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Slow and Steady: The Cautious Use of Neuroleptics in a Patient with Andersen-Tawil Syndrome

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Abstract

Long QT syndrome (LQT) is a disease of cardiac repolarization caused by alterations in the transmembrane potassium and sodium currents. This results in prolongation of the QT interval on electrocardiography (EKG) and can result in torsade de pointes and sudden cardiac death. We present a case of a patient who has Anderson Tawil syndrome; a congenital long QT syndrome, with a history of cardiac arrhythmias who developed acute paranoid schizophrenia that was refractory to treatment with non-QT-prolonging drugs and required institution of neuroleptics to control her psychiatric symptoms.

Keywords

Long Q-T Schizophrenia, Neuroleptic, Anderson Tawil Syndrome, Congenital Long QT Syndrome

1. Introduction

Congenital long QT syndrome (LQTS) refers to a group of heterogeneous cardiac electrophysiologic disorders that are characterized by abnormal ion function [1] [2]. This can lead to changes, including QT prolongation and T-wave abnormalities which are detected on an electrocardiogram (ECG). It is diagnosed using clinical presentation, family history, and typical ECG characteristics [1]. While most patients are asymptomatic and diagnosed incidentally on ECG, patients can present with syncope, dizziness or palpitations [3] [4]. The syncope here typically occurs during exercise and high emotions and is usually abrupt and without warning, differentiating it from orthostatic or vasovagal syndrome.

Additionally, sudden death can also occur due to the development of Torsades de Pointes [1].

The cornerstone of managing patients with LQTS is avoiding QT-prolonging medications that can decrease repolarization reserve and subsequently lead to an increased risk of malignant and potentially fatal arrhythmias [5]. However, there may be situations where these medications may be unavoidable. We describe the case of a patient with Andersen-Tawil syndrome who was admitted to the medical service for careful titration of her antipsychotic medications.

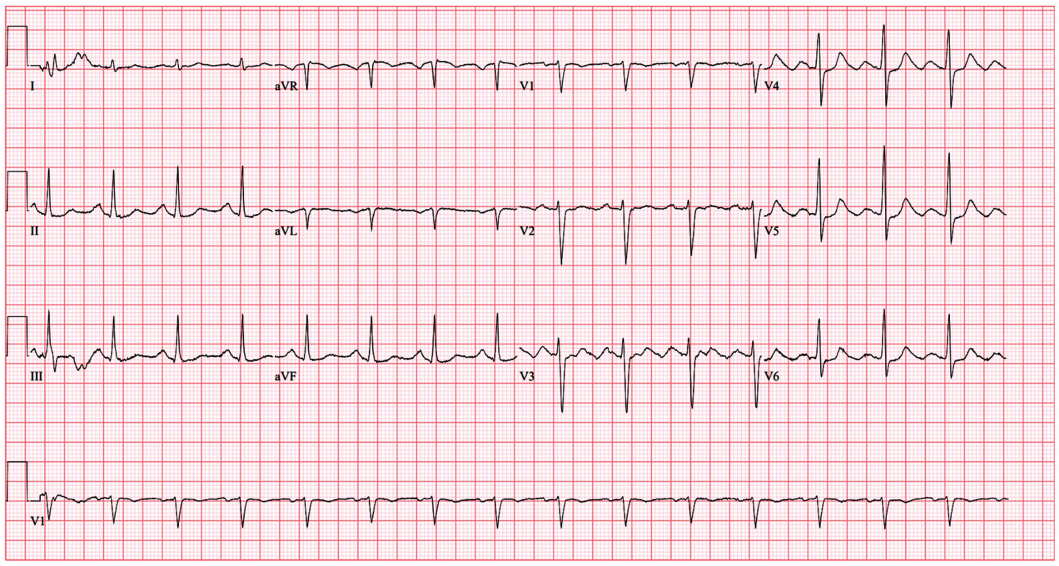
2. Case Presentation

A 37-year-old female with a past medical history of Long QT syndrome with bidirectional PVCs consistent with Andersen-Tawil syndrome and schizophrenia was admitted to the intermediate medical care unit from the psychiatry unit to initiate antipsychotic pharmacotherapy while closely monitoring her cardiac function. Prior to arrival at our unit, the patient was admitted to a local community hospital with a working diagnosis of schizophrenia after she was found to have homicidal ideation. She was at this hospital for over a month, where she has continued on her home medications of Flecainide 100 mg BID and metoprolol 25 mg daily. She was also given lorazepam PRN for agitation but received no treatment for her schizophrenia, as any medication that would prolong her QT interval could cause a potentially fatal arrhythmia. The hospital's inpatient Cardiology and patient's outpatient cardiologist were both consulted, and it was recommended that the patient could only be safely treated with neuroleptic medication if she was on continuous cardiac monitoring.

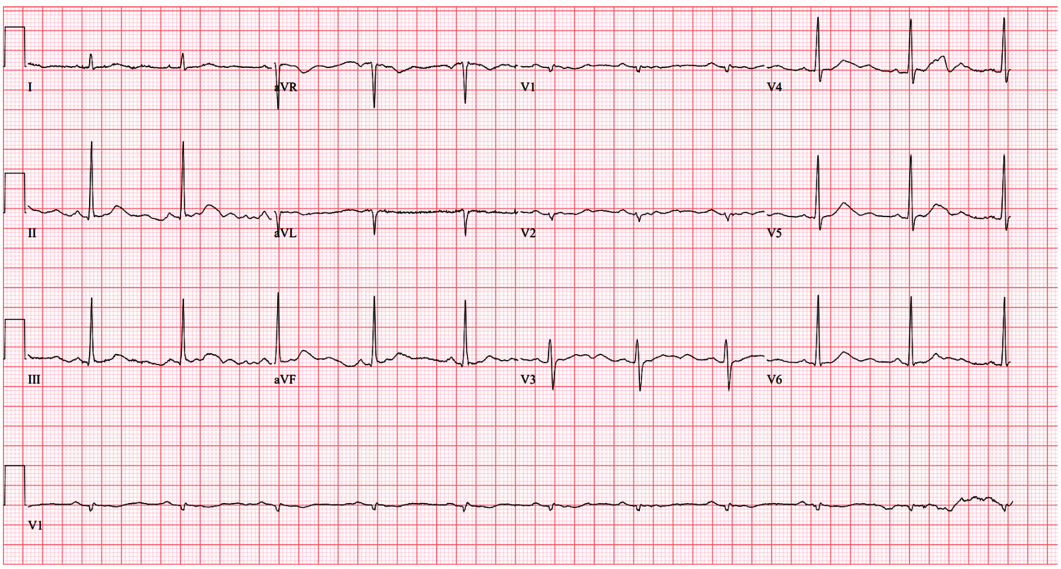
The patient first presented to a cardiologist at the age of 23 for the management of her bidirectional ventricular tachycardia. Her cardiac history began at the early age of 8, at which time she was diagnosed with an episode of severe bronchitis and was noted to have ventricular ectopy on an EKG. Pediatric notes prior to the age of 8 had noted a normal cardiac exam and documented normal cardiac rhythm. She subsequently underwent a routine physical exam at the age of 15 prior to starting high school, during which time a 12-lead EKG was done, demonstrating bidirectional ventricular tachycardia. She was diagnosed at that time of probably having had a prior episode of myocarditis. Based on these ECG findings, she was advised to curtail her exercise regimens. She moved to Russia at the age of 20 and, while there, had a Holter monitor, which showed significant ventricular ectopy with nearly 40,000 extra beats. She returned to the United States 3 years later and had several cardiology visits for persistent episodic palpitations that failed treatment with B-Blockers, calcium channel blockers, and amiodarone. Over the next 8 years, the patient continued to have episodes of palpitations with PVCs, atypical chest pain, and paroxysmal ventricular tachycardia. At the age of 31, she had DNA testing and was found to have a mutation in the *KCNJ2* gene and given the diagnosis of Anderson-Tawil syndrome.

She was admitted to the inpatient service, and Cardiology was consulted. The decision to start the neuroleptic medication was put into action with the patient

receiving Zyprexa (olanzapine) 10 mg PO every night along with Ativan (lorazepam) 2 mg PRN. Her initial potassium and magnesium were low and were repleted and kept on the higher end of the normal reference ranges before initiation of therapy. Over the course of a few days, she was slowly up titrated to 15 mg daily with improvement in her psychotic symptoms. The patient had EKGs twice daily and was also on continuous cardiac monitoring. Her Qtc ranged from 440 s to 470 s which seemed to be consistent with her baseline readings (Figure 1). There was no ventricular arrhythmia during her telemetry stay and hospitalization. On discharge, she was linked to an outpatient clinic for psychiatric follow-up.



(a)



(b)

Figure 1. ECG before (a) and after up-titration to 15 mg of olanzapine (b). Both show normal sinus rhythm with a rate of 60 - 75 beats per minute. Initial QTC of 457, which lengthened to 482 after olanzapine.

3. Discussion

Andersen-Tawil syndrome (ATS) is a form of periodic paralysis which is a set of rare neuromuscular disorders that are inherited in an autosomal dominant pattern. They cause mutations in skeletal muscle sodium, calcium, and potassium channel genes. They usually present in the 20 s or 30 s with episodic flaccid weakness, brought on by diet or rest after exercise [6]. Anderson-Tawil syndrome has a characteristic clinical presentation of episodic flaccid muscle weakness (*i.e.*, periodic paralysis); ventricular arrhythmias and prolonged QT interval. There are associated physical anomalies including low-set ears, widely spaced eyes, small mandible, fifth-digit clinodactyly, syndactyly, short stature, and scoliosis [4] [7]. It has been linked to mutations in the *KCNJ*2 genes on chromosome 17q23 which encodes the alpha subunit of the K^+ channel protein Kir2.1 (ATS type 1) that is expressed in skeletal muscle, heart, and the brain [6] [7]. The diagnosis of ATS can be difficult due to its high degree of phenotypic variability and significant non-penetrance in individuals with a *KCNJ*2 mutation [7]. The triad of paralysis, arrhythmias, and phenotypic characteristics has been reported in 58% - 78% of patients with a confirmed mutation while 32% - 81% of individuals have any two features of the triad [7]. The clinical diagnosis of ATS is made when individuals have two of three clinical features of the syndrome or have one of the three features as well as a family member with two of the three criteria [6]. The diagnosis of ATS is established in individuals with clinical characteristics and ECG findings that support the diagnosis of ATS or by identifying a pathogenic variant in the *KCNJ*2 gene [6]. However, a mutation in the *KCNJ*2 gene is estimated to be present in only 60% of patients with ATS [7].

Cardiac involvement is a major feature of ATS. A prolonged QT is seen in 50% of patients with ATS. Additionally, 84% of patients have ventricular arrhythmias, with bidirectional ventricular tachycardia (BVT) being the most common rhythm abnormality and is found in 32% of patients. Cardiac arrest can occur in around 10% of patients with ATS. Finally, patients may have ECG findings that reflect abnormalities in repolarization. These include a prolonged terminal T-wave downslope, biphasic and large U waves, and a wide TU wave pattern. These ECG findings may be absent in patients with clinical ATS but with no mutation in the *KCNJ*2 gene [5]. Annual screening with a 12-lead EKG and 24-hour Holter monitor for asymptomatic individuals with a *KCNJ*2 pathogenic variant is recommended [8].

Accurate QT measurement may be challenging because the presence of U waves makes it difficult to determine the end of the T-wave, but the QT interval can be easily measured using the "tangent method" if automated measurement is not available or appears incorrect (**Figure 2**). Correct QT measurement is key to minimizing the risks of over- or under-estimating the QT interval and wrongly stratifying patient risk. To minimize inconsistencies, it is best to measure the tangent of the descending T-wave to baseline in leads II or V5. This technique has been found to be the most reproducible among experts and non-experts alike [9].

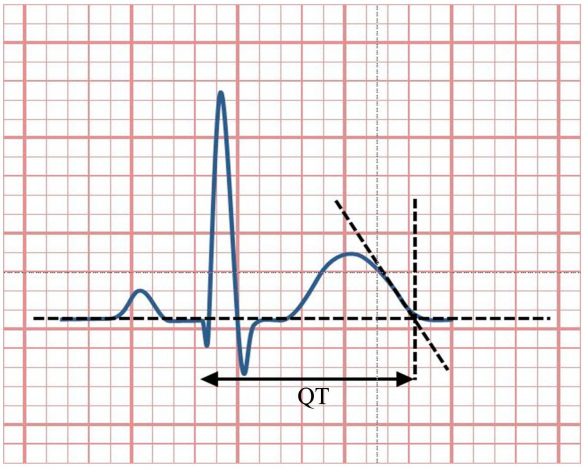


Figure 2. Cartoon showing measurement of the QT interval, (Own work, peaBrianC) [10].

The most widely used formula for calculating the QTc is the Bazett formula, given by $\mathrm{QTcB} = \mathrm{QT}/\sqrt{\mathrm{RR}}$. RR denotes the length of time between the QRS complexes (the RR interval). It is commonly abbreviated as QTcB. Barret formula is inaccurate for heart rates that are not in the normal range but it still remains the most used due to the lack of a widely accepted technique and is often reported on ECG machines [9]. For patients with a higher heart rate, the Fridericia correction formula is suitable (QTc = QT/RR0.33). The normal patients, the normal value of the QTC length is around 400 ms (can reach up to 460 ms for women and 450 ms for men), and QTc intervals longer than 500 ms are considered to be a major risk factor for the development of Tdp [11].

The approach to pharmacological interventions consists of therapy to abort acute attacks and chronic preventive therapy to reduce attack frequency. The cornerstone of treatment of patients with congenital prolonged QT involves avoiding drugs that prolong QT and the use of antiadrenergic therapy with B -blockers is a class I recommendation for all symptomatic, and asymptomatic patients with QT ≥ 470 ms. Left cardiac symptomatic denervation is recommended in patients in whom B-blockers are not effective, contraindicated or not tolerated. This is also the recommendation for patients who refuse or are unable to get implantable cardioverter-defibrillator or beta blockers [12]. For patients with reduced left ventricular function with significant, frequent ventricular arrhythmias, empiric treatment with flecainide should be considered and has been shown to suppress exercise-induced ventricular arrhythmia [13].

The treatment of patients on antipsychotics depends on the type of antipsychotic drug and the severity of QT duration (**Table 1** and **Table 2**) [14]. The use of ICD in patients with schizophrenia may be difficult and depend on their ability to tolerate the ICD. Due to this, the decision to implant an ICD is not straightforward.ICD is indicated as primary prophylaxis is used in patients with non-sustained torsades de pointes or persistent prolonged QTC (e.g. >550 ms) or discontinuing medication that caused the prolonged QT is impossible [14].

Table 1. Effect of antipsychotic drugs in QT.

The effect of psychotropics on QTc	
No effect:	Brexipiprazole, Cariprazine and Lurasidone
Low effect (Overdose or <10 ms increase in QTc)	Aripiprazole, amisulpride, clozapine, flupentixol, fluphenazine, perphenazine, prochlorperazine, olanzapine, risperidone, sulpiride, loxapine, paliperidone
Moderate effect (>10 ms QT prolongation at clinical doses)	Amisulpride, chlorpromazine, levomepromazine, iloperidone, melperone, quetiapine, ziprasidone
High effect (>20 ms QTc prolongation at average clinical doses)	Pimozide, Sertindole Any single drug or combination of drugs that are used in doses above recommended upper limits

Table 2. QTc duration severity and appropriate treatment.

QTc < 440 ms (Men) or <470 ms (Women)	No action required unless abnormal T-wave morphology—consider cardiac review if in doubt.
QTc > 440 ms (Men) or >470 ms (Women), but <500 ms	Consider reducing dose or switching to drug of lower effect; repeat ECG and consider cardiology review.
QTc > 500 ms	Stop suspected causative drug (s) and switch to drug with a lower effect: immediate cardiology review is needed. If the patient has syncope or pre-syncope, immediate ECG monitoring for ventricular arrhythmias should be performed.
Low-risk antipsychotics lurasidone,	cariprazine or brexpiprazole.

4. Conclusion

Anderson Tawil syndrome is a congenital long QT syndrome that presents with cardiac arrhythmia and may lead to sudden cardiac death. Drugs that prolong the QT level are always avoided as much as possible for these patients. Our patient with Anderson Tawil syndrome developed schizophrenia and needed a neuroleptic drug to control her symptoms. Under the supervision of both psychiatrist and cardiologist with telemetry evaluation, the patient was treated and discharged. We recommend the development of appropriate treatment guidelines for treating patients with Prolonged QT who needs neuroleptics.

Informed Consent

Informed consent was taken from the patient.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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