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Long QT syndrome with a functional 2:1 block and multilevel conduction disease☆

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ABSTRACT

A 2-year-old female presented acutely following a three-week history of intermittent fever and lethargy. She was paradoxically bradycardic in the context of fever. An electrocardiogram illustrated multilevel conduction disease and a markedly prolonged QT interval with functional 2:1 atrioventricular block and multilevel conduction disease. Routine baseline aetiological investigations confirmed normal renal and thyroid biochemistry and no evidence of an infective cause or systemic inflammatory response. There was no past history of autoimmune conditions in the patient or her mother. Long QT syndrome type 3 (LQTS3) was suspected and a pacemaker implanted. Routine phenotypic screening of her asymptomatic first-degree relatives was unremarkable. Genetic testing of the proband identified an SCN5A mutation of uncertain pathogenicity, precluding predictive testing of her parents for diagnostic purposes. The proband remains well and event-free.

1. Case Report

A previously well 2-year-old female presented to her local pediatric emergency department following a three-week history of intermittent fever and lethargy. She was paradoxically bradycardic (60 beats per minute) in the context of fever, whilst there was no evidence of electrolyte disturbance or thyroid dysfunction. Baseline investigations failed to identify an infective or inflammatory process. A 12-lead electrocardiogram (ECG) demonstrated a prolonged corrected QT interval (470 msec) with non-conducted P-waves falling within or before the T-wave, reflecting functional 2:1 atrioventricular (AV) block (Fig. 1). The T-waves were late-peaking and preceded by a long, isoelectric ST-segment, whilst there was no T-wave alternans. The conducted PR interval was prolonged (180 msec) and the QRS complexes, broad (116 msec). This constellation of ECG abnormalities, comprising multilevel conduction disease, both above (prolonged PR interval) and below the His bundle (prolonged QRS duration), in combination with corrected QT interval (QTc) prolongation affecting functional 2:1 AV block, was highly suggestive if not diagnostic of long-QT syndrome type 3 (LQT3), reflecting cardiac sodium channel disease.

On confirmation of a structurally and functionally normal heart, a dual-chamber epicardial pacing system was implanted to mitigate against pause-dependent torsades de pointes (TdP) and a beta-blocker (Propranolol) was introduced. She has thrived subsequently with improved energy levels and no syncope or symptoms suggestive of arrhythmia. Follow-up was arranged in the dedicated Inherited Arrhythmia clinic given the suspicion of sodium channelopathy. We confirmed no past or maternal history of autoimmune disease, making an acquired inflammatory or maternal antibody-mediated congenital conduction disease unlikely. She had no history of seizures or febrile convulsions. Her parents are asymptomatic, non-consanguineous and of north African origin. Her two older siblings are entirely well, whilst there was no history of sudden or unexplained death, syncope, cardiac arrhythmia, or intracardiac device implantation in the extended family. We arranged prompt phenotypic screening of her first-degree relatives, confirming a normal resting 12-lead ECG with no unmasking of a type 1 Brugada pattern with leads placed in high right precordial positions, and normal echocardiography in each case. In the absence of an overt channelopathy phenotype in her asymptomatic parents, we sought a causative gene mutation in the proband, identifying heterozygosity for a missense point mutation in the *SCN5A gene* (p.Glu1053Lys; E1053K), which is considered a variant of uncertain significance (VUS).

2. Discussion

Long QT syndrome was first described in 1957 by two Norwegian physicians, Drs. A. Jervell and F. Lange-Neilson, who described a family in which four of six children were deaf and suffered from repeated

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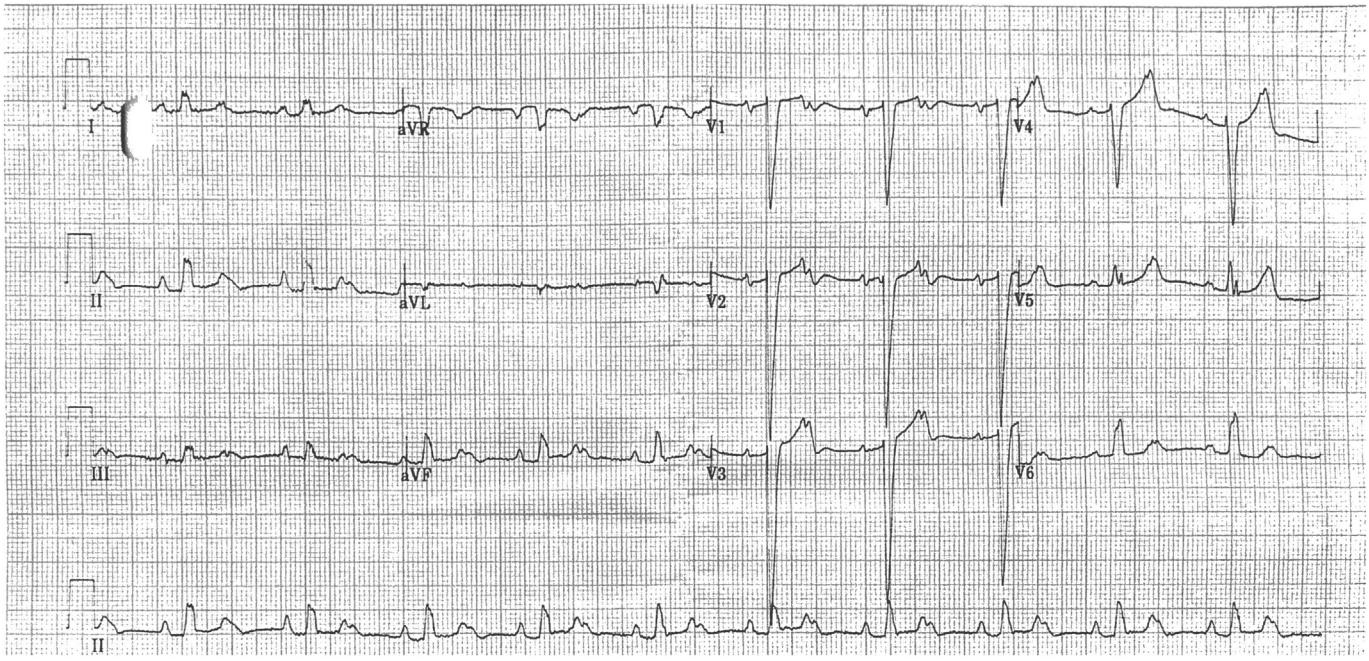

Fig. 1. 12-lead ECG demonstrating prolongation of the PR interval, QRS duration and QTc with functional 2:1 AV block.

syncopal episodes [3]. Those affected were found to have QT interval prolongation, with three of the four subsequently dying suddenly following syncope [3]. Romano et al. [29] and Ward [30] subsequently described families characterized by QT prolongation, syncope and sudden death in the absence of deafness, noting this to be considerably more common [4].

Long QT syndrome (LQTS) is a disorder of ventricular repolarisation reflecting a genetically inherited cardiac ion channel disease with a tendency towards malignant ventricular arrhythmia and sudden death in young people [3]. It is rare, affecting up to an estimated 1:2500 people in the general population, though due to its hereditary nature, clusters exist in families and smaller communities [2]. Diagnosis hinges partly on the duration of the QTc interval, though the threshold for this remains controversial (current practice is ≥450 ms in males and ≥460 ms in females) and measurement, subjective [2]. In phenotypically unaffected individuals who carry a known pathogenic LQTS mutation (genotype-positive/phenotype-negative), a risk of ventricular arrhythmia exists, albeit lower than in phenotypically affected individuals thus observation is warranted [2].

Hundreds of mutations have been identified in twelve different genes accounting for more than 80%of all hereditary LQTS presentations [2]. LQTS is classified by phenotype and genotype, with up to twelve different subtypes described [2]. Mutations in three genes predominate, accounting for at least 75% of cases including KCNQ1 and KCNH2, coding proteins integral to potassium channel structure and function in the cardiac myocyte [2]. Loss-of-function mutations in the KCNQ1 and KCNH2 genes manifests LQT1 and LQT2, respectively [2,5]. The SCN5A gene encodes a membrane protein integral to voltage-gated sodium channels in the cardiac myocyte[1]. Mutations in this gene disrupt the rapid inactivation of cardiac sodium channels, and as well as giving rise to LQT3, are closely associated with Brugada syndrome [5]. The most common LQTS subtype is LQT1, which typically presents with syncope and sudden death in the context of adrenergic stress such as physical exertion or emotional stress [5]. The LQT2 phenotype is characterized by syncope or sudden death occurring with stress or at rest, but typically, in response to loud noises such as an alarm [5]. Arrhythmic events in LQT3 (and Brugada syndrome) typically occur at rest or disproportionately often during sleep [6].

In the case we describe, present also is the important but uncommon characteristic of a functional 2:1 AV block. Patients presenting as such have been reported sporadically over recent decades [8]. As in this case, the non-conducted P-waves occur at the onset of, or even prior to, the preceding T-wave [7]. This coincides with ventricular refractoriness such that the depolarisation wavefront is not conducted beyond the AV node, thus no QRS follows [9]. This is particularly likely to be observed when a short sinoatrial cycle length is espoused with a long ventricular refractory period [9]. The functional nature of the AV nodal block is illustrated by intermittent 1:1 conduction, often at random, though sometimes induced with vagal maneuvers [8]. Interestingly, whilst LQTS has an approximately equal gender distribution, three quarters of those with associated functional 2:1 AV block are female [8]. Futhermore, as with our case, those with functional 2:1 AV block at presentation are less likely to have a family history than those with 'simple' LQTS (7% versus 60%) [8]. Affected infants typically present incidentally with asymptomatic bradycardia and even with close surveillance and active treatment, have higher rates of sudden cardiac death, implying this to be a very poor prognostic factor [8].

Miura et al. report another patient, presenting with bradycardia, prolonged QT interval and a functional 2:1 AV block in the context of a SCN5A mutation, describing a strategy of cardiac pacing to prevent pause-dependent TdP, the signature malignant ventricular arrhythmia of LQTS [9].

SCN5A mutations have also been described in the context of phenotypic Brugada syndrome, Progressive Cardiac Conduction Disorder (PCCD), congenital Sick Sinus Syndrome, familial atrial fibrillation (AF) and various combinations thereof [10]. Brugada syndrome is a rare cardiac channelopathy, defined by the presence of cove-shaped ST-segment elevation in the right precordial leads (in the absence of ischaemia or structural abnormality) and a tendency to ventricular arrhythmia and sudden cardiac death [10]. A hitherto occult Brugada ECG morphology may be unmasked by placement of the ECG electrodes in high right precordial positions, fever, or pharmacological provocation with class I anti-arrhythmic drugs, such as Ajmaline or Flecainide. While uncommon in the general population, it is thought that Brugada syndrome is responsible for at least 20% of all sudden cardiac deaths with a structurally normal heart [11].

PCCD describes conduction deterioration through the His-Purkinje system with left or right bundle branch block, a prolonged QRS