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The Relationship Between the Mutation of Cardiac Potassium-Channel and Early Repolarization and the Importance of the Arrhythmia Marker Tests in this Population

Kardiyak K Kanal Mutasyonunu ile Erken Repolarizasyon İlişkisi ve Aritmi Belirteci Testlerinin bu Populasyondaki Önemi

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Abstract

Aim

Early repolarization (ER) electrocardiographic pattern is not rare in the general population. This electrocardiographic (ECG) abnormality, which has been accepted as benign for years, has attracted attention with its association with sudden cardiac death (SCD). The association of fatal arrhythmia history and this pattern of ECG is defined as ER syndrome (ERS). Several tests can help clinicians to understand which ER patterns cause a risk for malignant arrhythmias. As in the other channelopathies, ion channel-related gene mutations have also been reported in ERS. In this study, we investigated the presence of the mutation in KCNJ8, which has been described for the first time in ERS in the groups with and without ER and which leads to an electrical functional change in the potassium (K) channel, causing an arrhythmia. In addition, we attempted to determine the risk for arrhythmia with 24-hour ECG monitoring and signal-averaged electrocardiogram (SAECG).

Materials and Methods

A total of 100 patients who met the ECG criteria, and 50 of whom had ER patterns underwent rhythm Holter evaluations. The presence of SAECG and late potentials (LP) were studied.

Öz

Amaç:

Erken repolarizasyon (ER) elektrokardiyografik (EKG) paterni toplumda nadir değildir. Yıllardır benign kabul edilen bu EKG anormalliği, ani kardiyak ölümler (AKÖ) ile olan ilişkinin ortaya konmasıyla dikkatleri üzerine çekmiştir. Ölümcül aritmi öyküsü ile EKG'de bu paternin birlikte bulunması ER sendromu (ERS) olarak tanımlanır. Hangi ER paterninin malign aritmiler açısından riskli olduğunun anlaşılması için ise birtakım testler klinisyene yardımcı olabilir. Diğer kanalopatilerde olduğu gibi ERS'de de iyon kanalı ilişkili gen mutasyonları bildirilmiştir. Biz bu çalışmamızda ER bulunan ve bulunmayan gruplarda ERS'de ilk olarak tanımlanmış olan ve K kanalında elektriksel fonksiyon değişikliğine yol açıp aritmiye neden olan KCNJ8 genindeki mutasyonunun varlığını araştırdık. Ayrıca ER paterni bulunan grupta 24 saatlik EKG monitörizasyonu ve sinyal ortalamalı EKG (SOEKG) ile aritmi risklerini belirlemeye çalıştık.

Materyal ve Metod

Çalışmaya dahil ettiğimiz EKG kriterlerine uygun 50'si ER paterni bulunan toplam 100 hastanın ritm holter değerlendirmeleri yapıldı. SOEKG ile geç potansiyellerin varlığına bakıldı. PCR yöntemi ile KCNJ8 gen mutasyonu araştırıldı.

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KCNJ8 gene mutation was investigated with the Polymerase Chain Reaction (PCR) method.

Results

The majority of the patients in the ER pattern group were in ER type 1 pattern. Although not statistically significant, QTc intervals were shorter in the ER group. There were no significant ventricular arrhythmias in rhythm Holter records in both groups. Heart rate variability (HRV) was decreased by 26%, and late potentials (LP) were found in 14% of the patients in this group with SAECG. No correlation was found between the investigated KCNJ8-S422L genetic mutation and ER pattern.

Conclusion

At the end of the study, the investigated genetic mutation was observed in the control group, and not in the ER group. This can be explained by the fact that the majority of the patients in the ER group were asymptomatic for cardiac symptoms, and they had no family history of SCD. Furthermore, comprehensive studies with a larger population of patients at risk will shed light on the importance of arrhythmic tests and possible gene mutation.

Keywords: Early: repolarization, arrhythmia, KCNJ8 gene mutation

Bulgular

ER paterni bulunan grubun çoğunluğunun tip 1 ER paternde olduğu görüldü. EKG'de QTc mesafelerinin istatistiki anlamlılığa ulaşmasa da ER grubunda daha kısa olduğu görüldü. Ritm holter kayıtlarında iki grupta da anlamlı ventriküler aritminin olmadığı görüldü. ER grubunun kalp hızı değişkenliğinin (KHD) %26 oranında azalmış olduğu, SOEKG ile bakıldığında ise %14'ünde geç potansiyellerin (LP) olduğu görüldü. Araştırılan KCNJ8-S422L genetik mutasyonu ile ER paterni arasında ise ilişki izlenmedi.

Sonuç

Çalışmanın sonucunda araştırılan genetik mutasyon ER grubunda değil kontrol grubunda izlendi. ER grubununun çoğunluğunun kardiyak açıdan asemptomatik olması, kendilerinde ve ailelerinde AKÖ hikayelerinin bulunmaması dolayısıyla düşük risk profilinde olmaları bu durumu açıklayabilir. İleride yapılacak olan daha geniş populasyonlu ve riskli hastalardaki çalışmalar aritmi testlerinin ve olası gen mutasyonun önemine ışık tutabilir.

Anahtar kelimeler: erken repolarizasyon, aritmi, KCNJ8 gen mutasyonu

Introduction

Early polarization (ER) pattern is defined as at least 1 mm (0.1 mV) elevation of the J point from to isoelectric line, mostly at 2 inferior and/or lateral consecutive leads on 12-lead standard ECG. Studies have shown that the ER pattern is more frequently seen in young people and athletes, although it varies between 1% and 5% in the general population (1-3). This pattern, which we have known to be innocent for long years, has drawn attraction upon it has been detected in idiopathic ventricular fibrillation (IVF) and sudden cardiac death (SCD) cases (4-8). According to the last consensus report; if a resuscitated person had experienced unexplained VF and polymorphic ventricular tachycardia (VT) causing SCD, and if an ER pattern had been observed on ECG, this is ERS (9). We know that SCD is a death state of cardiac causes in which the patient died within one hour after symptom-onset, and it is seen in people with underlying structural heart disease and especially in coronary artery disease (CAD) related mortal arrhythmias (10-12). In nearly 10% of these cases, the cause is hereditary arrhythmogenic disorders that were named as 'cardiac channelopathies' in the literature (13). Brugada Syndrome (BRS) and ERS are included in a spectrum, known as "J wave syndrome" because of their electrophysiological similarities (14). Most cases in ERS are associated with sporadic mutations and familial history is rarely shown. Many gene mutations have been described in ERS just as in BRS. First of these is the KCNJ8 mutation encoding subunit of the ATP-sensitive potassium channel (IK-ATP). In addition, genetic mutations associated with L-type Ca channel and Na channel protein have also been reported (15-18). In this study, we investigated the presence of KCNJ8-S422L genetic mutation and sensitivity of arrhythmic tests in persons with ER ECG patterns.

Material & Methods

This study included 50 patients with ER patterns and 50 with a normal pattern on ECG. The study protocol was approved by the ethics committee of the Istanbul Bilim University (Approval No:15.08.2011/199) and signed informed consent forms were received from all participants. Patients without CAD and structural heart dis-

ease as a result of echocardiographic assessment were included in the study. Patients with an ECG compatible with ER at the isolated right precordial derivations were excluded from the study, because type 4 ER pattern is accepted as BRS ECG pattern. Patients using antiarrhythmic drugs affecting the autonomic nervous system and those with known chronic renal failure (CRF) and diabetes mellitus (DM) that cause autonomic dysfunction and patients with permanent pacemakers were also excluded. Patients' age, gender, detailed history, cardiac history (chest pain, dyspnea, tachycardia, and syncope), and family history (if any) were recorded. All patients underwent echocardiographic examination with GE Vivid 3 device (Tirat Camel, Israel). Except for the patients who underwent coronary angiography that revealed normal coronary artery, the presence of CAD was ruled out with the Bruce protocol exercise test (Kardiyosis Treadmill exercise test system, Turkey) in patients without a history of angiography.

ER ECG pattern was typed in the ER group: Type 1: confined with lateral precordial leads, Type 2: seen in the inferior or inferolateral lead, Tip 3: included all derivations (lateral, inferior and, right precordial). Corrected QT (QTc) with Bazett formula was found in both groups. Holter monitoring, heart rate variability (HRV), and the presence of LP were studied in the ER group. 24-h rhythm Holter records were taken with 24-h ECG monitoring (Biyomedikal system version (V:2.0), (device model: Biyomedikal DL-700,system VX3). The recordings were transferred to the computer, analyzed, visually examined and the areas

Table 1. The demographic data and the ER patterns of the individuals

	ER group	Control group	P value
Age (years)	33.1±9.7	45.8±9.9	0.02
Males (%)	%78	%40	0.04
LVEF %	63.9±1,8	62.0±7.7	0.696
IVS (cm)	0.96±0.08	0.99±0.09	0.590
PW (cm)	0.92±0.73	0.94±0.19	0.512
LVEDD (cm)	4.5±0.35	4.6±0.50	0.464
LVESD (cm)	3.0±0.28	3.0±0.62	0.412
LASD (cm)	3.5±0.16	3.7±0.34	0.258
RASD(cm)	2.3±0.12	2.3±0.17	0.704
SPAB (mmHg)	21.5±3.2	24.3±3.5	0.204
MET SCORE	12.7±2	10.4±2	0.314
History of syncope	2 (%4)	0	0.12
Type 1 ER	27 (%54)		
Type 2 ER	21 (%42)		
Type 3 ER	2 (%4)		

LVEF: left ventricular ejection fraction, L**VEDD:** left ventricular end diastolic diameter, **LVESD:** left ventricular end systolic diameter, **IVS:** interventricular septum thickness, **PW:** posterior wall thickness, **LASD:** left atrial systolic diameter, **RASD:** right atrial systolic diameter, **SPAB:** systolic pulmonary artery pressure.

Table 2. QTc values in ER and the control groups the relationship between ER and syncope

	ER group	Control group	P value
QTc (mean)	371±28.7 msn	381±31.4 msn	0.09
QTc (max)	422 msn	479 msn	
QTc (min)	320 msn	320 msn	
History of syncope	2 (%4)	0	0.15

with parasites were excluded from the analysis. Rhythm, conduction defects, minimum, maximum and mean heart rates, atrial early pulse (if any), atrial tachycardia, premature ventricular complex (PVC) (single, couplet, bigeminy, and trigeminy), and VT attack (if any) were recorded. Time-dependent parameters for (HRV) (SDNN, SDANN, PNN50, RMSSD, Triangular index) and frequency-based parameters (VLF, LF, HF) were automatically calculated via 24-h ECG recordings through Holter software. For SAECG, clamp tipped bipolar XYZ patient wire and EKG Master USB device (tepa® Ltd, Turkey) were used and the data obtained were calculated using HiRes and WinEKG Pro XYZ software (Tepa® Ltd, Turkey,2005). SAECG records were taken in a quiet room closed to external stimuli, using a high resolution ECG analysis system for 5 minutes between 09:00-11:00 in the morning. Whereas, 40-250 default filters were used for the LP. Two of three parameters (HFQRS (MSN), HFLA<40, RMS40 (μV)) being in abnormal ranges was considered the presence of LP.

Genetic study

Genomic DNA Isolation

DNA isolation was performed using a kit (HibriGen Quick Blood DNA isolation kit). The centrifuged fluid (2 cc peripheral blood sample in EDTA tubes) that contained genomic DNA was kept at +4oC until the analysis. For the mutation analysis, the allele involving the S422L mutation region was amplified by Polymerase Chain Reaction (PCR) using specifically designed primer pairs.

Agarose Gel Electrophoresis

A 5X TBE stock prepared as an electrophoresis running buffer was diluted 1/10 with dH2O. The prepared 2.5% (w/v) agarose gel was loaded with 5-6 μl PCR product mixed with 2-3 μl loading buffer and after running at 120 V for 20 minutes, the gel was examined under UV light to determine whether the DNA units were replicated in mutant and wild type tubes for the S422L mutation of the KCNJ8 gene.

Statistical Analysis

Data obtained in the study was statistically analyzed using "Statistical Package for Social Sciences (SPSS) 16.0 for Windows, USA" package software. When evaluating the study data, besides descriptive statistical methods (mean, standard deviation), on comparison of the quantitative variables, independent samples t-test was used for the comparison of the normally distributed parameters between the groups. Categorical data were expressed as a percentage and compared with the Chi-square test and Fisher Exact Chi-square test. $p<0.05$ values considered statistically significant.

Results

The mean ages among the groups were 33.1 years (78% male) and 45.8 years (40% male) respectively. In the study, type 1 ER pattern was found in 54% and type 2 ER pattern in 42% of the patients. Type 3 ER pattern was observed only in two patients. Demographic and echocardiographic data are shown in Table 1. Although not statistically significant, the mean QTc value was shorter in the ER group (mean QTc: 371±28.7 MSN and QTc: 381±31.4 MSN; p =0.08, respectively). Neurological examinations of the patients in the ER group were normal, 2 patients had a history of syncope, while no statistically significant correlation was found between ER and syncope (p=0.15) (Table 2). In the ER group; the mean HR was 74±8 /min, max average HR was 145/min and minimum

Table 3. Heart rate variability values with time domain based methods

	ER group	Normal values
Mean HR	74±8	
Mean Minimum HR	46±7	
Mean Maximum HR	145±16	
SDNN	164±50	141±39
SDANN	146±56	127±35
Triangular index	617±167	37±15
RMSSD	52±33	27±12
PNN50	15±12	20±16
HFQRS (msn)	98±8	>114-120 msec
HFLA<40	31±8	<20 μV
RMS40 (μV)	44±4	> 39 msec

HR: heart rate, **SDNN:** standart deviation of all NN intervals, **SDANN:**standart deviation of 5 minutes segments of mean NN intervals, **Triangular index:** distribution intensity integral derived from division of distribution intensity of NN intervals by maximal distribution intensity, **RMSSD:** the mean square root of the values derived from sum of the square roots of substracted adjacent NN intervals , **PNN50:** the ratio of number of NN50 to total number of NN interval, **HFQRS:** filtered vector quantity signal time, **HFLA<40:** time of the region smaller than 40 μV leftwards after high frequency vector quantity activity, **RMS40:** RMS value of the last 40 msec of high frequency vector quantity, **LP:** late potentials

average HR was 46/min in the Holter records. None of the patients showed couplet, triplet PVC, or non-sustained ventricular tachycardia attack. First degree AV block was observed in nine patients. Sinus pauses and severe AV block were not detected in any patient. When evaluated with time-domain analysis, HRV was decreased by 26%, while the presence of LP was found with SAECG in 14% of the patients (Table 3). Genetic mutation was observed only in one patient in the control group (CT heterozygous mutant genotype (Table 4).

Discussion

ER pattern is more commonly seen in healthy young people and is fairly benign. It has been defined together with BRS as J wave syndromes due to their ECG similarities. Transmural voltage gradient occurs between the epicardium and endocardium in people with ER. In the early phase of the epicardial action potential, increased outward K current and decreased Na and Ca currents into the cell cause a shortening of the action potential in the epicardium. Thus, repolarization dis-

persion occurs between the epicardium and endocardium. This morphologically is seen on ECG as notching in QRS wave (positive J wave in the spike-wave morphology) or slurring of the terminal part (a slow shifting from QRS wave to ST-segment) (19). This common ER ECG pattern that we accept as innocent, has led us to question our approach since it was observed in persons who had experienced SCD. However, it was reported in a meta-analysis that, SCD was reported only in 0.07% of those with ER (20)

The association of ER and SCD was reported for the first time by Haissaguerre et al. (7). This multi-center study included 206 patients who survived after idiopathic VF and 412 matched control persons. ER pattern was detected at inferior and/or lateral leads in 31% of the patients in the idiopathic VF group and only in 5% of the patients in the control group. In addition, recurrent VF was higher in SCD related ER group. In a study by Rosso et al., comparing 45 patients who developed IVF and age and gender-matched control group, J point elevation in the inferior leads and D1, aVL was more common in the IVF group. However, interestingly J point elevation observed at V4-6 was similar between the two groups (8). In the CASPER study by Derval et al. (21), among 100 patients who developed SCD, ER pattern was observed in 6 of 44 with an etiology that could be clarified, and 13 of 56 patients with unknown pathology and who were considered to have idiopathic VF. These studies have raised the issue of which ER patterns are more risky. Tikkanen et al., published further analysis with subgrouping of the individuals with ER in Finland population according to ECG characteristics, based on the ST-segment morphology with a notching or slurring J wave. The authors observed that J wave being notching or slurring did not create a difference, but it caused a higher risk especially at inferior leads compared to those with a horizontal or downsloping ST-segment. In the same study, it was found that the upsloping ST-segment following J wave was the most commonly observed pattern in athletes, and a 2 mm elevation of J wave was associated with a high arrhythmic event in this group (22,23). Therefore, it can be said that types 2 and 3 ER patterns are more dangerous ER. Although there are studies reporting that the presence of a short QT is risky in J wave syndromes (24), in their study Roten et al. (25) ER patients who had experienced VT had a longer QT and stated that an increased J wave amplitude and decreased T/R ratio are arrhythmic risk factors. In our study, type 2 ER pattern was found in 42% and type 3 pattern only in two patients. QTc was shorter compared to the control group. However, in our study, there was no history of VF or SCD in the patients or their families. Only two patients with normal neurological evaluations had a history of syncope that we thought to be vasovagal, but the correlation between ER and syncope did not reach statistical significance.

Heart rate, beta-adrenergic, and parasympathetic tone is known to play a role in the ER pathophysiology. HRV is often used in the evaluation of autonomic function. Increased HRV is associated with long-term survival. HRV is evaluated with time and frequency-based measurements on 24-h rhythm records. Among the time-based parameters, RMSSD correlates with HF, which is a frequency-based parameter, shows parasympathetic activity, while SDNN is correlated with LF and shows

Table 4. Relationship between ER and KCNJ8-S422L genetic mutation

	ER group	Control group
KCNJ8-S422L mutation	0	1
Gene sequence	CACA**TCG** GAATC....(TCG; Ser)	CACA**TTG** GAATC....(TTG; Leu)

sympathetic activity. An increased HF/LF ratio is associated with increased parasympathetic activity. LP are the parameters used especially in predicting malignant ventricular arrhythmias in some patient groups (8). Riera et al. (26) reported that parasympathetic activity is predominant and the incidence of sinus bradycardia increases in individuals with ER. They found 1st degree atrioventricular block in 1% to 5% of the patients. Soliman et al. (27) compared the presence of LP using PVC, HRV, and SAECG with rhythm Holter records between the ER and control groups. Among the studied parameters only mean HR was low in the ER group. Other than that, they did not see any significant difference in HRV. Besides, they did not find a statistical difference in terms of LP. The rate of LP was 11% for both groups. In our study, HRV was decreased by 26% in the ER group and it was thought that this decreased response might be associated with the suppression of the parasympathetic response. Similar to the previous studies, LP was found by 14% with SAECG.

The first stated in ERS is KJN8-S422L mutation, which is the genetic mutation of the ATP-sensitive the K channel subunit. As a result of this epicardial mutation, K channel gains a half-open feature and can cause malignant arrhythmias with outward loss of K current, repolarization dispersion between the epicardium and endocardium, and phase 2 re-entry. In the current study, we examined the presence of this genetic mutation in the group, which was non-syndromic and only had ECG ER pattern, and the group with normal ECG. We observed KCNJ8 S422L gene mutation only on one female patient who had undergone coronary angiography which revealed normal coronary arteries.

Recent recommendations are that further arrhythmic testing will not provide additional benefit in the asymptomatic ER pattern group. However, a family history of SCD at a young age and having a personal history of syncopes warrant electrophysiological study (EPS). Implantation of an implantable cardioverter-defibrillator (ICD) is needed in ERS patients with a history of cardiac arrest. If a person has a history ıf syncope and ER pattern at inferior leads, and if VF is induced by isoproterenol or quinidine in EPS, ICD should be considered. ICD can be thought of in the presence of an increased J amplitude or horizontal/downsloping ST-segment and a family history of SCD at a young age regardless of the presence of the pathogenic genetic mutation (9,28). The monophasic action potential (MAP) technique, which is one of the novel invasive arrhythmic tests, facilitates direct measurement of action potential features, and has the potential to characterize transmural repolarization gradients in detail. Using this novel technique, ER patients carrying the moderate-to-high risk of SCD can be identified (29)

Conclusion

Since very few patients with ER pattern will develop arrhythmias during follow-up, determination of this minority of patients will be challenging for the clinician, although those with the risk of ER ECG pattern, and a family history of SCD or syncope should alert the clinician and the patient should be referred to an arrhythmia specialist.

Study Limitations

The major limitations of this study include the relatively small number of patients and lack of long-term follow-up. The importance of how to follow-up these low-risk patients with simple arrhythmic tests or examination of the presence of genetic mutation will be understood under the light of further studies with a larger population and longer follow-up.

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