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ECG Changes and Their Prognostic Effect in Acute Ischemic Stroke Patients Without Cardiac Etiology

Kardiak Etiyoloji Dışlanan Akut İskemik İnme Hastalarında EKG Değişiklikleri ve Prognostik Etkileri

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Abstract

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

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

Results: 123 patients had right hemisphere infarcts and 118 patients had left hemisphere infarcts with same mean ages. HT was more prevalent in right hemisphere infarcts (p=0.013). The most common ECG abnormalities were; QTc extension (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).

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

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

Öz

Amaç: Akut iskemik inme, 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 Yöntemler: Çalışma 241 akut iskemik inme hastalarını içermektedir., Çalışmaya kardiak aritmi ve inme öyküsü olmayanlar ile EKG ritmi ve süresini etkileyen ilaç kullanımı, akut veya kronik MI öyküsü ve elektrolit dengesizliği olmayanlar dahil edildi. İnme vasküler risk faktörleri, 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 depresyonu (% 24)'ydı. Sağ hemisferik ve serebellar enfarktı olan hastalarda CK-MB ve TnI düzeyleri anlamlı olarak daha yüksekti. NIHSS skorları ve enfarkt hacimleri sol hemisferde ve serebellar enfarktlarda daha yüksekti (p <0.05). 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.

vAkut 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 accepted as cardioregulator 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 myositolysis, contraction band necrosis, calcium discharge and reperfusion injury are the possible mechanisms of cardiac dysfunctions (6,7,8). There are several studies suggesting that the parasympathetic effect of the anterior hypothalamus causes bradyarrhythmia, while posterior hypothalamus causes tachycardia and extra systoles through sympathetic activity (9,10). Studies in literature demonstrated that cortical stimulation of left insula leads to bradycardia and right insula leads to tachycardia (11). Moreover the prolongation of the QT interval in insular cortical infarctions was also 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 findings (14,15,16). Cardiac enzymes are also studied in stroke patients. In some studies it was demonstrated that 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 acute ischemic stroke patients and investigated association between these changes and stroke localizations and prognosis.

Materials and Methods

Study group

We reviewed 1457 acute ischemic stroke patients admitted to emergency service 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 ethic committee of education and research hospital (18.10.2016 /decision no: 20). This article does not contain any studies with animals performed by any of the authors. Informed consent was obtained from all individual participants included in the study.

The study included 241 acute ischemic stroke patients except cardioembolic stroke with known sources (AF or any cardiac pathology); patients with normal echocardiography findings except left ventricle hypertrophy (LVH), without cardiac arrhythmia, acute or chronic MI history, long QT syndrome, 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 endocrinological disorders and patients using drugs affecting the pattern and duration of ECG rhythm 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 NIHSS scores at admission to the emergency service and at discharge.

Electrocardiography

ECG records of ischemic stroke patients were performed with a 12-channel ECG device at admission within 24 hours in emergency and neurology service respectively and re-interpreted by a blind 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, V1-V6 derivations. The QRS interval >120 msn, RR interval >100 msn and PR interval >200 msn were accepted as prolongation. The normal range of RR interval is 60-100 msn and PR interval is 120-200 msn. QTc were calculated using Bazett's method which was formulated as $QTc = QT / (\sqrt{RR})$. The results > 440 msn for female and >420 msn 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 during admission to the emergency and neurology service in all patients within the first 24 hours in routine laboratory tests.

Statistical Analyses

All data were evaluated using the SPSS 22 version (statistical package for the social sciences for windows). Student T-test and Chi square test or Fischer exact test were used to compare parametric and nonparametric data. ANOVA test was used in the comparison of multiple groups. $P < 0.05$ is accepted as statistically significant.

Results

241 patients (117 males, 124 females) were examined. The mean age was 68,135±11,98 years. ECG abnormalities were determined in 66% of all patients. Most common ECG abnormalities were QTc prolongation (31%), ST depression (24%), QRS prolongation (7%) and PR prolongation (4%), RR prolongation (1.5%). TnI levels were high in 17% and CK-MB levels were high in 6% of the patients. The mortality rate in one month was %3. 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 prognosis were compared for each group.

123 patients had right hemisphere infarcts and 118 patients had left hemisphere infarcts. HT, CK-MB and Troponin I 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 groups ($p>0.05$). NIHSS scores of patients with left hemisphere infarcts at admission and discharge were significantly higher than patients with right hemisphere infarcts ($p<0.05$).

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
Gender	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 (msn)	95.26±14.93	93.69±12.98	0.383
QTc (msn)	419.10±29.54	416.31±26.96	0.444
PR interval (msn)	169.43±25.91	163.82±27.93	0.077
RR interval (msn)	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 ¶NIHSS: National Institute of Health Stroke Scale

196 patients had hemispheric, 29 had brainstem and 16 patients had cerebellar infarcts. HT, DM and HCL ratios were significantly higher in brainstem and cerebellar infarct groups than hemispheric group as shown in Table 2 ($p<0.05$). There were statistically significant differences between 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 the other groups ($p<0.05$).

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

116 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.

Number of patients with QTc, PR, RR, QRS prolongation in ECG was presented in Table 4 according to localization and lateralization of infarcts.

Discussion

In the literature, there are several studies about ECG changes observed in acute ischemic stroke patients. In some studies there is an uncertainty if these changes are secondary to stroke, it is thought that stroke may affect cardiac rhythm directly or indirectly (20). It was reported that the incidence of ECG abnormality after acute ischemic stroke is 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 the patients. 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, severity or mortality in our analysis. In literature, it was indicated that QTc prolongation is more frequent in right hemisphere infarcts than left hemisphere infarcts seconder to sympathomimetic effect (24,25). It has been demonstrated that the prognosis is worse in the patients with QTc prolongation (26,27,28) and it even increases the mortality causing ventricular arrhythmia (23).

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

Another unexplained issue is the cardiac enzyme elevation in acute ischemic stroke patients (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 acute stroke patients was similar to other studies. Many studies suggested that sympathoadrenal system and catecholamine release are 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 significant elevation of TnI values in cerebellar infarcts. It is known that anterior cerebellum has sympathetic and posterior has parasympathetic effect (32). The elevation of TnI levels in cerebellar hemisphere lesions may be the result of the autonomic effect of cerebellum on cardiovascular system.

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
Gender	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 (msn)	93.87±14.07	94.17±12.02	102.75±14.69	0.050
QTc interval (msn)	416.83±28.28	422.41±28.05	420.31±29.51	0.572
PR interval (msn)	166.46±26.86	167.27±29.33	168.31±28.19	0.959
RR interval (msn)	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 ¶NIHSS: National Institute of Health Stroke Scale

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 score (NIHSS> 15). We also determined that the severity of stroke was higher and ECG changes were more prevalent in the patients who died.

The most common cause of mortality is cardiac complications in acute stroke patients (33). Saposnik et al. investigated the causes of early mortality in 12.262 acute ischemic stroke patients and indicated that AF, stroke severity and coronary artery disease increase the risk of mortality in those patients (34).

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

Vascular risk factors were also compared between groups; HT ratio was significantly higher in the right hemisphere strokes. This may be explained by vascular anatomical 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.

Our study has some limitations firstly to investigate ECG changes in stroke patients, comparison of ECG rhythms before and after acute stroke can be more valuable, but we could only evaluate them in acute phase, most of the patients did not have pre-stroke ECG recordings. Secondly the control ECG records of patients were not performed. ECGs after the first week and the first month could be recorded and compared. However, since most patients were selected retrospectively, we did not have this opportunity. Thirdly 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 underwent 24-hour Holter ECG monitoring or transesophageal echocardiography, so we could not exclude unknown cardioembolic sources which may lead to ECG changes or higher enzyme levels.

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

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 not only in the acute phase, but also in subacute and chronic phase of ischemic stroke to determine long term effects of stroke on cardiovascular system.

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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
Gender	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 (msn)	93.83±15.69	95.46±12.28	94.17±12.02	102.75±14.69	90.33±8.17	0.083
QTc (msn)	418.94±30.29	409.69±23.27	422.41±28.05	420.31±29.51	423.29±26.63	0.159
PR interval (msn)	169.05±26.48	164.98±27.01	167.27±28.33	168.31±28.19	157.41±27.20	0.407
PR interval (msn)	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

Table 4. Number of patients with pathologic ECG 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

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