Case Letter

Andersen-Tawil syndrome associated with myopathy

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Dear editor,

Andersen-Tawil syndrome (ATS) is a rare cause of periodic paralysis. The inheritance pattern of ATS is autosomal dominant. It is characterized by periodic paralysis, arrhythmias, and distinctive appearances.[1] ATS has been linked to mutations in the KCNJ2 gene that causes defective inward-rectifier potassium channel Kir2.1,[2] which plays an important role in stabilizing resting membrane potential in both skeletal and cardiac muscles.[3] There are few reports[4,5] concerning ATS in the Chinese population. The potentially reversible muscular weakness and potentially life-threatening ventricular arrhythmia require early diagnosis. In this report, we presented one case of ATS who had the symptoms of persistent bilateral proximal limb weakness and mildly elevated creatinine kinase. This patient was initially diagnosed with myopathy. Periodic paralysis, dysmorphic feature, and heterozygous mutation of R218Q in KCNJ2 led us to the diagnosis of ATS.

CASE

A 15-year-old boy was admitted to our clinic with bilateral proximal limb weakness in the last three years. He described that it was difficult to walk upstairs and lift his hands above his shoulder owing to the weakness. Initially, the weakness was episodic, each episode lasted 3–4 days, and resolved spontaneously. Over the last year, he often felt mild but persistent weakness, without clear fluctuation. He reported no myalgia, cramp, or stiffness. He had been in good health except for a continuous murmur accidentally of heart, which was found in a health screening test. The result of electrocardiogram (ECG) was normal. However, echocardiogram demonstrated a patent ductus arteriosus (PDA). Six months ago, he received a catheter intervention in our hospital. The interventional catheter procedure was successful, and the PDA was corrected. ECG revealed normal QTc and wave patterns. On questioning, he admitted that he did not feel palpitation, syncope, chest pain, or dyspnea after the operation. He did not receive any drug treatment that may contribute to myopathy, including statin, cimetidine, steroid, and alcohol. Motor, language, and adaptive social functions were developed with no delay. There was no family history of neuromuscular or cardiac disease.

Examination revealed that the patient had low-set ears and micrognathia (Figure 1A). Neurologic examination revealed he had lower bilateral proximal upper and lower extremity strength and positive Gower's sign. He had a waddling gait. Deep tendon reflexes of him were hypoactive, without muscle fasciculation. Babinski sign was bilaterally negative. There were no signs of sensory loss or no myotonia. Muscle bulk was normal. Cranial nerves were intact, with no signs of ptosis, dysarthria, or dysphagia. No skin ulcers, Gottron papules, or subcutaneous calcinosis was present.

Investigations for muscle weakness showed serum creatine kinase was mildly elevated (497 to 796 IU/L) on three separate tests. Potassium levels were normal, ranging from 3.68 to 4.98 mEq/L on three separate tests. Complete blood count, erythrocyte sedimentation rate, C-reactive protein (CRP), liver function test, thyroid function test, 25-hydroxy vitamin D, antinuclear antibody, and anti-Jo1 antibody were normal. The symptoms of proximal limb weakness and mildly elevated creatinine kinase indicated the patient had myopathy. By blood tests, the endocrine, infective, and inflammatory causes were ruled out. The result of the left bicep brachialis biopsy showed marked muscle atrophy and suggested a non-specific myopathy (Figure 1 B–E). No myophagocytosis, inflammatory infiltrates, or vacuoles were recognized in the results. Nicotinamide adenine dinucleotide (NADH), succinate dehydrogenase (SDH), cyclooxygenase (COX), periodic acid-Schiff (PAS), and oil red O (ORO) staining also revealed no abnormality.

Considering the fact that he had episodic proximal limb weakness as an initial presentation, a clinical diagnosis of periodic paralysis was made. With his dysmorphic facial features, we highly suspected the patient suffered from ATS. The result of genetic testing

revealed a heterozygous mutation of R218Q (G-G/A) in KCNJ2 (Figure 1 F–H). R218Q mutation in KCNJ2 was associated with ATS.[3,6] Yet no mutation was found from his father and his mother.

Within days of starting carbonic anhydrase inhibitor and oral daily potassium supplements, he had a noticeable improvement in baseline muscle strength. A 24-hour Holter monitoring was ordered after the operation of the interventional catheter. The result revealed no arrhythmia except for ventricular premature contractions, and the maximal QTc was 398 ms. There was no evidence of a potentially life-threatening cardiac arrhythmia. However, a long-term follow-up is recommended for patients who have been suspected of ATS.

DISCUSSION

ATS is one of the first detected channelopathies. The features of this case were constant muscle weakness with no clear episodic pattern at hospital admission, normal potassium, and thyroid hormone level. These features made it difficult for clinicians to definite the subtypes of periodic paralysis at the beginning. First of all, about a third of periodic paralysis patients develop permanent weakness as muscle degenerates,[7] but this feature cannot be used to distinguish ATS from other subtypes of periodic paralysis. Secondly, weakness episodes of ATS patients can occur in the hypokalemic, hyperkalemic, or normokalemic situations,[8] which are similar to other subtypes of periodic paralysis. Therefore, this case is not a typical ATS patient

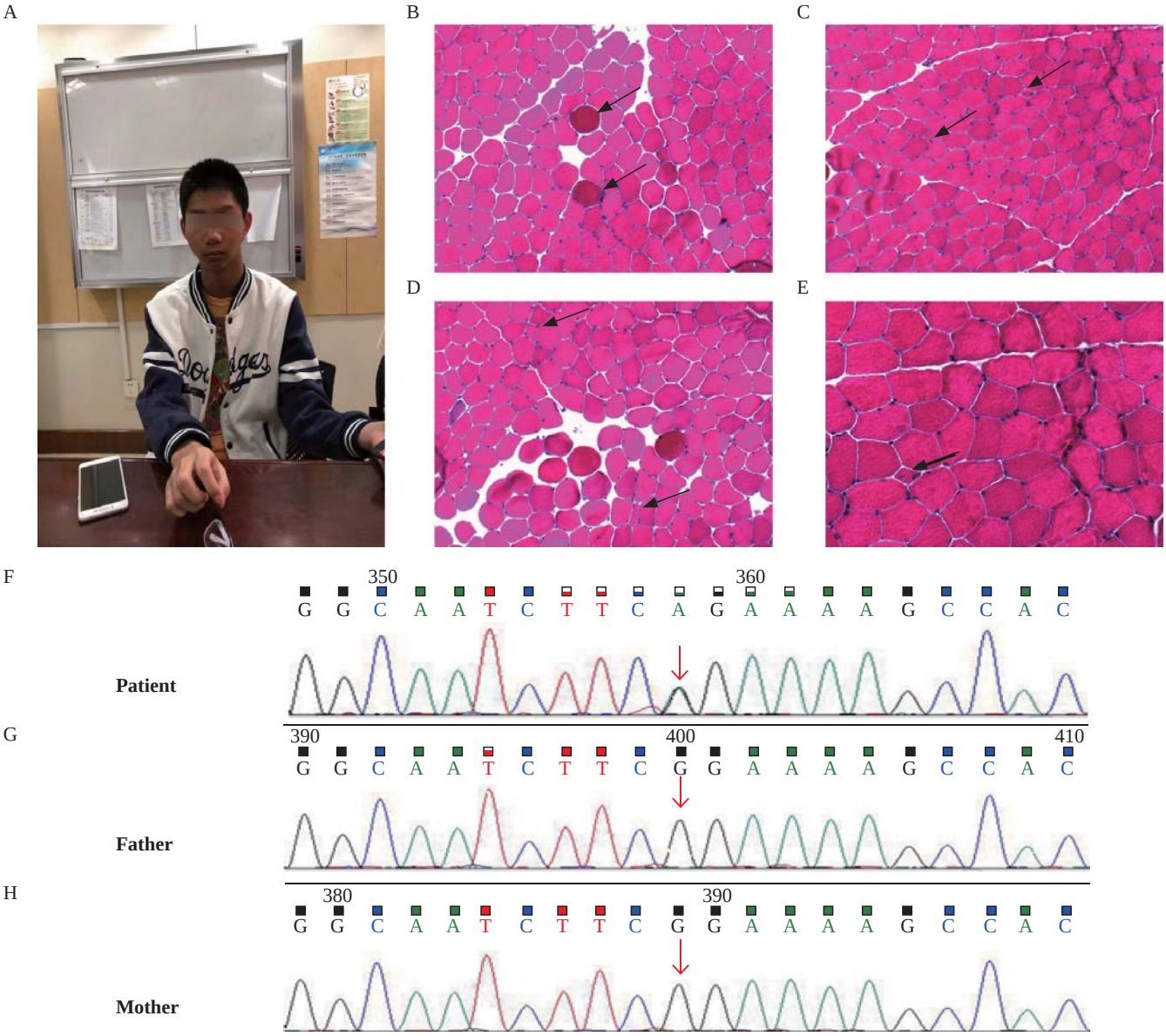

Figure 1. Skeletal-craniofacial features, clinical manifestations of left bicep brachialis and the sequencing analysis of the KCNJ2. A: the skeletal-craniofacial features of the patient; B–D: HE staining (×100); E: HE staining (×200); the black arrows represented atrophic muscle fibers; F: the partial sequence of KCNJ2 for the patient; G: the partial sequence of KCNJ2 for his father; H: the partial sequence of KCNJ2 for his mother, the red arrows represented mutation (R218Q for the patient) or unmutated site (R218 for his father and his mother).

and has some unusual features that need to be noticed.

Except for periodic paralysis, mildly elevated creatinine kinase and non-specific myopathic findings on muscle biopsy could guide clinicians to consider a variety of inherited myopathies rather than ATS. Some researchers[9-10] have reported that hypokalemia and hyperkalemia induced myopathy and creatinine kinase elevation. The symptoms of proximal limb weakness and mildly elevated creatinine kinase indicated the patient had myopathy. However, the result of the left bicep brachialis biopsy showed this patient was not inherited myopathies but a non-specific myopathy. Some researchers have reported the patients of ATS are often accompanied with myopathy. Yet, myopathic changes in ATS patients were less reported. The level of serum creatine kinase or potassium for this case was normal, which was not a diagnostic criterion for ATS.

For genetic testing, the heterozygous mutation (R218W) in KCNJ2 has also been reported as a notable feature for clinicians to find ATS.[1,4,11] R218 in KCNJ2 is within the C-terminal interaction domain in Kir2.1 channel,[12] takes part in phosphatidylinositol 4,5-bisphosphate (PIP2) binding and leads to Kir2.1 channel activation.[12] R218 mutation, such as R218Q, exerts a dominant-negative effect on wild-type channels, weakening channel-PIP2 interaction.[13] The mutation of KCNJ2 for our patient is R218Q, which is also a feature of ATS. However, no mutation was found from his father and his mother, which indicated this patient was a sporadic ATS patient. The cases of sporadic ATS patients have not been reported before. Except for the mutation of KCNJ2, the feature of weakness makes a difference among different ATS cases. Child et al[1] reported chronic persistent limb weakness in adulthood but did not mention childhood weakness patterns. Lefter et al[11] reported one case of nonfluctuating weakness developed into fluctuating weakness with fixed myopathy. For our patient, he experienced episodic weakness pattern and shifted into chronic permanent weakness. Different cases of ATS have unique features. Therefore, more clinical presentation patterns need to be found.

CONCLUSIONS

ATS is a rare and phenotypically heterogeneous condition. This patient was diagnosed with ATS by the standards of periodic paralysis, dysmorphic feature, and heterozygous mutation of R218Q in KCNJ2. However, some unusual features were found, such as normal ECG but PDA presented in this patient, and no mutation of R218Q in KCNJ2 in his father and his mother. These features suggest the patient should be a sporadic ATS patient, and clinicians should pay more attention to the differences in every case of ATS. This case also underscores the importance of recognizing the characteristic phenotypic features and other tests such as ECG and PDA. These tests can avoid some unnecessary invasive procedures such as muscle biopsy, which may be unhelpful. In addition, ATS is an important subtype of periodic paralysis. When a patient has more than two classic symptoms like periodic paralysis, cardiac abnormalities, and distinctive appearances, the ATS should be considered.

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