Epilepsi 2018;24(2):69-74 DOI: 10.14744/epilepsi.2018.97769

ORIGINAL ARTICLE / KLİNİK ÇALIŞMA

Early Seizures in Patients with Acute Ischemic Stroke: Incidence, Predictive Factors, and Clinical Outcome


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Akut İskemik İnmeli Hastalarda Erken Nöbetler: İnsidans, Prediktif Faktörler ve Prognoz Üzerine Etkisi

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Summary

Objectives: Cerebrovascular disease is one of the major causes of epileptic seizures in the elderly. The aim of this study was to identify the incidence and predictive factors of early seizures after ischemic stroke (ESAIS) and the effect of early seizures on clinical outcome.

Methods: The medical records of 619 patients with acute ischemic stroke were retrospectively reviewed. Early seizures were defined according to the International League Against Epilepsy within 7 days of stroke onset. Patient demographics, risk factors, National Institutes of Health Stroke Scale (NIHSS) score, thrombocyte count, and C-reactive protein (CRP) level on admission; modified Rankin Scale (mRS) score in the follow-up period; and details of the location of lesions observed on diffusion-weighted imaging were recorded and analyzed.

Results: A total of 22 (3.6%) patients with ESAIS [10 females, 45.5%; mean age: 66.55±15.3 years (range: 35–91 years)] and 597 (85.5%) patients with non-ESAIS [280 females, 46.9%; mean age: 69.5±13.3 years (range: 23–103 years)] were included. The mean NIHSS score on admission, CRP level, thrombocyte count, in-hospital mortality, mean follow-up mRS, and the recurrent stroke rate were significantly higher in the ESAIS group ($p<0.05$). Logistic regression analysis revealed that only the NIHSS score on admission, thrombocyte count, and recurrent stroke rate were significantly associated with ESAIS ($p<0.05$).

Conclusion: An elevated thrombocyte count and severe stroke on admission are possible major risk factors for ESAIS.

Keywords: Early seizures; ischemic stroke; predictive factors.

Özet

Amaç: Serebrovasküler hastalıklar özellikle ileri yaştaki hastalarda epileptik nöbetlerin önemli nedenlerinden biridir. Bu çalışmanın amacı akut iskemik inmeli hastalarda görülen erken nöbetlerin insidansını, prediktif faktörlerini ve prognoz üzerine etkisini araştırmaktır.

Gereç ve Yöntem: Bu çalışmada akut iskemik inmesi olan 619 hastanın dosyaları incelendi. Erken nöbetler, Uluslararası Epilepsi ile Savaş Derneği (ILAE) kriterlerine göre inmeden sonraki bir hafta içinde ortaya çıkan nöbetler olarak tanımlandı. Hastaların demografik özellikleri, risk faktörleri, başvuru sırasındaki National Institutes of Health Stroke Scale (NIHSS) skorları, serum C-reaktif protein (CRP) düzeyleri ve trombosit sayıları ile hastaların takiplerindeki modifiye Rankin Skalası (mRS) skorları ve diffüzyon ağırlıklı görüntülemede lezyon yerleşimi kaydedildi.

Bulgular: Çalışmaya 22 (%3.6) erken nöbet geçiren (10 kadın [45.5%]; ortalama yaş, 66.55±15.3 yıl) ve 597 (%85.5) erken nöbet geçirmeyen (280 kadın [%46.9]; ortalama yaş, 69.5±13.3 yıl) hasta dahil edildi. Başvuru sırasındaki NIHSS skoru ortalaması, CRP düzeyleri ve trombosit sayıları, hastanede mortalite, izlemde mRS skoru ve rekürren inme oranları erken nöbet geçiren grupta anlamlı olarak daha yüksek idi ($p<0.05$). Lojistik regresyon analizinde başvuru sırasındaki NIHSS skoru, trombosit sayısı ve rekürren inme, erken nöbetler ile anlamlı olarak ilişkili bulundu ($p<0.05$).

Sonuç: Artmış trombosit sayısı ve başvuru sırasındaki inme şiddeti akut iskemik inme hastalarında erken nöbetler için ana risk faktörleri olarak görünmektedir.

Anahtar sözcükler: Erken nöbetler; iskemik inme; prediktif faktörleri.

Submitted *(Geliş)*: 24.06.2017
Accepted (Kabul) **:** 15.01.2018
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Introduction

Cerebrovascular disease is one of the most important causes of epileptic seizures in the elderly.[1–15] Seizures after stroke may be with early or late onset. According to the International League Against Epilepsy (ILAE), early seizures are defined as those occurring within the first 7 days of stroke.[2] In literature, hemorrhagic stroke, cortical involvement, and large lesions have been reported as risk factors for the development of early seizures after stroke.[3]

The aim of this study was to identify the incidence and predictive factors of early seizures after ischemic stroke (ESAIS) and the effect of early seizures on clinical outcome in our stroke patients.

Materials and Methods

We retrospectively reviewed the medical records of 619 consecutive patients who were admitted to the stroke unit with acute ischemic stroke from January 2011 to November 2014. Approval was obtained from the research ethic committee at the start of the study. All patients had acute ischemic lesion on diffusion-weighted imaging (DWI). The magnetic resonance imaging scans of all patients were reviewed by investigators blinded to the history of the patients. The patients were divided into two groups: ESAIS group, patients with ESAIS; non-ESAIS group, patients without ESAIS.

According to ILAE, early seizures are defined as paroxysmal disorders of the central nervous system with or without loss of consciousness or awareness and with or without motor involvement within 7 days from stroke onset2. Thus, patients with history of epilepsy and those with any past episodes of subarachnoid hemorrhage (SAH) and cerebral venous sinus thrombosis were excluded.

Patient demographics and medical risk factors, including the history of hypertension, diabetes, hyperlipidemia, atrial fibrillation, congestive heart failure, coronary artery disease, previous transient ischemic attack, and previous stroke, as well as the National Institutes of Health Stroke Scale (NIHSS) scores, C-reactive protein (CRP) level, and thrombocyte count on admission were collected using a standard data collection form and entered in an institutional database. Hypertension was defined as a blood pressure of ≥140/90 mmHg on repeated measurements or prior use of antihypertensive medication; diabetes mellitus was defined as a fasting blood glucose level of ≥126 mg/dL on repeated measurements or the use of medications to lower blood glucose. Atrial fibrillation was defined based on findings in the history or detection on ECG or Holter. Coronary artery disease was defined based on any history of angina, myocardial infarction, or coronary revascularization.

A single rater (MHS) determined the etiologic stroke subtypes using the automated Causative Classification System (CCS, available at https://ccs.mgh.harvard.edu).[4] The CCS subtypes include supra-aortic large artery atherosclerosis (LAA), cardioaortic embolism, small artery occlusion, other causes, and undetermined causes. The etiologic work-up includes vascular imaging studies, such as carotid Doppler ultrasonography, computerized tomography angiography, magnetic resonance angiography or digital subtraction angiography, transthoracic or transesophageal echocardiogram, 24-h cardiac rhythm monitoring, and laboratory tests for hypercoagulability and vasculitis. In-hospital mortality, follow-up mRS scores, and stroke recurrence were considered as the outcome measures. Stroke recurrence was diagnosed based on both clinical and imaging findings. The modified Rankin Scale (mRS) scores were recorded according to the follow-up visits of the patients.

Statistics

Statistical analysis was performed using the Statistical Package for the Social Sciences 16.0 version (SPSS Inc. Chicago, Illinois, USA). Descriptive statistics are expressed as means ± standard deviations for normally distributed continuous variables and as median (interquartile range) for non-normally distributed variables. Statistical analysis was performed to determine the incidence, predictive factors, and clinical outcome of early seizures in patients with acute ischemic stroke in our registry. The group rates were compared using a chi-squared test, and the means were compared using Student's t test; $p<0.05$ was considered to be statistically significant. Logistic regression analysis was performed to determine the risk factors and clinical outcome measures associated with ESAIS.

Results

A total of 22 (3.6%) patients with ESAIS [10 females (45.5%); mean age, 66.55±15.3 (35–91) years] and 597 (85.5%) patients with non-ESAIS [280 females (46.9%); mean age, 69.5±13.3 (23–103) years] were included. Patient demographics and medical risk factors are shown in Table 1.

No between-group differences with respect to history of hypertension, diabetes, hyperlipidemia, atrial fibrillation, congestive heart failure, coronary artery disease, previous transient ischemic attack, or previous stroke were observed (p>0.05) (Table 1).

Levetiracetam (n=15), phenytoin (n=8), valproic acid (n=6) and carbamazepine (n=1) were taken by patients in the ESAIS group. Fourteen patients took monotherapy and eight took dual therapy.

The mean NIHSS score on admission was 8.95±5.7 (range, 1–26) in ESAIS group and 5.96±4.5 (range, 0–26) in the non-ESAIS group. The mean NIHSS score on admission was significantly higher in the ESAIS group than in the non-ESAIS group (p=0.002). The mean admission CRP level was 53.1±74.6 mg/l in the ESAIS group and 22.6±38.2 mg/l in the non-ESAIS group (p=0.012). The mean admission thrombocyte count was 284.5±168.8 mm^3 in the ESAIS group and 241.3±86.1 mm^3 in the non-ESAIS group (p=0.028). The mean admission CRP level and thrombocyte count was significantly higher in the ESAIS group than in the non-ESAIS group (p<0.05) (Table 1).

In the ESAIS group, four (18.2%) patients had LAA, 12 (54.5%) had cardioaortic embolism, and one (4.5%) had stroke due to other causes; the etiologic subtype of five (22.7%) patients remained undetermined. In the non-ESAIS group, 148 (24.8%) patients had LAA, 244 (40.9%) had cardioaortic embolism, 32 (5.4%) had small artery occlusion, and 34 (5.7%) had stroke due to other causes; the etiologic subtype of 139 (23.3%) patients remained undetermined (Table 1). Appro-

Table 1. Epidemiologic and clinical characteristics of patients with ESAIS and non-ESAIS

	ESAIS (n=22)	Non- ESAIS (n=597)	p
Age, year, Mean±SD	66.55±15.3 (35–91)	69.5±13.3 (23–103)	0.41
Sex, n (%)			
Female	10 (45.5)	280 (46.9)	0.89
Male	12 (54.5)	317 (53.1)	
Medical history, n (%)			
Hypertension	17 (77.3)	415 (69.5)	0.44
Diabetes mellitus	6 (27.3)	177 (29.6)	0.81
Atrial fibrillation	6 (4.8)	119 (19.9)	0.4
Hyperlipidemia	2 (9.1)	156 (26.1)	0.07
CAD	3 (13.6)	141 (23.6)	0.28
CHF	2 (9.1)	68 (11.4)	0.71
Previous stroke	5 (22.7)	101 (16.9)	0.48
Previous TIA	1 (4.5)	47 (7.9)	0.57
CCS classification, n (%)			
Large-artery atherosclerosis	4 (18.2)	148 (24.8)	0.48
Cardio-aortic embolism	12 (54.4)	244 (40.9)	0.20
Small vessel disease	–	32 (5.4)	0.26
Other rare causes	1 (4.5)	34 (5.7)	0.82
Undetermined causes	5 (22.7)	139 (23.3)	0.95
NIHSS score on admission, Mean±SD	8.95± 5.7	5.96±4.5	0.002
Cortical infarct, n (%)	19 (86.4)	367 (61.5)	0.018
CRP mg/dL, Mean±SD	53.13±74.61	22.55±38.17	0.012
Thrombocyte mm^3, Mean±SD	284.5±168.8	241.3±86.1	0.028
Recurrent stroke, n (%)	3 (13.6)	10 (1.7)	0.009
Mortality rate, n (%)	6 (31.6)	71 (20.2)	0.03
Follow up mRS, Mean±SD (Min-Max)	3.6±2.2 (0–6)	2.5±2.4 (0–6)	0.04

ESAIS: Early seizures after ischemic stroke; SD: Standard deviation; CAD: Coronary artery disease; CHF: Congestive heart failure; TIA: Transient ischemic attack; CCS: Causative Classification System; mRS: The modified Rankin Scale; NIHSS: the National Institutes of Health Stroke Scale; CRP: C-reactive protein.

Table 2. Logistic regression analysis of ESAIS

	OR	95%, CI	p
NIHSS score on admission >4	1.13	1.021–1.243	0.018
Thrombocyte count >450/mm^3	1.10	1.002–1.010	0.005
Recurrent stroke	9.96	1.975–50.296	0.005

ESAIS: Early seizures after ischemic stroke; NIHSS: The National Institutes of Health Stroke Scale; OR: Odds ratio; CI: Confidence intervals.

priate therapeutic drugs were given to all patients according to the etiologic subtypes of ischemic stroke.

Nineteen patients had cortical infarct in the ESAIS group. The cortical infarct is significantly associated with the ESAIS group (p=0.018) (Table 1).

The in-hospital mortality was significantly higher in the ESAIS group (31.6%, n=6) than in the non-ESAIS group (20.2%, n=71) (p=0.03).

The follow-up information was available for only 308 patients (16 patients in the ESAIS group and 292 patients in the non-ESAIS group). The mean follow-up time of the patients was 9 (range, 1–32) months, with 11.09 (range, 1–28) months in the ESAIS group and 8.92 (range, 1–32) months in the non-ESAIS group. The mean mRS was 3.6±2.2 (range, 0–6) in the ESAIS group and 2.5±2.4 (range, 0–6) in the non-ESAIS group during the follow-up period. The outcome was significantly better in the non-ESAIS group than in the ESAIS group (p=0.04). Recurrent stroke occurred in three (13.6%) patients with ESAIS and 10 (1.7%) patients without ESAIS. It was significantly higher in the ESAIS group than in the non-ESAIS group (p=0.009) (Table 1).

According to the results of the logistic regression analysis, NIHSS score on admission >4, thrombocyte count >450/mm^3, and recurrent stroke were the factors that were significantly associated with ESAIS (Table 2).

Discussion

Incidence

In literature, the incidence of early seizures is reported to be 2.13%–33.14% depending on the variability of period used in early seizure definition.[5–7] Some studies, which included patients with hemorrhagic stroke, have reported that early seizures were more common in hemorrhagic stroke than in ischemic stroke; however, other studies found no difference.[7–9] In one study, the incidence of ESAIS was reported as 3.9%, with 10% in patients with intracerebral hemorrhage and 2.4% in those with ischemic stroke.[10] In this study, we included only patients with ischemic stroke, and the incidence of ESAIS was 3.6%. This data was consistent with those reported in the literature.[4–10]

Predictive factors

In accordance with previous studies, there was no correlation between the risk factors of ischemic stroke and early seizures and we found that high NIHSS score on admission and cortical involvement were associated with early seizures.[11,12] In a prospective multicenter study including 1897 patients with stroke, cortical location and stroke disability were shown as independent risk factors for seizures after ischemic stroke on multivariate analysis.[13] In a more recent prospective study, it was revealed that alcoholism, NIHHS score on admission, hemorrhagic stroke, and cortical location were the predictors of early seizures.[11]

Previous studies have reported controversial results for the relationship between early seizures and etiology of ischemic stroke.[9,13,14] Although some authors report cardioembolic infarction as a risk factor for developing seizures,[7,14] other studies have shown no association between stroke etiology and early seizures.[9] We also did not find any significant correlation between stroke etiology and early seizures.

The pathophysiology of seizures after stroke is still not clearly understood. It was demonstrated that there is an up-regulation of pro-inflammatory mediators in the experimental models of epileptogenesis.[15] There have been several reports about the potential contribution of inflammation in the damaged hyper-excitable brain tissue, which causes spontaneous seizures.[16,17] In this study, the high CRP levels and platelet count on admission in patients with early seizures could be associated with this condition. However, high CRP levels in the ESAIS group were not found to be statistically significant.

Clinical outcome

The effect of early seizures on clinical outcome is controversial. Some studies have reported early seizures as a risk factor for mortality;[11,13,17] conversely, others have shown no association between early seizures and an adverse outcome at discharge.[9] A multicenter study including 5027 patients investigating the mRS scores and mortality rates during discharge and 30th day mortality rates after discharge reported that patients with ischemic stroke who had early seizures showed poor prognosis.[18]

The outcome was significantly better in patients with non-ESAIS than those with ESAIS regarding in-hospital mortality, follow-up mRS, and recurrent stroke, but only recurrent stroke was significantly higher in the ESAIS group. These results may be explained by higher NIHSS scores on admission. Previous studies have also shown that a high NIHSS score is associated with a higher risk of recurrent stroke.[19,20] In addition, it is demonstrated that recurrent epileptic seizure activity increases the lesion volume and ruins the functional recovery in experimental stroke models.[21] Mortality was higher in the ESAIS group. This may also be related to generalized seizures, unconsciousness, need for sedative benzodiazepines, or risk of aspiration pneumonia.

There are several limitations to this study, including its retrospective design and a relatively short follow-up period. In addition, the cohort was chosen from a single medical center. However, all of our patients underwent a detailed work-up for determining the causative mechanism of ischemic stroke. Acute ischemic lesions were identified with DWI in all patients. In contrast to the previous studies, the etiologic subtypes of ischemic stroke were determined systematically, according to CCS, in our patients.

In conclusion, elevated thrombocyte counts and severe stroke at admission appear to be the major risk factors for early seizure in patients with acute ischemic stroke. The recurrent stroke rate was significantly higher in patients with ESAIS. Further studies with larger patient numbers are needed to clarify this issue.

Ethics Committee Approval

Ethics committee approved.

Peer-review

Externally peer-reviewed.

Conflict of interest

The authors declare that they have no conflict of interest.

Authorship Contributions

Concept: S.E., M.H.S.; Design: S.E., M.H.S.; Data collection &/or processing: Z.K., M.K., Ç.U., H.Ç.L., İ.Ş.Ö., S.T., S.R., V.Y.; Analysis and/or interpretation: S.E., M.H.S., R.Y.; Literature search: S.E., M.H.S.; Writing: S.E.; Critical review: M.H.S., C.T.I.

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