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ATYPICAL PRESENTATION OF ANDERSEN-TAWIL SYNDROME: HEART FAILURE WITH REDUCED EJECTION WITHOUT PERIODIC PARALYSIS OR DYSMORPHIC FEATURES

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ABSTRACT

Background: Andersen-Tawil syndrome (ATS) is a rare autosomal dominant disorder caused by variants in the *KCNJ2* gene. It is associated with periodic paralysis, dysmorphic features and cardiac arrhythmias. The syndrome exhibits incomplete penetrance, leading to a broad spectrum of clinical manifestations, making diagnosis challenging.

Case description: A male in his mid-20s with class 3 obesity presented to the emergency department with a week-long history of worsening chest pain, orthopnoea and fatigue. His family history was significant for sudden cardiac death affecting both his mother and brother, with his father having died from complications of Wolff-Parkinson-White syndrome. Cardiovascular examination revealed an S3 heart sound and elevated brain natriuretic peptide levels at 875 pg/ml, with undetectable troponins; potassium level on admission was 3.6 mEq/l. An electrocardiogram showed normal sinus rhythm, first-degree heart block, left atrial enlargement, left bundle branch block and a prolonged QTc of 486 ms. A transthoracic echocardiogram demonstrated a 15-20% reduction in ejection fraction with global left ventricular hypokinesis and left atrial enlargement. Ultimately, he was diagnosed with non-ischaemic dilated cardiomyopathy and referred for genetic testing, which revealed a *KCNJ2* variant. Shortly after discharge, he experienced a 55-second run of ventricular tachycardia, necessitating the placement of a single-chamber ICD. Currently, the patient remains on guideline-directed medical therapy and is listed for a heart transplant.

Conclusions: Dilated cardiomyopathy, although a rare manifestation in ATS, can profoundly increase the risk of fatal arrythmias, necessitating the need for a low threshold of suspicion, to ensure timely diagnosis and management.

KEYWORDS

Andersen-Tawil syndrome, long QT syndrome, *KCNJ2*, periodic paralysis

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LEARNING POINTS

- Andersen-Tawil syndrome (ATS) can present with heart failure with reduced ejection fraction, even without the typical triad of periodic paralysis, dysmorphic features and arrhythmias. Early genetic testing is essential for confirming ATS, especially in atypical cases with unexplained heart failure or arrhythmias.
- ATS has incomplete penetrance so it may present without the typical features, making diagnosis challenging and requiring a high suspicion in cases with unexplained arrhythmias or family history of sudden cardiac death.

INTRODUCTION

Long QT syndrome (LQTS) is the most common inherited arrhythmia, with an estimated incidence of at least 1:2000 live births[1]. Since the discovery of the genes underlying LQTS in 1995, over the years a total of 17 genes have been implicated in the aetiology of LQTS, coding for various ion channels governing depolarisation and repolarisation of the cardiac myocytes[1]. Anderson Tawil syndrome type 1 (also termed LQTS 7) is a genetic disorder characterised by loss-of-function variants in *KCNJ2*, the gene coding the strong inward-rectifier potassium channel Kir2.1, which forms an essential membrane protein controlling cardiac excitability[1]. It is an autosomal dominant disorder with incomplete penetrance. ATS is exceedingly rare, with a prevalence of 1 per 1,000,000 live births[1]. There are at least two phenotypes related to this disorder. ATS type 1 is inherited in an autosomal dominant pattern and is caused by variants in the *KCNJ2* gene which encode the alpha subunit of the K channel protein Kir2.1. ATS type 2 is linked to a rare variant in the *KCNJ5-GIRK4* gene that encodes the G protein-sensitive-activated inwardly rectifying K channel Kir3.4. ATS is usually marked by a triad of periodic paralysis, life-threatening cardiac arrhythmias and dysmorphic features, but its expression is variable and not all patients with a phenotype linked to ATS have a known genetic alteration[1].
This report discusses a young male with a confirmed *KCNJ2* variant who presented with heart failure with reduced ejection fraction (HFrEF), a manifestation not commonly associated with ATS, prompting an exploration of potential mechanisms and clinical implications.

CASE DESCRIPTION

A male in his mid-20s with a history of class 3 obesity presented to the emergency department with a week-long history of gradually worsening chest pain, orthopnoea, shortness of breath and fatigue. He was unable to climb a single flight of stairs. Additionally, he experienced two episodes of nocturnal awakening due to chest pressure and one episode of non-exertional syncope. He did not any history of periodic paralysis. The patient's family history was notable for sudden cardiac death (SCD) with both his mother and brother dying in their early 40s and late 20s, respectively, while his father had passed away from complications of Wolff-Parkinson-White (WPW) syndrome in his late 50s.
On examination, the patient appeared anxious but afebrile. His vitals were: blood pressure 129/85 mmHg, heart rate 97 beats/min, respiratory rate 14 breaths/min and oxygen saturation 97% on room air. Cardiovascular examination revealed an S3 heart sound but no lower extremity oedema; the rest of his physical exam was unremarkable. No dysmorphic features were appreciated. Initial laboratory results showed mild leukocytosis and transaminitis, with otherwise normal complete blood count and comprehensive metabolic panel. His serum potassium was 3.6 mEq/l on admission. A urine drug screen was negative, and thyroid stimulating hormone levels were normal. Brain natriuretic peptide was elevated at 875 pg/ml, but troponins were undetectable. An electrocardiogram indicated normal sinus rhythm, first-degree heart block, left atrial enlargement, left bundle branch block and a corrected QT interval (QTc) of 486 ms *(Fig. 1)*. No prior electrocardiogram was

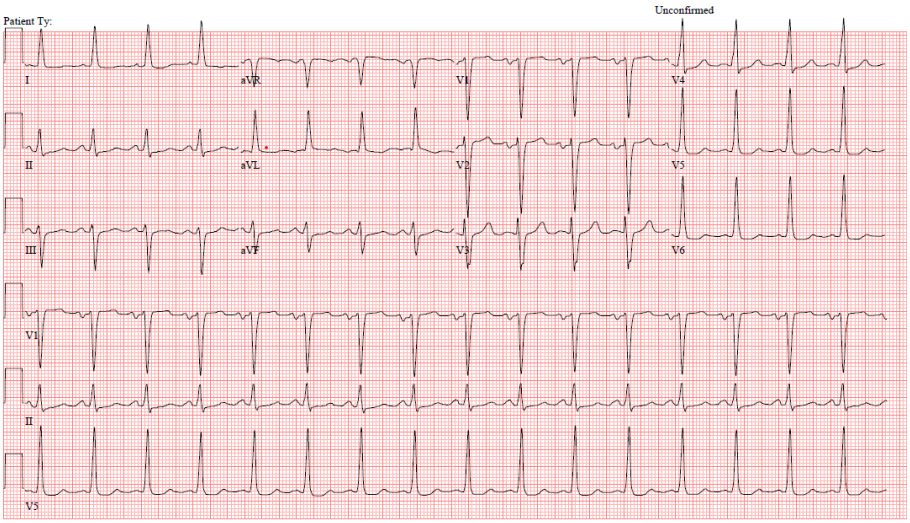


Figure 1. Electrocardiogram showing normal sinus rhythm, first-degree heart block, left bundle branch block and QTc of 486 ms.

available for comparison. Chest X-rays (posterior-anterior and lateral views) revealed pulmonary venous congestion and cardiomegaly *(Fig. 2)*. A transthoracic echocardiogram showed an ejection fraction of 15-20%, global hypokinesis of the left ventricle and left atrial enlargement *(Fig. 3)*.

The patient was started on furosemide and guideline-directed medical therapy for heart failure (HF). Due to his body habitus, cardiac computed tomography angiography was deemed unsuitable. Right and left heart catheterisation was performed the following day; left heart catheterisation revealed patent coronaries but an elevated left ventricular end-diastolic pressure. Right heart catheterisation, on the other hand, could not be completed due to a Swan-Ganz catheter malfunction. The patient was diagnosed with NYHA (New York heart association) class II, stage C, non-ischaemic HFrEF, likely due to familial cardiomyopathy. Before discharge, he was fitted with a LifeVest®, scheduled for an HF clinic follow-up and referred for a comprehensive genetic panel evaluating 168 genes linked to arrhythmias, cardiomyopathies and sudden unexpected death in epilepsy. The patient underwent a cardiac MRI, which revealed a severely dilated left ventricle (iLVEDV 186 ml/m^2), a right ventricle at the upper limits of normal (iRVEDV 105 ml/m^2) and a severely dilated left atrium *(Fig. 4)*. Left ventricle systolic function was severely reduced (Left ventricular ejection fraction of 22%), as was the right ventricular systolic function (RVEF 27%). Global severe hypokinesis was noted, with mid-myocardial hyperenhancement in the basal anteroseptum suggestive of a mid-myocardial scar. Cardiac MRI findings were consistent with severely dilated non-ischaemic cardiomyopathy with a mid-myocardial scar *(Fig. 4)*. Genetic testing revealed a *KCNJ2* c.23G>A (p.Arg8His) heterozygous variant.

Before his next follow-up, the patient experienced an episode of palpitations and shortness of breath, accompanied by his LifeVest® sounding an alarm. He managed to abort the shock, and the episode resolved spontaneously. Upon presenting to the nearest emergency department, a 55-second run of ventricular tachycardia was confirmed, as evidenced by a wide complex tachycardia strip from his LifeVest®. The patient was started on an amiodarone drip and referred for single-chamber implantable cardioverter-defibrillator (ICD) placement. The LifeVest® strip showed an intrinsicoid deflection greater than 100 milliseconds (from R to S) between 11 and 24 seconds, with significant artefacts appearing afterwards, after which the patient spontaneously converted to sinus rhythm *(Fig. 5)*.

Subsequently, he underwent single-chamber ICD placement under moderate sedation and was started on sotalol before discharge. A repeat echocardiogram conducted two months after ICD placement and sixteen months after his initial presentation revealed an improved left ventricular ejection fraction of 35%. Despite this improvement, the left ventricular cavity remained severely dilated with global hypokinesis. The left atrium also remained severely dilated, while the right ventricle and right atrium were moderately

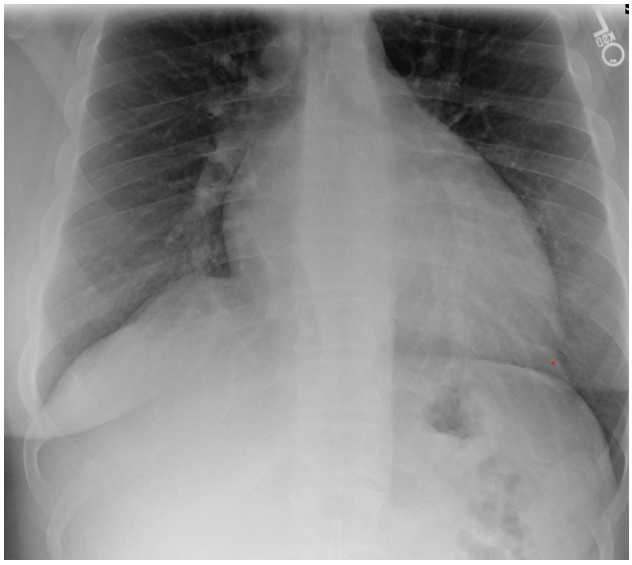


Figure 2. Chest X-ray (posterior-anterior) depicting pulmonary venous congestion and cardiomegaly.

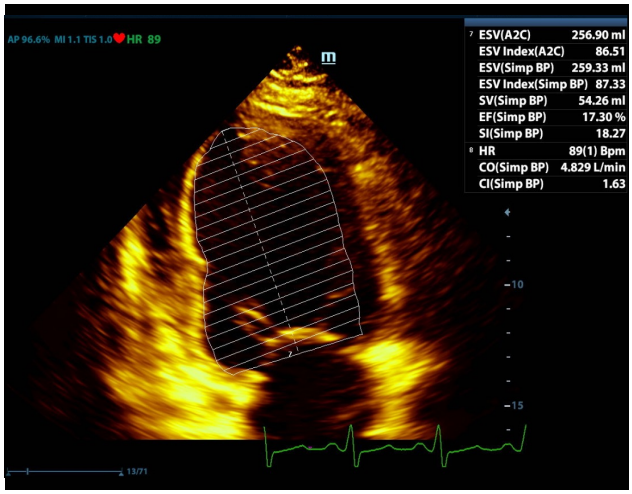


Figure 3. Transthoracic echocardiogram (apical view) showing an ejection fraction of 15-20% via Simpson's biplane rule, global hypokinesis of the left ventricle and left atrial enlargement.

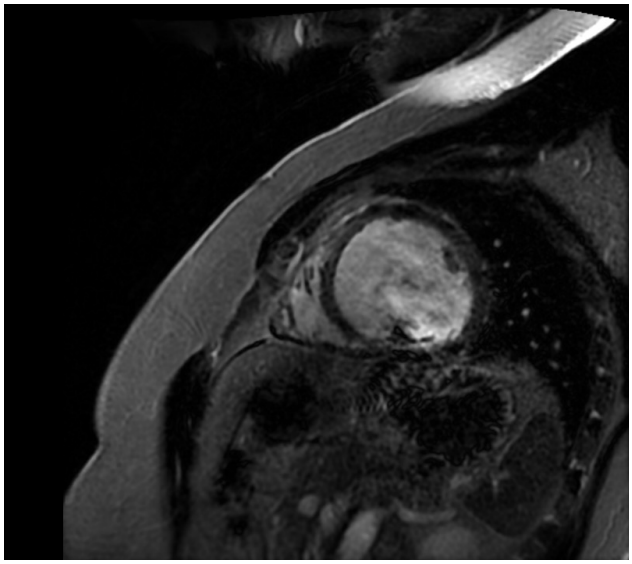


Figure 4. Cardiac MRI, which revealed a severely dilated left ventricle (iLVEDV 186 ml/m^2), a right ventricle at the upper limits of normal (iRVEDV 105 ml/m^2).

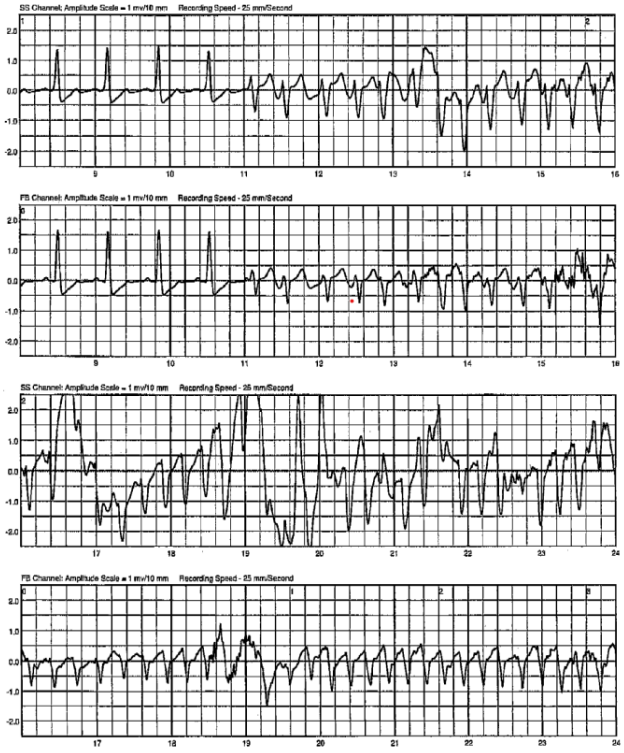


Figure 5. Holter monitor indicating a run of ventricular tachycardia.

dilated. Currently he remains on guideline-directed medical therapy, is attending cardiac rehabilitation and is on the waiting list for cardiac transplantation.

DISCUSSION

This case presents an unusual manifestation of ATS, characterised by severe HF without the typical triad of features generally associated with the disorder. ATS is an autosomal dominant condition caused by variants in the *KCNJ2* gene, which encodes the inward-rectifier potassium channel, Kir2.1. Incomplete penetrance is a hallmark of the syndrome, with only a portion of patients exhibiting the characteristic triad of periodic paralysis, dysmorphic features and cardiac arrhythmias[2]. Some patients may have isolated symptoms while others may remain asymptomatic, further complicating the diagnostic process.

Heart failure is not commonly associated with ATS, where arrhythmias and periodic paralysis tend to dominate the clinical picture. The presence of HF in this patient, despite the absence of secondary causes such as ischaemic heart disease, viral myocarditis, drugs or infiltrative cardiomyopathy, suggests the *KCNJ2* variant as the underlying pathology. Reports describing HF in ATS are exceedingly rare[3-4]. One case, reported by Schoonderwoerd et al. described a family in which both a patient and her mother, carriers of the *KCNJ2* variant, developed dilated cardiomyopathy, alongside dysmorphic features and polymorphic ventricular tachycardias[3]. Our patient's presentation with predominantly cardiac symptoms and a family history of SCD bears similarities; notably, however, he did not exhibit any other typical ATS features observed in previous cases.

In the few documented cases, the clinical picture is primarily dominated by ventricular arrhythmias and hallmark ATS features, with HF assuming a secondary role, often presenting years after an ATS diagnosis. In contrast, HF took centre stage in our patient's clinical presentation, with ATS diagnosed only after the clinical evaluation for HF. This may indicate a milder form of ATS in our patient, which would also account for the subtlety of typical manifestations, delaying the need for seeking medical care. Over time, the compounded effects of arrythmia and obesity likely contributed to the unmasking of the underlying pathology as HF. SCD is relatively rare in ATS compared to other types of LQTS[5]. Additionally, the patient's father had documented WPW syndrome, further complicating the clinical picture. WPW has only been rarely reported together with LQTS, with their co-existence attributed to an elevated risk of SCD. Unfortunately, confirmation of the same variant within the patient's family was not possible, as he was no longer in contact with them.

Variants in the *KCNJ2* gene, which codes for the Kir2.1 potassium channels, disrupts the inward-rectifier potassium current IK1, crucial for repolarisation and resting membrane potential. Disruption of this current leads to electrical instability, arrhythmias and possibly structural heart changes, contributing to cardiomyopathy and HF. Although several other ion channel variants have been linked to HF and dilated cardiomyopathy, a direct causal relationship between *KCNJ2* variants and HF is not fully established, as most ATS patients do not develop significant cardiomyopathy. It is hypothesised that in some cases, the variant may lead to progressive myocardial damage, as indicated by the myocardial scar observed in our patient, secondary to recurrent arrhythmic episodes. A previous animal model study demonstrated that arrhythmias precede cardiac remodelling and HF in LQTS[6]. The myocardial damage resulting from these factors may also significantly compound the risk of SCD, as ATS itself is not usually associated with SCD.

Management of ATS involves addressing both the cardiac and skeletal muscle manifestations of the disorder. Cardiac therapy focuses on controlling arrhythmias and reducing the QTc interval to prevent precipitation into torsades de pointes. ATS is associated with periodic paralysis in the literature; however, it is variably present. Potassium replacement can shorten the QTc interval, decreasing the risk of lethal arrythmias; however, supplementation can exacerbate skeletal muscle weakness. In patients with hypokalaemic periodic paralysis and ATS, significant treatment challenges exist. In hypokalaemic periodic paralysis, a drop in extracellular potassium levels can cause depolarisation of muscle cells, leading to muscle weakness or paralysis. Muscle cells rely on a high intracellular potassium concentration to maintain their resting membrane potential. During the periodic paralysis attacks, extracellular potassium levels drop, resulting in muscle cell depolarisation. Supplementing potassium repolarises muscle cells, relieving the paralysis. In ATS, the Kir2.1 potassium channels are defective, further

complicating normal homeostasis. Rapid correction of serum potassium can cause abnormal skeletal muscle excitability, worsening the paralysis. There is no consensus in the literature regarding treatment strategies for these patients. Our patient had an atypical presentation and had no history of periodic paralysis.

Long-term therapy with beta blockers is used for arrythmia control and reducing the risk of SCD. ICDs are recommended for high-risk patients for the prompt correction of serious life-threatening arrhythmias. Cardiac resynchronisation therapy may also be considered for patients with significant HF symptoms. Alongside medical management, regular follow-up and lifestyle adjustments are essential in managing the condition[2].

This report highlights an atypical presentation of ATS, marked by severe HF in the absence of classical features. The patient's presentation highlights the complex nature of ATS, where incomplete penetrance can obscure diagnosis. Our case contributes to the limited literature on ATS-related HF, emphasising the need for heightened clinical awareness and comprehensive management strategies. Considering the highly variable presentations of the syndrome, the threshold for suspicion should be kept low to ensure timely diagnosis and management.

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