ORIGINAL ARTICLE

Short QTc in Epilepsy Patients Without Cardiac Symptoms

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SUMMARY

Epilepsy patients have a higher mortality rate than the general population. Sudden unexpected death in epilepsy (SUDEP) is a major cause of mortality for these patients. The possibility of cardiac involvement in the pathogenesis of SUDEP has been suggested by many previous studies. This study compared the QT interval in epilepsy patients and normal controls, and identified the factors that affected the QT interval. Standard 12-lead ECGs were recorded from 70 consecutive epilepsy patients from the neurology clinic of HUKM and 70 age, race and gender matched controls. The mean QT interval corrected for heart rate (QTc) was calculated and compared. The mean QTc among the epilepsy patients was 0.401 ± 0.027s. It was significantly shorter than the QTc (0.420 ± 0.027s) in the control group (p<0.0005). Thirty five epilepsy patients (50%) and 17 matched controls (24.3%) had a mean QTc shorter than 0.40s (p=0.001). Among the epilepsy patients, the mean QTc did not significantly differ between patients in the duration (F=0.836, p=0.438) of the epilepsy, frequency (F=0.273, p=0.845) and types of seizures (p=0.633). There was no significant difference in the mean QTc between the epilepsy patients on different number of antiepileptic agents (F=0.444, p=0.643). Patients with cryptogenic epilepsy had a mean QTc of 0.392 ± 0.029s, which was significantly shorter than patients with symptomatic epilepsy (QTc = 0.410 ± 0.027s, p = 0.015). The mean QTc of the same subjects showed no significant interobserver difference (p=0.661). This study, for the first time, demonstrates that epilepsy patients have a significantly shorter QTc than controls, particularly in the subgroup of patients with cryptogenic epilepsy.

KEY WORDS:
QT interval, Shortened, Epilepsy, SUDEP, Cryptogenic

INTRODUCTION

A seizure is a paroxysmal event due to abnormal, excessive, hypersynchronous discharges from an aggregate of central nervous system neurons[1]. Patients with epilepsy have a mortality rate of two to three times that of the general population[2]. Epilepsy related causes of death include "sudden unexpected death in epilepsy" (SUDEP). The reported incidence varies from 1/1000 to1/100 and SUDEP accounts for 8-17% of deaths in this population. The possible risk factors for SUDEP are summarized in Table I[3,4].

Nonfatal pathologic findings, including fibrosis of the conductive system, have been reported in 33% of SUDEP patients. Increases in weight and venous congestion, indicating right cardiac failure, were documented in the majority of cases[3].

Cardiac arrhythmias also may play an important role in the pathogenesis of SUDEP. Erickson[5] systematically studied ictal ECG changes for the first time. Erickson[5] reported tachycardia, cardiac arrhythmia, and T-wave flattening secondary to a right temporal lobe seizure. Initial bradycardia, followed by tachycardia, was documented in as many as 64% of petit mal and 100% of generalized tonic-clonic seizure attacks. More recent studies, documenting simultaneous EEG and ECG, reported tachycardia in 74-92% of complex partial seizures. Persistent bradycardia is less common and is reported in 3-7% of complex partial seizures[6]. Ictal cardiac rhythm and conduction abnormalities have been reported in 5-42% of patients with partial seizures[7].

Drake *et al*[8] reviewed resting ECGs in 75 epilepsy patients and compared the ventricular rate, PR interval, QRS duration, and QT interval corrected for heart rate (QTc) with ECGs recorded in age-matched patients without cardiac or neurological disorders. No potentially lethal arrhythmias were noted in the seizure patients. Patients who fit the previously-described profile of high risk of SUDEP (Table I) had more abnormal ECGs and faster ventricular rates than in other epileptics. No differences were noted in QRS duration or PR interval. The QT interval was longer in patients with complex partial seizures than in control ECGs or other epilepsy patients.

Controversy exists regarding which lead should be used for the measurement of the QT interval and QT offset, the method of correction for changes with heart rate, and the correct limits of the normal range. Measured QT intervals (from the onset of QRS complex to the point at which the T wave ends) vary significantly among leads[9]. Lead II typically is used and most normal reference ranges are based upon measurements from this lead[10]. However, some suggest using whichever limb lead best shows the end of the T wave; or leads V2 or V3, in which QT measurements are typically the longest; or leads V5 or V6, because of the clarity of the Q-wave onset and T-wave termination[10]. Although this is somewhat arbitrary, the QT interval should be measured for three to five consecutive beats and averaged[11].

The upper normal limit usually cited for the QTc is 0.44 to 0.46 sec (440 to 460 msec). A QTc of more than 0.44 sec is considered prolonged in men; the normal range generally is extended to 0.45 to 0.46 sec in women[12-15]. Although these

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figures serve as useful guidelines, genetic studies have demonstrated that QTc measurements overlap in individuals who are carriers and noncarriers of an LQTS gene, resulting in potential misclassifications based upon QTc measurements alone. In one report of 199 family members (83 of whom were carriers of LQT1), QTc intervals were 0.41 to 0.59 sec in carriers, compared to 0.38 to 0.47 in noncarriers. A QTc $\geq$0.47 sec in males and $\geq$0.48 sec in females was completely predictive but resulted in a false negative diagnosis in 40 percent of male carriers and 20 percent of female carriers. On the other hand, use of QTc $\geq$0.45 sec resulted in a false positive rate of 11 percent[16].

The aims of the present study were to determine if epilepsy patients demonstrated a higher frequency of prolonged QT interval as compared to normal controls and to analyse factors that affect the QT interval. Abnormalities of the QT interval may provide clues to the underlying mechanisms of SUDEP and help identify epilepsy patients at risk. There is only one previous study that showed a longer QT interval in patients with epilepsy compared with normal controls.

MATERIALS AND METHODS

This was a comparative cross sectional study. Seventy epilepsy patients on antiepileptic drugs from the neurology clinic HUKM and 70 age, race and gender matched controls were recruited. The epilepsy patients were selected consecutively during their scheduled neurology clinic follow-up from December 2004 till March 2005. The healthy volunteers were recruited from the staff of HUKM as well as the visitors of non-epileptic patients in the medical wards. Individuals with preexisting heart disease and on medication that can cause prolonged QT interval in the past one month were excluded. The following information was recorded during recruitment: age, race and gender and aetiology, type, duration and treatment of the epilepsy as well as a thorough drug history.

A standard 12-lead electrocardiogram (ECG) was performed for all subjects recruited. The QT interval was measured manually from the beginning of the QRS complex to the end of the T wave using calipers with the smallest measurement being 0.005cm or 0.0002s (Figure 1). The lead with a large T wave and a distinct termination was used; generally, this was lead II. The time-corrected QT interval (QTc) was calculated using the Bazett formula, in which the QT interval was adjusted for heart rate by dividing it by the square root of the R-R interval. Three readings were taken and averaged for each sample. Mean QTc of less than 0.400 seconds was considered shortened. (Figure 2)

Data recorded were analysed using the SPSS version 11.5 software. Normality was evaluated by using Kolmogorov-Smirov statistics, and a non significant result, p>0.05 indicates normality. Outliers were identified by the histogram, box plot and statistical test.

All continuous variables (QT interval) were expressed as mean and standard deviation. Parametric tests (independent T test and ANOVA) were used to determine the association between quantitative variables (mean QT interval, which was normally distributed) and qualitative variables (epilepsy patients and normal controls, different subgroups of epilepsy patients). Statistical significance was set at a p value of less than 0.05 (p <0.05).

Ethical considerations

The study was approved by the Medical Research and Ethics Committee of the Medical Faculty, Universiti Kebangsaan Malaysia.

RESULTS

Demographic data

Seventy epilepsy patients and 70 age, race and gender-matched healthy volunteers were recruited. The mean age in the epilepsy patients was 34.2 $\pm$ 15.1 years and in the control group 34.1 $\pm$ 14.9 years. The distributions according to mean age, gender and ethnicity are shown in Table II. The largest number of patients and controls was in the 20 to 29 years age group.

Clinical characteristics

The distribution of patients according to duration of epilepsy and frequency of seizure is shown in Table III. Out of 70 patients, 42 (60%) had generalized seizures. The majority of patients (n=29, 41.4%) had symptomatic epilepsy, due to congenital cerebral abnormalities in 11 patients with hippocampal sclerosis in 9 patients, stroke in 5 patients to space occupying lesions in 2, and head injury in 2. Idiopathic and cryptogenic epilepsy constituted 25.7% and 32.9% of cases respectively.

Corrected QT interval (QTc)

There was no significant difference between different age groups (F=0.967, p=0.455), race (F=0.571, p=0.568), and gender (p=0.418) in the control group. There was also no significant difference in the mean QTc between different age groups (F=0.392, p=0.881) and race (F=0.982, p=0.380) among the epilepsy patients, but that males showed a significantly shorter mean QTc (0.388 ± 0.025s) than females (QTc=0.412 ± 0.024s, p<0005). The mean QTc among the epilepsy patients was 0.401 $\pm$ 0.027s. It was significantly shorter than the QTc (0.420 $\pm$ 0.027s) in the control group (p<0.0005).

Among the epilepsy patients, 35 (50.0%) had QTc intervals shorter than 0.40s, whereas only 17 (24.3%) of the matched controls had QTc shorter than 0.40s (p=0.001). Among the epilepsy patients, the mean QTc did not significantly differ with duration of epilepsy (F=0.836, p=0.438), frequency (F=0.273, p=0.845) or type of seizures (p=0.633). There was no difference in the mean QTc between the epilepsy patients on monotherapy, dual therapy or more than two antiepileptic agents (F=0.444, p=0.643).

Patients with cryptogenic epilepsy had a mean QTc of 0.392 $\pm$ 0.029s, which was significantly shorter than patients with symptomatic epilepsy (QTc = 0.410 $\pm$ 0.027s, p=0.015). There was also no significant difference in the QT interval between the symptomatic-idiopathic group (p=0.103) and cryptogenic-idiopathic group (p=0.532). When we merged the cryptogenic epilepsy with the symptomatic group, we found no significant difference in the QT interval between this combined group of patients and the idiopathic group (p=0.076).

When comparing the mean QTc of the same subjects measured by the second observer, there was no significant interobserver difference (p=0.661).

DISCUSSION

Sudden unexpected death in epilepsy (SUDEP) is a major diagnostic category in studies of mortality in epilepsy[3]. The aetiology for SUDEP remains elusive and may be multifactorial. Alterations of autonomic control of cardiac activity in epilepsy patients have been reported by several studies in the past; both ictal and interictally. Drake *et al*[8] also demonstrated that patients without cardiac symptoms who fit the previously-described profile of high risk of SUDEP had more abnormal ECGs and a faster ventricular rate. In addition, pathological changes, though they may not be the

Table I: Summary of possible risk factors for SUDEP[4]

Variable	High risk
Patient-related risk factors	
Age	28-35 years
Gender	Male
Race	African American
Health	Developmental delay
Seizure-related risk factors	
Seizure aetiology	Symptomatic
Seizure type	Generalized tonic-clonic
Age of seizure onset	Younger
Duration of seizure disorder	Longer than 10 years
Severity of seizure	Increased number of attacks
Treatment-related risk factors	
Antiepileptic medication serum levels	Subtherapeutic
Number of antiepileptic medications	Greater
Antiepileptic medication regimen	Recently changed
Other treatment	Surgery

Table II: Demographic data of epilepsy patients and their controls

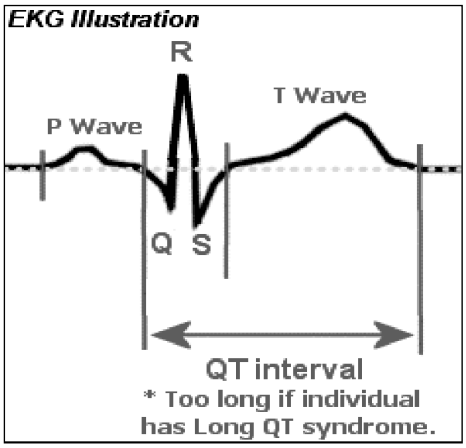
	Epilepsy patients n = 70	Controls n = 70	p value
Age (years)			
mean	34.2	34.1	0.97
SD	15.1	14.9	
Gender			
male	34 (48.6%)	34 (48.6%)	1.00
female	36 (51.4%)	36 (51.4%)	1.00
Ethnic			
Malay	27 (38.6%)	27 (38.6%)	1.00
Chinese	25 (35.7%)	25 (35.7%)	1.00
Indian	18 (25.7%)	18 (25.7%)	1.00

Level of significance p<0.05

Table III: Clinical characteristic of epilepsy patients

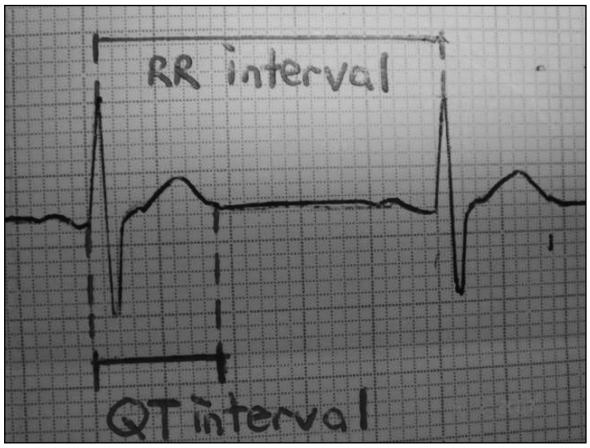
	Frequency	Percentage
Duration of epilepsy (year)		
<3	4	5.7
3-5	11	15.7
>5	55	78.6
Frequency of seizures (per year)		
<1	13	18.6
1-5	26	37.1
6-10	4	5.7
>10	27	38.6
Number of AEDs		
1	42	60.0
2	17	24.3
>2	11	15.7
Choice of AEDs		
PHT monotherapy	42	60.0
CBZ monotherapy	17	24.3
VPA monotherapy	11	15.7

PHT - Phenytoin
CBT - Carbamozepine
UPA - Sodium Valproate



Bazett formula: QTc = QT interval ÷ square root of the RR interval

Fig. 1: ECG illustration of measurement of a QT interval



QT interval = 0.342 second, RR interval = 0.998 second => QTc = 0.342 second

Fig. 2: ECG of a patient with short QT interval

direct cause of death, were described in 33% of the SUDEP patients[6,7].

The QT interval is an ECG reflection of ventricular repolarization. Its upper normal limits are clearly recognized, and QT interval prolongation is considered as an independent risk factor for sudden death. There are many data on congenital and acquired long QT syndromes and their relation to mortality. In contrast, little is known about the causes and prognostic value of QT interval shortening[17]. Unlike previous studies, the present study is the first study to demonstrate a shortened QT interval among epilepsy patients; a finding that was not foreseen during the design of the study.

The first data suggesting that not only too long but also too short a QT interval may be associated with increased mortality appeared in 1993. In a population study of 6693 Holter recordings, Algra *et al*[17] found that both long and short (<400 ms) QT intervals were associated with a twofold increased risk of sudden death.

Gaita *et al*[18] studied several members of two different families who were referred for syncope, palpitations, and resuscitated cardiac arrest in the presence of a positive family history for sudden cardiac death. At baseline ECG, all patients exhibited a QT interval ≤280 ms (QTc ≤300 ms). During electrophysiological study, short atrial and ventricular refractory periods were documented in all and increased ventricular vulnerability to fibrillation in three of four patients. Sudden death in the presence of short QT interval occurred in several generations, in both male and female subjects, which suggests an autosomal dominant mode of inheritance. Noninvasive and invasive evaluation revealed structurally normal hearts, and autopsies were not indicative of cardiac disease. Therefore, a short QT interval constitutes another primary electrical abnormality responsible for sudden death in the young. Nevertheless, the risk of sudden death might be present throughout life, because in the studied families, it occurred both in children <1 year old and in patients >60 years old.

The prevention of sudden cardiac death in patients with short QT syndrome is of great importance. Up to now, implantable cardioverter defibrillators (ICD) are the only available method of treatment in these patients; however, a high percentage of inappropriate ICD discharge due to T-wave oversensing has been reported[19]. In terms of pharmacological treatment, Gaita *et al*[18] evaluated different drugs that can potentially prolong the QT interval (class IC and III antiarrhythmic drugs) and found that only quinidine can prolong the QT interval observed on the ECG and prolong the ventricular refractory period, thereby decreasing the inducibility of ventricular fibrillation. This may be considered as an alternative treatment.

Although there have been no previous studies reporting a shortened QT interval in epilepsy patients, and its association with SUDEP, cardiac arrhythmias have been postulated to play an important role in the pathogenesis of SUDEP. Fatal arrhythmias can occur both during the seizure and interictally.

The shortened QTc in epilepsy patients may be related to the associated increase in ventricular rate and alteration of the autonomic tone observed in previous studies. Electrolytes abnormalities, particularly hypercalcaemia and hyperkalaemia may also cause shortened QTc in epilepsy patients. Not surprisingly, there may be direct alterations of the cardiac ionic channel with repeated seizure attacks as intractability and higher frequency of seizures have been associated with a higher risk of SUDEP.

CONCLUSION

This study demonstrates that epilepsy patients have a significantly shorter QTc than controls, particularly in the subgroup of patients with cryptogenic epilepsy, a hitherto unrecognized finding. Thus, epilepsy patients. Thus, epilepsy patients need to be actively screened for QTc as both shortened and prolonged QTc are associated with increased risk of sudden cardiac death. However the clinical significance of QTc abnormalities, observed in the present

study; in relation to the pathogenesis of SUDEP merits further investigation.

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REFERENCES

1. Lowenstein DH. Seizure and Epilepsy. In: Harrison TR, Braunwald E, Facia AS, Kasper DL (editors). Harrison's principle of internal medicine, USA: McGraw-Hill Companies, 2001; 2354-5.
2. Cockerell OC, Johnson AL, Sander SW, Hart YM. Mortality from epilepsy: results from a prospective population-based study. Lancet 1994; 334: 918-21.
3. Lhatoo SD, Langan Y, Sander JW. Sudden unexpected death in epilepsy. Postgrad Med J 1999; 75: 706-9.
4. Kloster R, Engelskjon T. SUDEP: a clinical prospective and search for risk factors. J Neurol Neuosurgery Psychiatry 1999; 67: 439-44.
5. Erickson T. Cardiac activity during epileptic seizure. Arch Neurol Pshych 1939; 41: 511-8.
6. Maromi N, Reginald T, Frank W, *et al*. EEG and ECG in sudden unexpected death in epilepsy. Epilepsia 2004; 45: 338-45.
7. Devinsky O, Price BH, Cohen SI. Cardiac manifestations of complex partial seizures. Am J Med 1986; 80: 195-202.
8. Drake ME, Reider CR, Kay A. Electrocardiography in epilepsy patients without cardiac symptoms. Seizure 1998; 7: 91-6.
9. Cowan JC, Yusoff K, Moore M, *et al*. Importance of lead selection in QT interval measurement. Am J Cardiol 1988; 61: 83-9.
10. Moss A. Measurement of the QT interval. Am J Cardiol 1993; 72: 23-9.
11. Al-Khatib SM, LaPointe NM, Kramer JM, Califf RM. What clinicians should know about the QT interval. JAMA 2003; 289: 2120-7.
12. Funck-Brentano C, Jaillon P. Rate-corrected QT interval: techniques and limitations. Am J Cardiol 1993; 72: 17-22.
13. Hnatkova K, Malik M. "Optimum" formulae for heart rate correction of the QT interval. Pacing Clin Electrophysiol 1999; 22: 1683-9.
14. Bazett HC. An analysis of the time-relations of electrocardiograms. Heart 1980; 7: 353-63.
15. Eggeling T, Hoeher M, Osterhues HH *et al*. Significance of noninvasive diagnostic techniques in patients with long QT syndrome. Am J Cardiol 1992; 70: 1421-7.
16. Kaufman ES, Priori SG, Napolitano C, *et al*. Electrocardiographic prediction of abnormal genotype in congenital long QT syndrome: experience in 101 related family members. J Cardiovasc Electrophysiol 2001; 12: 455-64.
17. Algra A, Tijssen JGP, Roelandt JRTC, *et al*. QT interval variables from 24 hour electrocardiography and the two year risk of sudden death. Br Heart J 1993; 70: 43-8.
18. Gaita F, Giustetto C, Bianchi F, *et al*. Short QT syndrome: A familial cause of sudden death. Circulation 2003; 108: 965-70.
19. Gussak I, Brugada P, Brugada J, *et al*. ECG phenomenon of idiopathic and paradoxical short QT intervals. Card Electrophysiol Rev 2002; 6: 49-53.