Sudden cardiac death in Andersen–Tawil syndrome

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Andersen–Tawil syndrome (ATS) is an autosomal dominant or sporadic disorder characterized by periodic paralysis, dysmorphic features, and ventricular arrhythmias. Although ventricular tachycardia burden is quite high sudden cardiac death in ATS is rare. We describe a case with sudden cardiac death due to electrical storm a few days after ICD implantation in KCNJ2 mutation-negative ATS.

KEYWORDS
Cardiac arrest; Bidirectional ventricular tachycardia; Polymorphic ventricular tachycardia; Genetic disorder; KCNJ2 mutation-negative

Andersen–Tawil Syndrome (ATS) is a heterogeneous autosomal dominant or sporadic disorder characterized by the clinical triad of periodic paralysis, dysmorphic features, and ventricular arrhythmias.1,2 While mutations in KCNJ2 account for the majority of ATS cases, ~35% of patients with the ATS phenotype are KCNJ2 mutation-negative.1 Electrocardiographic manifestations of ATS include mild QTc prolongation, pronounced QUC prolongation, and prominent U-waves in KCNJ2 mutation-positive cases.3,4 Ventricular ectopy is a common finding and includes frequent premature ventricular complexes (PVCs), bigeminy, polymorphic ventricular tachycardia (VT), and bidirectional VT.1,3,5 Tachycardia burden is quite large in some ATS individuals,6 with >50% of beats documented to be ventricular in origin. Despite a large tachycardia burden, most ATS patients are remarkably asymptomatic and sudden cardiac death is exceedingly rare.1 Moreover, a family history of sudden cardiac death is rarely described.5 Here, we describe the clinical characteristics of an individual with KCNJ2 mutation-negative ATS who presented with severe life-threatening ventricular arrhythmias and ultimately expired despite ICD implantation.

Case report
A 48-year-old male with a past medical history of schizophrenia presented to a local emergency department with pre-syncopal symptoms and ECG documentation of spontaneous polymorphic ventricular ectopy and bidirectional VT at a rate of 135 bpm after development of periodic facial paralysis (Figure 1 A and B).

After intravenous administration of 300 mg amiodarone, the patient developed rapid monomorphic VT (Figure 1C) associated with circulatory collapse. This rhythm degenerated into ventricular flutter that spontaneously converted into polymorphic VT. Ultimately, the polymorphic VT converted to bidirectional VT (Figure 1D) with stabilization of the patient’s haemodynamic status. Subsequently, the bidirectional VT spontaneously reverted to sinus rhythm, and the patient was referred to our institution for further evaluation and management.

The patient was receiving amisulprid 200 mg once daily for treatment of his schizophrenia. Standard ECG revealed QTc interval prolongation without T-wave abnormalities or prominent U-waves on this medication, measuring 520 ms (Figure 1E). Following discontinuation of amisulprid, the QTc shortened to 350–370 ms (Figure 1F). Despite beta-blockade therapy, the patient continued to have frequent ventricular bigeminy, polymorphic VT, and bidirectional VT related to episodes of periodic facial paralysis. Family history of the patient was uneventful. Transthoracic echocardiography confirmed a structurally and functionally normal heart. Coronary angiography was normal. An ajmaline challenge was performed, but did not elicit coved ST segment elevation and right bundle branch block pattern in right precordial leads typical of Brugada syndrome. Bicycle stress test did not reveal...
exercise-induced bidirectional VT, thus ruling out catecholaminergic polymorphic VT. Serum electrolyte levels were normal with and without episodes of periodic facial paralysis.

The diagnosis of ATS was suggested by episodes of periodic paralysis of the facial musculature. Furthermore, the patient demonstrated evidence of mild dysmorphic features that included hypertelorism, thoracic scoliosis, and clinodactyly of the left fifth finger. Molecular genetic analysis was performed at the University Hospital of Münster, Germany. Direct sequencing of KCNJ2 revealed no evidence for any sequence variation. Furthermore, no mutations were detected in other genes known to cause LQT syndrome, including KCNQ1, KCNH2, and SCN5A.

On the basis of the initial resuscitation and recurrent episodes of ventricular arrhythmias an ICD (Medtronic, Marquis DR, Minneapolis, MN, USA) was implanted. Programming included a VT zone at 171 bpm and ventricular fibrillation zone at 200 bpm. Within 8 days of ICD implantation, the patient developed recurrent syncope and 6 ICD discharges as an outpatient. He was evaluated at an outside emergency department, where he was noted to be haemodynamically stable despite polymorphic VT at a rate of 250 bpm (Figure 2). Without knowledge of his previous medical history, 200 mg intravenous amiodarone was administered which resulted in haemodynamic instability requiring cardiopulmonary resuscitation. The patient was transported to our institution, where he received multiple cardioversion attempts, intravenous magnesium boluses, and intravenous short acting beta-blockers. Following 3 h of resuscitation efforts, the patient ultimately expired while in a rhythm consistent with electromechanical dissociation. Stored electrograms of the ICD showed rapid polymorphic VT’s with an RR interval of 250–270 ms and short efficacy of each defibrillation shock with spontaneously recurrent VT.

Discussion

Andersen–Tawil syndrome is a rare disorder and as such, relatively little is known regarding the natural history of cardiac disease. Ventricular ectopy is a common cardiac manifestation of ATS, including frequent PVCs, ventricular bigeminy, and non-sustained polymorphic and bidirectional VT. Although tachycardia burden may be large in some individuals with ATS, life-threatening arrhythmias are uncommon and sudden death is rare.3,4 The individual reported here warrants careful review and consideration in light of his ultimate demise from uncontrollable ventricular arrhythmias.

Mutations in KCNJ2 account for the majority of ATS cases.5 KCNJ2 encodes the Kir2.1 channel which is the major component of the inward rectifier K⁺ current, Iₖ₁. A reduction in Kir2.1, caused by transfection of dominant-negative constructs, induces spontaneous electrical activity in normally quiescent ventricular myocytes.7,8 In silico reduction of Iₖ₁ causes prolongation of the most terminal portion of the cardiac action potential and induces spontaneous depolarizations triggered by forward mode of the Na⁺/Ca²⁺ exchanger.3,9 The molecular basis for KCNJ2-mutation negative ATS is not known. However, KCNJ2 mutation-negative ATS patients are phenotypically indistinguishable from mutation-positive individuals with respect to periodic paralysis, cardiac arrhythmias, and skeletal dysmorphisms.1 This suggests that mutation-negative patients harbour a mutation in a gene that ultimately results in reduced function of Kir2.1 or Iₖ₁ channels.

Complicating this patient’s history was the treatment of his schizophrenia with amisulpride. QTc prolongation in the setting of amisulpride toxicity10–12 and dose-dependent QTc prolongation, torsade de pointes, and lethal ventricular fibrillation13 have been described.

A genetic predisposition has long been proposed as a risk factor for acquired LQTS.14 The current patient’s predisposition to acquired LQTS was not due to a mutation or rare polymorphism in the common genes that cause inherited LQTS, as this was excluded by molecular genetic analysis. We cannot fully discount the possibility that he harboured a mutation or polymorphism in an as-of-yet unidentified LQTS gene (at most 5–10%). However, we propose that the predisposition to acquired LQTS was exacerbated by KCNJ2.
mutation-negative ATS. Indeed, simulations of ATS mutations in virtual ventricular tissue indicate that the contribution of \( I_{Kr} \) to phase 3 repolarization increases substantially in the setting of reduced \( I_{K1} \). Thus, ATS patients may be particularly susceptible to changes in \( I_{Kr} \), given the baseline reduced repolarization reserve and the dependence upon \( I_{Kr} \) as a substitute for reduced \( I_{K1} \).

In addition to amisulpride, the patient received intravenous amiodarone, which is also reported to prolong QTc. However, unlike many QTc-prolonging agents, amiodarone is rarely torsadogenic primarily due to its propensity to block multiple channels resulting in reduced transmural dispersion of repolarization. This may be less predictable in ATS patients with \( K^+ \) channel dysfunction. We suggest that the pro-arrhythmic effect of amiodarone was related, in part, to an underlying reduced repolarization reserve as a consequence of ATS. It remains unclear, why the patient subsequently developed rapid polymorphic VT while off amisulpride that was refractory to internal and external cardioversion.

The use of ICD secondary prevention in ATS population has not been systematically assessed, primarily due to the rarity of catastrophic events in this disease. The frequent yet asymptomatic VT typical of ATS evokes the question of optimal programming strategy. We believe that ICD implantation was indicated in this patient with syncope and documented VT. Ventricular tachycardia detection zone set at 171 bpm should have been sufficient to avoid repeated ICD discharges given that the rate of bidirectional VT was <150 bpm. Yet, the patient developed an electrical storm and was not stabilized (or worsened) by amiodarone and recurrent defibrillation attempts.

In summary, ATS is a rare channelopathy that complicates our understanding of the natural history of ventricular arrhythmias. Although ATS subjects are predisposed to ventricular arrhythmias, these arrhythmias rarely degenerate...
into lethal ventricular fibrillation. The clinical course in this patient was likely affected by the use of pharmacological agents that prolong QTc. Although clearly part of the recommendations in patients with LQTS, the avoidance of agents that lengthen repolarization has not become a routine recommendation in ATS patients. In light of the lethal clinical course of the patient reported here, we recommend against the use of any QTc-prolonging medication and urge extreme caution in treating ventricular arrhythmias in patients with documented or suspected ATS.

References