Int Cardiovasc Res J.2022;**16**(1):36-44.icrj.120859

International Cardiovascular Research Journal
www.ircrj.com

Electrocardiography Changes in Children with Epileptic and Non-epileptic Seizures Compared to Controls

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ARTICLE INFO

Article Type:
Research Article

Article History:
Received: 1 Nov 2021
Revised: 16 Jan 2022
Accepted: 15 Mar 2022

Keywords:
Electrocardiography
Epilepsy
Febrile Convulsion
Children

ABSTRACT

Background: Epilepsy, febrile convulsion, and breath-holding spells are neurological diseases affecting the heart.

Objectives: This study aimed to evaluate electrocardiography alterations in children with epilepsy, febrile convulsion, and breath-holding spells compared to controls.

Methods: This case-control study was conducted on 360 children aged 0.5 - 5 years in Zahedan, Iran. The children with epilepsy, febrile convulsion, and breath-holding spells were diagnosed by a single neurologist based on the standard definition. Electrocardiography was also performed by a pediatric cardiologist. The data were analyzed using the SPSS 20.0 software, and $P < 0.05$ was considered statistically significant.

Results: Among the participants, 160 (44.4%) were female. Females also comprised 45.6%, 42.2%, 38.9%, and 51.1% of the participants in the epilepsy, febrile convulsion, breath-holding spells, and control groups, respectively. QTd was different in the epilepsy group compared to the controls and patients with breath-holding spells ($P < 0.001$). Additionally, QTc was significantly different in the epilepsy group in comparison to the controls ($P < 0.001$) and patients with breath-holding spells ($P = 0.020$), in the controls compared to the patients with febrile convulsion ($P < 0.001$), and in the controls in comparison to the patients with breath-holding spells ($P < 0.001$). QTcd was also different in the epilepsy group compared to the controls ($P < 0.001$), patients with breath-holding spells ($P < 0.001$), and those with febrile convulsion ($P = 0.006$) as well as in the controls in comparison with the patients with febrile convulsion and breath-holding spells ($P < 0.001$). Finally, QT was different in the patients with breath-holding spells compared to those with epilepsy ($P = 0.005$), in the patients with breath-holding spells in comparison with the controls ($P = 0.002$), and in the patients with breath-holding spells compared to those with febrile convulsion ($P < 0.001$).

Conclusions: The present study findings indicated that QT dispersion was different in the epilepsy group compared to the patients with breath-holding spells, corrected QT was different in the epilepsy group compared with the patients with breath-holding spells, QTc dispersion was different in the epilepsy group in comparison with the patients with breath-holding spells and febrile convulsion, and QT was different in the patients with breath-holding spells compared to those with epilepsy and febrile convulsion.

1. Introduction

Autonomic Nervous System (ANS) regulates humans' physiological processes. This system is free of controlling conscious and consists of sympathetic and parasympathetic components. In ANS, ganglions contain numerous nerve cells located outside the Central Nervous System (CNS). Every nerve that enters into an organ is accompanied by sympathetic and parasympathetic fibers. In this process, heart rate and other cardiac outputs increase with sympathetic fibers and decrease with parasympathetic ones (1).

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Epilepsy is a chronic disease triggered by increased impulsiveness of nerve cells in the brain and may require a lifelong treatment. Epilepsy is confirmed by two or more unprovoked seizures in more than 24 hours (2). Febrile Convulsion (FC) is another type of seizure occurring due to fever over 38 °C without a history of convulsion, CNS infection, electrolyte imbalance, metabolic disorder, intoxication, and trauma. Evidence has shown a link between epilepsy and FC, such a way that the prevalence of FC was 2-5% amongst children. The prevalence of epilepsy was also 3%, with children comprising half of the patients. Additionally, the incidence of epilepsy was 10% after FC (3). Moreover, epilepsy was not accompanied by fever or CNS infection, with 1 - 2 deaths per 500 individuals, but its annual death rate varied from 1 to 2 in every 500 individuals when FC had both conditions (fever and CNS infection) with lower morbidity and mortality (3-5). Unlike epileptic seizures, there are non-epileptic seizures such as Breath-Holding Spells (BHs) that affect children's behaviors and often look like epileptic seizures. They mostly occur in 6-18-month-old children and rarely in those aged up to four years (6). Among BHs, 5% are due to crying up to a minute followed by losing consciousness, which do not have any risks for children's lives (6, 7). Although BHs mechanisms have remained unknown, autonomic imbalance with cerebral anoxia, anemia, and genetic disorders may play a role (8). Sudden death, prolonged asystole, and status epilepticus have been observed in BHs and autonomic dysregulation may have a key role in BHs pathophysiology (9). Cardiovascular changes have also been reported to be associated with seizures (2) and BHs (10).

QT parameters refer to the time from the Q wave to the end of the T wave. One of these parameters is QT dispersion that has been defined as the difference between the longest and shortest QT intervals within a 12□lead Electrocardiography (ECG) (11). QT parameters elongation show the danger of dysrhythmia and unexpected sicknesses such as cardiomyopathy, mitral valve prolapse, ischemic coronary illness, and kidney disorders (11). Many investigators have reported changes in QT parameters in various diseases (12) such as diabetes mellitus (13), celiac disease (14), thalassemia (15), epilepsy (10) BHs (9), FC (16), and febrile seizure (17). QT has also been found to change in the general population due to medications, electrolyte abnormalities, or endocrine diseases (18).

2. Objectives

The present study aims to evaluate changes in QT parameters amongst children with BHs and FC compared to healthy children.

3. Methods

3.1. Study Design and Participants

This case-control study aimed to evaluate changes in ECG parameters among children with epilepsy, BHs, and FC compared to healthy children in pediatric cardiology and neurology centers of Ali-Ibn- Abitalib and Ali Asghar hospitals affiliated to Zahedan University of Medical Sciences in 2018. The participants included 360 individuals divided into groups containing 90 members. During the one-year study, almost 327 children were referred to the abovementioned centers due to seizure. Among these children, 97, 122, and 108 had seizures due to epilepsy, FC, and BHs, respectively. In the final stage, 90 children were allocated to each group. The children were entered into the study continuously after the confirmation of diagnosis. From the children who had referred to the centers due to seizures, those suspected of epilepsy were confirmed by a neurologist based on the definition of having two or more unprovoked seizures in 24 hours (15). Among the children who had referred to the centers due to simple seizures, FC was confirmed by the same neurologist based on the definition of FC; that is, convulsions occurring in children aged 6 – 60 months with a body temperature of 38 °C (100.4 °F) or higher that is not the result of CNS infection or any metabolic imbalance and in the absence of a history of afebrile seizures (17). Additionally, some children had referred to the centers due to cyanotic attacks and/or fainting and were diagnosed with BHs by observing typical attacks during examination or by history taking (19). The exclusion criteria of the study were abnormal laboratory tests, using drugs that could affect ECG such as calcium, potassium, magnesium, blood glucose lowering drugs, anti-psychotics, and anti-arrhythmia medications, taking antibiotics such as aminoglycosides and anti-depressants, and suffering from such diseases as iron deficiency, impaired kidney function, cardiovascular disease, trauma, meningitis, encephalitis, seizure-inducing syndromes, and structural disorders. Furthermore, healthy individuals were selected randomly from those who had referred to the clinics for the routine checkup and met all the exclusion criteria considered for the patient groups.

3.2. Electrocardiography Measures

Thirty minutes or two hours after seizures, ECG was performed by an experienced nurse using Sa'adat device (made in Iran). In doing so, both patients and controls were requested to rest in supine position in a quiet room for ten minutes. Then, standard ECG was conducted at a voltage of 10 mm/mv and the results were recorded at a paper speed of 25 mm/s. After that, the recorded papers were used by a pediatric cardiologist to measure the intended parameters. QT interval was measured as the distance from the beginning of the Q wave to the end of the T wave at least in eight leads from the standard ECG. In each lead, the duration from the beginning of the Q wave to the end of the T wave was calculated in milliseconds and the average was obtained (QT average) for three consecutive beats. The maximum and minimum durations of the QT wave were selected from the 12 leads of the surface ECG. The difference between maxQT and minQT was defined as QTd. The average QTc was calculated using the same QT interval measured using the Bazett formula ($QTc = QT/\sqrt{RR}$). The difference between the longest and shortest QTc was calculated (QTcd), as well (10). Finally, the left ventricular mass in ECG was calculated using the Left Ventricular Mass (LVM) formula:

(g) = 0.026 (RaVL+SV3) + 1.25 Weight + 34.4 for boys, and 0.020 (RaVL+SV3) + 1.12 Weight + 36.2 for girls (10, 15).

3.3. Statistical Analysis

The data were analyzed using the SPSS software, version 20.0 (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp). The statistical difference for all the ECG parameters was investigated using Kruskal–Wallis test, and multiple comparisons were made via Dunn's test and Bonferroni test for adjusting the significant level. Additionally, the correlations between the variables were assessed through Pearson's correlation coefficient. $P < 0.05$ was considered statistically significant.

4. Results

This study aimed to compare the patients and controls with respect to ECG parameters. The patients were divided into epilepsy, febrile seizure, and BHs groups. From the participants, 160 (44.4%) were female. Females also comprised 45.6%, 42.2%, 38.9%, and 51.1% of the participants in the epilepsy, FC, BHs, and controls groups, respectively. The results of chi-square test showed that the gender distribution was similar in the three groups ($X^2 = 2.9710$, $P = 0.396$). However, the data did not follow normal distribution ($P < 0.001$) and, consequently, non-parametric tests were used.

Comparison of the patients and controls regarding the study variables has been presented in Table 1. Accordingly, the three groups were similar in terms of age ($P = 0.553$). However, height, weight, and RR interval were higher in the controls than in the patients. Heart rate was significantly higher in the patients compared to the controls ($P < 0.001$). S in V_1 was significantly higher in the controls compared to the patients ($P < 0.001$), while R in aVL was higher in the patients compared to the controls ($P < 0.001$). In addition, LVM by ECG had lower first (46.31 vs. 48.53), second (48.53 vs. 51.97), and third (50.81 vs. 54.25) quartiles in the patients compared to the controls ($P < 0.001$). Considering QT dispersion also, first (0.03 vs. 0.01), second (0.04 vs. 0.02), and third (0.04 vs. 0.03) quartiles were higher in the patients compared to the controls. Similar trends were also observed for corrected QT; first (0.41 vs. 0.39), second (0.44 vs. 0.42), and third (0.46 vs. 0.44) quartiles were higher in the patients. This was also the case regarding QTc dispersion; first (0.04 vs. 0.02), second (0.06 vs. 0.03), and third (0.06 vs. 0.04) quartiles were higher in the patients. Among the highlighted ECG parameters, QT had similar values in the control and patient groups ($P = 0.316$).

The results of Kruskal–Wallis test have been presented in Table 2. Accordingly, all the variables had different quartiles (first, second, and third) in the four groups (epilepsy, control, FC, and BHs). Thus, Dunn's multiple comparison test was applied and the p-values were adjusted by Bonferrini test whose results have been presented in Table 3. The results revealed a significant difference between the epilepsy and control groups ($P = 0.49$), epilepsy

Table 1. Mann–Whitney U Test for Comparing the Patients and Controls

Variables	Groups	Median (Q1,Q3)	Mann–Whitney U	P-value
Age	Patients	2.00 (1.29,3.00)	11644.5	0.553
	Controls	2.50 (1.78,3.00)		
Weight	Patients	11.00 (9.00,13.00)	6868.5	< 0.001
	Controls	14.00 (11.00,16.00)		
Height	Patients	80.00 (74.00,90.00)	6016.5	< 0.001
	Controls	96.00 (85.00,101.25)		
RR Interval	Patients	0.52 (0.44,0.60)	9265	0.001
	Controls	0.59 (0.48,0.63)		
HR	Patients	120.00 (100.00,140.00)	8879.5	< 0.001
	Controls	103.00 (93.00,126.25)		
S in V_1	Patients	0.40 (0.20,0.70)	7597	< 0.001
	Controls	0.70 (0.48,1.00)		
R in V_5	Patients	0.83 (0.60,1.30)	10934.5	0.154
	Controls	1.05 (0.70,1.20)		
R in aVL	Patients	0.30 (0.20,0.50)	7102	< 0.001
	Controls	0.20 (0.10,0.30)		
S inV_3	Patients	0.70 (0.39,1.00)	10973	0.167
	Controls	0.60 (0.40,0.80)		
LVM	Patients	48.53 (46.31,50.81)	7071.5	< 0.001
	Controls	51.97 (48.53,54.25)		
QTd	Patients	0.04 (0.03,0.04)	4779	< 0.001
	Controls	0.02 (0.01,0.03)		
QTc	Patients	0.44 (0.41,0.46)	7322	< 0.001
	Controls	0.42 (0.39,0.44)		
QTcd	Patients	0.06 (0.04,0.06)	4201	< 0.001
	Controls	0.03 (0.02,0.04)		
QT	Patients	0.32 (0.29,0.34)	11304	0.316
	Controls	0.32 (0.28,0.33)		

Abbreviations: RR, R-R interval; HR, heart rate; R in v5, the amplitude of R wave in the left precordial lead; S in v1, the amplitude of S wave in the right precordial lead; R in aVL, the amplitude of R wave in the left hand lead; S in V5, the amplitude of S wave in the left precordial lead; LVM, left ventricular mass; QT, a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle; QTc, QT/√ RR; QTd, QT max-QT min; QTcd, QTc max-QTc min.

and FC groups (P = 0.006), and epilepsy and HBs groups (P = 0.004) concerning age. A significant difference was also detected between the epilepsy and control groups (P = 0.03), control and FC groups (P < 0.001), and control and BHs groups (P < 0.001) regarding weight. Height was also significantly different in the epilepsy group compared to the controls (P < 0.001), in the BHs group in comparison with the controls (P < 0.001), and in the FC group compared to the controls (P < 0.001). Moreover, the results revealed a significant difference between the epilepsy and control groups (P < 0.001), epilepsy and BHs groups (P < 0.001), control and FC groups (P = 0.002), and FC and BHs groups (P = 0.001) with regard to RR interval. Additionally, a significant difference was found between the epilepsy and control groups, epilepsy and BHs groups, control and FC groups, and BHs and FC groups in terms of heart rate. A significant difference was also observed between epilepsy and FC groups, epilepsy and BHs groups, control and FC groups, control and BHs groups, and FC and BHs groups in terms of S in V_1. Besides, the results indicated a significant difference between epilepsy and BHs groups, control and BHs groups, and FC and BHs groups concerning R in V_5. R in aVL was also different between all the pairs, except for the epilepsy group compared to the BHs group and the control group compared to the FC group. LVM was also different in all pairwise comparisons, except for the epilepsy group compared to the controls and the FC group in comparison with the BHs group. Furthermore, the results demonstrated a significant difference between the epilepsy and control groups (P < 0.001), epilepsy and BHs groups (P = 0.012), controls and the FC group (P = 0.001), and controls and the BHs group (P < 0.001) regarding QTd. QTc was also different in the epilepsy group compared to the controls (P < 0.001), in the controls compared to the FC group (P < 0.001), and in the controls compared to the BHs group (P = 0.001). QTcd was also different between all the pairs (P < 0.05), except for the epilepsy group compared to the FC group. Finally, QT was different in the epilepsy group compared to the BHs group (P = 0.015), in the controls compared to the BHs group (P = 0.012), and in the FC group compared to the BHs group (P < 0.001).

The frequency of abnormal QTd, QTc, and QTcd in the study groups has been presented in Table 4. The results related to prolonged QTd, QTc, and QTcd defined per cut-point for each have been depicted in Table 5. In the epileptic, control, FC, and BHs children, 16.7%, 0.00%, 5.6%, and 3.3% had abnormal QTd, respectively (X^2 = 23.548, P < 0.001). Besides, 46.7% of the epileptic children, 2.20% of the controls, 28.90% of the children with FC, and 28.90% of those with BHs had abnormal QTc (X^2 = 46.364, P < 0.001). Finally, 48.9% of the epileptic children, 4.40% of the controls, 16.70% of the FC children, and 14.40% of those with BHs had abnormal QTcd (X^2 = 60.173, P < 0.001).

The correlations between the QT parameters and age,

Table 2. Kruskal–Wallis test for Comparing the Patients and Controls

Variables	Groups	Median (Q1,Q3)	X^2	P-value	Variables	Median (Q1,Q3)	X^2	P-value
Age	Epilepsy	2.75 (1.50, 4.00)	15.22	0.002	R in aVL	0.30 (0.20,0.50)	54.66	< 0.001
	Control	2.50 (1.78,3.00)				0.20 (0.10,0.30)		
	FC	2.00 (1.20,3.00)				0.25 (0.20,0.40)		
	BH	1.87 (1.13,3.00)				0.40 (0.30,0.50)		
Weight	Epilepsy	12.00 (10.00,15.00)	55.78	< 0.001	S in V_3	0.80 (0.40,1.20)	46.07	< 0.001
	Control	14.00 (11.00,16.00)				0.60 (0.40,0.80)		
	FC	11.00 (9.00,13.00)				0.80 (0.58,1.00)		
	BH	10.00 (8.48,12.00)				0.50 (0.30,0.60)		
Height	Epilepsy	80.00 (75.00,85.00)	52.02	< 0.001	LVM	49.65 (47.4,53.03)	54.34	< 0.001
	Control	96.00 (85.00,101.25)				51.97 (48.53,54.25)		
	FC	80.50 (73.00,90.00)				48.48 (46.31,50.78)		
	BH	81.50 (74.00,91.00)				47.23 (45.54,49.65)		
RR Interval	Epilepsy	0.48 (0.40,0.53)	42.7	< 0.001	QTd	0.04 (0.04,0.04)	96.83	< 0.001
	Control	0.59 (0.48,0.63)				0.02 (0.01,0.03)		
	FC	0.48 (0.44,0.60)				0.04 (0.03,0.04)		
	BH	0.56 (0.52,0.64)				0.04 (0.02,0.04)		
HR	Epilepsy	127.00 (107.75,148.50)	48.25	< 0.001	QTc	0.44 (0.41,0.48)	37.05	< 0.001
	Control	103.00 (93.00,126.25)				0.42 (0.39,0.44)		
	FC	127.00 (106.75,145.00)				0.44 (0.41,0.46)		
	BH	110.00 (90.00,120.00)				0.43 (0.41,0.45)		
SinV_1	Epilepsy	0.50 (0.20,0.90)	45.59	< 0.001	QTcd	0.06 (0.05,0.06)	113.32	< 0.001
	Control	0.70 (0.48,1.00)				0.03 (0.02,0.04)		
	FC	0.50 (0.30,0.80)				0.06 (0.04,0.06)		
	BH	0.30 (0.20,0.50)				0.05 (0.03,0.06)		
RinV_5	Epilepsy	1.05 (0.60,1.40)	18.57	< 0.001	QT	0.32 (0.28,0.34)	16.96	0.001
	Control	1.05 (0.70,1.20)				0.32 (0.28,0.33)		
	FC	1.00 (0.68,1.40)				0.31 (0.29,0.33)		
	BH	0.80 (0.60,1.00)				0.32 (0.32,0.34)		

Abbreviations: FC, febrile convulsion; BH, breath holding; RR, R-R interval; HR, heart rate; R in v5, the amplitude of R wave in the left precordial lead; S in v1, the amplitude of S wave in the right precordial lead; R in aVL, the amplitude of R wave in the left hand lead; S in V5, the amplitude of S wave in the left precordial lead; LVM, left ventricular mass; QT, a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle; QTc, QT/√ RR; QTd, QT max-QT min; QTcd, QTc max-QTc min.

Table 3. Multiple Comparisons by Dunn-Bonferroni Tests

Variables	Group (i)	Group (j)	Test Value	P-value	Adjusted P	Variables	Test Value	P-value	Adjusted P
Age	Epilepsy	Control	26.9	0.082	0.49	R in aVL	79.994	< 0.001	< 0.001
		FC	51.022	0.001	0.006		40.583	0.008	0.047
		BH	52.144	0.001	0.004		24.956	0.102	0.615
	Control	FC	24.122	0.118	0.711		-39.411	0.001	0.059
		BH	25.244	0.102	0.614		104.950	< 0.001	< 0.001
	FC	BH	1.122	0.942	1		-65.539	< 0.001	< 0.001
Weight	Epilepsy	Control	-43.461	0.005	0.03	S in V 3	44.872	0.040	0.022
		FC	40.639	0.009	0.052		-4.394	0.776	1.000
		BH	63.711	< 0.001	< 0.001		86.700	< 0.001	< 0.001
	Control	FC	84.1	< 0.001	< 0.001		-49.267	0.001	0.009
		BH	107.172	< 0.001	< 0.001		41.828	0.007	0.041
	FC	BH	23.072	0.136	0.815		91.94	< 0.001	< 0.001
Height	Epilepsy	Control	-90.122	< 0.001	< 0.001	LVM	-39.050	0.012	0.071
		FC	6.411	0.679	1		41.456	0.008	0.045
		BH	-4.178	0.787	1		67.106	< 0.001	< 0.001
	Control	FC	96.533	< 0.001	<0.001		80.506	< 0.001	< 0.001
		BH	85.944	< 0.001	< 0.001		106.156	< 0.001	< 0.001
	FC	BH	-10.589	0.495	1		26.650	0.098	0.589
RR Interval	Epilepsy	Control	78.3	< 0.001	< 0.001	QTd	129.672	< 0.001	< 0.001
		FC	-23.222	0.132	0.793		17.289	0.227	1.000
		BH	-83.456	< 0.001	< 0.001		44.128	0.002	0.012
	Control	FC	55.078	< 0.001	0.002		-112.383	< 0.001	< 0.001
		BH	-5.156	0.738	1		-85.544	< 0.001	< 0.001
	FC	BH	-60.233	< 0.001	0.001		26.839	0.061	0.366
HR	Epilepsy	Control	79.656	< 0.001	< 0.001	QTc	91.094	< 0.001	< 0.001
		FC	10.989	0.478	1		24.672	0.112	0.670
		BH	82.606	< 0.001	< 0.001		34.033	0.028	0.169
	Control	FC	-68.661	< 0.001	< 0.001		-66.422	< 0.001	< 0.001
		BH	2.956	0.849	1		-57.061	< 0.001	0.001
	FC	BH	71.617	< 0.001	< 0.001		9.361	0.546	1.000
S in V1	Epilepsy	Control	-55.217	< 0.001	0.002	QTcd	155.628	< 0.001	< 0.001
		FC	-11.667	0.451	1		33.817	0.029	0.175
		BH	48.372	0.002	0.01		79.778	< 0.001	< 0.001
	Control	FC	43.55	0.005	0.029		-121.811	< 0.001	< 0.001
		BH	103.589	< 0.001	< 0.001		-75.850	< 0.001	< 0.001
	FC	BH	60.039	< 0.001	0.001		45.961	0.003	0.018
R in V5	Epilepsy	Control	2.083	0.893	1	QT	0.872	0.955	1.000
		FC	3.917	0.8	1		11.350	0.458	1.000
		BH	56.356	0.001	0.002		-46.333	0.002	0.015
	Control	FC	1.833	0.906	1		10.478	0.493	1.000
		BH	54.272	< 0.001	0.003		-47.206	0.002	0.012
	FC	BH	52.493	0.001	0.004		-57.683	< 0.001	0.001

Abbreviations: FC, febrile convulsion; BH, breath holding; RR, R-R interval; HR, heart rate; R in v5, the amplitude of R wave in the left precordial lead; S in v1, the amplitude of S wave in the right precordial lead; R in aVL, the amplitude of R wave in the left hand lead; S in V5, the amplitude of S wave in the left precordial lead; LVM, left ventricular mass; QT, a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle; QTc, QT/√ RR; QTd, QT max-QT min; QTcd, QTc max-QTc min.

weight, height, and some ECG measures have been shown in Table 5. Based on the results, QTd was correlated to age (r = 0.133, P = 0.029), QTc was correlated to RR (r = -0.515, P < 0.001), heart rate (r = 0.158, P = 0.009), and S wave in V^3 (r = 0.148, P = 0.015), QTcd was correlated to RR (r = -0.203, P = 0.001), heart rate (r = 0.260, P < 0.001), and S wave in V^3 (r = 0.121, P = 0.046), and QT was correlated to RR (r = 0.237, P < 0.001) and heart rate (r = -0.491, P < 0.001). Considering the patients with epilepsy, the results indicated that QTc was correlated to RR (r = -0.609, P < 0.001), QTcd was correlated to S wave in V1 (r = -0.229, P = 0.030), and QT was correlated to RR (r = -0.513, P < 0.001) and R wave in V_5 (r = 0.249, P = 0.018). Regarding the FC patients, QTc was correlated to RR (r = -0.653, P < 0.001), heart rate (0.0330, P = 0.002), S wave in V_1 (r = -0.340, P = 0.001), and R wave in aVL (r = 0.263, P = 0.012), QTcd was correlated to RR (r = -0.498, P < 0.001), heart rate (r = 0.354, P = 0.001), and S wave in V1 (r = -0.236, P = 0.025), and QT was correlated to RR (r = 0.523, P < 0.001) and heart rate (r = -0.684, P < 0.001). In the patients with BHs, QTd was correlated to RR (r = -0.210, P = 0.047), QTc was correlated to RR (r = -0.279, P = 0.008) and S wave in V1 (r = 0.347, P = 0.001), QTcd was correlated to RR (r = -0.401, P < 0.001), and QT was correlated to RR (r = 0.622, P < 0.001) and S wave in V3 (r = 0.216, P = 0.041).

Table 4. Distribution of Abnormal QTd, QTc, and QTcd in the Study Groups

Variables	Groups	Statistics	Groups of Participants				Total	X^2	P-value
			Epilepsy	Control	FC	BH			
QTd	< 0.05	N	75	90	85	87	337	23.548	< 0.001
		%	83.3%	100.0%	94.4%	96.7%	93.6%		
	≥ 0.05	N	15	0	5	3	23		
		%	16.7%	0.0%	5.6%	3.3%	6.4%		
QTc	< 0.45	N	48	88	64	64	264	46.364	< 0.001
		%	53.3%	97.8%	71.1%	71.1%	73.3%		
	≥ 0.45	N	42	2	26	26	96		
		%	46.7%	2.2%	28.9%	28.9%	26.7%		
QTcd	< 0.06	N	46	86	75	77	284	60.178	< 0.001
		%	51.1%	95.6%	83.3%	85.6%	78.9%		
	≥ 0.06	N	44	4	15	13	76		
		%	48.9%	4.4%	16.7%	14.4%	21.1%		
	Total	N	90	90	90	90	360		
		%	100.0%	100.0%	100.0%	100.0%	100.0%		

Abbreviations: FC, febrile convulsion; BH, breath holding; QTc, QT/√ RR; QTd, QT max-QT min; QTcd, QTc max-QTc min.

Table 5. The Correlations between the QT Parameters and Age, Weight, Height, and Some Electrocardiography Measures

Groups of Participants	Patients				Epilepsy			
QTs	QTd	QTc	QTcd	QT	QTd	QTc	QTcd	QT
Statistics	r (p)	r (p)	r (p)	r (p)	r (p)	r (p)	r (p)	r (p)
Age	0.133 (0.029)	-0.026 (0.668)	0.096 (0.116)	0.036 (0.561)	0.116 (0.278)	-0.119 (0.265)	0.047 (0.661)	0.073 (0.492)
Weight	0.097 (0.111)	0.017 (0.783)	0.108 (0.077)	-0.080 (0.187)	0.027 (0.799)	-0.140 (0.189)	-0.019 (0.859)	-0.023 (0.829)
Height	-0.002 (0.970)	-0.023 (0.704)	-0.003 (0.961)	-0.014 (0.821)	0.067 (0.529)	-0.061 (0.568)	0.039 (0.715)	-0.006 (0.953)
RR Interval	0.089 (0.146)	-0.515 (0.000)	-0.203 (0.001)	0.237 (0.000)	0.191 (0.071)	-0.609 (0.000)	-0.153 (0.149)	0.164 (0.123)
HR	0.095 (0.120)	0.158 (0.009)	0.260 (0,000)	-0.491 (0.000)	0.048 (0.650)	0.062 (0.559)	0.201 (0.058)	-0.513 (0.000)
S in V_1	-0.028 (0.651)	-0.088 (0.150)	-0.073 (0.232)	0.047 (0.444)	-0.147 (0.168)	-0.118 (0.269)	-0.229 (0.030)	0.118 (0.267)
R in V_5	0.009 (0.881)	-0.010 (0.869)	-0.009 (0.883)	0.050 (0.410)	-0.064 (0.548)	-0.026 (0.810)	-0.134 (0.209)	0.249 (0.018)
R in aVL	-0.039 (0.521)	0.095 (0.118)	0.004 (0.953)	0.013 (0.834)	-0.120 (0.258)	-0.009 (0.934)	-0.068 (0.527)	-0.086 (0.419)
S inV_3	0.111 (0.067)	0.148 (0.015)	0.121 (0.046)	0.017 (0.777)	0.056 (0.598)	0.135 (0.206)	0.036 (0.734)	0.161 (0.131)
LVM	0.079 (0.194)	0.006 (0.916)	0.091 (0.136)	-0.080 (0.187)	0.035 (0.740)	-0.145 (0.174)	-0.011 (0.917)	-0.026 (0.808)
Groups of participants	**Febrile convulsion**				**Breath holding spells**			
QTs	QTd	QTc	QTcd	QT	QTd	QTc	QTcd	QT
Statistics	r (p)	r (p)	r (p)	r (p)	r (p)	r (p)	r (p)	r (p)
Age	-0.076 (0.478)	0.007 (0.949)	-0.099 (0.355)	0.120 (0.262)	0.114 (0.283)	0.007 (0.945)	0.125 (0.241)	-0.021 (0.842)
Weight	-0.091 (0.392)	0.084 (0.432)	-0.056 (0.598)	0.010 (0.923)	0.135 (0.203)	0.059 (0.579)	0.191 (0.071)	-0.120 (0.259)
Height	-0.157 (0.138)	0.084 (0.429)	-0.105 (0.324)	0.033 (0.761)	0.023 (0.828)	-0.106 (0.322)	0.045 (0.675)	-0.100 (0.346)
RR interval	-0.151 (0.155)	-0.653 (0.000)	-0.498 (0.000)	0.523 (0.000)	-0.210 (0.047)	-0.279 (0.008)	-0.401 (0.000)	0.622 (0.000)
HR	0.053 (0.620)	0.330 (0.002)	0.354 (0.001)	-0.684 (0.000)	-0.085 (0.425)	-0.086 (0422)	-0.076 (0.478)	-0.086 (0.422)
S in V_1	-0.126 (0.238)	-0.340 (0.001)	-0.236 (0.025)	0.128 (0.229)	0.132 (0.216)	0.347 (0.001)	0.191 (0.071)	0.062 (0.560)
R in V_5	0.023 (0.833)	-0.016 (0.883)	-0.024 (0.824)	0.120 (0.262)	0.065 (0.541)	-0.036 (0.739)	0.088 (0.407)	-0.083 (0.435)
R in aVL	0.094 (0.377)	0.263 (0.012)	0.168 (0.114)	0.059 (0.578)	-0.020 (0.852)	0.080 (0.452)	-0.017 (0.876)	0.044 (0.680)
S inV_3	0.067 (0.529)	0.087 (0.413)	0.081 (0.445)	-0.062 (0.561)	-0.018 (-.869)	0.145 (0.172)	-0.049 (0.645)	0.216 (0.041)
LVM	-0.091 (0.394)	0.094 (0.379)	-0.055 (0.606)	0.019 (0.857)	0.057 (0.593)	-0.001 (0.994)	0.094 (0.380)	-0.095 (0-371)

Abbreviation: RR, R-R interval; HR, heart rate; R in v5, the amplitude of R wave in the left precordial lead; S in v1, the amplitude of S wave in the right precordial lead; R in aVL, the amplitude of R wave in the left hand lead; S in V5, the amplitude of S wave in the left precordial lead; LVM, left ventricular mass; QT, a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle; QTc, QT/√ RR; QTd, QT max-QT min; QTcd, QTc max-QTc min.

5. Discussion

The present study aimed to evaluate ECG parameters in children with epileptic and non-epileptic seizures compared to the controls. The results revealed the highest heart rate in the epileptic children and the highest RR interval in those with BHs. LVM, as a measure that shows the size of myocardial fibers in the main cardiac pumping chamber, had the largest size in the controls followed by epileptic, FC, and BHs children. In pairwise comparisons, QTd had similar values in the children with epilepsy and those with FC as well as in the FC and BHs children, but significantly different values in other pairs. Additionally, the longest QTc was observed in the epilepsy group followed by the FC children. QTcd also showed the longest interval in the epilepsy group, while the FC and BHs groups were approximately similar in this respect. Moreover, the results

indicated that QTd had a significant negative correlation with weigh, height, and LVM and a significant positive correlation with age, heart rate, and S in V_3. QTc also was negatively associated with height and RR interval and positively correlated to R in aVL, heart rate, and S in V3. Besides, QTcd had a negative correlation with weight, height, RR, S in V1, and LVM and a positive correlation with heart rate, R in aVL, and S in V_3. Finally, QT had a positive relationship with RR and a negative correlation with heart rate.

Generally, epilepsy (15), BHs (9), and FC (16) are important events in children, exerting significant impacts on cardiac features. Biet et al. (19) observed prolonged QT in epilepsy, which was similar to a study performed by Kolsal et al. (20) who found QTd prolongation in patients with epilepsy compared to the control group. Movahedian et al. (21) and Noori et al. (16) also disclosed that QT, QTc, QTd, and QTcd were higher in epilepsy patients than in controls. In the same line, El-Rashidy et al. (22) concluded that QTc and QTd were significantly higher in epilepsy children. Sheng and Cheng (23) also observed that QTd was prolonged during epilepsy. Similarly, Seyal et al. (24) reported prolonged QT in epilepsy patients. All these results were in agreement with those of the present research, except for QT that was similar in the patients with epilepsy and the controls. Epidemiological studies have consistently shown that epileptic children had a higher prevalence of cardiac diseases (25). In this regard, cardiovascular disease was found to be a cause of higher mortality in epilepsy (26). De Sousa et al. (27) reported that patients with epilepsy had significantly longer QTc and QTd. Besides, Surges et al. (28) demonstrated that patients with refractory epilepsy had abnormal cardiac repolarization at rest, during or after seizures. They also had long or short QTc postictal and QTd prolongation. In the same vein, Lamberts et al. (29) referred to long QTc in epilepsy. Furthermore, Nie et al. (30) came to the conclusion that exercise had a strong effect on QT prolongation. About 10% of abnormal electrical discharges in brain cause seizures that increase in patients with stroke or brain damage, but a single and simple seizure is not a cause for epilepsy (24). These results cannot confirm those of the present investigation, because the studied patients belonged to different age groups and suffered from different underlying diseases. In addition, ECG parameters were detected during hypoxia within different intervals after seizures in the previous studies, while these parameters were measured 30 minutes or 2 hours after seizures in the current research.

In a prior study by Kandler et al. (31), 23.3% of children with FC had long QTc two hours after general seizures. Brotherstone et al. (32) also found that the majority of epileptic patients had long QTc during epileptic seizures. Additionally, Katibeh et al. (33) showed that only 1% of patients had long QTc, regardless of sex and age. Consistent with the present study findings, Noori et al. (16) reported that QTd, QTc, and QTcd were prolonged in FC children two hours after seizures. Similar results were also obtained by Kandler et al. (31).

BHs in children is a frightening non□epileptic event for parents and a clinically challenging paroxysmal for physicians (34). Akpinar et al. (35) conducted a study to assess ECG changes in children with BHs and found differences between these children and controls in terms of QTc, QTd, and QTcd, which was in agreement with the present study findings. Additionally, Tomoum et al. (36) revealed a longer QTd in the BHs group compared to controls, which was on the contrary to the results of the research carried out by Olsen et al. (37). Akalın et al. (9) found that BHs children and controls were similar in terms of heart rate, RR interval, QT, and QTc, while QTd and QTcd were significantly increased in the cases. Nonetheless, Al-Shahawy et al. (38) showed a significant decrease in heart rate in BHs patients compared to the controls. Furthermore, Amoozgar et al. (39) reported that the mean of QTcd was longer in BHs patients, while no significant differences were found regarding QTd.

In the present study, QT prolongation was similar in epileptic, FC, and control groups, but lower compared to the children with BHs. However, QTc, QTd, and QTcd were longer in the epileptic children compared to the controls, while being similar in BHs and FC groups. Noori et al. (15) showed an increase in heart rate in both epilepsy and FC groups compared to the controls. They also found that LVM in ECG was lower in FC children compared to those with epilepsy. Moreover, QTd, QTc, and QTcd were longer in the epilepsy group compared to the FC group. In another study, Noori et al. revealed longer QTd, QTc, and QTcd in epileptic children in comparison with those with BHs (40). In the present study, the seizure groups had a longer QTc compared to the BHs group and the controls. Among the seizure groups, the patients with epilepsy had longer QTd, QTc, and QTcd compared to those with FC. Up to now, limited trials have been conducted on this issue, but retrospective studies have suggested that improvement of seizure control may prevent ictal asystole (41).

Amongst seizures, FC is the most common cause of convulsion in children, but its pathophysiology is unclear. Increase in sympathetic hyperactivity can be a reason for muscle contraction, which is the cause of hypoxia that may be a reason for the hyperactivity of the ANS (2). Despite the unknown mechanism of FC, several theories can be highlighted. Firstly, elevated brain temperature alters many neuronal functions. Secondly, fever and hyperthermia share common mechanisms in provoking seizures. Thirdly, hyperthermia-induced hyperventilation and alkalosis have been proposed as pivotal elements in FC generation, since brain alkalosis provokes neuronal excitability and contributes to seizure pathophysiology (15).

In general, a higher QTd indicates a more heterogeneous ventricular repolarization throughout the ventricular wall and neighboring areas. This is a potential cause of ventricular arrhythmias that can facilitate ventricular microcircuits, eventually leading to reentrant tachycardia (42). The present study results demonstrated that R in aVL, LVM, QTd, and QTcd were significantly higher in the epilepsy group compared to the FC group. Seizures may also affect numerous autonomic parameters, but cardiovascular manifestations seem to be the maximum outstanding expression. Sympathetic responses predominate

during maximum seizures, causing tachycardia, tachypnea, improved blood pressure, pupillary dilatation, diaphoresis, and facial flushing (43). They may also result in functional ANS changes including a decrease in heart rate variability (44). The autonomic dysregulation, in turn, leads to alterations in cardiac features such as heart rate whose variability controls cardiac capabilities through efferent fibers to the vasculature of the heart (45).

Based on what was mentioned above, changes in ECG parameters in BHs may be considered a sign of cardiac arrhythmia. BHs are frequently confused with epilepsy and routine tests are not beneficial for differential diagnosis. To date, the specific cause of BHs has not been determined. However, it may be due to psychological or routine problems. The crucial issue in this regard is the absence of lesions and neurological problems in the brain, so that it may be considered a natural problem that exists in some children. In other words, BHs can almost never cause any damage to the brain and, consequently, will not lead to any physical or mental problems. Thus, there is a confusion regarding the use of ECG parameters in BHs patients.

The main limitation of this study was the lack of proper cooperation by the participants or their parents, which resulted in a small sample size.

5.1. Conclusion

The present study results indicated that QT dispersion was different in the epilepsy group compared to the BHs group, corrected QT was different in the patients with epilepsy in comparison with those with BHs, and QTc dispersion was different in the epilepsy group compared to the BHs and FC groups. QT was also different in the BHs group compared to the epilepsy and FC groups. Furthermore, QT dispersion, corrected QT, and QTc dispersion were higher in the children with epilepsy compared to those with BHs and FC and the control group. Therefore, it is necessary to refer children with epileptic or non-epileptic diagnosis of epilepsy, FC, and BHs to pediatric neurologists or cardiologists, and electroencephalography is an appropriate investigation in initial evaluation. To maintain a good strategic treatment in patients with seizure, there is a need to assess alternations in ECG parameters, especially QTc and QTd changes, which can lead to better comprehensive autonomic changes.

5.2. Ethical Approval

Consent forms were obtained from the participants or their guardians. The study was approved by the Ethics Committee of Zahedan University of Medical Sciences, Zahedan, Iran (IR.ZAUMS.REC.1397.257).

5.3. Informed Consent

The consent form has been attached to the project.

Acknowledgment

There is no acknowledgement.

Authors' Contribution

Study concept and design: N.N. and A.K.; acquisition of data: N.N., A.K., and E.S.S.; analysis and interpretation of data: A.T.; drafting of the manuscript: N.N. and A.T.; critical revision of the manuscript for important intellectual content: N.N. and A.T.; statistical analysis: A.T.; administrative, technical, and material support: N.N. and A.T.

Funding/Support

The authors have no funding/support related to the material in the manuscript.

Financial Disclosure

The authors have no financial interests related to the material in the manuscript.

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