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Resuscitated Sudden Cardiac Death in Andersen-Tawil Syndrome

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Introduction

Andersen-Tawil Syndrome (ATS) is an autosomal dominant or sporadic disorder characterized by ventricular arrhythmias, periodic paralysis and distinctive facial and skeletal dysmorphology [1-3]. ATS is notable for its variable penetrance (not all subjects manifest all three phenotypes) and variable expressivity (the severity of the expressed phenotype varies considerably). The neuromuscular manifestations of ATS consist of intermittent weakness, often in the setting of progressive interictal weakness. The distinctive physical characteristics include low-set ears, micrognathia, syndactyly, clinodactyly, short stature and scoliosis. Cardiac manifestations of ATS include QT and QU interval prolongation, prominent U waves, frequent premature ventricular contractions (PVCs), polymorphic ventricular tachycardia (VT) and bidirectional VT [3,4]. Although the burden of ventricular ectopy is often high in patients with ATS [5], degeneration into life-threatening arrhythmias is relatively uncommon [6]. Distinguishing individuals with stable, but frequent ventricular ectopy and those at risk for sudden cardiac death remains a challenge.

Dominant-negative mutations in *KCNJ2*, the gene encoding the inward rectifier potassium channel Kir2.1, account for the majority of ATS cases. However, nearly 30% of ATS patients do not have an identifiable mutation in *KCNJ2*, confirming the genetic heterogeneity of this disorder [7]. Interestingly, there are no obvious phenotypic differences that distinguish individuals with and those without a mutation in *KCNJ2*. Likewise, it is not clear that patients with *KCNJ2* mutations are at greater, lower or similar risk of life-threatening arrhythmias, compared to those who are *KCNJ2*-mutation negative. In this report, we present a 15-year-old female with *KCNJ2*-mutation negative ATS who experienced a life-threatening cardiac event with devastating clinical consequences.

Clinical Course

This patient is a female who first developed symptoms of intermittent muscle weakness at 8 years of age. She developed progressive, significant weakness such that she required a scooter for ambulation. At 12 years of age, she developed several, self-limited episodes of shortness of breath associated with palpitations, that the family described as a “panic attack”. She was

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evaluated at a local emergency department during one such episode where she was noted to have runs of non-sustained VT on an ECG rhythm strip. A subsequent Holter monitor revealed frequent single PVCs, bigeminy and nonsustained bidirectional VT up to 14 beats in duration (rate 120-150 bpm, Figure 1). She was referred to the Division of Pediatric Electrophysiology at the University of Utah for further evaluation and management. On physical examination, she was noted to have hypertelorism, micrognathia, clindactyly of the fifth digit and 2-3 toe syndactyly. Her cardiac examination and echocardiogram were normal. 12-lead ECG revealed sinus rhythm with a normal QTc (430 ms) and prominent U waves in leads V2 and V3 (Figure 2). A rhythm strip revealed bigeminy and non-sustained polymorphic VT. She underwent genetic testing and no mutation, insertion or deletion was identified in *KCNJ2* by direct sequencing. Of note, her family history was negative for periodic paralysis, syncope, seizures or sudden death. Neither parent had any physical stigmata of ATS.

Over the course of the next 2 years, the patient underwent 24-hour Holter monitoring on 4 occasions. On her initial study, ventricular ectopic beats constituted 2.3% of all recorded ventricular complexes (Table 1). After starting extended-release metoprolol 100 mg once daily, a repeat Holter monitor revealed ventricular ectopic complexes constituting 1.5% of all beats. While most of her serum potassium levels were within the normal limits, she did have a single episode of borderline hypokalemia (3.5 mM/L), after which she was placed on 40 meq KCl orally 3 times daily. The combination of metoprolol and KCl was temporally related to an improvement in the frequency of ventricular ectopy (0.6% ectopic beats). However, 6 months later a Holter monitor revealed an interval increase in the frequency of ventricular ectopy up to 10% of all complexes. Thus, we concluded that medical management was not effective in suppressing her ventricular arrhythmias. Interestingly, her ventricular ectopy transiently resolved during administration of propofol anesthesia for a tonsillectomy and adenoidectomy. Prior to propofol infusion, her telemetry revealed ventricular bigeminy and frequent ventricular couplets. She received a loading dose of 240 mg of propofol, followed by a continuous infusion. Throughout the hour-long infusion, the patient remained in sinus rhythm with no ventricular ectopy. However, within minutes following discontinuation of the propofol infusion, her ventricular ectopy returned to a baseline of bigeminy with ventricular couplets.

Over the 2 years following her diagnosis of *KCNJ2* mutation-negative ATS, the patient exhibited acute, paroxysms of apparent paralysis preceded by lightheadedness and diaphoresis. During these episodes, she collapsed to the ground and was unable to move or respond, although she was aware of her surroundings. On average, the episodes lasted 45 minutes, but some lasted as long as 2 hours. These episodes tended to occur at school and emergency services were frequently mobilized. Upon arrival of emergency services, her blood pressure was always noted to be normal and she was in her baseline sinus rhythm with frequent PVCs. An event recorder during one of the episodes also captured sinus rhythm with frequent PVCs. Palpitations or post-ictal symptoms were never associated with these episodes. While no obvious precipitating factors were identified, the episodes tended to occur during periods of anxiety. Therapy for her episodic weakness consisted of acetazolamide 500 mg twice daily. This did not alter the frequency or severity of her neurological manifestations.

The patient had at least 2 episodes of syncope, interspersed between the more frequent episodes of acute collapse. One episode occurred in the shower, where the patient fell and hit her head, requiring evaluation in the emergency department. With further questioning, it was not clear whether this episode represented a true syncopal event or whether this was a consequence of her severe muscle weakness. Subsequently, the patient had a brief episode of loss of consciousness that occurred just after urinating. She stood up, felt dizzy, sat back down again and then collapsed to the ground. The mother discovered her on the floor. In light of these episodes of apparent vasovagal syncope in the setting of the more bizarre episodes of acute collapse, we elected to implant an insertable loop recorder (ILR). The first IRL interrogation

included 3 patient-activated events and 5 automatically recorded events. The patient's rhythm was sinus, alternating with bigeminy and at other times, sinus rhythm with ventricular couplets that were typical of her baseline rhythm. However, several months later, she was found unconscious in the school bathroom and required full resuscitation. ILR interrogation revealed sinus rhythm with PVCs followed by rapid polymorphic VT, then monomorphic VT, asystole and ventricular fibrillation. Although successfully resuscitated, the patient suffered severe hypoxic encephalopathy.

Discussion

We report a case of an adolescent female with *KCNJ2* mutation-negative ATS who experienced resuscitated sudden cardiac death and devastating neurological consequences. While the burden of ventricular ectopy is often high in patients with ATS, degeneration into a life-threatening arrhythmia is relatively uncommon. In the largest series of *KCNJ2* mutation-positive ATS reported to date, the incidence of life-threatening arrhythmias was ~3% [6]. However, identifying the patients at risk for lethal arrhythmias remains a challenge. Moreover, it is not clear whether the risk of sudden death is different between ATS patients with and without identified *KCNJ2* mutations. In a recent report, a young man with *KCNJ2* mutation-negative ATS succumbed to rapid VT after receiving medications known to cause acquired Long QT Syndrome [8]. This observation supports the concept of reduced repolarization reserve in ATS patients, corroborated by *in silico* studies of a dominant-negative Kir2.1 channel mutation [9].

The patient reported here experienced 2 syncopal episodes with vasovagal characteristics. While an implantable cardioverter-defibrillator (ICD) was considered at that time, we opted to implant an ILR, given the historical low incidence of life-threatening arrhythmias in ATS together with the vasovagal properties of the patient's episodes. However, her subsequent event was devastating in its clinical outcome. The fact that she was found unresponsive in the bathroom and had a previous event following micturition, suggests a possible link between autonomic function and arrhythmia trigger. An acute autonomic trigger in the setting of frequent ventricular ectopy and post-ectopic pauses might provide sufficient electrical instability to induce a lethal tachyarrhythmia. The link between autonomic function and arrhythmia is further supported by the observation that the patient's ventricular ectopy transiently resolved during propofol infusion. Propofol is a widely-used intravenous anesthetic that activates central inhibitory GABA_A receptors, although there is evidence that propofol blocks neuronal Na⁺ channels [10]. Cardiovascular side-effects are generally mild and include bradycardia and hypotension [11]. Propofol was reported to block cardiac L-type Ca²⁺, transient outward K⁺ (*I*_{TO}) and the slowly activating delayed rectifier K⁺ (*I*_{Ks}) currents [12]. The precise mechanism whereby propofol reduced the frequency of ventricular ectopy in this patient remains unclear, but may be related to overall central depression of autonomic function.

The underlying mechanism of this patient's episodes of acute collapse was never clearly explained. The presence of flaccid, areflexic weakness during the episodes would have supported the contention that these episodes were due to periodic paralysis. Unfortunately, cursory documentation of neurological findings during emergency room visits allows no such conclusions. Moreover, acute weakness of this magnitude has never been reported in the periodic paralysis literature. A primary cardiac etiology was unlikely in that her rhythm was documented to be her baseline (sinus with frequent PVCs), captured by an event recorder during one such episode. We had entertained the possibility of a conversion disorder, as the episodes usually occurred at school and often during times of anxiety. However, we cannot exclude the possibility that the acute collapse represented a primary manifestation of her underlying ATS. The patient was given an empirical trial of acetazolamide, an established therapy for periodic

paralysis but it had no appreciable effect on the degree of weakness or the frequency of the episodes of acute collapse.

ICD therapy has been efficacious in ATS patients with life-threatening arrhythmias [5]. Indications for ICD placement include cardiac arrest, unexplained syncope or rapid/sustained VT. Given the relationship between autonomic function and arrhythmia in this patient, vasovagal syncope may represent a primary cardiac manifestation of this disease. ICD therapy in ATS patients is challenging as the large VT burden predisposes to multiple ICD shocks. Thus, programming must be tailored to minimize the risk of ICD discharges while treating lethal arrhythmias [13]. It is possible that pacing may be of additional benefit by providing heart rate stabilization and prevention of pause-dependent arrhythmias, as reported for a sub-group of LQTS patients [14].

In summary, we report a case of an adolescent female with *KCNJ2*-mutation negative ATS who experienced resuscitated sudden death with severe neurological consequences. Medical therapy was not effective at suppressing her ventricular ectopy, with the exception of transient improvement during propofol anesthesia. Given the paucity of ATS patients at any individual institution, a collaborative, multi-center study is necessary to identify arrhythmia triggers, determine the efficacy of pharmacological therapy and to define risk stratification for sudden death.

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Figure 1.
12 lead ECG rhythms strip obtained upon first evaluation in Pediatric Cardiology Clinic.
Manual QTc 430 ms. Note prominent U waves in leads V2 and V3.

Figure 2.
Holter monitor recording demonstrating bigeminy with nonsustained run of bidirectional VT
(best seen in lead 3).

Figure 3.
Loop recorder rhythm strip demonstrating the onset of rapid polymorphic VT, alternating with monomorphic VT, deteriorating into asystole.

Table 1

24 hour Holter monitor results

Ave HR (bpm)	total ventricular beats	% ventricular beats	couplets	runs > 3	Longest run	Fastest run (bpm)
72	2254	2.3	79	3	14	153
78	1359	1.5	3	1	4	150
66	571	0.6	0	0		
58	8171	10	471	105	7	153