Changing ischaemic lesion patterns in adult moyamoya disease

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ABSTRACT

Objectives: Ischaemic stroke is a frequent manifestation in patients with adult moyamoya disease (MMD), but the relationship between the lesion pattern and disease severity has rarely been investigated.

Methods: Data were collected on a consecutive series of 65 adult patients with MMD who visited our hospital between 1999 and 2006. Among them, 32 patients with first ever ischaemic stroke were included. The ischaemic lesions were categorised by location and compared as follows: (1) cortical versus subcortical involvement and (2) anterior (fronto-temporal) versus posterior (parieto-occipital) involvement. The lesions were also compared by disease severity, as determined by the extent of intracranial artery involvement (Suzuki's grading method) and by perfusion status visualised on single photon emission computed tomography (SPECT).

Result: Disease severity was significantly greater in patients with cortical involvement than in those with subcortical involvement (Suzuki's grade 4.17 (0.72) vs 2.70 (0.73); $p<0.001$). Disease severity was also significantly greater in patients with posterior involvement than in those with anterior involvement (4.50 (0.53) vs 2.83 (0.76); $p<0.001$). In most of the patients (83.3%) the perfusion defect area shown on SPECT was larger than the ischaemic lesion area shown on MRI.

Conclusions: Patients with advanced stage adult MMD tended to have ischaemic lesions involving the cortex and posterior part of the brain and the stroke mechanism in these patients was largely associated with haemodynamic compromise. Our results suggest that the lesion pattern of ischaemic stroke may change along with the extent of arterial involvement.

Moyamoya disease (MMD) is a rare cerebrovascular occlusive disorder characterised by progressive occlusion of the bilateral carotid forks associated with a fine vascular network, namely the moyamoya vessels.[1] The disease is known to have a progressive course, even in adult onset,[2] and several studies have reported large territorial infarctions in patients with MMD.[3 4] In addition, even asymptomatic MMD should not be regarded as a silent disorder because it could potentially lead to subsequent ischaemic or haemorrhagic stroke.[5] Considering the progressive nature and possibility of developing large infarction, it is important to understand the disease course and mechanism of stroke in adult patients with MMD in order to prevent serious outcomes.

Although ischaemic stroke is a frequent clinical manifestation in patients with adult MMD, there have been very few studies investigating the relationships between the lesion patterns of ischaemic stroke, disease severity and mechanism of stroke in adult MMD. The lesion pattern may be different at each stage of the disease because the involvement of the intracranial arteries spreads from the anterior to the posterior circulation, and collateral moyamoya vessels are exhausted at the end. Research on the area prone to ischaemia and perfusion defect patterns according to disease severity will provide valuable information that may help physicians decide on the best treatments for patients with adult MMD.

METHODS

Patients

Between 1999 and 2006, we studied adult patients with MMD whose initial symptoms began after 14 years of age. The diagnosis of MMD was based on the guidelines established by the Research Committee on Moyamoya Disease (Spontaneous Occlusion of the Circle of Willis) of the Ministry of Health and Welfare of Japan.[6] Sixty-five subjects were diagnosed with adult MMD at our hospital between 1999 and 2006. Among them, only those with first ever ischaemic strokes were selected because inclusion of recurrent stroke lesions may make it difficult to determine disease severity and haemodynamic status. We also did not include patients with MMD without ischaemic lesions in the corresponding area on brain MRI. Thus a total of 32 patients were finally included in the study. Mean age of the patients at the time of brain imaging was 44.6 (SD 12.8) years, and the mean age of symptom onset was 38.3 (12.4) years.

Localisation of the ischaemic lesion

All ischaemic lesions were confirmed by brain MRI, which included diffusion weighted imaging, fluid attenuated inversion recovery and T2 weighted imaging. MR imaging was performed in the horizontal plane using a 1.5 T MR system (Sonata; Siemens, Germany) with standard parameters. The ischaemic lesions were categorised by location as follows: (1) cortical versus subcortical involvement and (2) anterior (fronto-temporal) versus posterior (parieto-occipital) involvement. We did not categorise the lesions according to vascular territory involvement in this study because the vascular territories involved in patients with MMD change considerably as a result of large arterial occlusion and the development of moyamoya vessels. The cortical involvement group included patients with infarctions in the cortex with or without subcortical (subcortical white matter and basal ganglia) involvement, whereas the subcortical group included patients with infarctions only in the subcortex. Anterior involvement is considered when the infarction is limited

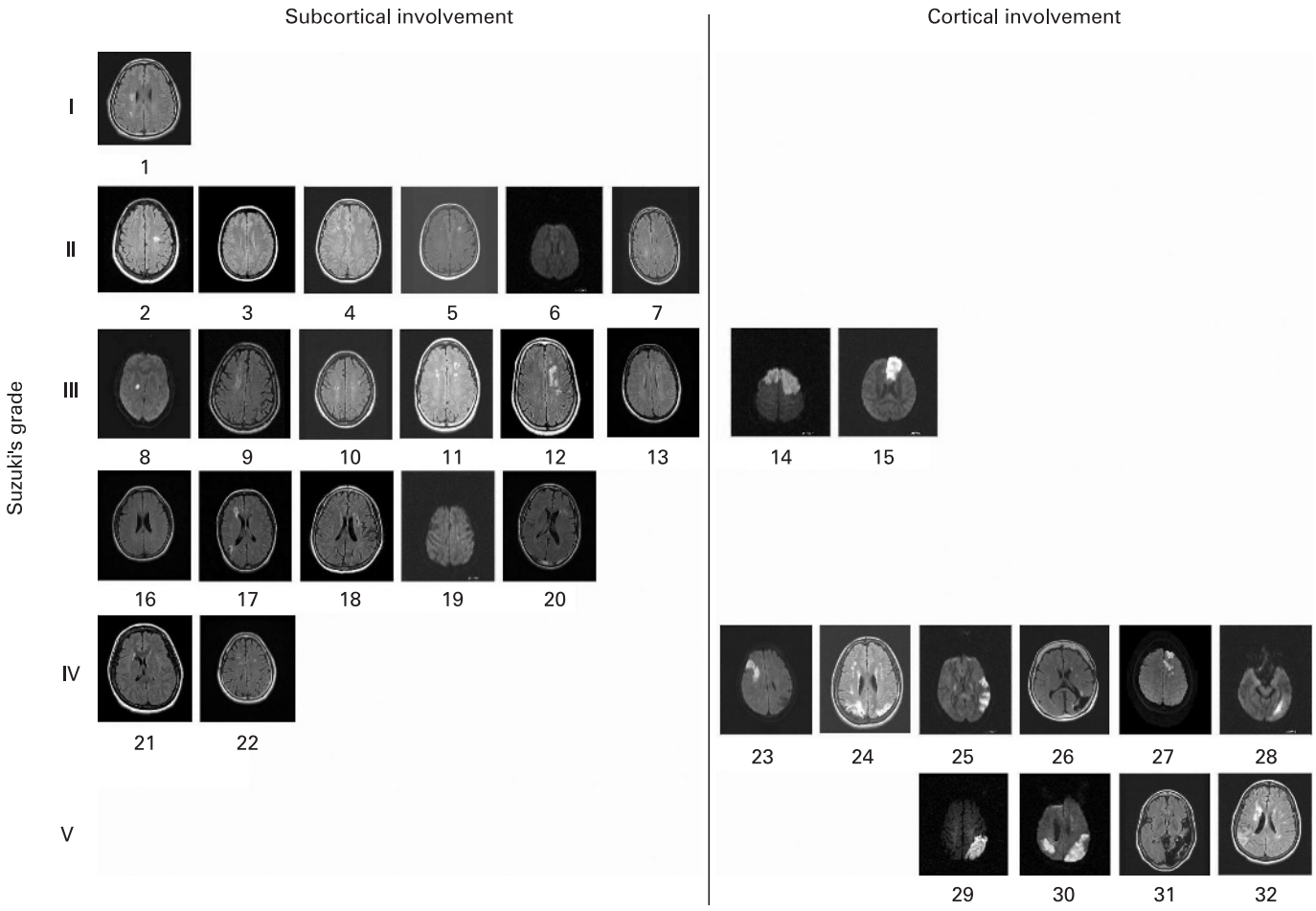

Figure 1 Lesion pattern of ischaemic stroke in 32 patients. The number below each photograph indicates the patient's identification number.

to the fronto-temporal area without the involving parieto-occipital area. Infarctions involving the parietal or occipital lobe were regarded as having posterior involvement.

Evaluation of disease severity

During the admission period, all 32 patients underwent cerebral angiography, including bilateral internal and external or common carotid arteriography, and unilateral or bilateral vertebral arteriography. Intracranial arterial involvement was determined according to Suzuki's grading method[1 7] by two independent investigators (JMK and SHL) who were blinded to the patient's medical information.

Evaluation of perfusion status

Brain perfusion single photon emission computed tomography (SPECT) was performed according to the following protocols.[8] For the basal study, 9.25 MBq/kg of 99m Tc-hexamethylpropyleneamine oxime (HMPAO; Amersham, Buckinghamshire, UK) were intravenously injected, and acquisition began after 5 min. Acetazolamide (20 mg/kg) was injected 10 min before the end of basal study acquisition, and 18.5 MBq/kg of 99m Tc-HMPAO were injected 5 min after the end of basal study acquisition in order to perform the acetazolamide stress study, which was initiated 5 min after the second injection of 99m Tc-HMPAO. Acetazolamide stress images were obtained by decay corrected subtraction of basal images from the corresponding stress images. The brain SPECT was acquired using a triple head gamma camera (Prism 3000; Picker International, Cleveland, Ohio, USA) with a high resolution fan beam collimator and reconstructed with filtered back projection using a 128×128 matrix. We obtained images from 30 patients during the admission period (not conducted in two patients). We reviewed both basal and acetazolamide stress images (post-stress images) to estimate perfusion status. Two independent investigators (JMK and SHL) performed visual interpretation of the SPECT images. The SPECT images were assessed as either "preserved" or "decreased" regional perfusion of each lobe. Decreased perfusion was defined as cerebral perfusion of acetazolamide stress SPECT that fell into a lower colour range from basal SPECT of the corresponding brain lobe. We categorised the perfusion defects into four groups: normal; focal, perfusion decreased only in one of the frontal, temporal, parietal and occipital lobes; extended, two or three lobes involved; and global, all four lobes involved.

Statistical analysis

Mann–Whitney U tests were used to compare the lesion patterns with disease severity, as determined by Suzuki's grading method. Linear by linear association analysis was performed in order to evaluate the relationship between intracranial artery stenosis and perfusion status. Two tailed values of $p<0.05$ were considered to be significant.

RESULTS

Ischaemic lesion patterns

The study subjects were seven male and 25 female patients with MMD. A total of 32 MR images showing ischaemic lesions are

Table 1 Number of patients with ischaemic lesions according to location and Suzuki grade

	Subcortical vs cortical		Anterior vs posterior	
Suzuki's grade	Subcortical (n = 20)	Cortical (n = 12)	Anterior (n = 24)	Posterior (n = 8)
I	1	0	1	0
II	6	0	6	0
III	11	2	13	0
IV	2	6	4	4
V	0	4	0	4
Mean grade	2.70 (0.73)	4.17 (0.72)	2.83 (0.76)	4.50 (0.53)
p Value*	<0.001		<0.001	

*Mann–Whitney U tests were used.

illustrated in fig 1. Two of the patients visited our hospital more than 3 months after symptom onset, and therefore the lesions in these patients appeared as tissue loss on MRI. Most of the ischaemic lesions did not correspond with the vascular territories—for example, patient No 14 had lesions in the bilateral partial frontal lobes and patient Nos 26 and 30 had lesions in the bilateral parietal lobes.

There were 12 patients with ischaemic lesions involving the cortical area and 20 patients with lesions involving deep subcortical structures without cortical involvement. In the early stages of MMD (Suzuki grade I or II), the ischaemic lesions were found only in the deep subcortical structures. As disease severity increased, the ischaemic lesions tended to show more cortical involvement, and cortical lesions were predominant in patients with advanced stage MMD (Suzuki grade IV and V). Disease severity was significantly higher in patients with cortical involvement (4.17 (0.72)) than in those with non-cortical involvement (2.70 (0.73); $p<0.001$) (table 1). In addition, the ischaemic lesions involving the cortex tended to be larger than those without cortical involvement.

As shown in fig 1, patients with grade IV or V MMD had ischaemic lesions mainly involving the posterior part of the brain (parieto-occipital lobes) (patient Nos 24, 25, 26, 28, 29, 30, 31 and 32). The rest of the patients (n = 24) had lesions predominantly involving the anterior part of the brain (fronto-temporal lobes). Patients with posterior involvement had a higher grade of severity (4.50 (0.53)) than patients with anterior involvement (2.83 (0.76); $p<0.001$) (table 1).

Patients with transient ischaemic attack (TIA) tend to have infarction in the subcortical and anterior areas compared with patients without TIA. Of the 18 patients with TIA as an initial manifestation, 14 had subcortical infarction and four patients had cortical infarction ($p = 0.07$). In terms of the anterior versus posterior involvement, there were 16 patients with infarction in the anterior region and two patients with infarction in the posterior region ($p = 0.05$). However, with regard to age, there were no clear associations with infarction pattern (subcortical versus cortical involvement, $p = 0.415$; anterior versus posterior involvement; $p = 0.094$ by linear by linear association) and disease severity ($p = 0.531$ by Spearman's correlation). Moreover, gender was not related to the location of the lesions ($p = 0.379$), and not related to disease severity ($p = 0.408$).

Mechanism of ischaemic stroke: haemodynamic compromise

Most of the patients showed perfusion defects on SPECT imaging, except for one patient who had normal perfusion status on both basal and post-stress images. Both basal and post-stress perfusion defects tended to broaden as the Suzuki grade increased, as shown in fig 2 (basal: $p = 0.025$; post-stress: $p = 0.001$).

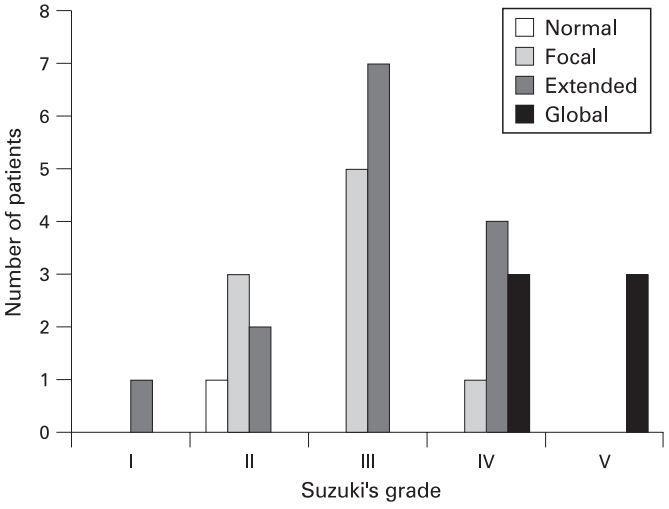

Figure 2 Distribution of the severity of perfusion defects shown on post-stress single photon emission computed tomography images according to Suzuki grade.

Most patients had perfusion defects that were larger than the ischaemic lesions shown on brain MRI (25 out of 30 patients, 83.3%), suggesting that haemodynamic compromise was the major mechanism of ischaemic stroke (fig 3, group A). However, two patients demonstrated normal perfusion status in the hemisphere with the ischaemic lesion and perfusion defects in the contralateral hemisphere, but had the same degree of intracranial artery stenosis (grade 3) on each side. Two other patients had perfusion defects that were the same size as the ischaemic lesion (fig 3, group B). Thus embolism might have been a mechanism of ischaemic stroke in these four patients. None of our patients had a potential cardioembolic source.

DISCUSSION

Our results showed that the locations of ischaemic lesions in patients with adult MMD varied and that as the disease progressed, the location of the lesions changed from the subcortical area and anterior part of the brain to the cortical area and posterior part of the brain. In addition, haemodynamic compromise was responsible for the ischaemic lesions in most of the patients. Although this is not a prospective follow-up study, these results suggest that the ischaemia prone area changes dynamically from the inner to outer cortical structures and from anterior to posterior brain regions as the disease progresses. To our knowledge, this is the first study to report changing ischaemic lesion patterns in adult MMD.

During the initial stages of MMD, the large arteries in the anterior circulation are narrowed, with moyamoya collaterals supplying the deep subcortical structures.[1 7] The initial involvement of the deep subcortical structures might result from the regression of moyamoya vessels. As the posterior cerebral arteries are involved in the advanced stages of MMD, cortical infarctions may occur with insufficient collaterals from the posterior circulation, which was consistent with the previous results.[3 4] In this context, the anterior part of the brain might be more susceptible to ischaemic insult than the posterior part. In addition, it has been reported that the incidence of ischaemic stroke increases when the posterior cerebral arteries are involved.[4] The ischaemic lesions in child onset MMD tend to

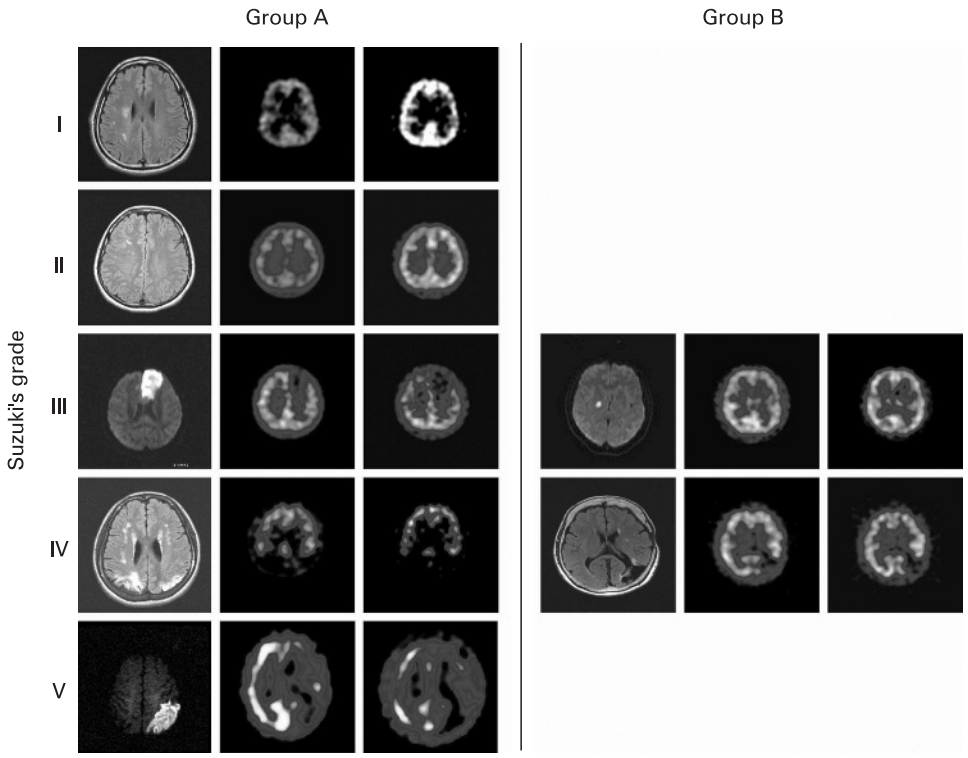

Figure 3 Representative brain MRI and single photon emission computed tomography (SPECT) images according to Suzuki grade. The SPECT images show that the perfusion defect area broadens as the Suzuki grade increases. The findings in group A indicate that the perfusion defect area is larger than the ischaemic lesion and is located on the same side as the ischaemic lesion, suggesting haemodynamic compromise as a mechanism of ischaemic stroke. In contrast, the findings in group B indicate that the perfusion defect area is located in the contralateral hemisphere to the ischaemic lesion or limited only to the ischaemic lesion, suggesting arterial embolism as a mechanism of stroke.

occur in the watershed area initially and then spread to a wider area involving the cortex and posterior part of the brain as the posterior cerebral arteries narrow.[3]

Haemodynamic compromise was the primary mechanism of ischaemic stroke in this study population. Because there were two patients with ischaemic lesions on the opposite side and one patient with normal perfusion status, embolism might be a potential underlying mechanism of ischaemic stroke. Large artery steno-occlusion increases not only the risk of haemodynamic infarction, but also the risk of embolic infarction.[9] Transcranial Doppler ultrasonography may provide additional information by detecting embolic signals,[10] but it was not routinely performed in the present study. Several studies have reported arterial embolic events in patients with adult MMD.[11 12] Despite these reports, there is no doubt that haemodynamic compromise is the principal mechanism of ischaemic stroke in MMD,[13] which was confirmed in the present study. As the disease progresses, the haemodynamically compromised area becomes wider and increases the risk of developing a large infarction with cortical involvement.

There are some important caveats of this study. Firstly, because this was not a prospective follow-up study, there are no data to indicate that the ischaemia prone area changes in each patient. In this population, two patients with small subcortical infarctions experienced recurrent ischaemic strokes with cortical involvement, but cerebral angiography was not conducted during the second attack. If cerebral angiography had been performed during the second attack, it might have provided additional evidence that would reinforce our hypothesis. Secondly, this study used brain MRI, including diffusion weighted imaging sequences, and thus provided more accurate information on the lesion pattern of ischaemic stroke than previous studies based on brain CT. In addition, we performed brain SPECT in most of the patients, which provided important data on the mechanism of ischaemic stroke.

Based on our results, surgical treatment may be justified as a treatment option for patients with a significant perfusion defect in order to prevent further ischaemic insult. It has been known that surgical revascularisation restores brain perfusion in patients with MMD,[8 14 15] even though there has not been a randomised controlled trial. There were several observational studies suggesting the superiority of surgical treatment to medical treatment in patients with MMD.[16–18] The efficacy and safety of antithrombotic treatments has not yet been determined[2 11 19] but they may be cautiously administered when the mechanism of ischaemic stroke is suspicious of arterial embolism. Our results indicated that the lesion pattern of ischaemic stroke in adult MMD changes dramatically according to disease severity and that the underlying mechanism of ischaemic stroke is largely a result of haemodynamic compromise. Our results should be confirmed in future prospective follow-up studies.

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Ethics approval: Ethics approval was obtained.

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