

Atrial pacing for the management of ventricular arrhythmias in Andersen-Tawil syndrome



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Introduction

Andersen-Tawil syndrome (ATS) is a rare autosomal dominant or sporadic disorder defined by a triad of periodic muscle paralysis, ventricular arrhythmias (long QT-7), and dysmorphic features. The estimated prevalence is 1 in 1,000,000.^{1,2} The underlying mutation is in the *KCNJ2* gene encoding the inward rectifier potassium channels (Kir2.1) present in both skeletal and cardiac muscles. About 80%–90% of ATS cases have an identified *KCNJ2* mutation, and these cases are classified as ATS1, with the rest designated ATS2.¹ The clinical phenotype of the cardiac presentation is varied, ranging from prolonged QT interval, prominent U wave, and premature ventricular complexes (PVCs) to bidirectional ventricular tachycardia and, rarely, ventricular fibrillation or sudden cardiac death (SCD). Ventricular arrhythmias are precipitated by adrenergic stimuli like exercise or intense emotion, which accounts for the use of beta-blockers as standard therapy.³ We present a case of ATS with ventricular arrhythmias not responsive to different antiarrhythmics including beta-blockers and managed successfully with atrial pacing.

Case report

A 58-year-old white woman with a lifelong history of hyperkalemic periodic muscle paralysis and bidirectional ventricular tachycardia diagnosed 50 years prior presented to the clinic for follow-up of symptomatic PVCs. She had no known history of coronary artery disease. She had been treated with sequential monotherapy of multiple antiarrhythmic agents, including quinidine, mexiletene, dronedarone, and propranolol, without significant suppression of PVCs.

KEYWORDS Andersen-Tawil syndrome; Atrial pacing; Electrophysiology; Implantable cardioverter-defibrillator; Long QT syndrome; Ventricular arrhythmia

ABBREVIATIONS ATS = Andersen-Tawil syndrome; ECG = electrocardiogram; PVC = premature ventricular complex; QT_c = corrected QT interval; SCD = sudden cardiac death
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A single-chamber implantable cardioverter-defibrillator was implanted for recurrent syncope with prolonged corrected QT (QT_c) interval noted on electrocardiogram (ECG) and nonsustained runs of ventricular tachycardia noted on ambulatory monitoring. She was on acetazolamide for control of periodic paralysis. There was no family history of SCD or periodic muscle paralysis. Physical examination was significant for a regularly irregular cardiac rhythm and the presence of dysmorphic features—microcephaly, facial asymmetry, thin helices, pinched nose, small alae nose, thin upper lip, small fingers, fifth finger clinodactyly bilaterally, small feet, and 2-3 toe syndactyly bilaterally. ECG showed frequent PVCs in a bigeminy pattern and a QT_c of 535 ms, as shown in Figure 1. A PVC burden of 35,000 per day was noted on Holter monitoring. Electrophysiology testing showed that the focus of the PVCs was at the base of the papillary muscles. The patient underwent 2 PVC ablations but had recurrence of different PVC morphologies. She continued to remain symptomatic.

Owing to the presence of the typical triad, there was a suspicion of ATS. Subsequent genetic testing confirmed she was a heterozygote for the *KCNJ2* gene mutation *C.407C>T, P.S136F*. Ventricular arrhythmias had not been responsive to multiple antiarrhythmic agents or PVC ablation. On electrophysiology testing, vagal stimuli slowed the sinus rate and allowed the abnormal rhythm to take over while atropine promoted normal sinus rhythm. A recent case report from Japan indicated that atrial pacing was successful in reducing PVC burden after findings of increased PVC frequency after meals or during sleep, suggesting PVCs were vagal-dependent.⁴ Therefore, an atrial lead was implanted in our patient to provide continuous overdrive pacing at 80 beats per minute. There was a reduction in the PVC burden in the postoperative period. One year later, she continues to have a low PVC burden (24 per day), normalized QT_c of 385 ms, absent PVCs on ECG (Figure 2), and improvement in quality of life.

Discussion

There are no randomized clinical trials that have evaluated the efficacy of current management strategies for ventricular

KEY TEACHING POINTS

- Andersen-Tawil syndrome is a differential diagnosis of bidirectional ventricular tachycardia. In the clinical setting of ventricular arrhythmias since childhood, periodic muscle paralysis, and dysmorphic features, the diagnosis of Andersen-Tawil syndrome should be considered.
- The first-line therapy of ventricular arrhythmias due to Andersen-Tawil syndrome is beta-blockers, along with avoidance of QT-prolonging medications.
- Atrial pacing at a higher rate than the intrinsic pacemaker stimulus is a consideration for management of ventricular arrhythmias resistant to first-line therapy.

arrhythmias in ATS owing to extremely low incidence. Fortunately, compared to other long QT syndromes or catecholaminergic polymorphic ventricular tachycardia, the occurrence of malignant tachyarrhythmias is relatively uncommon in ATS.¹ Although most patients are asymptomatic from the PVCs, those who are symptomatic experience a reduction in quality of life, like our patient. There is also the risk of tachycardia-induced cardiomyopathy, hence the need to control ventricular arrhythmias.⁵

One of the key management principles is to avoid QT-prolonging medications that can precipitate torsades. Intense adrenergic stimuli can sometimes precipitate an episode of arrhythmia, which accounts for the use of beta-blockers

(usually propranolol) as first-line treatment based on consensus.³ Beta-blockers are not always successful in reducing ventricular arrhythmias. There are reports of cases where arrhythmias are insensitive to catecholamines and were suppressed during periods of intense activity, such as exercise.⁶ Other medications including calcium-channel blockers, flecainide, and amiodarone have been used in a few cases, with varying success rates.^{3,7,9} A unique combination of flecainide and verapamil was found to be successful in a single case study by Janson et al.¹⁰ SCD is rare but has been reported.^{4,11} For this reason, the implantation of an implantable cardioverter-defibrillator may be considered for prevention of SCD in patients at high risk.^{1,11} However, there are no guidelines available for identifying these high-risk cases. The index case presented had failed 2 episodes of PVC ablation. Similarly, a retrospective French study did not find any benefit for ablation in patients with confirmed KCNJ2 mutation.¹²

Overdrive pacing in long QT syndromes (not ATS specifically) has been around for many years but is not well defined.¹³ There is no clear indication whether it should be considered for all symptomatic long QT syndrome patients or restricted to only those who have failed beta-blocker therapy. Similarly, the effectiveness of overdrive pacing in all genotypes of long QT syndrome is unknown, as available studies did not look at pacing effectiveness by genotype.¹⁴ Viskin et al¹⁵ in 2000 carried out an extensive review on cardiac pacing in this patient population and suggested that genotypes 2 and 3 were more likely to benefit from pacing, but cautioned that the absence of evidence of the efficacy of pacing in other genotypes should not be taken as evidence of

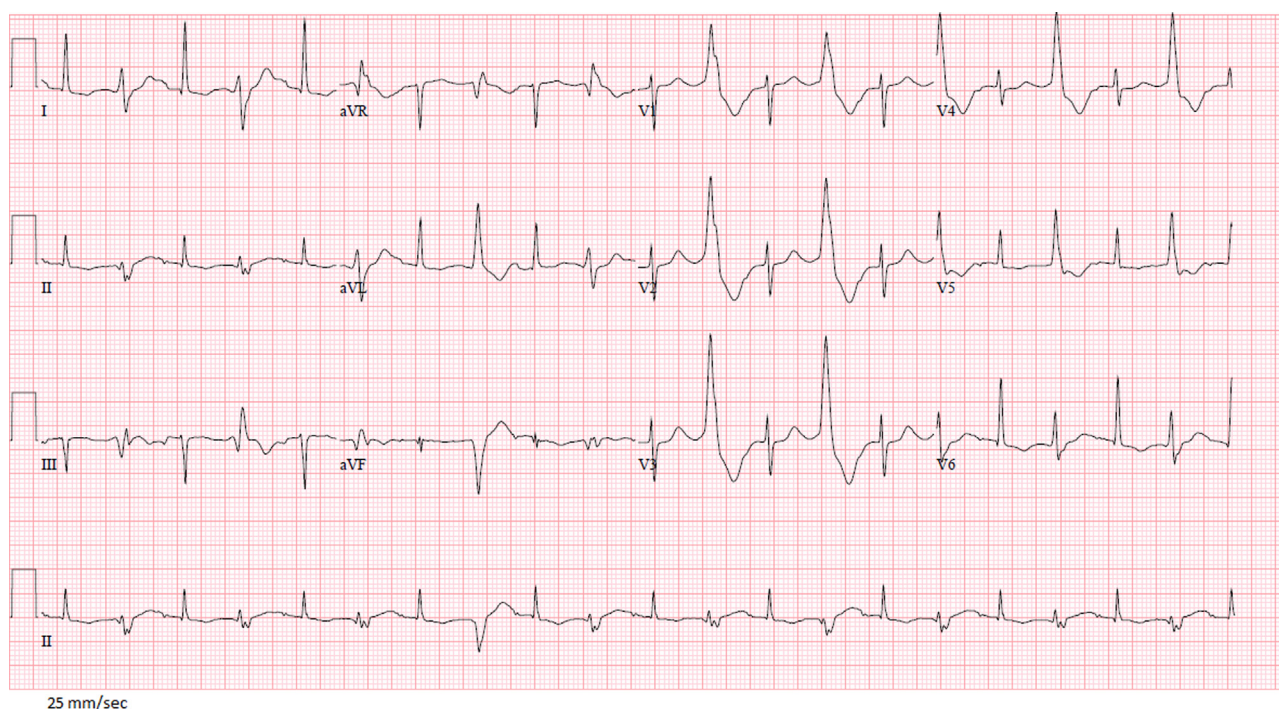


Figure 1 Resting 12-lead electrocardiogram at age 59 years (prior to atrial pacing) showing premature ventricular complexes in a bigeminy pattern with prolonged QT_c of 535 ms.

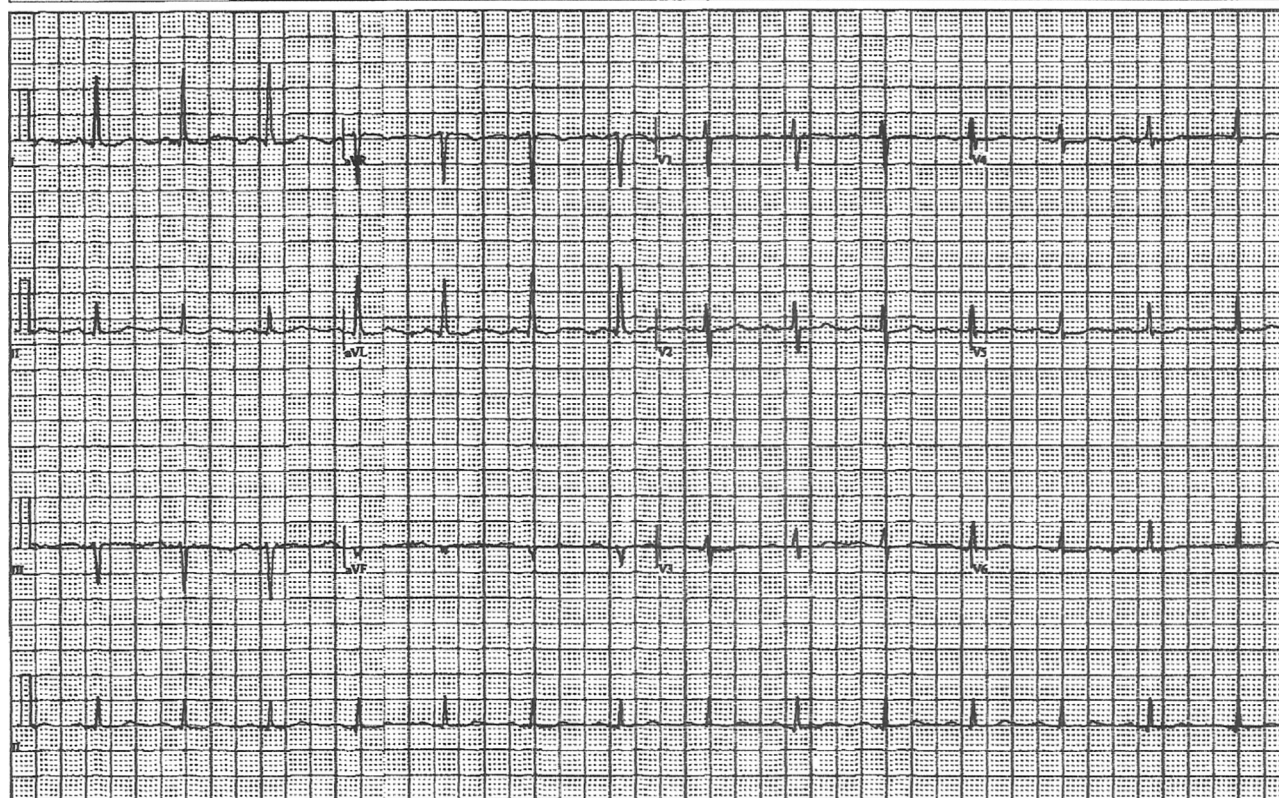


Figure 2 Resting 12-lead electrocardiogram a year post-pacing showing normalization of corrected QT interval (385 ms) and absence of premature ventricular complexes.

nonbenefit. The optimum pacing rate in long QT syndrome is unknown, although 80 beats per minutes is usually selected based on observational studies.¹³ However, this does not preclude the use of faster rates in patients who continue to have arrhythmias at a paced rate of 80 beats per minute.

This is the second case report, to our knowledge, that shows that atrial overdrive pacing may control ventricular arrhythmias in ATS. This was first reported by Kuramoto et al⁴ in 2012, when they found their patient had an increased frequency of PVCs and ventricular tachycardia during periods of increased vagal stimuli. Her paced rate was increased to 70 beats per minute, which subsequently decreased the frequency of PVCs and ventricular arrhythmias. In our patient, following the placement of an atrial lead and pacing at 80 beats per minute, her PVC burden decreased and there was subsequent improvement in symptoms and quality of life. Symptom improvement has persisted for greater than 15 months.

Conclusion

This report identifies the second case of ATS with confirmed *KCNJ2* mutation whose ventricular arrhythmias were successfully managed with atrial pacing. We propose that further studies are necessary to confirm findings, but that atrial overdrive pacing combined with beta-blockers should be considered in ATS patients with symptomatic tachyarrhythmias.

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