Concealed congenital long QT syndrome during velopharyngeal dysfunction correction: a case report

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The congenital long QT syndrome (LQTS) is an inherited cardiac disorder characterized by increased QT intervals and a tendency to experience ventricular tachycardia, which can cause fainting, heart failure, or sudden death. A 4-year-old female patient undergoing velopharyngeal correction surgery under general anesthesia suddenly developed Torsades de pointes. Although the patient spontaneously resolved to sinus rhythm without treatment, subsequent QT prolongation persisted. Here, we report a case of concealed LQTS with a literature review.

Keywords: Electrocardiogram; Long QT Syndrome; Torsades de Pointes.

INTRODUCTION

QT interval prolongation on the electrocardiogram (ECG) is a rare condition in which the repolarization of the heart is delayed. Congenital long QT syndrome (LQTS) is a cardiac ion channel disease (channelopathies) and a high proportion of untreated patients end up with cardiac arrest and sudden death [1]. Although symptomatic congenital LQTS is characterized by recurrent syncope, cardiac arrest, and seizures, only 60% of patients are symptomatic at the time of diagnosis [2]. Congenital LQTS commonly presents with normal corrected QT (QTc) interval especially in the early years of life and asymptomatic carriers of the gene. Moreover, LQTS patients are known to be at risk of developing life-threatening arrhythmias after exposure to several medications such as anesthetics, antibiotics, and decongestants [3]. Clinical identification of LQTS is difficult in asymptomatic LQTS patients with normal QTc. The diagnosis of LQTS based on family history and electrophysiologic criteria such as QTc may be unreliable especially in variants of the disease and asymptomatic carriers [4]. Approximately 25–40% of patients with genetically proven congenital LQTS have a nondiagnostic resting QTc ("concealed LQTS") [5]. To date, there are still no established gold-standard diagnostic methods.

We report a case of concealed congenital LQTS newly manifested during velopharyngeal dysfunction correction with a literature review.

a. At birth (HR:125 bpm, QTc: 445 ms)

b. Pre-operation (HR:94 bpm, QTc: 445 ms)

c. During operation after TdP (HR:105 bpm, QTc: 556 ms)

d. POD 1 (HR:113 bpm, QTc: 521 ms)

e. POD 5 after β blocker use (HR:101 bpm, QTc: 457 ms)

f. Four month later (HR: 88bpm, QTc: 441 ms)

g. Before epinephrine stress test (7 Month later)
(HR: 91 bpm, QTc: 439 ms)

h. During epinephrine (0.15 ug/kg/min) stress test
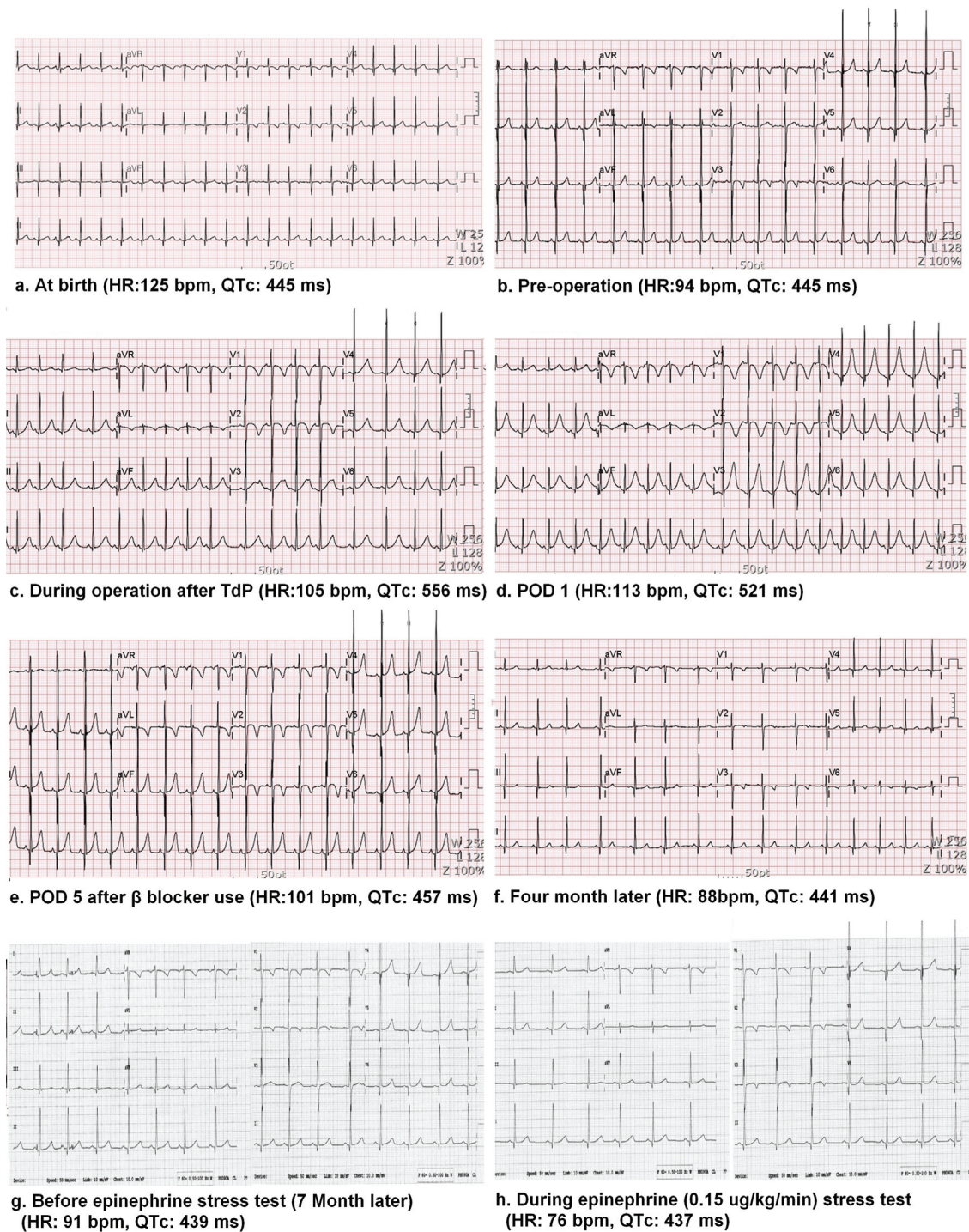(HR: 76 bpm, QTc: 437 ms)

Fig. 1. Electrocardiogram. QTc is significantly prolonged at c and d.

CASE REPORT

A 4-year-old female patient weighing 22 kg was admitted for treatment of velopharyngeal dysfunction and programmed for general anesthesia. She had undergone cleft palate surgery at the age of 10 months, but at that time, there was no event during the administration of general anesthesia. She had no history of bradycardia, syncope, or palpitation. Physical examination was normal.
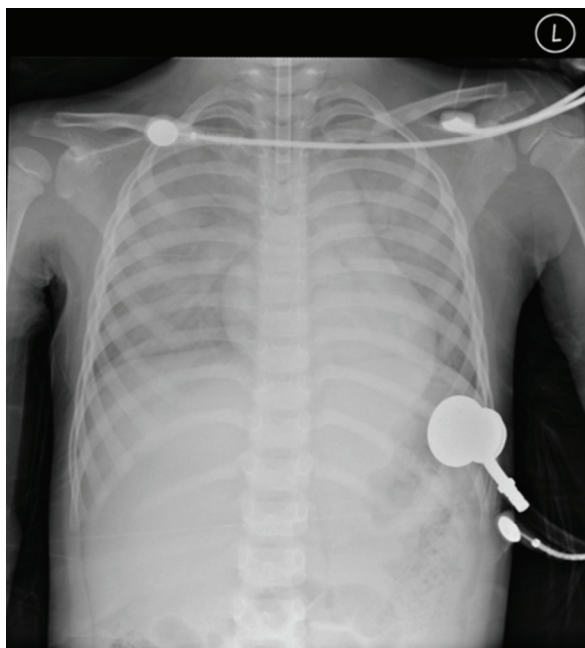
Fig. 2. Postoperative chest X-ray. Mild diffuse pulmonary edema of both lung field and mild thickening of right major fissure with right pleural effusion were seen.

Laboratory investigations revealed a sodium level of 140 mmol/L (the normal range 135-145 mmol/L), a potassium level of 4.6 mmol/L (the normal range 3.5-5 mmol/L), Cl 102.4 mmol/L, and ionized calcium level of 1.31 mmol/L with a normal albumin level. Her chest X-ray was normal. The ECG of the patient at birth is presented in Fig. 1a. On baseline ECG, heart rate (HR) was 94 beats/min with normal sinus rhythm (Fig. 1b). Borderline QTc interval prolongation [3] of 445 ms (all corrected QT intervals were calculated using the Bazett correction formula, Fig. 1) was observed without T wave abnormality.

On arriving operating room, standard monitoring devices were used. Anesthesia was induced using thiopental 100 mg and rocuronium bromide 20 mg intravenously. After tracheal intubation, the anesthesia was maintained with sevoflurane. After tracheal intubation, the patient was ventilated with oxygen and air (FiO$_2$, 50%), and the end-tidal CO$_2$ was maintained between 35 and 40 mmHg. For hemostasis and a clear local field, 1 ml of 1% lidocaine with 1 : 100,000 epinephrine solution (approximately 10 μg of epinephrine) was injected in the soft palate and posterior part

of the pharynx by the surgeon. Suddenly, her blood pressure (BP) increased from 100/60 to 150/70 mmHg, HR also increased from 113 to 175 bpm, and Torsades de pointes (TDP) was detected. Her HR was then 200-210 bpm and her BP was unmeasurable during TDP. Pulse oximetry could not detect the peripheral oxygen saturation and a cyanotic blood color was detected by the surgeon. After stopping sevoflurane, we ventilated the patient with 100% oxygen. While preparing for cardiac resuscitation and medication, TDP was converted to normal sinus rhythm without medication and chest compression/defibrillation after about 60 seconds. BP was 82/42 mmHg and dopamine 4.0 ug/kg/min were administered. After confirming that the patient's vital signs were stable for 10 minutes, the planned surgery proceeded under sevoflurane anesthesia. QT prolongation (QTc = 556 ms, Fig. 1c) continued until the end of the surgery. During the rest of the period, the operation went on without any events. After confirming consciousness and spontaneous breathing, the patient was admitted to the surgical intensive care unit.

Postoperative laboratory findings were within the normal range as follows: sodium level of 139.1 mmol/L (the normal range 135-145 mmol/L), a potassium level of 4.43 mmol/L (the normal range 3.5−5 mmol/L), Cl 103.4 mmol/L, magnesium 0.83 mmol/L, and ionized calcium level of 1.25 mmol/L. Transthoracic echocardiography showed normal systolic function, but chest X-ray revealed pulmonary edema (Fig. 2). The change in QTc and T wave alternans was demonstrated in Fig. 1c. The patient was referred to the pediatric department and diagnosed with a high probability of LQTS following Schwartz criteria with a score of 5 (QTc > 480 ms, TDP, and T wave alternans). The pediatrician prescribed the propranolol 10 mg ter *in die* and QT interval and chest X-ray findings were normalized 5 days after the event (Fig. 1d and 1e). The patient was discharged after planning of genetic workup and prophylactic propranolol was maintained for 3 months. The ECG of the patient 4 months after surgery is presented in Fig. 1f. In the family workup, her parents did not have any history of

arrhythmia, but her grandfather had an undefined arrhythmia with cardiac pacemaker insertion. Genetic testing was conducted only for LQT1 (KCNQ1) and showed a negative result. No other genetic tests were performed with parental rejection due to the high cost. Seven months later, the patient underwent an epinephrine QT stress test. Even at 0.15 μg/kg/min infusion rate of epinephrine, her response was negative (QTc = 437 ms, Fig. 1g and 1h). Her parents refused any further evaluation. In the subsequent months of observations, the patient reported no obvious events.

DISCUSSION

LQTS is a malfunction of cardiac ion channels resulting from mutations involving genes that code for critical ion channels of the heart (congenital LQTS), or caused by metabolic abnormalities, or drugs (acquired LQTS) [5]. Congenital LQTS may manifest anytime from infancy to old age. In this case, concealed congenital LQTS was unmasked after exposure to complex stimuli such as anesthesia, operative stress, and QT-prolonging medications in an asymptomatic 4-year-old pediatric patient.

LQTS occurs in about one out of 5,000 people and might be asymptomatic for life or cause fainting, seizures, or sudden death at a young age. LQTS usually occurs due to prolongation of action potential duration and increased susceptibility to TDP, ventricular fibrillation, and sudden cardiac death [6]. The "short–long–short" sequence heralding TDP is the hallmark of both congenital and acquired LQTS. TDP usually reverts spontaneously to sinus rhythm in most instances but degenerates to ventricular fibrillation in others.

LQTS might be diagnosed by the QTc interval on ECG, clinical symptoms, and family history. However, many patients with normal QTc genetically unproven LQTS have the possibility of being the 'concealed LQTS' patients. Thus, the diagnosis of LQTS is challenging. The Schwartz criteria are commonly used as a diagnostic tool

[7], however, one-third of the patients do not meet the diagnostic criteria at the time of diagnosis. In some patients with suspected LQTS who are not diagnosed with the Schwartz criteria and ECG, genetic testing or the epinephrine QT stress test might be needed.

Till date, genetic testing that identifies diagnostic changes in one or more of the 17 genes known to be associated with LQTS – of which KCNH2 (LQTS2), KCNQ1 (locus name LQTS1), SCN5A (LQTS3), KCNE1 (LQT5), and KCNE2 (LQT6) are most common [8,9]. The LQT1, LQT2, and LQT3 genotypes account for an estimated 70% to 75% of LQTS, and the majority of genotype-phenotype relationships pertain to these 3 LQTS genotypes [8]. The epinephrine QT stress test can unmask concealed type 1-LQTS (KCNQ1) with a high degree of accuracy [10,11]. Normally, enhanced sympathetic activity shortens the ventricular action potential duration and QT interval whereas increased sympathetic activity can prolong the QT interval in LQTS 1 and 2. However, there is some variation in the degree of response to sympathetic activation depending on the type of LQTS [12].

In this case, the young female patient had the prolonged QT interval and the self-terminated TDP after injection of 10 μg of epinephrine into the surgical field. In LQTS, cardiac events are uncommon after the age of 40 years; when present, they are often triggered by administration of a QT-prolonging drug, hypokalemia, or are associated with the LQTS type 3 phenotype [4]. We suspected congenital LQTS after consideration of the patient's age, family history, QT prolongation in ECG for 5 days even after the effects of epinephrine disappeared and improvement with propranolol medication. Although we clinically diagnosed the patient with congenital LQTS, no genetic mutations were found in the KCNQ1 genetic test and no further genetic tests were performed due to parental refusal. Moreover, the epinephrine QT stress test showed a negative result. Although the epinephrine QT test has been shown to be a powerful tool to predict the genotype of LQTS 1, in other types of LQTS, more than 50% of patients showed a negative response to

epinephrine [13]. Thus, the patient can be diagnosed with congenital LQTS because she meets the criteria, but the diagnosis is not LQTS 1 because the KNCQ1 gene and epinephrine stress test were negative.

Anesthesiologists should consider the possibility of the presence of LQTS and special attention to ECG changes during anesthesia is needed. These subsets of patients are highly prone to various ventricular arrhythmias and sudden cardiac death and hence should be evaluated and treated to normalize the QT interval, prior to anesthetic exposure.

Moreover, phenotypically mild (subclinical) mutations or polymorphisms in LQTS genes could be present in the general population, and it has been suggested that these patients could be predisposed to drug-induced or hypokalemia-induced arrhythmias.

When QT-prolongation-inducing drugs were administered or during other conditions favoring QT prolongation such as bradycardia or hypokalemia, the "repolarization reserve" was exhausted, leading to QT prolongation and TDP. Therefore, the molecular genetic analysis might be extended to those with acquired LQTS and their family.

Some anesthetic agents like sevoflurane, thiopentone, and other drugs are known to prolong the QT interval, the strength of association in precipitating TDP and ventricular fibrillation in these patients is unknown.

Flurane can affect cardiac repolarization and cause LQTS, which is common in patients with old age, electrolyte abnormalities, and ischemic heart disease [14]. Volatile anesthetics such as halothane, enflurane, isoflurane, and sevoflurane could prolong the QT interval to some extent, however, they have been successfully used in patients with congenital LQTS receiving beta-blocker therapy [15,16].

Thiopental prolongs the QT interval in healthy patients. Despite this effect, thiopental has been used safely in patients with congenital LQTS. Because of its prolongation of the action potential duration, thiopental may in fact reduce the heterogeneity of action potential dispersion through the ventricular wall (i.e., reduce

transmural dispersion of repolarization). This effect would theoretically prevent the spontaneous onset of TDP [17,18]. Glycopyrrolate has also been shown to lengthen the QT interval in healthy subjects [19].

A case of sevoflurane-associated TDP in a LQTS 2 patient was reported [20]. Pulseless ventricular tachycardia was sustained and ended after defibrillation in the patient. In LQTS 2, the risk of sudden death is reportedly high. As in other cases, TDP in our case was triggered after sevoflurane use and epinephrine injection, however, it ended automatically a minute after stopping sevoflurane and 100% oxygen ventilation, featured as a mild form.

Current evidence suggests that 5−10% of persons in whom TDP develops on exposure to QT-interval− prolonging drugs conceal mutations associated with LQTS and can, therefore, be viewed as having a subclinical form of the congenital syndrome.

β-Blockade is the first-line treatment LQTS with a resting QTc greater than 470 ms. Moreover, in asymptomatic patients with LQTS having resting QTc less than 470 ms, prophylactic treatment with β-Blockade is recommended to reduce the risk of event recurrence [21,22].

In the case of TDP, acute therapy should follow advanced cardiovascular life support guidelines. According to the 2015 American Heart Association (AHA) Pediatric Advanced Life Support (PALS) guidelines, wide Complex Tachycardia (QRS > 0.09 secs) with hypotension, altered level of consciousness, or signs of shock requires immediate synchronized cardioversion [23]. Because of the polymorphic nature of TDP, synchronized cardioversion may not be possible, and the patient may require unsynchronized defibrillation [22].

Magnesium sulfate (2 g) should also be administered intravenously to shorten the QT interval and potentially stabilize the cardiac cell membranes from early after depolarization-type premature ventricular complexes, which can promote TDP [23]. As a nonpharmacological treatment, implantable cardioverter-defibrillator (ICD) therapy could be considered in patients with congenital LQTS and history of aborted cardiac arrest, recurrent

cardiogenic syncopal events despite β-blockade or patients who cannot tolerate medical therapy [24-26].

In conclusion, anesthesiologists should be aware of the presence of QT prolongation in preoperative ECG and prepare for TDP and cardiac arrest if QT prolongation observed in the perioperative period. Several drugs that prolong the QT interval should be cautiously used. Genetic workup or epinephrine QT stress test for an accurate diagnosis of LQTS might be needed after surgery.

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FOOTNOTE: This case report followed the CARE guidelines for case reports. The Hospital Institutional Review Board (IRB) designated this project as exempt (IRB number: H-2004-002-089). Written informed consent was obtained from the patient's guardian for publication of this case report. At the time of consent, the patient had recovered from her illness.

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