Overt long QT syndrome in children presenting with seizure disorders in Pakistan

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ABSTRACT

Background and Objective : **The long QT syndrome (LQTS) is a repolarization defect of heart involving potassium linked channels and it usually manifests clinically as seizures, syncope, or sudden cardiac death syndrome in children secondary to its characteristic ventricular tachy-arrhythmia like torsades de pointes. The reason behind epilepsy or seizures like activity in this disease is the sequelae of prolonged cerebral hypoperfusion secondary to the cardiac dysrhythmia. The aim of study is to look for clinical spectrum and risk factors associated with LQTS among children presenting with epilepsy, which can predict the early diagnosis of LQTS.**

Materials and Methods **For this observational study, 422 patients having epilepsy presenting for the first time in a 3-year period were enrolled. Demographical profile, LQTS measures, and various factors under observation were recorded.**

Results : **Among the 422 enrolled children (M: F 1.8:1) with age ranging from 4 to 87 months (median 23 months), 8 (1.9%) children who presented with epilepsy had LQTS. Among those, mean QTc on electrocardiogram was 454 ± 31 msec and mean Schwartz score >3. Half of the patients with LQTS had deafness (P = 0.002) and 37.5% had a positive family history (P = 0.0045). Nearly a third (37.5%) presented with syncope and 87.5% patients with LQTS had no postictal drowsiness or sleep ($P \leq 0.004$).**

Conclusions : **LQTS is underestimated in children presenting with epilepsy and LQTS should be considered as an alternate diagnosis in children with recurrent seizures or syncopal attacks. The brief period of seizures with no postictal drowsiness, syncope, and strong family history are the features which may help in segregating LQTS from epilepsy.**

Keywords : Children, epilepsy, long QT syndrome, QT interval, torsades de pointes

INTRODUCTION

In 1856, Meissner reported the death of a deaf girl who collapsed and died in a school event related to emotional stress. The girl's two siblings also had similar kind of history and sudden death, and probably, it was the first description of the long QT syndrome (LQTS).[1] LQTS affects approximately 1 in 2000 people.[2] The LQTS is a repolarization defect of heart involving potassium linked

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channels and having many types, the most common of them is Romano–Ward syndrome (genetically LQT1-6 and LQT9-16), an autosomal dominant form in which the electrical activity of the heart is affected without involving other organs. A less commonly seen form is Jervell and Lange-Nielsen syndrome, an autosomal recessive form of LQTS combining a prolonged QT interval with congenital sensorineural deafness.[3] LQTS usually manifests clinically as seizures, syncope or sudden cardiac death syndrome in children secondary to its characteristic ventricular tachyarrhythmia like torsades de pointes (TdP).[4] Patients with LQTS can be misdiagnosed as seizure disorder or epilepsy and treated with antiepileptic drugs (AEDs). It has been documented in literature that 11% patients of LQTS have presented with seizures or seizure-like episodes and 1.6% has been diagnosed with epilepsy.[5] The developed world where diagnostic facilities have reached to the level of genetic studies show that there are many genes responsible for different types of LQTS and they usually encode a potassium channel to activate the syndrome for variable manifestations. However, in developing countries, labeling of LQTS is still based on clinical history, electrocardiogram (ECG), and certain criteria.[4] The LQTS predisposes the heart to ventricular tachycardia and fibrillation that may result in sudden death and in some cases may present just like epilepsy.[6] LQTS presenting with seizures has significant morbidity and mortality, which is reduced with appropriate management. However, usually the children presenting with seizures are not being investigated properly for LQTS and are usually treated by the pediatrician or neurologist as epilepsy.[7,8] This results in delayed recognition of the disease and sometime leads to catastrophic consequences in the form of severe morbidity and social and psychological trauma to the family.[9]

In this study, we aimed to evaluate clinical spectrum of LQTS, risk factors, and family history that distinguishes it from the children presenting as epilepsy, so that we can screen these children at early stage to pick the arrhythmias and make a better management plan accordingly. The identification of such factors would help in planning focused screening of such patients so that they can be diagnosed early to avoid fatal outcome. This will not only decrease the chances of life-threatening complications but also minimizes the cost to treat them. It will also help us to decrease psychosocial trauma to family.

MATERIALS AND METHODS

This observational study (prospective and retrospective surveillance of patients with LQTS) was conducted at the Department of Cardiology and Neurology, the Children Hospital Faisalabad, Pakistan over a period of 3 years from January 1, 2018 till December 31, 2020. This is a tertiary care center in the province of Punjab with a population of over 120 million[10,11] where we get referrals from other tertiary care hospitals in the region for diagnostic and management issues. Institutional Review Board of the hospital approved the study protocol. All patients presenting to the hospital for the first time and diagnosed with epilepsy were evaluated for the inclusion in the study. After obtaining informed consent from patient's parents, evaluation was performed with confirmation of diagnosis through electroencephalogram, ECG, and Holter monitoring. The demographic profile, residence, type of seizures, deafness, family, and siblings history were recorded on a specially designed questionnaire pro forma through interview-based information by the author (UR) from direct caregivers including mother, father or the guardian. The diagnosis of LQTS was made using criteria in patients and their families, which included both a corrected QT (QTc) interval of >440 msec in either lead II or V_5 (Bazzett's Formula) and an absolute QT interval greater than the 98th percentile for heart rate in lead V_5 along with combination of clinical parameters.[12] Schwartz scores were also calculated for the likelihood of LQTS. Patients with score of 1 or less have a low probability of LQTS, scores of 1.5–3 have an intermediate probability and scores of 3.5 or greater have a high probability of LQTS.[13] The patients who showed any evidence of secondary causes such as hypoxia, hypocalcemia, or any signs of known neurological injuries were excluded from the study. The children who were asymptomatic or did not present with the epilepsy or syncope but subsequently have the diagnosis of LQTS were also excluded from the study.

Statistical analysis

Data were entered in IBM SPSS Statistics package version 20.0(SPSS Inc., Chicago, U.S.A) and analyzed using its statistical package. Frequency was calculated for the qualitative variables including gender, ECG abnormality, and deafness. Mean and standard deviation were calculated for the quantitative variables such as age and weight. Univariate and multivariate analyses were performed to determine the significance of various factors in prediction for long QT and seizures. $P < 0.05$ was considered statistically significant.

RESULTS

In this study, 422 participants were recruited over a 3-year period. There were 271 (64.2%) boys with boys to girls' ratio of 1.8:1. The median age at the time of presentation was 23 months (range 4–87 months). Nearly 67.3% patients belong to the rural areas. Overall, 418 (99.1%) patients presented with epilepsy as their first presentation and 4 (0.9%) patients presented with syncope. Majority (81%; n = 342) had postictal sleep or drowsiness after the seizure

episode. Thirty-seven (8.8%) patients had a duration of seizures <1 min, 65.2% (n = 275) had 1–5 min duration, and 26.1% (n = 110) had >5 min duration. Majority (n = 318; 75.4%) of children were not taking medication for seizures before their presentation to the hospital. Only 7.3% (n = 31) had a positive family history of epilepsy in their first-degree relatives.

Out of the patients who presented with seizures, 1.9% (n = 8) had LQTS and 98.1% (n = 414) were having QT interval <440 msec. Among the LQTS patients, 87.5% (n = 7) were male. Only three children (37.5%) presented with syncope. Of these 8 children, 37.5% (n = 3) had QTc interval of 440–460 msec, 50% (n = 4) had QTc of 460–470 msec, and 12.5% (n = 1) had QTc of >470 msec. The median Schwartz score was 3.2 ± 0.79 (range 3–5) with 62.5% children (n = 5) having a Schwartz score of 3, and 37.5% (n = 3) having a score of >3. The average QTc measured at first time was a mean of 454 ± 31 msec and with re-evaluation on subsequent ECG, it was 467 ± 23 msec [Table 1]. Five children (62.5%) had a duration of seizures <1 min with no postictal drowsiness or sleep. Majority (75%) were taking AEDs for their seizures/epilepsy before their confirmation of diagnosis as LQTS.

Deafness, positive family history, sudden unexplained death in siblings, syncope had a strong association with the LQTS and were statistically significant (P < 0.05). The odd ratios (OR) and P value are given in the Table 2. There was no correlation between age, gender, and LQTS (P = 0.72 and P = 0.28). There was a significant association between LQTS and family history (P < 0.003, OR 42.7) and sibling death (P < 0.001, OR 70.0). Syncope was a prominent feature in patients with LQTS as compared to patients with normal QTc (P < 0.002, OR 34.3). Schwartz criteria are significant in diagnosing the LQTS as the criteria score of 3 or more than 3 was constant in patients with LQTS (P > 0.001). All the patients diagnosed with LQTS were put on beta blocker therapy and AEDs were discontinued in 75% of patients who were taking them prior to diagnosis and majority (62.5%) of them were event free for more than 6 months. One patient had three episodes of seizures even on beta blocker therapy and TdP were documented on Holter. However, his symptoms were also improved when the dose of beta blockers was increased. The patient who had repeated episode of seizures on follow-up had a QTc of 472 msec and Schwartz criteria of >4. Other two patients had QTc of 462 msec and 467 msec and Schwartz criteria of 3.5 each.

DISCUSSION

Most well-known symptomatic triad stemming from TdP (Trademark dysrhythmia of LQTS) is syncope, epilepsy, and sudden death.[14] The reason behind epilepsy or seizure like activity is the sequelae of prolonged cerebral hypoperfusion secondary to the cardiac dysrhythmia like ventricular tachycardia or TdP (i.e., torsadogenic seizures). Because these patients usually present with apparent generalized seizures, it is not uncommon for patients with LQTS to be misdiagnosed as epilepsy and treated with AEDs.[6,14] This is a diagnostic dilemma that not only results in bearing the risk of taking multiple AEDs but also can be fatal and lead to sudden death.

There was male predominance in our study, and it is comparable with the literature.[14,15] This may highlight a possible change in genetic substrate in the Asian population resulting in higher incidence in males

Table 1: Demographics of children diagnosed with long QT syndrome

Characteristics	Mean±SD or *n* (%)		*P*
	Main group (*n*=414)	LQTS group (*n*=8)	
Median age of diagnosis in months (range)±SD	23 (4-87)±15.7	25 (11-52)±13.0	<0.003
Median age at presentation in months (range)	20 (3-80)±13.8	22 (10-31)±6.7	<0.001
Gender male: female	1.8:1	7:1	NA
Average QTc on 1st ECG (ms)	367±24	454±31	0.02
Average QTc on subsequent ECG (ms)	389±19	467±23	0.02
Median schwartz score (range)	1 (1-2)	3.2 (3-5)	0.001
Family history			
LQTS in 1st degree relative	0	3 (37.5)	0.0001
Deafness in sibs	5 (1.2)	3 (37.5)	0.0001
Sudden unexplained death	1 (0.2)	3 (37.5)	0.001
Diagnosis of epilepsy in 1st degree relative	89 (21.5)	1 (7.0)	0.23
Symptoms			
Syncope	11 (2.6)	3 (37.5)	0.002
Palpitation	8 (1.9)	0	0.43
LOC	13 (3.1)	2 (12.5)	0.031
Treatment prior to presentation (AED)	104 (25.2)	6 (75.0)	0.002
Treatment after presentation			
B blocker	0	8 (100)	0.0001
ICD	0	0	-

LQTS: Long QT syndrome, AED: Anti-epileptic drugs, ICD: Implantable cardiac defibrillator, LOC: Loss of consciousness, ECG: Electrocardiogram, SD: Standard deviation, NA: Non significant, QTc: Corrected QT

Table 2: Risk factors and predictors of long QT syndrome

Risk factor	LQTS (*n*=08)	Non-LQTS (*n*=414)	OR (95% confidence limit for OR)	*P*
Deafness	4	1	50.0 (16.2-154.5)	0.0001
Family history	3	1	42.7 (17.1-141.2)	0.003
Postictal sleep	1	341	0.03 (0.004-0.26)	0.058
Sudden sibling death	2	0	70.0 (31.6-154.9)	0.001
LQTS in 1st degree relative	3	2	14.3 (3.1-68.5)	0.0001
Syncope	4	0	34.3 (12.3-98.7)	0.002
Gender	7	264	0.13 (0.001-27.3)	0.281

LQTS: Long QT syndrome, OR: Standard deviation

rather than equal gender distribution in the Western population. Another factor is cultural and social norms wherein a male gets more attention and is more likely to be brought to medical attention earlier than a female child. The median age at the presentation in the study represents the common cohort of children documented in the literature.[16] There were some patients who were diagnosed with epilepsy and treated with AEDs, but actually they had the diagnosis of LQTS. Some studies suggested that the misdiagnosis of LQTS under umbrella of epilepsy remained uncorrected for almost 11.2 years,[17] but in our data, the median delay was 8 months (Range 2–27 months). QTc measurement appears to be very simple, but it is reported that only 50% of cardiologists and 40% of noncardiologists interpret it correctly and this leads to a delay in the diagnosis of such children.[18]

Out of 422 children who presented with seizures, 1.9% (n = 8) had LQTS. In the literature, the association of LQTS with seizures is different in a variety of studies and range up to 6%–10% of children.[5,19] However, this difference is also contributed by the genetic testing of high-risk patients rather than simple ECG and Schwartz criteria for the diagnosis of LQTS. In our study, the QTc of >470 msec was observed in 12.5% of cases which is comparable to the international literature where it is 13% in Sadrnia *et al.*[16] and 16% in Taggart *et al.*[15] Half of the patients (50%) with LQTS (0.01% of all patients with seizures) had a history of deafness which is comparable with the study by Ocal *et al.*[20] where it was 0.57%. Three patients (37.5%) reported a history of parents, siblings or first-degree relatives who were diagnosed as LQTS, and it is comparable with literature.[15] The average QTc difference between the first and subsequent ECGs was 13 msec (P = 0.003) with the overestimation of subsequent ECG depicts the shortcoming in calculation of QTc[18] and it is comparable to international literature.[15] The median Schwartz criteria score was 3.2 ± 0.79 (Range 3–5). The patient with score of 5 was the patient who had recurrent seizures and his symptoms controlled with the high dose of betablockers.

The most dramatic case included a 4-year-old boy who was on AEDs for almost 9 months and had recurrent seizures despite multiple anticonvulsants. During an outpatient department visit for screening ECG, he developed seizure episode during ECG recording which showed. TdP and after immediate resuscitation, the rhythm was reverted back to normal and his QTc was 469 ms. He was put on beta-blocker therapy, and all the AEDs were discontinued and since then he is seizure free for the last 1.5 years.

All the patients with LQTS were put on beta-blockers as Implantable Cardiac Defibrillator facility was not available and 62.5% (n = 5) of these patients are event free with no seizures for at least 6 months' follow-up. Remaining 37.5% (n = 3) had recurrence of the symptoms in 6 months follow-up. In these three patients, 1 patient had recurrent seizures and he visited the outdoor patient department twice with a history of seizures of almost 1 min duration. Initially, the starting dose of beta-blocker was 1 mg/kg/day and subsequently it was titrated to 3 mg/kg/day and heart rate reduction was almost 25% and seizures stopped subsequently. Other two patients had 1 episode of syncope only, and it is well managed with 2 mg/kg/day dose of beta blocker. The patients who had recurrent seizures are now controlled by optimizing the dose of beta blockers. Two patients are still under observation after starting treatment and had a follow-up period <6 months till the completion of study and are event free. This is comparable to the study by Koponen *et al.*[21] that depicts that despite optimizing the dose of beta-blocker still 30% of patients can have the episode of seizures in the course of their follow-up.

A group of experts on LQTS proposed following guidelines for measuring QT interval:[22,23]

1. Use a limb lead that best reveals the end of the T-wave
2. Measure from beginning of QRS complex to the end of the T-wave and include a U-wave if it is large enough to be merged with T-wave
3. Adjust QT interval for heart rate.

Study limitations

There was an inherent limitation of collection of data from one or two tertiary care hospital settings in the study and it only included the patients who did reach to such facilities and may have missed some patients who presented to GP clinics. Genetic testing was also not done for LQTS due to nonavailability of facility and only ECG

and Schwartz criteria were used for diagnosis that may affect the yield of LQTS, but this may be useful in a way for the resource constrained countries.

CONCLUSIONS

In this study, we conclude that LQTS is underestimated in children presenting with epilepsy and it should be considered as an alternative diagnosis in children with recurrent seizures or syncope attacks. The brief period of seizures with no postictal drowsiness, syncope, and strong family history are the features which can predict LQTS. To avoid missing diagnosis of LQTS, physicians working in pediatric emergency department must obtain a detailed clinical history and should be familiar with reliable interpretation of QT interval.

Ethical approval

Institutional review board approved the ethical aspect of the study.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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