

A Rare Case of Anderson Tawil Syndrome

Sagar Nagpal^{1*} | Sindhu C. Pokhriyal² | Pooja Bhandari³ | Mohammad Amaan Parvez¹ | Rami Dalbah¹ | Suyog Patel⁴ | Keerthana C. Gottipati⁵

*Correspondence: Sagar Nagpal

Address: ¹Department of Internal Medicine, East Tennessee State University, Johnson City, Tennessee; ²Department of Internal Medicine, Interfaith Medical Center, Brooklyn, New York; ³Department of Internal Medicine, University of Buffalo, New York; ⁴B.J Medical College, Ahmedabad; ⁵Washington University of Health and Science, Belize

e-mail ✉: Nagpals@etsu.edu

Received: 03 April 2023; Accepted: 08 May 2023

Copyright: © 2023 Nagpal S. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided that the original work is properly cited.

ABSTRACT

Andersen Tawil Syndrome (ATS) is a rare disorder, the prevalence of which is one in a million. We present case of a 37-year-old female with a long-standing history of periodic paralysis, and ventricular arrhythmias. She presented with generalized weakness which resolved with potassium supplementation. Genetic workup revealed KCNJ2 mutation.

Keywords: *Electrophysiology, Genetic Disorders, Anderson Tawil Syndrome, Ventricular Tachycardia*

History of Presentation

A 37 years old short-statured lady presented with the chief complaints of generalized weakness in all extremities. Patient-reported having episodes of generalized weakness since the age of 12 but most often these episodes typically lasted for a very brief period and were self-resolving with no residual weakness. Extensive family history revealed a history of sudden cardiac deaths in several members including her siblings who had similar symptoms in their early life (Fig. 1). On the physical exam, she had motor strength of 1+ in all the extremities and had notable short stature with a height of 140 cm along with small hands.

Past Medical History

She had a history of asthma and was status post-AICD placement for recurrent symptomatic non-sustained ventricular tachycardia at the age of 29.

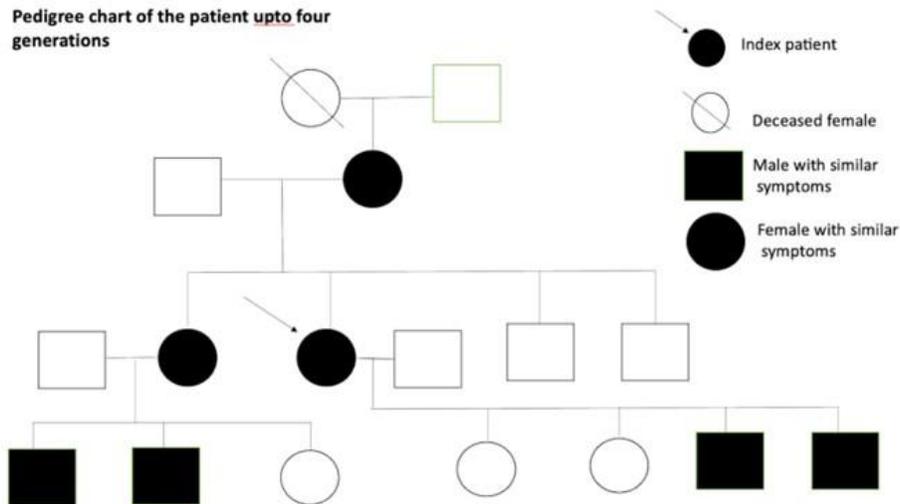


Figure 1: Pedigree chart of the patient up to 4 generations. Multiple family members including her kids were having similar symptoms.

Differential Diagnosis

There are several causes of periodic paralysis. However, ATS is associated with the classic triad of hypokalemia and dysmorphic physical characteristics alongside paralysis. Whenever we see hypokalemia with paralysis the first and most commoner diagnosis that crosses our minds is that of hypokalemic periodic paralysis. However, those who have hypokalemic periodic paralysis lack the cardiac and characteristic physical appearance of ATS. Any person with severe weakness and significant hypokalemia should also be evaluated for thyrotoxic periodic paralysis which is more common in men of Asian ethnicity. TSH, T4, and T3 concentrations in the serum are measured to rule out this diagnosis. Romano-Ward Syndrome and Jervell Lange-Nielsen Syndrome (JLNS) are also long QT syndromes that can be confused with ATS as ATS can also present with long QT on EKG as a complication of hypokalemia. However, these syndromes are clearly differentiated from ATS due to their association with congenital deafness. ATS is also different from Timothy Syndrome which is associated with structural abnormalities of the heart and long QT interval on EKG. Patients with Timothy syndrome are also at an increased risk of cardiac events, like ATS. Timothy syndrome and JLNS are both regarded as the most dangerous LQT syndromes. Anderson Tawil syndrome has characteristic TU prolongation which can be mistaken as prolonged QT interval. In our case hypokalemia likely contributed to prolonged QT interval in the absence of U waves.

Investigations

Workup demonstrated hypokalemia (2.5 mmol/l). Thyroid function and electrolytes including Magnesium were normal. EKG showed prolonged QTc of 642 msec (Fig. 2). Echocardiogram done was

normal with an ejection fraction of 55-60%. Holter studies done before ICD placement revealed multiple episodes of isolated premature ventricular contractions and non-sustained ventricular tachycardia with no acute ST changes. Echocardiogram was done which showed ejection fraction of 55-60% and mild concentric left ventricular hypertrophy. Stress test done before the ICD placement was normal with an ejection fraction of 59%. Stroke evaluation was negative. Genetic studies revealed KCNJ2 mutation which confirmed the diagnosis of ATS.

Management (Medical/Interventions)

Potassium supplementation was commenced, and the weakness improved dramatically with complete resolution within 24 hours of potassium supplementation. Repeat EKG showed QTc interval of 450 msec (Fig. 3). The patient was commenced on Nadolol for long QT syndrome. Dichlorphenamide was started with the aim of reducing the number of episodes of periodic paralysis.

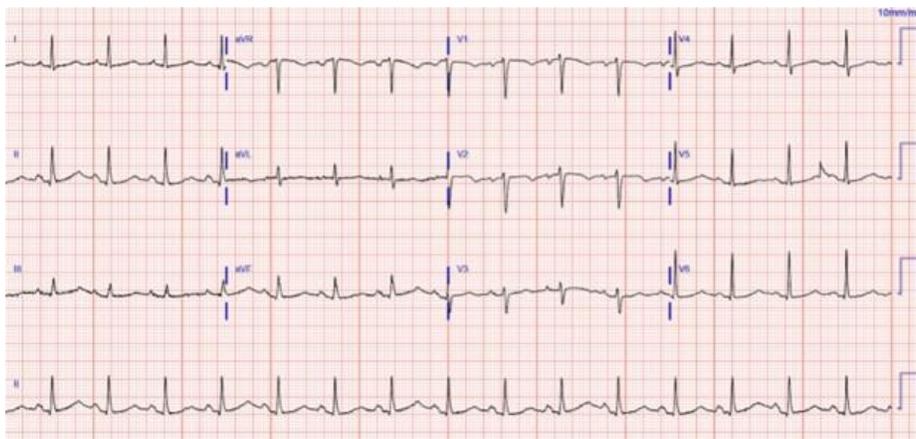


Figure 2: EKG on admission. Sinus rhythm with a heart rate of 61 bpm, QTc of 642 msec.

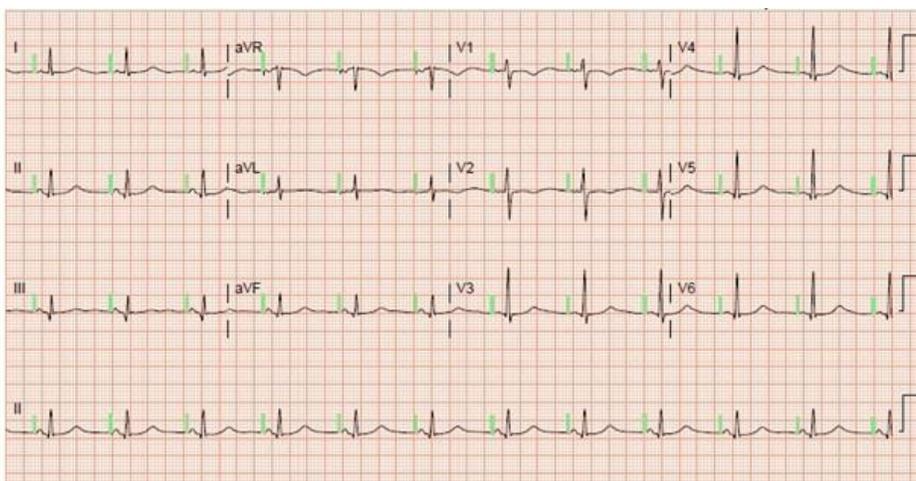


Figure 3: EKG after replacement of potassium and resolution of symptoms. Sinus rhythm with a heart rate of 93 and QTc of 450 msec.

Discussion

Anderson Tawil syndrome is characterized by a triad of periodic paralysis, ventricular arrhythmias, and dysmorphic features like micrognathia, hypertelorism, short stature, clinodactyly, low-set ears, and scoliosis (Zhang *et al.*, 2005). 60% of those who are affected exhibit all three characteristics, while 80% express two of the three cardinal traits. These characteristic physical features are often helpful in arriving at a diagnosis of ATS but may not always be present. ATS is predominantly associated with hypokalemia and presents with prominent U waves and characteristic TU pattern on EKG. Ventricular arrhythmias associated with ATS are bidirectional ventricular tachycardia (BiVT), premature ventricular contractions (PVCs), and rarely polymorphic ventricular tachycardia (Pegan *et al.*, 2006). There is a high occurrence of sudden cardiac death in patients with ATS due to these arrhythmias. Some patients exhibit learning disabilities and other neurocognitive disabilities. Family history can be helpful during differential diagnosis due to the autosomal dominant nature of the disease.

Several electrophysiological tests including Holter, long exercise protocol, and routine nerve conduction electrophysiology have been used in the work up of these patients. While nerve conduction may be normal between episodes of periodic paralysis, long exercise protocol may detect an aberrant decrease in the compound motor action potential amplitude immediately following exercise, and hence is a more sensitive test.

Diagnosis is usually established by characteristic clinical and EKG findings and can be confirmed by genetic analysis. There are two types of ATS. ATS1, which accounts for 60% of cases, is caused by a mutation in the inward rectifier potassium channel subfamily J member 2 (KCNJ2) which disrupts the insertion of the channel into the cell membrane (Kim and Chung, 2009; Kukla *et al.*, 2014). ATS2 is believed to be caused by a mutation in the KCNJ5 gene, but the exact mechanism of ATS2 remains elusive. Thus, the gold standard method of diagnosis is genetic testing of the KCNJ2 gene using PCR.

Single-gene testing, multigene panels, and whole-genome sequencing are all examples of gene-targeted testing methods used to diagnose ATS. Small intragenic deletions/insertions, as well as missense, nonsense, and splice site variants, can be detected through serial single-gene testing using sequence analysis. The most cost-effective method of identifying the genetic cause of the condition while minimizing the identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype is to use a multigene panel that includes KCNJ2, KCNJ5, and other genes of interest. However, the usual approach involves examining the KCNJ2 gene's sequence first.

Management encompasses treating the clinical findings as well as reducing the frequency and severity of attacks of periodic weakness. Treatment of periodic paralysis includes oral or IV potassium supplementation until serum concentration normalizes. Giving 20-30 mEq/ L of oral potassium every 15-30 minutes (with the maximum amount not exceeding 200 mEq in a 12-hour period) is the first line treatment if the serum potassium content is lower than 3.0 mmol/L in the setting of periodic paralysis (Pitt GS, 2016). This has been known to typically shorten an attack of paralysis. In order to prevent secondary hyperkalemia, close monitoring of serum potassium levels and the EKG are required during potassium replacement therapy.

Other measures are avoiding high carbohydrate meals, QTc prolonging agents, and diuretics. Ventricular arrhythmias are difficult to treat in ATS. Antiarrhythmic drugs of Class I cause neuromuscular symptoms and Class III cause prolonged QT interval, hence both are used with caution or better avoided. An implantable Cardioverter defibrillator is often advised to prevent sudden cardiac death in patients of ATS. Genetic counseling is extremely necessary to reduce the incidence of this syndrome in future generations.

Follow-Up: The patient was advised to follow up in the cardiology clinic every 3-6 months. She had remained free of any episodes of periodic paralysis in her last appointment.

Conclusion

Early diagnosis and treatment of this rare disease are crucial in improving the survival and prognosis of these patients.

Learning Objectives

1. To understand the clinical presentation of ATS and to establish a diagnostic algorithm while differentiating it from other common causes of periodic paralysis.
2. To emphasize the importance of proper genetic counselling of the patient and family members which can help in reducing the prevalence of ATS as well as facilitate early diagnosis and treatment.

Abbreviations:

1. LQT- Long QT syndrome
2. ATS- Anderson Tawil syndrome
3. PCR- Polymerase chain reaction

References

Kim JB, Chung KW. Novel de novo mutation in the KCNJ2 gene in a patient with Andersen-Tawil syndrome. *Pediatr Neurol* 2009; 41: 464-466.

Kukla P, Biernacka EK, Baranchuk A, Jastrzebski M, Jagodzinska M. Electrocardiogram in Andersen-Tawil syndrome. New electrocardiographic criteria for diagnosis of type-1 Andersen-Tawil syndrome. *Curr Cardiol Rev* 2014; 10: 222-228.

Pegan S, Arrabit C, Slesinger PA, Choe S. Andersen's syndrome mutation effects on the structure and assembly of the cytoplasmic domains of Kir2.1. *Biochemistry* 2006; 45: 8599-8606.

Pitt GS, editor. Ion channels in health and disease - 1st Edition. *Academic Press*; 2016 Jul 11. (Available at: <https://www.elsevier.com/books/ion-channels-in-health-and-disease/pitt/978-0-12-802002-9>)

Zhang L, Benson DW, Tristani-Firouzi M, Ptacek LJ, Tawil R, Schwartz P, George AL, Horie M, Andelfinger G, Snow GL, Fu YH, Ackerman MJ, and Vincent M. Electrocardiographic features in Andersen-Tawil syndrome patients with KCNJ2 mutations. Characteristic TU-wave patterns predict the KCNJ2 genotype. *Circulation* 2005; 111: 2720-2726.