Clinical presentation of Long QT Syndrome in a case series study in Iraq

Amar T. Alhamdi* MRCP(UK), FRCP(Ed.)

Abstract:

Background: Long QT syndrome is an important cause of arrhythmic death, and it is characterized by electrocardiographic changes and a prolonged QT interval. Patients may present with sudden cardiac death, recurrent syncope, and palpitation.

Objective: Clinical orientation for the Long QT syndrome and minimizing its misdiagnosis to achieve high diagnostic index.

Patients and Methods: Patients presenting with ventricular arrhythmias, syncope, dizzy spells, and prolonged, non-drug-induced QT interval from 2004 until 2019 at Al Nasiryah Heart Center, Al Sulaimanya Heart Hospital, and Al Nahrain Teaching Hospital were enrolled in this study. All patients studied clinically and followed up. Management included beta blocker drug therapy and ICD implantation.

Results: Forty-two patients were included within 15 years, comprising 22 pediatric and 20 adult patients (26 males, 16 females). Ventricular fibrillation reported in 18 patients and ventricular tachycardia in five patients. Thirty-eight patients received beta blockers, and 85% showed marked reduction in ventricular arrhythmia events. Implantable cardioverter-defibrillator (ICD) was implanted in 34 patients. The diagnosis of Long QT syndrome was missed in 85% of cases during the provisional medical contacts.

Conclusion: In this case series study patients with LQTS presented with syncope, recurrent dizzy spells or palpitation. The diagnosis requires high index of diagnostic suspicion. This case study is intended to orient physicians to diagnosis this fatal problem.

Keywords: Long QT-syndrome, clinical presentation, Iraq.

Introduction:

Congenital long QT syndrome (LQTS) is a life-threatening disease that represent an important cause of sudden death. It is characterized by ECG changes including prolonged QT interval and ventricular arrhythmias that cause symptoms of syncope, dizzy spells, and palpitations.1,2,3 People with LQTS may present with sudden cardiac death (SCD) due to ventricular fibrillation (VF), syncope, recurrent palpitations, or prolonged QT is incidentally found on routine electrocardiogram (ECG) for cardiac or non-cardiac symptomatics.4,5 If it is found during the evaluation of unexplained syncope, the diagnosis of ventricular arrhythmias resulting from LQTS becomes possible.6,7 LQTS may be misdiagnosed as epilepsy because of a syncope-like presentation.8 Occasionally LQT may be seen in asymptomatic patients where ECG was obtained for other reasons.2,3 LQTS is commonly inherited but it can be caused by drugs when it should be distinguished from inherited LQT5.1,2 The incidence of LQTS among the general population is uncertain, but an incidence of 1/3000–1/20,000 has been reported.9 LQTS genotypes are mainly determined by mutations in many defined genes.10, 11, 12 LQTS1 (43%), LQTS2 (45%), and LQTS3 (7%) account for 95% of the identified mutations. Other LQTS 4, 5, 6, 7 are rare.11-15 LQTS is a disease of cardiac repolarization that is expressed as corrected LQT (LQTc) at the superficial ECG, and there is a risk of syncope and seizures’ attacks and SCD16. The ventricular tachycardia (VT) of the Torse de point (Tdp) type can terminate spontaneously, resulting in syncope or it can degenerate into fatal VF and SCD. To date, there are 17 LQTS-susceptible genes, which accounts for approximately 85% of the clinical disease, but the most common three types are LQT1, which shows mutations in the KCNQ1 gene, LQT2, which shows in the KCNH2 gene, and LQT3, which shows mutations in the KCN5A gene.1,2,12 LQTS treatment has developed remarkably since the use of Beta blockers (BB), left cardiac sympathetic denervation (LCSD), and implantable cardioverter defibrillator (ICD) implantation to prevent SCD and terminate VT and VF.17-19, 20,24-26 Mapping and ablation of ventricular premature beats (VPCs) that trigger VF has become possible, and it has remarkably reduced VF recurrence.27 In Iraq few reports of this condition was found and few local reports in the Arab

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Amar T. Alhamdi

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The aim of this clinical case study is studying the clinical presentation of long QT syndrome, minimize the misdiagnosis and offer the right treatment.

Patients and Methods:
The study design is a case series study. Patients were collected from Al Nasiriya Heart Center in Thiqar governorate, Al Sulaimanya Heart Hospital in Al Sulaimanya governorate, and Al Naharin Teaching Hospital in Baghdad from the January 2004 until November 2019. Patients who clinically presented with symptoms of dizzy spells, pre-syncope, syncope, palpitations, or resuscitated VF, and who were found to have a prolonged QTc by a 12-lead ECG according to their age and sex were included on this study. The cases either presented to the above mentioned cardiac centers or referred to the author for evaluation and further management. Previous medical causes and misdiagnosis before the diagnosis of LQTS were investigated. A family history of SCD or LQTS was taken. Patients with a positive family history of SCD or LQTS were asked about their parent’s consanguinity. ECG was obtained in all first degree family members of patients who were diagnosed with the condition to determine whether other members are affected by LQTS. Unexplained sudden death in young children and infants triggered family screening for the condition. The QT interval was measured manually using limb lead II or the lead that showed the longest QT interval. The measurement was performed independently by two electrophysiologists and the average of the two measurements was taken as the QT interval. The QTc interval was measured using the Bazett formula (QTc = QT/square root of RR interval) to correct the QT interval. A QTc that was longer than 450 msc in males and 460 msc in females was considered to be prolonged. All patients had 24- or 48-hour Holter monitoring to observe the daily QTc variation, to detect rhythm disturbances and monitor T wave changes. The LQTS was diagnosed based on the presence of one of the followings three criteria: 1) QTc greater than 450 msc in males or 460 msc in females; 2) QTc of 440 msc and T-wave (TW) abnormalities or sinus bradycardia; or 3) syncope in a family member of the LQTS or SCD patient and prolonged or borderline QTc interval. The rhythm disturbance in each patient was identified either using a 12-lead ECG and or Holter monitor in the emergency room or at the clinic. In addition to the long-QT interval, LQTS1 was diagnosed if the TW has a high amplitude and a broad base, and LQTS2 is indicated by bifid TW (biphasic) in the precordial leads and an ST-T segment that has a low amplitude at the limb leads. LQTS3 shows a peaked TW with a narrow base and it is preceded by a long isoelectric ST-T segment. Patients in whom drug intake causes a long QT like erythromycin, chloroquine, sotalol and tricyclic antidepressants were excluded, and electrolytes including the calcium level were normal in all patients. This excludes drug-induced or electrolyte disturbances causing the long QTc. Patients over the age of 45 years had coronary angiogram, those with a normal coronary angiogram excluded ischemic heart disease. Those under the age of 45 yr did not go to coronary angiogram. Unfortunately, molecular genetic studies were not available in Iraq at the time this paper was written. The treatment offered to our patients included BB therapy in patients who tolerated the drug well and had no contraindications. ICD implantation was used if the LQTS patients had family history of SCD, documented VT/VF that was recurrent despite a maximal BB dose, or syncope with a family history of LQTS or SCD. Descriptive statistics was used.

Results:
Forty-two patients where included in this study over the last 15 years. There were 22 pediatric patients with an age range of 8 months to 14 years. Twenty adult patients had an age range from 18 to 54 years. Patients were either referred to the author for evaluation and management after having been diagnosed with LQTS or the patients were diagnosed by the author when they presented with the following symptoms: Syncope in 26, dizzy spells in 12, palpitation in 20, and poorly controlled epilepsy in one patient. Some patients may have more than one symptom. There were 26 males and 16 females. Twenty-four (57%) patients had a family history of SCD, while in 18 (43%) patients, there was no family history of SCD or LQTS. All patients were Iraqis, of whom 24 were Arabs and 18 were Kurds. Among the patients who were enrolled, three of the families included in the study were consanguineous, Table 1. Medical consultation before reaching the diagnosis of LQTS was reported in 85% of children and 50% of adults, with an average of three consultations where the cases were misdiagnosed as anemia, retarded growth or unexplained syncope in children, anxiety and stress, unexplained palpitation or syncope and ischemic heart disease (IHD) in adults, Table 2. All children who were referred after a diagnosis of LQTS by their physicians had family history of SCD. Table 3 shows that monomorphic VT was diagnosed in five patients, Torse de Pointe (TdP) in three patients. One VT was induced during ventricular programmed stimulation (VPS) by an electrophysiological study. Resuscitated VF was seen in 18 patients who were diagnosed and treated using ICD, nine of them were documented clinically and 9 through the ICD. Atrial fibrillation was seen in four patients, among whom three were clinically documented and one was diagnosed by the ICD. Additionally, 2:1 atrioventricular block (AVB) was seen in one 45-year-old female patient, which was clinically documented. History, ECG and T-wave morphology suggested that 22 (52%) patients had LQTS1, 16 (38%) patients had LQTS2, and 4 (10%) patients had LQTS3 (Table 2 and Figures 1, 2, and 3). There are eight cases where the ECG changes were not typical of one type, but dominantly showed LQTS1 and included as such, occasionally TW changes that did not fit classically with either LQTS2 or LQTS3 but included within LQTS2 (Figure 3). Thirty-eight patients received BB.

In 32 patients, propranolol was the BB that was used in doses based on body weight in children (3–5 mg/kg/day in divided doses). Four patients were taking atenolol, and two patients were on metoprolol. Sixteen patients were in the pediatric group and 22 patients were adults. Thirty-four patients underwent ICD implantation; Table (2).
We could not offer LCSD to four patients who needed this procedure because of their poor response to BB or because recurrent VF needed defibrillation by the ICD. The unavailability of LCSD was thoroughly discussed with thoracic surgeons, but we could not offer this type of therapy.

Table 1: Sociodemographic characteristics, presentation and family history of patients with LQTS

<table>
<thead>
<tr>
<th>Variables and categories</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Male 26 (62) Female 16 (38)</td>
</tr>
<tr>
<td>Age</td>
<td>Pediatric: 8 M-14 Y 22 (52) Adults: 18 - 54 Y 20 (48)</td>
</tr>
<tr>
<td>Presenting symptoms</td>
<td>Syncope 26 (62) Dizzy spells 12 (29) Palpitation 20 (48) Fits 1 (2)</td>
</tr>
<tr>
<td>Family history</td>
<td>Positive 24 (57) Negative 18 (43)</td>
</tr>
<tr>
<td>SCD</td>
<td>Arabs 24 (57) Kurds 18 (43) Consanguinous Families 3 (7)</td>
</tr>
<tr>
<td>Total</td>
<td>42 (100)</td>
</tr>
</tbody>
</table>

Table 2: Distribution of the cases by selected clinical variables

<table>
<thead>
<tr>
<th>Variables and categories</th>
<th>Paediatric (No.)</th>
<th>Adult (No.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of LQTS</td>
<td>LQTS1* 22 (52)</td>
<td>LQTS2 16 (38)</td>
</tr>
<tr>
<td>Provisional diagnosis</td>
<td>Anemia: 12</td>
<td>IHD: 10</td>
</tr>
<tr>
<td>initial medical presentation before LQTS was diagnosed</td>
<td>Retarded growth: 5</td>
<td>Anxiety &amp; stress: 7</td>
</tr>
<tr>
<td>LQTS was diagnosed</td>
<td>Unexplained syncope: 19</td>
<td>Unexplained syncope &amp; palpitation: 4</td>
</tr>
<tr>
<td>Treatment modalities</td>
<td>BB: Propranolol 16</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>BB: Atenolol    0 4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>BB: Metoprolol 0 2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ICD 18 16</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>22 20</td>
<td></td>
</tr>
</tbody>
</table>

* In 8 cases of LQTS1 the type is rather undifferentiated fully by ECG but dominantly of LQTS1 and included as such.

Table 3: Distribution of the types of arrhythmia encountered in LQTS patients and method of diagnosis

<table>
<thead>
<tr>
<th>Type of arrhythmia</th>
<th>Diagnosis</th>
<th>Clinical diagnosis</th>
<th>Electro-physiologic al testing</th>
<th>Implantable cardioverter defibrillator</th>
</tr>
</thead>
<tbody>
<tr>
<td>ventricular tachycardia</td>
<td>Torse de Pouttes</td>
<td>2 1 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Resuscitated ventricular fibrillation</td>
<td>9 9 18</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Atrial fibrillation</td>
<td>3 1 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2:1 Atrio-ventricular block</td>
<td>1 1 1</td>
<td></td>
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</tbody>
</table>

The ECG in figure (1 A) shows a QTc of 449 msc and a broad base peaked TW, which suggests LQTS1. Atrial pacing by the dual chamber ICD that was implanted in this patient is indicated by the arrow. Figure (1 B) shows the dual chamber ICD endocardiogram (EGM) of defibrillated VF in the same patient.

Figure 1A: ECG from a 20-year-old member of a family with LQTS.

Figure 1B: Dual chamber ICD endocardiogram of defibrillated VF. A, atrial signal; V, ventricular signal.
Clinical presentation of Long QT Syndrome in a case series study in Iraq.

Amar T. Alhamdi

Figure 2, Twelve leads ECG of 12 y age boy(brother of patient in Figure 1). Showing a QTc of 576msc with bifid, biphasic and inverted TW(arrow) suggesting a LQTS2, In lead II strip, please note beat to beat variation in T-wave shape and amplitude (solid arrows) which is called T-wave alternance(TWA), a risk marker in LQTS (see text for details).

Figure (3) is a 12-lead ECG from a 4-year-old boy with LQTS showing a QTc of 644 msc and a TW at V1 with a high peak and narrow base, which suggests LQT3 (arrow). In leads V4, V5, and V6, a bifid TW is visible, suggesting LQT2 (arrow). There was a change in TW in the strip lead II at the bottom.

Figure 4A. A 12-lead ECG of a 45-year-old woman with 2:1 AVB and a prolonged QTc of 474 msc

Figure 4B. Torse de pointes (Tdp) in the same patient as in Figure 4A.

Tdp is typically initiated by a short–long–short interval. Figure (4B) shows a premature ventricle complex (PVC) (asterisk) follows shortly after the sinus beat (short, solid line). The PVC is followed by a compensatory pause (long, dashed line). The following beat has a longer QT interval. If the next beat follows shortly thereafter, there is a good chance that this third beat falls within the QT interval, resulting in the R on T phenomenon and subsequent Tdp is preceded by a short (solid line), long (dashed line), and short (solid line) coupling interval.

Discussion:

Based on the history of symptoms and triggers, family history, and ECG changes in our series, we found that LQTS1 was the most common type, which comprised 52% of the cases, while LQT2 comprised 38% and LQT3 comprised 10% of the cases. This finding is comparable with other findings such as those in Schwartz and Moss’ series.1,5 Misdiagnosis of LQTS during the first, second and even a third medical contact occurred in 85% of our cases before the LQTS diagnosis was made. The strongest part of their medical history was the positive family history of SCD to suggest a diagnosis of LQTS to the physician. The unavailability of genetic testing in Iraq negatively affected the detailed understanding of the phenotypes and genotypes of LQTS, and could not be compared with Al-Hassani and AlSenaidi results of genetic testing29,30, but this should not delay the clinical diagnosis and implementation of life-saving measures. In the treatment strategy that was used in our patients, An excellent response was defined as a greater than 90% reduction in symptoms and a reduction of ventricular arrhythmias. In patients who responded well to BB with a negative family history of SCD, no ICD was implanted. In patients with LQTS1, we achieved almost 85% reduction in symptoms and ventricular arrhythmias (VA) incidence was monitored through the implanted ICD or by a Holter monitor, while in the LQT2 patients, an improvement was noticed in 45% of patients. In LQT3 patients, only one of four (25%) patients improved slightly. These findings are similar to those...
Clinical presentation of Long QT Syndrome in a case series study in Iraq.

Amar T. Alhamdi

of Moss and Vincent. However, the efficacy of BB was higher with LQT1 than with LQT2 and LQT3 compared to the less-common LQT. BB is recommended as a first-line therapy in most patients with LQTS. The 38 patients who received ICD were followed for 5–8 years, and 18 (47%) patients developed VF/VT despite the maximum BB dose. These patients were treated successfully by the device through direct – current DC shock (DC-shock). Two pediatric patients died after repeated VF and repeated unsuccessful shocks. These results are comparable to a series that was reviewed in Schwartz’s series 2010. The four patients who needed LCSD unfortunately could not be offered this therapy and two of them died with repeated DC-shocks and two patients were lost to follow-up. Conclusion: LQTS is a serious clinical problem which needs to be diagnosed in patients present with symptoms of syncope or palpitation. Misdiagnosing the syndrome may lead to serious outcome. In Iraq this is the first report which will orient physicians, paediatricians to this fatal disease.

References:

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Clinical presentation of Long QT Syndrome in a case series study in Iraq.

Amar T. Alhamdi

J Fac Med Baghdad 2020; Vol.62, No.3


الحالة السريرية لمتلازمة استطالة ك، دراسة سلسلة حالات في العراق

د. عمار طالب الحمدي

المقدمة: إن متلازمة استطالة الK تسبب مسحوق الوفاة بسبب أنظميات القلب البطينية وتمتاز بتغيرات تخطيط القلب المتمثلة باستطالة فترة الK.

هدف الدراسة: دراسة الوضع السريري والتوعية السريرية لمتلازمة استطالة الK ت لتقليل عدم تشخيص هذه الحالة المميتة.

الطريقة البصري والمرضى: أدرج في هذه الدراسة المرضى الذين عانوا من أنظميات بطينية، فقدان وعي أو نوبات دوار وظهروا إستطالة فترات الK.

النتائج: أدرج 42 مريضا جمعوا خلال 15 سنة، منهم 22 أطفال و20 بالغ، 26 ذكور و16 أنثى. تم التشخيص خلاف الزيارات الطبية الأولية في 85%، حيث ارتفعت بطين القلب في 18 مريضا وسارع بطين القلب في 5، أعلنت ثلاثينيات انطلاق فترة الK في 85%، صدرت النتائج ببيانات البداية القلبية. زرع جهاز الريحة في 34 مريضا.

الاستنتاج: إن حالات استطالة K ت تعاني من فقدان وعي، دوار مفاجئ، وخفقان. يحتاج التشخيص إلى دالة تشخيصية عالية. إن هذه الدراسة هدفت لتوعية الأطباء: متلازمة استطالة الK ت، الحالة السريرية، العراق.

الكلمات المفتاحية: متلازمة استطالة الK ت، الحالة السريرية، العراق