Frequency of Long QT Syndrome in Seizure Patients with no Underlying Cause

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Aim: The present cross-sectional study was conducted on seizure patients without any underlying causes. The data were collected using a questionnaire covering such variables as age, gender, and history of seizure and syncope. Electrocardiogram (ECG) was obtained from the patients in the first 2 h after the occurrence of seizure. Moreover, the distance from the beginning of the Q wave to the end of the T wave in the lead limb Ht was measured by the researcher. Finally, the collected data were analyzed in SPSS software (version 22).

Background and Aim: There are contradictory data regarding the changes of corrected QT interval (QTc) in seizure. Regarding this, the present study aimed to evaluate the frequency of long QT syndrome (LQTS) in seizure patients without underlying cause in Hazrat-e Masoumeh Hospital, Qom, Iran.

Materials and Methods: The present cross-sectional study was conducted on seizure patients without any underlying causes. The data were collected using a questionnaire covering such variables as age, gender, and history of seizure and syncope. Electrocardiogram (ECG) was obtained from the patients in the first 2 h after the occurrence of seizure. Moreover, the distance from the beginning of the Q wave to the end of the T wave in the lead limb Ht was measured by the researcher. Finally, the collected data were analyzed in SPSS software (version 22).

Results: The participants consisted of 67 males (55.8%) and 53 females (44.2%) with the mean age of 6.7±2.1 years. Long QT was observed in five patients. The gender of the participants had no significant relationship with the type of seizure and family history of syncope, sudden death, heart disease, and seizure (P≥0.05). The mean QT intervals in the males and females were 0.40±0.24 and 0.40±0.23 sec, respectively. Therefore, no significant difference was observed between male and female patients in this regard (P≥0.05).

Conclusion: Based on the results, LQTS in seizure patients without underlying causes was found in only five patients. However, in special cases, such as a family history of QTc disorders, history of suspected faint, and resistant or status epilepticus, the implementation of ECGs can be helpful for children.

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Introduction
Seizure is a transient disorder of the brain that is caused by abnormal electrical discharge in the brain nerve cells which creates a variety of symptoms, such as sudden loss of consciousness, muscle contraction, or sensory and behavioral changes (1). Some seizures have a cardiovascular cause (2). Long QT syndrome (LQTS) is a disorder in the heart electrical system which is caused by an increase in the duration of ventricular repolarization, which can be either congenital or medication-induced (3). This syndrome is a rare and life-threatening pathologic condition that affects 1 per 2,500 people with the mortality rates of 20% and 50% within the first and tenth years after diagnosis (4). Common symptoms of this syndrome include syncope, seizure, and sudden death (5). The QT interval
represents the time required for ventricular depolarization and repolarization. Heart rate affects these intervals; therefore, this variable should be considered during the measurement process. This interval is calculated via Bazett’s formula. The corrected QT (QTc) is considered to be less than 0.44; however, when this value increases, QT is regarded to be long (5–7). The LQTS often manifests itself in children as syncope, which results from exercise, fear in sleep, or sudden jumps. Patients may first experience seizures, pre-syncope, and palpitations; moreover, 10% of the cases undergo cardiac arrest (8). This syndrome is diagnosed by electrocardiography (ECG) and clinical history taking. The LQTS was first introduced by Jervvel and Lang-Nielsen in 1975 (9). Furthermore, Romano-Ward diagnosed several families with similar characteristics regarding QT length, recurrent syncope, and sudden death in 1963 and 1964 (10). Previous studies have shown that long QT may manifest itself as seizures or epilepsy; however, early detection can prevent sudden death in these patients (11). According to the literature, the misdiagnosis rate of long QT as seizure-related arrhythmias has been reported to be up to 35% (12). Furthermore, there are reports regarding the misdiagnosis of LQTS as seizure, resulting in the receipt of seizure-related therapy. Therefore, in order to prevent misdiagnosis and delay in correct diagnosis in the patients who are visited for seizures, they should be subjected to ECG, while considering the focal point of seizure (13). However, LQTS should be ruled out in every child with seizures through history taking and ECG (14). Studies conducted on this syndrome in Iran, especially on children, are limited. However, sudden death can be prevented in such patients by identifying these patients, obtaining ECG, and performing simple measures (e.g., using beta-blocker medications and avoiding medications that prolong the QT interval). With this background in mind, the present study aimed to evaluate the frequency of LQTS in seizure patients with no underlying cause in Hazrat Masoumeh Hospital to facilitate the adoption of proper treatment for special cases referring to hospitals.

Materials and Methods

This cross-sectional study was carried out in Hazrat-e Masoumeh Teaching Healthcare Center, Qom, Iran, in 2019. The study population of this study consisted of seizure patients with no underlying cause who referred to Hazrat-e Masoumeh Hospital. The required sample size was calculated as 120 cases. The data were collected using a questionnaire, which included such variables as age, gender, and history of seizures and syncope. The exclusion criteria were unwillingness to participate in the study on the part of patient or their family and affliction with seizure with an underlying reason (e.g., trauma, hypoxia, and known brain lesion). The ECG was obtained from the patients in the first 2 h after the seizure. Subsequently, the QT interval from the beginning of the Q wave to the end of the T wave was measured by the researcher via Bazett’s formula. The QTc was calculated at three different levels, and the longest interval was considered as our target. Our criterion for the measurement of the QT was the longest QT interval; accordingly, the maximum normal QTc interval was considered as 0.44. The distance in this study was measured via Bazett’s formula (QT interval/radical RR). The lead limb II was used in a complex containing a particular T and Q wavelength. After calculating the QTc in three different parts of the ECG, the longest QTc was selected as the target number. Patients who used medications that prolong the QT interval were excluded from the study. After calculating the QTc, the ionized calcium electrolyte in patients was checked, and all the data were included in the researcher-made checklist. Finally, all the families were ensured that the information would be kept confidential. Descriptive statistics, such as mean, standard deviation, and frequency tables, were used to describe the data. Chi-square test and independent t-test were also used for comparing the qualitative and quantitative data, respectively. The results were analyzed using SPSS software (version 20), and a p-value of less than 0.05 was considered statistically significant.

Results

The participants consisted of 44.2% (n=53) female and 55.8% (n=67) male. The mean age of the patients was estimated at 6.7±2.1 years.

Based on the results shown in Table 1, 38.3% (n=46), 12.5% (n=15) and 1.7% (n=2) of the patients had a family history of seizure, heart disease, and sudden death, respectively. In addition, there was a history of syncope in 10 (8.4%) patients. The route of delivery was natural in 71 patients (59.2%), and the most and least common types of seizure were generalized (n=58, 48.3%) and atonic (n=11, 9.2%), respectively.

According to the results indicated in Table 2, the most and least common types of seizure in male and female patients were generalized (n=33, 49.3% vs. n=25, 47.2%) and atonic seizure (n=8, 11.9% vs. n=3, 5.7%), respectively. Furthermore, no significant relationship was found between patient gender and the type of seizure (P=0.77). Based on the statistical tests, there was no significant relationship between the patient gender and family...
Table 1. Descriptive variables of the patients

| Variable                                | Number | Percentage |
|-----------------------------------------|--------|------------|
| Family history of seizures             | Yes    | 46         | 38.3     |
|                                        | No     | 74         | 61.7     |
| Family history of heart disease        | Yes    | 15         | 12.5     |
|                                        | No     | 105        | 87.5     |
| Family history of sudden death         | Yes    | 2          | 1.7      |
|                                        | No     | 118        | 98.3     |
| Syncope history                        | Yes    | 10         | 8.3      |
|                                        | No     | 110        | 91.7     |
| Route of delivery                      | Natural| 71         | 59.2     |
|                                        | Cesarean| 49        | 40.8     |
| Type of seizure                        | Generalized| 58    | 48.3     |
|                                        | Tonic  | 33         | 27.5     |
|                                        | Clonic | 18         | 15       |
|                                        | Atonic | 11         | 9.2      |

Table 2. Relationship between gender and type of seizure in the studied patients

| Gender  | Generalized | Tonic | Clonic | Atonic | Total | P-value |
|---------|-------------|-------|--------|--------|-------|---------|
| Male    | 33          | 15    | 11     | 8      | 67    |         |
| Percentage | 49.3%    | 22.4% | 16.4%  | 11.9%  |       |
| Female  | 25          | 18    | 7      | 3      | 53    | P=0.77  |
| Percentage | 47.2%    | 34.0% | 13.2%  | 5.7%   |       |
| Total   | 58          | 33    | 18     | 11     | 120   |         |
| Percentage | 48.3%    | 27.5% | 15.0%  | 9.2%   |       |

Table 3. Level of serum calcium and QT interval in study population

| Gender  | Total | Mean | Standard Deviation | P value |
|---------|-------|------|--------------------|---------|
| Level of serum calcium        | Male  | 67   | 9.62               | 0.72    | P=0.73  |
|                                  | Female| 53   | 9.67               | 0.75    |         |
| QTc                                | Male  | 67   | 0.39               | 0.02    | P=0.67  |
|                                  | Female| 53   | 0.39               | 0.02    |         |

history of syncope (P=0.69), family history of sudden death, (P=0.20), family history of heart disease (P=0.06), and family history of seizure (P=0.79).

Serum calcium levels in the male and female participants were 9.62±0.72 and 9.66±0.75, respectively. Therefore, no significant difference was observed between male and female patients in this regard (P=0.73). In addition, the mean QT interval in the male and female patients were estimated at 0.22±0.39 and 0.21±0.39 sec, respectively, indicating no significant difference between the genders (P=0.67) (Table 3).

Discussion

In the present study, 5 patients were inflicted with long QT, two of whom recovered after one month of treatment, and the rest were treated with high-dose propranolol. In a study performed on children within the age range of 0-14 years, Erikson and Koivikko observed partial seizure in 43% of patients. Moreover, 44%, 9%, and 4% of patients suffered from generalized, mixed, and uncategorized types of seizure, respectively. In the mentioned study, generalized seizures included absence (5%), atypical absence (2%), tonic colonic (27%), myoclonic (9%), atonic/static (3%), and infantile spasms (8%) (15). In the present study, 67 (55.8%) participants were male. Moreover, 46 (38.3%), 15 (12.5%), and 2 (1.7%) patients had a family history of seizure, heart disease, and sudden death, respectively. Moreover, there was a history of syncope in 10 (8.4%) patients. The route of delivery was found to be natural in 71 (59.2%) patients. In general, the most and least common types of seizure were generalized (n=58, 48.3%) and atonic (n=11, 9.2%), respectively. With regard to each gender, generalized seizure was found to be the most common type of seizure in both males and females (n=25, 47.2% vs. n=33, 49.3%), while atonic seizure was identified as the least common type (n=8, 11.9% vs. n=8, 11.9%). Moreover, no statistically significant relationship was observed between gender and type of seizure in patients.
The mean QT interval in male and female participants were respectively estimated at 0.22±0.39 and 0.21±0.39 sec, which indicated no significant difference between the two genders. Garson et al. studied LQTS in 287 children to determine low-risk and high-risk populations, as well as LQTS symptoms and the best treatment. In the aforementioned study, the investigated subjects were patients with less than 20 years of age, who had a QT of > 0.44 and referred to the hospital with syncope, seizure, or cardiac arrest as a result of stress or changes in the emotional state. The mean age of the patients was 6-8 years at the time of referral to the hospital. Based on the results, 9%, 26%, and 10% of the patients were suffering from cardiac arrest, syncope, and seizures, respectively. Furthermore, 39% and 31% of the patients had a family history of long QT and sudden death, respectively. A QT higher than 0.6 was observed in 13% of the patients. Since 9% of the patients had referred to the hospital with cardiac arrest and no prior symptoms, the researchers suggested the indication for prophylactic treatment in asymptomatic children (16). Lim et al. (2011) examined the association between fever and increase in QTc in a healthy adolescent patient. In this study case, fever prolonged QTc and ventricular fibrillation in the patient (17). Similarly, a recent clinical trial has shown that fever can be a risk factor for life-threatening ventricular arrhythmia in type II LQTS. Amin et al. showed that fever increased QT interval in patients with A558P mutation (18). Brotherstone et al. (19) investigated QTc during and after epileptic seizures on 39 patients in 2010. According to Bazett’s formula, in 21 seizures (9 patients) QTc increased to above the normal maximum level (20). Dagon et al. (21) conducted a study on 76 adult patients with well-controlled focal epilepsy and 66 healthy people. They obtained 12-lead ECGs of all the participants and calculated the QTc intervals. Finally, they concluded that the QTc interval was significantly higher in patients with well-controlled focal epilepsy than that in the control group. The results of the aforementioned study showed the important role of cardiac examination, even in patients with well-controlled epilepsy, in revealing serious cardiovascular issues. The multiple reports regarding the failure to diagnose this condition highlights the importance of considering long QTc in patients referring with seizures and adopting measures to rule out this diagnosis by obtaining ECG. Moreover, there was no statistically significant relationship between the patient’s gender and their history of syncope. Only 2 (3%) male patients had a family history of sudden death, while no such history was found in the female participants. Levels of serum calcium were estimated at 9.62±0.72 and 9.66±0.75 in the male and female patients, respectively, indicating no significant difference between the two genders in this regard. Sadri Nia et al. (2013) conducted a study with the aim of examining the relationship between seizures and long QT. In the mentioned case-control study, the control group consisted of patients hospitalized for seizure with no underlying cause, and the intervention group included patients suffering from conditions other than seizure. In the mentioned study, long QT was considered more than 0.46 sec. A total of 508 patients were studied who were divided into case (n=254) and control (n=254) groups. There were 66 children in the case group who suffered from seizures and long QT. Moreover, there were 48 children with long QT in the control group. The difference was statistically significant (P=0.02); however, no significant difference was observed between the two groups, regarding syncope and sudden death. Results of the present study showed that children with unrecognized seizures have longer QTcs, suggesting the possibility of arrhythmias in some seizures. Therefore, it is recommended that ECG be obtained from patients with no underlying causes of seizures (11). Teh HS et al. in a study examined the QT interval in seizure patients and normal subjects and identified the factors influencing the QT interval. They performed standard 12-lead ECGs on 70 seizure patients and 70 controls who were matched in terms of age and gender. The mean QTc for the seizure group was 0.401, which was significantly lower than that in the control group (QTc=0.420; P<0.0005). A total of 35 and 17 patients in the seizure and control groups had a QTc of < 0.4, respectively (P<0.0001). The mean QTc was not affected by the duration and type of seizure. The mean QTc in patients with cryptogenic seizures was significantly lower than that in the symptomatic seizure patients (22). The present study was the first attempt showing that the mean QTc was significantly lower in seizure patients, especially in cryptogenic epilepsy patients than in the control group.

Conclusion

There are contradictory reports on QTc changes in seizures. The results of the present study indicated that QTc levels were not high in children suffering from seizure with no underlying causes. However, the implementation of ECGs can be helpful for children, especially in certain cases, such as in those with a family history of QTc abnormalities, history of suspected faint, and
continuous or status seizures.

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Conflict of interest

There was no conflict of interest among the authors of the present study.

Suggestions

It is recommended that this study be repeated with a larger sample size, using a control group, and with the possibility of dividing patients into limited age ranges.

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