Risk Factors That Affect Stroke Recurrence

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ÖZET

İnmelerde tekrarlayıcılığı etkileyen risk faktörleri

Giriş: Tekrarlayan inme, önceki inmenin tamamlanması sonrası yeni gelişen serebrovasküler olaydır. İnme tekrarı, inmeye bağlı özürlülük-ölüm oranını arttırır. İnmeli olguların sistematik olarak değerlendirilmesi, inme tekrarlama riskinin azaltılmasını sağlayabilir

Amaç: Tekrarlama riski taşıyan inmeleri öngörebilmek üzere; risk faktörleri, inme tipi, inme etyolojileri ve inmeye bağlı özürlülük-ölüm oranlarına ilişkin bilgileri karşılaştırmak.

Yöntem: Bakırköy Ruh ve Sinir Hastalıkları Eğitim ve Araştırma Hastanesi nöroloji kliniklerine 1 Haziran 2002 - 28 Şubat 2003 tarihleri arasında başvuran inmeli hastalar, ardışık düzende, prospektif olarak inme veri tabanına kaydedildi. İnmeler; iskemik/hemorajik, ilk/tekrarlayan inmeler olarak gruplandırıldı. Tekrarlayan inmelerde önceki inme bilgileri kaydedildi. Risk faktörleri; hipertansiyon (HT), diabetes mellitus (DM), hiperlipidemi, atriyal fibrilasyon (AF), koroner arter hastalığı (KAH), migren, geçici iskemik atak (GİA) ve ailede serebrovasküler hastalık (SVH) öyküsü, oral kontraseptif (OKS) kullanımı, periferik damar hastalığı (PDH), konjestif kalp yetersizliği (KKY), diğer kalp hastalıkları, sigara ve alkol tüketimi olarak sınıflandırıldı. İnmeye bağlı özürlülük-ölüm oranları değerlendirildi. Tüm veriler ilk ve tekrarlayan inmeler için karşılaştırıldı.

Sonuçlar: Çalışmamızda 631 hasta değerlendirildi. Bu hastaların %52,3'ü kadın, %47,7'si erkekti. İnme sıklığı, 70 yaş üstü kadınlarda istatistiksel olarak yüksekti (p<0,001). İnmeler aynı tipte tekrarlıyordu. HT, ilk ve tekrarlayan inmelerde en yüksek oranda görülen risk faktörüydü. AF sıklığı yaşla birlikte artmaktaydı (p<0,001). Nedeni belirlenemeyen ve kardiyoembolik inmelerde özürlülük-ölüm oranları yüksek bulundu.

Tartışma: Etyolojik grubun bilinmesi inmenin tekrarlayıcılığı ve sağ kalım açısından bir öngörü sağlayabilir. İnme tekrarının en sık görüldüğü inme gruplarında tespit edilen değiştirilebilir risk faktörlerinin daha etkin tedavi edilmesinin, ileri yaştaki kadınlarda kardiyoembolik risk faktörlerinin araştırılmasına öncelik verilmesinin birincil ve ikincil inme korunması açısından önemli olduğunu düşünmekteyiz.

Anahtar kelimeler: İnme, tekrarlayan inme, risk faktörleri.

ABSTRACT

Risk factors that affect recurrence in strokes

Introduction: Recurrent stroke is defined as a new cerebrovascular event which occurs after the stabilization of the previous stroke. Recurrence of stroke increases likelihood of disability-mortality associated with stroke. Systematic evaluation of stroke cases can help to reduce the risk of recurrence.

Objective: In order to predict strokes which carry the risk of recurrence, we aimed to compare data related to risk factors, stroke type, etiology and disability-mortality rates associated with stroke.

Material And Method: Patients with stroke who referred to Bakırkoy Neurological and Psychiatric Diseases Training and Research State Hospital between June 1, 2002 and February 28, 2003 were recorded into the stroke database in a consecutive and prospective manner. Strokes were classified as ischemic/hemorrhagic and first/recurrent. For recurrent strokes, information about previous strokes was also recorded. Risk factors were classified as hypertension (HT), diabetes mellitus (DM), hyperlipidemia, atrial fibrillation (AF), coronary artery disease (CAD), migraine, transient ischemic accident (TIA), family history of cerebrovascular accident (CVA), oral contraceptive use, PAD, congestive heart failure (CHF), other heart diseases, smoking cigarette and alcohol consumption. Disability-mortality rates associated with stroke were evaluated. All data were compared for first and recurrent strokes.

Results: In our study, 631 patients were evaluated, 52.3% of whom were female and 47.7% male. Frequency of stroke was statistically high (p<0.001) in females over 70 years old. Recurrent strokes were of the same type. For the first and recurrent strokes, HT was the highest risk factor. AF frequency increased with age (p<0.001). The rate of disability-mortality was found high in strokes of undetermined and cardioembolic origin.

Conclusion: Knowledge of etiologic group can help to predict recurrence of stroke and prevent death. We think that effective treatment of modifiable risk factors identified in stroke groups where recurrence is the highest, and prioritising the investigation of cardioembolic risk factors in elderly women are significant in terms of primary and secondary stroke prevention.

Key words: Stroke, recurrent stroke, risk factors

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INTRODUCTION

Stroke is the clinical syndrome caused by neurological signs and symptoms that develop due to rapid onset of focal cerebral dysfunction with a vascular cause and that last more than 24 hours. Recurrent stroke is defined as a new cerebrovascular event which occurs after the stabilization of the previous stroke (1). Risk of stroke recurrence varies depending upon the types of cerebrovascular diseases (CVD) and risk factors. The risk of recurrence is highest for all types of cerebrovascular diseases in the first year after the stroke and it decreases gradually over time (2,3).

Cerebrovascular diseases are a leading cause of death and disability and cause individual and socioeconomic losses. Recurrent strokes increase the disability-mortality rates (1,4).

Systematic evaluation of stroke cases can help to identify risk factors and stroke better, to choose the appropriate treatments and to reduce the risk of recurrence. In this study, our objective is to compare data related to risk factors, types of strokes, etiologies and disability-mortality rates associated with stroke in order to predict which strokes carry a risk of recurring.

MATERIALS AND METHODS

Patients with stroke who admitted to Bakırköy Research and Training Hospital for Psychiatry, Neurology and Neurosurgery between June 1, 2002 and February 28, 2003 were included into the stroke database in a consecutive and prospective design.

Strokes were classified as ischemic and hemorrhagic strokes. Both types were classified as first and recurrent strokes and recurrent strokes were grouped according to the number of strokes experienced.

Risk factors were classified as hypertension (HT), diabetes mellitus (DM), hyperlipidemia, atrial fibrillation (AF), coronary artery disease (CAD), migraine, transient ischemic attack (TIA), family history of cerebrovascular accident (CVA), oral contraceptive use, cigarette smoking and alcohol consumption.

The "Trial of ORG 10172 in Acute Stroke Treatment" (TOAST) classification was preferred in ischemic strokes to classify them etiologically (5) (0: Stroke due to large-vessel atherosclerosis, 1: Cardioembolic stroke, 2: Stroke due to small-vessel atherosclerosis, 3: Unidentified cause of stroke, 4: Stroke due to more than one cause, 5: Stroke due to other known causes).

Hematocrite, platelet, triglyceride, cholesterol, HDL, LDL, erythrocyte sedimentation rate, activated prothrombin time and prothrombin time tests were conducted. When further investigations were necessary, VDRL, TPHA, HIV, lupus anticoagulant, antiphospholipid antibodies, homocysteine, FANA, Protein C, Protein S, Factor Leiden V mutation, active protein C resistance, antithrombin III, fibrinogen and cerebrospinal fluid examinations were conducted.

In order to determine the embolism resources, electrocardiography and transthoracic echocardiography were carried out and in necessary cases transesophageal echocardiography was conducted. Computed brain tomography and/or brain magnetic resonance imagining was conducted for all of the patients.

Carotid and vertebral artery Doppler duplex ultrasonography was performed in all patients and in necessary cases "digital subtraction angiography" was conducted as further examination. Predisease disability levels and postdisease disability levels of the patients were evaluated by using the Rankin disability scale. The relationhips between these identified parameters were assessed and the Chi-square test was used for statistical analysis.

RESULTS

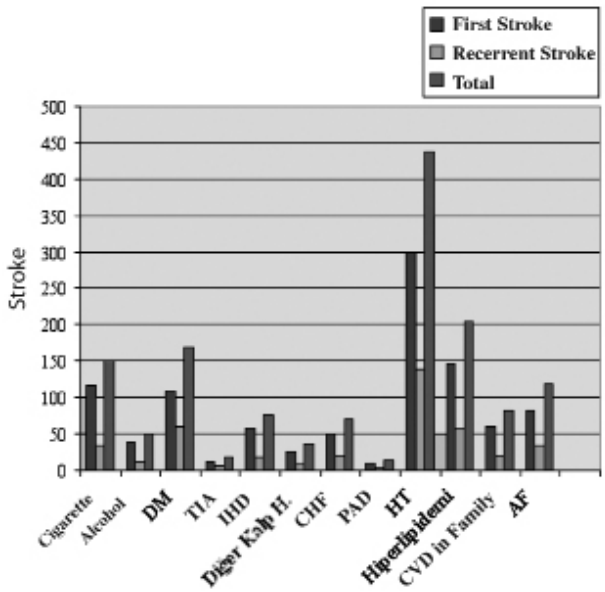
Seven hundred and fourteen patients with stroke diagnosis were included into the stroke database between June 1, 2002 and February 28, 2003 in a consecutive and prospective design. Seventy-three patients were excluded from the evaluation due to TIA diagnosis and 10 patients due to venous infarction. Three hundred and thirty patients (52.3%) of the remaining 631 patients were females and 301 patients (47.7%) were males. The mean age was 67.6 years in females (age range: 17-98) and 54.9 years in males (age range: 14-93). The frequency of stroke was relatively higher in males among patients younger than 70 years old and statistically significantly higher in females among patients over 70 years old ($p<0,001$). Five hundred and thirty-seven of the patients (85.1%) were ischemic type strokes and ninety-four of them (19.9%) were hemorrhagic type strokes (Table 1).

Table 1: The distribution of stroke type according to gender.

Type of stroke	Gender		
	Male	**Female**	**Total**
Ischemic	252 (%46,9)	285 (%53,1)	537 (%85,1)
Hemorrhagic	49 (%52,1)	45 (%47, 9)	94 (%14, 9)
Total	301 (%47,7)	330 (%52,3)	631 (%100)

The patients were grouped as first and recurrent strokes; 461 of them (73.1%) were first strokes and 170 of them (26.9%) were recurrent strokes. In both the first and recurrent strokes, the number of patients increased with advancing age. There was no significant difference between first and recurrent strokes regarding type of strokes.

When the types of strokes were evaluated, the previous stroke in 119 (81%) of 147 ischemic strokes was determined to be the ischemic type and 7 (4.8%) of them were the hemorrhagic type (p<0,001). The type of previous stroke was not determined in 21 (14.2%) of the recurrent strokes. In 10 (43.4%) of the recurrent hemorrhagic strokes, the previous stroke was the hemorrhagic type and 5 (21.7%) of them were ischemic type (p<0,001). These results were



Graph 1: The distribution of risk factors among first and recurrent strokes.

For hypertension in both group, p<0,0001.
DM: Diabetes Mellitus; TIA: Transient Ischemic Attack; IHD: Ischemic Heart Disease; CHF: Congestive Heart Failure; PAD: Peripheral Arterial Disease; HT: Hypertension; CVD: Cerebro Vascular Disease; AF: Atrial Fibrillation

Table 2: The distribution of etiological groups of ischemic strokes in the first and recurrent strokes.

Stroke	Etiological Groups of Ischemic Stroke *						
	0	**1**	**2**	**3**	**4**	**5**	**Total**
First stroke	48 (%12,3)	98 (%25,1)	55 (%14,1)	159 (%40,8)	26 (%6,7)	4 (%1,0)	390 (%72,6)
Recurrent stroke	23 (%15,6)	46 (%31,3)	20 (%13,6)	48 (%32,7)	8 (%5,4)	2 (%1,4)	147 (%27,4)
Total	71 (%13,2)	144 (%26,6)	75 (%14)	207 (%38,5)	34 (%6,3)	6 (%1,4)	537 (%100)

* According to TOAST classification.

Table 3: The distribution of etiological groups of ischemic strokes in the recurrent strokes.

Number of previous strokes	Etiological Groups of Ischemic Stroke *						
	0	**1**	**2**	**3**	**4**	**5**	**Total**
Once	18 (%17,5)	32 (%31,1)	17 (%16,5)	30 (%29,1)	4 (%3,9)	2 (%1,9)	103 (%70,1)
More than one	5 (%11,3)	14 (%31,8)	3 (%6,8)	18 (%40,9)	4 (%9,2)	-	44 (%29,9)
Total number of patient	23 (%15,6)	46 (%31,3)	20 (%13,6)	48 (%32,7)	8 (%5,4)	2 (%5,4)	147 (%100)

* According to TOAST classification.

statistically significant with regard to showing a trend of the same type of stroke for recurrence.

HT was the most frequent and statistically significantly highest risk factor observed in the first and recurrent strokes (in both group p<0,001). The other risk factors were hyperlipidemia, DM, smoking cigarette and AF, respectively. AF frequency increased with age (p<0.001) (Graph 1).

When the first and recurrent ischemic strokes were evaluated with regard to stroke etiologies, unidentified cause of strokes, cardioembolic strokes and strokes due to large-vessel diseases were seen to be the leading causes in both groups, respectively. There was no difference between two groups regarding the ordering of stroke etiologies (Table 2).

In recurrent strokes, the rates of unidentified cause of strokes (n=48; 32.7%) and cardioembolic strokes (n=46; 31.1%) were similar. But in recurrent strokes, while cardioembolic strokes were the most common type (31.1%) in the group with a previous stroke, unidentified cause of strokes was the most common type (40.9%) in the group that had more than one stroke (Table 3).

When the post-stroke disability levels were evaluated, advanced dependency and death were determined in 281 (61%) of first strokes and in 117 (68.8%) of recurrent strokes. There was no difference between the two groups regarding the rates of disability and death. When all recurrent strokes were classified according to etiologic groups, the rates of disability and death were found to be significantly higher in unidentified cause of strokes and cardioembolic strokes (in both groups p<0,001).

DISCUSSION

Cerebrovascular diseases are the leading causes of death, following cardiac diseases and cancer. Moreover, they also result in severe individual and socioeconomic losses by causing disability (4,6-9). Therefore, determination of predisposing factors and more effective treatment of high risk groups for this disease are important (10-12).

Many studies show that stroke rates are higher in men compared to women in the premenopausal period (11,13-15). In our study, we observed that stroke rates in both gender increased with age. There was no significant difference between first and recurrent stroke groups with regard to the age effect. These results are consistent with the literature (7,11,13,14,16,17). But the increase in stroke rate with age was marked in women over 70 years old and this was also statistically significant. This result is consistent with the high stroke rate observed in women over 64 years old and emphasized in the Turkish Multicenter Stroke Study conducted by Özdemir et al. in Turkey (18). The rates of men who had a previous stroke (45%) were found to be lower in the study conducted by Wiliams et al. In the study, this difference was explained by the decrease in number of the older male population at risk due to the impact of other lethal risks (11). In our study, 85% of all strokes were ischemic types and 14.9% hemorrhagic types. There was no difference between first and recurrent strokes regarding type. When the previous strokes in recurrent strokes were evaluated, the previous strokes were ischemic types in 80.9% of the ischemic strokes and hemorrhagic types in 43.4% of the hemorrhagic strokes and these results were statistically significant. The Hisayama study showed that most of the strokes in Japan's population recurred as the same type but the recurrence of lacunar infarction and intracerebral hemorrhage was variable (7,10,19-21).

Hypertension was the most frequently encountered and statistically significantly higher risk factor in the first and recurrent strokes in both the first and recurrent strokes. This finding is consistent with the literature (2,17,22,23). The other risk factors were hyperlipidemia, DM, cigarette smoking and AF, respectively. AF increased statistically significantly with age. This result is similar with the study conducted by Appelros et al. (13). In our study, the cardioembolic strokes were the leading types of strokes in the women and we thought that this condition was consistent with this information.

In the literature, the relation between risk factors and the recurrence of stroke shows considerable variation. According to the Copenhagen study, recurrence is related to TIA, AF, male gender and HT. No significant risk factors were found in the Rochester study (1). Barclay's compiler article emphasizes that the recurrence rate of stroke can be reduced by 30-40%. The same article states that while hyperlipidemia is an important risk factor for the first stroke, its effect is not clear

on the recurrent stroke. DM is correlated particularly with recurrent strokes. The cardioembolic stroke risk in patients with AF was 12% in each year in the study conducted by Boysen et al. Xu et al., found that stroke recurrence was correlated with HT, AF and cigarette smoking in the Chinese population and that getting controlling these risk factors decreased the recurrence rates considerably. The higher recurrence rates in Chinese compared to Western populations were attributed by the authors to modifiable risk factors which were not being managed (2,3,11,12,22-24).

When the etiological classification groups of ischemic strokes were evaluated, unidentified cause of strokes, cardioembolic strokes and strokes due to small vessel diseases were the leading type of strokes, respectively, both in the first and recurrent stroke groups. In many studies, the ordering of etiological groups showed different results in different countries. Cardioembolic strokes and unidentified cause of strokes were the leading type of strokes, respectively, in the study conducted in the USA by Petty et al. (25). Unidentified cause of strokes and cardioembolic strokes were the leading type of strokes, in similar frequencies, in the study conducted in Turkey by Sümer et al. (26). In RESQUE study, strokes due to small vessel diseases, strokes due to large-vessel atherosclerosis and cardioembolic strokes were the most common type of strokes, respectively (2). In the study conducted by Kolomisky et al. in Europe, cardioembolic strokes and strokes due to large-vessel atherosclerosis were the most common type of strokes, respectively (17). Kolomisky compared their study with Rochester and NOMASS cohort studies. Their results differed from the aforementioned studies and they explained this condition with the methodological differences. An example given for these differences was the inclusion of strokes developed due to various procedures in the Rochester study. The rate of these strokes was close to 31% and this group was in the stroke group due to large-vessel atherosclerosis. Again in the same study, recurrence rate of strokes due to large-vessel atherosclerosis were also found to be correlated with different distribution of risk factors in observed population. HT was higher in the Rochester and NOMASS studies compared to their own study. The other potential cause of difference is that both studies took place before 1990 (Rochester; 1985-1989, NOMASS; 1983-1988);early secondary stroke prevention was developed within the last decade in the USA and so risk factors have been partially managed since that time (17). Some of the differences between the studies also arise from methodological differences in hospital-based studies and population-based studies (17,26,27). For recurrent strokes, again, unidentified causes of strokes are the leading type of strokes in subgroup with more than one stroke. In addition, non-cardioembolic vascular risk factors in unidentified cause of strokes are relatively higher compared to the individuals who experienced a stroke earlier. We think that similar factors affect our results. The absence of further tests for most patients due to socioeconomic reasons might have also affected the rates of unidentified strokes in our study.

In letter to the editor, Cheung stated that 77% of the cardioembolic strokes, 65% of nonlacunar noncardiembolic strokes, 58% of intracerebral hemorrhages and 48% of lacunar infarcts in the study conducted by Yamamoto and Bogausslavky recurred in similar type with the first stroke (28). In the study conducted by Lovett et al., the recurrence rate in strokes due to large-vessel atherosclerosis was the highest. (29). The highest recurrence rate was found in cardioembolic strokes and the lowest recurrence rate for strokes due to large-vessel atherosclerosis at the end of a two year follow-up performed by Kolomisky et al. Again in the same study, the authors found that the survival rates of the individuals with strokes due to small vessel disease were 3 times higher than the survival rates of the individuals with cardioembolic strokes. With this result, they emphasized that TOAST classification could provide a significant prediction for long-term survival (17). When we evaluated cardiologic history of the patients in our study, we found that the recurrence trends of cardioembolic and unidentified cause of strokes and disability-death rates in unidentified cause of strokes was high. Therefore, we believe that TOAST groups can provide a limited prediction regarding the rates of stroke recurrence and disability and death.

According to the results of our study, we believe that knowledge of the etiologic group can help to predict recurrence of stroke and survival. Although stroke types vary according to the population in

which they are observed, follow-up of the strokes based on a certain classification can provide guidance for further planning. We think that more effective treatment of modifiable risk factors such as HT, DM and hyperlipidemia identified in stroke groups where recurrence is the highest before the stroke and after the first stroke, and prioritizing the investigation of cardioembolic risk factors in women over 70 years old, has great importance in terms of primary and secondary stroke prevention.

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