Risk Factors For Recurrent Ischemic Stroke in Turkey

Türkiye'de Reküren İskemik İnme Üzerine Etkili Risk Faktörleri

Esra YALÇIN[1], Murat YALÇIN[2], Yahya ÇELİK[3], Galip EKUKLU[4]

[1]Departments of Neurology, Samsun State Hospital, Samsun;
[2]Departments of Family Medicine, Medical Faculty of Ondokuz Mayıs University, Samsun;
Departments of [3]Neurology and [4]Public Health, Medical Faculty of Trakya University, Edirne

Objectives: The aim of the study is to determine the risk factors for recurrent ischemic stroke.

Patients and Methods: We compared the risk factors in 186 recurrent ischemic stroke patients (94 males, 92 females; mean age 66.85±11.21 years; range 20-95 years) with 300 first-ever stroke patients (control group) among 1150 ischemic stroke patients who had been treated in Neurology Department of Trakya University Medical Faculty over a period of three years.

Results: The recurrence rate was 16.1%. Within the recurrent patients, 89.7% had hypertension, 32.3% had atrial fibrillation, 24.4% had diabetes mellitus, 15.6% had transient ischemic attack, and 57.5% had several types of heart diseases. The most frequent recurrence etiology was embolic according to TOAST criteria (35.5%). Transient ischemic attack (OR= 2.98; 95% CI 1.54-5.76), hypertension (OR= 1.96; 95% CI 1.11-2.64) and atrial fibrillation (OR= 1.74; 95% CI 1.44-2.66) were found as the independent risk factors. The mean of the modified Rankin scores of the study group at their last charge were significantly higher than that of the control group.

Conclusion: Our findings emphasize the importance of the consistent anticoagulation therapy for patients with atrial fibrillation and close blood pressure control in patients with hypertension.

Key Words: Stroke; recurrence; ischemic; risk factors.

Amaç: Bu çalışmada reküren iskemik inmede risk faktörleri belirlendi.

Hastalar ve Yöntemler: Üç yıllık dönemde Trakya Üniversitesi Tıp Fakültesi Hastanesi Nöroloji Kliniği'ne başvuran toplam 1150 hasta içinden reküren inme geçiren 186 hasta (94 erkek, 92 kadın; ort. yaş 66.85±11.21; dağılım 20-95) ilk iskemik inmesini geçiren 300 hasta ile risk faktörleri açısından karşılaştırıldı.

Bulgular: Reküren inme oranı %16.1 idi. Reküren inme grubunda hastaların %89.7'sinde hipertansiyon, %32.3'ünde atrial fibrilasyon, %24.4'ünde diabetes mellitus, %15.6'sında geçici iskemik atak ve %57.5'inde değişik kalp hastalıklarının olduğu gözlendi. Reküren inmenin en sık görülen etyolojik nedeni TOAST sınıflamasına göre kardiyoembolizmdi (%35.5). Geçici iskemik atak (OR= 2.98; %95 CI 1.54-5.76), hipertansiyon (OR= 1.96; %95 CI 1.11-2.64) ve atrial fibrilasyon (OR= 1.74; %95 CI 1.44-2.66) reküren inme için bağımsız risk faktörü olarak bulundu. Hasta grubu ile kontrol grubu modifiye Rankin skoru için karşılaştırıldığında hasta grubunda bu skorun daha kötü olduğu izlendi.

Sonuç: Bizim bulgularımız hipertansif hastalarda kan basıncı kontrolünün, atriyal fibrilasyonlu hastalarda ise etkin antikoagülasyonun reküren inmeyi önlemede önemli olduğunu göstermiştir.

Anahtar sözcükler: İnme; rekürens; iskemik; risk faktörleri.

Correspondence (İletişim adresi): Dr. Yahya Çelik. Trakya Üniversitesi Tıp Fakültesi Nöroloji Anabilim Dalı, 22030 Edirne.
Tel: 0284 - 235 76 41 / 4514   Fax (Faks): 0284 - 235 27 30   e-mail (e-posta): celikyahyatr@yahoo.com

Stroke is the second most common cause of death globally. It claims the lives of about five million people annually, with another 30 suffering, to a greater or lesser extent, from its disabling effects.[1] The patient who is recovering from a stroke is at high risk of stroke recurrence, physical and intellectual disability, long-term institutionalization and death.[2] Recurrence of stroke is the major threat facing these patients and an important public concern. The long-term stroke recurrence rates range from 4% to 14% annually.[3,4] In the Framingham study,[5] the five-year cumulative recurrence rate for atherotrombotic brain infarction was 42% for men and 24% for women. In Rochester study[6] the same ratio was found as 29% with no sex difference. This high frequency of recurrence rates underscores the importance of secondary prevention. While the risk factors for ischemic stroke is relatively clear, there is a lack of knowledge about risk factors for recurrent stroke.[7,8] Although there have been several prospective studies which have identified specific risk factors, etiological features, and prognostic characteristics for recurrent strokes, the results are heterogeneous and remain controversial.[4,5,9] For many years risk factors like age, gender, hypertension, heart diseases, transient ischemic attacks (TIA), atrial fibrillation, diabetes mellitus, hiperlipedemia, alcohol usage and smoking are investigated in their role in recurrence ischemic stroke. But the contradictory results about the risk factors of ischemic stroke in different studies often limits to define ideal strategies in daily practice. Clinicians need more definite waypoints in order to challenge against stroke recurrence.

There are a few studies about this topic in Turkey with considerable lack of data about risk factors of recurrent ischemic stroke. For this purpose we investigated all of the hospitalized recurrent ischemic stroke patients for a period of three years in the Trakya University Department of Neurology in order to identify their risk factors and treatment features.

PATIENTS AND METHODS

Study design

This was a retrospective and consecutive study and we searched the files of the patients who had been treated between the dates January 1, 2000 and December 31, 2002 in Trakya University Medical Faculty Department of Neurology. Over a period of three years, 1150 ischemic stroke patients had been admitted to the department. Among them, 186 patients (94 males, 92 females; mean age 66.85±11.21 years; range 20-95 years) who had recurrent ischemic stroke were accepted as the study group. The control group consisted of 964 patients consequently. Initial and recurrent stroke was defined according to the World Health Organization criteria: Rapidly developed clinical signs of focal disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than vascular origin.[10] The cases that had intracerebral hemorrhage, subarachnoid bleeding and TIA, metabolic disturbances, toxemia and postictal situations were omitted from the study.

Every patient's demographic features and the associated risk factors were investigated from their medical charts. All of the subjects had computerized tomography imaging. Researchers investigated the recurrent ischemic stroke risk factors like hypertension, atrial fibrillation, diabetes mellitus, TIA and heart diseases from the medical charts. Total serum cholesterol, triglyceride and hematocrit values were investigated after their submission to hospital after their last stroke attack. Every patient's smoking status before the stroke attack were noted. Every stroke was classified according to the TOAST (Trial of Org 10172 in Acute Stroke Treatment) criteria that included etiology.[11] Modified Rankin Scale was used to identify the patients' clinical outcomes.[12]

Definition of risk factors

Hypertension was considered present if the systolic blood pressure was at least 140 mmHg or the diastolic blood pressure was ≥90 mmHg on each of two successive readings or if the subject was receiving antihypertensive medication. Diabetes was defined as the nonfasting blood glucose level ≥11.11 mmol/L (200 mg/dl) or the use of insulin or an oral hypoglycemic agent. Hypercholesterolemia was defined as serum cholesterol ≥200 mg/dl. Heart diseases were

Table 1. The baseline characteristics of the recurrence and control groups

| | Recurrence group | | | | | | | Control group | | | | | | |
| | Men | | | Women | | | | Men | | | Women | | | |
	n	%	Mean±SD	n	%	Mean±SD	p	n	%	Mean±SD	n	%	Mean±SD	p
Gender	94	50.5		92	49.5			163	54.3		137	45.7		
Mean age (year)			67.2±12.3			66.5±9.8	0.661			65.1±11.5			68.8±14.4	0.005
Smokers	51	54.8		5	5.45		0.001	88	54.0		16	11.7		0.001
Hypertension	80	48.9		85	51.1		0.226	123	75.4		117	85.4		0.001
Heart diseases	55	56.0		41	44.0		0.405	61	42.9		65	54.0		0.002
Myocardial infarction	11	18.3		13	27.6			27	38.5		9	12.1		
Valvular diseases	6	10.6		2	4.2			1	1.4		7	9.4		
Ischemic diseases	8	13.3		17	36.1			21	30.0		21	28.3		
Congestive heart disease	29	48.3		9	19.1			28	40.0		28	37.8		
Atrial fibrillation	21	31.1		45	68.9		0.001	45	27.6		43	31.3		0.012
Diabetes mellitus	29	52.7		26	47.3		0.306	25	15.3		34	24.8		0.057
Transient ischemic attacks	16	53.3		13	46.7		0.587	13	7.9		4	2.9		0.045
Hypercholesterolemia	40	44.9		49	55.1		0.070	91	55.8		94	68.6		0.023
Hematocrit (%)			42.1±5.4			39.4±5.2	0.001			41.5±5.3			39.3±4.7	0.001
Triglyceride (mg/dl)			143.6±85.1			150.0±78.3	0.611			137.1±73.7			147.7±77.6	0.228
Cholesterol (mg/dl)			196.4±53.8			214.30	0.020			195.9±50.9			222.2±59.7	0.001

defined as a large group of different diseases. This group consists of patients with myocardial infarction, valvular heart disease, ischemic heart disease and heart failure in electrocardiography (ECG). All of these diseases were confirmed with a cardiology consultation. Atrial fibrillation was diagnosed if chronic or paroxysmal atrial fibrillation or atrial flutter was present on electrocardiogram.

Statistical methods

All of the analyses were performed using SPSS (Statistical Package for Social Sciences, version 13.0). Different statistical tests like Chi-square, Mann-Whitney U, Pearson simple correlation and One-way ANOVA Tukey tests were performed to determine the relations between the groups and risk factors. After the known risk factors for ischemic stroke were investigated with univariate analyses, the significant factors were tested in a logistic regression model. A p value <0.05 was accepted as significant.

RESULTS

General characteristics of the study and the control group are shown in Table 1. Twenty-one (9.7%) recurrent ischemic stroke patients were unaware that they had hypertension and

they were significantly younger than the aware group (mean=68.16±9.15 versus 54.63±16.66 years) (Z= 3.510, p<0.001). In the aware group, 35 patients (35.4%) had regulated blood pressure (systolic <140 and diastolic <90 mmHg) at their admission.

Recurrent ischemic stroke ratios

Over a three-year period, 1150 ischemic stroke patients had been admitted to Trakya University. Among them, 186 (16.1%) patients had at least one ischemic recurrence. These patients had a mean of 2.16±0.40 recurrences (min. 2, max. 4). 186 patients had once, 28 had twice and two had three times recurrent ischemic stroke. The
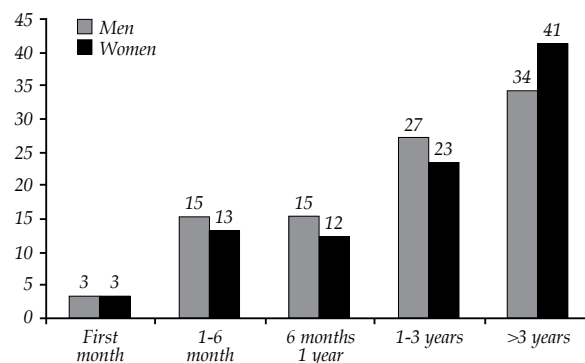

Fig. 1- *The intervals between the index stroke and the first recurrence attack.*

Table 2. Classification of the patients' index stroke and recurrences etiology according to the TOAST criteria

Etiology	Index Stroke		1st recurrence		2nd recurrence		3rd Recurrence	
	n	%	n	%	n	%	n	%
Atherotrombotic	56	30.1	60	32.3	9	32.1	1	50.0
Embolic	61	32.8	66	35.5	8	28.6	0	0.0
Lacunar	58	31.2	49	26.3	10	35.7	1	50.0
Undetermined	11	5.9	11	6.4	1	3.6	0	0.0
Total	186	186	28	2				

TOAST: Trial of Org 10172 in Acute Stroke Treatment.

intervals between the index stroke and the first recurrence is shown in Figure 1.

Etiology and classification

The subtypes of the recurrences according to the TOAST criteria is represented in Table 2. Cardioembolic subtype was the most frequent etiology for both index and first recurrent stroke. There was a significant relation between the age and the TOAST etiological type of the patients in their first recurrence (F=3.793 p=0.004). The patients with an undetermined etiology were the youngest followed by the lacunar, atherothrombotic, and lastly embolic group (mean age=58.45, 64.34, 67.77 and 69.49 years respectively). Seven patients (3.2%) had recurrence within the first month after the index stroke.

Recurrences were generally of the same type as the initial stroke (x^2=12.365, p<0.001) in 152 patients (81.7%). The patients with an index stroke of embolic etiology (n=61) had the same type of recurrence most, followed by undetermined (n=10), atherothrombotic (n=42) and lacunar (n=40) (100%, 90.9%, 75.0%, 67.8% respectively). Indeed, 23 patients (79.3%) who had a second recurrence had their three strokes in the same type.

Risk factors for recurrent stroke

A logistic regression model for age, gender (male), smoking, TIA, hypertension, diabetes mellitus, atrial fibrillation and lipid regulation was tested for recurrence risk factors. In this model TIA (OR=2.98), hypertension (OR=1.96) and atrial fibrilliation (OR=1.74) were found as independent risk factors for ischemic recurrent stroke. The result of the model is shown in Table 3.

Prevention treatment

According to the medical records of the patients, 80 (43.0%) patients were receiving regular antiplatelet or anticoagulant therapy before their first recurrence attack. Fifty-five patients (68.7%) were receiving acetylsalicylic acid in different doses (300 mg [n=48], 100 mg [n=5], 80 mg

Table 3. The logistic regression model for recurrent ischemic stroke risk factors

Variables	B	SE	WALD	P	R	OR	%95 CI	
							Lower	Upper
Transient ischemic attack	1.092	0.336	10.548	0.0012	0.1171	2.980	1.5419	5.7606
Hypertension	0.674	0.288	5.476	0.0193	0.0747	1.934	1.1159	3.4546
Atrial fibrillation	0.557	0.215	6.684	0.0097	0.0867	1.746	1.1444	2.6654
Gender	0.003	0.242	0.002	0.991	0.2541	1.003	0.856	1.254
Age	0.002	0.321	0.365	0.564	0.2454	0.854	0.521	1.002
Smoking	-0.150	0.240	0.376	0.542	1.2541	0.861	0.253	1.025
Diabetes mellitus	0.241	0.236	1.042	0.307	0.5482	1.273	0.568	1.549
Lipid regulation	-0.023	0.001	1.172	0.279	0.6572	0.988	0.368	1.257

[n=2]) and 25 (31.25%) were receiving different antiplatelet therapies (clopidogrel [n=8], ticlopidine [n=48], dipyridamole [n=7]). Two patients (2.5%) were receiving anticoagulation therapy (enoxaparine sodium and warfarin). Forty-seven of the patients (24.2%) were receiving irregular therapy while 61 (32.8%) were receiving none. One of our patients with atrial fibrillation (4.3%) was receiving anticoagulation treatment while 12 other patients (52.2%) were receiving 300 mg antiplatelet treatment.

Patient outcomes

The hospital outcomes of the recurrent patients were worse than control group. They were more disabled. The mean of the modified Rankin scores of the study group (3.26±1.81 points) at their last charge were significantly higher than that of the control group (2.43±1.88 points) (Z=4.867, p<0.001).

DISCUSSION

This study aimed to identify the risk factors of recurrent ischemic stroke in a large cross-sectional sample of Turkish patients. Our results had confirmed the importance of recurrence as a complication of ischemic stroke among our ischemic stroke patients. First of all the recurrence rate was very prevalent (16.1%) and second, the hospital outcomes which were indicated as modified Rankin scores were worse than control group in recurrence patients.

The clinicians treating stroke patients are confronted with the question of how to reduce the risk of a second stroke. The present strategies for prevention can be divided into management of comorbidities, life-style modifications, surgical, and pharmacological interventions.[13] Several comorbidities are known to influence the risk of recurrent stroke. In particular, hypertension, diabetes mellitus, carotid stenosis (>70%) and atrial fibrillation have been shown to be associated with the risk of recurrent stroke.

It was shown that blood pressure levels are directly and continuously associated with the initial occurrence of ischemic stroke.[14] However, there are fewer data about the associations with recurrence. Irei et al.[15] had investigated the

effect of blood pressure in the first admission and during follow-up with the recurrence rates in 368 hypertensive stroke patients. In that study, there was a J-type relation between poststroke diastolic blood pressure and recurrence stroke. The stroke recurrence rate was 3.8% per patient who had a poststroke diastolic blood pressure of 80-84 mm Hg, significantly lower than others. Hier et al.[4] had confirmed the preventing effect of the low diastolic blood pressure (≥100 mmHg) (OR: 1.0) in recurrence stroke. In three other major studies (Copenhagen Stroke Study, North Manhattan Stroke Study and Framingham study)[5,8,16] hypertension was identified as an independent risk factor for ischemic stroke. Lowering blood pressure strongly diminishes the risk for cardiovascular diseases but also few studies have evaluated the effect of antihypertensive treatment after stroke. In the United Kingdom TIA (UK-TIA) Trial, risk for recurrent stroke increased by 28% for every incremental increase of 10 mmHg in systolic blood pressure from 130 and 160 mmHg.[17] The results of the Perindopril Protection Against Recurrent Stroke Study (PROGRESS) showed that the blood pressure is lowered by 9/4 mm Hg on average in the active treatment group resulting in a 28% risk reduction of all kinds of major stroke.[18] This reduction of risk is extended to patients with and without hypertension, and those with and without diabetes. The most beneficial effect was observed in the patient group receiving the combination of perindopril plus indapamide rather than perindopril alone. This result suggested a hypothesis of that, diuretics in addition to their antihypertensive action; confer a specific cerebrovascular effect. Blood pressure-lowering therapy is now established as the most important measure for primary and secondary stroke prevention.[19] In the fact that the hypertension was associated with a 1.9 fold increase in recurrence underlies the importance of close monitoring of blood pressure in hypertensive patients with a previous stroke in our study.

Patients with atrial fibrillation and a first stroke run a high risk of a second stroke, 12% per year in European Atrial Fibrillation Trial (EAFT).[20] While in Warfarin-Aspirin Recurrent

Stroke Study (WARSS)[21] there weren't any difference between aspirin and warfarin for secondary prevention effect in non-cardioembolic stroke, in EAFT, anticoagulation therapy reduced the stroke risk by 75% as compared to 19% by aspirin. In atrial fibrillation and recent TIA or stroke, the number needed to treat any anticoagulation to prevent one event per year is in the range of 12 to 15. In the present study, a 1.7 relative risk of recurrence found in stroke patients with atrial fibrillation, emphasizes the need of routine use of anticoagulation therapy in these patients. Tight control of anticoagulation treatment targeting the International Ratio (INR) between 2.0 and 3.0 should be current practice.[13] But still the physicians are somewhat hesitant to prescribe this kind of treatment and stroke patients with atrial fibrillation have poor compliance.[22]

Although the recurrent subtype was not found as a risk factor for recurrence in this study, in Erlangen Stroke Register[23] the patients with cardioembolic etiology had higher risk for recurrence over a two-year follow-up (22%) than other etiological subtypes. Yamamoto and Bogousslavsky[24] showed that recurrent strokes were most often caused by the same mechanism, as the index strokes and the most frequent type was the embolic etiology. But they pointed out that in many patients, the second and third strokes had different etiologies than the first stroke. They pointed out that the recurrent strokes were often caused by the coexistent pathology, present at the time of the index event but not etiologically related to that event. They assumed that the preventive treatment should be directed to all potential causes of future strokes as well as all remediable stroke risk factors. But the use of anticoagulant therapy in patients who had their index stroke in cardioembolic stroke for secondary prevention is a logical and practical strategy.

As far as we know, this is the only regional study about this topic in Turkey. Although Trakya University is the most advanced referral center in Trakya region, our results might not represent the epidemiological data of the entire area. There might be some patients who was out of our hospital's referral system, neglected very mild symptoms, or had fatal episodes in other medical centers in the study period. These factors might decrease the apparent rate of recurrence rate.

In conclusion, the predictors for recurrence were TIA, hypertension and atrial fibrillation in our study. Our results emphasize the importance of close blood pressure monitoring and control in hypertensive patients and anticoagulation therapy in patients with atrial fibrillation in prevention of recurrence. The reasons for the lack of anticoagulation use in atrial fibrillation patients must be investigated in future researches.

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