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CASE REPORT

Asymptomatic ventricular tachycardia: diagnostic pitfalls of Andersen–Tawil syndrome—a case report

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Background Andersen–Tawil syndrome (ATS) is a rare arrhythmia disorder caused by a mutation in the KCNJ2 gene. Typical presentation includes a triad of cardiac arrhythmia, dysmorphia, and periodic paralysis. However, KCNJ2 mutations can mimic other disorders such as catecholaminergic polymorphic ventricular tachycardia (CPVT) making treatment challenging.

Case summary A 9-year-old asymptomatic female patient presented with an irregular heart rate noted at a well-child visit. Physical examination revealed short stature and facial dysmorphism. An initial rhythm strip showed intermittent runs of non-sustained bidirectional ventricular tachycardia with a prolonged QT interval of 485 ms at rest. Exercise testing showed no significant increase in ectopy from baseline at higher heart rates. Cardiac imaging was normal, and the burden of ventricular ectopy was significantly reduced on a beta-blocker and Class IC antiarrhythmic combination. Genetic testing marked a D71N mutation in the KCNJ2 gene.

Discussion Clinical distinction between ATS and CPVT is a challenge. Genetic testing in the above patient attributed a likely pathogenic variant for both ATS and CPVT to a single D71N mutation in the KCNJ2 gene. Further evaluation revealed no clinical CPVT, emphasizing the need for cautious interpretation of genetic results in inherited arrhythmia disorders.

Keywords Case report • Andersen–Tawil syndrome • CPVT • KCNJ2 gene mutation • Bidirectional VT • Antiarrhythmic • Asymptomatic VT • Long QT syndrome

Learning points

- Mutations in the KCNJ2 gene can manifest with phenotypic Andersen–Tawil syndrome (ATS) and catecholaminergic polymorphic ventricular tachycardia (CPVT).
- The ectopy in ATS-1 is often abundant but seldom causes sudden cardiac death (SCD).
- Clinical distinction is important because patients with the CPVT phenotype are at a risk for SCD.

Introduction

Andersen–Tawil syndrome (ATS), also known as Long QT syndrome Type 7 (LTQ7), is a rare electrophysiological disorder caused by a mutation in the KCNJ2 gene which encodes the inward-rectifying potassium channel Kir2.1. This ion channel plays a role in the cardiac action potential, contributing to Phase 4 repolarization and resting membrane potential, as well as in developmental signalling.[1]

Typically, patients with ATS present with a triad of cardiac arrhythmias, dysmorphic features, and periodic paralysis. However,

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mutations in the KCNJ2 gene are known to display a wide range of phenotypes that may mimic other electrophysiological disorders such as catecholaminergic polymorphic ventricular tachycardia (CPVT).[2] Patients exhibiting this type of 'phenotypic mimicry' may or may not display typical ATS characteristics but also exhibit exercise-induced arrhythmias characteristic of CPVT. Clinical differentiation is important because while most patients with only ATS will likely not have life-threatening arrhythmias, patients with the CPVT phenotype are at a risk for exercise-induced sudden cardiac death (SCD) and should be managed and treated as such.[1]

Timeline

Day 1	Irregular heart rate noted at paediatrician visit
Day 2	Paediatric cardiac outpatient visit: electrocardiogram revealed several runs of ventricular tachycardia
Day 2	Admission to inpatient paediatric cardiology for investigative work up
	Initial ventricular ectopy (VE) burden 45%
Day 3	Initiation of sotalol
Day 6	Sotalol stopped and propafenone initiated
Days 7–10	Escalating dose of propafenone and Metoprolol added to drug regime
Day 12	Patient discharged with a reduced ectopy burden of 6%
Months 2–12	Outpatient follow-up at 6–8 week intervals with VE burden stable at <15%
Months 12–18	Progressive increase in VE burden to 40%
Month 18	Inpatient admission. Propafenone and metoprolol stopped and flecainide and nadolol initiated.
Months 18–28	Doing well on outpatient follow-up with ectopy burden <5%

Case presentation

A 9-year-old clinically asymptomatic female patient was referred to paediatric cardiology for an irregular heart rate noted at an incidental well-child visit. An initial electrocardiogram (ECG) showed a prolonged QTc and runs of non-sustained bidirectional ventricular tachycardia (*Figure 1*), and she was admitted for further evaluation.

There was no family history of arrhythmogenic disorders, congenital heart disease, or sudden death. The only reported malformation in her mother and maternal grandmother was syndactyly. Physical examination revealed short stature, low set ears, mild micrognathia, wide spaced eyes, and dental abnormalities (*Figure 2*). She also had left iris heterochromia with half the iris blue and half green. Vitals including a heart rate, blood pressure, respiratory rate, and oxygen saturation were appropriate for age. Examination of the cardiovascular system revealed an irregular pulse rate and normal first and second heart sound. There were no additional cardiac sounds, murmurs, rub, or gallop noted. Examination of the respiratory, abdominal, and neurologic system were unremarkable. Initial investigations revealed a baseline ECG with a prolonged QTc of 485 ms and bidirectional VT on ECG and Holter with a ventricular ectopy (VE) burden of 40%. Laboratory testing included a complete blood count with differential, a comprehensive metabolic panel, cardiac enzymes (troponin and CK-MB), and thyroid function tests were within normal limits. Further exercise stress testing showed no significant increase in ectopy from baseline at higher heart rates. A transthoracic echocardiogram and cardiac magnetic resonance imaging showed a structurally normal heart with no evidence of ventricular dysfunction.

Genetic testing (GeneDx, Gaithersburg MD, www.genedx.com) revealed a *de novo* mutation in the KCNJ2 gene, D71N. This was described as likely pathogenic for both CPVT and LTQ7/ATS. In addition, the CPVT panel showed a G552W mutation in the SCN5A gene determined as a variation of uncertain significance (VUS).

After an inpatient investigative evaluation, sotalol was trialled with a maximum administered dose of 150 mg/m^2/day with no effect. We had initiated Sotalol for its combined beta blockage and Class III effects and monitored the QTc closely while on the medication. A significant reduction in VE from 40% to under 10% was obtained with a combination of propafenone (300 mg/m^2/day) and metoprolol (3 mg/kg/day) during the first admission. Close outpatient follow-up at 8–12 week intervals was performed, and the burden of ectopy on Holter monitoring progressively increased to up to 40% despite increasing doses of both medications. The patient was not experiencing any symptoms at this point; however, due to the long-term effects of VE on ventricular function we were attempting to reduce this burden to under 10%. Nine months later she was readmitted, and propafenone and metoprolol were stopped. She was then started on flecainide and nadolol both of which were titrated to achieve a discharge dose of flecainide (4 mg/kg/day) and nadolol (0.75 mg/kg/day) with a marked reduction in ectopy burden to 3%.

As she was clinically asymptomatic and had no phenotypic evidence of CPVT, no restrictions to her physical activity were imposed, and she was counselled as being a relatively low risk for SCD. She continues to do well and remains asymptomatic on close outpatient follow-up. Her most recent ECG showed a QTc of 472 ms, a normal echocardiogram, and a 24 h Holter with a VE burden of 1.8%. Most of the recorded ectopy occurs as single PVCs with a few couplets and triplets and one 5 beat run of slow VT at 128 b.p.m. A recent exercise stress test showed no increase in ectopy from baseline during exercise. Electrocardiograms performed on immediate family members (parents and siblings) were normal. Further variant specific gene testing was performed, and the KCNJ2 mutation was negative in all immediate family members. However, the SCN5A variant was present in the father.

Discussion

This case presents some useful insights into the management of inherited arrhythmia disorders. First, it highlights the need to practice careful consideration when interpreting results of genetic testing for arrhythmia syndromes. Next, it reinforces the need for attentive clinical evaluation of the patient to determine the significance of genetic variances. In the above case, D71N was clinically pathogenic for ATS, but not for clinical CPVT.

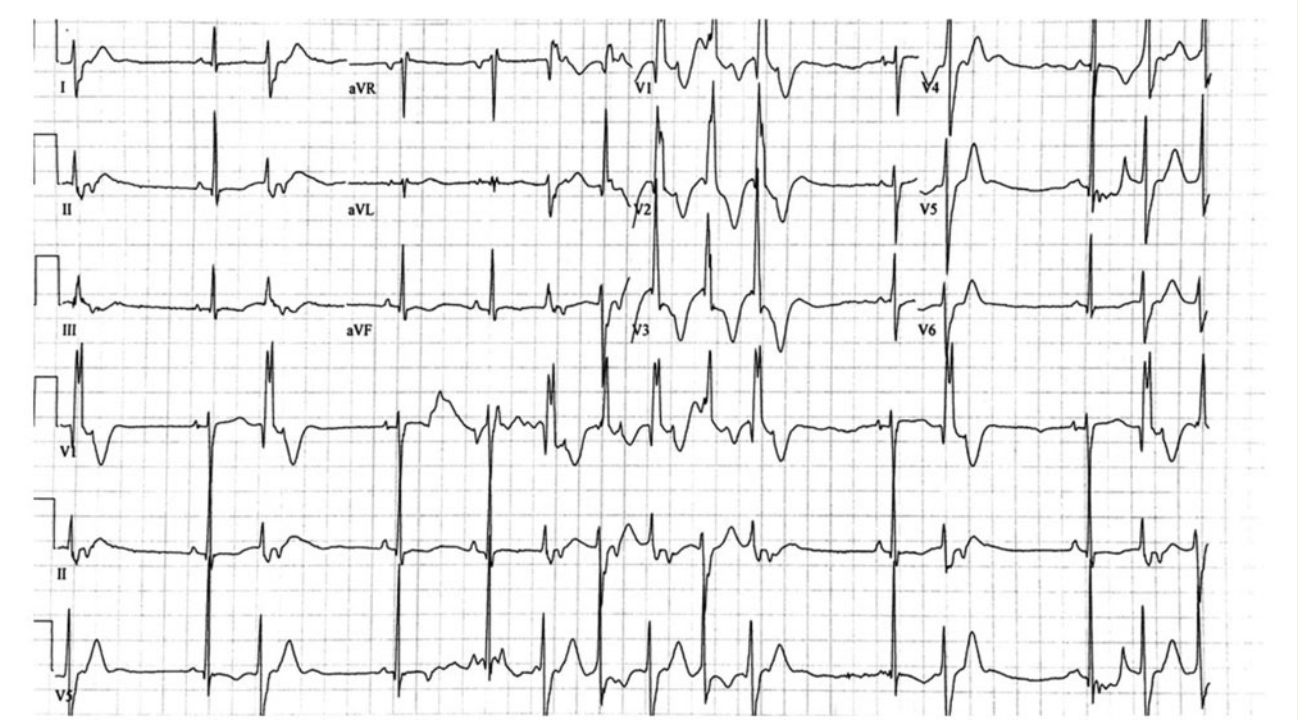

Figure 1 Presenting electrocardiogram showing a prolonged QTc at 485 ms and short runs of bidirectional ventricular tachycardia (evident in rhythm strip in lead II).

Figure 2 Patient frontal view and profile displaying some facial features of Andersen–Tawil syndrome.

The clinical distinction between ATS and CPVT can be a challenge. Catecholaminergic polymorphic ventricular tachycardia is an inherited arrhythmia disorder distinguished by life-threatening ventricular tachycardia and ventricular fibrillation induced by emotional or physical stress.[3] Catecholaminergic polymorphic ventricular tachycardia is classically caused by mutations in the RYR2 and CASQ2 genes but has recently been associated with KCNJ2 mutations and labelled as CPVT3.[1] Others have reported cases in which ATS displays 'phenotypic mimicry' of CPVT in which patients exhibit bidirectional VT and exercise-induced arrhythmias.[4] Kalscheur *et al.*[5] have acknowledged the controversy whether to label these cases as mimicry or true CPVT and pushed to create better definitions of these syndromes. This distinction is important because patients with the CPVT phenotype are at risk for sudden cardiac events, and a left sympathetic denervation should be considered as a treatment option. Contrastingly, ectopy in ATS is abundant but rarely degenerates into a fatal arrhythmia.

The increasing availability of genetic testing makes it simple for physicians to verify diagnosis for many inherited disorders. However, genotype reports may not always provide a clear answer. In the above case, our patient was reported to have a likely pathogenic D71N mutation in the KCNJ2 gene for ATS in keeping with the dysmorphic features and asymptomatic VT. This mutation was likely sporadic although the syndactyly in her mother and grandmother raises the possibility of gonadic mosaicism. The pathogenic mutation reported in the CPVT panel were not clinically significant for CPVT as her arrhythmia was suppressed rather than exacerbated on exercise. The G552W VUS in the SCN5A gene, also noted in her father was clinically non-significant in this patient. Van Ert *et al.* also advocate for using caution when interpreting genetic test results in inherited arrhythmia syndromes. Their case confirmed the R218L mutation in the KCNJ2 gene as pathogenic for ATS despite initial categorization as a VUS.[2] The authors recognize that their current interpretation may be limited by the young age of the patient who may with age develop clinical CPVT. Although initial presentation of CPVT occurs in childhood and adolescence, it has been reported to present in the 4th decade of life.[3]

Unrefined categorization and overlapping of symptoms between ATS and CPVT creates a problem for physicians dealing with

inherited arrhythmia disorders. In such cases of overlapping symptoms, Kalscheur *et al.* have concluded that it is best to manage and treat as clinical CPVT.[5] Studies by Barajas-Martinez *et al.*[1] and Van Ert *et al.*[2] support the effectiveness of flecainide therapy in this approach after failure of beta-blocker therapy.

In summary, genetic testing for a 9-year-old female patient with abundant polymorphic VT and long QTc resulted in a likely pathogenic variant for both ATS and CPVT from the same D71N mutation in the KCNJ2 gene. Further evaluation of this patient revealed no clinical CPVT, further emphasizing the need for cautious interpretation of genetic results in inherited arrhythmia disorders.

Consent: The author/s confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient's next of kin in line with COPE guidelines.

Conflict of interest: none declared.

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