Case Report

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A case with classical triad of Andersen Tawil Sydrome and KCNJ2:c,919A>G mutation

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Abstract

Andersen-Tawil Syndrome (ATS) is a rare channelopathy with distinctive features of periodic paralytic attacks, ventricular arrhythmias with long QT interval and dysmorphic features. The syndrome shows a high degree of phenotypic heterogeneity. Diagnosis can be confirmed by genetic testing where KCNJ2 is the most common causative gene. Here, we report a young patient with classical triad of ATS carrying KCNJ2:c,919A>G mutation, a mutation which was previously reported in only one patient who had no cardiac involvement. To our knowledge, our case is the first reported case with ventricular arrhythmias due to KCNJ2:c,919A>G (pMet307Val) mutation, and reflects the clinical heterogeneity of the disease when compared with previous reports.

Keywords: Andersen-Tawil Syndrome, periodic paralysis, ventricular arrhythmia, dysmorphic features

INTRODUCTION

Andersen-Tawil Syndrome (ATS) is a rare channelopathy with distinctive features of periodic paralytic attacks, ventricular arrhythmias with long QT and dysmorphic features (1). The syndrome shows a high degree of phenotypic heterogeneity. It constitutes less than 10% of periodic paralysis however as cardiac manifestations or dysmorphic features can be subtle, the disease should be considered in the differential diagnosis of all patients with periodic paralysis (2). Diagnosis can be confirmed by genetic testing. KCNJ2 is the most common causative gene, seen in 60% of the patients (3). While ATS is mainly inherited in an autosomal dominant pattern, de novo mutations occur in approximately 30% of the cases. Here, we present a case representing all the three cardinal features of ATS with 919A>G mutation of KCNJ2 gene.

CASE PRESENTATION

We report a 20-year-old female patient with sudden onset flaccid tetraparesis after she woke up in the morning. The patient complained of similar paroxysmal attacks since the age of 11, each of which consisted of weakness of the limbs, prominently in the lower extremities, lacking any sensory deficit and recovering gradually within a few days, seldomly attacks were severe enough to cause paraplegia. She reported stressful events or moderate intensity exercise a day before some of the attacks, but no dietary trigger. Until her present admission, she was evaluated several times at different centers mainly with an initial diagnosis of transverse myelitis, however magnetic resonance imagings of brain and spinal cord or analysis of cerebrospinal fluid did not reveal any pathology and finally her symptoms were accepted as psychogenic.

On gross examination she was a healthy looking young patient, with short stature, hypertelorism, low set ears, thin upper lip, dental abnormalities, and partial webbing (syndactyly) of second and third toes. She was alert and oriented. Cranial nerve examination was normal. She had severe proximal weakness (muscle research council scale (MRC) 3/5 deltoids and biceps and 0/5 psoas and quadriceps) with mild distal muscle involvement. Sensorial system examination was normal without any sensory level. Deep tendon reflexes were normal in the upper extremities, diminished on patella but Achilles reflexes were obtainable. Pathological reflexes were absent. Laboratory

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Figure 1. Long exercise test of the right abductor digiti minimi muscle in our patient
CMAP: compound motor action potential

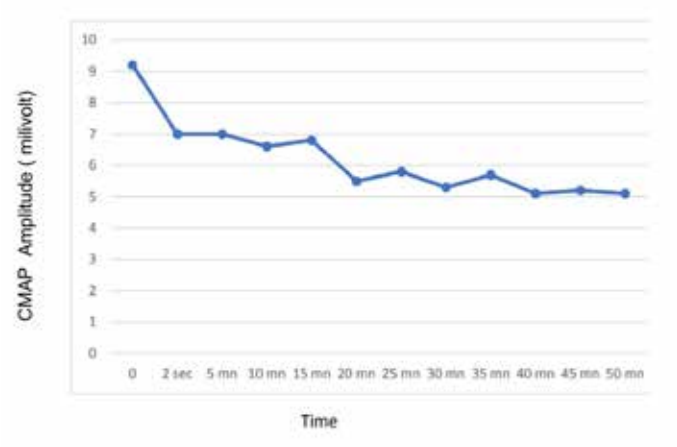
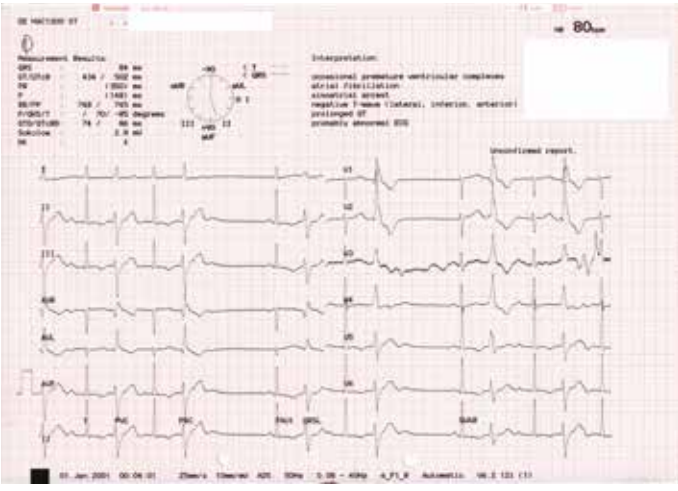


Figure 2. 12-lead electrocardiography of the patient showing bidirectional ventricular tachycardia



tests showed hypokalemia (3.4 mmol/L, normal range 3.5-5.1 mmol/L). Total blood count, liver enzymes, renal functions, thyroid function tests, serum sodium, magnesium, ionized calcium levels and serum creatine kinase level (125 U/L, normal range 29-168 U/L) were within normal limits. Oral potassium replacement provided improvement of weakness obviously within a few days.

Standard nerve conduction studies performed during the attack were normal and needle EMG showed no myotonia or myopathy. After the patient gained full strength, long exercise test on the right right abductor digiti minimi (ADM) muscle, and then a series of three short exercise tests were performed on the left ADM in accordance with the method that Fournier et al. reported previously (4). Compound muscle action potential (CMAP) amplitude decreased by 44.5% at 50th minute of the long exercise test (Figure 1), short exercise test did not reveal a decrease in CMAP amplitude.

In the light of neurological, electrocardiographic and phenotypic features we diagnosed the patient as ATS. Genetical analysis showed 46, XX female karyotype features without any numerical or structural chromosomal abnormality. DNA sequence analysis of KCNJ2 gene revealed pathogenic heterozygous variant KCNJ2:c,919A>G on the second exon of KCNJ2 gene leading to methionine displacement instead of valine amino-acid (KCNJ2:p.Met307Val).

Acetazolamide with oral potassium supplement reduced the frequency and severity of the paraplegic attacks in the follow up.

The patient also reported pre-syncope and palpitation attacks for the last 3 years. Electrocardiography (ECG) is shown in Figure 2. Premature ventricular contraction (PVC) burden was 27% on 24 hour holter ECG recording. Echocardiography revealed mild left ventricular systolic dysfunction, due to very frequent PVC it was not possible to calculate left ventricular ejection fraction using Simpson method. She was started on flecainide, a class Ic anti-arrhythmic agent, 100 mg bid. In the follow up PVC burden decreased to 2%.

It is unknown whether the mutation was de novo or autosomal dominantly inherited, because the patient's father died due to lung cancer at the age of 44. Other family members of the patient had no known cardiac or neurological symptoms, neither had any dysmorphic features.

Written informed consent was obtained from the patient.

DISCUSSION

Andersen Tawil Syndrome is a rare channelopathy with an estimated prevalence of 1: 500.000- 1.000.000 (2, 5). KCNJ2 gene mutation was the first shown gene related with the syndrome and was found in 60% of the cases (3). KCNJ2 encodes the inward rectifier potassium channel protein, Kir 2.1, which regulates resting membrane potential and cellular excitability of both cardiac and skeletal muscle. Clinically the disease has a typical triad of periodic paralysis, ventricular ectopy and dysmorphic features (1).

The syndrome accounts for less than 10% of all periodic paralysis (2). Periodic paralysis first develops during childhood or adolescence, can occur spontaneously or can be precipitated by stress, resting after long exercise, or carbohydrate rich food intake. Ictal potassium levels can be normal, elevated, but more frequently reduced (1, 6). This episodic weakness is thought to be caused by sodium channel inactivation and persistent membrane depolarization in the skeletal muscle due to the reduced inward potassium movement (7). Rarely there occurs persistent myopathy (8).

In the cardiac muscle, alteration of Kir2.1 function leads to prolongation of the most terminal phase of repolarization, so to delayed after-depolarization and Na+/Ca+-dependent

triggered activity (1). Electrocardiography can show prolongation of QT interval, prominent U waves and variable ventricular arrhythmias. Clinically the patient can be asymptomatic or can present with palpitations, pre-syncope, syncope or rarely with cardiac arrest (1). Both hypokalemia and hyperkalemia may precipitate serious ventricular arrhythmias.

Dysmorphic features related to ATS are broad forehead, hypertelorism, broad nasal bridge with bulbous tip, low set ears, short palpebral fissures, micro- and retrognathia, clinodactyly and syndactyly. Dental abnormalities like abnormal or missing lateral incisors, high-arched palate, cleft palate, relative microcephaly, small hands and feet, scoliosis are also reported. Dysmorphic features can be subtle, may involve any of these, but when present with paralytic attacks or long QT they can be hints for early diagnosis. The mechanism how potassium channel dysfunction in ATS leads to craniofacial defects is not clear. However, it is hypothesized that the effect of variant KCNJ2 on the resting membrane potential regionalization of ectodermal cells of craniofacial structures during early neurulation can be the responsible mechanism (9).

Here, we reported a patient with typical triad of ATS carrying a missense mutation of KCNJ2 gene, pathogenic heterozygous variant KCNJ2:c,919A>G (pMet307Val). This variant was recently defined in a Chinese ATS patient who had paralytic attacks and dysmorphic features (10). However that patient lacked any concomitant cardiac symptom or abnormalities in ECG.

To our knowledge, our case is the first reported case with ventricular arrhythmias due to KCNJ2:c,919A>G (pMet307Val) mutation, and reflects the clinical heterogeneity of the disease when compared with previous reports.

Informed Consent: Written informed consent was obtained from the patient who participated in this study.

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