

# Foetal 2:1 atrioventricular block in a patient with Timothy syndrome (LQT8) (RCDD code: VI-1B-1.2)

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## Abstract

Long QT syndrome (LQTS) may be a cause of foetal bradyarrhythmia and an important cause of death in children with arrhythmia. We present the case of a patient of Kadazan Iban descent with LQTS. He was detected prenatally to have foetal 2:1 atrioventricular (AV) block and tetralogy of Fallot. His postnatal electrocardiogram revealed a functional 2:1 AV block with QTc interval of 690 ms. Dysmorphism and cutaneous syndactyly of both hands and feet pointed to a diagnosis of classical Timothy syndrome (TS) type 1. This diagnosis was confirmed molecularly with a heterozygous mutation c.1216G>A. p. (Gly406Arg) at exon 8A in the CACNA1C gene. To the best of our knowledge, this is the first reported case of TS in a Kadazan Iban child. JRCD 2019; 4 (2): 42–46

**Key words:** rare disease, bradyarrhythmia, long QT syndrome, tetralogy of Fallot, syndactyly, electrocardiography, echocardiography

## Introduction

Foetal bradyarrhythmia can be a manifestation of long QT syndrome (LQTS) and about 50% of foetal bradycardias may have an underlying congenital heart disease [1]. LQTS is a hereditary cardiac disease characterised by a prolongation of the QT interval on basal electrocardiogram (ECG) and is associated with a high risk of life-threatening arrhythmias [1–2]. Early diagnosis is essential as it accounts for more than 10% of the causes of sudden infant death syndrome [1]. Here, we report a case of LQTS type 8 (LQT8) or Timothy syndrome (TS) in a patient who was noted to have foetal 2:1 atrioventricular (AV) block with underlying tetralogy of Fallot (TOF) and postnatal evidence of TS phenotype.

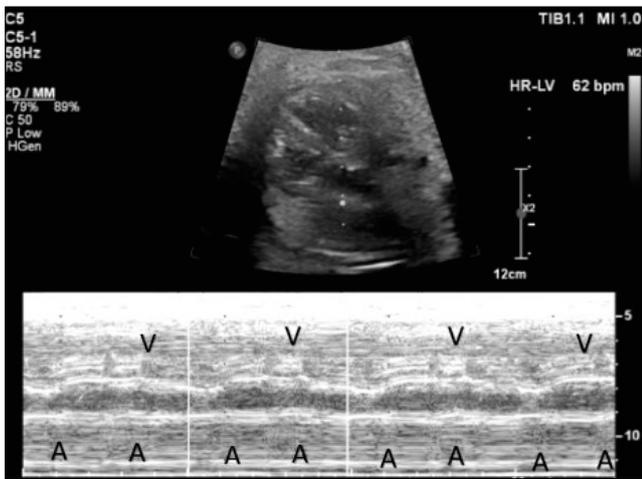
## Case presentation

A 32-year-old female of Iban descent presented at 32 weeks of gestation with foetal bradycardia. Her husband was 34 years old and of Kadazan descent; they were unrelated and this was their first child. There was no family history of sudden death or car-

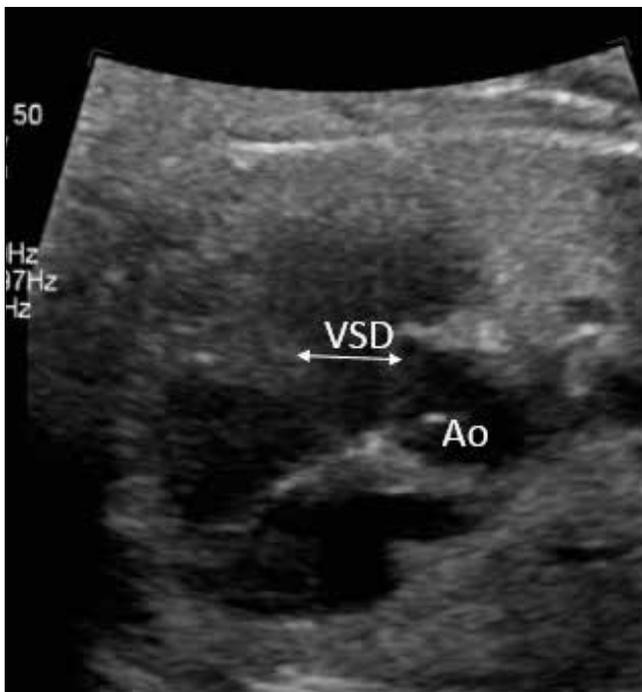
diac arrhythmia. Foetal echocardiography revealed a heart rate of 60 bpm with 2:1 conduction by M-mode (Figure 1). There was a large ventricular septal defect (VSD) with overriding aorta and small pulmonary valve annulus, which was suggestive of TOF (Figure 2). Prenatal counselling was provided with expectant management.

The baby boy was delivered via elective C-section at 38 weeks of gestation with good Apgar score and birth weight of 2.8 kg. He had a round face, sloping forehead, broad nasal tip, prominent columella, mild micrognathia, short neck, bilateral cutaneous syndactyly of thumbs and 2<sup>nd</sup> fingers as well as 3<sup>rd</sup>, 4<sup>th</sup>, and 5<sup>th</sup> fingers, and right cutaneous syndactyly of 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, and 4<sup>th</sup> toes as well as left 2<sup>nd</sup> and 3<sup>rd</sup> toes (Figure 3). His heart rate was 150 bpm with an intermittent rate of 60 bpm. There was a soft ejection systolic murmur over the pulmonary area. Examination of other systems was normal and he was haemodynamically stable.

His ECG showed intermittent bradycardia of 60 bpm with 2:1 AV block and QTc of 690 ms (Figure 4). Post-natal echocardiography confirmed the underlying TOF. On day 1 of life, he had symptomatic hypoglycaemia with a glucose level of 2.3 mmol/l and required intravenous dextrose infusion. This resolved within the next few



**Figure 1.** M-mode tracing through the left ventricle (LV) and right atrium (RA) reveals a 2:1 relationship between atrial and ventricular contraction



**Figure 2.** 2D foetal echocardiography of the left ventricular outflow tract shows a large ventricular septal defect with overriding aorta

days without recurrence. Molecular analysis of the CACNA1C gene by PCR and direct sequencing of exon 8A showed a heterozygous mutation c.1216G>A. p.(Gly406Arg). This mutation has been reported as pathogenic and results in the classic form of TS type 1. Both his parents' ECG were normal and family history was negative for the TS phenotype.

He was started on propranolol to maintain QT interval stability and to prevent ventricular tachyarrhythmia. The further management of this patient with regards to cardiac surgery, implantable cardioverter defibrillator and pacemaker was discussed with his parents and among cardiologists and electrophysiologists from

two Paediatric cardiac centres. A conservative medical approach was adopted in view of the guarded prognosis and limitation of resources.

At 6 months of age, he was found collapsed, with loss of consciousness at home. His mother, who is a staff nurse, performed cardiopulmonary resuscitation for 5–10 minutes. Upon arrival to the hospital, his ECG revealed macroscopic T-wave alternans in the precordial leads (Figure 5), arterial blood gas showed metabolic acidosis, blood glucose was normal, and chest radiograph showed cardiomegaly with oligemic lung fields. Repeated echocardiography showed the TOF anatomy with right ventricular outflow tract gradient of 65 mmHg and adequately sized pulmonary artery branches. The ventricular systolic function was impaired with an ejection fraction of 48%. We deduced a diagnosis of ventricular arrhythmia leading to cardiac arrest. He required invasive ventilation for 4 days and recovered.

The boy was most recently reviewed at 9-months-old. He has global developmental delay; developmental age is approximately 6-months-old. He is being treated with propranolol 2 mg b.d. and does not have further episodes of ventricular arrhythmia but has cyanotic spells secondary to TOF. He has neither seizures nor hypoglycaemia.

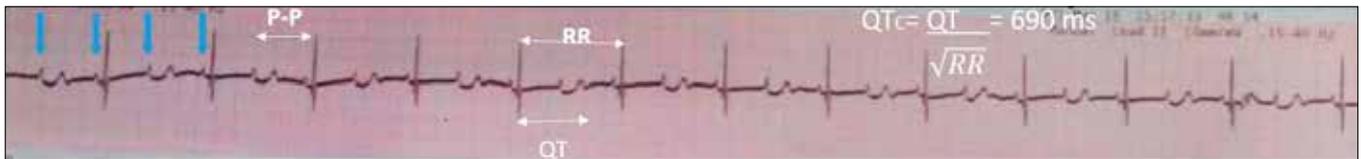
## Discussion

TS is a rare autosomal dominant multisystem disorder caused by a pathogenic variant in the CACNA1C gene which encodes for the CaV1.2 L-type calcium channel. It is characterised by facial dysmorphism, prolonged QT interval, congenital heart defects, syndactyly, immunodeficiency, hypoglycaemia, seizures, and behavioural and cognitive abnormalities [2]. TS is an extremely rare cause of LQTS, of which the exact prevalence is unknown. TS is diagnosed by clinical features and a pathogenic missense mutation in the CACNA1C gene. CACNA1C encodes the CaV1.2 L-type calcium channel which plays a central role in the excitation and contraction of the heart. Pathogenic variants in this gene result in reduced channel inactivation, thus contributing to maintained depolarisation and increased risk of arrhythmia [3]. Our patient presented with foetal bradyarrhythmia, a common presentation of this disorder. Others may present in the neonatal period or infancy with AV block due to QT prolongation and ventricular arrhythmias leading to cardiac arrest. These children are vulnerable to general anaesthesia which may provoke cardiac arrest in undiagnosed patients undergoing syndactyly surgery [4, 5]. Ventricular arrhythmia is the leading cause of death in TS, with the average lifespan being 2.5 years [1]. In addition, congenital heart defects are present in approximately 70% of individuals with TS. These include VSD, patent ductus arteriosus, hypertrophic cardiomyopathy, and TOF, as seen in our patient [1].

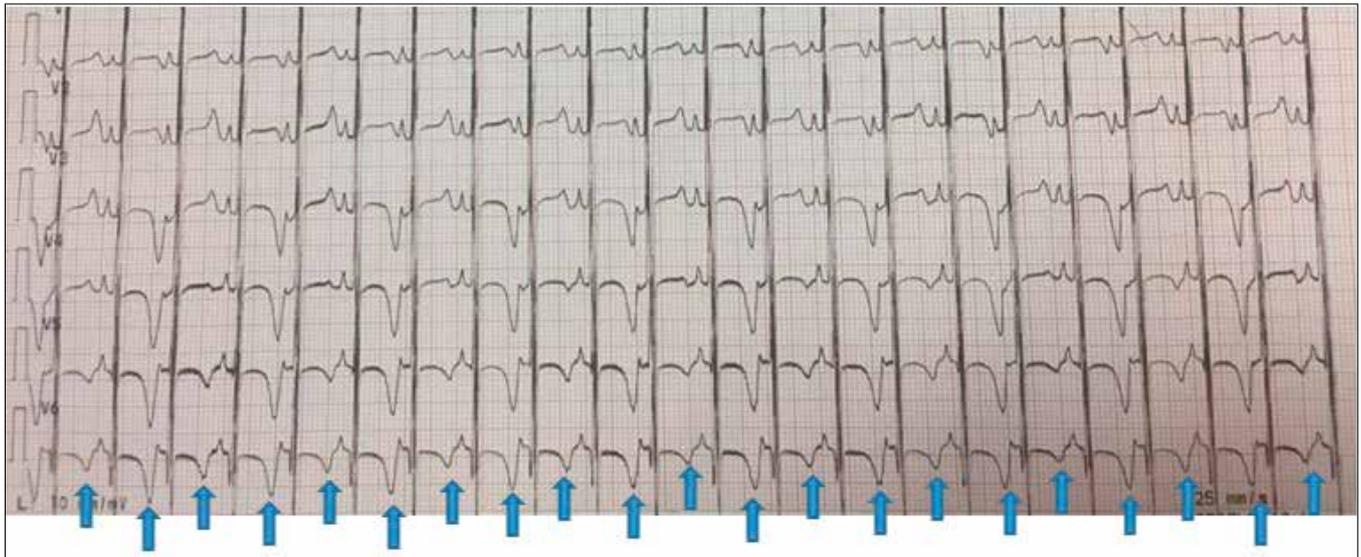
Two types of TS have been reported in the literature. TS type 1 (classic type) is characterised by unilateral or bilateral cutaneous syndactyly variably involving the 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup> and 5<sup>th</sup> fingers and bilateral cutaneous syndactyly of 2<sup>nd</sup> and 3<sup>rd</sup> toes. TS type 1 patients have milder cardiac symptoms with an average QTc of 580 ms, rare multiple arrhythmias, and most arrhythmias are associated with medications. In contrast, TS type 2 (atypical TS) patients do not



**Figure 3.** A round face, sloping forehead, broad nasal tip, prominent columella, cutaneous syndactyly of thumbs and 2<sup>nd</sup> fingers as well as 3<sup>rd</sup>, 4<sup>th</sup> and 5<sup>th</sup> fingers, cutaneous syndactyly of left 2<sup>nd</sup> and 3<sup>rd</sup> toes



**Figure 4.** Long lead II electrocardiogram (ECG) shows with 2:1 atrioventricular (AV) block with atrial rate of 120 bpm (P waves are represented by blue arrows) and ventricular rate of 60 bpm and marked QT prolongation with QTc (Bazett's formula) of 690 ms



**Figure 5.** Precordial lead electrocardiogram (ECG) reveals T-wave alternans (T waves represented by arrows) due to delay in repolarisation caused by abnormal L-type calcium channel activation

have syndactyly, but they do have a more severe cardiac phenotype with QTc range of 620 – 720 ms and multiple unprovoked arrhythmias. TS type 2 is caused by mutations in exon 8 rather than 8A of the CACNA1C gene [6–7]. Our patient has symmetrical syndactyly of both hands but asymmetrical involvement of the toes. Also, slightly distinct from the reported phenotype, our patient has a significantly prolonged QTc of 690 ms on presentation and 1 episode of unprovoked tachyarrhythmia with cardiac arrest at 6 months old.

Although the pathophysiology of all features of TS has not been fully elucidated, it is known that the CaV1.2 channel is expressed in organs other than the heart. In the brain, the CaV1.2 channel is essential for the development and function of neurons, giving insight into why autism and cognitive impairment may occur in affected children. In the pancreas, the CaV1.2 channel likely has a role in regulating blood sugar, hence the presence of hypoglycaemia in some patients, including ours [3, 6–8].

Due to its rarity, treatment of cardiac arrhythmias in TS has been based on anecdotal case reports and short case series. Beta-blockers have been used as well as other antiarrhythmic medications such as verapamil and mexiletine [4, 7]. However, the propensity for malignant arrhythmia in these patients, despite medications, may require the need for surgical interventions, e.g. insertion of a pacemaker or implantable cardioverter-defibrillator [7, 9]. These procedures, in turn, carry the high risk associated with anaesthesia in this group of children and the technical challenges in small infants. In our patient who has TOF in addition to LQTS, cardiac surgery would be associated with an extremely high risk. Additionally, due

to the limitation of resources in our country, conservative medical management was chosen for this patient.

TS is a panethnic inherited disorder with no gender predilection [4, 10]. To the best of our knowledge, we report the first case of a Kadazan Iban patient with this condition. Kadazan and Iban are natives of Borneo Island in the East of Malaysia. TS usually occurs as a result of de novo pathogenic mutation. To date, all literature report unaffected parents. However, rare instances of siblings being affected suggest parental gonadal mosaicism.

## Conclusions

In conclusion, foetal 2:1 AV block may point to a diagnosis of LQTS, and the co-occurrence of LQTS and syndactyly is a rare but distinguishing finding in TS that should be suspected early as it may lead to fatal ventricular arrhythmia. Early diagnosis is also essential to allow for appropriate planning of treatment and for genetic counselling to take place.

## Acknowledgements

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