Andersen–Tawil Syndrome: A Retrospective Analysis of Clinical and Electrocardiographic Characteristics

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ABSTRACT. Andersen–Tawil syndrome is an autosomal dominant, multisystem disorder characterized by periodic paralysis, dysmorphic features and cardiac arrhythmias. Mutations in the KCNJ2 gene, which encodes potassium channels, have been identified in individuals with Andersen–Tawil syndrome. These individuals can present with typical electrocardiographic findings that can prognosticate their tendency to develop lethal arrhythmias. However, literature on cardiac and clinical findings in this population is scarce. We analyzed the clinical characteristics, electrocardiographic patterns and the risk of potentially malignant cardiac arrhythmias in seven subjects with Andersen–Tawil syndrome. All patients reported episodes of palpitations. Forty-two percent had syncope or presyncope and 28% had a history of periodic paralysis. A family history of sudden death was present in 42.8%. Electrocardiogram analysis showed prominent U-waves in 57%. The mean QTc and QUc intervals were 432.7 ± 23.23 ms and 599.1 ± 83.82 ms, respectively. Exercise stress testing induced ventricular arrhythmias in all patients in the initial stages. The 24-h Holter monitoring showed frequent ventricular premature beats (85%) and episodes of non-sustained polymorphic or bidirectional ventricular tachycardia (71%). Patients with Andersen–Tawil syndrome have a significant clinical burden of ventricular arrhythmias that can progress to sudden cardiac death. The 24-h Holter monitoring and exercise stress test were highly efficient methods to detect the presence of potentially lethal ventricular arrhythmias and should be used in the diagnostic work-up of patients with Andersen–Tawil syndrome.

KEYWORDS. Andersen–Tawil syndrome, electrocardiographic interpretation, genetic disease, sudden cardiac death, ventricular arrhythmias.

Introduction
Andersen–Tawil syndrome (ATS) is an autosomal dominant, genetic or sporadic, multisystem disorder characterized by developmental, cardiac, and neuromuscular abnormalities.8 Although the first cases were reported in 1971 by Andersen and colleagues, the triad of cardinal clinical features (periodic paralysis, cardiac arrhythmias, and dysmorphic features) was first universally recognized in the 1990s.5 Mutations in the KCNJ2 gene, which encodes the α-subunit of the potassium channel Kir2.1, have been identified in patients with ATS.6 Currently, more than 20 mutations have been reported in the literature.7–12 The Kir2.1 potassium channel is responsible for the inward potassium rectifier current (IK1) during diastole.13–15 Disturbances during this phase of repolarization can result in significant arrhythmogenesis and potentially symptomatic
or life-threatening rhythms. However, KCNJ2 mutations are detectable in only 60% of patients with ATS making genetic screening limited as a universal diagnostic tool.\textsuperscript{10} The diagnosis of ATS remains elusive and sometimes difficult to distinguish from other primary electrical disorders.\textsuperscript{6}

Given the paucity of data in the literature, further studies are required to identify the clinical characteristics, electrocardiographic patterns, and risk of potentially malignant arrhythmias in ATS. In order to better define these distinctive features of ATS and enable earlier diagnosis, we conducted a retrospective standardized evaluation of seven subjects with clinically diagnosed ATS.

**Materials and methods**

**Study population**

Seven patients with ATS from a single academic center in Buenos Aires, Argentina, were included in the study. The clinical diagnosis of ATS was performed by the presence of at least two of the following criteria: 1) familial periodic paralysis; 2) characteristic facies, dental abnormalities, or small hands/feet, and at least two of low-set ears, widely spaced eyes, small mandible, fifth-digit clinodactyly, syndactyly; and 3) symptomatic cardiac arrhythmias or evidence from electrocardiograms (ECGs) of enlarged U-waves, ventricular ectopy, and prolonged QTc or QUc interval. Medical records of the patients were used to obtain demographics, and medical and treatment history. Patients were excluded from the study if they had any other known conditions that could cause the aforementioned ECG abnormalities or did not get a baseline ECG, exercise stress test and 24-h Holter monitoring. The study design was approved by the Ethics and Research Board at the Ramos Mejía Hospital in Argentina. All patients provided informed consent to participate in the study.

**Electrocardiographic analysis**

A 12-lead electrocardiogram (DM CARDIOSCAN Resting 12 Lead ECG 4.0, Beijing, China) at a paper speed of 25 mm/s was recorded at rest in the supine position during the patient’s first presentation prior to treatment. The RR, QT, and QU intervals were compared in all the patients. The T and U-waves were measured in the lead with the highest amplitude, usually in V2 or V3. The QT interval was measured from the onset of QRS to the end of the T-wave, at the point at which the T-wave down-slope crossed the isoelectric line.\textsuperscript{16} The U-wave was defined as an early diastolic deflection after the end of the T-wave.\textsuperscript{17} The QU interval (onset of QRS to the end of the U-wave) was also measured. The corrected QT and QU intervals (QTc and QUc) were calculated using Bazett’s formula and averaged from three consecutive sinus beats. The results were analyzed and calculated by two separate investigators.

**Exercise stress test**

All the patients underwent a uniform exercise protocol using a cycle ergometer. The initial phase consisted of 3 min of pedaling in an unloaded state followed by a ramp protocol involving an increasing work rate to maximal exercise. This was also conducted once during initial investigation prior to treatment.

**24-h Holter monitoring**

Holter monitor studies were performed for 24 h with a three-channel device (DM CARDIOSCAN II Premier 12.0). Similar to other investigations, the Holter monitoring was conducted once prior to treatment.

**Treatment and follow-up**

All patients were treated as per current standard of care by their clinician. All patients were followed up regularly as per their clinician’s judgment. Patients’ symptoms, medications, and any changes were recorded at each visit.

**Results**

**Clinical characteristics**

The average age at enrolment was 21 years. Four participants were female, the remaining three were male. All seven patients reported episodes of palpitations, while three of them associated it with presyncope or syncope (42.8%). Two subjects (28.5%) had a history of periodic paralysis. A family history of sudden death was present in three subjects (42.8%). All participants in the study had dysmorphic features such as short stature and micrognathia (Table 1).

**Baseline ECG analysis**

Baseline ECGs showed prominent U-waves in four subjects (Table 2, Figure 1). Ventricular bigeminy, polymorphic ventricular premature beats and bidirectional ventricular tachycardia was also observed in three separate participants (Table 2, Figure 2). The mean QTc interval was 432.7 ± 23.23 ms. However, the QUc interval was significantly prolonged at 599.1 ± 83.82 ms (Table 2).

**Exercise stress test**

Exercise stress testing revealed premature ventricular beats in all seven subjects that resolved during peak

**Table 1: Clinical characteristics of subjects in the study**

<table>
<thead>
<tr>
<th>Clinical characteristic</th>
<th>Number of subjects (%)</th>
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<tbody>
<tr>
<td>Age 21 ± 14 (years)</td>
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<tr>
<td>Female 4 (57)</td>
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<tr>
<td>Palpitations 7 (100)</td>
<td></td>
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<tr>
<td>Syncope or presyncope 3 (42.8)</td>
<td></td>
</tr>
<tr>
<td>Family history of sudden cardiac death 3 (42.8)</td>
<td></td>
</tr>
<tr>
<td>History of periodic paralysis 2 (28.5)</td>
<td></td>
</tr>
<tr>
<td>Dysmorphic features 7 (100)</td>
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Table 2: ECG characteristics, exercise stress testing, Holter monitoring and EPS results in seven subjects

<table>
<thead>
<tr>
<th>Baseline ECGs</th>
<th>Number of subjects (%)</th>
</tr>
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<tbody>
<tr>
<td>Prominent U waves</td>
<td>4 (57.1%)</td>
</tr>
<tr>
<td>Ventricular bigeminy</td>
<td>1 (14.3%)</td>
</tr>
<tr>
<td>Polymorphic ventricular beats</td>
<td>1 (14.3%)</td>
</tr>
<tr>
<td>Bidirectional ventricular</td>
<td>1 (14.3%)</td>
</tr>
<tr>
<td>QTc intervals</td>
<td>432.7 ± 23.23 ms</td>
</tr>
<tr>
<td>QUc intervals</td>
<td>599.1 ± 83.82 ms</td>
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</table>

Exercise stress testing
- Premature ventricular beats: 7 (100%)
- Bidirectional or polymorphic ventricular tachycardia: 1 (14.3%)

24-h Holter monitoring
- Premature ventricular beats: 6 (85.7%)
- Bidirectional or polymorphic ventricular tachycardia: 5 (71.4%)

Electrophysiological study
- Ventricular tachycardia/ventricular fibrillation: 1 (14.3%)

ATS is a heterogeneous autosomal dominant disorder characterized by the presence of muscular periodic paralysis, developmental abnormalities, and cardiac arrhythmias. The full triad of clinical features has been reported in up to 78% of mutation-positive patients in previous studies. Because of this, a clinical diagnosis of ATS has traditionally been made in individuals with two of the three cardinal features. However, many of these patients present with typical cardiac abnormalities. Sixty percent of patients with ATS present mutations of the KCNJ2 gene located on chromosome 17 (17q23), which provides the code for the synthesis of the rectifying potassium channel Kir2.1 activated during cardiac repolarization. The Kir 2.1 potassium channel is responsible for the IK1. In the cardiac myocytes, IK1 plays an important role in stabilizing resting potential and determining the shape of the terminal portion of the cardiac action potential. Disturbances during this phase of repolarization can result in significant arrhythmogenesis and potentially symptomatic or life-threatening rhythms. Several electrocardiographic abnormalities in patients with ATS have been described previously. Zhang et al. described prominent U-waves and prolonged QT-U interval compared with healthy individuals (650 ms versus 600 ms). They showed an abnormal T-U wave in 91% of their patients. These abnormalities included:
1. prolonged terminal portion of the descending T-wave (70%)
2. wide T-U wave junction (43%)
3. biphasic U waves (16%)
4. large U waves (73%).

**Discussion**

ATS is a heterogeneous autosomal dominant disorder characterized by the presence of muscular periodic paralysis, developmental abnormalities, and cardiac arrhythmias. The full triad of clinical features has been reported in up to 78% of mutation-positive patients in previous studies. Because of this, a clinical diagnosis of ATS has traditionally been made in individuals with two of the three cardinal features. However, many of these patients present with typical cardiac abnormalities. Sixty percent of patients with ATS present mutations of the KCNJ2 gene located on chromosome 17 (17q23), which provides the code for the synthesis of the rectifying potassium channel Kir2.1 activated during cardiac repolarization. The Kir 2.1 potassium channel is responsible for the IK1. In the cardiac myocytes, IK1 plays an important role in stabilizing resting potential and determining the shape of the terminal portion of the cardiac action potential. Disturbances during this phase of repolarization can result in significant arrhythmogenesis and potentially symptomatic or life-threatening rhythms. Several electrocardiographic abnormalities in patients with ATS have been described previously. Zhang et al. described prominent U-waves and prolonged QT-U interval compared with healthy individuals (650 ms versus 600 ms). They showed an abnormal T-U wave in 91% of their patients. These abnormalities included:
1. prolonged terminal portion of the descending T-wave (70%)
2. wide T-U wave junction (43%)
3. biphasic U waves (16%)
4. large U waves (73%).
Recently, Kukla et al. have proposed five new electrocardiographic criteria for the diagnosis of ATS: 1) “U on P” sign (U-wave masquerading P-wave) during sinus tachycardia, 2) pseudo “Tee-pee sign” during a premature ventricular contraction by prolongation of the descending limb of the T + U-wave, 3) post-extrasystolic “pseudo-LQTS-pattern” that mimics long-QT syndrome (LQTS), 4) the presence of U-waves in the inferior leads and precordial leads V2-V3, 5) and U-wave amplitude augmentation after adrenaline administration. In our study, four patients (57.14%) had prominent U-waves on ECG recording (Figure 1). This percentage was slightly lower than, but similar to, previous studies. Furthermore, the QUc interval was relatively shorter than previously reported (599.1 ms versus 650 ms). The differences between studies can be explained by small sample sizes and slightly differing definitions of large U-wave measurements. All four patients with large U-waves demonstrated the “U on P sign” during sinus tachycardia induced by exercise testing. Kukla et al. were able to observe this sign in five out of their six patients. The pseudo “Tee-pee sign,” the post-extrasystolic “pseudo-LQTS-pattern” and the presence of U-waves in the inferior leads were observed in two patients each. Previous studies have proposed ATS as LQT on the basis of an apparently long QTc interval and associated arrhythmias. Interestingly, given the significant tachycardia burden from ventricular ectopy in many patients, a large majority remain asymptomatic. However, in our study, all patients were symptomatic with palpitations and 42.8% of our subjects had a family history of sudden cardiac death. Premature ventricular beats and bidirectional or polymorphic ventricular tachycardia was identified in a majority of our subjects (Table 2). Bidirectional ventricular tachycardia is an extremely rare form of ectopy described in only three clinical settings: ATS, digitalis toxicity, and catecholaminergic ventricular tachycardia. This phenomenon has been previously observed in the literature. According to our findings, 24-h Holter monitors and exercise stress testing were highly efficient methods to detect the presence of potentially lethal ventricular arrhythmias. Given the potential for sudden cardiac death and the efficacy of testing in these patients, we recommend both...
a 12-lead ECG and a 24-h Holter monitoring as standard tests in the diagnostic work-up of individuals with suspected ATS. The management of patients with ATS is currently empirical and individualized. There still is no consensus on how to treat these patients. While medical therapy for polymorphic ventricular tachycardia has been minimally successful, β-blockers and calcium-channel blockers seem to be the most efficacious and commonly used. Most of our patients were on a β-blocker with good effect (Table 3). More recently, flecainide has been shown to be efficacious and safe in suppressing ventricular arrhythmias in patients with ATS. Importantly, clinical conditions that might trigger hypokalemia such as diarrhea or medications that could prolong the QT interval should be avoided. Potassium replacement should be promptly initiated and potassium-sparing medications, such as spironolactone, should be used when needed.

In general, genetic forms of ventricular ectopy and tachyarrhythmias have been difficult to induce in electrophysiological studies and have not been amenable to ablation. Most reports in the field have been case series, and no consensus for risk stratification or treatment indications have been established. The efficacy of an ICD for unstable ventricular tachycardia or ventricular fibrillation has been well characterized; however, the indications for ICD use in inherited arrhythmia syndromes remains unclear. Currently, a family history of an inheritable arrhythmogenic condition is considered a class IIb indication for ICD implantation; however, the presence of spontaneous sustained ventricular tachycardia is considered a class I indication for device placement. In our patients, we extrapolated the approach from other inherited arrhythmia disorders. If the Holter showed non-sustained polymorphic or bidirectional ventricular arrhythmias, EPS was performed to check for inducibility. An ICD was recommended when polymorphic VT/VF was easily induced with a non-aggressive protocol. Contraindications to ICD placement include disorders that are amenable to medical treatment of radiofrequency ablation; however, as mentioned earlier, many forms of ATS arrhythmias demonstrate resistance to such forms of therapy. Given the lack of clear guidelines for treating these patients, therapy should be individualized and tailored to the patient’s findings on clinical, ECG, and Holter examinations.
Andersen–Tawil Syndrome

Figure 5: 24-h Holter monitoring record for Patient 1. The recording shows spontaneous occurrence of premature ventricular beats (black asterisk) and runs of non-sustained bidirectional ventricular tachycardia.

Table 3: Treatment modality used in all subjects from enrolment to end of study

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Number of subjects (%)</th>
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<tbody>
<tr>
<td>Nadolol</td>
<td>4 (57.1)</td>
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<tr>
<td>Spironolactone</td>
<td>2 (28.5)</td>
</tr>
<tr>
<td>Atenolol</td>
<td>1 (14.2)</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>1 (14.2)</td>
</tr>
<tr>
<td>Propranolol</td>
<td>1 (14.2)</td>
</tr>
<tr>
<td>Implantable cardioverter-defibrillator</td>
<td>1 (14.2)</td>
</tr>
</tbody>
</table>

Limitations

Because of the lack of availability in performing genetic testing at the subjects’ centers, the diagnosis of ATS was based on clinical and electrocardiographic criteria.

Conclusions

Phenotypic and electrocardiographic heterogeneity limit the clinician’s ability to identify patients with ATS who are at the highest risk for life-threatening arrhythmias. Our study, in addition to previous reports, continues to demonstrate a high prevalence of ventricular arrhythmias, some of which may progress to potentially malignant arrhythmias causing sudden cardiac death. ECG findings consistent in patients with ATS can be used to identify those at high risk. Exercise stress testing and 24-h Holter monitoring were highly efficient methods to detect the presence of these lethal arrhythmias.

References


