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Clinical report

Unusual retrospective prenatal findings in a male newborn with Timothy syndrome type 1

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ABSTRACT

Timothy syndrome 1 (TS1) is a multisystem disorder characterized by severe QT prolongation and potentially lethal ventricular arrhythmias in the first years of life, plus other cardiac and extracardiac manifestations caused by mutation in the *CACNA1C* gene, a CaV1.2 L-type calcium channel. Here, we report retrospectively an unusual fetal presentation on a second patient with TS1 with fetal hydrops due to a congenital AV block and its postnatal diagnosis by a marked prolongation of the corrected QTc interval of 570 ms and a missense mutation, p.Gly406Arg, in exon 8A of *CACNA1C* gene. The observed manifestations in our patient during fetal period indicate a severe form and they were probably exacerbated by the maternal use of amitriptyline during the first 4 months of pregnancy. Unfortunately, he died at 3 months-old due a ventricular tachycardia and fibrillation related to a septic event. Although difficult to diagnose, possibly most fetuses with TS1 have symptoms of long QT syndrome. Despite the fatal outcome for our patient, an early diagnosis of TS may help to prevent life-threatening events or early death in future patients, especially in developing countries where availability of therapies such as cardioverter defibrillator are very limited, or require time for its funding.

1. Introduction

Timothy syndrome (TS, OMIM #601005), or long QT (LQT) syndrome type 8 (LQTS 8) is a rare multisystem disorder in most cases due to sporadic heterozygous mutations in the *CACNA1C* gene, characterized by cardiac anomalies potentially life-threatening (severe prolongation of the QT interval with a rate-corrected QT interval (QTc) of 480 ms–700 ms, arrhythmia–ventricular tachyarrhythmia, bradycardia, atrioventricular (AV) block, T-wave alternance and in 61%, several congenital heart defects) [Splawski et al., 2004]. Other extracardiac abnormalities include a typical cutaneous syndactyly in almost all patients, and facial dysmorphism, autism spectrum disorders, immunodeficiency, and severe hypoglycemia in some [Splawski et al., 2005]. Currently at least 30 patients with TS from have been reported [Yazawa and Dolmetsch, 2013]. The two forms of TS are, type 1 (TS1, classic) caused by mutations in the *CACNA1C* gene, a CaV1.2 L-type calcium channel and type 2, a rare form caused by mutations in an isoform of the same gene [Splawski et al., 2004; Splawski et al., 2006].

Fetal symptoms of LQT syndromes are very rare and its prenatal diagnosis is difficult [Horigome et al., 2010]. LQT syndromes

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account for 15–17% of fetal bradycardias among fetuses with a normally structured hearts, manifesting also other prenatal signs such as sinus or intermittent bradycardia <110 beats/min, or fetal heart rate <3rd percentile for gestational age, AV block, tachyarrhythmias, or pleural effusion and exceptionally, by fetal hydrops [Ishikawa et al., 2013; Mitchell et al., 2012]. Fetal hydrops as antenatal expression of TS1 has been reported previously in only one instance [Lo-A-Njoe et al., 2005, patient B], since most of them have been usually diagnosed during neonatal period or rarely, in late infancy. Here, we report retrospectively on a second patient of TS1 with fetal hydrops possibly related to congenital AV block as an unusual fetal presentation of this type of LQT syndrome and additionally, its postnatal evolution and molecular confirmation.

2. Clinical report

The *propositus* was the first child of a 23-year-old mother and 29-year-old father. During the first 4 months of pregnancy the mother received an antidepressive treatment with amitriptyline once daily, and during the same time-period, she smoked 8 cigarettes per day, and had consumed alcohol occasionally, but denies illicit drugs use, or other infectious illnesses, or trauma during the gestation. The ultrasound at 34 weeks of pregnancy found fetal rhythm irregularities with 2:1 AV block (ventricular and auricular rates of 58 and 129 beats/min, respectively) (Fig. 1, left), and also identified fetal hydrops by the presence of left hydrothorax (Fig. 1, right), ascites, and hydrocele, although without generalized edema. These findings on the fetal echocardiography persisted on subsequent evaluations until to its birth. Delivery was carried out via cesarean in the 36th week of gestation. Apgar scores were 2, 7, and 7 at 1, 5 and 10 min, respectively. The birth weight was 3400 g (>90th centile), the length was 48 cm (75th centile), and the occipitofrontal circumference (OFC) was 36 cm (>90th centile). Physical examination showed telecanthus, frontal hemangioma, heart murmur, abdominal distention and bilateral hydrocele. The hands showed mitten's appearance with bilateral cutaneous syndactyly involving fingers two to five with three to five synonychia, and mild syndactyly between the thumb and the index fingers, as well as bilateral cutaneous syndactyly of toes two to four, and right talipes equinovarus (Fig. 2a–l). He showed a severe respiratory insufficiency requiring intubation in the immediate neonatal period. A chest radiograph in the first day confirmed a bilateral hydrothorax, predominantly on the left side and additionally, mild ascites and 11 pairs of ribs. An intercostal tube was placed, draining a total of 150 ml of clear fluid over the following 10 days. Biochemically the effusion it was a transudate. The ECG at second day showed an auricular/ventricular rate of 120/57 bpm, respectively, 2:1 AV block, and marked prolongation of the QTc interval of 570 ms by the Bazett's formula (Fig. 2m). These clinical and electrocardiographic findings guided us to the TS diagnosis. Echocardiogram showed a patent ductus arteriosus and a patent foramen ovale. Hand radiographs corroborate absence of bony fusion on the syndactyly (Fig. 2c,f,i,l). CT scan of the brain was normal. Serology tests for congenital infections, serum glucose, and thyroid function test yield normal or negative results. Renal and abdominal ultrasound at age one month were normal and failed to found ascites or visceromegaly. Chromosome analysis at 550 band-level revealed a normal 46, XY karyotype.

After TS diagnosis, he started a management with propanol (3 mg/kg/d). At age of 35 days he was discharged, initiating efforts to secure funding for a cardioverter defibrillator. At aged of 2 months He was re-hospitalized during 7 days by an uncomplicated pneumonia. At the age of 3 months the patient presented a systemic inflammatory response syndrome related to a bloody diarrhea episode with a systemic inflammatory response syndrome accompanied by an arrhythmic event. On his admission to the hospital, intravenous fluids and antibiotic agents were administered, but he remained lethargic, depressed and febrile. He developed multiple episodes of ventricular tachycardia and fibrillation and unfortunately died. Infection was not confirmed because the blood cultures were negative. An autopsy was not performed.

2.1. Family data

The parents of the propositus were healthy and non consanguineous. The electrocardiograms of both parents were normal, as well as the rest of clinical and echocardiographic evaluations, which included the absence of syndactyly. The father has other two healthy children from a previous marriage and referred also, the history of two second-degree uncles with unilateral syndactyly in the hand and feet, respectively, and another two with an unspecified congenital cardiac anomaly. Despite that our cardiac evaluation was normal in the father of our patient, he and his father were

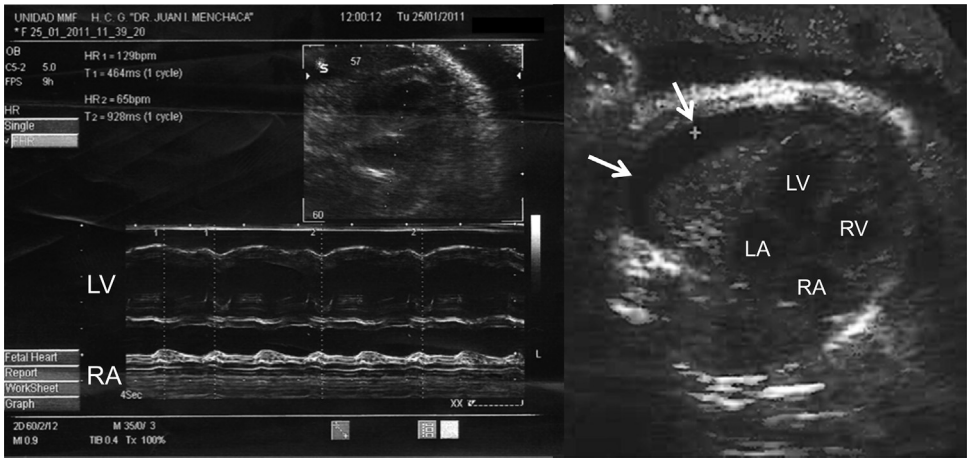

Fig. 1. M-mode fetal ultrasonography (Left), demonstrating 2:1 atrioventricular block with a normal atrial rate of 129 bpm, and a ventricular bradycardia of 65 bpm. The four-chamber view (Right), showing left hydrothorax (caliper and arrows). RA = right auricle, LA = left auricle, RV = right ventricle, LV = left ventricle.