CASE REPORT

Late-onset severe long QT syndrome

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We report a case of torsades de pointes arrhythmia as the first manifestation of congenital Long QT syndrome in a 77-year-old man with family history of sudden unexplained death. This case illustrates the importance of vigilant clinical assessment and genetic counseling in families with sudden death in order to identify properly asymptomatic relatives at risk for cardiac events. It also demonstrates that Long QT syndrome can still manifest with potentially fatal arrhythmias late in life in previously asymptomatic elderly patients.

KEYWORDS

channelopathy, genetic test, long QT syndrome, sudden death

1 | INTRODUCTION

Congenital Long QT syndrome (LQTS) is a genetically determined cardiac channelopathy characterized by a prolongation of the QT interval on the ECG and increased propensity to syncope, seizures, polymorphic ventricular tachycardia (typically torsades de pointes), cardiac arrest, and sudden death in individuals with structurally normal heart (Schwartz, Crotti, & Insolia, 2012). The pathophysiological mechanism underlying LQTS is delayed repolarization due to mutations in genes encoding ion channels that participate at the fine-tuning of the cardiac action potential. The disease typically presents in young individuals with recurrent cardiac events, but presentation at all ages has been described (Locati et al., 1998). The single-most important prognostic factor has been shown to be the duration of QTc; longer times are generally associated with more severe phenotype (Priori et al., 2003). The disease has multiple, gene-specific subtypes, but the most common are LQTS1, LQTS2 and LQTS3, caused respectively by mutations in *KCNQ1*, *KCNH2* (*HERG*), and *SCN5A* genes.

2 | CASE REPORT

A 77-year-old man was brought to the emergency department for evaluation of palpitations, a syncopal episode while seated with spontaneous recovery, and malaise which started an hour before following heavy physical work. He reported no dyspnea or chest pain. Past medical history included mild arterial hypertension controlled with lisinopril (20 mg

and hydrochlorothiazide (12.5 mg). The patient reported occasional smoking and only social alcohol intake. Family history was remarkable for sudden unexplained death in the sister at the age of 70. He reported no infections, diarrhea, vaccinations, or travel during the last year.

Shortly after arrival to the emergency department, the patient experienced a second syncopal episode. Torsades de pointes arrhythmia was recorded (Figure 1A), which was terminated after administration of magnesium sulfate (2×20 mmol). Upon recovery of the normal sinus rhythm at a frequency of 73 beats/min, a severely prolonged heart-rate corrected QT interval (QTc) of 713 msec (QT = 648 msec) with T-wave alternans (beat-to-beat variation in the amplitude or shape of the T wave) was evident on 12-lead electrocardiogram (ECG) (Figure 1B), consistent with the diagnosis of LQTS. The patient was afebrile. No electrolyte abnormalities were detected, and the patient denied use of any QT-prolonging medication. Physical examination and transthoracic echocardiography were normal. The doses of antihypertensive medications were adjusted. The patient refused an implantable cardioverter defibrillator (ICD) and pharmacotherapy with propranolol 160 mg was initiated.

The in-hospital care was uncomplicated, and no recurrent cardiac events were recorded. The patient was discharged in a stable condition on the fifth day of hospitalization.

3 | GENETIC TEST RESULTS

After obtained written informed consent, genetic testing was performed. Genomic DNA was extracted from EDTA-blood using

FIGURE 1 Electrocardiographic characterization of a patient with long QT syndrome. (a) recording of torsades de pointes, the hallmark arrhythmia of long QT syndrome, terminated after injection of magnesium sulfate. (b) 12-lead ECG showing heart-rate corrected Q-T interval (QTc) of 713 ms (QT = 648 ms, heart rate = 73/min), T-wave alternans (arrowheads), and frequent premature ventricular contractions

standard procedure. Targeted exome sequencing was performed by next generation sequencing on a MiSeq instrument using the TruSight One Sequencing Panel (Illumina, San Diego, CA, USA) which provides comprehensive coverage of exonic and exonic-intronic boundaries of 4,813 clinically relevant genes. Read alignment and local realignment of indels were performed using CLC Workbench v7.5.1 (CLC bio, Aarhus, Denmark). Subsequently, variants in 16 known LQTS-susceptibility genes (*KCNQ1*, *KCNH2*, *SCN5A*, *ANK2*, *KCNE1*, *KCNE2*, *KCNJ2*, *CACNA1C*, *CAV3*, *SCN4B*, *AKAP9*, *SNTA1*, *KCNJ5*, *CALM1*, *CALM2*, *CALM3*) (Online Mendelian Inheritance in Man, 2017) were

analyzed. Variants with a minor allele frequency <1% were further evaluated. Interpretation of these sequence variants was performed according to the guidelines established by the American College of Medical Genetics and Genomics (Richards et al., 2015). Identified variants were assigned a level of evidence for pathogenicity as very strong, strong, moderate or supporting, and, based on the calculated aggregate score, were further classified as pathogenic, likely pathogenic, benign, likely benign, or variant of uncertain significance (Richards et al., 2015). Putative pathogenic variants were confirmed by Sanger sequencing.

FIGURE 2 Family pedigree. The index patient is indicated with an arrow. The black symbol represents the affected individual. Symbols containing “n.a.” (not analyzed) indicate individuals with unknown genotype and phenotype. II.1: Sudden death at the age of 70. II.2: index patient who carries heterozygous c.1022C > T mutation in *KCNQ1* gene, and was diagnosed with long QT syndrome at the age of 77 years. III.1 and III.2: unaffected daughter and son evaluated at the age of 44 and 41, respectively

Screening of LQTS-associated genes revealed a heterozygous c.1022C > T missense variant in *KCNQ1*, predicting to substitute Alanine with Valine at position 341 (exon 7) of the Kv7.1 channel. The p.(Ala341Val) variant has been previously reported as pathogenic (rs12720459) (Kapa et al., 2009; Landrum et al., 2016), confirming the diagnosis of LQTS1 (Wang et al., 1996). The Kv7.1 channel mediates the slow delayed rectifying K^+ current (I_{Ks}) during the phase 3 repolarization. Mutations in *KCNQ1* (locus 11p15.5) are the most common cause of LQTS and explain 30%–35% of all cases (Ackerman et al., 2011).

Following the identification of the causative mutation, we performed clinical evaluation and extended the genetic testing to the 41-year-old son and the 44-year-old daughter of the index patient. Both were asymptomatic, did not report complaints in the past and both tested negative for p.(Ala341Val) mutation in *KCNQ1* (Figure 2).

4 | DISCUSSION AND CONCLUSIONS

We report a rare case of a torsades de pointes arrhythmia in a previously asymptomatic elderly patient with concealed LQTS and family history of sudden unexplained death. The *KCNQ1*-Ala341Val

FIGURE 3 Predicted topology of the Ala341Val mutation on the α subunit Kv7.1 (*KCNQ1*) of the IKs channel. Kv7.1 (KvLQT1) is composed of six membrane-spanning segments (S1–S6), including a voltage-sensing domain (VSD) (S1–S4), a pore loop, two cytoplasmic loops (S2–S3 and S4–S5), a NH_2 and a $COOH$ terminus domains. The Kv7.1 subunit interacts with accessory β subunit/MinK (*KCNE1*) and the A-kinase anchoring protein (AKAP) (Yotiao) to form the functional IKs channel complex. Conventional 1-letter abbreviation (A, alanine; V, valine) is used to show the *KCNQ1*-Ala341Val substituted identified in this case

mutation in our patient, has been mapped to the sixth transmembrane domain (S6) of the α subunit Kv7.1 (KvLQT1) of the IKs channel (Figure 3) (Smith, Vanoye, George, Meiler, & Sanders, 2007). The KCNQ1-A341V is considered a high risk LQTS1 mutation, and has been associated with a higher incidence of cardiac events compared with that reported for LQTS1 subjects in general (Brink et al., 2005; Priori et al., 2003). Usually, patients with this mutation have symptoms early in life, (Crotti et al., 2007) with a 14% incidence of sudden death before the age of 40 years (Brink et al., 2005). Functional studies of KCNQ1-A341V mutation conducted in Chinese hamster ovary cells stably expressing IKs identified a dominant negative effect of the mutation on wild-type channels, which explains its severe phenotype (Brink et al., 2005).

In population aged ≥ 40 years, the prevalence of prolonged QTc interval (≥ 480 criterion) is reported 0.42% in a representative Spanish cohort of nearly 8,000 participants (Awamleh Garcia et al., 2017). The vast majority of these patients are symptomatic and receive diagnosis at a younger age, but in some patients, LQTS is misdiagnosed and treated as a primary seizure disorder at young age, (Coto et al., 2017) and later recognized at older age after recurrent symptoms. It is also known, that LQTS can be asymptomatic for the entire life, or manifest clinically in certain conditions, such as hypokalemia or treatment with antipsychotic medications (Rabkin, 2015). Reports from International Long QT Syndrome Registry showed that LQTS subjects maintain a high risk for life-threatening cardiac events after the fourth decade of life (Goldenberg et al., 2008). The risk of sudden cardiac death is particularly high when the QTc is consistently prolonged in serial measurements (Niemeijer et al., 2015). The phenotypic expression of affected subjects is influenced by age-specific factors related to gender, clinical history, and the LQTS genotype (Goldenberg et al., 2008). As such, LQTS3 genotype (SCN5A) has been shown to be the most powerful predictor of poor outcome after age 40, with nearly a 5-fold increase in the risk of aborted cardiac arrest or sudden death compared with genotype-negative subjects, whereas the LQTS2 (KCNH2) genotype has been shown to be associated with intermediate risk, and the risk associated with LQTS1 (KCNQ1) was similar to that of genotype-negative subjects (Goldenberg et al., 2008). This case report nicely illustrates that severe LQTS1 may also present with life-threatening arrhythmias in previously asymptomatic elderly individuals. Since the benefit of β -blocker therapy in LQTS patients was shown to be maintained after age 40 years, (Goldenberg et al., 2008) preventive therapy in high risk individuals and close follow-up may allow to prevent LQTS-related cardiac fatalities.

Most of the genetic studies performed on sudden cardiac death victims exclude patients older than 40 years old, (Bagnall et al., 2016) since ischemic heart disease is the leading cause of sudden cardiac death in this age group (Chugh et al., 2004). As a result, among sudden cardiac death victims above 40 years, fatal LQTS and other genetic channelopathies usually remain undetected. We illustrate here that channelopathies can also be a cause of cardiac arrest at old age, and the precise prevalence of this problem in the elderly is unknown due to exclusion from most of the genetic studies performed before. Additionally, it is possible that the sudden

unexplained death in the sister of our index patient was caused by LQTS, however this could not be confirmed due to the lack of tissue available to perform genetic testing. This demonstrates the essential role of clinical evaluation and genetic counseling in families with sudden unexplained death for identifying asymptomatic relatives at risk for cardiac events.

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