Circumstance-dependent functional variants in the major long QT syndrome genes in patients with recurrent polymorphic ventricular arrhythmias: A case series

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Introduction

Long QT syndrome (LQTS) is a potentially life-threatening cardiac arrhythmia syndrome, characterized by a prolonged (heart rate–corrected) QT interval (QTc) on the electrocardiogram (ECG).[1] To date, many LQTS-susceptibility gene mutations have been discovered.[2,3] However, the burden of background genetic variants complicates interpretation of gene–disease associations in clinical practice. There is substantial evidence that certain common genetic variants previously described as benign could contribute to QT prolongation under specific circumstances, such as electrolyte imbalances, structural heart disease, fever, or other proarrhythmic states.[4,5] Genetic variants are generally classified as pathogenic or benign; however, this "all or none" approach has some pitfalls in capturing the arrhythmic risk imparted by many of LQTS-associated alleles. This case series reports on 2 potential circumstance-dependent (rare) functional variants for QT prolongation and polymorphic ventricular arrhythmias, highlighting the difficulties in individual risk assessment based on genetic variants.

KEY TEACHING POINTS

- Nonpathogenic rare functional long QT syndrome (LQTS) variants potentially enhance susceptibility to QT prolongation under specific circumstances.
- Specific circumstances may affect the pathogenicity of different LQTS variants.
- Understanding LQTS gene–disease associations enables personalized management.

Case reports

Case 1

A 53-year-old female patient presented to the emergency department with a sore throat and fever. Her medical history consisted of a depressive disorder for which she took paroxetine 20 mg daily. She reported no family history of sudden death. Just before presentation, she had taken doxycycline (a tetracycline antibiotic) and lost consciousness for a short time. At physical examination, she had a normal blood pressure but an irregular heart rate of 120 bpm. Body temperature was 38.4°C. Laboratory test results showed the following plasma levels: sodium 131 mmol/L (reference range 135–145); potassium 3.6 mmol/L (reference range 3.5–5.0); magnesium 0.71 mmol/L (reference range 0.7–1.0); and glucose 6.9 mmol/L (nonfasting reference range 3.3–7.8). Antibiotics were switched to penicillin and ciprofloxacin. Initially, her ECG showed sinus rhythm with a prolonged QTc interval of 580 ms and polymorphic premature ventricular complexes (Figure 1A). Later that day, nonsustained polymorphic ventricular tachycardias and torsades de pointes ventricular arrhythmias were documented (Figure 1B). Subsequently, paroxetine was permanently discontinued, and antibiotics were switched to cefuroxime, but the QTc interval remained prolonged. A temporary pacing wire was implanted to suppress ventricular ectopy. During admission, the patient underwent insertion of an implantable cardioverter-defibrillator. Genetic screening revealed a heterozygous missense mutation in the KCNQ1 gene (c.1597C>T; p.R533W) resulting in replacement of arginine by

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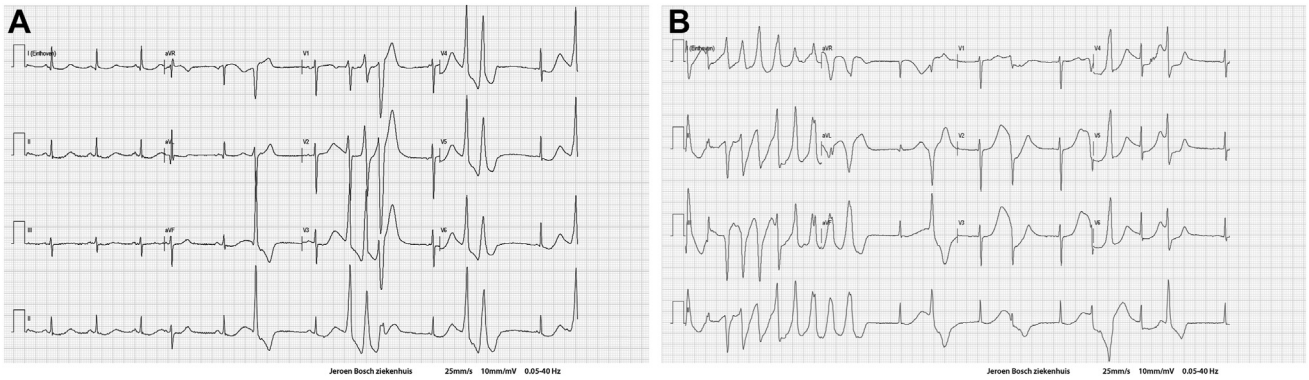

Figure 1 **A:** Case 1. Electrocardiogram (ECG) on admission shows sinus rhythm of 75 bpm with a prolonged QTc interval (580 ms, Bazett formula) and multiple polymorphic premature ventricular complexes. **B:** ECG during admission shows nonsustained polymorphic ventricular tachycardia, junctional escape rhythm, and premature ventricular complexes in bigeminy.

tryptophan, which is not listed in the Genome Aggregation Database (gnomAD) and has been classified elsewhere as of "uncertain significance."[6,7] However, it has been observed in an autosomal recessive form of Romano-Ward syndrome.[8] Additional experimental data suggest that this mutation alone has only a mild effect on channel function.[9] Risk factors for QTc prolongation in this case were fever, female sex, QTc-prolonging medication (paroxetine), and low-to-normal electrolyte levels. One year later, while the patient had a fever and again a prolonged QTc interval, she lost consciousness for a short time as a result of a polymorphic ventricular arrhythmia of 36 complexes with cycle length 200–250 ms, which spontaneously converted to sinus rhythm and was caught on device interrogation.

Case 2

A 36-year old female patient with hemophagocytic lymphohistiocytosis was admitted because of persistent fever with pancytopenia, based on a possible B-cell non-Hodgkin lymphoma or a primary Epstein-Barr virus infection. Family history included sudden death of her mother at the age of 45 years. Rituximab was administered and routine infusion with ceftazidime was started. Approximately 10 hours after infusion with rituximab and ceftazidime, the patient suffered from a cardiac arrest as a result of ventricular fibrillation for which she was successfully defibrillated. The patient's cardiac arrest was preceded by an exceptionally long QT interval of 690 ms measured on telemetry (Figure 2). Her body temperature was normal in the hours before and at the time of the cardiac arrest. Laboratory test results showed mild hyperphosphatemia, and normal corrected calcium, magnesium, and potassium plasma levels. Levels of cardiac markers were nonsignificantly elevated. In this case, risk factors for QTc prolongation consisted only of female sex. The patient recovered within 5 days, and a cardiac defibrillator subsequently was implanted. Six weeks later, she was discharged from the hospital in good clinical condition. Her QTc interval duration normalized within 2 months after admission. Genetic analysis revealed a heterozygous missense mutation in the SCN5A gene encoding the alpha subunit of the cardiac sodium channel (c.1715C>A; p.A572D) and a single nucleotide polymorphism on the same gene (c.1673A>G;

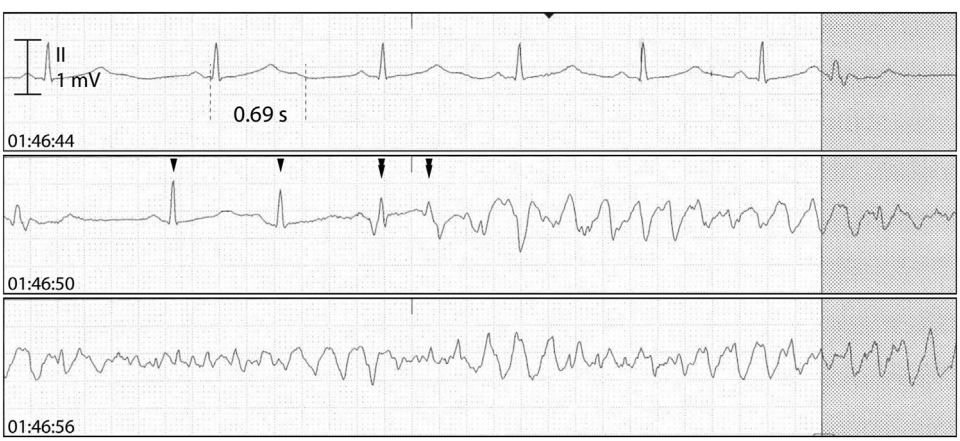

Figure 2 Case 2. Telemetric monitoring at initiation of torsades de pointes. QT-interval duration was 690 ms. *Single arrowheads* indicate conducted QRS complexes. *Double arrowheads* indicate premature ventricular complexes. The second premature QRS complex occurs in the relative refractory period (during the T wave), initiating a torsades de pointes polymorphic ventricular arrhythmia. The first premature QRS complex might already be a fusion complex between a sinus conducted complex and a premature ventricular complex, contributing to ventricular dispersion in refractoriness.

p.H558R). A frequency of 4.91×10^{-3} is reported for the former, which is classified as benign based on strong evidence of benign impact: benign strong (BS) 1; BS2 (observed in healthy adult individual with full penetrance expected at an early age); and BS3 (functional studies show no damaging effect on protein function or splicing) according to American College of Medical Genetics and Genomics guidelines.[6,10]

Discussion

This case series reports on 2 different rare variants that might contribute to QTc prolongation and enhance the susceptibility to polymorphic ventricular arrhythmias under specific circumstances. Case 1 had a heterozygous missense mutation in the KCNQ1 gene. Exogenous factors might have provoked ventricular arrhythmias, as our patient possibly was more prone to QT prolongation due to this specific variant. Possible pharmacologic factors for QTc prolongation in this case were ciprofloxacin, omeprazole, and paroxetine only under certain circumstances. Both levocetirizine and doxycycline currently are not classified.[11] One could argue whether implantable cardioverter-defibrillator placement was indicated in this case. However, our team desired to protect this relatively young patient from potential sudden cardiac death as a consequence of serious ventricular arrhythmias because underlying conditions such as fever, illness, or electrolyte imbalances can be expected to reoccur in the remaining lifetime of this patient and cannot be prevented.

Case 2 had a missense mutation in the SCN5A gene accompanied by transient QT prolongation, which ultimately resulted in ventricular fibrillation in a patient treated for a hemophagocytic syndrome. Of note, the risk categories for QTc prolongation for both rituximab and ceftazidime are still not known.[11] In a previously reported case, Epstein-Barr virus had been linked to myocarditis with the potential to induce arrhythmias.[12] However, the fact that the patient did not complain of chest pain and did not have significantly elevated cardiac markers make this alternative explanation less likely, although it cannot be completely ruled out. Overall, this case series suggests that some (rare) variants are potentially clinically relevant, with increased susceptibility to cardiac arrest in individual patients under specific circumstances compared to noncarriers, albeit without a (known) association with LQTS on the population level.

Current literature reports that depending on multiple endogenous and/or exogenous factors, missense variants can cause altered ion function resulting in disease phenotype.[5,13] The wide phenotypic range varies from absence of any clinical or ECG features to relevant QT-interval prolongation with arrhythmic events or even sudden cardiac death. This might be partly explained by incomplete penetrance, variable expressivity, and the coexistence of modifier gene alleles, altering arrhythmia susceptibility. Therefore, the paradigm recently shifted from a monogenetic disease-causing perspective to a perspective in which rare, functionally proarrhythmic variants can potentially contribute to oligogenic/polygenic LQTS or predispose to acquired forms of LQTS.[4,14] In order to accurately assess pathogenicity, variants can be classified as functional risk alleles only when there is supportive epidemiologic and/or experimental evidence.[4] Accordingly, Giudicessi et al[14] proposed that variants be classified as functional risk alleles if both substantial epidemiologic (ie, odds ratio >5 in case-control studies) and experimental (ie, well established *in vitro* cellular electrophysiological data) evidence are present. Based on these more tailored criteria, the variants found in both of our cases cannot be classified as definite functional risk alleles. Nevertheless, reporting on circumstance-dependent functional variants facilitates further exploration of these variants and their possible contribution to symptomatic LQTS. Moreover, incorrect interpretation of genetic information can lead to harmful results.[15]

Our results should be interpreted with caution because this series describes only 2 cases, and the existence of other (unknown) variants or gene modifiers cannot be ruled out. QTc values before hospitalization were not available. In addition, some potential risk factors for acquired LQTS were unavailable. However, these cases highlight the importance of genotype–phenotype associations and emphasize that specific circumstances may affect the pathogenicity of variants. Better understanding of these mechanisms combined with a tailored method of reporting potential pathogenicity of different variants is paramount to enable personalized management of patients with LQTS or LQTS susceptibility.

Conclusion

Based on the findings in both cases, we suggest that genetic variants in LQTS genes previously described as nonpathogenic can potentially enhance susceptibility and contribute to QT prolongation and can even provoke symptomatic LQTS in the presence of exogenous factors.

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