weakness, aphasia</td>
<td>No attack for 1 year</td>
<td>Playing the flute</td>
</tr>
<tr>
<td>16</td>
<td>13/F</td>
<td>Numbness</td>
<td>+ + +</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>14/M</td>
<td>Weakness</td>
<td>No attack for 5 years</td>
<td>Eating hot noodles</td>
</tr>
<tr>
<td>18</td>
<td>14/M</td>
<td>Right weakness</td>
<td>No attack for 6 years</td>
<td>Eating hot soup</td>
</tr>
<tr>
<td>19</td>
<td>15/F</td>
<td>Right hemiparesis</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>16/F</td>
<td>Left hemiparesis</td>
<td>+</td>
<td>Playing the harmonica</td>
</tr>
</tbody>
</table>

F, female; M, male; + + +, > 1 attack/week; + +, 1-4 attacks/month; +, 1 attack in several months.
Figure 1. Typical angiogram in Moyamoya disease (right carotid angiogram of Case 10).

There was no significant difference between the 2 groups. However, rCBF of the younger group was again significantly higher than that of the older group (p<0.005). From the results for the 9 children in whom rCBF values were measured during both rest and hyperventilation, the CO₂ response expressed as the rCBF change/Paco₂ change was 1.30.

Age and rCBF

Figure 2 shows the relations between age and rCBF during rest and hyperventilation. Younger children had higher rCBF, but there was a significant and progressive decrease in rCBF with advancing age in both states. The closed circle in Figure 2 indicates Case 4, who cried at the end of the rCBF measurement and showed transient hemiparesis after completion of the measurement.

Discussion

The frequency of occurrence of TIAs in MMD is highest in the first decade, and the attacks tend to cease with advancing age. The present study confirms that younger children have more frequent TIAs. The children with MMD examined in this study had certain precipitating factors for TIAs, which included crying, eating hot noodles, playing the flute, or blowing up a balloon. Kuriyama et al found Paco₂ decreased during crying or eating hot noodles, indicating that these behaviors are related to hyperventilation. Some reports have emphasized hyperventilation as a triggering factor for TIAs in MMD. In this study, crying in particular was observed to precipitate ischemic symptoms more frequently in younger children with MMD, as Nishimoto et al have stressed. Rebuildup is also frequently provoked by hyperventilation and at times accompanies clinical ischemic symptoms in young children with MMD. It is well known that hyperventilation reduces cerebral blood flow (CBF). Therefore, it seems probable that a decrease in CBF due to hyperventilation may play an important role in the occurrence of ischemic manifestations in children with MMD. On the other hand, precipitation of TIAs or EEG abnormalities by hyperventilation is rarely encountered in adults with MMD.

It still remains unclear why ischemic manifestations of MMD occur more frequently in younger children and tend to cease with advancing age. To resolve this question, three explanations are possible. First, in MMD, impairment of cerebral circulation in younger children may be more serious than that in older children. In the presence of severely impaired cerebral circulation, cerebral dysfunction may be readily induced by a moderate reduction of CBF such as that due to hyperventilation. In the present study, the rCBF of children with MMD was greater in the younger age group and progressively declined with advancing age. Previous CBF studies in MMD have also indicated that younger children had a higher cerebral blood flow than older children. Thus, the first explanation seems unlikely.

Second, younger children may have better cerebral vasoconstrictive responses to hyperventilation than adults. If so, a profound decrease in rCBF may occur due to hyperventilation, resulting in the manifestation of ischemic symptoms. Gotô et al and Yamaguchi et al reported a superior cerebral vasoconstrictive response to hypocapnia in a younger age group. Nishimoto et al found an impaired CO₂ response but preserved hyperventilatory response in children with MMD. Also in this study, the cerebral vasoconstrictive response to hyperventilation was preserved in children

Table 2. rCBF During Rest and Hyperventilation in Children With Moyamoya Disease

<table>
<thead>
<tr>
<th></th>
<th>Younger group (n=8)</th>
<th>Older group (n=8)</th>
<th>Younger group (n=6)</th>
<th>Older group (n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>rCBF</td>
<td>68.8±8.96</td>
<td>55.8±6.82</td>
<td>59.1±12.4</td>
<td>41.4±5.65</td>
</tr>
<tr>
<td>Paco₂ (mm Hg)</td>
<td>39.0±2.68</td>
<td>41.1±1.72</td>
<td>29.0±3.50</td>
<td>28.0±2.18</td>
</tr>
<tr>
<td>MABP (mm Hg)</td>
<td>84.8±5.73</td>
<td>82.9±15.2</td>
<td>85.0±9.82</td>
<td>81.1±15.8</td>
</tr>
</tbody>
</table>

rCBF, regional cerebral blood flow; MABP, mean arterial blood pressure.
with MMD. However, the CO2 response of children with MMD (1.30) did not differ greatly from the value for adult TIA patients (1.05) measured previously in our laboratory. Furthermore, rCBF during hyperventilation was still higher in the younger than in the older children. These results indicate that an excellent CO2 response alone is not responsible for the frequent occurrence of ischemic symptoms in younger children with MMD.

Third, there may be an essential difference in the susceptibility to ischemia of brains of children and adults. It is well known that during the first decade of life, children have much higher cerebral oxygen consumption than adults.17,18 When normal cerebral function is maintained by high cerebral oxygen consumption in childhood, a high CBF may be needed. The greater cerebral metabolic demand of the juvenile brain requires a higher CBF. Therefore, even a moderate reduction in CBF could precipitate cerebral dysfunction. The results of the present study therefore seem to be in accordance with this third explanation.

The frequent occurrence of ischemic manifestations in very young children may also be related to the intellectual or emotional immaturity of the subjects. For example, younger children tend to cry readily in response to an uncomfortable experience. Such a tendency to cry could be another potent factor in the frequent occurrence of TIAs. It is likely that multiple factors participate in the frequent occurrence of TIAs in younger children with MMD and that one of the most important factors is the large metabolic demand of the juvenile brain.

References


KEY WORDS • Moyamoya disease • rCBF • transient ischemic attacks • age
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