

Effects of fluorosis on QT dispersion, heart rate variability and echocardiographic parameters in children

Çocuklarda QT dispersiyonu, kalp hızı değişkenliği ve ekokardiyografik parametrelere florozisin etkileri

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ABSTRACT

Objective: Chronic fluoride poisoning is called fluorosis. The aim of the study was to investigate effects of fluorosis on cardiovascular system in children by measuring QT dispersion (QTd), corrected QT dispersion (QTcd), heart rate variability (HRV) and echocardiography findings.

Methods: Thirty-five children with dental fluorosis and 26 children as control group were included in this cross-sectional study. Dean index was used for the clinical diagnosis. The fluoride levels of subjects measured by ion electrode method in spot urine higher than 0.6 ppm were included in the study. Serum electrolytes and thyroid function tests were analyzed. Electrocardiography (ECG), echocardiography and 24-hour ambulatory Holter monitorizations were applied, and all the data were analyzed for measuring HRV, and calculation of QTd and QTcd intervals. Corrected QT (QTc) intervals were determined with the Bazett formula. Difference between the longest and shortest intervals was considered as dispersion. Statistical analysis was performed Kruskal-Wallis test and Pearson correlation test.

Results: Low free thyroxine hormone (FT4) (Control Group, Group 2 1.11 (0.85-1.64) ng/dL, 0.96 (0.85-1.11) ng/dL, p<0.05), calcium (Control Group, Group 1, 2, 9.80 (9.30-10.70) mg/dL, 9.60 (8.90-10.70) mg/dL, 9.50 (8.90-10.10) mg/dL, p<0.05) and high serum sodium levels (Control Group, Group 2 139 (136-142) mEq/L, 141 (138-148) mEq/L, p<0.01), increased QT (Control Group, Group 2 329.8 (300.0-363.5) msec, 351.8 (318.0-372.0) msec, p<0.05) and QTc intervals (Control Group, Group 1 390.6 (309.0-418.5) msec, 366.8 (318.2-468.5) msec, p<0.05) were found in subjects with fluorosis. No significant difference was found with respect to echocardiography and HRV variables.

Conclusion: Endemic fluorosis is a risk factor for decrease in calcium and FT4 levels, increase in sodium levels and QT prolongation. These findings might be related with some cardiovascular system dysfunctions such as arrhythmias or syncope. Subjects with fluorosis should be monitored in terms of long QT and QTc intervals. (*Anadolu Kardiyol Derg 2011; 2: 150-5*)

Key words: Fluorosis, QT interval, QTc dispersions, heart rate variability, child

ÖZET

Amaç: Kronik flor zehirlenmesine florozis denilir. Bu çalışmanın amacı, çocuklardaki florozisin kardiyovasküler sistem üzerine olan etkilerini, QT dispersiyonu (QTd), düzeltilmiş QT dispersiyonu (QTcd), kalp hızı değişkenliği (KHD) ve ekokardiyografi (EKO) bulguları ile incelemektir.

Yöntemler: Enine-kesitli bu araştırmada, dental florozisli 35, sağlıklı 26 çocuk çalışmaya alınmıştır. Klinik tanı Dean indeksi kullanılarak konulmuştur. Spot idrarda flor seviyesi iyon elektrot metodu ile 0.6 ppm üzerinde ölçülen olgular çalışmaya alınmıştır. Serum elektrolit seviyeleri, tiroit fonksiyon testleri ölçülmüştür. Elektrokardiyografik, ekokardiyografik ve 24-saatlik ambulator Holter monitorizasyonları uygulanmış ve tüm veriler KHD ölçmek için değerlendirildi, QT ve QTcd aralıkları hesaplanmıştır. Düzeltilmiş QT aralığı Bazett formülü ile belirlenmiştir. En uzun ve en kısa ölçümler arasındaki fark dispersiyon olarak adlandırılmıştır. Grupların karşılaştırılması Kruskal-Wallis testi ve Pearson korelasyon testi kullanılmıştır.

Bulgular: Florozisi bulunan olgularda serbest T4 (ST4) (Kontrol Grup, Grup 2, 1.11 (0.85-1.64) ng/dL, 0.96 (0.85-1.11) ng/dL, sırasıyla, p<0.05) ve kalsiyum seviyelerinde (Kontrol Grup, Grup 1, Grup 2, 9.80, (9.30-10.70) mg/dL, 9.60, (8.90-10.70) mg/dL, 9.50, (8.90-10.10) mg/dL, p<0.05) azalma, serum sodyum değerlerinde artma (Kontrol Grup, Grup 2, 139 (136-142) mEq/L, 141 (138-148) mEq/L, p<0.01), QT (Kontrol Grup, Grup 2, 329.8 (300.0-363.5) msn, 351.8 (318.0-372.0) msn, p<0.05) ve QTc sürelerinde bir uzama (Kontrol Grup, Grup 2 390.6 (309.0-418.5) msn, 366.8 (318.2-468.5) msn, p<0.05) saptanmıştır. Ekokardiyografik ve kalp hızı değişkenliği değerlendirilmesinde anlamlı bir fark gözlenmemiştir.

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Sonuç: Endemik florozis azalmış kalsiyum ve ST4, artmış sodyum seviyeleri, QT uzaması açısından risk faktörüdür. Bu bulgular senkop ve aritmi gibi bazı kardiyovasküler sistem disfonksiyonlarıyla ilişkilidir. Florozisli olgular, QT ve QTc süresi uzaması açısından takip edilmelidir. (*Anadolu Kardiyol Derg 2011; 2: 150-5*)

Anahtar kelimeler: Florozis, QT, QTc dispersiyonları, kalp hızı değişkenliği, çocuk

Introduction

Fluoride is a halogen and is found in soil, water, rocks, air, plants and animals in different quantities. Fluoride is a necessary element for body and mainly stored in bones and teeth. Under normal circumstances, people should receive some amounts of fluoride compounds, which are not harmful, on a daily basis. However, if the amount of daily fluoride consumption exceeds the security threshold for a long time, chronic fluoride poisoning may occur and it is called as fluorosis. In various regions of the world, high fluoride levels in drinking water poses a public health problem (1-3).

Isparta is one of the endemic regions of fluorosis. Ground waters with high fluoride concentrations occur in many area of Turkey including not only in Isparta, but also, Samsun-Havza, Vezirköprü, large parts of East Anatolia (Tendürek Mountains, Ağrı, Van) Eskişehir-Beylikova/Kızılcaören villages, Kırşehir-Kaman/Bayındır-Çamalak villages, as well (5). Therefore, fluoride pollution in drinking water is a national health problem as the fluoride presents often at levels above acceptable limits. Furthermore, there was also a presence of high risk factors for chronic fluoride poisoning in some industrial areas. Toothpastes, tea, drugs and fluoridated salts usages may also cause fluorosis (6). Until 1970s, fluorosis had been detected in 70% of the people living in Isparta (5). In recent years, the amount of fluoride in water has been reduced. However, especially some areas of Isparta, still, contain higher amounts of fluoride in drinking water. Some of inhabitants continue to consume high fluoride level water (6).

Fluorosis has some hormonal, gastrointestinal, hematological, skeletal, renal, respiratory, cardiovascular, immunological, neurological and developmental side effects (1-4).

The effect of fluoride on the cardiovascular system was not studied extensively in previous years. Most of these studies were conducted as experiments with animals (1-4). Previous studies have shown that excess of fluoride induces some electrocardiographic changes and fatal arrhythmias in adults (7).

According to the literature, we could not find the studies, which investigated the cardiovascular side effects of fluorosis in children.

This study was aimed to investigate the effects of fluorosis on cardiovascular system in children by echocardiographic findings and measuring QT dispersion, corrected QT dispersion, and heart rate variability.

Methods

Study population and design

Study was conducted at the Department of Pediatrics of Süleyman Demirel University Medical Faculty, between June-

August 2008. Thirty-five patients (20 girls, 15 boys) aged 7-16 years with the diagnosis of endemic fluorosis were included in this cross-sectional observational analysis. The clinical diagnosis of endemic fluorosis was modified from the criteria of Wang et al. (8): 1. Living in the endemic fluorosis region since birth, 2. Having dental fluorosis, 3. Consuming drinking water with a fluoride level more than 1.2 ppm, and 4. The urine fluoride level greater than 0.6 ppm. Assessment of fluorosis was carried out using the Dean index (9). This index scores two teeth that are most affected. The index grades fluorosis from very mild, mild, moderate or severe and notes the percentage of the labial surface that is affected by fluorosis. Patients were subdivided into two groups. Group 1 consisted of 22 subjects with very mild, mild, and moderate fluorosis. Group 2 consisted of 13 subjects with severe fluorosis. Control Group included 26 (13 girls, 13 boys) volunteers living in a non-endemic region.

Children having acute or chronic illness by either history or physical examination were excluded.

The study was approved by the Ethics committee of our institution. Informed consents were obtained from all parents.

Clinical examinations

Detailed histories were noted and full physical examinations with blood pressures were performed. Chest X-ray, 12 channel electrocardiography (ECG) estimations (Nihon Kohden, Japan), (AEK), were studied in all patients.

Echocardiographic analysis

All patients underwent complete transthoracic echocardiographic studies with a GE Vingmed SystemV (Horten, Norway) with a 3.5-MHz phased-array probe (SK, ŞO). According to the American Society of Echocardiography guidelines (10), standard M-mode, 2-dimensional and Doppler echocardiographic studies were performed. Aortic diameter, ejection fraction, left ventricular end diastolic diameter, interventricular septum thickness and left ventricular posterior wall thickness of all patients were measured.

Laboratory analyses

Biochemical analyses were performed by enzymatic methods on analyzer (autoanalyzer, Abbott Aeroset, III., USA). Serum free thyroxine (FT4), free triiodothyronine (FT3), and thyroid stimulating hormone (TSH) levels were measured to evaluate thyroid functions. We measured FT3, FT4, and TSH levels for evaluation of thyroid function because free thyroid hormones are the active form of the thyroid hormone and usually they are initially affected with TSH in thyroid disorders. Serum levels of

FT3, FT4, and TSH were determined using chemiluminescent micro-particle immunoassay (CMIA, USA). Reference ranges for FT3, FT4, and TSH were 1.71-3.7 pg/mL, FT4: 0.7-1.47 ng/dL and TSH: 0.35-4.94 µIU/mL respectively.

Urine fluoride was analyzed by using an ion specific electrode (Orion Research, Inc.500 Cummings Center, Beverly, MA 01915-6199) (11). Spot urine fluoride level higher than 0.6 ppm was considered as elevated (1).

Measurements of QT interval and QT dispersion

ECG's with a duration of 10 second (s) were recorded, using the same system at 25 mm/s paper speed and standardized at 0.1 mV/mm. QT intervals were measured by a single observer manually in all the 12 leads in blinded manner from the onset of the QRS complex to the end of the T wave as previously described (12). When U waves were present, the QT interval was measured to the nadir of the trough between the T and U waves. If the end of the T wave could not be identified, the lead was not included. Three consecutive QT intervals were measured and averaged for each lead. QT dispersion was defined as the difference between the longest and shortest QT intervals. Minimum of nine leads in which QT intervals could be measured, was required for QT dispersion to be determined. By means of Bazett's formula, QT and QT dispersion were corrected as QT corrected (QTc) and QT corrected dispersion (QTcd) for heart rate (12-14).

Heart rate variability (HRV) analysis

A 24-hour ECG monitoring was performed. All the tapes were subsequently analyzed measuring HRV in the time and frequency domain, using a commercially available program (ELA medical Multichannel-Multiday Version 3.10, Italy). The normal and aberrant complexes were discriminated, and all adjacent intervals between normal beats (NN) were collected over a period of 24 hour. All of the normal intervals were analyzed employing the time domain method. The time domain analysis of HRV included the mean of all normal R-R intervals (N-N), the standard deviation of N-Ns (SDNN), the standard deviation of 5 min mean values of N-Ns (SDANN), the root mean square successive difference of N-Ns (rMSSD), and the percentage of successive N-N differences of 50 ms for each 5-min interval (pNN50%). The recordings, and the collection and elaboration of the results, were done in accordance with guidelines of the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (15).

Statistical analysis

Statistical Package for Social Sciences statistical package SPSS version 11.0 (Chicago, IL, USA) was used for statistical analysis. Genders of the subjects were analyzed among groups by Pearson's Chi-square test. All data are represented as median (minimum-maximum) values. The scale variables of the three groups were tested by Kruskal -Wallis test with posttest multiple comparisons to identify differences in pairs of groups. Bland-

Altman plot was used to assess intra-observer variations for dispersion analysis. All of the explanatory variables were plotted against each other using Pearson correlation coefficients. A p<0.05 value was considered as significant in all of the tests.

Results

Demographic properties

Subject groups were comparable for age, sex, weight, height, and body mass index (p>0.05). The demographics are shown in Table 1. Systolic blood pressure was not different statistically but diastolic blood pressure levels of groups 1 and 2 were lower than of control one (p<0.05).

Urine fluoride levels were significant different between the study groups and the control group (p<0.01).

Laboratory findings

TSH and FT3 levels were not different between groups, but FT4 levels of Group 2 were lower than in Control group (p<0.05). Sodium levels of Group 2 were higher than in Control group (p<0.01). Calcium levels in groups 1 and 2 were lower than in controls (p<0.05) (Table 2).

ECG findings

Heart rate, P, PR, QTd, QTcd values were not different (p>0.05) between studied groups. QT and QTc interval durations of Group 2 were longer than in controls (p<0.05 for both Table 3).

Table 1. Demographic characteristics

Variables	Control Group (n =26)	Group 1 (n =22)	Group 2 (n =13)	Chi-square	p
Age, years	13.5 (8.5-16)	11.5 (8-15)	12 (8-16)	6.0	0.05
Gender, n					
Male	13	10	5	-	-
Female	13	12	8	-	-
Body weight, kg	40 (22-56)	38 (21-53)	42 (24-57)	1.95	0.37
Height, cm	146 (123-175)	146 (126-168)	150 (118-184)	0.55	0.71
BMI, kg/cm ²	18.4 (13.9-25.7)	17.9 (14.1-23.6)	20.0 (12.1-27.5)	4.50	0.1
Systolic blood pressure, mmHg	100 (85-125)	100 (80-120)	100 (90-130)	2.44	0.29
Diastolic blood pressure, mmHg	70 (50-80)	60 (50-80)*	70 (50-90)**	9.36	<0.0001
Urine fluoride, ppm	0.20 (0.08-0.54)	0.74 (0.62-0.97) [†]	0.90 (0.61-1.2) ^{††}	44.16	<0.0001

Data are represented as median (min-max) and number values

Kruskal-Wallis test

*Between Group 1 and control multiple comparison posttest p=0.04

**Between Group 2 and control multiple comparison posttest p=0.02

[†]Between Group 1 and control multiple comparison posttest p<0.0001

^{††}Between Group 2 and control multiple comparison posttest p<0.0001

BMI - body mass index

Echocardiographic findings

According to echocardiography, aortic diameter, ejection fraction, left ventricular end-diastolic diameter, interventricular septum thickness and left ventricular posterior wall thickness of patients and control groups were not different ($p>0.05$, Table 4).

Heart rate variability

The time domain analysis of HRV results, included the mean of all normal R-R intervals, SDNN, SDANN, rMSSD, and pNN50% of patients and control groups were not different ($p>0.05$, Table 5).

Table 2. Laboratory findings of the subjects

Variables	Control Group (n=26)	Group 1 (n=22)	Group 2 (n=13)	Chi-square	p
FT3, pg/mL	3.62 (2.69-4.41)	3.46 (2.74-4.14)	3.42 (2.69-4.41)	2.03	0.36
FT4, ng/dL	1.11 (0.85-1.64)	1.11 (0.63-1.53)	0.96 (0.85-1.11)*	9.60	0.08
TSH, μ U/mL	1.81 (0.80-3.43)	2.14 (0.82-3.47)	1.56 (1.21-3.52)	0.92	0.63
Sodium, mEq/L	139 (136-142)	140 (136-147)	141 (138-148)**	9.84	0.01
Potassium, mmol/L	4.05 (3.30-4.70)	4.00 (3.60-5.20)	4.00 (3.40-5.30)	0.38	0.82
Chloride, mEq/L	108 (102-114)	109 (101-112)	109 (104-113)	0.58	0.74
Calcium, mg/dL	9.80 (9.30-10.70)	9.60 (8.90-10.70) [†]	9.50 (8.90-10.10) ^{††}	9.45	0.01
Albumin, g/dL	5 (4.21-5.50)	4.82 (4.02-5.31)	4.85 (4.62-5.31)	4.55	0.10

Data are represented as median (min-max) values

Kruskal-Wallis test

*Between Group 2 and control multiple comparison posttest $p=0.03$

**Between Group 2 and control multiple comparison posttest $p<0.0001$

[†]Between Group 1 and control multiple comparison posttest $p=0.04$

^{††}Between Group 2 and control multiple comparison posttest $p=0.01$

Table 3. ECG findings of the subjects

Variables	Control Group (n=26)	Group 1 (n=22)	Group 2 (n=13)	Chi-square	p
Heart rate, betas/min	78 (62-110)	80 (62-101)	76 (58-100)	1.45	0.48
P-wave, msec	78 (68-98)	78 (64-94)	74 (60-88)	3.80	0.14
PR-interval, msec	140 (80-210)	120 (72-194)	124 (74-208)	1.15	0.56
QT interval, msec	329.8 (300.0-363.5)	333.7 (308.0-382.5)	351.8 (318.0-372.0)*	6.41	0.04
QTc interval, msec	390.6 (309.0-418.5)	383.8 (342.2-419.5)	366.8 (318.2-468.5)**	7.32	0.03
QTd, msec	26 (20-32)	26(24-28)	28 (22-32)	3.63	0.16
QTcd, msec	54.5 (21-66)	51.5 (27-61)	42 (22-62)	1.34	0.51

Data are represented as median (min-max) values

Kruskal-Wallis test

*Between Group 2 and Control multiple comparison posttest, $p=0.04$,

**Between Group 2 and Control multiple comparison posttest, $p=0.04$

ECG - electrocardiogram, QTd - QT interval dispersion, QTc - QT corrected interval QTcd - QT corrected interval dispersion

Relationship between ECG and laboratory markers

There was a significant correlation between QT, QTc and serum calcium level (for QT- $r=-0.11$, $p<0.005$ and for QTc- $r=-0.07$, $p<0.001$). However, there was no significant correlation between the QT, QTc and serum sodium level and FT4 level either. Intraobserver variation for dispersion analysis was 17%.

Discussion

In this study we examined the deleterious effect of fluorosis on cardiovascular system including detailed ECG with dispersion analysis, echocardiography, and HRV with Holter analysis in children. We found statistically significant low T4 levels, hypocalcemia and hyponatremia, increased QT and QTc interval in children with dental fluorosis. Our results show that fluorosis might increase risk of arrhythmia indirectly, due to its hypocalcemic, hypernatremic, and hypothyroidism effects.

Although acute toxic effects of fluoride on the heart are fairly well known, information about the chronic effects is still very limited. Fluoride produces deleterious effects on the skeleton, teeth, and soft tissues, but the mechanisms are not fully understood. Acute toxic level exposures lead to vomiting, cramps, diarrhea, and finally lethal ventricular fibrillation (16).

Various studies showed hypotension in animal models when exposed at a toxic level (17, 18). In our study, diastolic blood pressure was low in severe fluorosis. This finding supports previous experimental studies.

High fluoride exposures lead to low FT4 levels and high uptake of FT3 in rats (1-4). Zhao et al. (19) examined low iodine uptake in mice thyroid tissue after high fluoride exposure. Michael et al. (20) found high FT4 levels of the people living in endemic fluoride regions. The same study revealed high serum epinephrine and norepinephrine levels. Bachinskii et al. (21) showed thyroid uptake levels lower than controls in the people of endemic fluorosis regions. These studies tell us high fluoride exposures may cause hypothyroidism. Hypothyroidism may also be related to cardiac pathologies, such as impaired cardiac contractility, decreased cardiac output, increased systemic vascular resistance, and cardiac electrical abnormalities. Electrocardiographic changes such as bradycardia, low voltage, and varying degrees of heart block are commonly recognized in hypothyroid patients (22-24). Low FT4 levels were found in Group 2. Despite low FT4 levels, no significant difference was found according to heart rate. Probable cause of this finding is that, FT4 levels were within normal ranges.

Fluoride ion has an extremely strong affinity to cations and an inhibitor affect on various enzyme systems. Fluoride strongly binds to calcium. It results in hypocalcemia, and hyperkalemia (25, 26). Calcium levels were significantly lower in both study groups than control group. However, those levels were within the normal ranges. Sodium levels of Group 2 were higher than control group. These results were same with the previous studies that showed hypocalcemic and hypernatremic effects of fluoride.

Table 4. Echocardiographic findings

Variables	Control Group (n =26)	Group 1 (n =22)	Group 2 (n =13)	Chi-square	p
Ao, mm	23.0 (17-27)	21.9 (18-25.9)	22.5 (19-24)	0.00	0.99
Ejection fraction, %	74.0 (61.0-79.0)	74.0 (62.0-88.0)	72.5 (62.0-79.0)	0.26	0.87
Left Ad, mm	26.0 (23.0-31.7)	25.0 (23.0-36.0)	26.0 (24.0-31.7)	0.49	0.78
LVEDd, mm	41.0 (24.6-45.0)	41.0 (27.0-44.0)	40.5 (27.0-43.0)	0.53	0.76
IVS, mm	6.5 (4.9-7.5)	6.4 (4.7-7.9)	7.4 (4.7-9.5)	1.61	0.44
LVPWd, mm	7.2 (4.8-8.2)	7.2 (4.0-9.4)	7.4 (4.7-9.5)	0.17	0.91

Data are represented as median (min-max) values
Kruskal - Wallis test, p>0.05
Ao - aortic diameter, IVS - interventricular septum diameter, Left Ad - left atrium diameter, LVEDd - left ventricular end-diastolic dimension, LVPWd - left ventricular posterior wall diameter

Table 5. Heart rate variability parameters

Variables	Control Group (n =26)	Group 1 (n =22)	Group 2 (n =13)	Chi-square	p
Minimum HR, beat/min	46.0 (36.0-56.0)	46.0 (42.0-58.0)	46.0 (35.0-52.0)	0.13	0.93
Mean HR, beat/min	81.5 (64.0-120.0)	81.0 (68.0-92.0)	81.5 (82.0-173.0)	0.49	0.78
Maximum HR, beat/min	163.0 (135.0-200.0)	163.0 (125.0-199.0)	176.0 (125.0-205.0)	5.20	0.07
Mean RR, msec	726.0 (582.0-939.0)	739.0 (649.0-947.0)	702.0 (604.0-859.0)	2.54	0.28
PNN50, %	27.4 (7.1-46.6)	32.2 (4.7-41.8)	30.5 (5.2-39.9)	2.20	0.33
PNN30, %	42.9 (18.9-52.3)	49.7 (18.3-87.9)	42.0 (14.6-65.9)	3.26	0.19
RMSSD, %	61.8 (31.9-140.6)	86.8 (26.7-119.9)	84.6 (27.8-119.9)	2.80	0.24
Variability index	5.1 (2.8-9.6)	6.1 (2.5-8.6)	6.4 (2.6-8.6)	3.00	0.22
SDNN, msec	78.8 (50.8-130.4)	92.8 (40.1-130.4)	94.4 (49.4-140.8)	3.74	0.15
SDANN /5 min, msec	142.7 (81.2-248.3)	148.7 (103.5-254.1)	147.9 (99.6-205.2)	1.72	0.42
SD, msec	160.9 (117.0-288.2)	177.9 (121.1-258.2)	185.4 (119.7-255.7)	2.90	0.23

Data are represented as median (min-max) values
Kruskal-Wallis test, p>0.05
HR - heart rate, PNN50 - percentage of successive difference of RR>50 msec for each 5-min interval, RMSSD - root mean square of successive difference of RR intervals, Variability index - percentage of successive difference of RR intervals, SD - standard deviation of all RR intervals for an hour, SDANN/5min - standard deviation of 5 min mean values of RR, SDNN - standard deviation of all RR intervals

In a study, they detected sinusoidal bradycardia, prolongation of PR in sheep that rendering to high fluoride (25). Same findings were observed in residents of Japanese village (27).

Abnormal ECG findings, sinus bradycardias, arrhythmias, low voltage, ST and T-wave changes were demonstrated in Chinese residents of endemic fluorosis areas (28). In metallurgical industry workers, sinus bradycardias, arrhythmias, various conductive blocks, T-wave changes, premature beats, and ischemia were detected (29).

In our study, we did not find any statistical difference between groups in ECG variables including P, PR, QTd and QTcd durations. But, QT and QTc intervals were significantly longer in Group 2 than in controls. It is probably related to low calcium levels, which we detected in our fluorosis groups. Both calcium levels and QT, QTc intervals were within reference range so the subjects were asymptomatic. However, one must remember that, severely affected subjects might be admitted to clinics with the complaint of syncope.

Hypocalcemia provokes myocardial smooth muscle dysfunction, arrhythmias, diastolic dysfunction. Myocardial contraction depends on membrane depolarization after intracellular entrance of calcium (30). Left ventricular dysfunction sometimes is the result of severe hypocalcemia. In dilated cardiomyopathies, typical echocardiographic findings are left ventricular dilatation, interventricular septum and posterior wall thinning and reduction in ejection fraction (30). Fibrous necrosis, dissolution of nuclei, fibrinolysis, interstitial edema, hemorrhages, and infiltration of histiocytes, lymphocytes and granulocytes in the myocardium were observed under the microscopic evaluation of mice specimens (27-30). A direct relationship between degree of fluorosis in the dental areas and cardiac dilatation was observed (27-30). In our study, we did not find significant difference between study and control groups when considering aortic diameter, ejection fraction, left atrial diameter, left ventricular end diastolic diameter, interventricular septum and left ventricular posterior wall thickness in echocardiography.

Fluorosis causes sympathetic nervous system activation via increment in catecholamine activity. Increase in catecholamine levels results in increment in heart rate and cardiac muscle contraction. At the same time, it induces angiotensinogen secretion. Increment in aldosterone secretion results in sodium and water retention. This information showed us fluorosis might affect HRV (31). According to our HRV results, we found no significant difference between study and control groups.

Study limitations

This study was conducted with a small number of cases. Fluorosis causes sympathetic nervous system activation via increment in catecholamine activity. Increase in catecholamines result with increment in heart rate and cardiac muscle. The measurement of serum catecholamine would have been useful. This could be considered limitation of the present study.

Conclusion

Endemic fluorosis is a risk factor for cardiovascular system dysfunction. Our study shows that decrease in calcium and FT4

levels, increment of sodium levels, due to fluorosis may affect ventricular repolarization. These findings show us that fluorosis make patients more vulnerable for developing arrhythmias, and syncope. Intermittent evaluation of the subjects living in endemic fluorosis area concerning this side effect is very important.

Our results belong to children. Further studies concerning cardiovascular effect of fluorosis in both adults and children are needed.

Conflict of interest: None declared.

References

1. Fawell J, Bailey K, Chilton J, Dahi E, Fewtrell L, Magara Y. Fluoride in drinking water. IWA, London, UK. World Health Organization. 2006
2. Brouwer ID, Dirks OB, De Bruin A, Hautvast JG. Unsuitability of World Health Organization guidelines for fluoride concentrations in drinking water in Senegal. *Lancet* 1988; 1: 223-5.
3. Li J, Cao SR. Recent studies on endemic fluorosis in China. *Fluoride* 1994; 27: 125-8.
4. U.S. Department of Health and Human Services Public Health Service Agency for Toxic Substances and Disease Registry. Toxicological Profile for Fluorides, Hydrogen Fluoride and Fluorine. 2003.
5. Usmen E. Isparta il, ilçe ve köylerinde dış fluorosisi. *İ.Ü. Dış Hek Fak Derg* 1976; 10: 285-96.
6. Öztürk M, Kişioğlu AN, Akdoğan M, Demirel R, Kırbıyık S, I Malgr İ. Isparta'daki içme su kaynakları, depoları ve çeşme sularının fluor düzeylerinin dağılımlarının incelenmesi. VIII. Ulusal Halk Sağlığı Kongresi, Diyarbakır. 2002; 434-6.
7. Baltazar RF, Mower MM, Reider R, Funk M, Salomon J. Acute fluoride poisoning leading to fatal hyperkalemia. *Chest* 1980; 78: 660-3.
8. Wang Y, Yin Y, Gilula LA, Wilson AJ. Endemic fluorosis of the skeleton: radiographic features in 127 patients. *AJR Am J Roentgenol* 1994; 162: 93-8.
9. Rozier RG. Epidemiologic indices for measuring the clinical manifestations of dental fluorosis: overview and critique. *Adv Dent Res* 1994; 1: 39-55.
10. Lai WW, Geva T, Shirali GS, Frommelt PC, Humes RA, Brook MM, et al; Task Force of the Pediatric Council of the American Society of Echocardiography; Pediatric Council of the American Society of Echocardiography. Guidelines and standards for performance of a pediatric echocardiogram: a report from the Task Force of the Pediatric Council of the American Society of Echocardiography. *J Am Soc Echocardiogr*. 2006; 19: 413-30.
11. Savaş S, Çetin M, Akdoğan M, Heybeli N. Endemic fluorosis in Turkish patients: relationship with knee osteoarthritis. *Rheumatol Int* 2001; 21: 30-5.
12. Garson A Jr. How to measure the QT interval--what is normal? *Am J Cardiol* 1993; 72: 14B-16B.
13. Sagie A, Larson MG, Goldberg RJ, Bengtson JR, Levy D. An improved method for adjusting the QT interval for heart rate (the Framingham Heart Study). *Am J Cardiol* 1992; 70: 797-801.
14. Tutar HE, Öcal B, İmamoğlu A, Atalay S. Dispersion of QT and QTc interval in healthy children, and effects of sinus arrhythmia on QT dispersion. *Heart* 1998; 80: 77-9.
15. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability: standards of measurement, physiological interpretation and clinical use. *Circulation* 1996; 93: 1043-65.
16. Martínez MA, Ballesteros S, Piga FJ, Sánchez de la Torre C, Cubero CA. The tissue distribution of fluoride in a fatal case of self-poisoning. *J Anal Toxicol* 2007; 31: 526-33.
17. Öncü M, Gülle K, Karaöz E, Gültekin F, Karaöz S, Karakoyun İ, et al. Effect of chronic fluorosis on lipid peroxidation and histology of lung tissues in first and second generation rats. *Toxicol Ind Health* 2006; 22: 375-80.
18. Takamori T. The heart changes of growing albino rats fed on varied contents of fluorine In: Gordonoff T, editor. *The Toxicology of Fluorine Symposium* 1962; 15-17.
19. Zhao W, Zhu H, Yu Z, Aoki K, Misumi J, Zhang X. Long-term Effects of Various Iodine and Fluorine Doses on the Thyroid and Fluorosis in Mice. *Endocr Regul* 1998; 32: 63-70.
20. Michael M, Barot VV, Chinoy NJ. Investigations of soft tissue functions in fluorotic individuals of North Gujarat. *Fluoride* 1996; 29: 63-71.
21. Bachinskii PP, Gutsalenko OA, Naryzhniuk ND, Sidora VD, Schliaktha AI. Action of the body fluorine of healthy persons and thyroidopathy patients on the function of hypophyseal-thyroid the system. *Probl Endokrinol* 1985; 31: 25-9.
22. Wang H, Yang Z, Zhou B, Gao H, Yan X, Wang J. Fluoride-induced thyroid dysfunction in rats: roles of dietary protein and calcium level. *Toxicol Ind Health* 2009; 25: 49-57.
23. Gammage M, Franklyn J. Hypothyroidism, thyroxine treatment, and the heart. *Heart* 1997; 77: 189-90.
24. Fazio S, Biondi B, Carella C, Sabatini D, Cittadini A, Panza N, et al. Diastolic dysfunction in patients on thyroid-stimulating hormone suppressive therapy with levothyroxine: beneficial effect of beta-blockade. *J Clin Endocrinol Metab* 1995; 80: 2222-6.
25. Dure-Smith BA, Farley SM, Linkhart SG, Farley JR, Baylink DJ. Calcium deficiency in fluoride-treated osteoporotic patients despite calcium supplementation. *J Clin Endocrinol Metab* 1996; 81: 269-75.
26. Khandare AL, Kumar PU, Shankar NH, Kalyanasundaram S, Rao GS. Effect of Calcium deficiency induced by F intoxication on lipid metabolism in rabbits. *Fluoride*. 2007; 40: 184-9.
27. Çiçek E, Aydın G, Akdoğan M, Okutan H. Effects of chronic ingestion of sodium fluoride on myocardium in a second generation of rats. *Hum Exp Toxicol* 2005; 24: 79-87.
28. Dönmez N, Çınar A. Effects of chronic fluorosis on electrocardiogram in sheep. *Biol Trace Elem Res* 2003; 92: 115-22.
29. Zhiliang Y, Yihua L, Liansheng Z, Zhengping Z. Industrial fluoride pollution in the metallurgical industry in China. *Fluoride* 1987; 20: 118-25.
30. Xu R, Xu R. Electrocardiogram analysis of patients with skeletal fluorosis. *Fluoride* 1997; 30: 16-8.
31. Bauer A, Malik M, Schmidt G, Barthel P, Bonnemeier H, Cygankiewicz I, et al. Heart rate turbulence: standards of measurement, physiological interpretation, and clinical use: International Society for Holter and Noninvasive Electrophysiology Consensus. *J Am Coll Cardiol* 2008; 52: 1353-65.
32. Genovesi S, Prata Pizzala DM, Pozzi M, Ratti L, Milanese M, Pieruzzi F, et al. QT interval prolongation and decreased heart rate variability in cirrhotic patients: relevance of hepatic venous pressure gradient and serum calcium. *Clin Sci* 2009; 116: 851-9.