A nationwide survey on unilateral moyamoya disease in Japan

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None.

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Abstract

Objective Moyamoya disease (MMD) is an unique occlusive disease of the bilateral internal carotid arteries; compensation for occlusion results in rich arterial collaterals at the base of the brain. The clinical features of unilateral MMD, confirmed by typical angiographic evidence of MMD unilaterally and normal or equivocal contralateral findings, are not well known. To identify the clinical features of unilateral MMD in Japan, a nationwide survey was conducted.

Patients and Methods The questionnaire was directly mailed to 241 departments that reported treating unilateral MMD patients in a primary survey. We ascertained the sex, age, family history, clinical manifestation, radiological findings, treatments, course of the disease, and daily activity of unilateral MMD patients.

Results A total of 114 departments replied to the questionnaire. The data of 203 patients (118 female and 85 male; female to male ratio 1.4) were registered and analyzed. The mean age was 40.2 years old with a peak occurring in the fifties. Twenty-one patients (10.7%) exhibited familial MMD. The clinical symptoms are motor weakness 57 (26.8%), headache 37 (17.4%), transient ischemic attack 35 (16.4%), and no symptom 30 (14.1%). The MMD types determined by imaging included ischemic type in 64 patients (32.5%), bleeding type in 51 (25.9%), and normal in 82 (41.6%). The development of moyamoya vessels was mild in 78 patients (43.9%) and most patients (81.1%) were accompanied with cerebral hypoperfusion. Medical treatment or vascular reconstruction was employed for the more than half of the patients. **Conclusion** The

clinical feature of unilateral MMD were revealed in this nationwide study. Unilateral MMD was predominant in adults and the development of moyamoya vessel was relatively less prevalent.

1. Introduction

Moyamoya disease (MMD) is characterized by idiopathic steno-occlusion at the terminal portion of the internal carotid artery (ICA) with concomitant abnormal vascular networks (1). Whether unilateral lesion, confirmed by typical angiographic evidence of MMD unilaterally and normal or equivocal contralateral findings, is an early form of definite MMD remains controversial (2-5). The progression of the contralateral side in patients with predominantly unilateral MMD is reported especially in young patients (3). Thus, familial occurrence of unilateral MMD was observed in the definite MMD pedigree (6, 7). On the other hand, moyamoya-like vasculopathy more often tend to occur unilaterally in the genetic or acquired syndromes (8, 9).

We conducted a nationwide epidemiological survey on MMD, unilateral MMD, and quasi-MMD in 2006 (10). The annual incidence rate of MMD and unilateral MMD are 1.13/100,000, and 0.23/100,000 respectively, and the prevalence is 5.22/100,000 and 0.66/100,000, respectively. Because unilateral MMD is quite a rare disease, single center studies are not feasible to identify the associated clinical features. Based on this earlier study, we conducted a secondary survey to determine the clinical features of unilateral MMD.

2. Materials and Methods

The criteria prepared by the Research Committee on Moyamoya disease (Spontaneous

Occlusion of the Circle of Willis) of Japan were used for the clinical diagnosis of MMD. A diagnostic algorithm was used to appropriately diagnosis of each type of MMD (Fig. 1A). “Bilateral MMD” is bilateral ICA terminal steno-occlusion with bilateral development of moyamoya vessels. “Unilateral MMD” is unilateral ICA terminal steno-occlusion with development of moyamoya vessels. “Definite MMD” describes adult cases of bilateral MMD. In pediatric cases, “unilateral MMD” is also considered to be “definite MMD” if steno-occlusion is indentified on another side of the ICA terminal. The questionnaire was directly mailed to 241 departments that reported answered treating unilateral MMD patients in the primary survey. We ascertained the sex, age, associated disorders, clinical manifestation, radiological findings (subtype, degree of moyamoya vessels, location of steno-occlusive lesion, and Suzuki’s angiographic stage in each sides), cerebral blood flow (CBF), treatments including medical and surgical methods, course of the disease, initial and follow-up modified Rankin Scale (mRS), follow-up period, follow-up imaging studies and the results, and family history of quasi-MMD patients. For the evaluation of moyamoya vessels, typical moyamoya vessels observed in definite MMD was categorized as severe. Each angiographical example was enclosed (Fig. 1B-D). The medical fees of definite MMD patients were supported by a Grant-in-Aid for Intractable Diseases from the Ministry of Health, Labor and Welfare of Japan. Unilateral MMD patients received this support on a case by case basis.

3. Results

A total of 114 departments replied to the questionnaire (response rate; 47.3%). The data of 203 patients (85 male and 118 female) were registered and analyzed. The mean age was 40.2 years old with an upper peak in the fifties and a lower peak among children (Fig. 2). Twenty-one patients (10.7%) exhibited familial MMD.

The initial clinical manifestations included motor weakness in 57 patients (26.8%), headache in 37 patients (17.4%), transient ischemic attack in 35 patients (16.4%), and no symptoms in 30 patients (14.1%) (Table 1). The imaging study subtypes included the ischemic type in 64 patients (32.5%), bleeding type in 51 patients (25.9%), and normal type in 82 patients (41.6%) (Fig. 3A). The development of moyamoya vessels were mild in 78 patients (43.9%), moderate in 42 patients (23.6%) and severe in 58 patients (32.6%) (Fig. 3B). The right side was involved in 109 cases (53.7%) and the left side was involved in 94 patients (46.3%). Steno-occlusive lesions were observed at the ICA in 134 patients (70.2%), the middle cerebral artery (MCA) in 41 patients (21.5%), the MCA and the anterior cerebral artery (ACA) in 15 patients (7.9%), and the ACA in 1 patient (0.5%) (Fig. 3C). On the contralateral side, steno-occlusive lesions were observed at the ICA in 14 patients (8.4%), the MCA in 10 cases (6.0%), the MCA and the ACA in 2 patients (1.2%), and the ACA in 15 patients (9.0%) (Fig. 3D). Collateral from external carotid arteries developed in 23 patients (13.0%). In terms of cerebral circulation, hypoperfusion was observed in 101 patients (63.5%) and vasoreactivity was impaired in 28 patients (17.6%).

Antithrombotic agents were given to 86 patients (40.0%), anticonvulsant were

given to 21 patients (9.8%), and antihypertensive drugs were given to 20 patients (9.3%) (Fig. 4A). Eighty-two patients (38.1%) ware not medically treated. Vascular reconstruction was performed on 110 patients (89 patients underwent direct reconstruction; 44.3%, 21 patients underwent indirect reconstruction; 10.4%) (Fig. 4B). Eighty-three patients (41.3%) were not treated surgically. During follow-up, 42 patients (23.3%) experienced improved symptoms, 127 patients (70.6%) experienced no change and symptoms worsened in 3 patients (1.7%) (Fig. 5A). Among the 42 patients showing symptom improvement, 35 patients (83.3%) had been treated surgically and 28 patients (66.7%) had been treated medically. Cerebral hemorrhage occurred in 5 patients (2.8%). In addition, disease progressed in the contralateral side in 3 patients (1.7%). Both initial and follow-up mRS scores are shown in Figure 5B. Approximately 80% of patients had an initial mRS score of 0-2 and were relatively better during follow-up.

Finally, the medical fees of 84 patients (54.5%) were supported by the government.

4. Discussion

Unilateral lesions, confirmed by typical angiographic evidence of MMD unilaterally and normal or equivocal contralateral findings, have been defined as probable MMD (3). The term of “probable” may be confusing because this may indicate poor diagnoses or insufficient examination of the patient. Therefore, per the MMD guidelines, published in 2011, the term “unilateral MMD” replaces the term “probable” (11).

Unilateral lesions frequently develop to bilateral lesions in pediatric patients (2, 12). Familial occurrence has been reported in approximately 10% of MMD patients (13-16). In this unilateral MMD study, the prevalence of familial occurrence was 10.7%. The coincidence of unilateral and definite MMD within a single family indicates that they reflect different phenotypes cause by the same genetic defects (6). In unilateral cases, there was a predominance of female cases and it has been reported that the female to male ratio of definite case was approximately 2-fold (14, 16). In this study, that female to male ratio of unilateral cases was 1.4. In terms of patient ages, we observed two peak patterns in the age distribution in unilateral cases as definite MMD. Consistent with previous reports, the adult onset rate is higher in unilateral cases than in definite cases (3, 4, 17, 18). Acquired disease such as atherosclerosis may be a cause of the moyamoya like steno-occlusive disease. It is well known that atherosclerosis predominantly occurs elderly males. The results of the sex and age analyses indicate that unilateral MMD might be influenced by acquired diseases including atherosclerosis.

The clinical manifestations of unilateral MMD are divided into focal sign and non-specific symptoms such as headache and unconsciousness. In this study, half of the patients had focal signs and while the remaining patients had non-specific symptoms or were asymptomatic. From our experience, unilateral MMD tends to be found with coincidentally (19). The imaging subtype study included ischemic type in 64 patients (32.5%), bleeding type in 51 patients (25.9%), and normal type (only vascular lesion) in 82 patients (41.6%). It is well known that the pediatric patients presenting with ischemic

attack and adult patients tend to suffer from intracranial bleeding (14, 16). Although unilateral MMD was predominant in adults, bleeding was relatively less common. Recent MMD diagnostics using magnetic resonance (MR) imaging and MR angiography makes it possible to detect asymptomatic patients (20).

Steno-occlusive lesions were mainly observed in the ICA. This feature differentiates unilateral MMD from idiopathic MCA occlusion. Regarding with the contralateral side, ACA or MCA were occasionally involved. Kelly et al. reported that unilateral patients with contralateral equivocal arterial stenotic changes are at an increased risk of disease progression (4). Because the development of moyamoya vessels is the most important finding in the diagnosis of MMD, we evaluated the degree of moyamoya vessels development. The development of moyamoya vessels was mild or moderate in two-thirds of the patients. Thus, collateral from the external carotid arteries was observed in only 13% of patients. Lower levels of collateral vessel development occurred in unilateral MMD patients compared with definite MMD patients. CBF was impaired in approximately 80% of cases. It is speculated that the CBF was mainly evaluated with single photon emission computed tomography (SPECT) because SPECT is widely used in Japan and MMD guideline recommend CBF measurement for the treatment of MMD (11).

Approximately 60% of patients were medically treated. Refracting cerebral hypoperfusion and antithrombotic agents were the most frequently employed medical treatments. Anticonvulsants were prescribed for symptomatic epilepsy. Because the age of the patients was relatively higher, they may also have arteriosclerosis or hypertension.

As a result, antihypertensive drugs would be indicated. Approximately 60% of patients were treated surgically. Because most cases occurred in adults, the incidence of direct bypass, most likely of the superficial temporal artery-MCA anastomosis, was much greater than indirect bypass such as encephalo-duro-arterio-synangiosis. This is a retrospective study and all treatments were chosen by the physicians. Interestingly, a significant proportion of patients were not treated medically or surgically.

During follow-up, the clinical status improved among 23.3% of patients. Clinical symptoms worsened in only 1.7% of patients in the lesion side and in only 1.7% of patients in the contralateral side. Cerebral hemorrhage also occurred rarely. Activities of daily living were done independently in approximately 80% of patients initially and in approximately 90% of patients during follow-up.

The medical fees of patients with definite MMD were supported by the government. Doctors designated from each prefecture certified the diagnosis of the patient according to the MMD criteria. Although unilateral cases should not be certified as definite MMD, over half of the unilateral cases were certified as definite MMD cases in this study. Sympathy for the patients might be a cause of this violation.

5. Conclusions

In conclusion, the clinical features of unilateral MMD were determined by the analyses of a nationwide survey. Unilateral MMD was predominant in adults and the development of moyamoya vessels was relatively low.

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The authors would like to express their heartfelt thanks to the doctors who devoted their time to this investigation.

Source of Funding

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Disclosure

None.

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Figure legends

Fig. 1

A: A diagnostic algorithm of definite moyamoya disease, unilateral moyamoya disease and quasi-moyamoya disease. ICA indicates internal carotid artery. MMD indicates moyamoya disease.

B: Angigraphical example of mild moyamoya vessels.

C: Angigraphical example of moderate moyamoya vessels.

D: Angigraphical example of severe moyamoya vessels.

Fig. 2 Distribution of the patients' age

Fig. 3

A: Subtype found by the imaging studies

B: Degree of the moyamoya vessels

C: Location of the steno-occlusion of the arteries (lesion side)

D: Location of the steno-occlusion of the arteries (contralateral side)

Fig. 4

A: Status of the medical treatment

B: Status of the surgical treatment

Fig. 5

A: Clinical status

L; lesion side, C; contralateral side

B: Initial and follow-up modified Rankin Scale scores

Fig. 1A

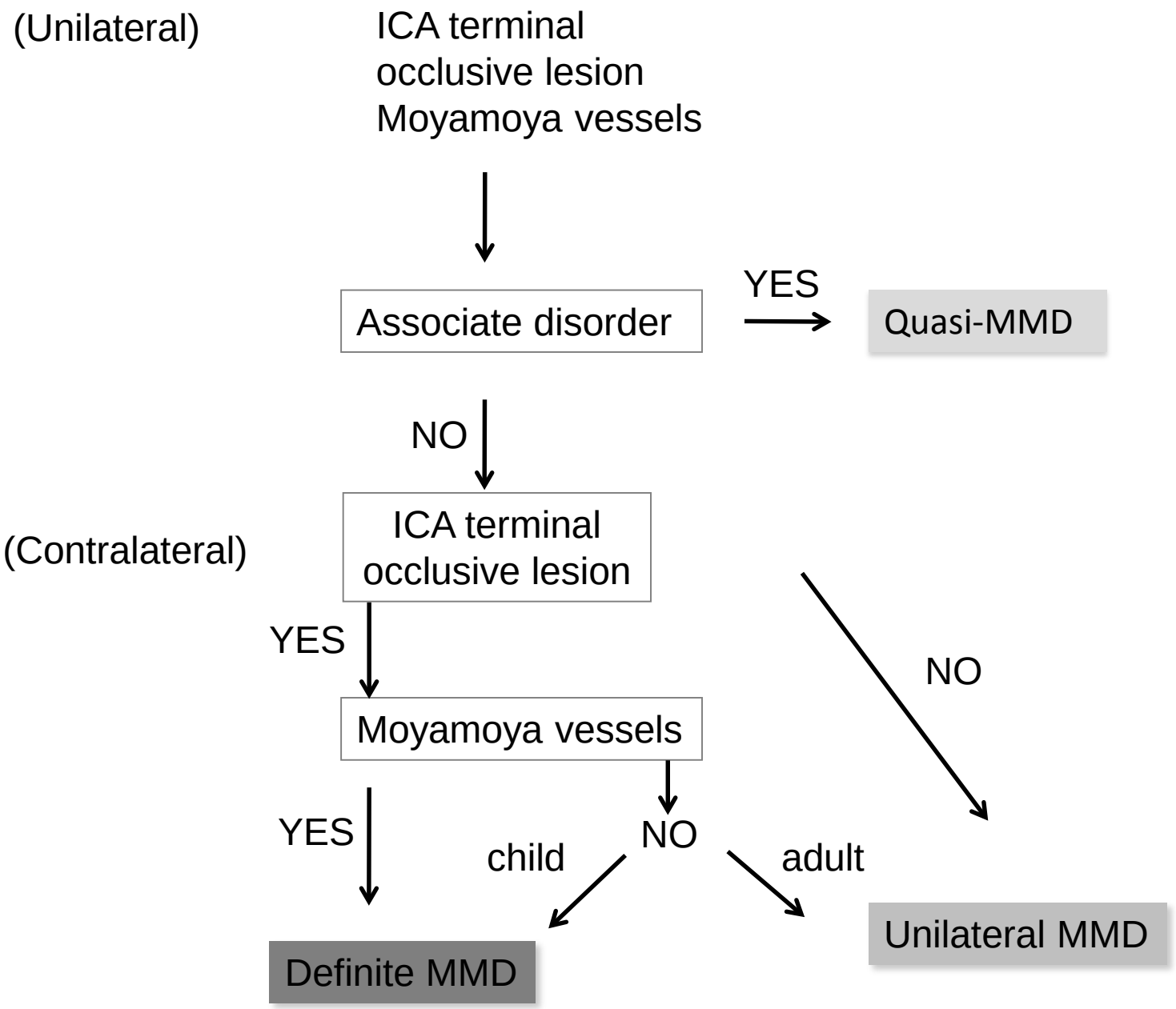
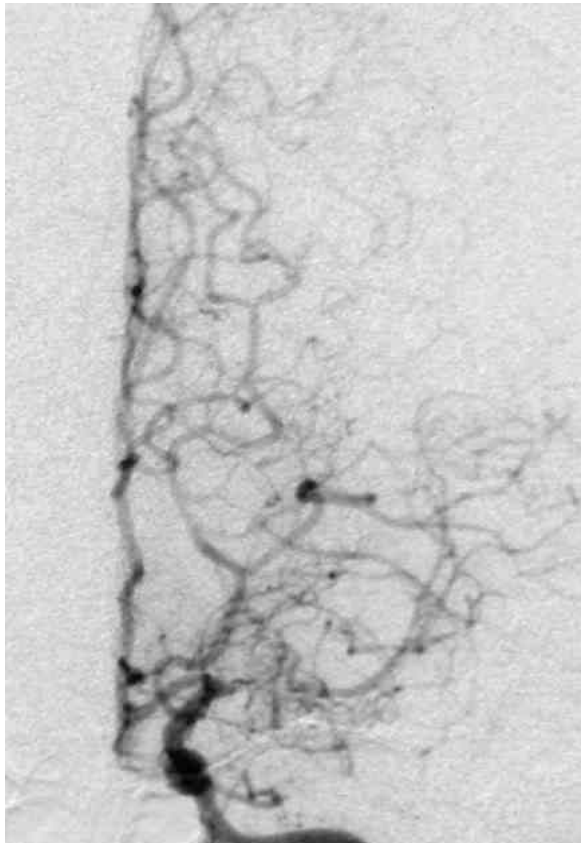
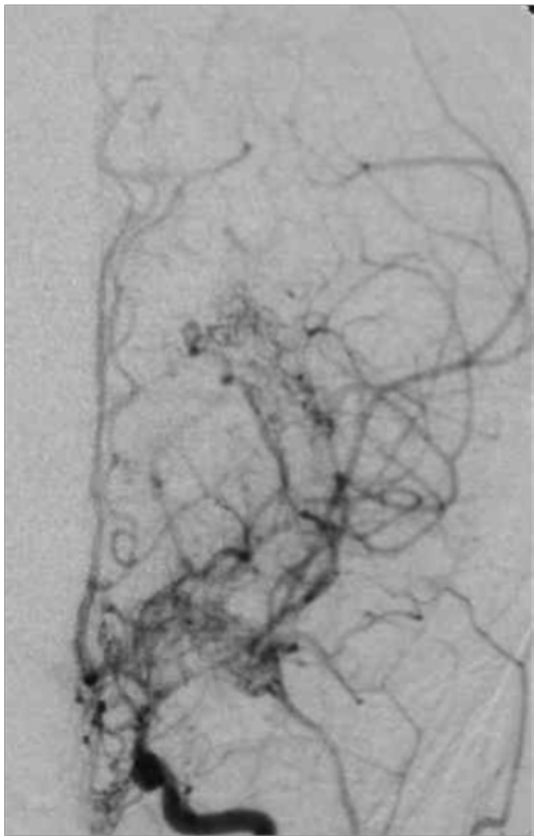

(Unilateral)
ICA terminal occlusive lesion Moyamoya vessels
Associate disorder
YES
Quasi-MMD
NO
(Contralateral)
ICA terminal occlusive lesion
YES
NO
Moyamoya vessels
YES
NO
child
adult
Unilateral MMD
Definite MMD

Fig. 1

B



C



D

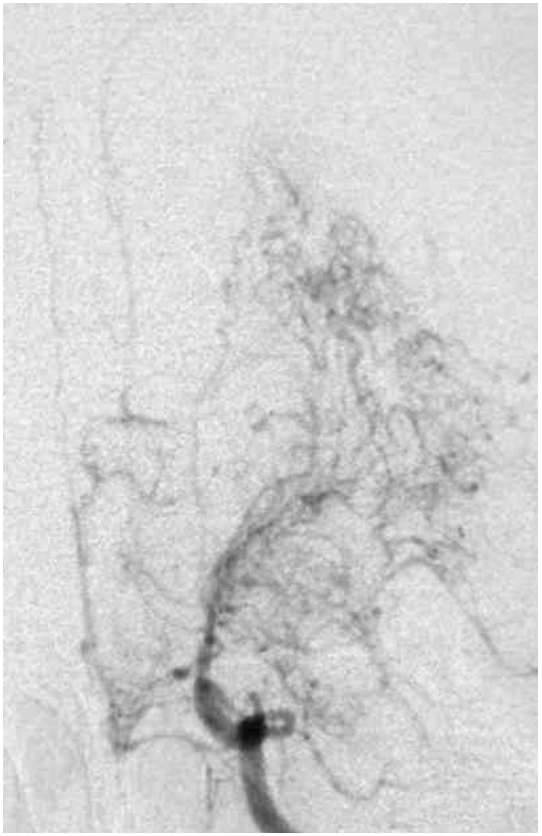


Fig. 2

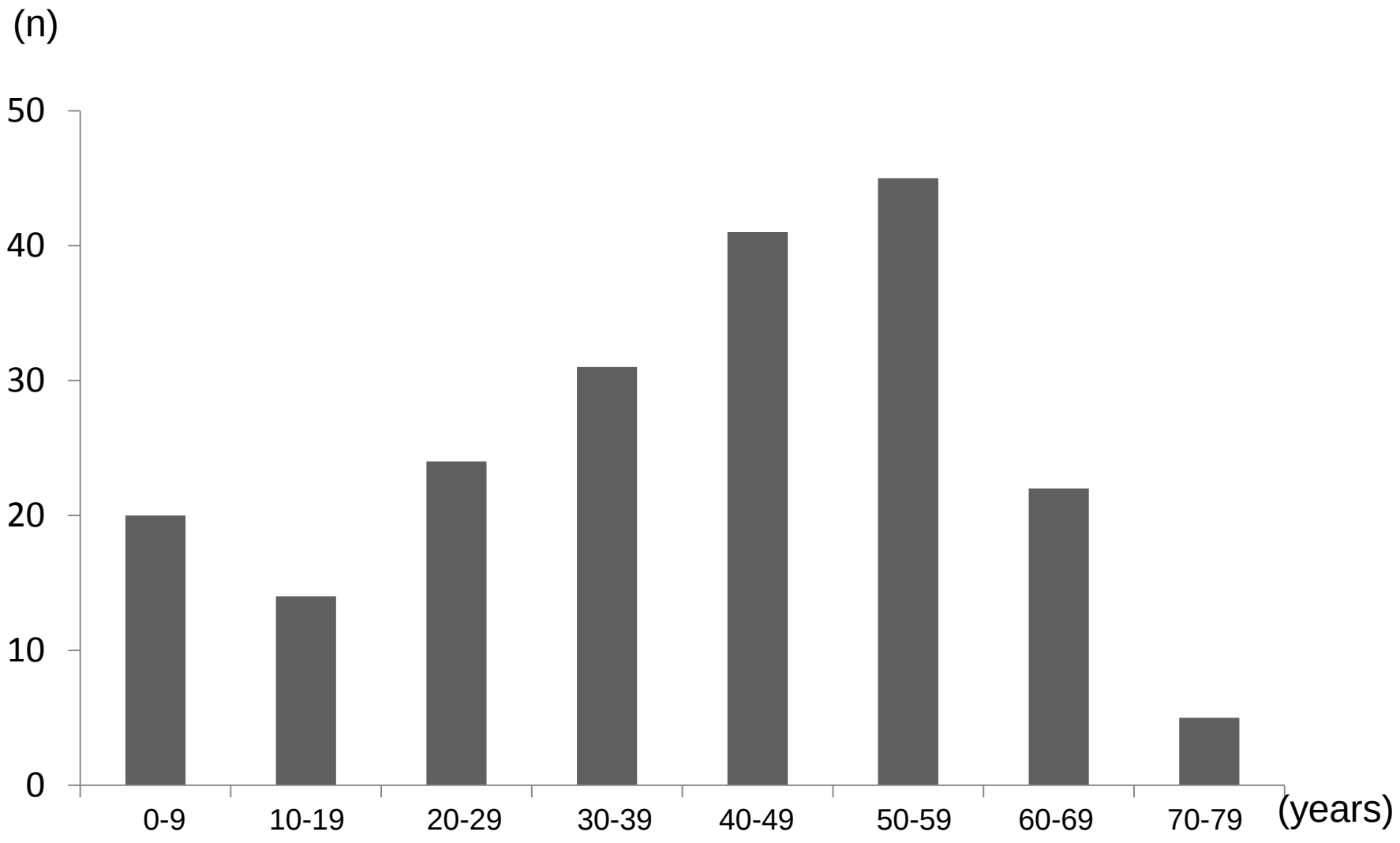
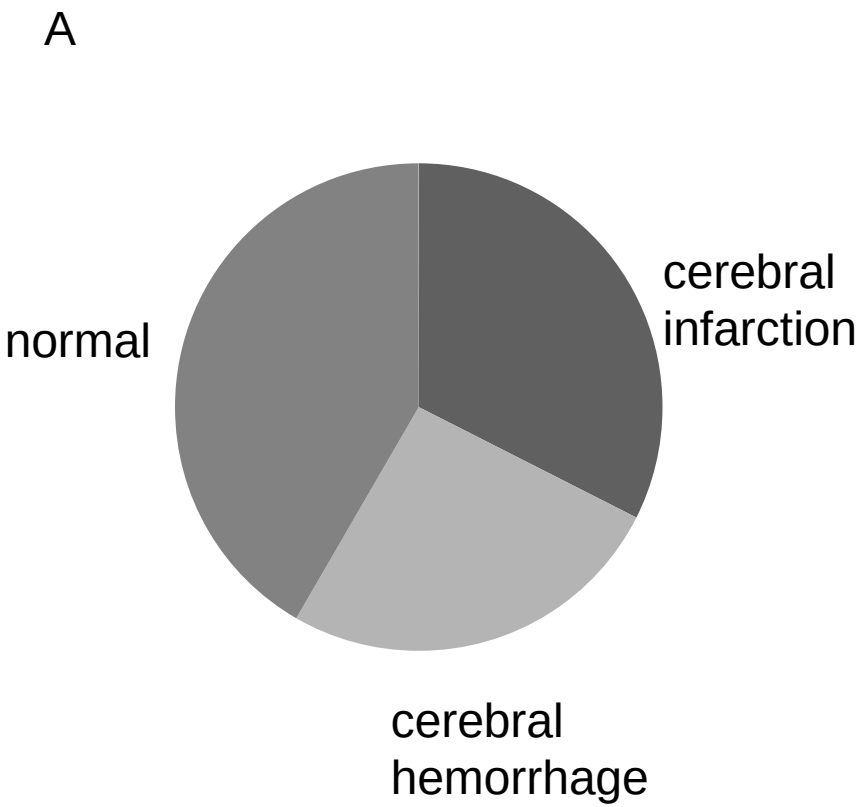


Fig. 3


A
normal
cerebral
infarction
cerebral
hemorrhage

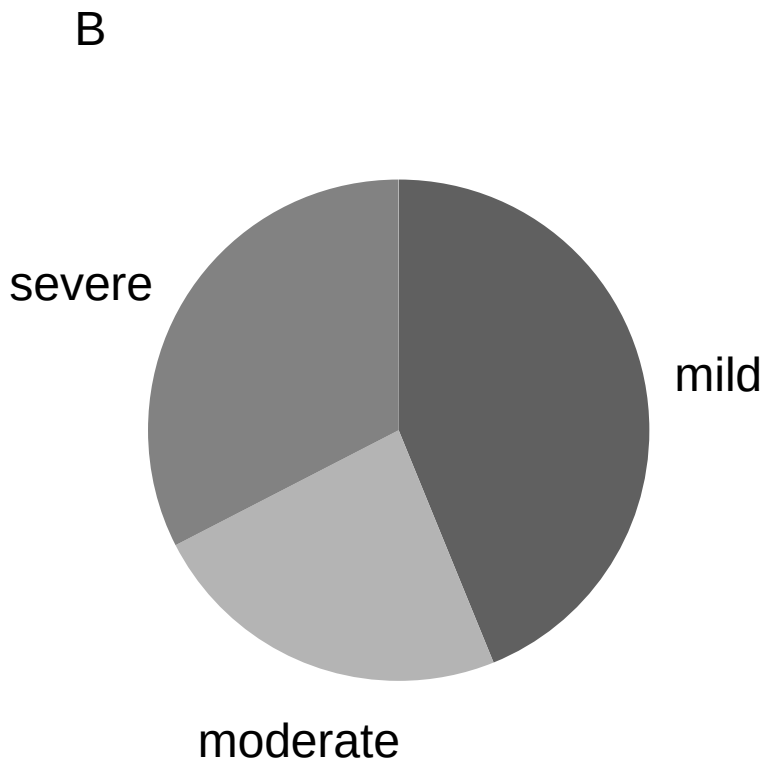

B
severe
mild
moderate

Fig. 3

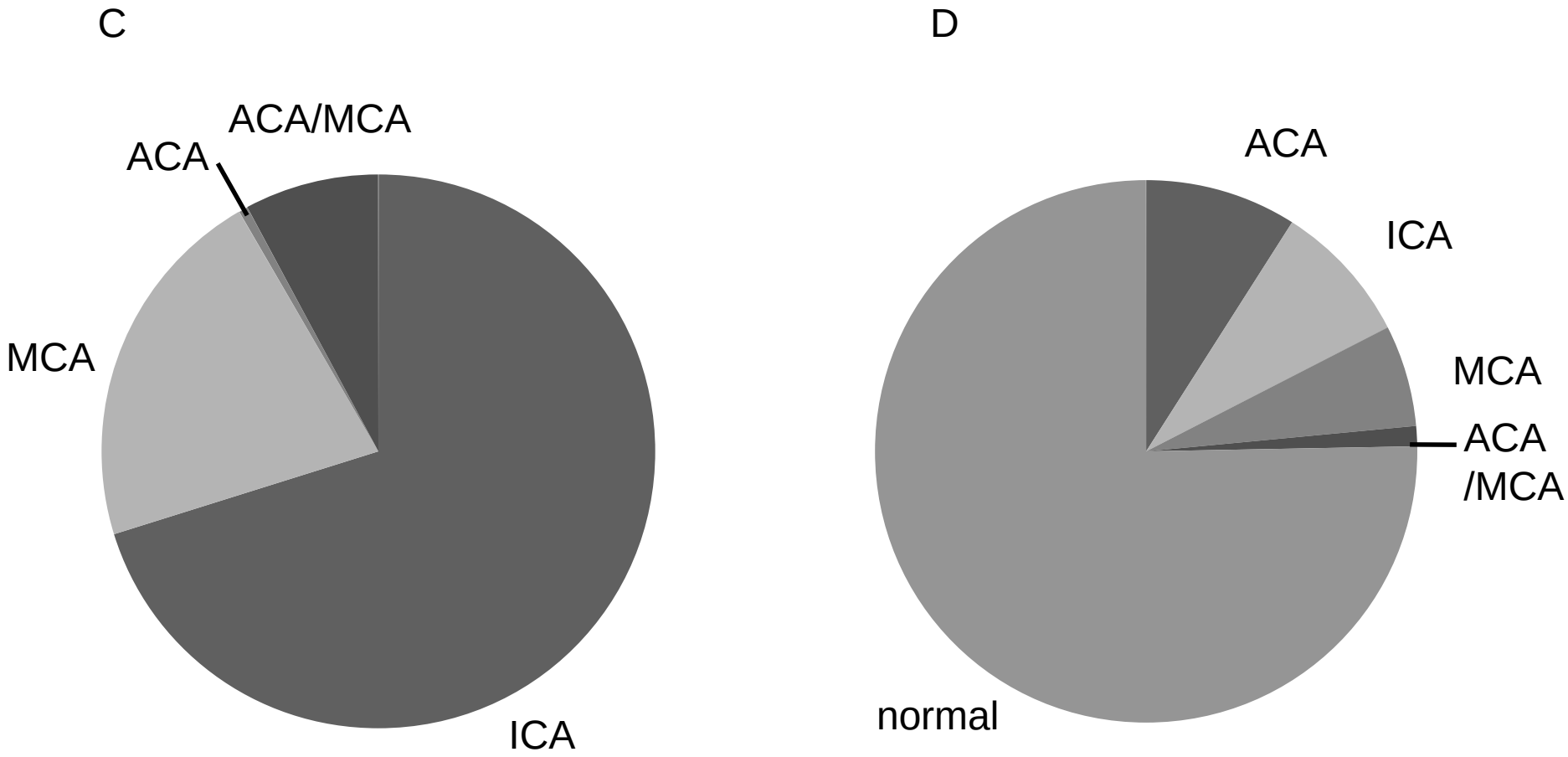


Fig. 4

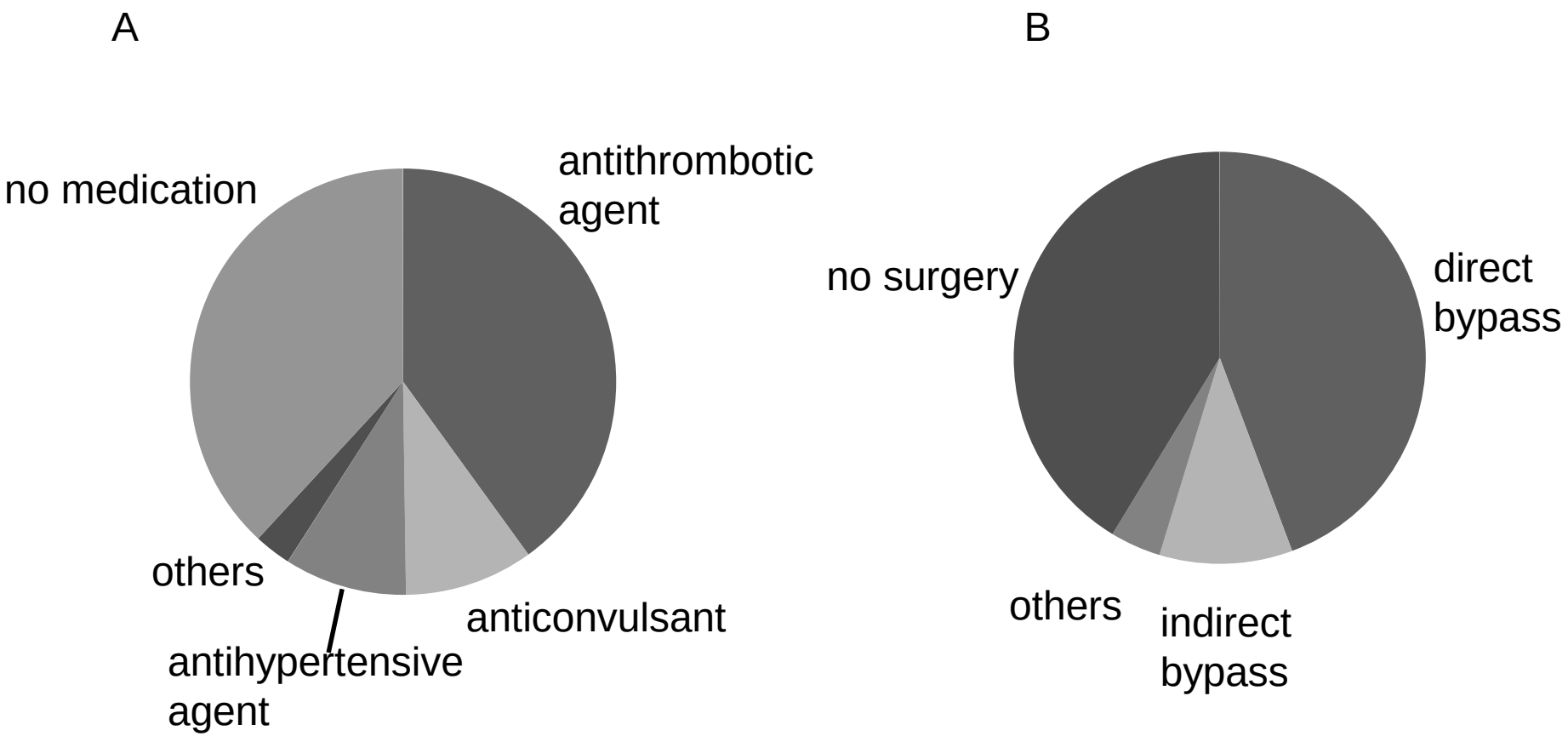
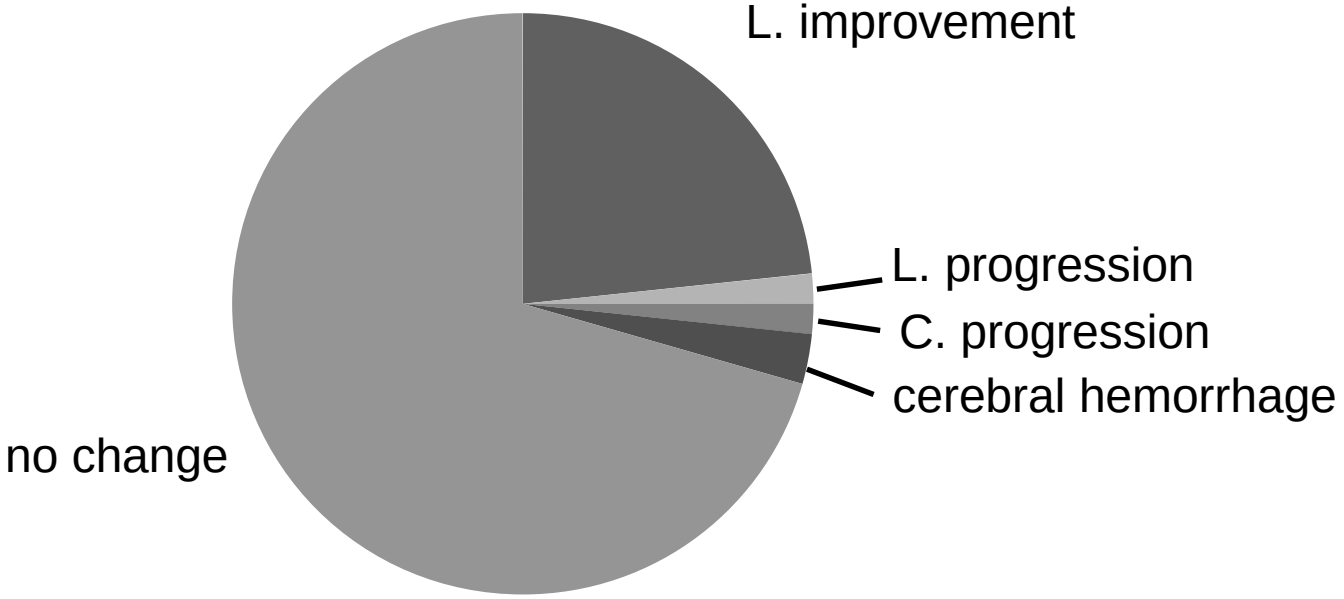

A
no medication
antithrombotic agent
others
anticonvulsant
antihypertensive agent
B
no surgery
direct bypass
others
indirect bypass

Fig.5

A


L. improvement
L. progression
C. progression
cerebral hemorrhage
no change

B

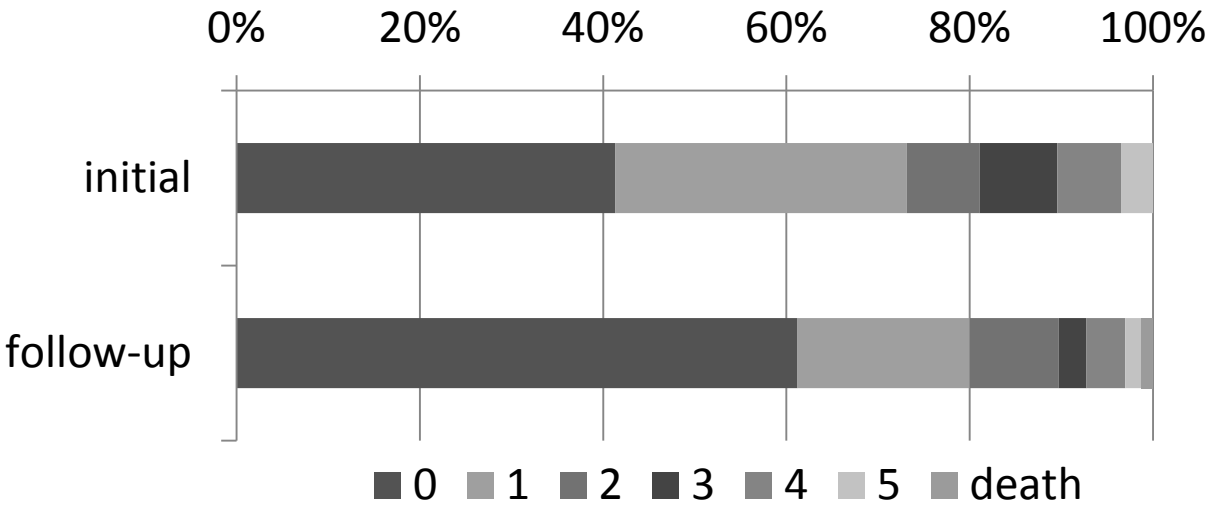

0%
20%
40%
60%
80%
100%
initial
follow-up
0
1
2
3
4
5
death

Table 1 Clinical manifestation of unilateral moyamoya disease

	n	%
motor weakness	57	26.8
headache	37	17.4
TIA	35	16.4
consciousness disturbance	17	8
sensory disturbance	14	6.6
aphasia	12	5.7
other neurological deficit	8	3.8
seizure	3	1.4
asymptomatic	30	14.1

TIA; transient ischemic attack