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Electrocardiography Findings in Children with Epilepsy Compared with Healthy Children

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Abstract

Background

Epilepsy is one of the most common neurological diseases. Over the last decades the hypothesis of cardiovascular effects from sudden seizure has been raised, and cardiac rhythm and ECG changes in these patients have been highlighted. The study aimed to evaluate the electrocardiography findings in children with epilepsy compared with healthy children.

Materials and Methods

In this case-control study, 90 patients aged between 6 months and 18 years who were matched with equal number of healthy children who referred to pediatric ward the of 'Ali Ebne Abi Talib' hospital in Zahedan, Iran. The study was performed in multicenter of Neurology and Cardiology centers. In the patients, the epilepsy was confirmed by a unique pediatric neurologist based on the definition of having at least two unprovoked seizures in 24 hours. ECG was captured from all participants by a pediatric cardiologist.

Results

In patients, 45.6% (n= 41) were females and in healthy 51.1% (n= 46) were females. Mean age of participants was similar in patients and healthy children (p=0.060). ECG findings such as QT min (p=0.001), R-R interval (p<0.001), Heart rate (p<0.001), S in V1 (p=0.002), R in aVL (p<0.001), S in V3 (p=0.003), QTd (p<0.001), QTcd (p<0.001), QTc max (p<0.001), and LV mass (p=0.007) were different in patients compared to controls. In patients, from ECG parameters, R in V5 was higher in male patients (p=0.043).

Conclusion

Based on the results, QTc, QTd, QTcd were prolonged in patients with epilepsy and, R in V5 was higher in male patients. To prevent abnormality rhythm in epilepsy, it is needed to evaluate QT to recognize the autonomic changes.

Key Words: Children, Electrocardiography, Epilepsy.

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1- INTRODUCTION

Epilepsy is one of the most common neurological diseases of children globally, and is a major complication leading to sudden death (1, 2). Epilepsy-induced death is a sudden and unexpected death, whose prevalence is two or three times higher in patients with seizure than in the normal population (1, 3). Over the last decades, especially since the 1970s, the hypothesis of cardiovascular effects from sudden seizure has been raised and cardiac rhythm and electrocardiography (ECG) changes in these patients have been studied several times (4, 5). At present, 40% of children with seizure have eccentric cardiac arrhythmia including benign idiopathic sinus arrhythmia, irregular heart rhythm, and changes in QT (6). Indeed, QT changes and prolongation during seizure and changes in the autonomic system can lead to ventricular tachycardia and fibrillation. Most importantly, torso des de point causes death in the affected person (4). Several mechanisms cause QT prolongation, including the fact that the ictal phase is associated with respiratory changes including hypoxia and hypercapnia. Hypoxia and hypercapnia develop in response to cardiac reperfusion, and a sympathetic increase in the sinus node leads to prolongation of QT in these patients (7, 8). Seizure also leads to changes in the neutralization and neurological functions in different regions of the brain, leading to sympathetic and parasympathetic effects, followed by significant production of adrenaline and noradrenaline, which persist for several hours (8, 9). The sympathetic stimulation that occurs while standing affects the QT interval independent of the concomitant tachycardia. Such adrenergic stimulation would be expected to exert different effects on patients with normal versus abnormal QT interval (10). Brain injury leads to disturbances in autonomic networks and cardiovascular dysfunction. Changes in the heart also lead to arrhythmias in which ventricular repolarization and QT changes are the most common (11). On the other hand, seizure induced rapid repolarizations in the Purkinje system and the development of ventricular molecular changes in the heart and in ionic channels, such as sodium, excess sodium channel expression can lead to prolonged activity, causing arrhythmia and increased QT interval (4). Therefore, neurologic disease can result in cardiac arrhythmias which is supported by observations that cortical networks regulate cardiovascular function (12). Considering above relationship between heart and nervous systems to verify the changes of ECG parameters in epilepsy, the present study aimed to evaluate and compare the ECG findings in patients with epilepsy and healthy children.

2- MATERIALS AND METHODS

In this case-control study, 90 patients aged between 6 months and 18 years were matched with an equal number healthy children who referred to 'Ali Ebne Abi Talib' hospital in Zahedan, Iran, in 2018. The patients were randomly selected from the epileptic children children who were diagnosed by a pediatric neurologist based on the definition that a child has two or more unprovoked seizures in 24 h duration (13). The controls were selected from those who referred to the hospital for routine checkup.

2-1. Exclusion Criteria

First, the patient was clinically examined and received the routine tests. Here, the exclusion criteria included 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. If any participant had seizure or seizure-induced fever, they were also excluded from the study.

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. 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 ($QTc= QT/\sqrt{RR}$); among all derivations, the difference between the longest and shortest QTc was calculated (QTcd) (9). 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 (14).

2-4. Statistical analysis

Data analysis was performed using SPSS software (version 20.0). 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 student t-test were employed; otherwise non-parametric tests, such as Mann-Whitney U test and Chi-square test, were used. The significance level was considered as $p<0.05$.

3- RESULTS

In the present study 180 participants were analyzed with case-control ratio of 1:1. From the patients, 45.6% and 54.4% were female and males respectively. In the controls, this distribution was 51.1% and 48.9%. Sex distribution showed similarity in the groups (p=0.456) (**Figure. 1**). Mean age of participants was similar in case and control (p=0.060). But weight and height were different in case and controls in favor of controls with the significance levels of p= 0.003 and p <0.001, respectively (**Table.1**). **Table.2** shows normality for the variables in the study for all participants and patients. The table showed that amongst participants and patients all the variables had free distribution (abnormal) (p<0.05). Mean age of participants was similar in case and control (p=0.060). But weight and height were different in case and controls in favor of controls with the significance levels of p= 0.003 and p <0.001, respectively. ECG findings such as QT min (P=0.001), RR interval (P<0.001), heart rate (P<0.001), S in V_1 (P=0.002), R in aVL (p<0.001), S in V_3 (P=0.003), QTd (P<0.001), QTcd (P<0.001), QTc max (P<0.001), and LV

mass (P=0.007) were different in case and controls. The findings of heart rate, R in aVL, S in V_3, QTd, QTcd and QTc max were significantly higher in patients when the findings of R-R, S in V1 and LV mass were lower (**Table.2**). Mean age of patients was different in females and males (P=0.021). But weight and height were similar in patients. From ECG findings R in V_5 was different in patients' groups based on gender that was higher in males (P=0.043). All other ECG findings were similar in gender groups of patients (**Table.3**).

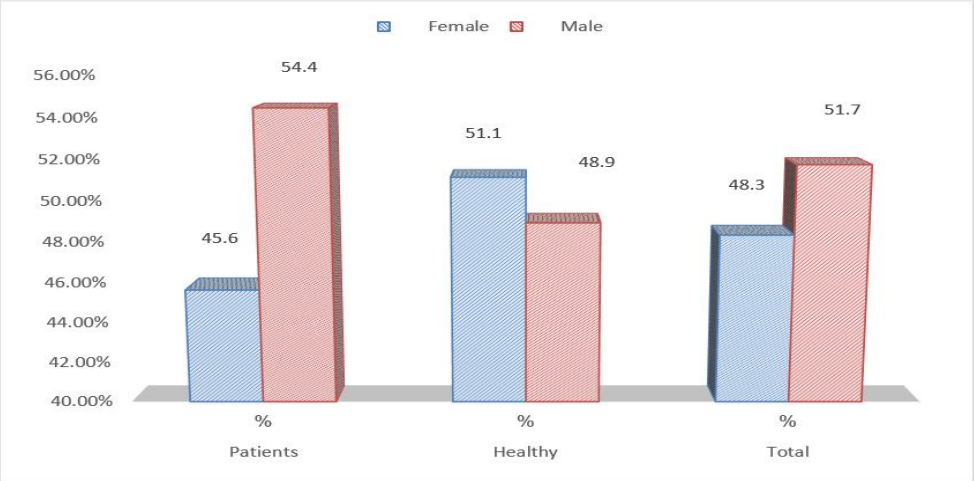

Fig.1: Sex distribution in patients with epilepsy and healthy children.

Table-1: Test of normality distribution for the variables in the study for both patients and healthy children combined and patients with epilepsy.

	Patients and Healthy Participants				Patients Participants			
Variables	Mean	SD	K.S	P-value	Mean	SD	K.S	P-value
Age	4.16	2.32	0.13	<0.001	3.95	2.43	0.20	<0.001
Weight	13.44	6.71	0.22	<0.001	12.27	3.12	0.13	0.001
Height	87.41	16.06	0.10	<0.001	82.37	11.46	0.18	<0.001
QT min	0.28	0.04	0.16	<0.001	0.27	0.04	0.17	<0.001
QT max	0.31	0.04	0.18	<0.001	0.31	0.04	0.20	<0.001
RR	0.55	0.37	0.29	<0.001	0.53	0.51	0.36	<0.001
HR	119.49	28.78	0.09	0.001	129.64	27.63	0.11	0.007
S in V_1	0.65	0.41	0.12	<0.001	0.58	0.45	0.17	<0.001
R in V_5	1.04	0.49	0.07	0.016	1.06	0.54	0.09	0.048
R in aVL	0.33	0.27	0.21	<0.001	0.43	0.32	0.18	<0.001
S in V_3	0.74	0.44	0.12	<0.001	0.85	0.49	0.10	0.031
QTd	0.03	0.02	0.27	<0.001	0.04	0.02	0.41	<0.001
QTc min	0.39	0.04	0.12	<0.001	0.39	0.05	0.15	<0.001
QTcd	0.05	0.03	0.21	<0.001	0.06	0.03	0.32	<0.001
QTc max	0.43	0.05	0.11	<0.001	0.45	0.06	0.12	0.002
LV M	51.28	8.24	0.22	<0.001	49.90	3.74	0.11	0.006

SD: Standard Deviation, K.S: Kolmogorov–Smirnov, RR: 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-2: Comparison of the ECG parameters in patients with epilepsy and healthy children

Variables	Groups	Mean	SD	Mean Rank	Sum of Ranks	M W.U	P-value
Age	Case	3.95	2.43	81.88	7369.50	3396.00	0.060
	Control	4.37	2.20	99.12	8920.50		
Weight	Case	12.27	3.12	79.18	7126.50	3031.50	0.003
	Control	14.61	8.84	101.82	9163.50		
Height	Case	82.37	11.46	70.58	6352.00	2257.00	<0.001
	Control	92.45	18.33	110.42	9938.00		
QT min	Case	0.27	0.04	77.52	6976.50	2881.50	0.001
	Control	0.29	0.03	103.48	9313.50		
QT max	Case	0.31	0.04	90.09	8108.50	4013.50	0.915
	Control	0.31	0.03	90.91	8181.50		
RR	Case	0.53	0.51	72.43	6519.00	2424.00	<0.001
	Control	0.57	0.11	108.57	9771.00		
HR	Case	129.64	27.63	109.14	9823.00	2372.00	<0.001
	Control	109.33	26.35	71.86	6467.00		
Sin V_1	Case	0.58	0.45	78.63	7077.00	2982.00	0.002
	Control	0.71	0.36	102.37	9213.00		
R in V_5	Case	1.06	0.54	92.70	8343.00	3852.00	0.570
	Control	1.01	0.44	88.30	7947.00		
R in aVL	Case	0.43	0.32	109.98	9898.00	2297.00	<0.001
	Control	0.24	0.16	71.02	6392.00		
S in V_3	Case	0.85	0.49	102.16	9194.50	3000.50	0.003
	Control	0.64	0.37	78.84	7095.50		
QTd	Case	0.04	0.02	119.99	10799.50	1395.50	<0.001
	Control	0.02	0.01	61.01	5490.50		
QTc min	Case	0.39	0.05	89.27	8034.00	3939.00	0.750
	Control	0.39	0.03	91.73	8256.00		
QTcd	Case	0.06	0.03	122.92	11062.50	1132.50	<0.001
	Control	0.03	0.02	58.08	5227.50		
QTc max	Case	0.45	0.06	109.18	9826.50	2368.50	<0.001
	Control	0.42	0.04	71.82	6463.50		
LV Mass	Case	49.90	3.74	79.98	7198.00	3103.00	0.007
	Control	52.67	10.90	101.02	9092.00		

M W.U: Mann-Whitney U. K.S: Kolmogorov–Smirnov. RR: 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-3: Comparison of the ECG parameters in Male and Female children with epilepsy

Variables	Gender	Mean	SD	Mean Rank	Sum of Ranks	M W. U	P- value
Age	Female	4.32	2.21	44.84	1838.50	720.00	0.021
	Male	3.65	2.58	46.05	2256.50		
Weight	Female	11.69	2.74	41.43	1698.50	837.50	0.173
	Male	12.77	3.34	48.91	2396.50		
Height	Female	81.07	10.21	43.76	1794.00	933.00	0.561
	Male	83.45	12.41	46.96	2301.00		
Qt min	Female	0.26	0.04	42.27	1733.00	872.00	0.265
	Male	0.27	0.04	48.20	2362.00		
Qt max	Female	0.30	0.04	40.57	1663.50	802.50	0.089
	Male	0.32	0.04	49.62	2431.50		
RR	Female	0.47	0.09	42.85	1757.00	896.00	0.375
	Male	0.59	0.68	47.71	2338.00		
HR	Female	133.12	27.98	48.61	1993.00	877.00	0.301
	Male	126.73	27.27	42.90	2102.00		
S in V1	Female	0.57	0.49	43.94	1801.50	940.50	0.602
	Male	0.58	0.41	46.81	2293.50		
R in V5	Female	0.92	0.51	39.41	1616.00	755.00	0.043
	Male	1.18	0.55	50.59	2479.00		
R in aVL	Female	0.35	0.19	42.01	1722.50	861.50	0.241
	Male	0.49	0.39	48.42	2372.50		
S in V3	Female	0.80	0.49	42.45	1740.50	879.50	0.310
	Male	0.89	0.49	48.05	2354.50		
QTd	Female	0.04	0.02	41.17	1688.00	827.00	0.072
	Male	0.05	0.02	49.12	2407.00		
QTc min	Female	0.39	0.05	43.83	1797.00	936.00	0.577
	Male	0.38	0.06	46.90	2298.00		
QTcd	Female	0.06	0.03	41.63	1707.00	846.00	0.169
	Male	0.07	0.02	48.73	2388.00		
QTc max	Female	0.44	0.05	42.44	1740.00	879.00	0.307
	Male	0.45	0.06	48.06	2355.00		
LV Mass	Female	49.31	3.08	42.54	1744.00	883.00	0.325
	Male	50.39	4.18	47.98	2351.00		

M W.U: Mann-Whitney U. K.S: Kolmogorov–Smirnov. RR: 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.

4- DISCUSSION

Epilepsy is one of the most common neurological diseases of children around the world and is one of the most important and most complicated disorders which occasionally ends in sudden death (5). In the present study we aimed to evaluate electrocardiography findings in children with epilepsy compared with healthy children and resulted that QT min, RR interval, Heart rate, S in V1, R in aVL, S in V3, QTd, QTcd, QTc max, and LV mass were different in case and controls. The findings of Heart rate, R in aVL, S in V_3, QTd, QTcd, and QTc max were higher in patients. R inV_5 was different in the patient groups of males and females. By definition, QT is the duration of discharge and cardiac contraction, which can be a risk factor for arrhythmia and sudden death when one thousandth of the general population also have gene mutations (4).

Epilepsy also affects the ionic channels in the heart and brain, leading to changes in the heart and arrhythmia. Meanwhile, hypoxia and hypercapnia developed during epilepsy can also result in arrhythmia and ultimately sudden death (4). In some studies, sinus tachycardia has been described as the most common cause of heart rhythm changes, as well as reparation and conduction abnormalities (2, 3). Lin et al., (15) reviewed a new perspective on cardiovascular effects on 30 patients under the age of 18 years, in which QT was less than normal, which was not a coherent study. The reason for this was because of rapid changes in heart rhythm, which resulted in a higher rate of QT shortening. They also observed the prolongation of QTd in girls. Compared with the present study, it was revealed that QT min decreased in patients which is similar to Lin et al.'s study but was dissimilar considering all other QT measures. However, Seyal et al. (7) examined coronary heart disease in seizure hypoxemia on 17 patients aged between 12 and 35 years. They observed prolonged QT in epilepsy patients, which was in line with the present study. This similarity probably cannot confirm our results, because their patients were older and underlying disease was coronary heart disease. Further, in their study, ECG parameters were detected during hypoxia and SPo_2 less than 90% within 2 minutes after seizure, while in the present study, the ECG parameters were measured in 30 minutes - 2 hours duration time after the seizure. Also, Biet et al. (2), observed prolonged QT in epilepsy, where the findings of their study were not consistent with the present study. The effect of this can be the chronicity of seizure in their study. In this study, children with the first epilepsy seizure were studied. In this study, QTd was significantly different in children with epilepsy compared with healthy individuals. However, in a study by Kolsal et al. (5), on 20 children with recurrent epilepsy, 20 children with epilepsy and 20 healthy children aged less than 18 years old with changes in their heart rhythm, they found significant QTd changes during epilepsy, suggesting that epilepsy leads to a prolonged QTd.

Lin et al. (15) also tested 25 patients with epilepsy under the age of 18 and looked at the effects of QT and tachyarrhythmia after epilepsy. The distribution was the same in boys and girls. Sheng and Cheng (16), also analyzed QT on 687 patients older than 3 years with epilepsy. In this study, 448 subjects were male and 239 were female. They observed that QTd was prolonged during epilepsy. They concluded that the prolongation of QT dispersion and the occurrence of T wave alteration increase severe autonomic dysfunction in patients with epilepsy who are prone to sudden cardiac death. These results to some extent, confirm our related findings. It could be stated that the prolongation of the QTd may be due to changes in the autonomic system.

Also, during epilepsy, ventral depolarization as well as atrioventricular and synoventricular nodes can lead to autonomic dysfunction and increased QTd. Increased QTd also results in VF and ultimately, sudden death. In this study, the mean QTc size in children with epilepsy was significantly different from that of their healthy counterparts. Surge et al. (17) conducted a study on 70 children with epilepsy and analyzed QT and tachyarrhythmia. They observed shortened QTc, which contradicts the results of this study. The reason for this discrepancy could be patient heterogeneity. However, Brotherstone et al. (8) reviewed QTc in 39 patients between the ages of one month and 16 years old, with 25 girls and 14 boys. They found an increase in QTc in epilepsy. Indeed, prolonged corrected QT may have a role in sudden unexplained death in epilepsy. Sevcencu and Struijk (3) also suggested prolongation of QTc in the study of cardiac changes in epilepsy, which is consistent with the present study.

Note that epilepsy-induced impulses and direct cardiopulmonary effects bypass the development of an asystole, yielding a substantial adrenergic effect in the sympathetic pathways causing the development of ventricular tachycardia and ultimately QTC prolongation. Further, heightened amplitude during epilepsy leads to sodium peak. Changes in the channels in the brain and heart cause ventricular reperfusion and QTc increase. In the present study, the mean QTcd size in children with epilepsy was significantly different from that in healthy subjects. Dogan et al. (18) conducted a study on children with well-controlled epilepsy under the age of 18 years. They resulted no statistically significant differences in terms of ECG intervals including HR, duration of P wave, duration of QRS wave, RR, and PR intervals between epileptic and the control groups. QTc max and QTcd intervals were significantly higher in the epileptic group than those of the control group. In their study significant difference between the groups regarding the QTc min intervals was not observed. These changes are consistent with the present study. The hypoxia occurring during seizure results in augmented QTcd. Accordingly, autonomic changes and cardiac changes caused by epilepsy lead to an increase in QTc, QTd, QTcd; even without QT changes, QT prolongation is generally accompanied by an increase in sudden death. De Sousa et al. (19) conducted a study on adult patients and controls. They found no difference in heart rate and R-R interval between the groups, but the QTc interval was longer in patients. In addition, pathologic QTd and left atrial enlargement were significantly more frequent in patients. In comparison with this study, we achieved dissimilar results regarding HR and RR. However, concerning QT the results are similar with different age groups for the participants.

Movahedian et al. (20) conducted a study on 50 children aged 3 months to 15 years with syncope attacks and compared them with controls. To compare QT, QTc, QTd, and QTcd values in groups, these parameters were higher in patients than controls. In comparison with the present study, it is observed that the results related to QT are dissimilar due to the age difference of participants in the studies and the type of patients. Measuring the above values in children's ECG, once could predict whether syncope attack would happen in the future or not. El-Rashidy et al. (21) performed a study on 60 patients with idiopathic epilepsy in comparison with controls to detect ECG findings. They concluded that the mean values of QTc and QTd were significantly higher in patients similar to our findings. Ali et al. (22) confirmed the association of ventricular alterations following convulsive status epilepticus in children. They reached the conclusion that prolonged seizures may have detrimental

effects on the stability of ventricular electrical properties. They also found that children with epilepsy exhibit the highest prevalence of ECG abnormalities, the minimum QT/RR coupling, and the greatest beat-to-beat QTc interval variability, suggesting that these children may be at the highest risk for ventricular instability.

4-1. Study Limitations

The study limitations were lack of proper cooperation in the study especially healthy children. The study was also limited by the lack of the evaluation of autonomic functions and antiepileptic drugs in detail.

5- CONCLUSION

From the present study it was concluded that ECG parameters such as QTc, QTd, QTcd increased in epilepsy patients, and in patients, males had higher amplitude in R in V_5. To maintain a strategic distance in epilepsy patients, there is a need to assess ECG parameters alterations especially QT changes that lead to comprehending the autonomic changes.

6- CONFLICT OF INTEREST: None.

7- ACKNOWLEDGEMENT

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