Syndactyly and long QT syndrome ($Ca_V1.2$ missense mutation G406R) is associated with hypertrophic cardiomyopathy

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Introduction

Long QT syndrome (LQTS) is a heterogeneous ion channel disorder caused by mutations in either the cardiac potassium channel genes or the cardiac sodium channel gene SCN5A.[1] Manifestations of LQTS during fetal or neonatal life are uncommon and usually indicate a severe form of the disease.[2–4] A specific cardiac L-type calcium channel dysfunction has been reported to cause LQTS and syndactyly.[5] This disorder, also called *Timothy syndrome,* is caused by the *de novo* $Ca_V1.2$ missense mutation G406R. It appears to be a multiorgan disease that includes congenital heart disease, recurrent infections, hypoglycemia, and autism. The syndrome is characterized by severe QT prolongation and lethal ventricular arrhythmias in the first years of life. In this report, we describe two neonates with Timothy syndrome and extend the phenotype to include hypertrophic cardiomyopathy and ventricular systolic dysfunction.

Case reports

Patient A

Patient A, male, birth weight 3,270 g, presented with a fetal heart rate of 70 bpm due to 2:1 AV block. Physical examination at birth revealed cutaneous bilateral syndactyly of the third fourth and fifth fingers. Subsequent ECGs showed marked QT prolongation (QTc 570 ms), T-wave alternans, and intermittent functional 2:1 AV block (Figure 1). The family history was negative for sudden cardiac death, syncope, syndactyly, and epilepsy. ECGs of the father, mother, and sister showed normal QT intervals. Serial echocardiography showed marked hypertrophy of both ventricles as well as ventricular systolic dysfunction (left ventricular shortening fraction 25%) (Figure 2). A small patent arterial duct was present, with delayed closure after age 3 weeks. Diuretic therapy was administered for congestive heart failure. Additional treatment consisted of epicardial dual-chamber pacing, high-dosage propranolol (5 mg/kg/day), and potassium supplementation. Two episodes of sepsis with *Escherichia coli* and *Staphylococcus aureus* were successfully treated with antibiotics.

Short runs of polymorphic ventricular tachycardia were documented after age 3 weeks despite therapy, and the patient died suddenly at age 30 days. No autopsy was performed. Sequencing of the LQT genes revealed no abnormalities. Three years later, postmortem DNA analysis showed the $Ca_V1.2$ missense mutation G406R, which was not identified in either parent. For that reason, exon 8a of the CACNA1C gene was amplified with primers CACNA1C_8AF CTCGGTTGCTGAGTGTGCCTC and CACNA1C_8AR CAGCCAGGAATAGCAGAAAGAATA. Sequence reactions were performed using the BigDye Terminator v 1.1 Cycle Sequencing Kit (Applied Biosystems, Foster City, CA) and analyzed using an ABI 3100 Analyzer (Applied Biosystems).

Patient B

Patient B, male, birth weight 3,030 g, was born by caesarian section at 33 weeks of gestation because of fetal hydrops and bradycardia. Physical examination at birth showed a hydropic neonate with a heart rate of 70 bpm. Cutaneous syndactyly

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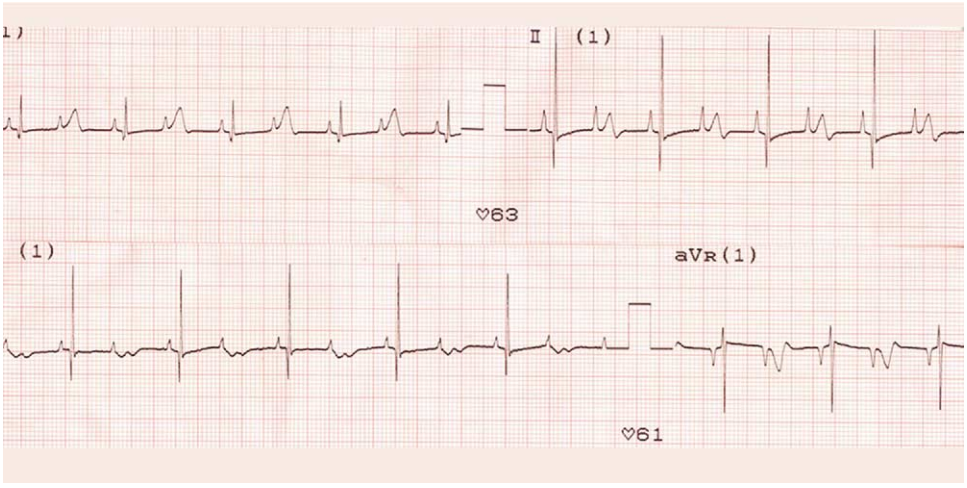

Figure 1 ECG of patient A showing functional 2:1 AV block (60 bpm) and QTc of 570 ms.

between the fourth and fifth fingers of the left hand was noted. ECG showed severe QT prolongation (QTc 650 ms), intermittent functional 2:1 AV block, and T-wave alternans (Figure 2). The family history was negative for syndactyly, syncope, and sudden death. ECGs of the father, mother, and sister showed normal QT intervals. Echocardiography showed hypertrophic cardiomyopathy with decreased left ventricular systolic function (left ventricular shortening fraction 20%) (Figure 3). Therapy consisted of diuretics, high-dose beta-blocker, and a ventricular pacemaker (Microny II, St. Jude) placed at birth to prevent functional 2:1 AV block. After 1 month, the patient developed frequent episodes of torsades de pointes and syncope. Mexiletine 15 mg/kg and oral potassium supplementation were added to the therapy. The patient remained in the hospital. At age 3 months, weighing 4 kg, the patient underwent insertion of an extracardiac single-chamber implantable cardioverter-defibrillator (ICD), with a subcutaneous patch array placed in the left lateral thorax and an ICD unit placed submuscularly in the right upper abdomen (Figure 4). The defibrillation threshold was 6 J, and the backup pacing rate was VVI 95 bpm. As in patient A, DNA analysis revealed the $Ca_V1.2$ missense mutation G406R, which similarly proved to be absent in both parents. During 12-month follow-up, the patient received nine successful ICD shocks for polymorphic ventricular tachycardia. The initiating sequence was not particularly pause dependent, although bigeminy of ventricular extrasystolic or aberrantly conducted supraventricular beats, which did not lead to marked variation in R-R intervals, preceded the arrhythmia several times.

The hypertrophic cardiomyopathy and left ventricular dysfunction remained stable during follow-up echocardiography. To date, psychomotor development appears normal, and no signs of autism have been detected. Neurologic, eye, and hearing evaluation have been normal. Two episodes of severe diarrhea and one clinical episode of sepsis have occurred. Extensive immunologic testing and fasting glucose and insulin levels have been normal.

Table 1 lists the presence and absence in patients A and B of other phenotypic hallmarks of Timothy syndrome as reported in literature.[5]

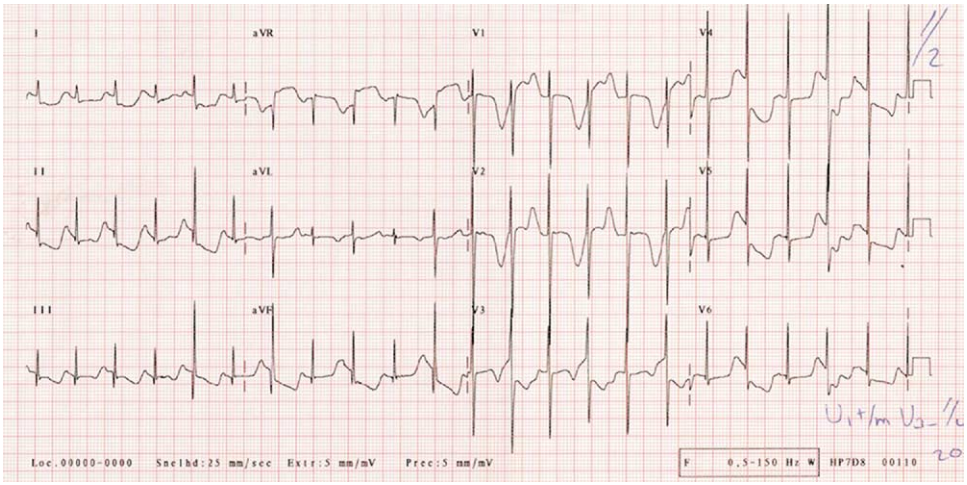

Figure 2 ECG of patient B showing QT prolongation (QTc 650 ms) and T-wave alternans.