Posterior Circulation and High Prevalence of Ischemic Stroke among Young Pediatric Patients with Moyamoya Disease: Evidence of Angiography-Based Differences by Age at Diagnosis

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**BACKGROUND AND PURPOSE:** At diagnosis, the primary clinical manifestations of pediatric Moyamoya disease are TIA or CSs. CSs are reported to be more prevalent in younger than in older children. We sought to determine whether age-related differences in clinical manifestations are associated with age-related angiographic differences.

**MATERIALS AND METHODS:** We divided 78 patients diagnosed with Moyamoya disease before 16 years of age into four 4-year age groups and examined the relationships between age at diagnosis and clinical manifestations and angiographic and MR imaging findings.

**RESULTS:** Among the 4 diagnostic age groups, in those younger than 4 years of age, the prevalence of CSs and of infarctions on MR images was highest, and along with severity of steno-occlusive lesions of the PCA, the prevalence was significantly higher than that in the next diagnostic age group (4–7 years), though the severity of steno-occlusive lesions in the ICA and the degree of transdural collaterals did not differ significantly. The prevalence of CSs and infarctions did not differ significantly in the 3 oldest diagnostic age groups, whereas ICA and PCA lesions and transdural collaterals correlated positively with diagnostic age.

**CONCLUSIONS:** The high prevalence of CSs and infarctions in patients diagnosed before 4 years of age is associated with advanced steno-occlusive lesions of the PCA. In patients 4 years of age and older at diagnosis, transdural collaterals develop in parallel with advancement of ICA and PCA lesions, which may contribute to the nearly constant prevalence of CSs.

**ABBREVIATIONS:** ACA = anterior cerebral artery; ant-MCA = anterior half of the territory of the MCA; ant-watershed = the anterior watershed area of the ACA and MCA; CS = completed stroke with permanent neurologic deficit; ECA = external carotid artery; ICA = internal carotid artery; MCA = middle cerebral artery; N.S. = no significant difference or no significant relationship with diagnostic age; PCA = posterior cerebral artery; post-MCA = posterior half of the territory of the MCA; postwatershed = posterior watershed area of the MCA and PCA; TIA = transient ischemic attack.
years; 75th percentile, 10.25 years), who were definitively diagnosed with Moyamoya disease at our institution or affiliated hospitals between 1997 and 2008 and were registered at the time of diagnosis with the Research Committee on Spontaneous Occlusion of the Circle of Willis (Moyamoya Disease) of the Ministry of Health and Welfare, Japan (hereafter referred to as Ministry Research Committee).10,11

Clinical Manifestations at Diagnosis
In all 78 patients, we reviewed the clinical manifestations at diagnosis registered with the Ministry Research Committee.10,11 and on the basis of symptoms and MR imaging findings, either of 2 neurosurgeons classified the clinical manifestations as a categoric variable.

Findings at Diagnosis
In all 78 patients, we reviewed the clinical manifestations at diagnosis and 12, by time-of-flight MR angiograms plus MR imaging without conventional or MR angiograms. MR images included T1-weighted, fluid-attenuated inversion recovery, and diffusion-weighted images. We divided the right and left cerebral hemispheres into the basal ganglia, the thalamus, and 6 corticospinal subcortical zones. The 6 corticospinal subcortical zones included the territory of the ACA, the ant-watershed, the ant-MCA, the post-MCA, the postwatershed, and the territory of the PCA from anterior to posterior in the hemisphere. The ant-MCA and post-MCA were divided at the central sulcus, and the temporal lobe was included in the post-MCA. We used the number of infarcted zones, including the basal ganglia and thalamus, and the distribution of the infarcted zones, excluding the basal ganglia and thalamus (corticospinal subcortical infarcted zones), as ordinal variables in each hemisphere.

Two radiologists (S.M. and S.H.), blinded to patient identity and clinical manifestations, evaluated MR images and either conventional or MR angiograms. MR images were interpreted without knowledge of either conventional or MR angiographic findings. When interpretations were inconsistent, final evaluation was reached by consensus. Initial interobserver agreement between the 2 radiologists was 84% in interpreting MR images and 90% in interpreting conventional or MR angiograms. The intraobserver agreement of the first radiologist was 90% in interpreting MR images and 88% in interpreting conventional or MR angiograms. The intraobserver agreement of the second radiologist was 85% in interpreting MR images and 90% in interpreting conventional or MR angiograms.

Age at Time of Diagnosis
Diagnostic age was defined as the age at diagnosis based on conventional or MR angiography findings. In an earlier study, Kim et al divided the age categories unevenly into 3 groups (younger than 3 years, 3–6 years, 7–16 years of age) without a clear explanation. In contrast, to avoid such arbitrary groups, we assigned our pediatric patients, whose ages ranged from 10 months to 15 years, into 1 of 4 diagnostic age groups of 4 years each before analysis: younger than 4 years (14 patients; median age, 2 years); 4–7 years (29 patients; mean age, 5 years); 7–11 years (21 patients; median age, 9 years); and 12–15 years (14 patients; median age, 12 years). We used each patient’s diagnostic age group as a categoric or ordinal variable.

Analysis and Statistics
We measured 7 variables—diagnostic age and clinical manifestations in each patient and 5 imaging findings in each hemisphere (ICA stage, PCA stage, number of transdural collaterals, number of infarcted zones, and distribution of corticospinal subcortical infarcted zones). Therefore, variables did not correspond 1 to 1. In addition, the corticospinal subcortical infarcted zones were multiple-choice variables (for example, ant-watershed and post-MCA in 1 hemisphere) and could be determined only in the limited hemispheres with corticospinal subcortical infarctions. To minimize the impact of such variations on statistical analysis and to determine the possible correspondence between age-related differences in clinical manifestations and imaging findings, we analyzed the 6 single factors, treating diagnostic age as an independent variable and the other 6 variables as dependent variables.

A recent study showed that CSs were more prevalent in the youngest patient age group (younger than 3 years of age) than in the next older age group (3–6 years) but not substantially different between patients 3–6 years and those 7–16 years of age.13 In this study, therefore, we focused mainly on the characteristics of the youngest age group (diagnosed before 4 years of age).

To avoid exploratory analysis as far as possible, we analyzed statistics according to the analyses plan in common among all the 6 single-factor analyses. First, among the 4 diagnostic age groups, we used the Fisher exact test to compare clinical manifestations and the Kruskal-Wallis test to compare the aforementioned 5 imaging findings. When we observed significant differences among the 4 diagnostic age groups, between patients diagnosed before 4 years of age and those diagnosed from 4 to 7 years, we used the Fisher exact test to assess the differences in clinical manifestations and the Wilcoxon rank sum test to assess the differences in imaging findings. Among the
3 oldest diagnostic age groups, we used the Fisher exact test to assess the differences in clinical manifestations, the Kruskal-Wallis test to assess the differences in imaging findings, and the Spearman rank correlation test to test the correlation between diagnostic age and imaging findings.

Statistical significance was defined as 2-tailed $P < .05$. The Fisher exact test was performed by using R, Version 2.8.1 (http://cran.md.tsukuba.ac.jp/bin/windows/) and the Kruskal-Wallis and Wilcoxon rank sum tests, by using JMP 6.0 J software for Windows (SAS Institute, Cary, North Carolina).

**Results**

Among the 4 diagnostic age groups, we detected significant differences in all 6 dependent variables: clinical manifestations (Fig 1A, $P = .0040$), number of infarcted zones (Fig 1B, $P = .0020$), distribution of corticossylveal infarcted zones (Fig 1C, $P = .0258$), ICA stage (Fig 1D, $P = .0009$), PCA stage (Fig 1E, $P = .0132$), and degree of transdural collaterals (Fig 1F, $P = .0033$).

Patients diagnosed before 4 years of age had the highest prevalence of CSs (85.7%, 12 of 14 patients) and the highest number of infarcted zones. CSs (85.7%) predominated over TIAs (14.3%, 2 of 14 patients), but TIAs (62.1%, 18 of 29 patients) predominated over CSs (34.5%, 10 of 29 patients) in patients diagnosed from 4 to 7 years of age.

Clinical manifestations ($P = .0028$), number of infarcted zones ($P = .0024$), distribution of corticossylveal infarcted zones ($P = .0035$), and PCA stages ($P = .0222$) differed significantly between patients diagnosed before 4 years of age and those diagnosed from 4 to 7 years, but ICA stage ($P = .7081$) and degree of transdural collaterals ($P = .7820$) did not. Figure 2 shows a typical case of a patient diagnosed before 4 years of age.

We observed infarctions in 77 (49.4%) of 156 hemispheres,
which included 128 corticosubcortical zones and 4 basal ganglia. In patients diagnosed before 4 years of age, the prevalence of infarctions in ant-MCA (26.7%, 12 of 45 hemispheres with corticosubcortical infarcted zones) and post-MCA zones (33.3%, 15 of 45 hemispheres) was higher than the prevalence in those diagnosed from 4 to 7 years (17.1%, 7 of 41 hemispheres in the ant-MCA and 17.1%, 7 of 41 hemispheres in the post-MCA zone).

We observed infarctions in the basal ganglia in 4 hemispheres of 2 patients, 1 each from the age groups diagnosed before 4 years of age and at 8–11 years, and 2 from the group diagnosed from 4 to 7 years. Two hemispheres of 2 patients had infarctions in the basal ganglia without corticosubcortical infarction. In no patient did we observe infarction in the thalamus.

Among the 3 oldest diagnostic age groups, we observed neither significant differences with respect to clinical manifestations ($P = .7751$), number of infarcted zones ($P = .6394$), and distribution of corticosubcortical infarcted zones ($P = .4561$) nor a significant relationship to diagnostic age with respect to the number infarcted zones ($P = .5059$) and the distribution of corticosubcortical infarcted zones ($P = .2229$).

In contrast, differences were significant for ICA stage ($P = .0008$), PCA stage ($P = .0207$), and degree of transdural collaterals ($P = .0037$); and the relationship to diagnostic age was significantly positive for ICA stage ($P = .0005$), PCA stage ($P = .0243$), and degree of transdural collaterals ($P = .0007$). Figure 3 shows a typical case of a patient diagnosed from 4 to 7 years; Fig 4 shows a case diagnosed from 12 to 15 years.

**Discussion**

The prevalence of CSs and the number of infarcted zones were highest in patients diagnosed before 4 years of age, in whom CSs, infarctions, and PCA lesions were more prevalent than in patients diagnosed from 4 to 7 years, despite the absence of a significant difference between ICA stage and transdural collaterals between the 2 groups. Among the 3 oldest diagnostic age groups, clinical manifestations and number of infarcted zones were approximately constant, though ICA and PCA stages were higher.

The explanation for CSs being more frequent in patients diagnosed before 4 years of age is unclear, but the literature notes that children younger than 3 years of age cannot report T1A symptoms and thus appear symptomatic only when they develop CSs apparent to their caregivers. Although this hypothesis may be correct, it is unlikely the sole explanation for recent evidence that Moyamoya disease has a more progressive clinical course in children younger than 3 years of age than in older children, with additional CSs likely to occur even during the short interval between diagnosis and surgery.

To explain the high prevalence of CSs prior to age 4, we propose 3 other hypotheses regarding age-related differences in PCA stage and transdural collaterals derived from the present study and in blood demand derived from the literature.

First, in the group diagnosed before 4 years of age, PCA stages were significantly more advanced than in those diagnosed from 4 to 7 years ($P = .0222$; Fig 1E), whereas differences in ICA stage were not significant (Fig 1D). This unique pattern of PCA involvement in patients diagnosed before 4 years of age prompted us to perform additional subgroup analysis in the 117 hemispheres with less advanced (stage I or II) ICA lesions (Fig 5). PCA stages in the group diagnosed before 4 years of age were significantly more advanced than in those diagnosed from 4 to 7 years ($P = .0054$). In contrast, there was neither significant difference ($P = .9919$) nor signifi-
The distribution of corticosubcortical infarcted zones differed between the patients diagnosed before 4 years of age and those diagnosed from 4 to 7 years, but no significant difference was observed among the 3 oldest diagnostic age groups. This may be related to early involvement of the PCA, even with less advanced ICA lesions, in patients diagnosed before 4 years of age. In the group of children younger than 4 years at diagnosis, the high prevalence of infarctions, including the ant- and post-MCA zones, and the largest number of involved zones indicate the high prevalence of infarctions, particularly in the MCA territory, in this age group. In Moyamoya disease, the leptomeningeal collaterals from the uninvolved PCA generally compensate somewhat for the cerebral blood flow in the MCA territory. However, when steno-occlusive lesions also involve the PCA and decrease the leptomeningeal collaterals to the MCA territory, infarctions result in that territory.

Our second hypothesis, stemming from age-related differences we observed in the transdural collaterals, is that less developed transdural collaterals (Fig 1F) in patients diagnosed before 4 years of age may be related to the high prevalence of CSs in this age group and represent a need for further development of the collaterals. More developed collaterals found in the older groups, 8–11 years and 12–15 years of age, may be attributable to a longer interval of latency from the onset of the steno-occlusive disease process to clinical onset, which allowed the collaterals time to develop well. In contrast, in patients diagnosed before 4 years of age, the interval from the onset of the steno-occlusive disease process and clinical onset may have been too short for the full development of the transdural collaterals.

Our last hypothesis to explain the high prevalence of CSs in
patients diagnosed before 4 years of age is the temporal serial changes in blood demanded by the developing brain. Previous evidence indicated that in the normally developing brain, cerebral blood flow increases beginning in the neonatal period, increases most rapidly before 4 years of age, reaches a maximum at approximately 6 years, and gradually decreases thereafter to the adult level. The serial changes in normal blood flow of the developing brain may derive from the increasing demand for blood characteristic of the brains of younger children and at least partially account for the highest prevalence of CSs in the very young group. This hypothesis may well explain why Moyamoya disease has a more progressive clinical course in children younger than 3 years of age.

It is unclear why the clinical manifestations and prevalence and distribution of infarction remain approximately constant among the 3 oldest diagnostic age groups despite advanced ICA and PCA stages. Our study findings indicate that the development of the transdural collaterals increase with diagnostic age, which may compensate for the decrease in cerebral blood flow from the ICA and PCA. In the normally developing brain, blood demand gradually decreases beginning at 6 years of age. Along with the development of the transdural collaterals, this serial alteration in demand may explain our observation of the relatively constant prevalence of CSs with infarctions in older children despite progressing ICA and PCA lesions.

Our study is limited by its retrospective nature and because the invasive nature of conventional arteriography precluded some patients from undergoing the procedure. In addition, to include all consecutive patients in the study, we evaluated ICA and PCA staging only on MR angiograms and did not evaluate the degree of transdural collaterals in such patients. As well, the number of transdural collaterals is an insufficient substitute for the degree of cerebral blood flow from such pathways.

Our study is further limited by our analytic methods. We only indirectly showed the relationship between age-related differences in clinical manifestations and angiographic differences. On the other hand, a direct relationship would be clarified by multivariable analysis by using hemispheric-based clinical symptoms or the number of infarcted zones as dependent variables and diagnostic age and angiographic findings as independent variables, adjusting for confounding among in-

**Fig 4.** A 12-year-old boy (diagnostic age group, 12–15 years) with right and left transient motor paresis. His clinical manifestation was TIA. A, Axial time-of-flight MR angiogram shows advanced steno-occlusive changes bilaterally at or around the terminal parts of the ICAs, with no apparent ACA and MCA branches (ICA stage IV, bilaterally). Advanced steno-occlusive lesions bilaterally in the PCAs with well-developed Moyamoya vessels from the PCA are seen (PCA stage III, bilaterally). B, Anteroposterior view of the vertebral angiogram shows advanced steno-occlusive lesions bilaterally in the PCAs (PCA stage III, bilaterally). C and D, Lateral view of the arterial (C) and capillary (D) phases of the right external carotid angiograms shows that the dilated posterior branch of the middle meningeal artery (large arrow) and the meningeal branch of the occipital artery (arrowhead) provide transdural collaterals mainly to the right posterior part of the cerebral hemispheres. The frontal branch of the superficial temporal artery (small arrow) and medial branches of the internal maxillary artery provide transdural collaterals to the frontotemporal region. Three transdural collaterals are seen on the right. The right cerebral hemisphere is largely supplied through the transdural collaterals (D). Three transdural collaterals were seen on the left (left external carotid angiogram, not shown). E, Axial T2-weighted MR image shows an old small infarction in the left anterior MCA territory. No infarcted regions are seen on the right, but 1 is seen on the left. Note that this patient has severe steno-occlusive PCA changes that parallel the advanced ICA lesions. This progressive state should have provoked the development of transdural collaterals, which might have prevented a large infarction and CS.
dependent variables. In other words, such analysis would not clarify the age-related angiographic differences, including the PCA, which may explain the high prevalence of CS or infarctions in patients diagnosed before 4 years of age. Clarifying the age-related angiographical differences including PCA is the advantage of our adopting 6 single-factor analyses that treat diagnostic age as an independent variable and the other 6 variables as dependent variables.

Conclusions
Steno-occlusive PCA lesions are closely related to the presentation of CS with infarctions in children diagnosed with Moyamoya disease before 4 years of age. Despite the general neglect of the posterior circulation in the literature, our findings provide important information for therapeutic planning.

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References