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Original Article / Özgün Araştırma

Electrocardiographic Changes and Their Prognostic Effect in Patients with Acute Ischemic Stroke without Cardiac Etiology

Kardiyak Etiyoloji Dışlanan Akut İskemik İnme Hastalarında Elektrokardiyografik Değişiklikler ve Prognostik Etkileri

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Abstract

Objective: Acute ischemic stroke has an effect on electrocardiography (ECG) results and cardiac enzyme levels, but its mechanism has not been clearly established. Our aim was to research ECG and cardiac enzyme changes in acute ischemic stroke and to investigate the association between these changes and stroke localizations and prognosis.

Materials and Methods: The study included 241 patients with acute ischemic stroke. Patients without cardiac arrhythmia, history of previous stroke, use of drugs affecting the pattern and duration of ECG rhythm and without acute or chronic myocardial infarction history and electrolyte imbalance were included. The vascular risk factors for stroke, creatine kinase-MB (CK-MB), and troponin I (TnI) levels, and ECG results were examined.

Results: One hundred twenty-three patients had right hemisphere infarcts and 118 patients had left hemisphere infarcts with the same mean ages. HT was more prevalent in right hemisphere infarcts (p=0.013). The most common ECG abnormalities were QTc prolongation (31%) and ST depression (24%). CK-MB and TnI levels were significantly higher in patients with right hemispheric and cerebellar infarcts. QRS durations were longer in cerebellar infarcts (p=0.05).

Conclusion: The most common ECG abnormality was QTc prolongation in patients with acute ischemic stroke within 24 hours. CK-MB and TnI levels were higher in patients with right hemisphere and cerebellar infarcts.

Keywords: Acute ischemic stroke, ECG changes, TnI levels, stroke prognosis, cerebellar infarcts

Öz

Amaç: Akut iskemik inme, elektrokardiyografi (EKG) sonuçları ve kardiyak enzim düzeyleri üzerinde etkili olmakla birlikte mekanizması açık bir şekilde belirlenememiştir. Amacımız akut iskemik inmede EKG ve kardiyak enzim değişikliklerini incelemek ve bu değişiklikler ile inme lokalizasyonu ve prognoz arasındaki ilişkiyi araştırmaktır.

Gereç ve Yöntem: Çalışma 241 akut iskemik inme hastalarını içermektedir. Çalışmaya kardiyak aritmi ve inme öyküsü olmayanlar ile EKG ritmi ve süresini etkileyen ilaç kullanımı, akut veya kronik miyokardiyal enfarktüs öyküsü ve elektrolit dengesizliği olmayanlar dahil edildi. İnme vasküler risk faktörleri, kreatin kinaz-MB (CK-MB) ve TnI düzeyleri, EKG sonuçları incelendi.

Bulgular: Yaş ortalamaları benzer olan 123 hastada sağ hemisfer enfarktı ve 118 hastada sol hemisfer enfarktı vardı. HT sağ hemisfer infarktlarında daha sıktı (p=0,013). En sık karşılaşılan EKG anormallikleri; QTc uzaması (%31), ST depresyonuydu (%24). Sağ hemisferik ve serebellar enfarktı olan hastalarda CK-MB ve TnI düzeyleri anlamlı olarak daha yüksekti. QRS süreleri serebellar enfarktlarda daha uzun saptandı (p=0,05).

Sonuç: Akut iskemik inmeli hastalarda 24 saat içinde en sık görülen EKG anormalliği QTc uzamasıydı. Sağ hemisfer ve serebellar enfarktlı hastalarda CK-MB ve TnI düzeyleri belirgin yüksek bulundu.

Anahtar Kelimeler: Akut iskemik inme, EKG değişiklikleri, TnI düzeyleri, inme prognozu, serebellar enfarkt

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Introduction

The main control of cardiac functions is in the medulla oblongata, which is accepted as the cardioregulatory center (1,2). The sympathomimetic autonomic effect is thought to be due to catecholamine discharge and the parasympathomimetic effect via vagal stimulation (3). The findings of autonomic system changes in electrocardiography (ECG) are represented as arrhythmias and repolarization changes (4,5). Intracardiac catecholamine discharge, coagulated myocytolysis, contraction band necrosis, calcium discharge, and reperfusion injury are the possible mechanisms of cardiac dysfunction (6,7,8). There are several studies suggesting that the parasympathetic effect of the anterior hypothalamus causes bradyarrhythmia, and the posterior hypothalamus causes tachycardia and extra systoles through sympathetic activity (9,10). Studies in the literature demonstrated that cortical stimulation of the left insula leads to bradycardia and the right insula leads to tachycardia (11). Moreover, prolongation of the QT interval in insular cortical infarctions has also been reported (12). It has also been asserted that cardiac arrhythmias cause mortality, especially in MCA infarcts with right insula involvement (13). In the literature, the most common cardiac rhythm anomalies are atrial fibrillation (AF), QTc prolongation, T inversion, ST depression, and left ventricular hypertrophy (LVH) findings (14,15,16). Cardiac enzymes are also studied in patients with stroke. In some studies, it was demonstrated that troponin I (TnI) levels were associated with prognosis and involvement of the right insular cortex (17,18,19).

In this study, we researched ECG findings and cardiac enzyme changes in patients with acute ischemic stroke and investigated the association between these changes and stroke localizations and prognosis.

Materials and Methods

Study Group

We reviewed 1457 patients with acute ischemic stroke who were admitted to emergency department in the first 24 hours after the onset of symptoms and internalized to the neurology service or neurology intensive care unit between January 2012 and October 2016. The study was approved by the Local Ethics Committee of Izmir Tepecik Training and Research Hospital (18.10.2016/ decision no: 20).

The study included 241 patients with acute ischemic stroke except cardioembolic stroke with known sources (AF or any cardiac pathology); patients with normal echocardiography findings except for LVH, without cardiac arrhythmia, acute or chronic MI history, long QT syndrome, and valvular heart disease were included.

Patients with a history of cardioembolic stroke, intracranial hemorrhage and electrolyte imbalance, use of an antiarrhythmic drug, a history of cardiac pacemaker and cardiac surgery or any cardiac pathology determined during routine examination in neurology service were excluded. In addition, patients with severe metabolic or endocrinologic disorders and patients using drugs affecting the pattern and duration of ECG rhythms were also excluded.

The vascular risk factors for stroke [hypertension (HT), diabetes mellitus (DM), hypercholesterolemia (HCL)], ECG parameters (QTc interval, PR interval, QRS duration, RR interval and ST depression), LVH, laboratory tests (sedimentation, hemogram, routine biochemistry tests, CK-MB and TnI levels) and drugs used were recorded.

Patients were followed up for prognosis using National Institute of Health Stroke Scale (NIHSS) scores at admission to the emergency service and at discharge.

Electrocardiography

ECG recordings of patients with ischemic stroke were performed with a 12-channel ECG device at admission within 24 hours in emergency and neurology wards, respectively, and re-interpreted by a blinded cardiologist according to the modified Minnesota criteria. The QTc interval, PR interval, QRS duration, RR interval, and ST depression were evaluated according to these criteria. ST depressions ≥1 mm were considered to be pathologic in DI, DII, aVL, aVF, and V1-V6 derivations. The QRS interval >120 msec, RR interval >100 msec, and PR interval >200 msec were accepted as prolongation. The normal range of RR interval is 60-100 msec and PR interval is 120-200 msec. QTc were calculated using Bazett's method, which was formulated as $QTc=QT/(\sqrt{RR})$. The results >440 msec for female and >420 msec for male patients were accepted as QTc prolongation.

Cardiac Enzymes

The normal range of CK-MB was 0-5 U/L and serum TnI >0.06 ng/mL was considered as pathologic. Cardiac enzymes were measured on admission to the emergency and neurology wards in all patients within the first 24 hours in routine laboratory tests.

Statistical Analysis

All data were evaluated using the Statistical Package for the Social Sciences for Windows (SPSS, version 22. Student's t-test and the chi-square test or Fischer's exact test were used to compare parametric and nonparametric data. The ANOVA test was used in the comparison of multiple groups. $P<0.05$ was accepted as statistically significant.

Results

Two hundred forty-one patients (117 males, 124 females) were examined. The mean age was 68.13±11.98 years. ECG abnormalities were determined in 66% of all patients. The most common ECG abnormalities were QTc prolongation (31%), ST depression (24%), QRS prolongation (7%), PR prolongation (4%), and RR prolongation (1.5%). TnI levels were high in 17% and CK-MB levels were high in 6% of patients. The mortality rate in one month was 3%. The highest NIHSS scores were reported in brainstem infarcts. Patients were divided into groups according to infarct localizations. Demographic findings, ECG parameters, cardiac enzymes, and stroke prognoses were compared for each group.

One hundred twenty-three patients had right hemisphere infarcts and 118 patients had left hemisphere infarcts. HT, CK-MB, and TnI levels were significantly higher in patients with right hemisphere infarcts as indicated in Table 1 ($p<0.05$). There were no statistical differences in terms of other parameters.

There were no statistically significant differences in terms of ECG parameters between the groups ($p>0.05$). The NIHSS

scores of patients with left hemisphere infarcts at admission and discharge were significantly higher than those of patients with right hemisphere infarcts (p<0.05).

One hundred ninety-six patients had hemispheric infarcts, 29 had brainstem, and 16 patients had cerebellar infarcts. HT, DM, and HCL ratios were significantly higher in the brainstem and cerebellar infarct groups than in the hemispheric group, as shown in Table 2 (p<0.05). There were statistically significant differences between the groups in terms of QRS duration and TnI levels (p<0.05). Especially in patients with cerebellar infarcts, QRS durations were longer and TnI levels were significantly higher than in the other groups (p<0.05).

Table 1. Comparison of right and left hemisphere infarcts

Parameters	Right hemisphere (n=123)	Left hemisphere (n=118)	p value
Age	68.07±11.37	68.20±12.59	0.993
Sex	55	62	0.224
HT	108	89	**0.013**
DM	79	65	0.148
HCL	81	73	0.519
ST depression (mm)	29	31	0.629
LVH	80	67	0.189
QRS (msec)	95.26±14.93	93.69±12.98	0.383
QTc (msec)	419.10±29.54	416.31±26.96	0.444
PR interval (msec)	169.43±25.91	163.82±27.93	0.077
RR interval (msec)	82.40±10.98	83.61±12.13	0.418
CK-MB (U/L)	2.09±2.33	1.58±1.43	**0.041**
Troponin I (ng/mL)	0.15±0.67	0.03±0.50	**0.037**
Admission NIHSS	6.88±5.11	8.30±5.80	**0.045**
Discharge NIHSS	6.23±5.02	7.82±3.34	**0.046**

HT: Hypertension, DM: Diabetes mellitus, HCL: Hypercholesterolemia, LVH: Left ventricle hypertrophy, CK-MB: Creatine kinase-MB, NIHSS: National Institute of Health Stroke Scale

There were statistically significant differences between the groups in terms of NIHSS scores at admission and discharge (p<0.05). The highest NIHSS scores were determined in brain stem infarcts.

One hundred sixteen cortical, 56 subcortical, 29 brainstem, 16 cerebellar infarcts and 24 multiple infarcts were determined. HT and HCL were more frequent in the group with brainstem infarcts (p=0.051, p=0.023 respectively). As shown in Table 3, there was a statistically significant difference between the groups in terms of TnI levels (p<0.05) and the highest mean value was observed in cerebellar infarcts.

The number of patients with QTc, PR, RR, and QRS prolongation in ECG is presented in Table 4 according to the localization and lateralization of infarcts.

Discussion

In the literature, there are several studies about ECG changes observed in patients with acute ischemic stroke. In some studies, there is an uncertainty if these changes are secondary to stroke, it is thought that stroke might affect cardiac rhythm directly or indirectly (20). It was reported that the incidence of ECG abnormality after acute ischemic stroke was between 45% and 90%. Although there were differences between the studies, the most common ECG abnormalities were QTc prolongation, ST depression, and AF (21,22,23).

In our study, ECG abnormalities were observed in 66% of patients. The most common ECG changes were QTc prolongation (31%), ST depression (24%), QRS prolongation (7%), and PR interval prolongation (4%).

The most common ECG abnormality was QTc prolongation, but it was not associated with stroke localization, or severity and mortality in our analysis. In the literature, it was indicated that QTc prolongation was more frequent in right hemisphere infarcts than left hemisphere infarcts secondary to a sympathomimetic effect (24,25). It has been demonstrated that prognosis is worse in

Table 2. Comparison of hemispheric, brainstem and cerebellum infarcts

Parameters	Hemispheric (n=196)	Brain stem (n=29)	Cerebellum (n=16)	p value
Age	68.81±12.15	65.93±10.21	68.13±11.96	0.162
Sex	94	14	9	0.815
HT	154	28	15	**0.028**
DM	109	24	11	**0.016**
HCL	122	24	8	**0.049**
ST depression (mm)	46	9	5	0.565
LVH	119	20	8	0.451
QRS (msec)	93.87±14.07	94.17±12.02	102.75±14.69	**0.050**
QTc interval (msec)	416.83±28.28	422.41±28.05	420.31±29.51	0.572
PR interval (msec)	166.46±26.86	167.27±29.33	168.31±28.19	0.959
RR interval (msec)	83.24±11.42	83.13±11.33	79.75±13.71	0.509
CK-MB (U/L)	1.77±1.61	1.72±2.39	2.93±3.94	0.070
Troponin I (ng/mL)	0.07±0.27	0.06±0.20	0.45±1.61	**0.008**
Admission NIHSS	7.37±5.37	9.82±6.79	6.06±2.95	**0.041**
Discharge NIHSS	6.26±5.04	7.92±5.53	5.80±3.3	**0.048**

HT: Hypertension, DM: Diabetes mellitus, HCL: Hypercholesterolemia, LVH: Left ventricle hypertrophy, CK-MB: Creatine kinase-MB, NIHSS: National Institute of Health Stroke Scale

patients with QTc prolongation (26,27,28) and it even increases mortality by causing ventricular arrhythmia (23).

In our study, QRS durations were significantly longer in cerebellar infarcts (p=0.05). This is a novel finding that needs to be proven by large randomized studies. The other ECG abnormalities were not significantly different between the groups.

Another unexplained issue is the cardiac enzyme elevation in patients with acute ischemic stroke (29). Elevation of serum troponin levels after acute ischemic stroke was reported as 0-34% in different studies (30,31). In our study, TnI levels were normal (<0.06 ng/mL) in 199 patients and higher (>0.06 ng/mL) in 42 patients. The ratio of troponin elevation (17%) in patients with acute stroke was similar to other studies. Many studies suggested that the sympathoadrenal system and catecholamine release were more common in right hemisphere infarcts, as demonstrated in our study, cardiac enzymes were significantly higher in right hemisphere infarcts.

Another novel finding of the present study was the significant elevation of TnI values in cerebellar infarcts. It is known that the anterior cerebellum has sympathetic and posterior has parasympathetic effects (32). The elevation of TnI levels in cerebellar hemisphere lesions may be the result of the autonomic effect of the cerebellum on the cardiovascular system.

In the follow-up of our patients, the mortality rate in one month was 3%. Disability was significantly higher in patients with high stroke severity scores (NIHSS >15). We also determined that the severity of stroke was higher and ECG changes were more prevalent in patients who died.

The most common cause of mortality is cardiac complications in patients with acute stroke (33). Saposnik et al. (34) investigated the causes of early mortality in 12,262 patients with acute ischemic stroke and indicated that AF, stroke severity, and coronary artery disease increased the risk of mortality in those patients.

In the present study, the highest NIHSS scores were reported in brainstem infarcts. In addition, NIHSS scores of left hemisphere infarcts were significantly higher than those of the right hemisphere, may be due to aphasia.

Vascular risk factors were also compared between the groups; the HT ratio was significantly higher in right hemisphere strokes. This may be explained by vascular anatomic differences. Moreover, the ratios of HT, DM, and HCL were significantly higher in brainstem infarcts (p<0.05). These findings suggest the importance of vascular risk factors in brainstem infarcts.

Study Limitations

Our study has some limitations. First, to investigate ECG changes in patients with stroke, comparison of ECG rhythms

Table 3. Comparison of cortical, subcortical, brainstem, cerebellum, and multiple infarcts

Parameters	Cortical (n=116)	Subcortical (n=56)	Brainstem (n=29)	Cerebellum (n=16)	Multiple (n=24)	p value
Age	69.70±12.84	67.05±9.87	65.93±10.21	68.13±11.96	68.58±13.38	0.240
Sex	50	31	14	9	13	0.541
HT	95	42	28	15	17	0.051
DM	66	31	24	11	12	0.069
HCL	77	28	24	8	17	**0.023**
ST depression (mm)	29	9	9	5	8	0.383
LVH	74	33	20	8	12	0.511
QRS (msec)	93.83±15.69	95.46±12.28	94.17±12.02	102.75±14.69	90.33±8.17	0.083
QTc (msec)	418.94±30.29	409.69±23.27	422.41±28.05	420.31±29.51	423.29±26.63	0.159
PR interval (msec)	169.05±26.48	164.98±27.01	167.27±28.33	168.31±28.19	157.41±27.20	0.407
PR interval (msec)	83.19±10.86	82.75±11.81	83.13±11.33	79.75±13.73	84.62±13.40	0.775
CK-MB (U/L)	1.68±1.41	1.93±1.97	1.72±2.39	2.93±3.94	1.84±1.57	0.201
Troponin I (ng/mL)	0.07±0.30	0.03±0.06	0.06±0.20	0.45±1.61	0.13±0.41	**0.035**

HT: Hypertension, DM: Diabetes mellitus, HCL: Hypercholesterolemia, LVH: Left ventricle hypertrophy, CK-MB: Creatine kinase-MB

Table 4. Number of patients with pathologic electrocardiography findings according to infarct localization and lateralization

Number of patients with	QTc prolongation	QRS prolongation	PR prolongation	RR prolongation
Right hemisphere infarcts	43	9	5	3
Left hemisphere infarcts	22	8	6	1
Cerebellar infarcts	6	1	1	0
Brainstem infarcts	11	1	1	1
Cortical infarcts	30	8	8	2
Subcortical infarcts	13	3	3	1
Multiple infarcts	4	2	2	0
Total	n=129	n=32	n=26	n=8

before and after acute stroke would be more valuable, but we could only evaluate them in the acute phase; most of the patients did not have pre-stroke ECG recordings. Secondly, follow-up ECG recordings of patients were not performed. ECGs after the first week and the first month could be recorded and compared. However, because most patients were selected retrospectively, we did not have this opportunity. Finally, we could not analyze control levels of cardiac enzymes, which might be important in the follow-up.

Further, in our retrospective study the patients did not undergo 24-hour Holter ECG monitoring or transesophageal echocardiography, so we could not exclude unknown cardioembolic sources that might lead to ECG changes or higher enzyme levels.

Conclusion

In conclusion, besides neurologic examination, follow-up of cardiac monitoring and enzymes are vital for preventing and treating cardiovascular complications in patients with acute ischemic stroke. These strategies will be effective in reducing or preventing poor prognosis and mortality because cardiac complications are the most common cause of mortality in stroke.

According to the findings of the study, it is important to analyze TnI levels and ECG changes in cerebellar and right hemisphere-localized infarctions for prognosis and treatment. Investigation and comparison of ECG records and cardiac enzymes can be useful in the acute phase and in subacute and chronic phases of ischemic stroke to determine the long-term effects of stroke on the cardiovascular system.

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All of the authors declare that they participated in the design, execution, and analysis of the paper, and that they approved the final version. Additionally, there are no conflicts of interest in connection with this paper, and the material described is not under publication or consideration for publication elsewhere.

Ethics

Ethics Committee Approval: The study was approved by the Local Ethics Committee of Izmir Tepecik Training and Research Hospital (18.10.2016/decision no: 20).

Informed Consent: Patients' surveys were scanned during this retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Data Collection or Processing: A.K., Y.A., Analysis or Interpretation: Y.A., Ö.Ö., U.Ş., Literature Search: A.K., Y.A., Y.Z., F.T., Writing: A.K., Y.A.

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