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Original Article / Özgün Araştırma

Etiologic Subtypes, Risk Factors and Early Outcome of Acute Ischemic Stroke in Females

Kadınlarda Akut İskemik İnmenin Etiyolojik Alt Tipleri, Risk Faktörleri ve Erken Dönem Prognozu

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Abstract

Objective: It has been reported that the mortality due to ischemic stroke is higher and the prognosis is worse in women compared with men. The aim of this study was to determine the etiologic subtypes, risk factors, and prognosis of acute ischemic stroke (AIS) in females.

Materials and Methods: We reviewed the medical records of 957 patients who were admitted with AIS between January 2011 and May 2017. The patients' records were analyzed and the demographic data, risk factors, National Institutes of Health Stroke Scale (NIHSS) scores at admission, and modified Rankin Scale (mRS) in the follow-up were recorded. We determined etiologic stroke subtypes using the Automated Causative Classification System.

Results: In the study, 432 (45.1%) female patients [mean age: 71.2±14.7 (range: 21-100) years] and 525 (54.9%) male patients [mean age: 67.2±12.9 (range: 25-103) years] were included. The women were older than the men ($p<0.001$). Atrial fibrillation (AF) and congestive heart failure were more common in females ($p<0.001$). Otherwise, coronary artery disease was more common in males ($p<0.001$). NIHSS score at admission and the number of patients with mRS scores over 2 in the follow-up after discharge were higher in female patients than in male patients ($p<0.05$). The most common ischemic stroke etiology in females was cardioembolism (48.4%), whereas it was in major large artery atherosclerosis in males (31.6%). On logistic regression analysis, AF and cardio-aortic embolism were significantly associated with female sex ($p<0.05$).

Conclusion: In our series, AIS was more severe and caused more disability in females compared with males. AF was more common as an underlying etiology of ischemic stroke in females. These results reveal the importance of AF screening and anticoagulant treatment prophylaxis in the older female population.

Keywords: Acute ischemic stroke, female, ischemic stroke etiology, risk factors

Öz

Amaç: Kadınlarda erkeklere göre iskemik inmeye bağlı mortalitenin daha yüksek ve prognozun daha kötü olduğu bildirilmiştir. Bu çalışmanın amacı kadınlarda akut iskemik inmenin (Aİİ) etiyolojik alt tiplerini, risk faktörlerini ve erken dönem prognozunu belirlemektir.

Gereç ve Yöntem: Ocak 2011 ve Mayıs 2017 arasında Aİİ nedeniyle hastanemize başvuran 957 hasta çalışmaya alınmıştır. Hastaların kayıtları incelenerek demografik verileri, risk faktörleri, başvuru Ulusal Sağlık İnme Enstitü Ölçeği (NIHSS) skorları ve taburculuk sonrası modifiye Rankin Skalası (mRS) skorları ile klinik seyirleri kaydedilmiştir. İnme subtipleri otomatize "The Automated Causative Classification System" kullanılarak tespit edilmiştir.

Bulgular: Hastaların 432'si kadın (%45,1), 525'i erkekti (%54,9). Kadın hastaların ortalama yaşı 71,2±14,7 iken, erkek hastalarınki 67,2±12,9 olarak saptandı. Aİİ ile başvuran kadın hastaların erkeklere göre daha ileri yaşta olduğu görüldü ($p<0,001$). Atriyal fibrilasyon (AF) ve konjestif kalp yetmezliğinin kadınlarda daha fazla olduğu saptandı ($p<0,001$). Öte yandan koroner arter hastalığı erkeklerde daha fazla idi ($p=0,001$). Ortalama NIHSS skoru kadınlarda anlamlı olarak daha yüksekti ($p<0,001$). Rekürren inme ve hastanedeki mortalite oranları açısından fark saptanmazken, taburculuk sonrası mRS 2 veya üzerinde olan hastaların sayısının, kadın grubunda anlamlı olarak daha yüksek olduğu görüldü ($p=0,021$). Kadınlarda en sık görülen iskemik inme etiyolojisi kardiyoembolizm (%48,4) iken, erkeklerde büyük arter aterosklerozuydu (%31,6). Çoklu regresyon analizi yapıldığında Aİİ'li hastalarda kadın cinsiyet ile AF ve kardiyo-aortik embolizm arasında anlamlı ilişkili bulunmuştur ($p<0,05$).

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Sonuç: Bizim serimizde kadınlarda Aİİ'nin daha şiddetli geliştiği ve daha fazla özürlülük yarattığı tespit edilmiştir. Kadın hastalarımızda öncelikli altta yatan inme nedeninin AF olduğu görülmüştür. Bu veriler; ileri yaş kadın popülasyonda AF taramalarının ve antikoagülan tedavi profilaksisinin önemini ortaya koymaktadır.

Anahtar Kelimeler: Akut iskemik inme, kadın, etiyoloji, risk faktörleri, prognoz

Introduction

Sex is among the unmodifiable risk factors for ischemic stroke. Studies have reported that stroke severity, mortality, and functional outcomes differ between the male and female (1,2,3,4,5,6,7, 8, 9,10,11,12,13,14,15,16,17,18,19,20,21,22). The lifetime risk of stroke is higher in women because the average life expectancy of women is longer than for men (22). However, in some studies, it has been reported that the mortality due to ischemic stroke is higher and the prognosis is worse in women aged 55-75 years compared with men (16,17,18).

The aim of this study was to determine the etiologic subtypes, risk factors, and prognosis of stroke in women who were admitted to our hospital with acute ischemic stroke (AIS) or transient ischemic attack (TIA).

Materials and Methods

The records of patients admitted to our hospital with AIS or TIA between January 2011 and May 2017 were retrospectively reviewed and included in the study. The study was initiated after it was approved by the Ankara University Ethics Committee (date: 13.07.2020, decision number: İ6-377-20). Informed consent forms were signed by all patients. Patients with hemorrhagic stroke were excluded from the study. The age, sex, among the risk factors of ischemic stroke in their history such as hypertension, diabetes mellitus, atrial fibrillation (AF), coronary artery disease, congestive heart failure, previous ischemic stroke or TIA the National Institutes of Health Stroke Scale (NIHSS) score at admission, location of acute ischemic lesion on diffusion magnetic resonance imaging (MRI), and modified Rankin Scale (mRS) score after discharge were recorded. The localization of the acute ischemic lesion in diffusion MRI was recorded as multiple if there were acute ischemic lesions in the anterior, posterior or both circulation areas. Electrocardiography, computed tomography or MR angiography, transthoracic/transesophageal echocardiography, rhythm Holter examinations performed for the etiology of stroke of the patients were evaluated and stroke subtypes were determined using the automated Causative Classification System (CCS). Follow-up mRS, mortality, and recurrent stroke rates of the patients were determined at discharge. Risk factors, stroke severity, etiologic subtypes, and early prognosis in women were compared with men.

Statistical Analysis

The analysis of the data was performed using the SPSS Windows 15 package program. Descriptive statistics are shown as mean ± standard deviation for variables with normal distribution, as median (min-max) for variables without normal distribution, and as the number of patients and percentage (%) for nominal variables. When the number of groups was two, the significance of the difference between the groups in terms of means was investigated using the t-test, and the significance of the difference in terms of median values was investigated using the Mann-Whitney U test. When the number of groups was more than two, the significance of the difference between the groups in terms of means was investigated using One-Way ANOVA, and the significance of the difference in terms of median values was investigated using the Kruskal-Wallis test. Nominal variables were evaluated using Pearson's chi-square or Fisher's Exact test. The risk factors affecting the dependent variable were determined using logistic regression analysis. A p value <0.05 was considered statistically significant.

Results

In the study, 957 (AIS n=886, and TIA n=71) patients who were screened retrospectively were included. Of the patients, 432 were female (45.1%) and 525 were male (54.9%). The mean age of the female patients was 71.2±14.7 years, and that of male patients was 67.2±12.9 years. It was observed that female patients presenting with AIS were older than men ($p<0.001$) (Table 1).

AF and congestive heart failure were found to be significantly more frequent in women ($p<0.001$). On the other hand, coronary artery disease was more common in males ($p=0.001$). The mean NIHSS score was significantly higher in women ($p<0.001$). There was no difference in terms of recurrent stroke and hospital mortality rates. The outpatient clinic follow-up information of 508 patients was reached and it was observed that the number of patients with an mRS score above 2 was significantly higher among the women ($p=0.021$) (Table 1).

Diffusion MRI was not performed in 78 patients. No acute ischemic lesion was detected in the diffusion MRI of 52 patients. Acute ischemic lesions in the anterior circulation were more common in female patients, whereas acute ischemic lesions occurring in the posterior circulation and both circulations at the same time were more common in male patients ($p=0.036$) (Table 2).

The most common ischemic stroke etiology in women was cardio-aortic embolism (48.4%), whereas it was large artery atherosclerosis (31.6%) in men (Table 3).

In multiple regression analysis, female was found to be significantly associated with AF and cardio-aortic embolism in patients with AIS ($p<0.05$) (Table 4).

Discussion

In this study, 957 patients who were admitted to our hospital's neurology clinic with a diagnosis of AIS between January 2017 and April 2019 were retrospectively evaluated. It was observed that female patients presenting with AIS were older than the men. AF and congestive heart failure were significantly more frequent in women, and coronary artery disease was more common in men. Acute ischemic lesions in the anterior circulation, the mean NIHSS score at admission, and the number of patients with follow-up mRS scores above 2 were found to be significantly

Table 1. Epidemiologic and clinical characteristics of male and female patients with acute ischemic stroke			
	Female n=432	**Male n=525**	**p**
Age, year, mean ± SD	71.2±14.7	67.2±12.9	**<0.001**
Risk factors			
Hypertension, n (%)	317 (73.4)	361 (68.8)	0.118
Diabetes mellitus, n (%)	137 (31.7)	168 (32)	0.924
Known AF, n (%)	112 (25.9)	55 (10.5)	**<0.001**
Hyperlipidemia, n (%)	88 (20.4)	132 (25.1)	0.081
CAH, n (%)	80 (18.5)	160 (30.5)	**<0.001**
CHF, n (%)	65 (43)	43 (8.2)	**0.001**
Prior TIA history, n (%)	33 (7.6)	48 (9.1)	0.406
Prior stroke history, n (%)	73 (16.9)	112 (21.3)	0.084
First NIHSS score, mean ± SD (min-max)	6.5±4.9 (0-27)	5.4±4.7 (0-26)	**<0.001**
CRP, mg/l	25.01±40.68	27.52±50.14	0.170
In-hospital mortality, n (%)	49 (11.3)	49 (9.3)	0.308
Follow-up mRS >2, n (%)	98/225 (44.3)	95/283 (33.6)	**0.021**
Recurrent stroke, n (%)	37 (8.6)	56 (10.7)	0.271

SD: Standard deviation, NIHSS: National Institutes of Health Stroke Scale, mRS: Modified Rankin Scale, DM: Diabetes mellitus, AF: Atrial fibrillation, CVH: Cardiovascular disease, CAD: Coronary artery disease, CHF: Congestive heart failure, TIA: Transient ischemic attack, min: Minimum, max: Maximum

Table 2. Location of acute ischemic lesions in diffusion MRI			
	Female n=381	**Male n=446**	**p**
Location of acute ischemic lesions			
Anterior circulation	284 (74.5)	296 (66.4)	
Posterior circulation	75 (19.7)	105 (23.5)	**0.018**
Multiple (anterior + posterior circulation)	22 (5.8)	45 (10.1)	

MRI: Magnetic resonance imaging

Table 3. Etiologic subgroups of ischemic stroke			
	Female n=432	**Male n=525**	**p**
CCS			
LAA	75 (17.4)	166 (31.6)	
CE	209 (48.4)	165 (31.4)	
SVD	23 (5.3)	27 (5.1)	**<0.001**
OC	31 (7.2)	31 (5.9)	
Stroke of unknown etiology	94 (21.8)	136 (25.9)	

CCS: Causative Classification System, LAA: Large artery atherosclerosis, CE: Cardio-aortic embolism, SVD: Small vessel disease, OC: Other causes

Table 4. Multiple regression analysis of female patients with acute ischemic stroke			
	Beta	**95% CI**	**p**
AF	0.12	0.38-2.83	0.01
CE	0.101	0.9-2.01	0.032

CE: Cardio-aortic embolism, AF: Atrial fibrillation, CI: Confidence interval

higher in women. In terms of ischemic stroke etiology, the most common stroke subtype according to CCS was found to be cardio-aortic embolism (48.4%) in women and large artery atherosclerosis (31.6%) in men (p<0.05). In multiple regression analysis, AF and cardio-aortic embolism were found to be significantly associated with AIS in female (p<0.05).

In the Middle East and North African countries, stroke mortality is higher in women. In developing countries other than these countries, it has been reported that the incidence, prevalence, and mortality of stroke is higher in men than in women. In European countries, the incidence of stroke is higher or similar in women (1). According to the 2019 statistics of the American Heart Association, the prevalence of stroke was similar between women and men between the ages of 20-59 years, whereas it was found to be higher in men aged 60-79 years and women aged 80 years or over (2). It is important to focus on stroke epidemiology in older women because women live longer than men and have a higher lifetime risk of stroke (after age 50, 17% for women vs. 15% for men) (3,4).

Blood pressure levels increase in women after menopause. Ullberg et al. (5) were reported that the rates of hypertension in patients with stroke were found to be higher in women (60%) compared with men (56%) (p<0.001). It was observed that there was no difference between men and women in terms of the effect of hypertension on stroke risk (6).

The effect of AF on stroke risk is greater in women than in men. In previous studies, it was shown that AF caused two fold higher risk of stroke in women compared with men and that the severity of stroke due to AF was more severe in women than in men (7,8). In the Framingham study cohort, women with diabetes were found to have a 3.5-fold increase in stroke risk compared with non-diabetic women, and men with diabetes were found to have a 2.1-fold increase in stroke risk compared with men without diabetes (11). In a meta-analysis that systematically evaluated 64 cohort studies, women with diabetes had 27% more stroke than men with diabetes (12). In a prospective diabetes study conducted in England, it was found that stroke-related fatality increased two-fold in women with diabetes mellitus compared with men (13). In the study conducted by Ho et al., the risk of fatal stroke in women with diabetes was found to be similar to women with a previous history of stroke but who were not diabetic (14).

In a meta-analysis by Peters et al. (15), dyslipidemia was shown to pose a slightly higher risk for stroke in men. However, when only the relative risk in terms of ischemic stroke was evaluated, no difference was found between the sexes (15). Women have been reported to have a poor prognosis after stroke than men, but this might be the result of having a stroke at an older age, worse pre-stroke functional status, and multiple comorbidities in women. However, in the study conducted by Lisabeth et al. (9), it was reported that women still had poor outcomes when the contribution of these factors was also eliminated.

In the study conducted by Hung et al. (16), 403 patients (female: 170, male: 233) who had their first AIS were included. There was no difference between the groups in terms of stroke severity, stroke subtypes, and co-morbidities. Outcomes of women were found to be worse, but female sex was not found to be a predictor of poor outcome. Age of 75 years or above, NIHSS score 8 or above, cardiac embolism, and large artery atherosclerosis were found to be predictors of poor outcome at 3 months. In the subgroup analysis, cardiac embolism, i.e. AF, in women, and large artery atherosclerosis in men were found to be independent predictors for poor outcome (16). In the study conducted by Gargano ve Reeves (17) 373 (femal: 210, male: 163) patients with AIS were included. It was found that the functional recovery at the end of the third month was less and the quality of life was worse in female patients (17).

In the study conducted by Caso et al. (18), 1.136 (female: 494, male: 642) patients with AIS were included. In that study, female patients were older and had higher NIHSS scores (p=0.002). Cardiac embolism was common in women (p=0.004), and lacunar stroke (p=0.002) and large artery atherosclerosis (p=0.01) were common in men. The mRS score at the end of the third month was higher in women (p=0.003). In multiple regression analysis, female sex was not found to be associated with poor outcome (18). In the study by Stróżyńska et al. (19), 185 (female: 100, male: 85) patients with AIS were included. AF (female 51%, male 22.4%), coronary artery disease (female 49%, male 28.2%) and acute ischemic lesions in the anterior circulation (female 37%, male 10.6%) were more common in female patients (p<0.05). In the study conducted by Frid et al. (20), 2.381 (female: 927, male: 1.454) patients with AIS who underwent diffusion-weighted MRI were included. Acute ischemic lesions in the posterior circulation in male patients (female: 231, 32%, male: 487, 68%, p<0.001) were significantly higher (20). In a prospective study by Foroozanfar et al. (21), 703 (female: 260, male: 443) patients with AIS were included. The mean age of the female patients was higher. In addition, stroke was more severe in female patients (NIHSS >16, female 4.6%, male 2.9%, p=0.007) and functional status was worse (mRS >2, female 55.4%, male 46.5%, p=0.023). The 28-day mortality rate was higher in females (8.17%) than in males (6.08%), although it was not statistically significant (p=0.299). Sex differences should be taken into account for us to better manage patients with stroke (21).

Study Limitations

While interpreting the results of this study, several limitations should be taken into account. The weaknesses of our study were that our study was conducted in a single center, that only inpatients were evaluated, and that patient records were analyzed retrospectively.

Conclusion

As a result, in our study, the severity of stroke and the prognosis after discharge were found to be worse in female patients. The worse prognosis in women after discharge might be due to higher NIHSS scores in women. In addition, the rate of cardio-aortic embolism was significantly higher in women. Previous studies have also reported that the severity of stroke due to AF was more severe in women than in men, and the prognosis of stroke due to cardio-aortic embolism was worse in women. Higher NIHSS scores in women and poor prognosis in follow-up may be associated with the incidence of stroke due to cardio-aortic embolism. In multiple regression analysis, the significant relationship between female sex and AF and cardio-aortic embolism was preserved in patients

with AIS. These data reveal the importance of AF screening and anticoagulant therapy prophylaxis in the older female population.

Ethics

Ethics Committee Approval: The study was initiated after it was approved by the Ankara University Ethics Committee (date: 13.07.2020, decision number: İ6-377-20).

Informed Consent: Informed consent forms were signed by all patients.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: M.H.S., C.T.I., Design: M.H.S., C.T.I., Data Collection or Processing: E.A.B., Z.Ö.A., T.A., O.B., S.E., F.T.K., A.N., B.Ö., C.Ö., T.Ş., Ö.E.Y., Z.Y., A.Y.Y., Analysis or Interpretation: E.A.B., M.H.S., M.E., C.T.I., Literature Search: E.A.B., C.T.I., Writing: E.A.B., M.H.S., C.T.I.

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