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Case Report

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Torsades de pointes in a patient with congenital long QT syndrome during the puerperium: Case report

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Abbreviations
ECG: Electrocardiogram
ICD: Implantable cardioverter-defibrillator
LQTS: Long QT syndrome
MVA: Malignant ventricular arrhythmias
SCD: Sudden cardiac death
TdP: Torsades de pointes

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ABSTRACT
Congenital long QT syndrome is a primary electrical disorder of the heart which predisposes to the occurrence of malignant ventricular arrhythmias. It is characterized by a prolongation of the QT interval on the electrocardiogram and the torsade de pointes is the main associated arrhythmia, resulting in syncope and sudden cardiac death. Pregnancy and puerperium increase the incidence of those events. We present the case of a patient who suffered from this disorder, and during the post-delivery period, she had events of faint and anxiety interpreted as psychogenic. Torsades de pointes without response to the available antiarrhythmic drugs was documented and she was transferred to the reference center (*Instituto de Cardiología y Cirugía Cardiovascular*), where the pacemaker stimulation frequency was increased and, subsequently, an implantable cardioverter-defibrillator was implanted. This is an infrequent case that was a real challenge for the comprehensive and emergent treatment, all of which enabled the survival of the patient.
Keywords: Congenital long QT syndrome, Torsades de pointes, Sudden cardiac death, Puerperium

Torsión de puntas en una paciente con síndrome de QT largo congénito durante el puerperio: Presentación de un caso

RESUMEN
El síndrome de QT largo congénito es una enfermedad eléctrica primaria del corazón que predispone a la ocurrencia de arritmias ventriculares malignas. Se traduce en una prolongación del intervalo QT en el electrocardiograma y la torsión de puntas es la arritmia que ocasiona síncope y, en ocasiones, muerte súbita. El embarazo y el puerperio aumentan la incidencia de estos eventos. Se presenta el caso de una puérpera afectada que presentó crisis de ansiedad y desmayos interpretados como psicógenos. Se documentó torsión de puntas sin respuesta a los fármacos antiarrítmicos diponibles y se trasladó al centro de referencia (Instituto de Cardiología y Cirugía Cardiovascular), donde se aumentó la frecuencia de estimulación del marcapasos y, posteriormente, se implantó un desfibrilador automático. Se trata de un caso infrecuente que constituyó un verdadero reto en el tratamiento integral y emergente, todo lo cual posibilitó la supervivencia de la paciente.
Palabras clave: Síndrome de QT largo congénito, Torsión de puntas, Muerte súbita cardíaca, Puerperio

INTRODUCTION

Congenital long QT syndrome (LQTS) is considered a disease characterized by a long ventricular repolarization, which translates in the surface electrocardiogram (ECG) as a prolongation of the QT interval[1]. It is considered a disease of the ion channels responsible for the action potential of the cardiac cells, and it has a varying clinical presentation, ranging from syncope to the aborted cardiac arrest secondary to malignant ventricular arrhythmias (MVA) or sudden death cardiac (SCD)[2]. Transmembrane ion channels are affected because of mutations in genes encoding their protein synthesis, which produces accelerations or delays in their physiology[1,2].

In 1957, Jervell and Lange-Nielsen[3], described the first family with congenital LQTS, in children with bilateral deafness, recurrent syncope, SCD and long QT; this disorder has an autosomal recessive inheritance pattern. Meanwhile, Romano[4] and Ward[5] described, years later, a more common familiar form, with similar clinical practice, but without deafness, which is transmitted with a pattern of autosomal dominant inheritance. In recent years, it has been confirmed that it is not always about mutations of isolated genes, but multiple genetic alterations that follow complex patterns, which cause several polymorphisms responsible for diverse phenotypic expressions of the disease[2].

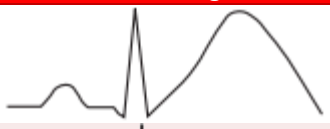
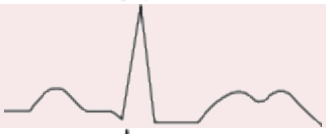
It is estimated that its prevalence oscillates in figures between 1:2 000 and 1:20 000 inhabitants, respectively, a difference that may be the result of the limitations in the diagnosis and the incidence of hidden and mixed forms[1,2].

More than 700 mutations in 13 genes have been described, which identify 13 types of congenital LQTS. Despite the development of genetics and the increasing identification of new subtypes, more than 75% of mutations are concentrated in three main genes: KCNQ1 (LQTS1), KCNQ2 (LQTS2) and SCN5A (LQTS3), which are well studied from the clinical-electrophysiological point of view. The rest of the LQTS are very rare and their reports in bibliography, almost anecdotal[6].

Congenital LQTS type 1 is the most common, due to mutations of the gene encoding the subunit α of the slow currents in the potassium channels (I_{Ks}) thus, there is a loss in the function of this channel; MVAs are related to exercises and physical or emotional stress (**Table 1**)[6,7]. This relation to stress and adrenergic discharge determines the positive response to beta-blockers and less need to resort to more aggressive therapies, such as the implantable cardioverter-defibrillator (ICD). The ECG also shows QTc interval ≥ 460 msec in women and QTc ≥ 450 msec in men, and broad-based T waves[1,6,7].

Mutations of the also called HERG gene are responsible for the congenital LQTS type 2, and the second in prevalence, encoding subunits α of fast potassium currents (I_{kr}). The MVAs are manifested with auditory stimuli (rings or alarms) and appear, especially, in the postpartum period. Until 50 or 60% of the MVAs may appear before 40 years old, with an annual incidence of SCD of 0.6%. In the ECG (**Table 1**), T waves of small amplitude can be found, which can be notched or biphasic[6].

Table 1. Main characteristics of congenital long QT syndrome.

C-LQTS	Current	Incidence	Pattern on the electrocardiogram	Triggers
Type 1	Potassium (I_{Ks}) ↑	30 – 35%		Exercise (68%) Emotions (14%) Sleep, rest (9%)
Type 2	Potassium (I_{Kr}) ↑	25 – 30%		Exercise (29%) Emotions (49%) Sleep, rest (22%)
Type 3	Sodium (I_{Na}) ↓	5 – 10%		Exercise (4%) Emotions (12%) Sleep, rest (64%)

c-LQTS, congenital long QT syndrome; I_{Kr}, rapid currents of the α subunit of potassium channels; I_{Ks}, slow currents of the α subunit of potassium channels; I_{Na}, sodium channel.
Modified from Medeiros-Domingo et al[7]. Rev Esp Cardiol. 2007;60(7):739-52.

Mutations of the SCN5A gene, the least prevalent, originate congenital LQTS type 3, that is related to increased intracellular sodium (I_{Na}). Resting, sleeping or the slow heart rates trigger events and its lethality is greater, with a high incidence of SCD. The ST-segment has a long isoelectric line (**Table 1**), with a narrow base[6,8].

Prolongation of the QT interval is associated with an increase of refractoriness and post potentials triggers of MVA; however, the heterogeneity of repolarization expressed by the increased dispersion of the QT has been identified as the main arrhythmogenic substrate of this channelopathy[1,3,6,8].

Torsades de pointes (TdP) is the more frequently associated polymorphic ventricular tachycardia, and it is responsible for syncope and the degeneration in ventricular fibrillation causing the SCD of these patients[1-8].

Pregnancy and puerperium are physiological events in the life of a woman and, at the same time, they are a critical period for those affected by these mutations, as in the case of congenital LQTS type 2[9]. All that is given by the role of postpartum hormonal fluctuations (high levels of estrogen and progesterone), which are involved in the physiology of the ion channels of myocardiocytes, associated with nausea, sleep deprivation, stress and noise (child's crying) as possible triggers for TdP during puerperium, even nine months postpartum, according to bibliography[10,11]. In spite of its low incidence, the welfare of the pairing mother-fetus or mother-child are a source of concern, and multidisciplinary action that includes genetic counseling, −to mothers already diagnosed or with strong personal medical history of first line− as well as the inclusion or keeping the treatment with beta-blockers during pregnancy and puerperium, which have been shown to decrease the incidence of MVA and SCD[11,12].

Here we present the case of a young mother of three children, with a history of known congenital LQTS since childhood, that, during the second postpartum month of her last child, presented recurrent events of palpitations and fainting, and a TdP refractory to the initial medical treatment was registered. This is the first case of this type treated in our center, which represented a real challenge in the treatment of this infrequent clinical situation.

CASE REPORT

A 25-years-old woman with history of bronchial asthma and congenital LQTS, diagnosed at the age of 7 years old. At that time, she was oriented a treatment with propranolol and an atrial (AAI) pacemaker was implanted in the *Cardiocentro Pediátrico Willian Soler*. When she reached the adulthood she was moved to the Department of Arrhythmia at the *Instituto de Cardiología y Cirugía Cardiovascular (ICCCV)* in Havana, Cuba, and at 15 years old, the treatment with beta-blockers was suspended, supposedly, because she started to have bronchial asthma and her evolution was favorable during the following years, even in the first two pregnancies and childbirths.

The patient had follow-up by the National Group of Attention to Pregnant Women with heart diseases, and the pacemaker's generator was changed two times (last time on April 2018). This time, after two months of her third childbirth, she began presenting events of general discomfort, strong palpitations and blurred vision at certain times, especially when breastfeeding her baby. She had never experienced such symptoms. She came to the Emergency Department sweaty and with irritability, her vital signs were normal and a suitable rhythm (spontaneous) was confirmed in the ECG at 62 beats per minute, alternating with the pacemaker's rhythm with atrial stimulation (**Figure, Panel A**), and the known long QTc (QTc = 500 msec). After two hours of observation the patient referred again discomfort, and frequent bigeminal premature ventricular contractions were documented in the monitor with events of TdP (**Figure, Panel B**), self-limiting at the beginning, then they were more frequent and lasting throughout the night. In **table 2** are presented some results of the blood cell count and blood chemistry analysis.

Management

Her admission to the intensive care unit was necessary, where a superficial sedation with intravenous midazolam was carried out, to limit the anxiety, as well correcting potassium through central vein in one hour. Isoprenaline at 0.07 mcg/kg/min was used, which produced supraventricular tachyarrhythmia (**Figure, Panel C**); in addition to two intravenous grams of magnesium sulfate. The patient, during all the night, and despite the therapeutic implemented, kept presenting self-limiting episodes of TdP. A coordination with the Department of Arrhythmias and Pacemakers of the ICCCV was made, and she was moved there in ambulance. In that center, the AAI pacemaker was reprogrammed and when increasing the pacing rate, the arrhythmias stopped. An ICD

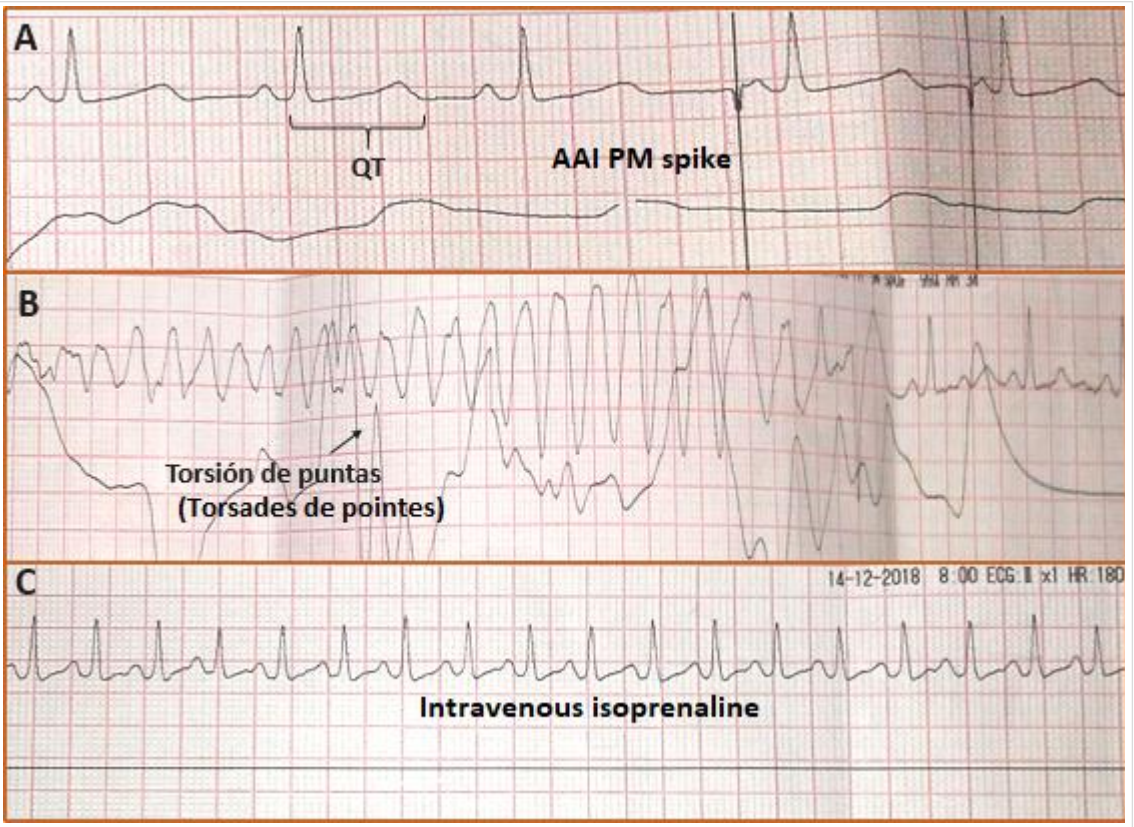


Figure. Segments of the electrocardiographic sequence performed during hospital admission. **A.** Sinus rhythm with prolonged QTc is observed, alternating with rhythm electro-stimulated by AAI pacemaker. **B.** Event of torsades de pointes (polymorphic tachycardia, with wide irregular QRS, without visible P wave, 300 beats per minute) that limits itself spontaneously. **C.** Supraventricular tachycardia (fibrillation *vs.* atrial tachycardia) triggered by the isoprenaline infusion. PM, pacemaker.

Table 2. Results of some blood parameters.

Parameter	Value
Potassium	3.01 mEq/L
Sodium	140 mEq/L
Chlorine	110 mEq/L
Hemoglobin	110 g/L
Leukogram	8.9 x 10^9/L
Glycemia	5.6 mmol/l

implant was decided and reinstated the propranolol, having in mind that she had been many years without respiratory symptoms. One week later, she was discharged, stable and asymptomatic. Currently, at six months of the event, the patient is symptom free.

COMMENTS

Several authors[1,10,11] have reported that the risk of MVA during pregnancy is reduced given the physiological changes that decrease these events, such as the increase in heart rate −particularly during the third trimester− because this phenomenon can be protective, especially in patients having a significant prolongation of the QTc at low heart rates. The genotype of LQTS2 is the most dangerous, compared to other genotypes[1,10,11]. While during the nine months after delivery there is a 2.7 times higher risk of experiencing these arrhythmic events, it can be substantially reduced with the use of beta-blockers[9,10,12]. This fact takes place because, after childbirth, there are a number of circulation, hemodynamic and neuroendocrine physiological changes favoring the distortion of the ductal function of the myocardiocyte[13].

Treatment with beta-blockers, especially the pro-

pranolol, is a choice for an initial treatment. This practice helps to significantly reduce syncopal episodes by MVA and SCD in most patients. These drugs are important for the prevention of events during pregnancy and postpartum, and –contrary to what many people believe– they are well tolerated by infants without increasing the number of malformations or abortions[12,13]. Stimulation in pacemakers is another option with special indication in cases in which the MVAs are associated with breaks (short-long-short cycles) with very long QTc intervals or associated with atrial-ventricular cardiac blocks[12-14].

In our patient, the QTc on arrival was 500 msec and, although she had a pacemaker implanted, she had constant arrhythmias that probably were recurrent because of the hypokalemia and the absence of beta-blockers in the treatment. A curious fact was her history of bronchial asthma, and there are reports of malignant associations between congenital LQTS and asthma, which confer a worse prognosis, perhaps due to disorders of modulation of beta receptors at the cardiac and bronchial level, genetically conditioned[15,16]. Another interesting thing is the fact that, although it was known from previous records, this patient was evaluated in two previous centers and the crises were attributed to psychosomatic causes linked to the recent childbirth and social burden of this young woman with three small children, which shows that there is still ignorance from many doctors concerning the deadly risks and implications of this disease.

A history of cardiac arrest or aborted SCD and the presence of recurrent syncope despite documented pharmacological treatment or sustained MVAs represent an indication for ICD. These devices can be effective for primary prevention in patients with a strong family history, intolerance to drug treatment or QTc ≥ 500 ms[1,17]. This patient was protected with the mentioned device given the described circumstances, even, the suspended beta-blockers with imprecise indications in the past were restarted.

In this patient was not possible, as in any other case in our country, to know the genotype of the syndrome, which is useful for stratifying the risk. As it is well-known, these are very expensive studies and often they are not available in all centers, globally[14,16]. It is believed that this was the case of congenital LQTS type 2, for its frequent associations with events during pregnancy and puerperium. Recently, Gallardo *et al*[11], published a number of pregnant women attended at the National Service of Heart Disease and Pregnancy of our country. They suggest that, during the pregnancy and the immediate postpartum period, there were no complications despite cases of very long QTc, and they accepted that a possible limitation of the study would be the fact that the follow-up was very short, unlike other international publications reaffirming the danger of MVA up to nine months after childbirth[9,10,12,15]. This patient is part of this example, and most likely, she was included in the previously mentioned registry; a fact we have not confirmed.

The fundamental merit of the present publication is to note that, although it is a rare disease, –consequently– this type of patients can come to our daily practice and we must be prepared to face situations that, many times, exceed our limit of action.

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