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Risk factors for multiple recurrent ischemic strokes

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Abstract:

BACKGROUND: Cardiovascular diseases, hypertension, diabetes mellitus, dyslipidemia, and atrial fibrillation are the most common modifiable risk factors for recurrent ischemic stroke. In this study, we aimed to find the risk factors associated with more than two recurrent ischemic strokes after the first-ever stroke.

METHODS: We collected the ischemic stroke patients in our stroke registry data bank, and the eligible patients were followed for recurrent ischemic stroke after 2008. Our study consisted of 927 patients who were followed up for 9 years after the first-ever stroke.

RESULTS: We found that 185 (20%) patients had a recurrent ischemic stroke, and another 32 (3.5%) patients had more than one recurrence after the first-ever ischemic stroke. The mean time for the first stroke recurrence was 1 year, and the mean time for the multiple stroke recurrences was 3 years. Significant risk factors for multiple recurrences were congestive heart disease ($P < 0.015$) and diabetes mellitus ($P < 0.006$).

CONCLUSIONS: We concluded that even with the appropriate treatments, patients with congestive heart disease and diabetes mellitus have a higher rate of multiple recurrences for ischemic stroke after the first-ever ischemic stroke, indicating that more attention should be paid to this issue.

Keywords:

Ischemic stroke, risk factors, stroke recurrence

Introduction

Ischemic stroke is a serious health problem both when it occurs for the first time and when it recurs. Although the risk factors for ischemic stroke are well defined, there may be differences between these risk factors in recurrent strokes. Cardiovascular disease, hypertension, diabetes mellitus, dyslipidemia, and atrial fibrillation are the most responsible modifiable risk factors for recurrent ischemic stroke.[1] Our study was conducted to reveal the risk factors in more than two recurrent ischemic strokes.

Methods

This was a single-center and hospital-based retrospective study and was approved by the noninterventional clinical research ethics committee (No.: 80558721/G-191, on 13 June 2017). Study data were compiled using the Stroke Data Collection Form created by the department of cerebrovascular diseases. The records of patients presenting with ischemic stroke from October 2007 to May 2017 were transferred to the database.

Patients who died after the first stroke, who could not be followed up, or who had incomplete examinations were not included in the study. Among the remaining patients, 927 patients who could be followed for 9 years after the first stroke and whose examinations were completed were included in the analysis.

Ischemic stroke patients were defined by demonstrating lesions with computed tomography or magnetic resonance imaging. Doppler ultrasonography and transcranial

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Doppler sonography of the patients were performed in the neurosonology unit of the department. Stroke subtypes were defined according to the Trial of ORG10172 in acute stroke treatment classification[2] and clinical stroke types according to the Oxfordshire Community Stroke Project classification.[3] Statistical analyses were performed with IBM, SPSS 24.0, Armonk, NY, USA, the parametric data were evaluated with one-way ANOVA, the categorical data were evaluated with the Kruskal–Wallis test, the *post hoc* analyses were done with the Mann–Whitney *U*-test, and odds ratio and confidence interval estimation were done with the crosstabs test.

Results

A single stroke recurrence was seen in 185 (20%) patients, and more than one stroke was observed in 32 (3.5%) of them. The first stroke recurrence was seen after an average of 1 year, and multiple stroke recurrences were seen after an average of 3 years.

The mean age of patients with recurrent stroke was 69.7 ± 12.2 years, and the mean age of patients with multiple recurrent strokes was 64.9 ± 15.8 years, whereas the mean age of patients without recurrent stroke was 68.1 ± 13.7 years; there was no significant difference between groups. Furthermore, there was no significant difference in terms of gender among patients with or without stroke recurrence [Table 1].

In acute treatment, 36 patients with large artery disease received thrombolytic treatment, and nine were treated with mechanical thrombectomy. In secondary prevention, all patients with large artery disease received antithrombotic treatment. An intra-arterial stent was placed in 86 patients and an endarterectomy was performed in 31 of them.

In acute treatment, 262 patients with cardioembolic stroke received thrombolytic treatment, and 16 were treated with mechanical thrombectomy. In secondary prevention, 81 patients with cardioembolic stroke received antithrombotic treatment, and 138 patients received anticoagulant treatment. There was a low level of adherence to preventive treatment in this patient group.

In acute treatment, 16 patients with lacunar infarction received thrombolytic treatment. In secondary prevention, 86 patients with lacunar infarction were on antithrombotic treatment.

In acute treatment, 91 patients with cryptogenic stroke received thrombolytic treatment, mechanical thrombectomy was performed on five patients, and an intra-arterial stent was placed in five patients. In secondary prevention, 176 patients with cryptogenic stroke were on antithrombotic treatment, and four were on anticoagulant treatment.

In acute treatment, six of the patients with stroke due to hematological reasons received thrombolytic treatment. In secondary prevention, three of the patients with stroke due to hematological reasons were under antithrombotic therapy, and six of them were under anticoagulant treatment.

When we evaluated the etiological subtype [Table 2] among patients who had a single stroke recurrence, there were 58/260 patients with large artery disease, 17/90 with small artery disease, 59/297 with cardioembolism, 47/250 with cryptogenic causes, and 1/9 with a hematological cause.

Furthermore, multiple stroke relapses occurred in 10/260 patients with large artery disease, 14/297 patients with cardioembolism, 5/90 patients with lacunar infarction, and 6/250 patients with stroke for cryptogenic reasons. Multiple stroke recurrences were not observed in patients with hematological causes. Although cardioembolism and lacunar infarcts are more common in multiple stroke

Table 1: The age and gender of the patients

	Patients without stroke recurrence (*n*=710)	Patients with recurrent stroke (*n*=185)	Patients with multiple recurrent stroke (*n*=32)	*P*
Age	68.1±13.7	69.7±12.2	64.9±15.8	NS
Gender (women/men), *n* (%)	288/422 (40.6/59.4)	75/110 (40.5/59.5)	12/20 (37.5/62.5)	NS

One-way ANOVA and Kruskal-Wallis test. NS: Not significant

Table 2: Stroke subtypes by etiological classification

	Patients without stroke recurrence (*n*=710), *n* (%)	Patients with single recurrent stroke (*n*=185), *n* (%)	Patients with multiple recurrent strokes (*n*=32), *n* (%)	*P*
Large artery atherosclerosis	192 (27.0)	58 (31.4)	10 (31.3)	NS
Cardioembolism	224 (31.5)	59 (31.9)	14 (43.8)	NS
Lacunar infarction	68 (9.6)	17 (9.2)	5 (15.6)	NS
Hematological	8 (1.1)	1 (0.5)	0	NS
Cryptogenic	197 (27.7)	47 (25.4)	6 (18.8)	NS

Kruskal-Wallis test. NS: Not significant

recurrence, no significant differences were found between multiple stroke recurrences due to etiologic causes.

When the radiologic types of ischemic stroke were evaluated [Table 3], a single stroke recurrence was observed in 13 patients in the total anterior circulation infarcts (TACIs) group, 135 patients in the partial anterior circulation infarcts (PACIs) group, 12 patients in the lacunar infarct (LACI) group, and 44 patients in the posterior circulation infarcts (POCI) group. A single stroke recurrence was significant in patients with PACI ($P < 0.001$).

Multiple stroke recurrences were not seen in patients with TACI ($P < 0.045$). Instead, patients with multiple stroke recurrences had clinical manifestations such as PACI in 23 patients, LACI in three patients, and POCI in eight patients.

According to the radiological classification, 41 (45%) patients with TACI, 22 (3.8%) patients with PACI, and 18 (4%) patients with POCI patients died. There were no deaths in patients with LACI (69 patients).

In the analysis of risk factors [Table 4], although not significant, atrial fibrillation, hyperlipidemia, and smoking rates were found to be high in multiple stroke recurrence patients. Occurrences of coronary artery disease, alcohol usage, obstructive sleep apnea, and patent foramen ovale did not differ between groups. Although hypertension was found to be high in the first recurrent stroke, it was less common in multiple recurrent strokes. Conversely, a single stroke recurrence was significantly higher in patients with congestive heart failure ($P < 0.004$) and diabetes mellitus ($P < 0.009$). In addition, diabetes mellitus was found to be significantly higher in multiple stroke recurrences ($P < 0.036$).

Discussion

There has been no significant change in stroke recurrence in the past 20 years,[4] and large artery disease and cardioembolic strokes have come to the forefront in recurrent strokes.[5] In our study, while the multiple recurrence rate was found to be high in cardioembolic and cryptogenic strokes, it did not make a significant difference. Since the rate of nonadherence to treatment is high in cardioembolic strokes, it may have played a role in multiple stroke recurrences. Although PACI showed a higher rate of recurrence among recurrent strokes, it did not make a significant difference. Since the mortality rate is very low in PACI patients, the recurrence rate may be higher. Similarly, since the mortality rate is higher in TACIs, the risk of recurrence is likely to be low.

In particular, hypertension and diabetes mellitus, atrial fibrillation, angina pectoris, ischemic heart disease, cardiomyopathy, and smoking have emerged as independent risk factors for recurrent strokes.[1,5] As

Table 3: Stroke recurrence data by stroke radiologic subtypes

	Patients without stroke recurrence (*n*=710), *n* (%)	Patients with single recurrent stroke (*n*=185), *n* (%)	Patients with multiple recurrent strokes (*n*=32), *n* (%)	*P*	OR with CI (95%)
TACI	80 (11.3)	13 (7.0)	0	0.045[a]	0.96 (0.94-0.97)
PACI	426 (60.0)	135 (73.0)	23 (71.9)	0.001[b]	1.80 (1.26-2.57)
LACI	54 (7.6)	12 (6.5)	3 (9.4)	NS	
POCI	152 (21.4)	44 (23.8)	8.(25.0)	NS	

[a]Between without recurrence and multiple recurrences, [b]Between without recurrence and single recurrence. Kruskal–Wallis test, *post hoc* analyses with Mann–Whitney test, and crosstabs test for OR and CI. NS: Not significant, OR: Odds ratio, CI: Confidence interval, TACI: Total anterior circulation infarct, PACI: Partial anterior circulation infarct, LACI: Lacunar infarct, POCI: Posterior circulation infarct

Table 4: Distribution of risk factors

	Patients without stroke recurrence (*n*=710)	Patients with single recurrent stroke (*n*=185)	Patients with multiple recurrent strokes (*n*=32)	*P*	OR with CI (95%)
Atrial fibrillation	183 (25.8)	47 (25.4)	11 (34.4)	NS	
Hypertension	471 (66.3)	136 (73.5)	18 (56.3)	NS	
Coronary artery disease	209 (29.4)	68 (36.8)	10 (31.3)	NS	
Congestive heart disease	155 (21.8)	59 (31.9)	9 (28.1)	0.004[a]	1.68 (1.17-2.40)
Diabetes mellitus	209 (29.4)	73 (39.5)	15 (46.9)	0.009[a]	1.56 (1.12-2.19)
				0.036[b]	2.16 (1.04-4.31)
Hyperlipidemia	301 (42.4)	85 (45.9)	16 (50.0)	NS	
Smoking	252 (35.5)	65 (35.1)	14 (43.8)	NS	
Alcohol usage	21 (3.0)	6 (3.2)	2 (6.3)	NS	
OSAS	1 (0.1)	0	0	NS	
Patent foramen ovale	11 (1.5)	0	0	NS	

[a]Between without recurrence and single recurrence, [b]Between without recurrence and multiple recurrences. Kruskal-Wallis test, *post hoc* analyses with Mann-Whitney test, and crosstabs test for OR and CI. NS: Not significant, OR: Odds ratio, CI: Confidence interval, OSAS: Obstructive sleep apnea syndrome

mentioned above, these risk factors have also become more prominent in long follow-up periods after a stroke. In the current study, diabetes mellitus was associated with a single stroke recurrence and multiple stroke recurrences similar to the previous report.[6] According to the Framingham study, hypertension and coronary heart diseases are among the primary risk factors for congestive heart failure. Rheumatic heart valve, diabetes mellitus, hyperlipidemia, and even atrial fibrillation are also included as risk factors. In the presence of these diseases, congestive heart failure occurs as a result of long-term follow-up.[7] In addition, the rate of congestive heart failure in our patient group was found to be higher than expected. A study yielded similar results.[8] Therefore, our results are as anticipated.

Conclusion

Finally, a single stroke recurrence was found to be significantly higher in patients with congestive heart failure and diabetes mellitus in our study. Despite appropriate treatments, diabetes mellitus and congestive heart failure can still lead to stroke recurrence, indicating that more attention should be paid to this issue.

The most important limitation of this study is that it is a retrospective evaluation. In this process, the loss of data on many patients caused a decrease in the number of patients included in the study. Apart from this, although our unit is the most comprehensive examination and treatment center in the region, hospital data do not reflect the entire population. Nevertheless, large differences were not found between population-based studies and hospital-based studies.[7] Still, well-designed population-based studies are needed to identify risk factors for multiple stroke recurrences.

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Conflicts of interest
There are no conflicts of interest.

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