Child Neurology: Andersen-Tawil syndrome

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Andersen-Tawil syndrome (ATS) is one of the periodic paralyses. This autosomal dominant disorder was initially named after Andersen, who in 1971 reported the case of a young boy presenting with intermittent muscle weakness, ventricular arrhythmias, and other developmental abnormalities. It was subsequently renamed Andersen-Tawil syndrome following the additional work of Dr. Rabi Tawil. Periodic paralysis, cardiac arrhythmias, and dysmorphic features are now recognized as the 3 characteristic features in patients with ATS.^{1,2}

CLINICAL CASE The proband is a 14-year-old boy who presented at the age of 9 years with recurrent episodes of leg weakness lasting several days. These episodes became more frequent, occurring at least once a month. The severity of the weakness during the episodes varied from mild weakness to inability to walk unassisted (2-3/5 weakness of proximal leg muscles). There were no clear triggers. Serum potassium levels measured during episodes of weakness were normal. Neurologic examination between episodes demonstrated proximal weakness (4/5) in the lower and upper extremities and a positive Gower sign. Treatment with potassium supplementation and acetazolamide resulted in mild clinical improvement. Family history revealed that his mother had had similar episodes that began during adolescence, improved with age, and resolved in her 40s. Potassium levels were reported to be low during her acute episodes. Sequencing of *CACNA1S* and *SCN4A* in the proband did not reveal any abnormalities. Several years after presentation, the proband's 14-year-old brother developed a ventricular tachycardia. He had no history of weakness and his neurologic examination was normal. The combination of periodic paralysis and family history of cardiac arrhythmia prompted the testing of *KCNJ2* for ATS. A pathogenic heterozygous missense c.652C>T (p.R216W) mutation was identified that segregated with the phenotype in the family. In retrospect, the proband, his brother, and his mother were noted to have mild dysmorphic features (micrognathia, clinodactyly of the 5th fingers of the hands, and syndactyly of the

2nd and 3rd digits of the left foot). ECG and cardiac Holter monitoring of the proband did not reveal any abnormalities.

DISCUSSION Clinical features. ATS is one of the first known channelopathies; causal mutations have been identified in *KCNJ2* on chromosome 17q24, which encodes the inward rectifier potassium channel 2 protein, Kir2.1.³ The dominant mutations in the Kir2.1 channel have a dominant negative effect on the potassium current (i.e., the mutated protein loses its normal function and adversely affects the function of the normal protein), resulting in prolonged depolarization of the action potential, thereby accounting for the cardiac and muscular symptoms.² Autosomal recessive mutations in Kir2.1 have also been reported.⁴ Recently, a mutation in *KCNJ5*, which encodes the Kir3.4 subunit, has been linked to ATS and is thought to exert an inhibitory effect on the inward rectifier potassium current.⁵

In ATS, episodes of periodic paralysis first develop during childhood or adolescence and typically last between several hours and several days. Serum potassium levels during the episodes may be normal, elevated, or reduced. Although most cases seem to be associated with hypokalemia, several recent studies suggest normal potassium levels in patients with ATS.^{1,6} Triggers of the paralytic episodes mainly include prolonged exercise, prolonged rest, rest after exercise, and emotional stress. Patients usually present with mild permanent proximal weakness.

Cardiac manifestations include ventricular arrhythmias as well as electrocardiogram abnormalities such as long QT interval, pronounced U waves, and long QTU interval.² Patients may develop fainting spells or, in some cases, present with cardiac arrest leading to sudden death. ATS is also classified as "long QT syndrome type 7" (LQTS7), although the QT interval is either normal or only slightly prolonged in most cases.⁷

In addition to skeletal and cardiac muscle abnormalities, patients with ATS have dysmorphic features that are usually subtle. In fact, the use of the term "distinctive facial features" may be more appropriate.²

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Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Dysmorphisms include broad forehead, hypoplastic mandible, hypotelorism, short palpebral fissures, short nose with fullness along the bridge and bulbous tip, thin upper lip, high arched or cleft palate, triangular facies, digit clinodactyly, syndactyly of the 2nd and 3rd toes, and short stature.^{2,8}

Patients with ATS have a distinct neurocognitive phenotype characterized by deficits in executive function and abstract reasoning.⁹

ATS is a syndrome with a very high degree of phenotypic variability and is therefore very difficult to diagnose. The characteristic triad of clinical features (ventricular arrhythmias, periodic paralysis, and dysmorphic features) is present in 58%–78% of patients with *KCNJ2* mutations, whereas between 32% and 81% present with involvement of only 2 of the 3 organ systems.¹⁰ Approximately 60% of the patients with a clinical diagnosis of ATS have causal mutations identified in *KCNJ2*.⁹ About 6%–20% of mutation-positive individuals do not exhibit any of the associated features, indicating that this disorder has incomplete penetrance.⁸

Differential diagnosis. The diagnosis of ATS should be considered in any individual who displays at least 2 of the characteristic triad of symptoms, i.e., periodic paralysis, cardiac abnormalities, and facial dysmorphism. The differential diagnosis of ATS includes other periodic paralyses, namely hypokalemic periodic paralysis, hyperkalemic periodic paralysis, and thyrotoxic periodic paralysis.

The onset, duration, and severity of attacks in patients with hypokalemic or hyperkalemic paralysis are similar to those in ATS.² Hypokalemic paralysis is associated with low serum potassium levels, whereas patients with hyperkalemic periodic paralysis generally have increased levels of serum potassium. In patients with ATS, periodic paralysis can occur with normokalemia, hyperkalemia, or hypokalemia. Nevertheless, the absence of the other typical features present in ATS (cardiac abnormalities and mild dysmorphic features) generally distinguishes patients with both hyperkalemia and hypokalemia from those with ATS. The presence of myotonia is characteristic of hyperkalemic periodic paralysis, and a majority of the patients with hypokalemic paralysis have mutations in the *CACNA1S* or *SCN4A* genes.¹¹

Management. Treatment strategies for ATS are generally directed toward the management of the periodic paralysis and cardiac arrhythmias. A thorough examination involving blood chemistry, including serum potassium concentration and thyroid function, should be done at baseline and during attacks. Cardiac evaluation including ECG and Holter monitoring should be performed, and patients should be

followed by a cardiologist. Characteristic abnormalities of the heart, including prominent U waves, prolonged Q-U intervals, premature ventricular contractions, and bidirectional ventricular tachycardia, may be noted on ECG. Similarly, the use of 24-hour Holter monitoring will aid in examining the presence, frequency, and duration of ventricular tachycardia. Carbonic anhydrase inhibitors (such as acetazolamide 250–1,500 mg/day and dichlorophenamide 50–200 mg/day) have been used to reduce recurrent attacks of paralysis.² Daily potassium supplements may be used in cases in which attacks are associated with hypokalemia. This can be an attractive option since elevated potassium levels shorten the QTc interval and decrease cardiac arrhythmogenicity.² Cardiac pacemaker or defibrillators may be required in some patients.

Analysis of mutations in *KCNJ2* is the only confirmatory genetic test so far. Genetic counseling, including thorough screening of family history, must be conducted, as it enables early treatment and prevention, especially of cardiac complications.

CONCLUSION ATS should be considered in the differential diagnosis of patients with periodic paralysis. The clinical triad of ATS consists of periodic paralysis, cardiac arrhythmias, and dysmorphic features. However, due to its phenotypic heterogeneity and subtle physical findings, ATS can be difficult to diagnose. Because some of the cardiac manifestations of ATS can be dangerous and life-threatening, establishing the accurate diagnosis of ATS is critical.

AUTHOR CONTRIBUTIONS

Mohammed Almuqbil drafted and revised the manuscript for intellectual content. Myriam Srour drafted and revised the manuscript for intellectual content.

ACKNOWLEDGMENT

The authors would like to thank the patient and his family for their valuable participation.

STUDY FUNDING

No targeted funding reported.

DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

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Neurology 2015;84:e78-e80

DOI 10.1212/WNL.0000000000001377

This information is current as of March 16, 2015

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Neurologic aspects of sweating and its disorders

Neurology® 2020;94:187. doi:10.1212/WNL.0000000000008730

In the Clinical Implications of Neuroscience Research article “Neurologic aspects of sweating and its disorders” by Minota et al.,¹ the Disclosure should have noted the grant support received from the NIH (R01 NS092625). The authors regret the error.

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Outcome of endovascular therapy in stroke with large vessel occlusion and mild symptoms

Neurology® 2020;94:187. doi:10.1212/WNL.0000000000008829

In the article “Outcome of endovascular therapy in stroke with large vessel occlusion and mild symptoms” by Manno et al.,¹ Dr. Heldner’s byline should read Mirjam R. Heldner, MD. The authors regret the error.

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Amyloid and cerebrovascular burden divergently influence brain functional network changes over time

Neurology® 2020;94:187. doi:10.1212/WNL.0000000000008830

In the article “Amyloid and cerebrovascular burden divergently influence brain functional network changes over time” by Chong et al.,¹ the label beside the blue line in panel A of figure 2 should have read “svMCI PiB-.” The authors regret the error.

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Child Neurology: Andersen-Tawil syndrome

Neurology® 2020;94:187. doi:10.1212/WNL.0000000000008828

Two images of patients in the article “Child Neurology: Andersen-Tawil syndrome” by Almuqbil and Srour,¹ published online March 16, 2015, have been removed because the patients requested that their consent for publication be withdrawn. The removal of the images does not invalidate the paper because an extensive verbal description of the patients was included within the text of the article. The American Academy of Neurology, who owns copyright of the article, the Editor of the journal, and the authors agreed that the images were unnecessary to the message of the paper and agreed to honor the request to remove them.

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