Original Article

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Ischemic Stroke Severity, Stroke Types and Early Mortality in Patients with End-stage Renal Disease

Son Dönem Böbrek Yetmezliği Olan Hastalarda İskemik İnme Şiddeti, İnme Tipleri ve Erken Dönem Mortalite

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ABSTRACT

Objective: To compare the demographic characteristics, vascular risk factors, stroke subtypes and early prognosis of patients with end-stage renal disease (ESRD)/normal renal function (NRF) with acute ischemic stroke (IS).

Methods: Demographic data and vascular risk factors of patients with acute stroke between August 1 2013-April 1 2015 were determined. Patients diagnosed with ESRD who were receiving dialysis treatment with a glomerular filtration rate below 15, were included in the study. Stroke severity was determined by using the National Stroke Health Stroke scale. To determine the types of IS, "Trial of Org 10172 in Acute Stroke Treatment" TOAST criteria were used. Deaths during hospitalization were used to determine early mortality.

Results: Of the 132 patients included in the study, 33.3% had ESRD and 66.6% had normal renal functions (NRF). Demographic characteristics and risk factors did not differ between ESRD and NRF groups. When stroke types were compared, it was determined that stroke with undetermined etiology with more than one etiology was higher in ESRD patients. Of all patients 10.6% died in hospital and this rate was 20.5% in ESRD patients. In the regression analysis, the presence of ESRD increased hospital mortality significantly (risk ratio: 11.6, 95% confidence interval 1.7-77, p=0.011).

Conclusion: Our results showed that more than one etiology was seen in acute IS patients with ESRD and ESRD significantly increased the risk of hospital mortality.

ÖZ

Amaç: Çalışmamızda akut iskemik inme (İİ) saptanmış son dönem böbrek yetmezliği (SDBY) olan ve böbrek fonksiyonu normal saptanan hastaların demografik özelliklerinin, vasküler risk faktörlerinin, inme alt tiplerinin ve erken dönem prognozunun karşılaştırılması amaçlanmıştır.

Yöntemler: Akut iskemik inme tanısıyla 1 Ağustos 2013-1 Nisan 2015 arasında başvuran hastaların demografik verileri ve vasküler risk faktörleri belirlendi. Glomerüler filtrasyon hızı 15 altında olan ve diyaliz tedavisi alan SDBY tanılı hastalar belirlenerek çalışmaya dahil edildi. İİ tipinin belirlenmesinde "Trial of Org 10172 in Acute Stroke Treatment" TOAST kriterleri kullanıldı. Hastaların inme şiddeti Ulusal İnme Sağlık ölçeği (NIHSS) ile belirlendi. Erken dönem mortalitenin belirlenmesinde hastane yatışı sırasındaki ölüm oranları kullanıldı.

Bulgular: Çalışmaya dahil edilen 132 hastanın %33,3'ünde SDBY varken geriye kalan %66,6'sında böbrek fonksiyonları normal bulundu. SDBY olan ve olmayan grup arasında demografik özellikler ve risk faktörleri farklılık göstermedi. İnme tipleri karşılaştırıldığında ise, SDBY olanlarda birden fazla etiyolojiye bağlı sebebi bilinmeyen inmenin daha yüksek oranda olduğu belirlendi. Tüm hastaların %10,6'sı hastanede eks olmuş olup, bu oran SDBY olanlarda %20,5 olarak bulundu. Regresyon analizinde SDBY varlığı hastanede ölüm oranını anlamlı derecede yükseltmekteydi (risk oranı: 11,6, %95 güven aralığı 1,7-77, p=0,011).

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Keywords: Stroke, end-stage renal disease, risk factors, stroke subtypes, early prognosis

Sonuç: SDBY olan akut İİ hastalarında birden fazla etiyolojinin daha fazla görüldüğünü ve SDBY'nin hastanede ölüm riskini anlamlı derecede yükselttiğini göstermiştir.

Anahtar Sözcükler: İnme, son dönem böbrek yetmezliği, risk faktörleri, inme alt tipleri, erken dönem prognoz

Introduction

Renal failure is a strong risk factor for cerebrovascular disease [(CVD), stroke], which is one of the most important causes of mortality and disability worldwide. It has been reported that patients with end-stage renal disease (ESRD), especially receiving dialysis treatment, have stroke 5-30 times more than the population without kidney disease. Although the case fatality rate differs among stroke subgroups, it reaches up to 90% (1). It has been stated that the increased risk of stroke in chronic renal failure (CRF) is associated with the interaction of renal failure-specific factors such as vascular comorbidities, malnutrition-inflammation-atherosclerosis complex, fluid overload, toxic molecules that cannot be excreted, and disruption of the coagulation mechanism. The reason why one third of the developing strokes are seen in the first 30 days following the start of dialysis has been attributed to the more frequent observation of risk factors such as diabetes, hypertension (HT), previous CVD and hyperlipidemia (HL) (1,2). For a disease such as CVD with a high incidence, disability and mortality, determining the risk factors and knowing the modifiable or non-modifiable factors that may affect the early and late prognosis gain importance in terms of both early treatment and preventive medicine. In our study, it was aimed to compare the demographic characteristics, risk factors, ischemic stroke (IS) subtypes, stroke severity, stroke subgroups and early death in acute IS patients with and without ESRD, and to investigate the effect of ESRD on stroke severity, subtype and early mortality.

Methods

In our study, all patients who were hospitalized, examined and treated in the neurology service and/or intensive care unit with the prediagnosis of IS in Van Regional Training and Research Hospital between January 1 2014 and August 1 2015, were retrospectively scanned. Being over the age of 18 was accepted as an inclusion criterion. The diagnosis of stroke was made by using computed brain tomography and diffusion-weighted imaging and apparent diffusion coefficient magnetic resonance imaging findings at the first admission. Patients with no signs of stroke in their cranial imaging and those with metabolic pathologies mimicking stroke (hypoglycemia, hyponatremia, etc.) were excluded from the study. Demographic data and risk factors of the patients were recorded. The following criteria were used to determine risk factors: systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg or using antihypertensive medication for HT; fasting blood glucose >140 mg/dL in 2 consecutive measurements or >200 mg/dL in glucose challenge test or using antidiabetic medication for diabetes mellitus (DM); stable or unstable angina pectoris, previous MI, diagnosis of coronary artery disease (CAD) with coronary angiography and therefore taking medication for CAD; total cholesterol >200 mg/dL, triglyceride >150 mg/dL low density lipoprotein cholesterol ≥100 mg/dL, high density lipoprotein cholesterol <40 mg/dL; or the use of antihyperlipidemic drugs for HL. Patients receiving dialysis treatment were patients with a calculated glomerular filtration rate (GFR) of less than 15 during their clinical follow-up or prior to hospitalization and undergoing dialysis.

All investigations for the etiology of stroke were reviewed. Stroke types of patients according to the TOAST criteria (3) were as follows: large artery atherosclerosis (LAA), small vessel occlusion (SVO), cardioembolism (CE), stroke of other determined etiology (SODE), and stroke of undetermined etiology (SUE). LAA was defined as more than 50% stenosis or occlusion in large vessels in MR angiography, CT angiography, or carotid and vertebral arteries doppler ultrasonography ipsilateral to the brain region where symptomatic stroke occurred. The diseases with or without atrial fibrillation (AF) leading to thrombus formation in the heart such as rheumatic heart disease, nonvalvular valve disease, sick sinus syndrome, recent heart attack, cardiac vegetation, akinetic left ventricle, atrial myxoma, dilated cardiomyopathy, prosthetic heart valve, and paradoxical embolism were accepted as sources of CE. Patients with one of the lacunar syndromes characterized by clinical findings, infarcts of less than 1.5 cm in neuroimaging and exclusion of CI and LAA were classified as having SVO. Rare diseases such as vasculopathies and hematological disorders without atherosclerosis, carotid and vertebral artery dissection, arteritis, migraine, diseases such as substance abuse vasculopathy, fibromuscular dysplasia, radiation arteritis, protein C and protein S deficiencies, antithrombin 3 deficiency, and IS due to other coagulation disorders were designated as SODE. The SUE group, on the other hand, was considered as those in whom no etiology could be found despite further evaluations, or those who were found to have two or more causes or those who were examined insufficiently.

The stroke severity of the patients was determined according to the The National Institutes of Health Stroke scale (NIHSS). Length of stay and hospital mortality status of all patients were noted. In order to determine the functional status of patients after stroke, the modified Rankin scale (mRS) score was recorded at the first admission and on the 15th day (4,5).

Statistical Analysis

The study was approved by the local ethics committee. After all data were collected in the SPSS 20 database, patients with ESRD and patients with normal renal functions (NRF) were compared in terms of demographic characteristics, vascular risk factors, IS etiology, stroke severity, and early functional outcome. Most of

the results were evaluated by descriptive statistical methods. Chi-square test was used in the analysis of ordinal variables. In the analysis of numerical variables, the Student's t-test was used for normally distributed data and the results were given as mean ± standard deviation, while the data were given as interquantile range when the Mann-Whitney U test was used for data that did not show normal distribution. Binary logistic regression model was used for multivariate analysis. The results were considered significant at the 95% confidence interval and significance level of $p<0.05$.

Results

A total of 132 patients (68 men, 51.5%) were included in the study, including 44 patients undergoing dialysis for ESRD and 88 patients with NRF. The mean age of all patients was 69.5±11.7 (minimum-maximum: 31-88). The mean age of the ESRD group was not different from the NRF group (71 and 73, p=0.395). Gender distribution did not differ between the groups. The distribution of risk factors in groups with and without ESRD is shown in Table 1. The history of stroke was more common in the ESRD group than the NRF group, but the difference did not reach statistical significance.

Comparison of the etiologies of IS is given in Table 2. It was seen that the SUE subtype was the most common in the ESRD group and the CE subtype was the most common in the NRF group (Table 2). Nineteen (43.2%) of the SUE in the ESRD group were due to the coexistence of more than one etiology.

When groups with and without ESRD were compared, the NIHSS scores at admission to hospital [9 (6) and 8 (8.8), p=0.396], and length of stay [8 (7.5) and 8 (4), p=0.234] did not differ.

Of patients with ESRD 20.5% (9 patients) and 5.7% (5 patients) of patients without ESRD died in hospital, and this difference was statistically significant (p=0.015). Initial NIHSS scores of patients who died in the hospital were significantly higher than those who did not die [16 (6) and 8 (8), respectively, p<0.0001]. Of the vascular risk factors, only HT differed significantly between the groups with and without mortality (13.6% and 0%, respectively, p=0.039). Age and gender adjusted regression analysis revealed that the presence of ESRD was significantly associated with hospital mortality (hazard ratio: 11.6, 95% CI 1.7-77, p=0.011).

Discussion

In this study, patients with ESRD presenting with IS were examined in terms of demographic characteristics, vascular risk factors, stroke severity and type, length of hospital stay and hospital mortality, and the results were compared with IS patients without ESRD.

IS patients with ESRD included in our study did not differ in terms of age, gender and vascular risk factors compared to patients without ESRD. Although there are many publications in the literature reporting a higher incidence of IS in hemodialysis (HD) patients, it is noteworthy that hemorrhagic stroke is mostly seen in this patient group. The reason for this difference is explained by genetic predisposition and uncontrolled high blood pressure, which rapidly decreases the GFR value and creates a situation that is unprotected against changes in blood pressure by reducing the resistance in the brain and renal vascular bed (6-8). Independent risk factors for stroke in the CRF population include African-American race, old age, DM, elevated systolic and diastolic blood pressure, left ventricular hypertrophy, GFR below 60 mL/min/1.73 m^2, male gender, and positive family history (9). In a 22-year single center study comparing CRF and stroke patients with stroke patients with NRF, it was reported that CRF patients were younger (mean age= 65.3; 70.5 years) (7).

In a study examining gender differences in CRF in the literature, it was reported that women had protective factors against CRF during the reproductive age and they had a tendency to develop CRF 10 years later than men. The studies of Wang et al. (10) and Ovbiagele (11) also supported that stroke was more common in men. Differently, in the study of J. Mattana et al. (12) in which they compared CRF and stroke patients with stroke patients with NRF, the male/female ratio was reported to be 50% in both groups. Age can also be evaluated as a strong long-term predictor for death after stroke. In the study of McWalter et al. (13), it was reported that mortality was 8 times more in patients older than 85 years of age who had a stroke compared to the group under 60 years of age. In HD patients, HT is a factor that increases the risk of both IS and hemorrhagic stroke, and it is thought that high

Table 1. Comparison of risk factors between groups with and without ESRD

	ESRD (n=44)	NRF (n=88)	p
HT, n (%)	38 (86.4)	65 (73.9)	0.122
DM, n (%)	16 (36.4)	30 (34.1)	0.847
CAD n (%)	14 (31.8)	33 (37.5)	0.567
HL n (%)	22 (50)	38 (43.2)	0.466
AF n (%)	9 (20.5)	30 (34.1)	0.156
Smoking n (%)	6 (13.7)	11 (12.5)	0.470
History of stroke n (%)	18 (40.9)	22 (25)	0.072

HT: Hypertension, DM: Diabetes mellitus, CAD: Coronary artery disease, HL: Hyperlipidemia, AF: Atrial fibrillation, ESRD: End-stage renal disease, NRF: Normal renal function

Table 2. Comparison of stroke types between groups with and without ESRD in IS patients

TOAST classification	ESRD (n=44)	NRF (n=88)	p
1. Large artery atherosclerosis	3 (6.8)	9 (10.2)	0.067
2. Cardioembolism	7 (15.9)	31 (35.2)	
3. Small vessel occlusion	5 (11.4)	10 (11.5)	
5. Stroke of undetermined etiology (including more than one etiology)	29 (65.9)	38 (43.2)	

ESRD: End-stage renal disease, NRF: Normal renal function, IS: Ischemic stroke

BP, which is difficult to control at the time of admission, may be a predisposing factor in the development of stroke (11). Other modifiable atherosclerotic risk factors such as smoking, HL and AF also increase the risk of IS. The facts that our study was a retrospective and single-center study and had a low number of patients maked it difficult to interpret our results.

In the literature, there are publications reporting that the frequency of HT in HD patients diagnosed with stroke reaches 92%. In the publications, it was reported that the most common comorbidity in both HD patients and non-HD patients with stroke was HT, and uncomplicated DM was the second most common (14,15). In our study, the frequency of HT was 88.3% in the ESRD group and 73% in the NRF group, and it was lower when compared to the literature. It has been reported that AF develops more in patients with CRF than in the normal population, and CRF develops more in patients with AF than in the normal population (16). AF was a risk factor on its own for stroke, and it was found that 24% of our patients had a history of AF and there was no difference between groups. It has been reported that HT is an important risk factor leading to the development of CAD in patients with CRF. It has been reported that DM also accelerates the development of CAD in patients with CRF (17). In our data, 1/3 of all patients had a history of CAD and there was no significant difference between the groups. Supporting the literature, HT was the most common comorbid disease in our patients, and HL and DM were also common. The presence of risk factors did not differ between the groups.

In our study, when evaluated according to IS subtypes in patients with ESRD, the most common one was SUE due to more than one risk factor in the patients. In patients with NRF, CE was the most common etiology. It was thought that the frequent observation of the SUE subtype might result from the coexistence of LAA and CE risk factors in patients receiving dialysis treatment, and the absence of a single etiologic cause. In a study in the literature examining CVD developing in ESRD patients receiving intermittent HD treatment, the distribution of IS subtypes was reported as 28% CE, 23% SUE, 20% SVO, 18% SODE, and 11% SUE (18). Tusukamoto et al. (19) examined the relationship between stage 3-4 kidney disease and IS. They found that 46% of patients with IS with CRF, 36% of patients with LAA, 31% of patients with SVO, and 26% of patients with SUE and SODE had stage 3-4 renal failure. Stage 4 CRF in this study included stage 4 and 5 CRF levels in our study. The increase in the frequency of AF in advanced ages is the most important factor that makes CE play an important role in the etiology of IS. Observation of CRF more frequently in patients with AF also increases the incidence of CE. While CE is more closely related to the degree of CRF, LAA increases significantly as the stage of CRF increases. The reason for the increased frequency of LAA is associated with an increase in carotid intima and media thicknesses independent of atherosclerotic risk factors in HD patients, and especially this increase in those with carotid stenosis decreases blood flow velocity in middle cerebral artery and impairs brain perfusion (19). Sandsmark et al. (20) examined 3,939 patients for the presence of stroke in CRF and reported that lacunar infarcts and white matter lesions were observed more frequently in cranial MR imaging as the GFR value decreased, and this increase was higher in those with albuminuria. Contrary to all these studies, we found significantly more critical stenosis and atherosclerotic changes in the NRF group in our own patients. One of the important factors in this might be that this group was older in our study.

Our results did not show any difference in terms of stroke severity between patients with and without ESRD. In a study in which HD patients with stroke were evaluated in the literature, the mean NIHSS score at admission was reported as 5.33 (21). In the study conducted by Ülker et al. (22) in our country, it was reported that the initial NIHSS score was very valuable in determining the early prognosis, and that the prognosis was much better after the second week in approximately 90% of patients with NIHSS ≤6 compared to those with NIHSS ≥16. In most studies with stroke patients, the presence of CRF has been found to be associated with increased stroke severity, 3-month mortality, and poor short-term prognosis, with more sequelae than strokes with other mechanisms. There are conflicting data regarding the post-stroke mortality rate in HD patients. For example, while this rate was reported as 8-9% in some studies in the literature, Mattana et al. (12) reported this rate as 23% (11). In our study, 10.6% of all patients died during hospitalization, and the mortality rate was found to be low compared to other studies. In patients with ESRD, this rate increased to 20.5% in our study. In the study of Ovbiagele (11), they found that younger patients with hemorrhagic strokes and women died at a higher rate in 25 patients with ESRD and stroke. In our study, patients with and without ESRD were included and only hospital mortality rates were evaluated. It was observed that the presence of ESRD significantly increased the risk of in-hospital mortality in patients with IS.

In the literature, it has been reported that the hospitalization period of patients with CRF is longer than that of patients with NRF (10,11). The reason for this is that there are often accompanying complex medical problems, infections and/or sepsis, and complications are more common in these patients. For example, in the study conducted by Ovbiagele (11), the average hospitalization time was reported as 3.9 days in the CRF group and 2.7 days in the other group. There was no difference between the groups in terms of the total length of hospital stay of the patients in our study. Even when the patients who died were excluded for more objective evaluation, there was no difference in terms of length of stay between the two groups. This can be attributed to the fact that patients with ESRD and undergoing HD are tried to be discharged as soon as possible before complications occur and infection is detected.

Study Limitations

The limitations of our study were that it was a retrospective and single-center study. Multicenter studies are still needed to determine stroke types in ESRD patients and to understand their effects on early and late prognosis.

Conclusion

In conclusion, in our study, it was shown that IS with more than one etiology was seen more frequently in patients with ESRD, and ESRD significantly increased the risk of mortality in the hospital. It is recommended to take more effective measures to prevent mortality during the treatment of IS patients with ESRD.

Ethics

Ethics Committee Approval: The study was approved by the Van Regional Training and Research Hospital Local Ethics Committee.

Informed Consent: Retrospective study.

Peer-review: Externally peer reviewed.

Authorship Contributions

Concept: S.Ö., T.K.Y., Design: S.Ö., Data Collection or Processing: S.Ö., F.İ.U., Analysis or Interpretation: S.Ö., F.İ.U., T.K.Y., Literature Search: S.Ö., F.İ.U., Writing: S.Ö., F.İ.U.

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