Systemic Vascular Changes in Spontaneous Occlusion of the Circle of Willis

Eiji Ikeda, MD

Background and Purpose: We examined the presence of systemic etiologic factors causing vascular changes in so-called “spontaneous occlusion of the circle of Willis” (cerebrovascular moyamoya disease) to determine whether extracranial, as well as intracranial, vessels are involved in this disease.

Methods: Histopathologic examination and morphometric analysis of the extracranial vessels were performed in 13 patients with this disease.

Results: The histopathologic findings of the extracranial vessels were as follows: 1) advanced intimal fibrous thickening similar to that of the intracranial vessels; and 2) characteristic intimal fibrous nodular thickening, which may indicate organization of mural thrombi, at the proximal portions of the pulmonary arteries in three of 13 patients. Morphometric analysis revealed significant intimal thickening of the pulmonary arteries (p<0.05), renal arteries (p<0.05), and pancreatic arteries (p<0.01) in patients with this disease as compared with age- and sex-matched control patients.

Conclusions: On the basis of these findings, it is highly likely that this disease has systemic etiologic factors, as well as focal etiologic factors, that work to create vascular change in both the intracranial and extracranial vessels.


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o-called “spontaneous occlusion of the circle of Willis,” or cerebrovascular moyamoya disease, was first described by a Japanese surgeon and is known to have a high incidence in the Japanese population.1-3 This disease is characterized by occlusive or stenotic lesions at or around the terminal portions of the internal carotid arteries and abnormal vascular networks at the base of the brain.1-6 The obstructive lesions are caused by fibrous thickening of the intima with minimal lipid deposition. The internal elastic lamina is well preserved, and no significant inflammatory cell infiltration is seen in the vascular wall.4,5 The etiology of this disease has not yet been clarified, although abnormal thrombogenesis,6,7 an inflammatory process, or an autoimmune process3,4 is thought to be responsible. To discuss the etiology of this disease, it is important to determine whether there are systemic etiologic factors causing the obstructive vascular lesions observed in the intracranial vessels. There have been reports of involvement of the extracranial vessels, especially the renal arteries,8-11 and in some patients, the extracranial vessels exhibited intimal fibrous thickening similar to that found in the intracranial vessels.8,9 Nevertheless, no studies have provided clear statistical evidence as to whether this disease affects the extracranial vessels as well as the intracranial vessels. The solution to this problem may shed light on the existence of systemic etiologic factors in this disease. In this report, we conducted histopathologic and morphometric analyses on both the intracranial and extracranial vessels in 13 autopsy cases of this disease.

Materials and Methods

We used the extracranial vessels from 13 autopsy cases of spontaneous occlusion of the circle of Willis diagnosed according to the criteria proposed by the Research Committee on Spontaneous Occlusion of the Circle of Willis (Moyamoya Disease) of the Ministry of Health and Welfare of Japan,12 consisting of 1) angiography revealing bilateral occlusive or stenotic lesions at or around the terminal portions of the internal carotid arteries, with abnormal vascular networks at the base of the brain visualized in the arterial phase, and 2) absence of known etiologic factors.

Histopathologically, the intracranial vascular lesions of these 13 patients were all typical for this disease. The ages of the patients ranged from 6 to 58 years (average age, 33 years) at the time of autopsy. There were four males and nine females. Our series confirmed the higher incidence of the disease among

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females and the existence of juvenile patients, as previously described.1-4,8

There were several significant findings in our patients' clinical histories. One 6-year-old girl had a history of hypertension from unknown causes; a 15-year-old boy with no familial incidence of the lesion had café au lait spots of the skin; a 16-year-old girl had renovascular hypertension with stenosis of a unilateral renal artery; a 24-year-old woman experienced onset of the disease during pregnancy; and a 36-year-old man had concomitant hepatocellular carcinoma. Aside from the evidence of cerebrovascular disease, the other patients had no significant findings in their clinical histories.

Eleven patients with no history of hypertension were selected from the autopsy cases with this disease for morphometric analysis to exclude the effects of systemic hypertension on the vascular lesions. The age distribution of these patients ranged from 15 to 58 years (average age, 37 years) at the time of autopsy. There were four males and seven females. For statistical analysis, an age- and sex-matched control group consisting of 22 autopsy cases was prepared from routine autopsies performed at Keio University Hospital and the National Children's Hospital. Two age- and sex-matched control patients were selected for each patient with the disease. The age distribution of the control patients was from 15 to 58 years (average age, 38 years). There were eight males and 14 females. No history of hypertension or focal disease that might have modified the vascular lesions was detected in any of the 33 patients used in this morphometric and statistical analysis. The autopsies did not disclose any hypertrophy of the heart.

Specimens from the extracranial organs were fixed in 10% formaldehyde and embedded in paraffin. Histological sections were stained with hematoxylin and eosin, elastic van Gieson, and elastic hematoxylin and eosin, and were observed under a microscope.

The extent of intimal thickening of certain arteries was compared between the patients with spontaneous occlusion of the circle of Willis and the control
patients. The arteries chosen were the coronary arteries (0.1–0.3 cm o.d.), pulmonary arteries (0.03–0.1 cm o.d.), renal arteries (0.03–0.1 cm o.d.), and pancreatic arteries (0.03–0.1 cm o.d.). Three random samples were taken from each of the examined arteries. The thickness of the intima and media was measured at both the side showing the most prominent intimal thickening and the opposite side of the vessel. Then the ratio of the total intimal thickness of these two sides to the total medial thickness (i/m ratio) was calculated (Figure 1). This ratio was calculated for each patient with the disease and then compared with the control patients using Student’s t test or Welch’s t test.

Results

Clinically, no specific complications common to all 13 patients with spontaneous occlusion of the circle of Willis were detected in this study. Hypertension was pointed out in two patients, a 6-year-old and a 16-year-old girl. Hypertension in the latter patient was caused by stenosis of a unilateral renal artery. Unfortunately, there was no chance to study the stenotic lesion of the renal artery pathologically.

Histopathologic observations revealed an age-related increase in the extent of intimal thickening of the extracranial vessels both in the patients with the disease and in the control patients. This tendency was confirmed by morphometric analysis. Intimal thickening that was relatively advanced for the patient’s age was observed in the extracranial vessels of patients with the disease (Figure 2). Advanced intimal thickening was found even in juvenile patients, whose intimal thickening is normally negligible. The degree of intimal thickening was about the same in each of the given arteries of individual patients, regardless of the size of the arteries examined.

The extracranial vessels exhibited essentially the same intimal lesions as the intracranial vessels, namely, fibrous thickening showing minimal intracellular or extracellular lipid deposition, minimal inflammatory cell infiltration, and no significant disruption of the internal elastic lamina (Figure 3). Advanced intimal thickening was observed not only in the systemic circulation but also in the pulmonary circulation.

As a characteristic histopathologic finding, the proximal portion of the pulmonary arteries showed fibrous nodular intimal thickening with neither significant inflammatory cell infiltration nor disruption of the internal elastic lamina in three of the 13 patients (Figure 4). Endothelization was found at the innermost layer of the fibrous nodular lesions. The intimal lesion contained varying numbers of elastic fibers. The media showed no remarkable changes. It was suggested that these intimal lesions had been
formed by the organization of mural thrombi, although fresh thrombi were not observed.\textsuperscript{13} The fact that this kind of intimal lesion was observed at the proximal portions of the pulmonary arteries in three of 13 patients with this disease was worthy of note.

In addition, the lumen of the peripheral portion of a pulmonary artery in one patient was filled with loose fibrous tissue containing evidence of recanalization, which was thought to be the result of organization of thromboemboli.

Mean values and standard deviations of the $i/m$ ratio for each of the given arteries are shown in Table 1. Intimal thickening of the pulmonary and renal arteries was significantly greater than that of control patients ($p<0.05$). Intimal thickening of the pancreatic artery was also significantly greater than that of control patients ($p<0.01$). Although the mean values of the $i/m$ ratio for the coronary artery were not statistically different between the two groups, some patients showed evidence of advanced intimal thickening relative to their age.

**Discussion**

Spontaneous occlusion of the circle of Willis can cause cerebral infarction, transient ischemic attack, intracranial hemorrhage, or epilepsy. The etiology of the obstructive vascular lesions at or around the terminal portions of the internal carotid arteries has not been clarified. To elucidate the causative factors in this disease, it is important to study the existence of systemic etiologic factors through histopathologic observation of the extracranial vessels.

In this study, the extracranial vessels of 13 patients with this disease showed advanced intimal thickening relative to age, a finding that has been described sporadically in the literature.\textsuperscript{9,11} The extracranial vascular changes were mainly confined to the intima and were similar to those in the intracranial vessels. The thickened intima contained minimal lipid deposition and minimal inflammatory cell infiltration. No evidence of vasculitis was apparent in the extracranial vessels in this study.

Morphometric analysis of 11 patients with this disease whose intimal thickening was not caused by hypertension showed statistically significant intimal thickening in the pulmonary artery, renal artery, and pancreatic artery. Although intimal thickening of the coronary artery was not statistically significant in this study, this result may be due to the paucity of patients (five of 11 patients) in whom histologic sections of the coronary artery were available for morphometric analysis. The morphometric findings strongly suggest that this disease involves not only the intracranial vessels but also the extracranial vessels and that there are systemic etiologic factors that cause intimal thickening in the systemic vessels.
The thickened intima of both the intracranial and extracranial vessels in the patients with this disease was histologically compatible with old organized thrombi. The formation of mural thrombi is frequently observed in the intracranial vessels. Therefore, thrombosis was thought to play an important role in the development of intimal lesions as well as in the progression of the obstructive vascular lesions. The fibrous nodular lesions of the intima observed in the proximal portion of the pulmonary artery in three of 13 patients in this study were also suggestive of a systemic tendency to form thrombi in this disease. Because of the frequent incidence of preceding infections, some authors regard inflammatory and autoimmune processes such as vasculitis as the cause of the obstructive vascular lesions in this disease. However, no apparent evidence of vasculitis, such as significant inflammatory cell infiltration or disruption of the internal elastic lamina, was observed in either the intracranial or extracranial vessels in this study. As previously mentioned, it is highly likely that patients with this disease have a systemic tendency to form thrombi.

Routine blood coagulation studies in this disease are known to show values within normal limits, although abnormalities in the neumaminidase content of platelets and plasma level of serotonin have been pointed out in some patients classified as having the infarct type. These abnormalities might be secondary. Abnormalities of the red blood cells have not been described. These findings support the idea that the systemic tendency to form thrombi in this disease is due to abnormalities of the vascular wall rather than to abnormalities of the blood.

It is almost certain that this disease has focal etiologic factors, including a rheological factor, that act around the terminal portions of the internal carotid artery to form the characteristic vascular lesions of this disease. However, in addition to focal etiologic factors, this disease might be characterized by systemic etiologic factors that lead to intimal fibrous thickening in both the intracranial and extracranial vessels. Further investigation of the vessels affected in this disease will be required to detect these systemic etiologic factors.

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Key Words • cerebral arteries • moyamoya disease

Table 1. Ratio of the Thickness of the Intima to the Media

<table>
<thead>
<tr>
<th>Spontaneous occlusion of the circle of Willis</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Coronary artery</strong></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>2.11</td>
</tr>
<tr>
<td>SD</td>
<td>1.85</td>
</tr>
<tr>
<td><em>(n=5)</em></td>
<td></td>
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<tr>
<td><strong>Pulmonary artery</strong></td>
<td></td>
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<tr>
<td>Mean</td>
<td>0.587*</td>
</tr>
<tr>
<td>SD</td>
<td>0.641*</td>
</tr>
<tr>
<td><em>(n=11)</em></td>
<td></td>
</tr>
<tr>
<td><strong>Renal artery</strong></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>1.10*</td>
</tr>
<tr>
<td>SD</td>
<td>0.94</td>
</tr>
<tr>
<td><em>(n=11)</em></td>
<td></td>
</tr>
<tr>
<td><strong>Pancreatic artery</strong></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>0.767†</td>
</tr>
<tr>
<td>SD</td>
<td>0.596</td>
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<tr>
<td><em>(n=11)</em></td>
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</table>

Numerals represent the means and standard deviations of the intima-to-media ratio for each artery in each group. The intimal thickening in the patients with spontaneous occlusion of the circle of Willis was significantly greater than that of control patients (*p<0.05, t p<0.01)*.

n, Number of cases examined.
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