Nationwide survey on quasi-moyamoya disease in Japan

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Abstract

Objectives -Moyamoya disease (MMD) is a unique occlusive disease of the bilateral internal carotid arteries with moyamoya vessels. A inherited or acquired disorders and conditions may present in conjunction with MMD. This condition is known as quasi-moyamoya disease. To identify the clinical features of quasi-MMD in Japan, nationwide survey was conducted.

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

Results-A total of 114 departments replied to the questionnaire. The data of 108 patients (66 female and 42 male; female to male ratio 1.57) were registered and analyzed. Mean age was 30.6 years old with a peak of the child. Seven patients (7%) exhibited familial MMD. The initial clinical manifestation was motor weakness, followed by transient ischemic attack, headache. Their imaging study type included ischemic type in 64 patients (63.4%), bleeding type in 7 (6.9%), and normal in 27 (26.7%). Stenoocclusive lesion was seen in internal carotid artery in more than half of the patients. Development of moyamoya vessels was mild in approximately 40% of the patients. Almost all cases were accompanied with cerebral hypoperfusion. About half of them were unilateral lesion. Vascular reconstruction was employed for the approximately 60% patients. The prognosis did not changed significantly.

Conclusion-Clinical feature of quasi-MMD were revealed in the nationwide study. In quasi-MMD, unilateral lesion is dominant, and the development of moyamoya vessels and intracranial hemorrhage are less.

Full title: Nationwide survey on quasi-moyamoya disease in Japan

Running title: Nationwide survey on quasi-moyamoya disease

Key words; moyamoya disease, quasi-moyamoya disease, nationwide survey, epidemiology

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. This disease has been reported in association with various disease entities including atherosclerosis, autoimmune disease, meningitis, brain tumor, von Recklinghausen disease, Down syndrome, cranial irradiation etc [11, 12, 14]. These conditions are distinguished from MMD according to the diagnostic criteria of the Research Committee on Moyamoya Disease (Spontaneous Occlusion of the Circle of Willis) of Ministry of Health and Welfare of Japan (RCMJ), and named as quasi-moyamoya disease [3, 21]. We have ever conducted nationwide epidemiological survey on MMD, unilateral MMD, and quasi-MMD in 2006 [9]. The annual incidence rate of MMD and quasi-MMD are 1.13/100,000, and 0.11/100,000 respectively, and the prevalence is 5.22/100,000 and 0.34/100,000 respectively. Since quasi-MMD is quite rare disease, the clinical features have been unclear and a consensus about treatment has not been established. Based on that study, we conducted secondary survey to reveal the clinical features of quasi-MMD.

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 clinical diagnosis of MMD. A

diagnostic algorithm was provided to appropriate diagnosis of each disease [9]. The questionnaire was directly mailed to 241 departments (Neurosurgery 186, Neurology 28, Pediatrics 27), where answered treating quasi-MMD patients in the primary survey. We ascertained the sex, age, associated disorders, clinical manifestation, type of radiological findings, radiological findings (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 seen in definite MMD was categorized as severe. Each angiographical example was enclosed.

For the diagnosis of quasi-MMD, previously reported associate disorders was announced as follows, atherosclerosis, autoimmune disease (systemic lupus erythematodes, antiphospholipid antibody syndrome, arteritis nodosa, Kawasaki disease, Sjogren syndrome), meningitis, von Recklinghousen disease, brain tumor, Down syndrome, head injury, irradiation, Turnar syndrome, Allagille syndrome, Williams syndrome , Noonan syndrome , Marfan syndrome, nodular sclerosis, Ito nevus, incontinence of pigment, Hirschsprung disease, diabetes mellitus Ia, Prader-Willi syndrome, Wilms tumor, primary oxalosis, sicklemia, Fanconi anemia, spherocyte, eosinophilic granuloma, plasminogen abnormality II, Leptospirosis, EV virus infection, protein S deficiency, Protein S deficiency, Pyruvate Kinase deficiency, fibrous dysplagia, polycystic kidney, retinitis pigmentosa oral contraceptives.

Results

A total of 114 departments (Neurosurgery 92, Neurology 13, Pediatrics 9) replied to the questionnaire (response rate; 47.3%). The data of 109 patients (42 male and 66 female, female to male ratio 1.57) were registered and analyzed. Mean age was 30.6 years old with a higher peak of the children and lower peak of forties to fifties (Fig. 1). Seven patients (7%) exhibited familial MMD.

The associated disorders are athrosclerosis in 27 patients (29%), Down syndrome in 14 (15.1%), von Recklinghausen disease in 13 (14%), brain tumor/irradiation in 7 (7.5%), autoimmune disease in 7 (7.5%), hyperthyroidism in 7 (7.5%), meningitis in 2 (2.2%), leukemia in 2 (2.2%), renal hypertension in 2 (2.2%), aortic coarctation in 2 (2.2%) (Fig. 2).

The initial clinical manifestation were motor weakness 38 (36.5%), transient ischemic attack 20 (19.2%), headache 10 (9.6%), seizure 10 (9.6%), speech disturbance 7 (6.7%), and no symptom 6 (5.8%) (Fig. 3A). Their imaging study type included ischemic type in 64 patients (63.4%), bleeding type in 7 (6.9%), and normal in 27 (26.7%) (Fig. 3B).

Angiographical findings are shown in Table 1. Approximately 60% was Suzuki's stage III, which is "intensification of moyamoya vessels". Stenoocclusive lesion was seen in ICA in more than half of the patients. Development of moyamoya vessels was mild in approximately 40% of the patients. Collateral flow from external

carotid arteries (volt-moyamoya vessels) was seen in approximately 30% of the patients. Totally 45.9% are unilateral lesion.

In terms of cerebral circulation, hypoperfusion was seen in 68 patients (90.7%) and vasoreactivity was impaired in 6 patients (8%).

Surgery underwent to 25 patients (25%) bilaterally and to 34 patients (34%) unilaterally. Forty-one patients (41%) were not treated surgically (Fig. 4A). Among surgical treatment, direct bypass was performed to 42 cases (49.4%) and indirect bypass was performed to 43 patients (50.6%) (Fig. 4B). The mean follow-up period was 77 months (range 3 to 277 months). During follow-up, symptoms were improved in 20 patients (20.2%), no changed in 66 patients (66.7%) and worsened in 11 patients (11.1%) (Fig. 5A). Cerebral hemorrhage occurred in only 2 patients (2%). Both initial and follow-up mRS were shown in Figure 5B. Approximately 80% of patients were mRS 0-2 initially and were not changed during follow-up.

The clinical features of quasi-MMD due to the atherosclerosis was separately analyzed. All 27 quasi-MMD cases with atherosclerosis are more than 40-years-old and the mean age was 53.5-years-old. That is 62.8% of quasi-MMD cases of more than 40-years-old. The female to male ratio was 0.9 and the ratio of male is relatively high. About half cases visited with motor weakness and transient ischemic attack. Imaging study included ischemic type in 60% and bleeding type in 2 (7.4%). Development of moyamoya vessels were mild in 4 (14.5%). Those findings were similar with total analysis. The unilateral lesion was seen in 18 cases (66.7%) and the ratio was slightly higher.

Discussion

Quasi-MMD had not been defined in diagnostic criteria of MMD. Several terms, such as quasi-moyamoya disease, akin-moyamoya disease, moyamoya syndrome, moyamoya phenomenon, moyamoya-like vasculopathy, moyamoya angiopathy, have been used [6, 21] and occasionally confused with unilateral MMD [2, 13]. It is clearly defined in the guideline as quasi-MMD [10], therefore we employed the term in this study.

In quasi-MMD patients, there was a female predominance as definite cases. In terms of patient ages, there seems to be two peak patterns in the age distribution in quasi-MMD as definite MMD. The child onset rate is higher in quasi-MMD may be due to the congenital disorders or pediatric onset brain tumor. And the acquired disorder such as atherosclerosis cause the lower peak of elderly patients. The pathologic and epidemiological facts suggest that genetic factors play a more important role in the pathogenesis of MMD than do acquired factors [5]. It is reported that the familial occurrence was approximately 10% of MMD patients [5, 16, 18, 20]. In this quasi-MMD study, the ratio of familial occurrence was 7.0%. Some of the congenital disorders may be related to the same gene with MMD. Another possibility is that MMD patients coincidentally accompanied with associated disorder and misdiagnosed as quasi-MMD.

Regarding with associated disorders, atherosclerosis is the most major since it is one of the most common disease nowadays. It is described that conventional

angiographic evaluation methods cannot easily differentiate MMD from intracranial atherosclerotic disease [15, 17] and genetic analysis or high resolution MRI is useful for the differentiation [15, 17]. It is well-known that Down syndrome and von Recklinghausen disease accompanies with moyamoya-like vasculopathy in the western countries. And it was confirmed in this Japanese study. Hyperthyroidism is a kind of autoimmune disease. Since the ratio of hyperthyroidism is relatively higher, it was categorized independently. On the other hand, irradiation and brain tumor were included same category, because most of irradiated cases appeared to be brain tumor.

The clinical manifestations are divided into focal sign such as motor weakness, and non-specific symptoms such as headache. In this study, most of them are focal sign. Therefore, their cerebrovascular disease might be found by the further examination rather than screening or coincidentally. In the questionnaire, which we sent, did not cover the systemic manifestations. Since most of the systemic disease such as Down syndrome or von Recklinghausen disease manifest systemic abnormality, percentage of cases with these systemic manifestations might be high. Their imaging study type included ischemic type in 64 patients (63.4%), bleeding type in 7 (6.9%), and normal in 27 (26.7%). It is well known that the pediatric patients present with ischemic attack and adult patients tend to suffer from intracranial bleeding [16, 20]. Main cause of intracranial bleeding is rupture of dilated, fragile moyamoya vessels due to hemodynamic stress and hemorrhage occurs in the basal ganglia, thalamus, or periventricular region. The ratio of intracranial bleeding is approximately 20% of definite MMD patients and approximately 50% of adult MMD patients [1, 4, 7]. In this

quasi-MMD study, intracranial bleeding was less (6.9%) and it was notable clinical feature.

About half of them are unilateral lesion. Consistent with previous reports on cerebrovascular lesion of Down syndrome or von Recklinghausen disease, the ratio of unilateral lesion was higher [11, 19]. Steno-occlusive lesion was mainly seen in the ICA. Since the development of moyamoya vessels is the most important finding to make diagnosis of MMD, we evaluated the degree of moyamoya vessels. The severe degree, which is typical moyamoya vessel seen in definite MMD, was only 20%. The development of moyamoya vessels is less in quasi-MMD. In another words, development of moyamoya vessels and bleeding from them are quite important feature of the definite MMD. Thus, collateral from external carotid arteries were seen in approximately 30% of cases. CBF was impaired in almost all cases. On the staging of the CBF, firstly reserve capacity is impaired and CBF decrease in the second stage. Therefore, hypoperfusion may includes reserve capacity impairment. Acetazolamide challenge is required to evaluate reserve capacity, however, it is not performed routinely since it has a risk of ischemic attack in case of critical condition. That is the reason why the reserve capacity impairment was low rate. Even in the temporary ischemic symptoms, CBF may decease.

Surgery underwent approximately 60% of patients. Since adult cases are predominant, the ratio of direct bypass, probably superficial temporal artery-middle cerebral artery anastomosis, is much more than indirect bypass such as encephalo-duro-arterio sinangiosis.

During follow-up, their statuses improved in 20.2% patients. The disease progressed 11.1%. Mostly their condition did not changed. Thus, cerebral hemorrhage was quite rare. This tendency is quite different with definite MMD. Activity of daily living is independent in approximately 80% initially and not changed during follow-up. As well as definite cases, medical treatment or vascular reconstruction may prevent disease progression. But some associated disorder such as brain tumor is usually progressive and others such as Down syndrome may be accompanied with mental retardation [8]. Taken together, their prognosis might not be changed so much.

The limitation of this study includes retrospective nature of the data analysis. Among 241 departments, which we sent questionnaire, 114 departments responded (response rate 47.3%). This study was based on the voluntary policy. No reward was paid. The doctors needed to investigate the MMD patients during their busy daily work. Then, collected information was limited. This secondary study was performed for quasi-MMD patients and the data of definite MMD is missing. The clinical features of definite MMD have been reported very well and we compared with previous reports.

Conclusions

In conclusion, clinical features of quasi-MMD were revealed in the nationwide survey. In quasi-MMD, unilateral lesion is dominant, and the development of moyamoya vessels and intracranial hemorrhage are less.

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Disclosure

None.

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Figure legends

Fig. 1 Distribution of the patients' age

Fig. 2 Associated disorders

Fig. 3

A: Clinical manifestations

TIA indicates transient ischemic attack.

B: Subtypes of imaging findings

Fig. 4 Treatment

A: Status of the surgical treatment

B: Ratio of direct bypass and indirect bypass

Fig. 5

A: Outcome

B: Initial and follow-up modified Rankin Scale

Fig. 1

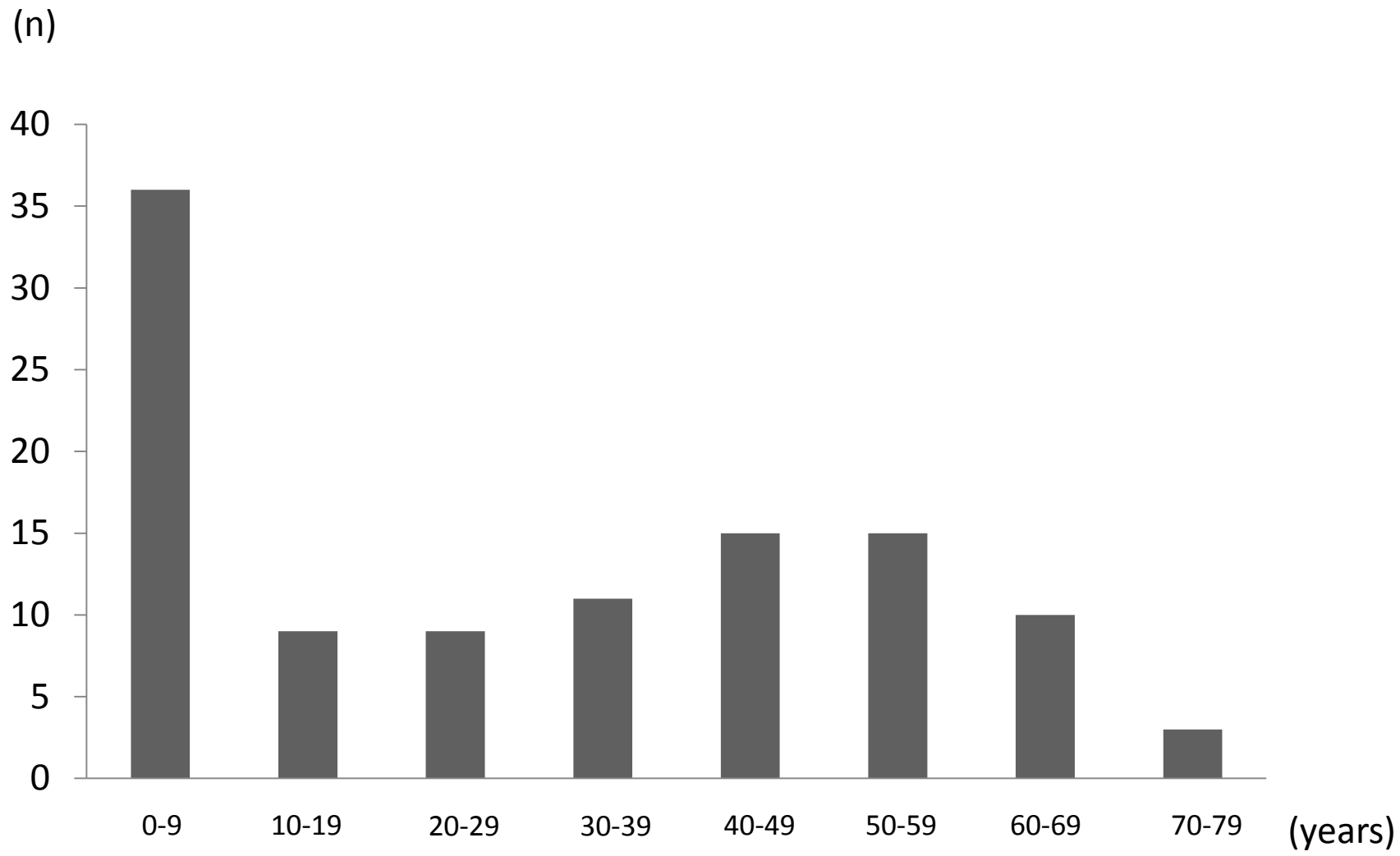
(n)
40
35
30
25
20
15
10
5
0
0-9
10-19
20-29
30-39
40-49
50-59
60-69
70-79
(years)

Fig. 2

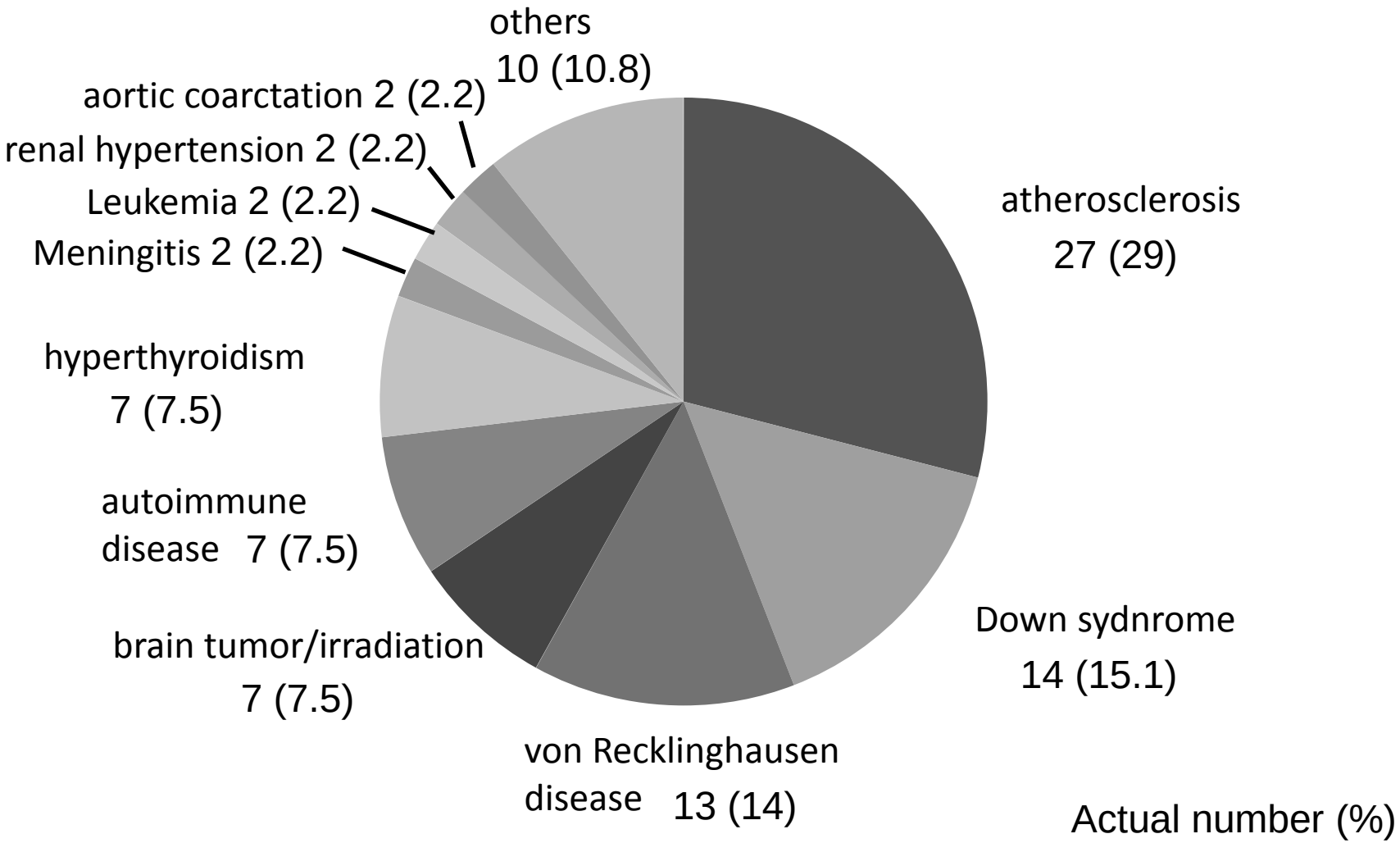
others
10 (10.8)
aortic coarctation 2 (2.2)
renal hypertension 2 (2.2)
Leukemia 2 (2.2)
Meningitis 2 (2.2)
hyperthyroidism
7 (7.5)
autoimmune
disease 7 (7.5)
brain tumor/irradiation
7 (7.5)
von Recklinghausen
disease 13 (14)
Down sydnrome
14 (15.1)
atherosclerosis
27 (29)
Actual number (%)

Fig. 3

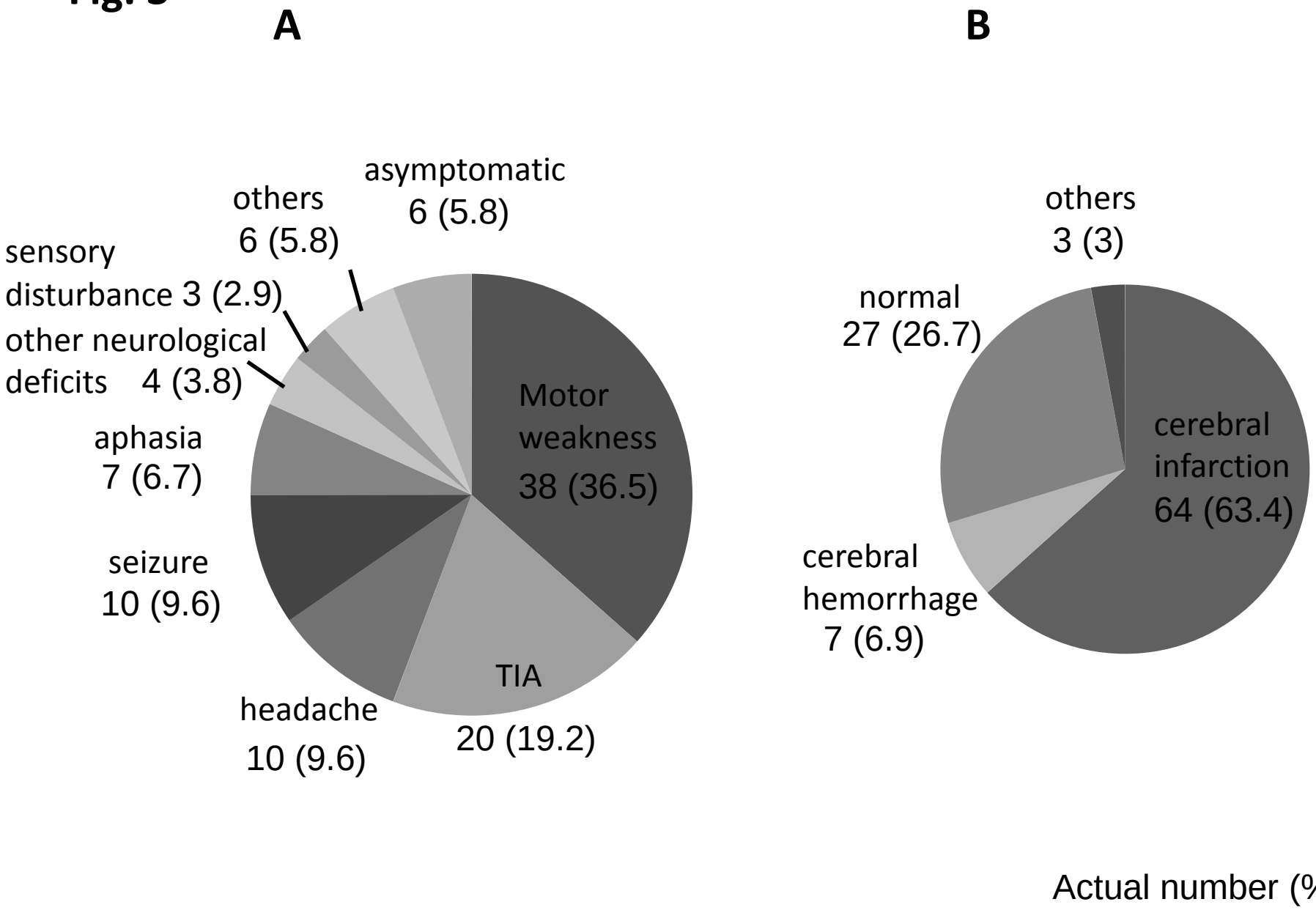
A
asymptomatic
6 (5.8)
others
6 (5.8)
sensory
disturbance 3 (2.9)
other neurological
deficits 4 (3.8)
aphasia
7 (6.7)
seizure
10 (9.6)
headache
10 (9.6)
TIA
20 (19.2)
Motor
weakness
38 (36.5)
B
others
3 (3)
normal
27 (26.7)
cerebral
infarction
64 (63.4)
cerebral
hemorrhage
7 (6.9)
Actual number (%)

Fig. 4

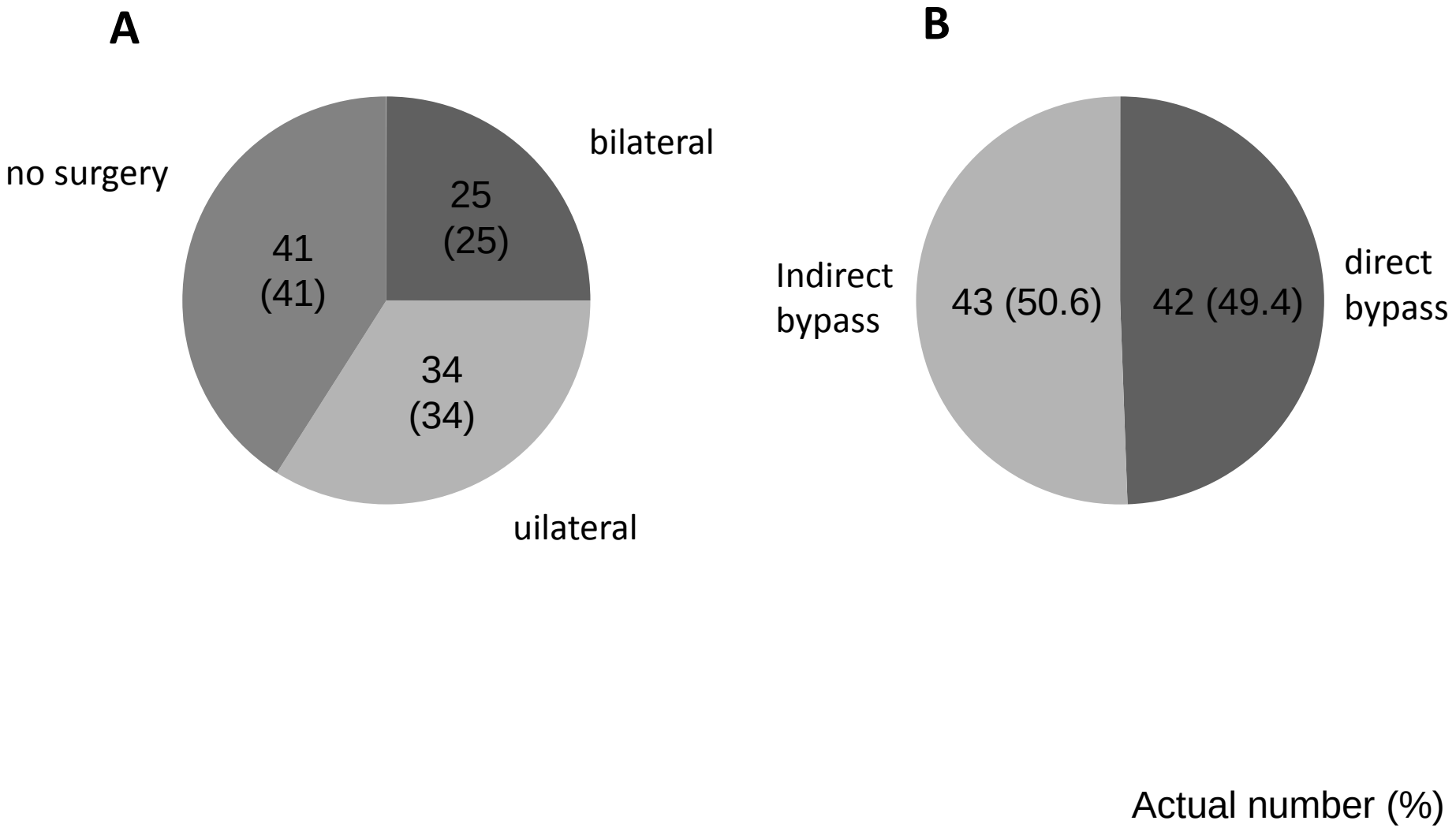
A
no surgery
bilateral
uilateral
41
(41)
25
(25)
34
(34)
B
Indirect
bypass
direct
bypass
43 (50.6)
42 (49.4)
Actual number (%)

Fig. 5

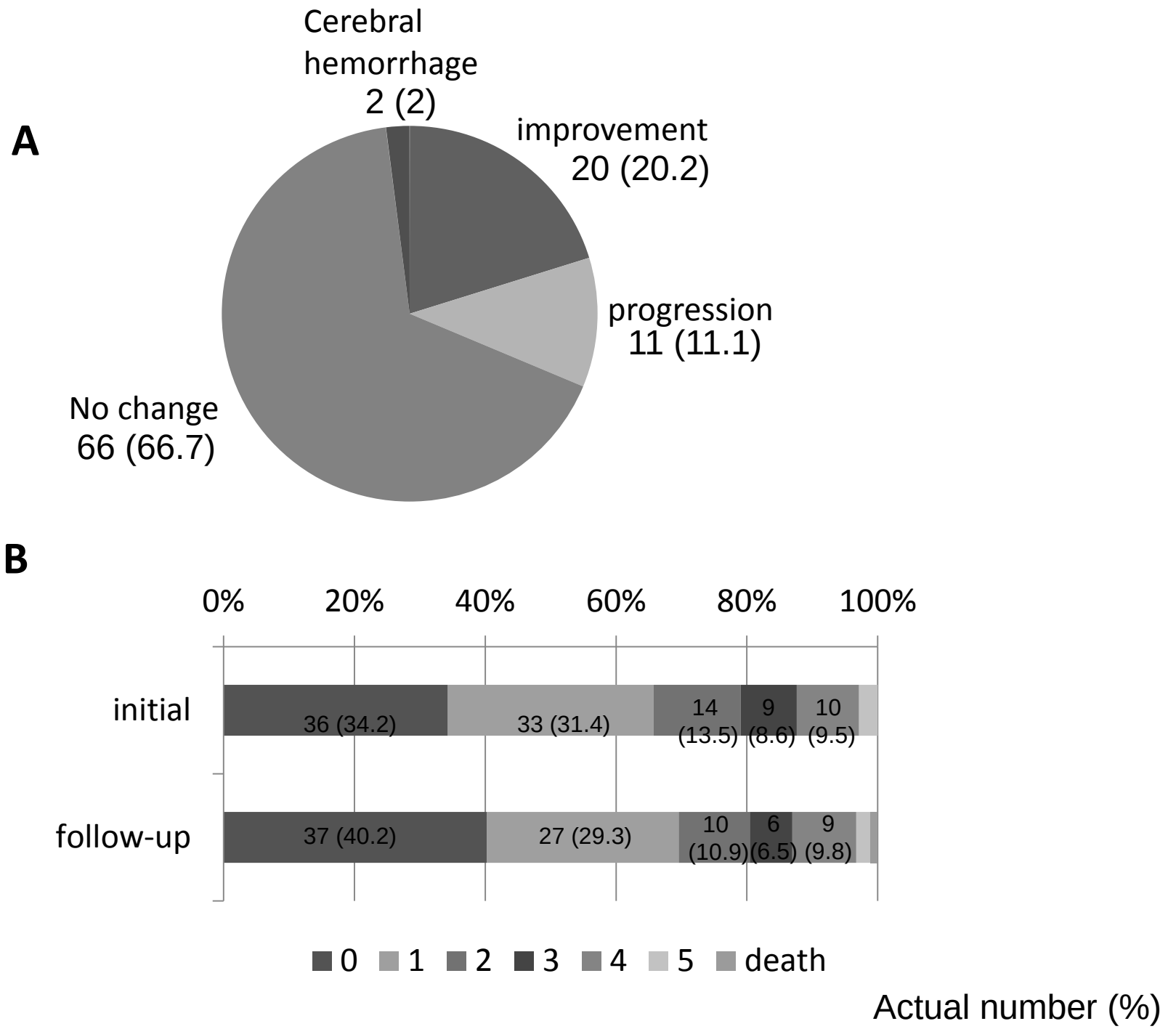
A
Cerebral hemorrhage 2 (2)
improvement 20 (20.2)
progression 11 (11.1)
No change 66 (66.7)
B
0%
20%
40%
60%
80%
100%
initial
follow-up
36 (34.2)
33 (31.4)
14 (13.5)
9 (8.6)
10 (9.5)
37 (40.2)
27 (29.3)
10 (10.9)
6 (6.5)
9 (9.8)
0
1
2
3
4
5
death
Actual number (%)

Table 1 summary of angiographical findings

	Right side	(%)	Left side	(%)
Suzuki's stage				
1	6	(7.1)	6	(7.3)
2	6	(7.1)	7	(8.5)
3	51	(60.7)	50	(61)
4	4	(4.8)	4	(4.9)
5	3	(3.6)	0	(0)
6	3	(3.6)	5	(6.1)
normal	11	(13.1)	10	(12.2)
Steno-occlusion				
ICA	58	(65.2)	54	(62.1)
MCA	12	(13.5)	13	(14.9)
ACA	1	(1.1)	3	(3.4)
ACA/MCA	8	(9)	8	(9.2)
no	10	(11.2)	9	(10.3)
Moyamoya vessels				
mild	34	(37.8)	38	(45.2)
moderate	16	(17.8)	8	(9.5)
severe	19	(21.1)	19	(22.6)
no	21	(23.3)	19	(22.6)
Volt-moyamoya vessels				
yes	23	(27.1)	23	(28.3)
no	62	(72.9)	58	(71.6)

ICA: internal carotid artery, MCA: middle cerebral artery, ACA: anterior cerebral artery

Table 2 Compartment of definite moyamoya disease and quasi- moyamoya disease

	Definite moyamoya disease	Quasi- moyamoya disease
Age	two peak	two peak
Sex	male < female	male < female
Symptom	motor weakness/TIA	motor weakness/TIA
Imaging type		
child	ischemia	ischemia
adult	ischemia/hemorrhage	ischemia
Moaymoya vessel	severe	mild
Lesion side	bilateral	unilateral
Cerebral blood flow	decrease	decrease
Treatment	medication	medication
	vascular reconstruction	vascular reconstruction