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Case report

A newborn with Timothy syndrome and torsades de pointes

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Abstract

Timothy syndrome (TS) is a rare multisystem disease with a characterized association of long QT syndrome (LQTS) type-8 with congenital cardiac and extracardiac malformations (neurological and dysmorphic facial features, syndactyly). It is caused by heterozygous mutations in the CACNA 1C gene, which participates in decoding the calcium channels. In this study, we describe a case of TS with systemic phenotypic characteristics associated with a long QT interval on the electrocardiogram. The LQTS predisposes to a characteristic life-threatening ventricular arrhythmia known as torsades de pointes or "twisting of the points". In this scenario, the authors describe the main clinical characteristics in a case of TS focusing on improving the ability of early diagnosis and on better management of LTQS type-8.

Key words: Timothy syndrome, torsade de pointes, echocardiography.

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Introduction

Long QT syndrome (LQTS) is a disorder that affects the repolarization of ion channels characterized by QT interval prolongation and T-wave abnormalities on the electrocardiogram (ECG). LQTS (congenital long QT) is an autosomal dominant or recessive disorder with an estimated prevalence of 1:2000–1:2500 people [1]. There is an association with the polymorphic ventricular tachyarrhythmias, typically torsade de pointes (TdP). TdP usually is self-limiting, causing a syncopal event, and is the most common symptom in individuals with a LQTS. In some cases, it degenerates to ventricular fibrillation and causes sudden cardiac arrest or death. Such cardiac events typically occur during physical or emotional stress, less often during sleep, and usually without prodromes. So far, there are 10 known types of LQTS according to the gene that is mutated [2].

The *CACNA 1C* gene (voltage-dependent L-type calcium channels) has been described in patients with Timothy syndrome (TS) or LQTS type-8. This gene is essential for the process of excitability, myocyte contraction, regulation of gene expression, and of the cardiac action potential plateau. Calcium channel dysfunction in TS is of autosomal dominant inheritance. The association of LQTS with the extracardiac phenotypes such as syndactyly, facial dysmorphism, seizures, and delayed neuropsychomotor development should draw attention to the TS [3]. In this study, we describe a newborn (NB) with an initial clinical picture of bradycardia, who progressed to episodes of ventricular tachycardia in which evidence of a long QT interval associated with syndactyly led to a diagnostic suspicion of this syndrome.

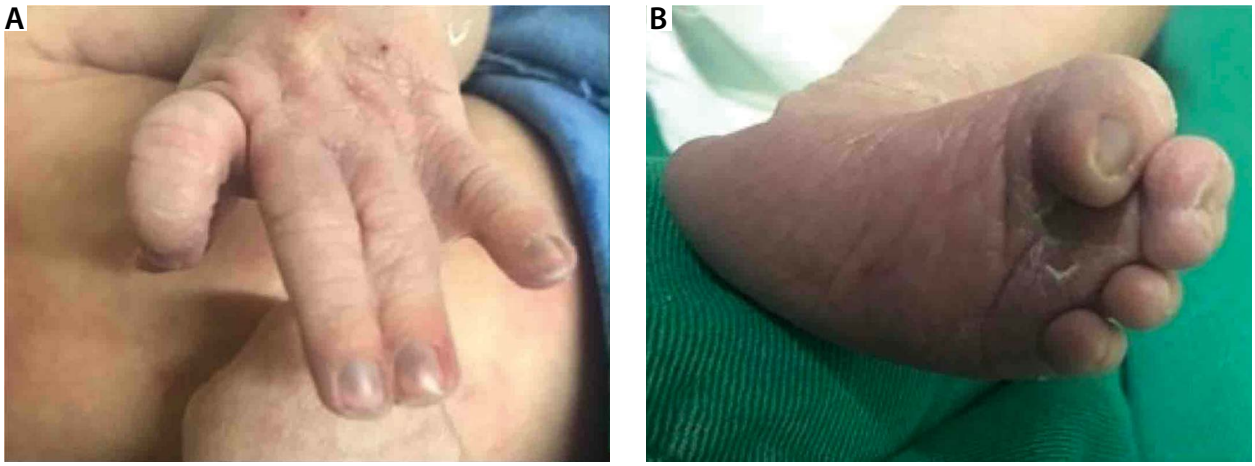

Figure 1. Complete syndactyly between (**A**) the third and fourth fingers and (**B**) second and third toes

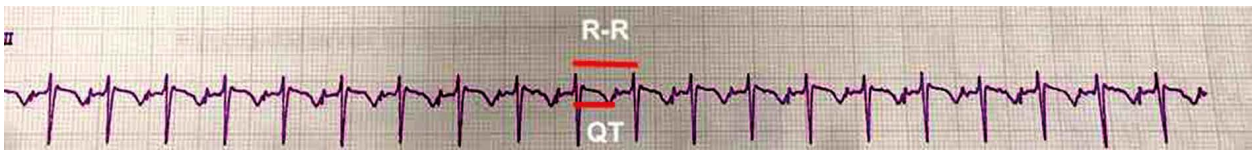

Figure 2. Electrocardiogram with long QT. Note the calculation of the QT interval for heart rate by the Bazett formula

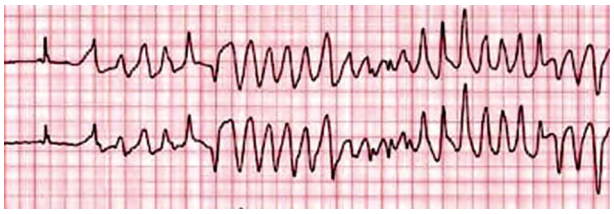

Figure 3. Electrocardiogram showing the ventricular arrythmia: torsades de pointes. Note the polymorphic nature of the tachycardia

Case report

A newborn, appropriate for gestational age (AGA), female, born by caesarean section due to acute fetal distress and marked oligohydramnios, birth weight 3020 g, 48 cm in length, Apgar 8/8, without any prenatal complications. She evolved with respiratory distress and bradycardia, and at 20 h of life was transferred to the neonatal intensive care unit. Physical examination showed syndactyly in the upper and lower limbs and on a cardiovascular examination, the heart rhythm was irregular (Figure 1). An ECG showed second-degree atrioventricular block, long QT interval (660 ms), and notch T waves or T-wave alternans. Follow-up ECG showed the remaining prolonged QT interval (Figure 2). An echocardiogram ruled out structural cardiac malformation, demonstrating the presence of a patent foramen ovale (physiological for age group). Drug treatment with beta-blocker propranolol was started (Initial dose: 2 mg/kg/day), but this did not reduce the QT interval. Even with a gradual adjustment of dose up to 5 mg/kg/day, the QT interval remained longer than 550 ms.

During the hospitalization, he had several episodes of low cardiac output with ventricular tachycardia: TdP (Figure 3).

Due to the condition compatible with the ST, the installation of a cardiac pacemaker was indicated, and this was performed at 21 days of life. After implantation of the pacemaker, voluminous chylothorax appeared on the right. Chest drainage was performed with antibiotic therapy.

The NB maintained haemodynamic stabilization after the implantation of the pacemaker, but due to infectious complications, she died.

Table 1. Morphological anomalies in fetuses with Timothy syndrome (TS)

Anomalies	Prevalence in TS
Syndactyly*	Almost all cases
Bradycardia AV block Ventricular tachyarrhythmias Structural heart defects	Fatal bradycardia due to 2:1 AV block accounts for around 1/4 of cases with prenatal diagnosis
Facial anomalies	
Pleural effusion Hydrops	Pleural effusion in LQTS is exceptional, but it has been described in TS

**The lack of syndactyly does not exclude this diagnosis.*
AV – atrioventricular, LQTS – long QT syndrome.

Discussion

Timothy syndrome is a rare multisystem disorder associated with a LQTS, TYPE-8, structural congenital heart disease, bilateral cutaneous syndactyly of the fingers and toes, dysmorphic facial features, and neurological symptoms including autism, seizures, and intellectual disability. It is caused by heterozygous mutations in the *CACNA 1C* gene that encodes a calcium channel. Cardiological changes are expressed on the ECG, characterized by QT interval prolongation. Morphological anomalies in fetuses with TS are described in Table 1.

QT prolongation can be assessed on the ECG measuring the QRS complex, ST segment, and T-wave (ventricular depolarization and repolarization). The erroneous inclusion of the

U wave and the non-correction of the QT interval for heart rate (HR) during bradycardia can falsify the prolongation of this interval. Several formulas to calculate the QT interval for HR (QTc) can be used, such as Framingham, Fridericia, and Bazett [4–6]. In the case reported, we used the formulas of Bazett and Fredericia, and both of the QTc values were prolonged (550 ms and 520 ms, respectively) (Figure 2). In general, QTc interval values > 480 ms are prolonged, with an indication for genetic testing of LQTS values ≥500 ms being acceptable in the absence of associated factor, hypocalcaemia, and medication use [7, 8]. Genetic research was not performed in this case report, not even in the family. Although there are several formulas for calculating the QTc, the diagnostic score for LQTS formulated in 1993 and updated in 2011 uses Bazett's formula to calculate this interval [9]. The criteria for LQTS are described in Table 2.

Torsade de pointes ventricular tachycardias are associated with LQTS. It is a ventricular rhythm with a high HR for the age showing variations in QRS complex morphology and/or axis. The peaks of QRS complexes appear to "twist" around the isoelectric line, giving rise to the denomination 'torsades de pointes.' Episodes could be self-limiting, as in the present report, or progress to a ventricular fibrillation with the risk of sudden cardiac arrest and death.

Classic TS is caused by a repeat de novo CA V 1.2 missense mutation (*G1216A* transition in the eighth exon alternative splicing of *G406R CACNA 1C*), causing a multisystem disorder including arrhythmia and autism. Despite syndactyly being a common feature of the classic form of TS, Ozawa et al. described 2 atypical patients with the severe heart defects and the absence of syndactyly, and a new *CACNA 1C* mutation was identified [10]. This fact expands the spectrum of ST.

According to the ECG findings, the characteristics of TS are second-degree AV block, long QT, and T-wave alternans (T waves with the different morphologies and formats), as in the presented case.

Patients with TS are clinically treated with antiarrhythmics of the B-adrenergic blocker type having the propranolol and nadolol being more effective [11, 12] Although studies have shown a reduction in the adverse cardiac events in STQL type-1, these antiarrhythmics are insufficient to prevent lethal arrhythmias in patients with a TS [11-13]. Therefore, new therapies for TS are still needed. Some studies suggested that roscovitine, a cyclin-dependent kinase inhibitor, could rescue the phenotypes in the cardiomyocytes derived from human-induced pluripotent stem cells (MCs) and neurons from TS patients [10, 14, 15]. However, the mechanisms by which roscovitine restores cardiac functions in MCs have not been fully elucidated. In this case report, propranolol beta-adrenergic blocker was used.

In general, in LQTS, implantation of a cardioverter defibrillator is indicated in patients who have survived cardiac arrest, in those with syncope(s) even on a full dose of B-adrenergic blocker, and exceptionally in those with signs of increased electrical instability (long pauses followed by alternating T waves) and QTc interval > 550 ms [13]. Left cardiac sympathetic denervation (removal of the third and fourth thoracic ganglia) by thoracotomy or thoracoscopy is an adjunctive therapy to the use of B-blockers to control the arrhythmic storm and repeated shocks of implantable defibrillator in the LQTS [13]. However, in Jervell and Lange-Nielsen LQTS (LQT types 1 and 3 associated with deafness) and in TS, due to the severity, it is recommended that therapies be associated with the use of B-adrenergic blockers such as cardioverter defibrillator and denervation.

Table 2. Clinical diagnosis of long QT syndrome (scoring system)

ECG and clinical characteristics	Findings	Points
ECG QTc values*	≥ 480 m 460—479 ms 450—459 ms ≥ 480 ms at the 4th min recovery from exercise stress test	3 2 1 1
ECG T-wave features, torsades de pointes, and HR#	Torsade de pointes T-wave alternans Notched T-wave in 3 leads Low HR for age	2 1 1 0.5
Clinical history	Syncope with stress Syncope with no stress	2 1
Family history	Family member(s) with definitive LQTS Unexplained sudden cardiac death aged < 30 years in the immediate family	1 0.5

**QTc calculated by Bazett's formula. #In the absence of medications or disorders known to affect these ECG findings.*
HR – heart rate, LQTS – long QT syndrome
Total score: ≤1.0 point = low probability of SQTL 1.5–3.0 points = intermediate probability of SQT ≥ 3.5 points = high probability of SQTL.
Adapted from: Schwartz PJ, Crotti L, Insolia R. Circ Arrhythm Electrophysiol 2012; 5: 868-877.

Conclusions

The authors recommend performing an electrocardiogram in suspicion of TS, to aid in the diagnosis, and before any procedures in patients with this syndrome.

Ventricular arrhythmias can occur spontaneously or during anaesthetic procedures, especially TdP. These arrhythmic events occur in up to 80% of the patients, which leads to death. Drug treatment and insertion of an implantable cardioverter defibrillator when indicated are imperative to avoid a sudden death in these patients.

Conflict of interest

The authors declare no conflict of interest.

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