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Case Report

Atypical muscular manifestations in Andersen-Tawil Syndrome

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Abstract

Andersen-Tawil syndrome (ATS) is a rare autosomal dominant disease that is characterized by a triad of augmented U waves on electrocardiography and/or ventricular arrhythmias, periodic paralysis, and dysmorphism. Many reports have focused on the etiology and management of arrhythmias based on the risk of lethal arrhythmias. In contrast, case reports on muscle manifestations in ATS are rare and, thus, its prognosis remains unclear. We herein describe an adolescent with ATS who presented with the muscle symptoms of a novel variant in the *KCNJ2* gene only and whose father had permanent muscle weakness. We propose an approach to diagnose atypical ATS by focusing on muscle manifestations.

Background

Andersen-Tawil syndrome (ATS) is a disease that is characterized by a triad of augmented U waves and/or ventricular arrhythmias, periodic paralysis, and dysmorphism of face and digits. The causative gene is the *KCNJ2* gene, which shows autosomal dominant inheritance. The prevalence of ATS is estimated to be 1 in 500,000[1)]. Many reports of ATS with ventricular arrhythmias and muscle symptoms or cardiac findings alone have been reported, with a focus on the cause and management of arrhythmias as the risk factor for lethal arrhythmias. In contrast, case reports on muscle manifestations in ATS are rare and, thus, its prognosis remains unclear.

We herein describe an adolescent with ATS who presented only with the muscle symptoms of a novel variant in the *KCNJ2* gene and whose father had permanent muscle weakness.

Case Presentation

A boy in his early teens presented to our hospital with lower extremity paralysis. He developed paralysis with difficulty climbing stairs and standing up after a physical education class three days prior to the visit. It was the first episode of paralysis, which gradually improved each day thereafter. He was born to nonconsanguineous parents. His neonatal course, developmental, and medical history were unremarkable. A family history of muscular disease was noted in his father.

The father reported difficulty in getting up and running in his adolescence and arrhythmias from school age. He was diagnosed with periodic paralysis when he developed difficulty in holding a cup in his early 20s. His muscle manifestations worsened over the years and became permanent. He had the ability to

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walk without aids, but had gait abnormalities and was unable to open bottle caps in his 40s.

A physical examination of the proband showed a height of 144 cm (−0.71 SD) and body weight of 63 kg. He had no dysmorphic features or abnormalities on chest auscultation. Neurological findings were unremarkable, except for a manual muscle test score of 4 in the bilateral quadriceps which completely recovered after one week.

Laboratory data of the proband revealed elevated serum muscle enzymes with creatine kinase (CK) of 1,173 U/L and aldolase of 12.6 IU/L, while his serum potassium level was normal at 4.2 mEq/L. A thyroid function test, blood amino acid analysis, and urinary organic acid analysis showed no significant findings. Furthermore, lactic and pyruvic acid levels were normal. Rest and exercise electrocardiograms (ECG) showed no ventricular arrhythmias and augmented U wave (Fig. 1). Echocardiography revealed no evidence of structural abnormalities.

Based on the father's history, hereditary periodic paralysis was suspected. Informed consent was obtained from the patient and his father, and a gene panel test (*CACNA1S*, *SCN4A*, *KCNJ2*, and *KCNJ5*) was performed. The results obtained revealed a heterozygous variant of c.660C>A (p.Ser220Arg) in the *KCNJ2* gene (NM_000891. 3). This variant is classified as "Likely Pathogenic" according to the criteria of the American College of Medical Genetics and Genomics. His father was confirmed to have the same variant, while his mother was not genotyped because she was deceased due to acute myocardial infarction in her mid-40s.

The proband was diagnosed with ATS based on his phenotype, family history and genetic test results. He was educated to avoid excessive exercise, endurance, and nighttime arousal, since fatigue and stress can trigger tetraplegia and arrhythmic attacks. There has been no recurrence without medications since the first episode of muscle weakness. Acetazolamide, which is commonly used and effective for muscle symptoms in ATS, is

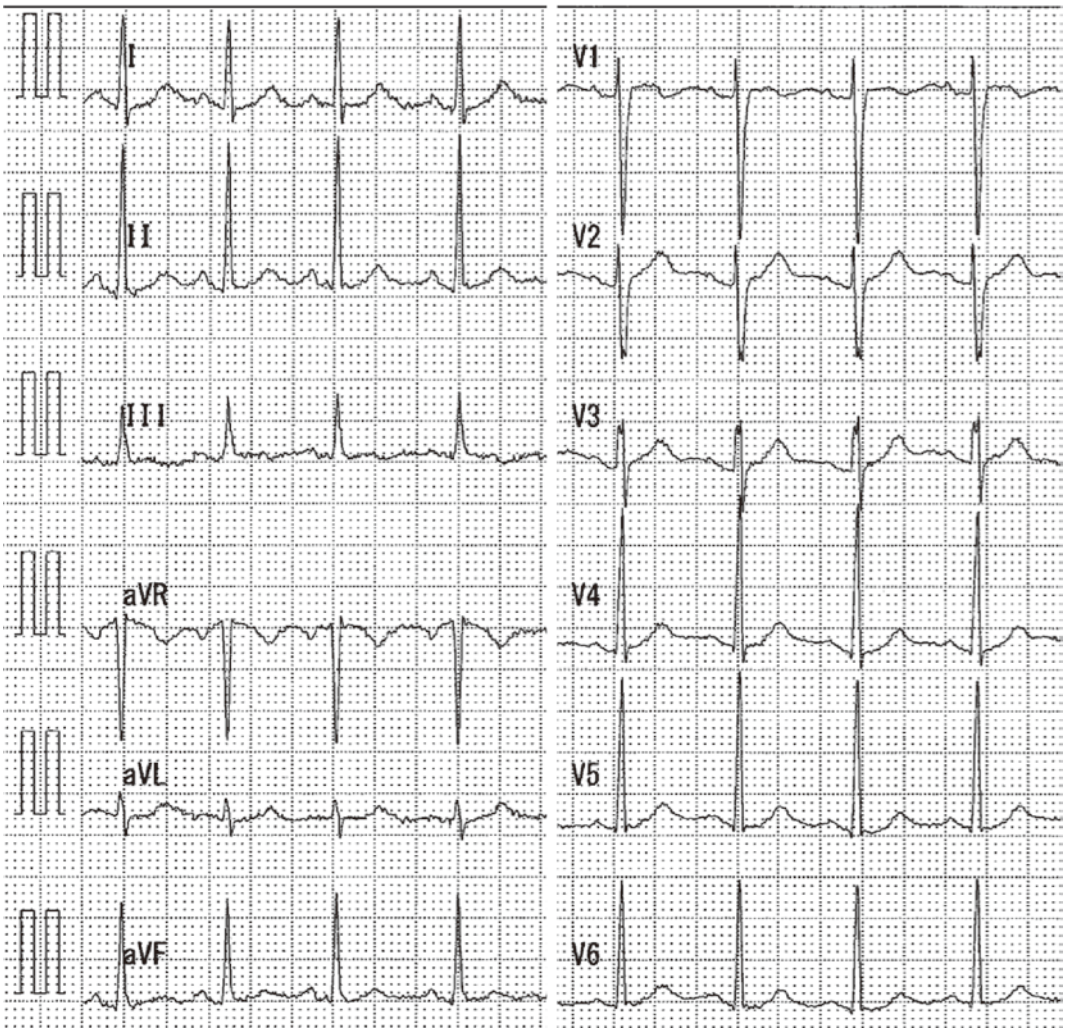

Fig. 1 Rest ECG of the proband
A resting 12-lead electrocardiogram revealed no ventricular arrhythmias and U waves.

planned when relapse occurs. In addition, we recommended that if he has palpitations or loss of consciousness, he should immediately visit a hospital for the evaluation of arrhythmic type. In high-risk ventricular arrhythmias like polymorphic premature ventricular contraction, antiarrhythmic drugs, especially flecainide which has been shown to be effective for ATS[2] needs to be considered.

After the diagnosis of this proband, his father was also diagnosed with ATS in his late 40s. He had no facial and digit dysmorphic features. The ECG of the arrhythmia in his teenage years was unavailable, but the ECG in his 40s (Fig. 2) showed right bundle branch block (RBBB) and U wave, which were common ECG findings in ATS. As for muscle symptoms, the present potassium level was 4.8 mEq/L with his persistent muscle weakness, while the potassium level at the time of the quadriplegia was unavailable.

Discussion

While typical ATS can be appropriately suspected with supportive diagnostic criteria[3] (Table 1), atypical ATS presenting only muscle manifestations in the first and second decades is difficult to diagnose. Furthermore, those muscle symptoms may be slowly progressive. *KCNJ2* gene testing is useful for diagnosing atypical ATS with muscular manifestations only.

The patient in this case had ATS with muscle symptoms, but no cardiac or dysmorphism phenotypes. A previous study reported that 58% of cases of ATS exhibited all three signs, while 81% had two or more signs[4]. ATS presenting with periodic paralysis alone accounts for 5%[5] or 11%[6] of ATS cases. In consideration of the prevalence of ATS, ATS with only periodic paralysis is a rare presentation. Two or more signs are practical to clinically suspect ATS, while a diagnosis is often difficult in cases with only one sign. Therefore, there may be an underestimation of the number of atypical ATS patients.

The 30-year course of his father's impaired activities of daily living indicates that the long-term prognosis of the muscle symptoms of ATS is unfavorable, at least in some cases. Previous studies showed that the frequency and severity of paralytic episodes of ATS decreased with age[7], whereas permanent mild muscle weakness was common[4]. A retrospective study in France reported the long-term courses of 35 ATS patients[6]; permanent muscle weakness was detected in 45.7% of cases and became per-

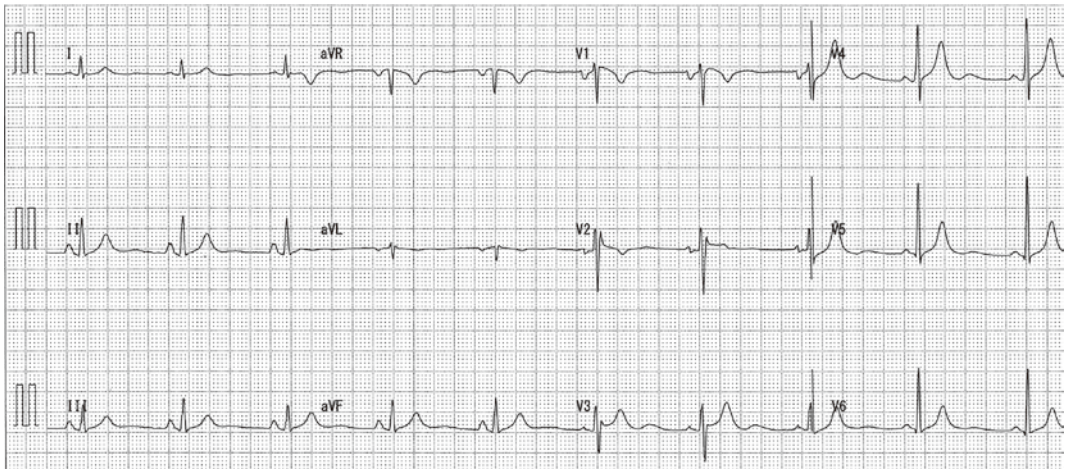

Fig. 2 Rest ECG of the father
A resting 12-lead electrocardiogram showed RBBB and U waves.

Table 1 Clinical criteria for suspecting Andersen-Tawil syndrome

A. Presence of 2 of the following 3 criteria :
   1. Periodic paralysis
   2. Symptomatic cardiac arrhythmias or ECG evidence of enlarged U-waves, ventricular ectopy or a prolonged QTc or QUc interval
   3. Characteristic facies, dental anomalies, small hands and feet, and at least 2 of the following :
      - Low-set ears
      - Widely spaced eyes
      - Small mandible
      - Fifth-digit clinodactyly
      - Syndactyly of toes 2 and 3

B. One of the above 3 in addition to at least 1 other family member who meets 2 of the 3 criteria.

sistent at an average of 7 years from disease onset. Research from a specialized neuromuscular facility suggests that a higher percentage of patients have muscle symptoms. Some adult cases with similar symptoms to the present case have been followed up as other diagnoses.

The *KCNJ2* gene analysis to diagnose atypical ATS with muscular symptoms alone is helpful. A review of periodic paralysis[3] suggests the differentiation of ATS from primary periodic paralysis based on the presence of arrhythmias and characteristic facial features. However, the overlap between muscular symptoms in ATS and periodic paralysis makes it difficult to clinically differentiate atypical ATS from primary periodic paralysis. Hyperkalemic paralysis is indicated when muscle stiffness is identified. An exercise test may differentiate periodic paralysis from other muscle diseases with a sensitivity of 71-81%[8,9], and long exercise tests were previously reported to be useful for differentiating ATS from normal controls[10,11]. Nevertheless, it is challenging to distinguish ATS only with periodic paralysis from primary periodic paralysis using these tests.

In the proband, a family history of periodic paralysis and arrhythmias prompted genetic testing even for the first episode of muscle weakness in the absence of ECG abnormalities. This highlights the significance of a family history for the diagnosis of atypical ATS. It is important to note that ATS may not show complete autosomal dominant inheritance because of its incomplete penetrance. Therefore, the rule in/out based on family trees needs to be applied with careful attention.

In the father's case, episodes of limb weakness and abnormal ECG findings may allow for an earlier diagnosis of ATS. However, some adult cases with atypical ATS have been followed up as other diagnoses, including primary periodic paralysis and unspecified myopathy. This is attributed to ATS studies progressing since the 1994 study by Tawil; therefore, it is reasonable to presume that the diagnosis of ATS was not made at the time of onset, as was the case for the father.

To diagnose atypical ATS followed up as permanent muscle weakness of unknown etiology, the time of onset is important. If disease onset is confirmed to be in adolescence or the 20s, ATS needs to be listed as a differential diagnosis. ECG is required to identify U waves and ventricular arrhythmias. Even if ECG is negative, the patient may have ATS with periodic paralysis only. In the clinical setting of a family history of ECG abnormalities or muscle disease, even if it is not complete autosomal dominant inheritance, genetic testing can be helpful to reach a diagnosis. When family history is not available, pediatricians and physicians should pay attention to the following two findings related to muscle weakness as a clue to differentiating atypical ATS. The first is the slowly progressive course over time, and the second is the change in characteristic of episodes from reversible to irreversible.

The *KCNJ2* gene encodes Kir2.1, an inwardly rectifying potassium channel, expressed in the heart and skeletal muscle. Mutant proteins of Kir2.1 showed a dominant negative effect on the wild-type protein[12]. The altered Kir2.1 could lower inward potassium transportation leading to a positive charge shift in the membrane potential and inactivation of voltage-gated sodium channels[13].

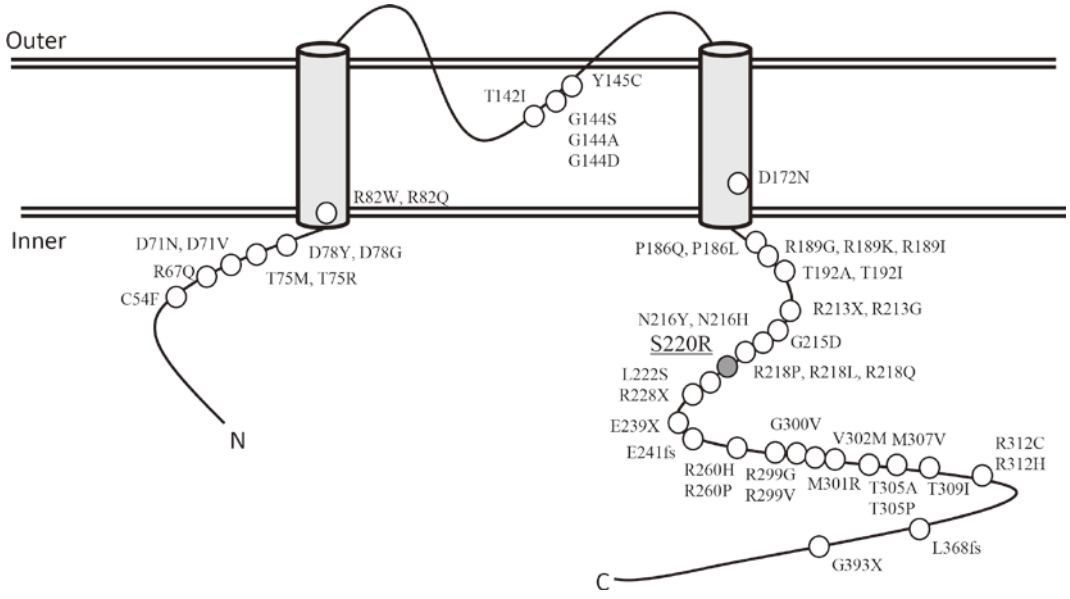

Fig. 3 Reported variants in *KCNJ2* gene
The white circles show variants reported as "Likely Pathogenic" or "Pathogenic" in Clinvar database.
The gray circle shows the variant found in this report.

To the best of our knowledge, this is the first case report of ATS with p.Ser220Arg in the *KCNJ2* gene (Fig. 3)[14]. The alteration from serine to arginine changes from a neutral to positive amino acid charge. In the well-characterized proximal p.Arg218 position, the change from a positive to neutral charge has been shown to make phosphatidylinositol 4,5-bisphosphate ineffective for binding to the site[15]. The serine to arginine alteration at position 220 changes the charge of the amino acid from neutral to positive. It may indirectly affect PIP_2 binding, leading to inadequate rest membrane potential of a modified potassium channel function. In vitro experiments using skeletal muscle cells edited with that variant would provide more details of altered *KCNJ2* effects.

Conclusion

ATS may present without cardiac or dysmorphic findings and only muscle manifestations in the first and second decades. Some adults with ATS may be followed up as persistent muscle weakness of unknown etiology. The *KCNJ2* analysis is useful for the diagnosis of atypical ATS either in patients with a positive family history of ECG abnormalities and/or muscular disease, or in patients in whom there is a change to irreversible muscle weakness.

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Andersen-Tawil 症候群の父子例における筋症状

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【要旨】 Andersen-Tawil 症候群（ATS）は、U 波の増大ないし心室性不整脈、周期性四肢麻痺および形態異常を 3 徴とする疾患である。その致死的不整脈のリスクから不整脈の原因と管理に重点を置く報告が多くされてきた。一方で ATS における筋の表現型のみを呈するケースの報告は稀であり、筋所見の予後に関して心所見ほどには理解が進んでいないのが現状である。この症例報告では、*KCNJ2* 遺伝子に新規バリアントを持ち、筋症状のみを呈した男児とその父親でみられた永続的な筋力低下の ATS の一家系について報告する。また、筋症状に関連する非典型的な ATS を適切に認識し、診断するためのアプローチについて考察した。

〈キーワード〉 Andersen-Tawil 症候群、筋力低下、周期性四肢麻痺、不整脈、家族歴