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Electrocardiography Parameters' Changes in Epilepsy and Breath- holding children compared to Healthy Children

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Abstract

Background: Breath holding spells (BHS) are paroxysmal events with apnea and postural tone with Electrocardiography (ECG) abnormality and epilepsy status reports. The study aimed to compare the ECG parameters' in epilepsy and breath-holding children compared with healthy children.

Materials and Methods: This case control study conducted on 270 participants consisted of 90 children in each group of epilepsy, breath-holding and control (healthy children) that were collected from pediatric clinics of Ali Asghar Hospital, Zahedan, Iran, for a period of one year starting in 2018. QT, QTd, QTc and QTcd were recorded after ECG for participants. Data were analyzed using SPSS 20.0 and the level of 0.05 was considered significant.

Results: From children, 45.6% were girls. Height and weight were the highest in controls and the lowest in breath-holding group, significantly ($p<0.001$). QT had the highest value in BHs, followed by epilepsy when dispersion QT, corrected QT had the highest values in epilepsy (448.62±56.14), and then BHS (433.00±32.76). QT abnormality in epilepsy, controls and BHs frequency of 16 (17.8%), 3(3.3%), and 7(7.8%), respectively (Chi-square=11.321, $p=0.003$). The abnormal individuals based on corrected QT frequency of 43(47.8%), 14(15.6%), and 26(28.9%) in epilepsy, controls and BHs groups and this trend was 44(48.9%), 9(10.00%), and 24 (26.70%) (Chi-square=33.611, $p<0.001$) for dispersion QTc,

Conclusion: It was concluded that QTd, QTc and QTcd were higher in epilepticus children compared with breath-holding and controls. To maintain a good strategic treatment in patients with epilepsy, there is a need to assess alternations in ECG parameters, especially QT changes that lead to better comprehensive autonomic changes.

Key Words: Breath holding, Children, Electrocardiography, Epilepsy.

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1- INTRODUCTION

Breath holding spells (BHS) as non-epileptic activities are benign, paroxysmal activities with apnea and postural tone adjustments that happen when a child stops breathing for up to 1 minute due to being frightened, upset, angry, or sudden shock or pain (1). It is normally harmless but can be frightening for parents the first time (2). Its prevalence has been anticipated between 0.1% and 4.6% inside the general population (3). Difficulties of BHS are unusual, however, unexpected loss of life, extended asystole, and status epilepticus have been reported. A distinct record and examination is critical to correctly diagnose BHs and help distinguish them from epileptic seizures and other reasons of syncope (4), because they may sometimes resemble a seizure. Epilepticus repute can cause cell damage in diverse mind regions, along with the cerebral cortex, hippocampus, thalamus, and cerebellum (5). Mechanisms underlying pathogenesis of the neuronal damage, and its confinement to selectively vulnerable regions, are unknown. Various contributing factors might include hypoxia, ischemia, hypoglycemia, hyperpyrexia, acidosis, free-radical generation and lipid peroxidation, and accumulation of intracellular Ca++ (5, 6).

Hypoxia and ischemia are the various first elements proposed to contribute to neuronal damage following epilepticus status. Ischemic damage was attributed to cerebral vasospasm or to compression of cerebral blood vessels, resulting from venous engorgement or edema. Also, systemic hypoxia and hypotension may contribute to cerebral hypoxia/ischemia during seizures (7). During later seizures, cerebral oxygenation decrease. The cerebral hypoxia is related to seizure without any changes in arterial PO2 (measurement of oxygen pressure in arterial blood). In addition, it has been stated that intense BHS in children could be a reason of cerebral hypoxemia (8). There are two cyanotic and pallid BHS. Few children have both of these spells during their lifetime (9). These spells have benign prognosis, but every so often some complications may appear as a loss of consciousness, tonic–clonic actions, or seizures. The prevalence of this circumstance is stated as 4 to 27% of children between 6 months and 6 years of age in studies (10). In a study (11) it was observed that the children with prolonged breath-holding spells experienced complications and reported syncopal attacks and hypoxic convulsion in 12.6% and 15.7%, respectively. Along with BHS, epilepsy is one of the most common neurological diseases in children, and is a major complication leading to sudden death (12). Epileptic populations similar to breath holding have a higher risk of death than general population and each year, about 1:500 to 1:1000 patients will die suddenly (13).

Electrocardiography (ECG) parameters are predictor factors of mortality in various diseases (14) including diabetes mellitus (15), celiac (16), thalassemia (17), epilepsy (18) breath holding (19), febrile seizure (20), and Kawasaki (21). Expanded QT dissipation has been found to demonstrate extension risk of dysrhythmia including cardiomyopathies, mitral valve prolapses, ischemic coronary disease and renal dissatisfaction (19). ECG parameters are straightforward strategies which are useful for non-intrusive evaluation of the heterogeneity of repolarization inside the ventricular myocardium utilizing the surface electrocardiogram such that QT dispersion (QTd), and QT correction (QTc) are associated with breath holding (22), and are generally considered to reflect autonomic nervous system activation that dissipates with seizure. On the other hand, seizure induced rapid repolarizations in the Purkinje system and the development of ventricular molecular

changes in the heart. Moreover, in ionic channels such as sodium, excess sodium channel expression can lead to prolonged activity, causing arrhythmia and increased QT interval (22); therefore, neurologic disease can result in cardiac arrhythmias (18). This study aimed to assess electrocardiography parameters' changes in children with breath-holding spells and epilepsy compared with healthy children.

2- MATERIALS AND METHODS

2-1. Study design and participants

This case-control and comparative study was carried out on 270 participants, 90 individuals in each group of BHs, epilepsy and healthy children that were aged between 6 months and 6 years. The participants were collected from children referred to Ali Asghar Hospital of Zahedan, Iran, during the year 2018. A child with epilepsy was randomly selected from the epileptic children who were diagnosed by a pediatric neurologist based on the definition that a child has two or more unprovoked seizures in 24 hour's duration (23). Similarly, a child with breath-holding was randomly selected from the breath-holding children who were diagnosed by the same neurologist as those who referred to the pediatric neurology clinics. Healthy individuals were selected randomly from those who were referred to the clinics for the routine checkup.

2-2. Ethical Approval

Consent form was obtained from the participants or their guardians after the study approval. The study was approved as a resident thesis (ID-code: 945) by the Ethics Committee of Zahedan University of Medical Sciences, Zahedan, Iran.

2-3. Criteria

First, the patients were clinically examined and received the routine tests. Those children with epilepsy or BHs who were aged from 6 months to 6 years were entered to the study. Same criteria were assumed for healthy children. Here, the exclusion criteria were abnormal laboratory results affecting the ECG, including calcium, potassium, magnesium, blood glucose, and history of using drugs such as anti-psychotics, anti-arrhythmia, and antibiotics such as aminoglycosides as well as anti-depressants, plus those with underlying cardiovascular disease, trauma, meningitis, encephalitis, seizure-inducing syndromes, and structural disorders. Children with electrolyte disturbance, hypoglycemia, Iron deficiency, impaired kidney function, those with abnormal neurological findings during examination, those who received or were receiving any medications for BHS, or those with a doubtful diagnosis were also excluded from the study.

2-4. Electrocardiography measures

Electrocardiogram (ECG) was detected with an electrocardiogram by Saadat device made in Iran initially from 30 minutes to 2 hours after seizure. ECG in standard scheme was obtained. Once the patients or controls had rested for 10 minutes in a supine position in a quiet room, all 12-ECG leads were simultaneously recorded at a paper speed of 25 mm/s and a voltage of 10 mm/mV. The following measurements were made by a single experienced investigator. To evaluate intra-observer variations, the same ECG leads were measured twice by the same observer on two separate occasions. QT interval was accepted as the distance from the beginning of the Q wave to the end of the T wave. In each lead, the duration from the beginning of the Q wave to the end of the T wave was calculated in milliseconds, the average was taken (QT average) for three consecutive beats. The maximum and minimum duration of the QT wave was selected from the 12 leads of the surface ECG. The difference between maximum and minimum duration was defined as QTd. The average QTc was

calculated using the same QT interval measured using the Bazett formula (QTc= QT/ √ RR); among all derivations, the difference between the longest and shortest QTc was calculated (QTcd) (16). To calculate left ventricular mass in ECG we used the following formulas: LV mass (g) =0·026 (RaVL+SV3) + 1·25 Weight + 34·4 for boys, and 0·020 (RaVL+SV3) + 1·12 Weight + 36·2 for girls (16, 17).

2-5. Statistical analysis

Data analysis was performed using SPSS software version 20.00 (SPSS Inc, Chicago, IL, USA). For quantitative data, the mean and standard deviation (SD), while for qualitative data, frequency and percentage were expressed. Before analysis, the assumption of normality was tested using Kolmogorov–Smirnov test (KS test). In the case of normality, parametric tests including analysis of variance and student t-tests were employed; otherwise non-parametric tests, such as the Kruskal–Wallis by rank and Mann-Whitney U and Chi-square test (X^2), were used. The significance level was considered as $p<0.05$.

3- RESULTS

The present study was conducted on 270 children (45.6% were girls) with breath-holding spells, epilepsy and who were healthy. The rates of girls in each group of epilepsy, controls and BHS children were 45.6%, 51.1% and 40.00%, respectively. This pattern of sex distribution among groups of participants was similar ($X^2=2.24$, $p=0.326$) (**Table.1**). Normality test showed that almost all the variables in the study had free distribution ($p<0.05$) that permitted using non-parametric test for analysis. **Table.2** shows mean comparison of the ECG parameters between the three groups of participants. All the ECG parameters were different in groups. Height and weight of children were the highest in controls and were the lowest in BHS children. These variations of height and weight in children's groups were significant ($p<0.001$). R-R interval was shorter in epileptic children compared with BHS children when HR was higher. S wave in lead V_1, R wave in lead V_5 and S wave in lead V_3 had the lowest values in BHS and then epilepsy significantly.

R wave in lead a VL had similar values in HBS and epileptic children and had significantly higher values than controls. LVM means in the groups of epilepsy, controls and BHS were 50.08±3.77, 52.85±10.87, and 47.32±6.19, respectively such that both groups of patients had significant difference with controls in addition to a significant difference between themselves. The most important parameters of ECG are QT, corrected QT, dispersion QT and dispersion QTc that were compared in the three groups of our participants. The resulted issued in the Table 2 showed that all were significantly different such that, QT had the highest value in BHS children followed by epilepsy, QTd had the highest value in epilepsy children followed by BHs children.

Table-1: Sex distribution of participants in Epilepsy, Breath Holding and Healthy children

Gender	Statistics	Groups			Total	Chi-square	P-value
		Epilepsy	Controls	BHs			
Girls	Number	41	46	36	123	2.24	0.326
	%	45.6%	51.1%	40.0%	45.6%		
Boys	n	49	44	54	147		
	%	54.4%	48.9%	60.0%	54.4%		
Total	n	90	90	90	270		
	%	100.0%	100.0%	100.0%	100.0%		

Table-2: Weight, Height and ECG parameters' comparison between participants' groups of Epilepsy, Breath Holding and Healthy children.

Variables	Groups	Mean	SD	Mean Rank	Chi-Square	P-value	Variables	Mean	SD	Mean Rank	Chi-Square	P-value
Weight	Epilepsy	12.17	2.32	140.29	50.81	<0.001	LVM	50.08	3.77	142.41	45.79	<0.001
	Controls	14.69	8.79	174.24				52.85	10.87	170.97		
	BHS	10.36	3.22	91.96				47.32	6.19	93.12		
Height	Epilepsy	84.16	9.45	119.47	42.46	<0.001	Dispersion QT	45.28	18.12	180.27	74.70	<0.001
	Controls	93.88	15.26	178.77				25.00	12.83	87.51		
	BHS	82.46	10.95	108.26				33.89	13.38	138.72		
RR	Epilepsy	0.53	0.51	94.68	37.41	<0.001	Corrected QT	448.62	56.14	168.07	35.46	<0.001
	Controls	0.57	0.11	154.39				411.20	36.74	99.10		
	BHS	0.57	0.09	157.43				433.00	32.76	139.33		
HR	Epilepsy	129.64	27.63	175.77	36.11	<0.001	Dispersion QTc	63.15	28.71	187.56	75.20	<0.001
	Controls	108.78	26.01	115.21				34.16	19.10	87.01		
	BHS	109.10	19.55	115.52				47.11	17.24	131.93		
S in V_1	Epilepsy	0.58	0.45	133.41	43.33	<0.001	QT	311.44	40.27	127.82	16.51	<0.001
	Controls	0.72	0.36	174.64				307.44	31.43	116.95		
	BHS	0.38	0.22	98.44				326.00	31.29	161.73		
R in V_5	Epilepsy	1.06	0.54	150.55	18.45	<0.001	S in V_3	0.85	0.49	166.68	28.85	<0.001
	Controls	1.02	0.43	149.22				0.64	0.37	135.41		
	BHS	0.78	0.32	106.73				0.50	0.32	104.41		
R in aVL	Epilepsy	0.43	0.32	149.47	50.10	<0.001						
	Controls	0.24	0.16	89.72								
	BHS	0.43	0.22	167.31								

R-R: R-R interval. HR: Heart Rate. 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. 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.

QTc had the highest values in the group of epilepsy (448.62±56.14), followed by BHs (433.00±32.76) then controls (411.20±36.74). This parameter had a significant difference between the two groups of patients. **Table.3** shows pairwise comparison in the groups of participants. **Table.4** shows the distribution of QTd, QTc and QTcd in the three groups of our participants. The distributions in all mentioned parameters had significant distribution in the groups. In QTd, the abnormal individuals in groups of epilepsy, controls and BHS had a frequency of 16(17.8%), 3(3.3%), and 7(7.8%), respectively (X^2=11.321, p=0.003). In QTc, the abnormal individuals in groups of epilepsy, controls and BHS had a frequency of 43(47.8%), 14(15.6%), and 26(28.9%), respectively (X^2=22.162, p<0.001). In QTcd, the abnormal individuals in groups of epilepsy, controls and BHS had a frequency of 44(48.9%), 9(10.00%), and 24(26.70%), respectively (X^2=33.611, p<0.001).

Table-3: Weight, Height and ECG parameters' pairwise comparison between participants' groups of Epilepsy, Breath Holding and Healthy children.

Variables	Groups	Groups	UMW	P-value	Variables	Groups	Groups	UMW	P-value
Weight	Epi	BHS	2390.000	<0.001	R in aVL	Epi	BHS	3554.000	0.152
		Control	2821.500	<0.001			Control	2297.000	<0.001
	BHS	Control	1791.500	<0.001		BHS	Control	1683.000	<0.001
Height	Epi	BHS	3614.000	0.212	LVM	Epi	BHS	2453.500	<0.001
		Control	2171.000	<0.001			Control	3075.000	0.005
	BHS	Control	2034.500	<0.001		BHS	Control	1832.500	<0.001
RR	Epi	BHS	2060.500	<0.001	Dispersion QT	Epi	BHS	2682.000	<0.001
		Control	2365.500	<0.001			Control	1388.500	<0.001
	BHS	Control	4034.500	0.964		BHS	Control	2392.500	<0.001
HR	Epi	BHS	2163.500	<0.001	Corrected QT	Epi	BHS	3074.000	0.005
		Control	2312.000	<0.001			Control	2095.000	<0.001
	BHS	Control	3962.000	0.800		BHS	Control	2729.000	<0.001
S in V1	Epi	BHS	3114.000	0.007	Dispersion QTc	Epi	BHS	2043.500	<0.001
		Control	2926.000	0.001			Control	1371.000	<0.001
	BHS	Control	1651.000	<0.001		BHS	Control	2365.000	<0.001
R in V5	Epi	BHS	2846.000	0.001	QT	Epi	BHS	3115.000	0.006
		Control	3899.500	0.666			Control	3806.500	0.479
	BH	Control	2664.500	<0.001		BHS	Control	2624.000	<0.001
S in V3	Epi	BHS	2263.500	<0.001					
		Control	3030.000	0.003					
	BH	Control	3038.500	0.004					

R-R: R-R interval. HR: Heart Rate. 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. 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.

Table-4: The abnormality distribution of QT measures in participants' groups of Epilepsy, Breath Holding and healthy children.

Variables	Cut point	Statistics	Groups			Total	Pearson Chi-Square	P-value
			Epilepsy	Controls	Breath Holding			
Dispersion QT	≤ 50	Number	74	87	83	244	11.321	0.003
		%	82.2%	96.7%	92.2%	90.4%		
	>50	Number	16	3	7	26		
		%	17.8%	3.3%	7.8%	9.6%		
Corrected QT	<450	Number	47	76	64	187	22.162	<0.001
		%	52.2%	84.4%	71.1%	69.3%		
	>=450	Number	43	14	26	83		
		%	47.8%	15.6%	28.9%	30.7%		
Dispersion QTc	<60	Number	46	81	66	193	33.611	<0.001
		%	51.1%	90.0%	73.3%	71.5%		
	>=60	Number	44	9	24	77		
		%	48.9%	10.0%	26.7%	28.5%		

4- DISCUSSION

Epilepsy (23), and BHS (19) are important events in children with significant impact on cardiac features. Although BHS are paroxysmal non-epileptic events, their pathogenesis is unknown and they occur due to imbalance between sympathetic and parasympathetic activities (24). In addition, it has been observed that autonomic dysregulation has consistently been postulated to have an important role in BHS pathophysiology (19). The autonomic dysregulation leads to alterations in cardiac functions resulting in brain hypoperfusion, seizure, and loss of consciousness. Heart rate variability which controls cardiac functions via efferent fibers to the vasculature of the heart as well as the sinoatrial node and myocardium, is an important marker for autonomic dysregulation (25). In the present study we aimed to evaluate and compare electrocardiography findings in children with epilepsy, BHS and controls. From the study it can be resulted that all the ECG parameters were different in both epilepsy and breath holding patients compared with controls. The significant parameters were RR interval that was higher in BHS than epileptic children but was the same as controls, heart rate was higher in epilepsy compared to both controls and BHS groups. LVM by ECG was lower in BHs. QTd, QTc and QTcd were extremely higher in epilepsy than controls and BHs compared with controls when QT was higher in BHs patients compared to controls and epilepsy. Epidemiological studies have consistently shown that children with epilepsy have a higher prevalence of structural cardiac disease than those without epilepsy (26). De Sousa et al. (27) reported that patients with epilepsy had significantly longer QTc interval and pathologic QTd. Lamberts et al. (28) observed QTc prolongations in epilepsy. El-Rashidy et al. (29), Sheng and Cheng (30), Seyal et al. (31), Biet et al. (32), Kolsal et al. (23), Movahedian et al. (33), and Noori et al. (23) observed prolonged QT measures in epilepsy patients compared to healthy children. All these studies had the same results and are similar with the present study but, QT did not change in epilepsy compared to controls in the present study. The similarity of ECG parameters, except QT between our results and the mentioned studies cannot confirm our results, because their patients were in different age groups and had different underlying disease. Overall, in these studies, ECG parameters were detected during hypoxia within different time after seizure, while in the present study, the ECG parameters were measured in 30 minutes or 2 hours after the seizure. Similarly, other conditions besides seizures are known to cause QTc prolongation such as; exercise like that shown by Nie et al. (34), and migraine by May et al. (35). Surges et al. (36) found those with refractory epilepsy had abnormal cardiac repolarization at rest, during or after seizures, and had QTc prolongation or shortening postictal and pathologic QTd. Ictal-related oxygen desaturation is accompanied by hypercapnia and in patients with seizures may be accompanied by severe oxygen desaturation and marked rise in end-tidal CO^2. This indicated that seizure-related respiratory dysfunction was associated with prolongation of QTc. Other factors contributing to seizure-related increase in QTc cannot be excluded as QTc increase also occurred with seizures that were not accompanied by a drop in oxygen saturation below 90% but with a lower likelihood than in seizures with accompanying hypoxemia (31). Akpinar et al. (37) conducted a study to assess ventricular repolarization changes in children with BHS and resulted in statistically significant differences between BHS and controls regarding the QT, QTc, QTd and QTcd, similar to the present study results. They concluded that the

increase in BHS may be considered as a sign of cardiac arrhythmia. Tomoum et al. (38) concluded a higher QTd in BHS patients compared to controls. They also observed higher durations of bradycardia during attacks and higher occurrences of dysrhythmia during cyanotic spells, which were more frequent in patients with prolonged BHS. Olsen et al. (39) found no changes in ECG parameters in patients with BHS. Akalın et al. (19), also concluded that there was no statistical difference in heart rate, R-R interval, QT and QTc intervals in patients and controls but QTd and QTcd significantly increased. Al-Shahawy et al. (40) reported a significant decrease in heart rate in the patients compared the control. Amoozgar et al. (41) reported that the mean of the QTcd was higher in patients. Meanwhile, no significant differences were found regarding QTd. From the results of the previous studies (41), it seems that there is some confusion when using the ECG parameters for assessing cardiac involvements in BHS patients because of contradiction in reports. Arrhythmias and particularly prolonged QT are useful in the differential diagnosis of BHS. Autonomic nervous system dysfunction leading to QT prolongation at the time of attack has been implicated, particularly in pallid BHS. It was reported that patients with prolonged and frequent spells had longer QT and T-wave dispersion than the control group (38). BHs are frequently confused with epilepsy, and routine tests are commonly known as not being beneficial inside the differential diagnosis. Although the presence of EEG abnormalities no longer constantly calls for a diagnosis of epileptic seizures nor does their absence exclude a natural cause, the absence of a trigger in epileptic seizures and detection of pathology in EEG may cause discrimination. To evaluate the frequency of odd contributors regarding QT measures the results of the present study showed that the proportion of members with the peculiar frame of dispersion QT, became higher in epileptic children (17.8%) compared with BHS children (7.8%). Similar pattern was observed for corrected QT and dispersion QTc such that in corrected QT, epileptic children were 47.8% compared with BHS, 28.9%. Dispersion QTc abnormality in epileptic children was 48.9% compared with BHs children, 26.7%. The specific cause of BHS hasnot been determined yet; however, it may be due to psychological or routine problems. The crucial issue in this regard is the absence of lesions and neurological problems inside the mind, and it may be considered a natural problem that exists in some children. There is almost never any damage to the mind due to BHS, and in the future, no physical or mental troubles are anticipated in these children. The action of neurons is to transmit nerve messages to different neurons. These messages are transmitted to subsequent neurons via chemical messengers known as neurotransmitters. The incidence of any seizure is due to the unexpected switch of a large number of neural messages in the mind, which typically must not be emitted from the mind. These messages can be simply produced in one part of the mind or the entire brain. Depending on where the messages start, the clinical picture of a seizure is also defined. For instance, in the event that they begin from the neurons in the motor area of the brain, the attack may start as a motion of the limbs. The exact cause of the seizure has not yet been determined. The autonomic nervous system is a motor system that is involved in regulating the function of smooth muscle, heart muscle, and glands. The parasympathetic nervous system controls breathing and reduces the baby's heart rate when children with epilepsy sleep more than healthy children. Autonomic nervous system dysfunction is thought to be the primary abnormality in the pathophysiology of BHS (42). Prolonged

expirations are mediated by cyanotic attacks effects, whereas pallid spells are mediated by autonomic effects. Both sympathetic and parasympathetic stimulation may affect QT interval. The higher rate of sudden death due to epilepsy compared to breath-holding can be a justification for longer QT measures in epileptic children (43).

4-1. Study Limitations

The main limitation of this study was the lack of patient follow-up. It is highly probable that by following up changes cardiac evaluation of these patients, more significant abnormal ECG findings will be found.

5- CONCLUSION

From the study it was concluded that dispersion QT, corrected QT and dispersion QTc incidence were higher in children with epilepsy compared to those children with breath-holding spells. These ECG findings were higher in both epilepsy and breath-holding children compared to healthy ones. To maintain a good strategic treatment in patients with epilepsy, there is a need to assess alternations in ECG parameters especially QT changes that lead to better comprehensive autonomic changes.

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7- CONFLICT OF INTEREST: None.

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