Angiographic Analysis of Moyamoya Disease
—How Does Moyamoya Disease Progress?—

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Abstract
Differences in the clinical presentation and angiographic stages of moyamoya disease were studied in 69 patients, 35 children (6.3 ± 2.9 years old) and 34 adults (44.6 ± 10.5 years old). The angiographic stage (Suzuki’s stage) was compared between childhood and adulthood, ischemic onset and hemorrhagic onset, and female and male. The distribution of the angiographic stage was not very different, but was significantly shifted from stage III to stage IV in adult cases. The angiographic stage in patients with hemorrhagic onset was not significantly different from those with ischemic onset. There was no significant difference between females and males. Angiographic change is not very remarkable between pediatric and adult moyamoya disease. The angiographic stage does not directly correlate with the distinct clinical presentations between pediatric and adult moyamoya disease. Other factors such as cerebral blood flow demand and arteriosclerotic change seem to cause these differences.

Key words: moyamoya disease, angiography, cerebral ischemia

Introduction
Moyamoya disease, the spontaneous occlusion of the circle of Willis, is a progressive disease with two peaks of frequency in pediatric (under 15 years old) and adult (over 16 years old) patients. There is continuity between these two peaks, but how pediatric moyamoya disease progresses to the adult type is not well understood. In addition, pediatric moyamoya disease and adult moyamoya disease have distinct differences in clinical presentation. Most cases of pediatric moyamoya disease present with ischemia, whereas some cases of adult moyamoya disease present with intracerebral hemorrhage. The most likely explanation is that there are some distinct differences in angiographic stage between pediatric moyamoya disease and adult moyamoya disease. However, there has been no systematic study analyzing the differences in angiographic stage between pediatric moyamoya disease and adult moyamoya disease. This study reviewed the angiographic stages in patients with pediatric moyamoya disease and adult moyamoya disease to analyze the correlation between the angiographic stage and clinical presentation.

Materials and Methods
Between 1986 and 1995, 69 patients with moyamoya disease were treated in Hokkaido University Hospital and its affiliated hospitals, including 35 children (under 15 years old) and 34 adults (over 16 years old). The initial clinical symptoms were definitely classified as hemorrhage or ischemia according to whether hemorrhage or infarction was seen on computed tomography scans or magnetic resonance (MR) images, and if obvious signs of transient ischemic attack after hyperventilation was seen even if neuroimaging was negative. Nontypical signs of ischemia such as seizure, involuntary movement, or poor mental development occurring mainly in pediatric moyamoya disease without obvious evidence of cerebral ischemia was also classified as ischemia (nonhemorrhage).

All symptomatic patients received surgical treat-
ment involving combined revascularization (direct bypass with superficial temporal artery-middle cerebral artery anastomosis and indirect bypass with encephalo-duro-arterio-myo-synangiosis). Basically, surgery was performed on only the symptomatic side. The details and results of surgery have been described elsewhere.\textsuperscript{21} Cases of so-called akin-moyamoya (or quasi-moyamoya) disease, which is associated with apparent arteriosclerotic disease in adulthood and systemic diseases such as Down’s syndrome and von Recklinghausen’s disease, were carefully excluded from this study.

All patients underwent conventional contrast angiography or digital subtraction angiography (DSA) before surgical treatment. MR angiography is a reliable modality for correct diagnosis as previously shown.\textsuperscript{19} However, stage differentiation by MR angiography is not reliable. Therefore, angiographic stage was determined by two of the authors (K.H., T.Y.) based exclusively on good conventional angiograms or DSA. Surgical revascularization drastically modifies the angiographic findings.\textsuperscript{1,21} Therefore, all angiographic stagings were based on preoperative angiograms. Angiographic staging was based on the criteria established by Suzuki and Takaku.\textsuperscript{19} Briefly, the disease is classified into six stages based on the findings of conventional angiography: I, stenosis of the intracranial bifurcation of the internal carotid artery; II, first appearance of moyamoya vessels (dilatation of the intracerebral arteries); III, increase of moyamoya vessels (disappearance of the middle cerebral and anterior cerebral arteries); IV, fine formation of moyamoya vessels (disappearance of the middle cerebral and anterior cerebral arteries); V,
shrinking of moyamoya vessels (disappearance of the intracerebral arteries); and VI, disappearance of moyamoya vessels and dominance of collateral circulation from only the external carotid system. Figure 1 shows typical angiograms selected from our study to demonstrate stages I, II, III, IV, V, and VI.

**Results**

The distributions of age, sex, and initial clinical symptoms clearly shows the two peaks of frequency in childhood and adulthood (Fig. 2). The mean age and SD was 6.25 ± 2.93 years old for pediatric patients and 44.56 ± 10.48 years old for adults. There were 22 males and 47 females, so 68% of the patients were female. All pediatric moyamoya patients (35 patients) had ischemic (nonhemorrhagic) onset, whereas 19 cases (56%) of adult moyamoya patients had hemorrhagic onset.

The correlations between angiographic stage and pediatric and adulthood occurrence, ischemic onset and hemorrhagic onset, and sex were analyzed. There were significant differences in angiographic stage between pediatric and adult cases as a whole (p < 0.02, Wilcoxon test). In addition, most pediatric moyamoya disease cases were clearly concentrated in stage III (p < 0.001, chi-square test), whereas adult moyamoya disease had shifted significantly toward the more advanced stage IV (p < 0.01, chi-square test) (Fig. 3). Stage I (normal or minimal change) was predominantly seen in the adult type, but there was no significant difference in the distribution. We also compared hemorrhagic onset and ischemic onset in adulthood, but there was no significant difference between these two groups (p > 0.10, Wilcoxon test). There was no significant difference between female patients and male patients (p > 0.10, Wilcoxon test).

**Discussion**

Previously, limited numbers of patients with moyamoya disease have shown drastic angiographic changes during the course of the disease.\(^ {19}\) However, no dynamic angiographic change has been reported in the follow-up of adult moyamoya disease except for unusual cases of unilateral moyamoya disease.\(^ {1,4,19}\) Our study also showed that there is no such drastic change between pediatric moyamoya disease and adult moyamoya. However, our results also demonstrated that stage III was occurred significantly more often in pediatric moyamoya disease than in adult moyamoya disease, whereas stage IV was seen more often in adult moyamoya disease. Therefore, it is most likely that pediatric moyamoya disease advances to adult moyamoya disease, although the extent of angiographic progression is very slight.

The problem then remains of how and when does moyamoya disease progress? Suzuki and Takaku\(^ {19}\) demonstrated several cases of pediatric moyamoya disease that showed a dynamic change in angiographic findings over a short period. Ezura et al.\(^ {4}\) reported cases with angiographic follow-up from childhood to

![Figure 2: Distribution of patients.](image)

*Fig. 2  Distribution of patients.  left: Ischemia (open column) and hemorrhage (shaded column).  right: Females (open column) and males (shaded column).*

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young adulthood, and concluded that moyamoya disease progresses in angiographic stage until adolescence, then stabilizes or almost stabilizes by the age of 20 years. At present, the most likely theory for the pathogenesis of moyamoya disease is that certain polygenes are related to the occurrence of this disease, although the mode of inheritance is unknown. Based on these facts, we suggest that moyamoya disease progresses very quickly in early childhood from stage I to stage III. Especially patients less than 2 years old may progress very quickly in a short period. Ito et al. have reported that patients with moyamoya disease less than 2 years old have a poor prognosis because of rapid angiographic progression. Moyamoya disease may then progress relatively slowly after the early pediatric stage and become stable in childhood and adolescence.

Questions remain about how and when this disease becomes symptomatic and why the clinical manifestation is so different between pediatric and adulthood. Our results indicated that there is no significant angiographic difference between females and males, between pediatric and adult occurrence, or between hemorrhagic and ischemic onset. Clearly symptomatic onset does not necessarily depend on the angiographic stage, but other factors such as cerebral blood flow demand in childhood and arteriosclerotic change of moyamoya vessels in adults contribute to the mechanism of clinical manifestation (Fig. 4). As we demonstrated elsewhere, the perfusion reserve detected by acetazolamide test is disturbed in pediatric moyamoya disease although mean cerebral blood flow is not always decreased. The cerebral blood flow necessary for development and maturation of the child’s brain is much higher than that required by an adult. Therefore, most pediatric patients manifest ischemic insults induced by loading such as hyperventilation or chronic ischemic brain damage causing mental retardation.

Patients may pass through childhood asymptotically, if cerebral blood flow and perfusion reserve is maintained. Most moyamoya patients remain asymptomatic during adolescence since the demand for cerebral blood flow decreases to the adult level and no significant arteriosclerotic process is seen. In adults, arteriosclerotic change involves the moyamoya vessels and other collateral vessels, resulting in two apparently different clinical presentations, hemorrhage and ischemia. Most hemorrhage seen in moyamoya disease is supposed to be due to microaneurysm (visible or invisible on angiography) rupture in the basal moyamoya vessels. These microaneurysms are closely related to arteriosclerotic
change, and may result in cerebral ischemia in some cases. We have rarely encountered asymptomatic adult moyamoya disease despite the development of screening examinations for cerebrovascular disease using MR angiography. In other words, most patients with moyamoya disease become symptomatic in adulthood even if the disease remains asymptomatic during childhood.

Moyamoya disease progresses in early childhood and becomes stable in adolescence and adulthood. The disease can be clinically divided into three stages: the ischemic stage, which is vulnerable to ischemia due to the demand for cerebral blood flow in childhood; the asymptomatic stage in adolescence and early adulthood, which is stable since there is no critical cerebral blood flow level or arteriosclerotic change of moyamoya vessels and collateral vessels; and the ischemic and hemorrhagic stage in adulthood, which manifests both hemorrhage and ischemia due to arteriosclerotic change of the abnormal vessels. Complete clarification of the clinical course of moyamoya disease requires a long-term angiographic follow-up study in the same series of patients.

References


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Commentary

While rapid progression until adolescence has been documented in some cases, the mode of progression of moyamoya disease in the majority of cases has remained elusive. Using the classification of angiographical appearance of moyamoya disease as advocated by Suzuki and Takaku, this study addressed the above question by comparing the distribution of angiographical stages between pediatric (under 15 y/o, n = 35) and adult (over 16 y/o, n = 34) patients who presented with ischemic or hemorrhagic events. The major findings were: the stage III was predominant in the pediatric group whereas the stage IV was in the adult group; the other stages were distributed evenly in the two groups; and hemorrhagic events occurred solely in the adult group. It is an important finding that stages I-II as well as stages V-VI occupied similar percentages among pediatric and adult patients, because this clearly indicates that the evolution of disease process takes place mostly during infancy, being self-limited in some cases. Thus, the authors' speculation that the hemorrhagic or ischemic events occurring in the adult patients is owing to the progression of cerebral arteriosclerosis which is accelerated by the hemodynamic alteration is strong and persuasive. In this regard, however, it is desirable to see whether the occurrence of cerebral ischemia or hemorrhage is associated with advanced angiographical stage, which is not clear from the results presented.

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I have read with interest the article by Houkin et al., which carefully analyzes the differences in angiographic stages between pediatric and adult moyamoya disease. This large study includes 69 patients — 35 pediatric and 34 adult — classified into hemorrhagic or nonhemorrhagic presentation of moyamoya disease. Importantly, the authors are careful to assign the angiographic stage on the basis of preoperative arteriograms, as it is well recognized that surgical intervention may alter the angiographic appearance. The results of this analysis clearly demonstrate two peaks of incidence of moyamoya, one between 3 and 10 years of age and a second between 41 and 50 years of age with an overall predominance in female patients. All pediatric patients presented with nonhemorrhagic manifestations of moyamoya disease, yet 56% of adult patients had hemorrhagic presentations. Despite the fact that pediatric cases were concentrated in angiographic stage III and there was a significant shift towards angiographic stage IV in adult cases, it does not appear that angiographic stage alone explains the rarity of hemorrhagic presentation in pediatric moyamoya and common hemorrhagic presentation in adults.

Although this epidemiologic study does not identify the factors other than angiographic stage that may influence the mode of presentation of moyamoya disease, the authors propose an interesting explanation for the discrepancy in presentation between children and adults. They propose that the predominance of nonhemorrhagic presentation of moyamoya in early childhood is related to increased demands for cerebral blood flow. This hypothesis is supported by evidence from other studies that cerebrovascular reserve is limited, even in the presence of relatively normal regional cerebral blood flows in young pediatric patients with moyamoya disease. The authors attribute that high incidence of hemorrhagic presentation in adult moyamoya disease to arteriosclerotic change in the moyamoya vessels. This hypothesis would also explain the group of adolescent patients that often times remains asymptomatic due to favorable changes in the demand for cerebral blood flow combined with a lack of arteriosclerotic changes within their abnormal cerebral vessels.

Clearly, further scientific work will be required to substantiate this hypothesis. These epidemiologic studies, however, are very important in contributing to our understanding of this enigmatic disease.

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