ARAŞTIRMA/RESEARCH

Diagnostic and management difficulties in congenitally long QT syndrome: a single centre experience

Konjenital uzun QT sendromunda tanısal ve yönetimsel zorluklar: tek merkez deneyim

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Abstract

Purpose: Long QT Syndrome (LQTS) is characterized by prolonged ventricular repolarization and tendency to malignant tachyarrhythmia. We reported 16 patient diagnosed congenitally LQTS as a tertiary centre's 12 years experience.
Material and Methods: Patients whom diagnosed as congenitally LQTS in Cukurova University Divison of Pediatric Cardiology between years 2001 to 2013 were included the study.
Results: Sixteen patients (6 female, 12 male) were diagnosed as congenitally LQTS. Mean age of patients was 10 years (2.6-20 years), mean follow up period was 35 months (11-120 months). Mean corrected QT interval was measured 520 ms (470-590 ms). At the diagnosis nine of sixteen patients (56%) had syncope, convulsion or cardiac arrest history, and three of them were misdiagnosed as epilepsy and were treated with antiepileptic drugs as well.
Conclusion: We want to underline the importance of electrocardiography monitoring at all family members and some patients who misdiagnosed as recurrent seizures.
Key words: Long QT Syndrome, syncope, sudden cardiac arrest.

Öz

Amaç: Uzun QT Sendromu (LQTS) uzamış ventriküler repolarizasyon zamanı ve malign taşikardiye eğilim ile karakterizedir. Bu yazıda doğumsal LQTS tanısı almış 16 hastamızda 12 yıllık deneyimimizi sunduk.
Gereç ve Yöntem: Çalışmamızda Çukurova Üniversitesi Pediatrik kardiyoloji bölümünde 2001-2013 yılları arasında konjenital olarak LQTS tanısı alan hastalar dahil edildi.
Bulgular: 16 hastaya (6 kadın, 12 erkek) konjenital LQTS tanısı konuldu. Hastaların ortalama yaşı 10 (2.6-20 yaş) ortalama takip süresi ise 35 ay idi (11-120 ay). Ortalama doğrulanmış QT intervali 520 ms (470-590 ms) olarak ölçüldü. Teşhis esnasında onaltı hastadan dokuzunda senkop, konvülsiyon veya kalp krizi hikayesi varken üç hastaya yanlış epilepsi teşhisi konarak antiepiletik ilaçlarla tedavi edilmiş.
Sonuç: Özellikle tüm aile bireylerinde yüzeyel EKG taramasının önemini ve bazen hastaların yanlış tanı alarak tekrarlayan dirençli nöbet olarak tedavi edildiklerini vurgulamak istedik.
Anahtar kelimeler: Uzun QT Sendromu, senkop, ani kardiyak ölüm

INTRODUCTION

Long QT Syndrome (LQTS) is an inherited disorder characterized by prolonged ventricular repolarization (QT interval prolongation) and a propensity for syncope and sudden death secondary to malignant polymorphic ventricular tachyarrhythmia such as Torsades de pointes.

Mutation of one of several genes lie behind this situation. These mutations tend to prolong the duration of the ventricular action potential, thus lengthening the QT interval.

LQTS remains an underdiagnosed disorder, because at least 10-15% of LQTS gene carriers have a normal QTc duration. The prevalence of LQTS is about 1 in 10000 individuals[1]. Episodes may lead to

palpitations, fainting, syncope and sudden death that provoked by various stimuli like during exercise, emotional stress, at rest, or at sleep depending on the type of mutation. Most important feature of LQTS is to be a leading cause of sudden death in children and adolescents. Excellent outcomes in the management of LQTS can be achieved with lifestyle modifications and therapeutic intervention, highlighting the importance of its identification. Although genetic testing remains the diagnostic gold standard, the diagnosis of LQTS remains challenging when electrocardiographic findings are borderline, which can occur in up to 50% of cases[2]. This occurrence emphasizes the importance of diagnosing LQTS in the presymptomatic period.

Resting 12-lead ECG and routine exercise testing is useful in predicting and directing genetic testing in LQTS[3]. Patient and family education about the nature of LQTS and avoidance of triggering factors are important. In this current paper we reported twelve years clinical experience with congenital LQTS in a tertiary Pediatric Cardiology Department.

MATERIAL AND METHODS

Patients whom diagnosed as congenitally LQTS in Cukurova University Divison of Pediatric Cardiology between years 2001 to 2013 were included the study. Inclusion criteria included a history of syncope or cardiac arrest and either the presence of an affected first-degree relative or a borderline to prolonged corrected QT interval ($\geq$440 ms in men and _$\geq$460 ms in women) on their resting 12-lead ECG.

The QT interval was measured as the time interval in milliseconds from the beginning of the QRS complex and the end of the T-wave. The QT interval was considered the longest interval of all 12 leads, primarily measured in lead II and V5. The mean of 3 QT intervals was used. The corrected QT (QTc) was calculated using the Bazett formula. For men, the QTc was considered normal if it was <440 ms, borderline if 441 to 460 ms, and prolonged if $\geq$460 ms. For women, a QTc of _<460 ms, 461 to 480 ms, and $\geq$480 ms was defined as normal, borderline, and prolonged, respectively[4].

Family histories were questioned to all patients. β-Blockers were recommended to all patients with a new diagnosis of LQTS, regardless of symptom status. β-Blocker use was predominantly propranolol at a daily dosage of 2 to 3 mg/kg, targeting a 30 beat

per minute reduction in peak treadmill heart rate at peak work load[5]. If this heart rate change was not achieved, the dose was increased and testing was repeated. As all data was acquired during routine clinical care, no informed consent was required.

Statistical analysis

Statistical analyses were performed using SPSS software version 17. Descriptive analyses were presented using mean ±SD, median (min-max value), and percentages were expressed where appropriate.

RESULTS

Sixteen patients (6 female, 12 male) were diagnosed as congenitally LQTS. Mean age of patients was 10 years (2.6 - 20 years), mean follow up period was 35 months (11-120 months). Mean corrected QT interval was measured 520 ms (470-590 ms). At the diagnosis nine of sixteen patients (56%) had syncope, convulsion or cardiac arrest history, and three of them were misdiagnosed as epilepsy and were treated with antiepileptic drugs as well.

Implantable Cardioverter Defibrillator (ICD) was implanted two patients with high risk. One of them was ten-year-old female with recurrent syncope attacks due to documented ventricular tachyarrhythmia, and the other was sixteen-year-old male patient that long pauses and bradyarrhythmia was documented on his 24 hours Holter ECG monitoring, also there was a sudden cardiac death history at his family.

Beta-blockade medication was admitted to all patients at diagnosis, and then maintenance dose adjustment was made through heart rate response to treadmill exercise test. Female patient that whom required ICD implantation was diagnosed as LQT3 later on follow up. She was prone to syncope during inactive periods and pause depended VT was documented. At first a VVIR pacemaker implanted, then high dosage propranolol therapy started safely. Because LQT3 is a disorder of sodium channel, oral Mexiletin was added.

When the pacemaker generator reached to the end of life, and the size of the patient was suitable for ICD, the device upgraded to an ICD. Family histories were questioned to all patients; there were seven patients (47% of all) with positive family history for sudden cardiac arrest. No cardiac arrest

event was observed at our patients during twelve year period. Two patients' asymptomatic first degree relatives were diagnosed LQTS on family ECG screening. Characteristics of patients were summarized in the Table 1.

Table 1. Characteristics of patients

Patient	Age (year)	Follow up (month)	QTc* (msn)	Symptom	SCA† history in family	Propranolol first dose kg/mg	Propranolol maintenance dose (kg/mg)
1	8.7	19	0.58	Cardiac arrest	Absent	2	4
2	8.8	13	0.49	Absent	Present	1,5	2
3	9.1	21	0.48	Absent	Present	2	2
4	10,1	67	0.47	Syncope	Absent	2	2
5	5,1	24	0.50	Absent	Absent	2	2
6	10	17	0.58	Syncope	Present	1,4	1.4
7	10	36	0.51	Syncope	Absent	2	2.7
8	10	18	0.49	Syncope	Absent	2	2.8
9	11.3	84	0.50	Absent	Absent	1.5	1.5
10	8.6	13	0.53	Syncope	Present	2	3
11	20	120	0.51	Absent	Present	2	2
12	7.3	13	0.58	Absent	Present	2	2
13‡	16	17	0.59	Syncope	Present	2	3
14	13	17	0.48	Absent	Absent	2	2
15	2.6	11	0.50	Syncope	Absent	2	3
16‡	10	72	0.56	Syncope	Absent	2	3

* QTc; corrected QT intervale, † SCA; sudden cardiac arrest,‡ ICD implanted patients

DISCUSSION

Congenital Long-QT syndrome is a significant cause of cardiovascular mortality, especially in structurally normal hearts. Mutation in at least twelve genes have been identified thus far in patients with genetic LQTS; the distinct genetic types are designated LQTS 1 through 12. The first three, LQTS1-3, are the most prevalent and most studied[6]. The diagnosis of LQTS is clear-cut when there is a marked prolongation of the QTc interval with a positive family history of the syndrome. In the absence of genetic screening, the diagnosis is often measured in probabilities. Schwartz and colleagues refined the diagnostic criteria in 1993 and then revised[4,5]. The diagnosis of LQTS was made according to QTc measurements at 12 lead ECG, clinical symptoms and family history in this current study.

Once the diagnosis has been made, the next step is to determine the patient's risk of malignant arrhythmias. Prior et al reported risk stratification on LQTS and QTc longer than 500 ms was found the single most powerful predictor of events[7]. Prior cardiac arrest, syncope with triggering factor on beta-blockade therapy, and recent syncope with QTc>500 ms were determined as the highest risk factors.

Eleven patients' (68%) QTc interval was longer than 500 ms in this serial and one patient was aborted cardiac arrest before. Beta-blocker agents are advised for the probands and affected family members in general management of LQTS. If a patient experience further syncope or aborted cardiac arrest on beta-blocker therapy, ICD implantation is recommended[8,9]. Two patients were determined as the highest risk group because one of them had recurrent syncope attacks, and the other had significant bradyarrhythmias on Holter ECG with a history of sudden cardiac arrest family member. ICD were implanted to these two patients. The remaining patients with QTc longer than 500 ms and one patient with aborted cardiac arrest history did not experience a new event on beta-blocker therapy. Maintenance dose of beta-blockade agent was determined as patients' response to adrenalin stimuli during Treadmill exercise test.

Convulsive syncope due to arrhythmias from QT prolongation is sometimes misinterpreted as a seizure[10]. Three patients whom misdiagnosed as epilepsy were treated with antiepileptic drugs as well. Antiepileptic drugs were discontinued after beta-

blockade therapy and no convulsive syncope was observed subsequently. Another important point to draw attention to this situation is some antiepileptic drugs may induce QT prolongation. Patients and family members education about nature of LQTS and critical importance of medical treatment with beta-blockers is essential. Also education about avoidance of medication that induces QT prolongation is important. Recommendation examples about triggering factors are, avoidance of alarm clocks in patients with LQTS2, and restriction of physical activity (particularly swimming) in those with LQT1.

A recommendation for genetic testing in LQTS is controversial. Comprehensive genetic testing for LQTS is definitely indicated in probands with definitive LQTS. Family member screening to definitive LQTS patient is crucial. Measurement of QTc on basal 12-lead ECG is useful for screening. But ECG is not useful at silent carriers that who have mutation on LQT1 but normal QTc. Silent carriers have lower risk of cardiac events but not zero. This is an important point to draw attention for genetic screening of family members of symptomatic individuals, even if the family members have normal ECG. All patients' family members were screened with basal ECG, and they were questioned about palpitation, syncope, aborted cardiac arrest. Two patients' asymptomatic first degree relatives were diagnosed LQTS on family screening and beta-blockade therapy was admitted. There were seven patients (two of them are siblings) with history of sudden cardiac arrest family member, and this was the remarkable result.

Congenital long QT syndrome should be suspected with presence of QT prolongation and characteristic T abnormalities on surface ECG and with history of syncope, epilepsy especially resistant to drugs and aborted cardiac arrest in the patient or patient's family. Beta-blockade agent is beneficial for most of LQTS subtype. Implantation of ICD is appropriate for high risky patients. Family members' ECG screening is crucial. Genetic screening to symptomatic individuals' family members with normal ECG is recommended. Education of patients and family members, avoidance of triggering factors are critical point of the management.

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