

Epidemiology and Characteristics of Recurrent Stroke : The Occurrence Type of Restroke is Similar as Previous Stroke

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Objective : Despite improvement of therapeutic regimen, incidence of stroke increases and it remains a leading cause of death. Our study aims at offering variable data on recurrent strokes.

Methods : There were 59 patients who admitted from Jan. 2002 to Dec. 2004 due to recurrent strokes. A retrospective longitudinal cohort study was done.

Results : Four-hundred-seventy five patients, diagnosed with acute stroke, experienced 491 strokes in 3 years, and there were 75 recurrent strokes (15.3%) in 59 patients. These 59 patients were included in the study. First hemorrhagic cases (H) were 19 (32%), and the first infarction cases (I) were 40 (68%). Subsequent strokes after first stroke were as follows : H→H 14 (23.7%) cases, H→I 5 (8.5%), I→H 8 (13.6%), I→I 32 (54.2%). A Cox regression analyses showed that the first type of stroke was a significant factor to the second stroke as follows : if one has had a hemorrhagic stroke, the possibility of second hemorrhagic attack (H→H attack) increase 3.2 times than ischemic type and in ischemic stroke (I→I attack) 3.6 times increased incidence of second ischemic attack.

Conclusion : The recurrence rate of stroke was 12.4% (59 of 475 patients). If the first stroke is hemorrhage or infarction, the next stroke would have high potentiality of hemorrhage, or infarction. The possibility of same type in second stroke increase over 3 times. In H→H group, the time interval between first and second stroke was shorter and the age of onset was earlier than in I→I group. Moreover, the infarction was more frequent than hemorrhage in multiple strokes. There was a correlation in lacunar type infarction between first and second attack.

KEY WORDS : Recurrent stroke · Cerebral infarction · Cerebral hemorrhage.

Introduction

In 2005, the percent distribution of population over 65 years old was increased to 9.1% in South Korea, and nowadays the diet pattern has been altered to take a lot of lipid and high-caloric food with a change of lifestyle. As expected the cerebrovascular diseases have increased with the high prevalence of hypertension and diabetes mellitus. According to Korea National Statistical Office¹⁾, the stroke was second most common cause of death in 2004 (death rate : 70.3/100,000 population, 13.9% of total dead population). Hence, the various treatment modalities of such disease have gained great attention and our greatest interest lies in its prevention. The risk of

subsequent stroke is highest in the period immediately after stroke^{4,9,17,19)}, so clinical goal of acute and long term management of stroke is to prevent its recurrence. Patients with recurrent stroke have greater disability and poorer outcomes than those with first stroke²⁰⁾. Whenever a stroke occurs, the patient and his/her family become anxious to find out the risk of another stroke, the likely timing of another stroke, and whether it can be prevented.

Usually, the cerebral hemorrhagic diseases are treated in the department of neurosurgery (76.8%), and ischemic diseases from the department of neurology (51.4%) and less commonly in neurosurgery (20.0%) in South Korea⁸⁾. Fortunately, hemorrhagic and ischemic patients have been treated in our

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department. Thus, study on the epidemiologic and clinical characteristics of both types of strokes could have been conducted without much difficulty. The purpose of this study was to evaluate the recurrent strokes of both types.

Materials and Methods

From January 2002 to December 2004, four hundred-seventy-five patients who admitted due to cerebral hemorrhage or infarction were drawn and performed a longitudinal cohort study. The 59 subjects had multiple strokes in their life span. We classified and studied them by stroke type, number and attack interval.

Those patients who had transient ischemic attack, subarachnoid hemorrhage, arteriovenous malformation, moyamoya disease, trauma, operation related hemorrhage, tumor bleeding and coagulopathy were excluded from the study. The hemorrhagic cases that related with treatment of infarction were also eliminated.

Etiologic subtypes of infarction were defined according to the Perth Community Stroke Study criteria¹⁾.

Statistical analysis

Independent t-test was used for comparison of age difference between hemorrhage and infarction group in first stroke. The paired t-test was used for the comparison of pathological subtypes of lacunar infarction between first and second strokes. The Kaplan-Meier technique was used to generate occurrence probability and time interval curve between first and second attack. A Cox regression analysis was used to determine the effect of first attack to second attack. The SPSS 12.0 for Windows was used for all statistical analysis.

Results

During three years, 475 patients were admitted, among whom 59 (12.4%) had multiple strokes. These 59 patients had 75 strokes (15.3%) during 3 years and 133 strokes in their whole lifetime (Table 1, 2). These 133 attacks were analysed in detail.

Age was ranged from 42 to 84 (mean 64.7) years at the time of admission (Table 3). But age distribution was from 41 to 82 (mean 58.6) years when they were adjusted to first attack age. In hemorrhage cases the adjusted mean age was 52.9 years [95% Confidence Interval (CI), 48.6, 57.2] and infarction cases 61.4 years (95% CI, 58.5, 64.3). These group differences of age were statistically significant ($p=0.02$, 95% CI, 3.4, 13.5). Thirty two (54.2%) were men.

Forty-eight patients had 2 strokes (81.4%, 48/59) in 3 years. And the infarction was more common than hemorrhage

Table 1. Incidence of strokes

Characteristics	Values
No. of admitted patients (2002–2004)	475
Hemorrhage	203 (42.7%)
Infarction	213 (44.8%)
Restroke	59 (12.4%)
No. of patients classified by restroke frequency	59
2 times	48
3 times	7
4 times	4
No. of strokes during whole lifetime in 59 restroke patients	133
Hemorrhage	47
Infarction	86

Table 2. Number of strokes in 475 patients (from 2002 to 2004)

	Single stroke	Multiple strokes	
Hemorrhage	203	29	232 (47.3%)
Infarction	213	46	259 (52.7%)
	416 (84.7%)	75 (15.3%)	491 (100%)

Table 3. Demographics and clinical characteristics by recurrent strokes in 59 patients

Characteristics	Values
Age (mean \pm SD at admission)	64.7 \pm 9.2
Hemorrhage	59.8 \pm 8.8
Infarction	67.0 \pm 8.6
Male:Female	32:27
Hypertension	47/59 (79.7%)
Diabetes mellitus	17/59 (28.8%)
Hyperlipidemia	20/57 (35.1%, 2 unknown)
Cardiac disease (AF, MI, Valvular disease)	10/57 (17.5%, 2 unknown)

AF: Atrial fibrillation, MI: Myocardial infarction

Table 4. A factor related to the occurrence of second stroke: A Cox regression analysis

Factor	RR (95% CI)	<i>p</i> value
H type of 1 st attack (in 2 nd HG)	3.21 (1.34 – 7.69)	0.009
I type of 1 st attack (in 2 nd IG)	3.55 (1.37 – 9.18)	0.009

CI: confidence interval, H: hemorrhagic, HG: hemorrhagic group, I: infarction, IG: infarction group, RR: relative risk

Table 5. Risk of occurrence of a second stroke after first-ever stroke within defined time intervals

	<6M	6–12M	1–2Y	2–3Y	3–4Y	4–5Y	6–10Y	>10Y
No.	4	3	4	9	6	7	17	9
% risk	6.8	5.1	6.8	15.3	10.2	11.9	28.8	15.3
% cumulative	6.8	11.9	18.6	33.9	44.1	55.9	84.7	100

in multiple strokes (Table 1, 2).

The associated diseases were hypertension in 80% (47/59 patients), hyperlipidemia 33.9% (20/59), diabetes mellitus 28.8% (17/57) and heart disease 16.9% (10/57) i.e. atrial fibrillation, valvular heart disease, myocardial infarction. Hypertension was the highest risk factor followed by hyperlipidemia, diabetes mellitus in descending orders (Table 3).

Table 6. Classification of recurrent strokes according to pathological subtype

	stroke				No.
	1st	2nd	3rd	4th	
Hemorrhage					
basal ganglia	9	4	1	1	15
Gt/thalamus	6	11	1	-	18
pons					
lobe	-	4	1	-	5
cerebellum	-	2	2	-	4
undetermined	4	1	-	-	5
	19	22	5	1	47
Infarction					
large-artery occlusion	7	6	2	-	15
lacunar	21	19	2	2	44
cardioembolic	3	6	2	1	12
boundary zone	1	5	-	-	6
undetermined	8	1	-	-	9
	40	37	6	3	86
Total	59	59	11	4	133

Gt : gangliothalamic

According to pathologic type, first-ever hemorrhages were 19 cases (32%) and first-ever infarctions 40 cases (68%). With the analysis of second strokes, infarctions as a second stroke after ischemic attack (I→I) were 54.2% (32/59), hemorrhages as a second stroke after hemorrhagic attack (H→H) were 23.7% (14/59), H→I 8.5% (5/59), I→H 13.6% (8/59). Also, the proportion of ischemic restrokes after first-ever ischemic strokes (I→I) were 80% (32/40) and hemorrhagic restrokes after first-ever hemorrhagic strokes (H→H) 74.7% (14/19) (Fig. 1, 2). These indicate that the types of second attack have a likelihood pattern that of a previous stroke. Namely, patients of hemorrhage will have a higher risk of recurrent hemorrhage than of ischemic stroke and vice versa. Kaplan-Meier technique shows statistical significance in both hemorrhagic and ischemic strokes (Log Rank test $p < 0.01$, Tarone-Ware test $p < 0.01$) (Fig. 3, 4). A Cox regression analyses showed that the first type of stroke was a significant factor to the second strokes as follows : if one has had a hemorrhagic stroke, the possibility of second hemorrhagic attack (H→H) increase 3.2 times than infarction and in ischemic stroke (I→I) increase 3.6 times than hemorrhage (Table 4).

Moreover, the analyses on third strokes showed higher, I→I→I course (5 of 11 cases) than the other types. In fourth stroke, there were 2 cases of I→I→I→I type.

The interval between first and second stroke was variable from one month to nearly 17 years. The occurrence of restroke according to interval between first and second attack is as follows (Table 5) ; 1 case, < 1 month ; 3, 1-6 months ; 3, 6-12 months ; 4, 1-2 years ; 9, 2-3 years ; 6, 3-4 years ; 7, 4-5 years ; 17, 6-10 years ; and 9, > 10 years. The restroke

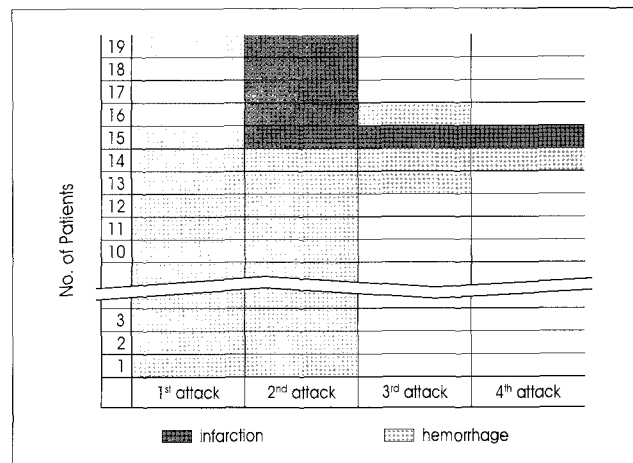


Fig. 1. Development of restrokes in first-ever hemorrhagic patients (No. of patients : 19, total number of strokes : 44).

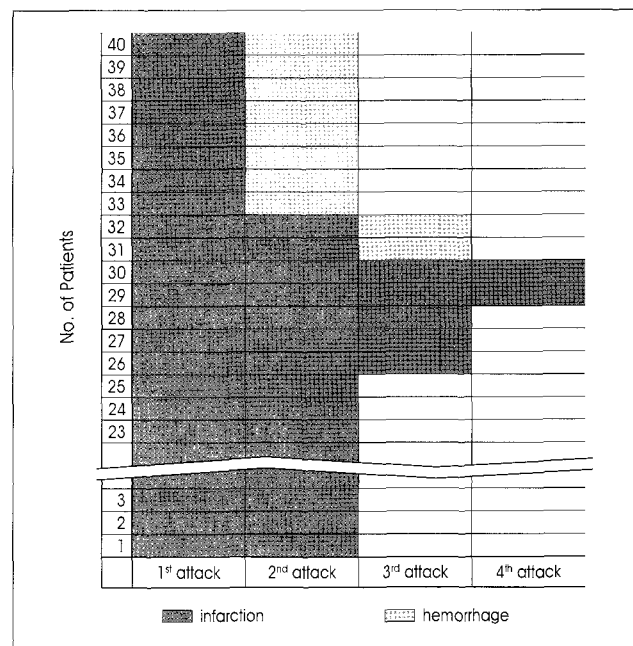


Fig. 2. Development of restrokes in first-ever infarction patients (No. of patients : 40, total number of strokes : 89).

rate was 11.9% under 1 year and 44.1% over 5 years. In 9 cases, the interval was over 10 years. In case of a third stroke patients after second attack, there were 5 cases (45.5%) who had an occurrence interval from 1 to 2 years. The time interval between first and second stroke was under 12 years (mean : 6.3 ± 0.9 years) in H→H group and under 17 years (mean : 12 ± 1.1 years) in I→I group (Fig. 3, 4). The mean age of onset was 51.9 ± 7.5 years in H→H group and 60.8 ± 9.1 years in I→I group.

The majority of hemorrhagic stroke were gangliothalamic/thalamic or basal ganglia type (33/47, 70.2%) and in ischemic cases lacunar types were predominant (44/86, 51.2%) (Table 6). The correlation of stroke according to subtypes between

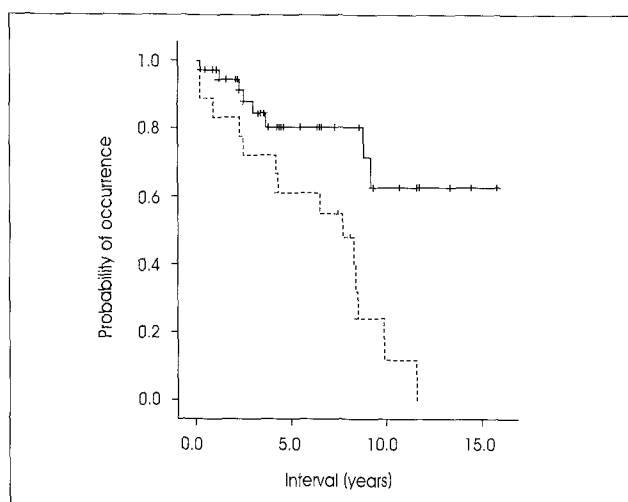


Fig. 3. Occurrence curve of second hemorrhagic strokes by first stroke. The x axis indicates the time interval between first and second strokes, and y axis indicates the probability of occurrence of second hemorrhagic stroke. Kaplan-Meier estimate of the occurrence curve of second hemorrhagic stroke is plotted (dotted line). (solid line is ischemic stroke, Log Rank test and Tarone-Ware test $p < 0.01$).

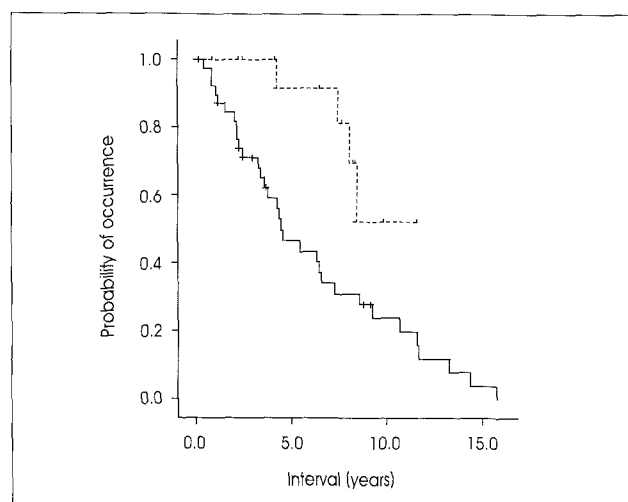


Fig. 4. Occurrence curve of second ischemic strokes by first stroke. The x axis indicates the time interval between first and second strokes, and y axis indicates the probability of occurrence of second ischemic stroke. Kaplan-Meier estimate of the occurrence curve of second ischemic stroke is plotted (solid line). (dotted line is hemorrhagic stroke, Log Rank test and Tarone-Ware test $p < 0.01$).

first and second attack were statistically significant only in lacunar infarction ($p = 0.001$).

Discussion

The morbidity rate of stroke in South Korea was 305/100,000 population at 2003, and in which ischemic brain disease account for 57.6%, intracerebral hematoma 15.3%, and subarachnoid hemorrhage 6.3% in order⁸⁾.

In this study, the prevalence of restroke during 3 years was 12.4% (59/475 patients), and 15.3% (75/491 attacks). The

risk of a recurrent stroke within 1 year after a first-ever stroke was about 11.9%, and this is similar to other reports (13%)^{4,7)}. The risk of another stroke occurring in the 1 year after a first stroke was 8.5 times greater than the risk of first stroke in the general population of the same age and sex⁷⁾. The risk of recurrent stroke is known highest (8.8%) in the first 6 months after stroke⁷⁾, but this was not observed in this study.

The studies indicate that the risk of recurrence after infarction varies from 1.7-4% in the first 30 days, and 6-13% in the first year, and 5-8% per year for the next 2 to 5 years, culminating in an absolute risk of recurrence within 5 years of 19-42%^{4,7,19)}. It has been speculated that the high rate of a recurrent ischemic stroke within the first year of first stroke is the hypothesis that atheroma is an acute-on-chronic disease, which cause recurrent episodes of thromboembolism before the endothelium of the ulcerated plaque heals⁷⁾.

In our study risk of recurrence was 56% within 5 years, and 44% was over 5 years. Although the occurrence rate of hemorrhage decrease in South Korea today, the prevalence of hemorrhage is still higher than the other countries, so the high rate of recurrence within 5 years is expected. Intracranial hemorrhage accounts for 10-15% of all stroke in the West²¹⁾, however the rate of hemorrhage was 47.3% (232/491) of all strokes and 39% (29/75) of all restrokes in this study. Bae et al.²⁾ reported the recurrence rate of hemorrhage to be 92.5% within 4 years and Lee et al.¹⁴⁾ 66.7% within 5 years in South Korea. In other studies, recurrence rate of hemorrhage has been reported to be about 6.4-24% in Europe^{12,16)}. Recurrent hemorrhagic stroke occurs at a rate of about 4% per patient-year, and most patients have a higher risk of recurrent hemorrhage than of ischemic stroke after cerebral hemorrhage³⁾ as observed in this study.

The factors which affect the occurrence of restroke were age and type of previous stroke in this study. When the factor was applied individually to the Cox regression analysis program, the results showed a statistical significance. However, when 2 factors applied simultaneously, the results were statistically insignificant: in infarction cases the age factor was not significant ($P = 0.08$) and in hemorrhagic cases the previous stroke factor was not significant ($P = 0.094$). These are the interference effect of factors, because these 2 factors are correlated strongly with occurrence of restroke.

In addition to age factor, which we already know, the type of previous stroke is also an important factor for restroke.

The time interval in H→H group between first and second stroke is shorter (within 12 years) than in I→I group (within 17 years), and the age of onset was also earlier. Eventually hemorrhagic restroke developed at younger age and had a shorter interval than infarction. These may be due to habitual changes of food intake and increased average life span.

There was a correlation in lacunar type infarction between first and second attack but not-significant statistically in gangliothalamic/thalamic or basal ganglia type.

There are several limitations of this study. The first is that there are many factors which might have affected for the occurrence of restroke i.e. continuous treatment of hypertension and diabetes mellitus, antiplatelet medication, cigarette smoking, alcohol abuse. As these factors can also affect the type or timing of recurrence, the study should have had considered them. But, since many of these patients have usually visited several hospitals in our country, close follow-up evaluation of these factors is nearly impossible, and perfect medical recording is difficult to obtain. Therefore, this study demonstrates the review only from our institution. A second limitation of our study is that the patients who had treated with herb medicine or in the other hospital in follow-up period might have been omitted. A third is that some cases with mild symptoms or who prefer the Oriental medical treatment were disregarded. A fourth problem is that there were difficulties in interpreting infarctions with non-diffusion MRI film in past days. The last is that there were a little cases of second and third restrokes, so proper statistical analysis on these cases were not performed.

The factors which have been associated with an increased risk of recurrent stroke include increasing age²²⁾, hypertension^{14,19)}, initial elevated blood pressure⁵⁾, low blood pressure¹⁰⁾, cigarette smoking⁴⁾, alcohol abuse¹⁸⁾, diabetes mellitus⁹⁾, elevated blood glucose¹⁸⁾, coronary heart disease¹⁵⁾, atrial fibrillation¹³⁾, valvular heart disease and congestive heart failure¹⁵⁾, atherosclerotic disease of the aortic arch⁶⁾, coronary artery disease⁵⁾, and the occurrence of dementia after stroke¹⁵⁾. A reduced risk of recurrent stroke has been associated with a low diastolic blood pressure, no history of stroke, and no history of diabetes⁹⁾. However, no single independent factor consistently has been associated with an increased or decreased risk of recurrence.

To obtain more the precise results in the future we have to choose and match the patients group that have good follow-up data and having well controlled risk factors, and exclude the patients who have above mentioned limitations.

Conclusion

The recurrence rate of stroke was 12.4% (59 of 475 patients). If the first stroke is hemorrhage, the next stroke has had high potentiality of hemorrhage. Also infarction had same tendency. Moreover, the infarction was more frequent than hemorrhage in multiple strokes. There was a correlation in lacunar type infarction between first and second attack. The possibility of second hemorrhagic attack (in H→H type) increases 3.2 times than infarction and in ischemic stroke (in I→I type) increases 3.6 times. In H→H group, the time

interval between first and second stroke is shorter and the age of onset was earlier than in I→I group.

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Commentary

I read with great interest this article which discusses about the recurrent stroke. The authors statistically analysed 59 patients with recurrent stroke and provided valuable information of the epidemiology and characteristics of restroke. I also think that the prevention of recurrent stroke is very important because of its fatal course and severe disability.

In the 10 years follow up study of Hardie et al.¹⁾, the risk of first recurrent stroke was 6 times greater than the risk of first-ever stroke in general population of the same age and sex. And the cumulative 10-year risk of a first recurrent stroke was 40%. Almost one half of survivors remained disabled and one seventh required institutional care. And the cumulative risk of death or new disability was very high.

This single center study may have some limitation to draw out reliable conclusive result. So, I think further cooperative study of multi-center about the risk factor of recurrent stroke is required in order to establish the effective strategies for prevention of recurrent stroke.

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