Electrocardiographic evaluation in patients with endemic fluorosis without clinically evident heart disease

Ercan Varol*, Selahattin Akçay*, İ. Hakkı Ersoy**,
Mehmet Özaydın*, Banu Kale Köroğlu**, Simge Varol***

* Süleyman Demirel Üniversitesi Tıp Fakültesi, Kardiyoloji AD, Isparta
** Süleyman Demirel Üniversitesi Tıp Fakültesi, Endokrinoloji AD, Isparta
*** Süleyman Demirel Üniversitesi Mühendislik Fakültesi, Jeoloji Müh, Isparta

Özet

Klinik olarak belirgin kalp hastalığı olmayan endemik florozisli hastaların elektrokardiyografik bulguları

Amaç: Bu çalışma endemik florozisli hastaların elektrokardiyogram (EKG) bulgularının incelenmesi açısından yapıldı. Ellialtı endemik florozis hastası ve yaş, cinsiyet ve vücut kütle indeksi eşitlenmiş 44 sağlıklı bireyin standart 12 derivasyon EKG'si, idrar flor düzeyi ve serum sodium, potasyum, kalsiyum ve fosfor analizi yapıldı. Temel EKG ölçümleri ve EKG değişkliklerinin frekansı değerlendirildi. Bulgular: İdrar flor düzeyleri florozis hastalarında kontrol grubuna göre anlamlı derecede yüksekti (1.9 ± 0.2 mg/l vs. 0.4 ± 0.1 mg/l sırasıyla; P<0.001). Yaş, cinsiyet, vücut kütle indeksi ve serum sodyum, potasyum, kalsiyum ve fosfor düzeyleri açısından kontrol grubu ve florozis hastaları arasında istatistiksel açıdan fark yoktu. Kalp hızı, temel EKG ölçümleri ve EKG değişiklikleri açısından kontrol grubu ve florozis hastaları arasında istatistiksel olarak anlamlı fark yoktu. Sonuç: Endemik florozisin EKG üzerine etkisi olmadığı sonucuna vardık.

Anahtar kelimeler: endemik florozis, elektrokardiyogram

Abstract

Objective: This study was carried out to analyse the electrocardiogram (ECG) in patients with endemic fluorosis. Methods: Fifty six patients with endemic fluorosis and 44 age, sex and body mass index (BMI) matched healthy controls with normal fluoride intake underwent standart 12-lead ECG, urine fluoride level and serum sodium, potassium, calcium and phosphorus determination. Basic ECG measurements and frequency of ECG abnormalities were evaluated. Results: The urine fluoride levels of fluorosis patients were significantly higher than control subjects as expected (1.9 ± 0.2 mg/l vs. 0.4 ± 0.1 mg/l respectively; P<0.001). There were no statistically significant differences between the two groups with respect to age, gender, BMI and serum levels of sodium, potassium, calcium and phosphorus. There were no statistically significant differences between controls and fluorosis patients with respect to heart rate, basic ECG measurements and ECG abnormalities. Results: We concluded that endemic fluorosis has no effect on ECG.

Key words: endemic fluorosis, electrocardiogram

Introduction

Fluoride is one of the chemical elements necessary for dental and body development. It also helps to maintain the integrity of bone (1). However, excessive intake of fluoride leads to chronic fluorosis, dental fluorosis (mottled teeth) and skeletal fluorosis. Although the prevalence of this disease has decreased considerably, it is still endemic in many places around the world such as India, China, and Africa (2-4). Endemic fluorosis is a public health problem in Isparta, a region situated in southern Turkey where fluorosis is endemic (1). The origin of fluoride was attributed to volcanic rocks in the Golcuk Lake area, located 6 km. southwest of the Isparta city centre. Golcuk area consists of sedimentary and volcanic rocks. Those are tephriphonolite, pyroclastic series and trachyandesite together with trachyite. These volcanic rocks consist of fluoride bearing minerals. These minerals are pyroxene, hornblende, biotite, fluorapatite and glassy groundmass (5). Although high fluoride-content drinking water has been diluted

Corresponding Address: Doç. Dr. Ercan Varol
Süleyman Demirel Ünivesitesi Tıp Fakültesi, Şevket Demirel Kalp Merkezi, Isparta, Türkiye
Tel: 0 532 3468258, Fax: 0 246 2324510
E-mail: drercanvarol@yahoo.com

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with some low fluoride-content drinking water sources with the object of supplying safe and sufficient water to the city population in recent years, the fluoride levels of drinking water are still high in some part of the city.

It has been reported that experimental fluorosis in rabbits produced pathological lesions in the myocardium (6-8). Similarly, changes in the electrocardiogram (ECG) in animals were also linked to fluoride (9,10). However, there are limited studies about effects of chronic fluorosis on ECG in humans subjects (11-13).

Fluoride produces its actions by various different mechanisms. However, the exact mechanism is not clear. It has been reported that fluoride causes disturbances in plasma sodium, potassium and calcium ion levels (14). These electrolytes are essential for normal electrical conduction, depolarization and repolarization of the cardiac cells. Therefore, disturbances of these electrolytes by fluoride toxicity might cause changes in the electrical activity of heart. Therefore, we aimed to analyse the ECG in patients with endemic chronic fluorosis to estimate the possible toxic effects of chronic fluoride intake through drinking water on myocardial tissue in clinical setting. We also studied serum electrolyte levels those can cause changes in ECG to clarify the possible relationship between ECG and electrolyte disorders.

Material and Methods

Fifty six patients with endemic fluorosis (32 males/24 females; mean age 32.8 ± 8.7 years) and 44 age, sex and body mass index (BMI) matched healthy controls (30 males/14 females; mean age 33.7±8.7 years) with normal fluoride intake were enrolled in this prospective study.

Endemic fluorosis was diagnosed according to the clinical diagnosis criteria, as described by Wang et al; 1) living in the endemic fluorosis region since birth, 2) having mottled tooth enamel, indicating dental fluorosis, 3) consuming water with fluoride levels above 1.2 mg/l (normal 1 mg/L), and 4) a urine fluoride level greater than 1.5 mg/l. (normal< 1.5 mg/l) (15). According to Isparta Health Organization data, the mean fluoride level in drinking water was 2.74 ± 064 mg/l in the endemic fluorosis region and 0.53 ± 0.06 mg/l in the non-endemic region (16). All patients met Wang's criteria.

Physical examination was performed in all patients and controls. The patients were also examined for having mottled tooth enamel which is one of the diagnostic criteria of endemic fluorosis. Body weight and height were recorded, and body mass index (BMI) was calculated for each patient as weight (kg)/height (m).[2]

Exclusion criteria of the study were the presence of any known cardiac disease (hypertension, angina pectoris) and lung disease, use of cardiac drugs, diabetes mellitus, chronic renal and hepatic diseases, serum electrolyte imbalance. Informed written consent was obtained from all subjects. This study was approved by the Ethics Committee.

Biochemical measurements

Urine samples were analyzed for fluoride by using an ion specific electrode (Orion 9609BN ionplus Sure-Flow Fluoride). Serum electrolyte profiles were determined by standard methods.

Electrocardiographic measurements

Twelve-lead ECG was recorded with a sensitivity of 10 mm/mv and a paper speed of 25 mm/s from all patients within 24 h after admission. ECG measurements were made manually. For all measurement, the lead II was used. The P wave duration, PR, QRS, QT intervals, T wave duration and P wave, QRS, T wave amplitudes were measured manually by two experienced cardiologist who was blinded to the study groups. Interobserver coefficients of variation were 2%, 3.6%, 5%, 1.6%, 4.4%, 6.4%, 1% and 2.4% for P wave duration, PR, QRS, QT intervals, T wave duration and P wave, QRS, T wave amplitudes respectively. The values of each measurement estimated by two cardiologists were averaged and used for analysis. QT interval was corrected by heart rate using Bazett's formula and was considered significant prolongation more than 0.44 s (17). Each ECG was also evaluated for sinus arrhythmia, sinus bradycardia, first-degree antrio - ventricular block, right axis deviation, left axis deviation, left ventricular hypertrophy, defined as the greatest measured depth of the S-wave in leads V1 or V2 added to the greatest height of the R-wave in leads V5 or V6?35 mm, nonspecific ST-segment and T-wave changes, right bundle branch block, left bundle brunch block, early repolarization, premature atrial contraction, premature ventricular contraction and r progression loss.

Statistical analysis

Data were analyzed with the SPSS software version 10.0 for Windows. Continuous variables from the study groups were reported as mean ± standard deviation, categorical variables as percentages. To compare continuous variables, the Student t-test or Mann-Whitney U test were used where appropriate. Categorical variables were compared with the chi-

squared test. Statistical significance was defined as $p<0.05$.

Results

Clinical characteristics and serum electrolyte levels of the controls and fluorosis patients were summarized in Table 1. Urine fluoride levels of fluorosis patients were significantly higher than control subjects as expected (1.9 ± 0.2 mg/l vs 0.4 ± 0.1 mg/l respectively; P<0.001). There were no statistically significant differences between fluorosis patients and the controls respect to age, gender, BMI and levels of sodium, potassium, calcium and phosphorus. Basic ECG measurements of the controls and fluorosis patients were shown in Table 2. There were no statistically significant differences between controls and fluorosis patients with respect to heart rate and basic ECG measurements. The frequency of ECG abnormalities in controls and fluorosis patients were shown in Table 3. There were no statistically significant differences between controls and fluorosis patients with respect to ECG abnormalities.

Table 1. Comparison of the clinical characteristics and serum electrolyte levels of the control and fluorosis patients.

	Control (n=44)	Fluorosis Patients (n=56)	P value
Age (years)	33.7 ± 8.7	32.8 ± 8.7	0.62
Sex (M/F)	30/14	32/24	0.25
BMI	25.5 ± 3.3	25.2 ± 3.8	0.68
Urine fluoride (mg/l)	0.4 ± 0.1	1.9 ± 0.2	< 0.001
Sodium (mmol/L)	137.3 ± 2.8	137.1 ± 3.2	0.72
Potassium (mmol/L)	4.1 ± 0.2	4.2 ± 0.2	0.16
Calcium (mg/dL)	9.9 ± 0.3	9.8 ± 0.4	0.40
Phosphour (mg/dL)	3.2 ± 0.4	3.1 ± 0.25	0.42

M/F: male to female, BMI: body mass index, P value is for comparison between control and study population.

Table 2. Basic electrocardiographic measurements of the control and fluorosis patients.

	Control (n=44)	Fluorosis Patients (n=56)	P value
Heart rate (bpm)	72.6 ± 9.8	73.3± 10.5	0.64
Interval/duration (s)			
P	0.06 ± 0.02	0.06 ± 0.02	0.43
PR	0.13 ± 0.01	0.13 ± 0.02	0.50
QRS	0.06 ± 0.01	0.06 ± 0.02	0.76
QT	0.37 ± 0.03	0,37 ± 0.02	0.77
QTc	0.41 ± 0.03	0,43 ± 0.05	0.11
T	0.14 ± 0.03	0.14 ± 0.05	0.90
Amplitude (mm)			
P	0.12 ± 0.03	0.12 ± 0.04	0.53
ORS	0.98± 0.40	1.04± 0.30	0.44
T	0.27± 0.09	0.27 ± 0.10	0.93

QTc: Corrected QT, P value is for comparison between control and study population.

Table 3. The frequency of ECG abnormalities in controls and fluorosis patients.

	Control (n=44)	Fluorosis patients (n=56)	P value
Sinus arrhythmia	4 (9%)	9(16%)	0.30
Sinus bradycardia	1 (2%)	2 (3%)	0.70
Sinus tachycardia	0 (0%)	1 (2%)	0.37
First-degree AV block	0 (0%)	0 (0%)	
Right axis deviation	3 (7%)	2 (4%)	0.46
Left axis deviation	2 (5%)	2 (4%)	0.80
LVH	0 (0%)	0 (0%)	
ST-T	2 (5%)	5 (9%)	0.39
RBBB	0 (0%)	1 (2%)	0.37
LBBB	0 (0%)	0 (0%)	
Early repolarization	2 (4%)	0 (0%)	0.10
PAC	1 (2%)	3 (5%)	0.43
PVC	1 (2%)	1 (2%)	0.86
R progression loss	1 (2%)	4 (7%)	0.26

AV: Atrioventricular, LVH: Left ventricular hypertrophy, ST-T: ST-T wave changes, RBBB: Right bundle branch block, LBBB: Left bundle brunch block, PAC: Premature atrial contraction, PVC: Premature ventricular contraction, P value is for comparison between control and study population.

Discussion

There are limited studies on effects of chronic fluorosis on ECG especially in human subjects. The two of these studies are on animals. Donmez et al found prolonged P–Q interval and sinus bradycardia in the sheep with chronic fluorosis when compared with healthy sheep (9). Kilicalp et al found prolonged P–Q interval and sinus bradycardia in the dogs with chronic fluorosis (10). They assumed that this effect in animals with chronic fluorosis could be due to insufficient synthesis and secretion of iodine and thyroid hormones according to the previous reports (18,19). In addition, Kilicalp et al reported that duration and amplitude of T wave was longer and higher in the fluorosis group than control group (10). This finding was similar to the previous study in which T wave peaking was observed in ECG of dogs during acute sodium fluoride infusion (20).

There are also limited studies about effects of chronic fluorosis on ECG in human subjects. Takamori et al reported myocardial damage and dilatation of the cardiac muscle and established a direct relationship between increased myocardial damage and mottled enamel by means of ECG (11). Zhou et al studied the ECG changes in 271 dental fluorosis cases and they found that 29.5% had abnormal heart rhythms, and 12.8% had reduced myocardial function (12). Xu et al also reported abnormal ECG findings (sinus irregularity, sinus bradycardia, low voltage, ST and T wave changes) in patients with skeletal fluorosis (13). But there is less certainty about the nature of

these effects. Recently, Olgar et al studied the effects of chronic fluorosis on cardiovascular system in thirty-five childrens with dental fluorosis. They found significantly low sodium, calcium and T4 levels and increased QT and QTc intervals in children severely effected with dental fluorosis (21). Other ECG parameters were within normal limits in children with dental fluorosis in their study as in our study. Our study population consisted of young adults and sample size of our study was larger than this study. Several reports showed that acute fluoride poisoning caused electrolyte abnormalities and fatal arrhythmia in experimental animal studies (22,23). There are also few reports in human subjects about electrolyte abnormalities and associated ECG findings in acute fluoride poisoning. McIvor reported a 19-year-old man who presented with acute fluoride poisoning with delayed fatal hyperkalemia (24). The electrolytes of the patients were normal initially, but two hours later he developed ECG findings of hyperkalemia followed by refractory ventricular fibrillation. Baltazar et al reported a patient with acute fluoride intoxication who developed peaking of the T waves, an ECG evidence of hyperkalemia, before developing refractory ventricular fibrillation (25). It has been proposed that cardiovascular effects of acute fluoride poisoning developed from hypocalcemia and hyperkalemia. In vitro studies have shown that fluoride binds to calcium and cause hypocalcemia. Paradoxically while decreasing extracellular calcium levels, fluoride increases intracellular calcium, which is thought to trigger calcium-dependent potassium channels and produce a potassium efflux causing hyperkalemia (22-25). It has been thought that hyperkalemia was responsible from fatal arrhythmia and death from acute fluoride poisoning. Recently, subacute toxic effects of fluoride have been reported. Kant et al showed a significant increase in P-R, Q-T and S-T intervals, prolongation of T wave duration and bradycardia after subacute exposure of fluoride for 30 days in healthy goats (26). Kant et al also studied the various biochemical parameters during subacute toxicity of fluoride and showed decrease in plasma sodium concentration and no significant changes in plasma calcium, phosphorus, and potassium after exposure of sodium fluoride for 30 days in healthy goats (27). We also found no statistically significant differences between fluorosis patients and controls with respect to levels of sodium, potassium, calcium and phosphorus. Our results are consistent with previous study (27) except sodium levels. As a difference, our study population consisted of patients with endemic chronic fluorosis. There are conflicting results about electrolyte disorders and ECG abnormalities in chronic fluorosis. In an animal experimental study, Das et al reported that plasma calcium concentration of fluoride treated rabbits were significantly lower than those of controls after exposure of sodium fluoride for 18 months (28). Shivashankara et al also reported that children with chronic fluorosis had reduced serum potassium and urea concentrations (29). In another study, increased sodium and potassium levels have been reported in patients with endemic fluorosis (30). Recently, Sharifian et al studied serum calcium and parathyroid hormone levels in aluminum potroom workers exposed to fluoride and they found that serum calcium levels were within the normal range in all workers (31).

In the present study, we investigated the effect of chronic fluorosis on electrocardiogram in patients with endemic fluorosis without clinically evident heart disease. We found that chronic fluorosis had no effect on ECG contrary to previous studies. We also studied serum electrolyte levels those can influence ECG. We found no significant differences in electrolyte levels between chronic fluorosis patients and control subjects.

One of the reasons of normal ECG findings in fluorosis patients might be normal electrolyte levels in fluorosis patients. Our fluorosis patients were also relatively young. The mean age of our fluorosis patients was 32.8± 8.7 years. However, fluorosis patients of the previous study (13) were relatively older (aged between 39 and 56) than our fluorosis patients. Young study group can be another cause of normal ECG findings in our fluorosis patients. We can expect that ECG abnormalities increase as the age increase. We also used strict exclusion criteria in our fluorosis patients to eliminate the other factors those can influence ECG. This also can be another cause of normal ECG findings in our fluorosis patients. The previous studies investigated only electrolyte disorders or only electrocardiographic abnormalities in acute or chronic fluorosis separately. To the best of our knowledge, there is only one study investigating electrolyte disorders and ECG abnormalities at the same time in chronic fluorosis patients (21). We also studied electrolyte disorders and ECG abnormalities at the same time in chronic fluorosis patients in the present study.

In conclusion, we found that chronic endemic fluorosis

has no effect on ECG in contrary to previous studies. The small sample size was study limitation of our study. Further studies and other cardiovascular evaluations are needed to clarify cardiovascular disturbances in endemic fluorosis patients.

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