

# Andersen-Tawil syndrome – a review of the literature and a case report

## *Zespół Andersen i Tawila – przegląd piśmiennictwa i opis przypadku*

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**Słowa kluczowe:** zespół Andersen i Tawila, napadowe porażenie mięśni.

### Summary

Andersen-Tawil syndrome is a rare form of channelopathy, i.e. disease caused by defective structure and function of the proteins that form the ion channels within the cell membrane. In patients with Andersen-Tawil syndrome, mutations of the KCNJ2 gene result in defective Kir 2.1 protein. The protein forms potassium ion channels. The clinical picture includes periodic muscular weakness occurring after physical exercise, cardiac arrhythmias and dysmorphic features (short stature, hypoplasia of mandible, short fingers and toes).

### Introduction

Andersen-Tawil syndrome is a rare disorder characterized by paroxysmal muscle paralysis, ventricular arrhythmias and developmental anomalies.

Two cases of familial periodic paralysis associated with ventricular ectopy were described for the first time in 1963 by Klein et al. [1]. In 1971, Ellen D. Andersen and co-workers [2] reported a new case of an 8-year-old boy and suggested syndromic association of muscular alterations and ventricular extrasystoles. Later, Rabi Tawil and colleagues [3] reviewed 10 previously reported cases and 4 new ones, and found that the condition is inherited in a predominantly autosomal dominant pattern. They used the term “Andersen syndrome”, which was renamed “Andersen-Tawil syndrome” in 2003 [4] in recognition of the

### Streszczenie

Zespół Andersen i Tawila jest rzadką postacią kanałopatii, tj. choroby uwarunkowanej defektem struktury i funkcji białek tworzących kanały jonowe w błonie komórkowej. W zespole Andersen i Tawila dochodzi do mutacji genu KCNJ2 kodującego białko Kir 2.1, tworzące kanał potasowy. Objawami klinicznymi choroby są okresowe napady osłabienia mięśniowego występujące po wysiłku, zaburzenia rytmu serca i wady rozwojowe (niski wzrost, niedorozwój żuchwy, krótkie palce u rąk i stóp).

contribution of Rabi Tawil, who refined understanding of the syndrome.

### Molecular genetics and pathology

Andersen-Tawil syndrome is a potassium ion channelopathy. The defective gene is located on chromosome 17q23 [6]. Mutation of a gene encoding proteins that are responsible for ion channel functioning is responsible for clinical features of the syndrome. Initially, three channel genes located within the chromosome region were considered as suitable candidate genes. They were SCN4A, CACNG1, and KCNJ2. The SCN4A gene mutations are known to be associated with periodic paralysis without heart and developmental abnormalities. The protein encoded by CACNG1 gene was not detected in the heart, and thus

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the KCNJ2 gene was considered as associated with Andersen-Tawil syndrome.

The KCNJ genes encode the inward rectifier potassium channel protein Kir. The Kir protein family is subdivided into seven members according to the extent of amino acid sequence homology [6]. The Kir protein consists of two transmembrane helical segments (M1 and M2), the loop between them is a pore-forming domain and the two terminal regions anchor the protein intracellularly. The channel is formed by four molecules that co-assemble in various manners.

The genes of the KCNJ family are expressed in various tissues of the body including the muscle, heart, brain, epithelial tissue and other tissues [7].

Three inherited human diseases have been linked to mutations of the KCNJ gene family. Mutation of KCNJ1 (=Kir 6.2) gene results in Bartter's syndrome (an autosomal recessive disorder characterized by hypokalaemia and salt wasting). The defective gene product is Kir 1.1 protein. Mutations in KCNJ11 (=Kir 6.2) gene are responsible for the syndrome of persistent hyperinsulinaemic hypoglycaemia. The defective protein in this syndrome is Kir 6.2 and the associated protein SUR1. The Andersen-Tawil syndrome is caused by mutations of the KCNJ2 gene. Additionally, mutation resulting in abnormal Kir 3.2 protein is a cause of severe ataxia in mice.

A number of mutations of the KCNJ2 gene have been described. Bendahton et al. [7] reported 19 mutations, and recently 6 new ones were reported by Davies et al. [8]. They include missense mutations in the amino-terminal and carboxy-terminal regions. Three similar mutations were reported in the P (pore) region. Additionally, deletions in the M1 helical region and carboxy-terminal region were shown. It is possible that new mutations will be discovered because the clinical picture of the Andersen-Tawil syndrome remains variable.

## Clinical manifestations

Various mutations and possible other alterations, i.e. different co-assembly of the subunits of the channel protein complex, are responsible for different severity and clinical presentation of the syndrome.

The clinical presentation of the syndrome includes muscle and cardiac manifestations and dysmorphic features.

## Skeletal and cardiac muscle involvement

Episodic muscular weakness or paralysis is usually the main clinical feature that leads the patient to seek

medical help. Cardiac involvement in patients with Andersen-Tawil syndrome are numerous due to phenotypic expression variability. Most of them need to be evaluated with electrophysiological methods and some manifestations are life-threatening. Electrocardiographic evaluation revealed QT interval prolongation or prominent U waves in the anterior precordial leads, although these findings are visible in some patients only. The U waves in the patients with Andersen-Tawil syndrome are recorded at higher heart rates, suggesting that they are not a normal variant seen in healthy individuals at low heart rates or hypokalaemia. A variety of arrhythmias can be detected in the patients, from isolated premature ventricular beats to complex ventricular ectopy and polymorphic ventricular tachycardias such as bidirectional ventricular tachycardia [9].

In addition to rhythm and conduction cardiac disturbances, structural anomalies of the cardiovascular system have been reported. They include bicuspid aortic valve insufficiency with or without aortic coarctation, and stenosis of the pulmonary artery valve. A family with Andersen-Tawil syndrome and dilated cardiomyopathy has recently been reported [10].

## Dysmorphic features

Dysmorphic manifestations are a basic feature of the Andersen-Tawil syndrome because they are not common in other channelopathies. Various features have been reported, including short stature, low-set ears, wide-set eyes (hypertelorism), clinodactyly (medial or lateral curvature of a finger or toe), and mandibular hypoplasia. Other abnormalities have also been reported: cryptorchidism, vaginal atresia, hyperthyroidism, unilateral kidney dysplasia as well as earlier described cardiovascular abnormalities [11].

## Disease course

Muscular weakness or paralysis is a key phenomenon for early diagnosis of the syndrome. The onset of episodes usually precedes the cardiac abnormalities. Typically, the manifestations occur after prolonged physical exertion. Muscular weakness is found during physical examination and may be associated with muscular wasting. The signs and symptoms are pronounced in the proximal muscles. The serum potassium level is not diagnostically significant as it may be higher, lower or normal in the patients and usually is unaltered in the patients' relatives. In some patients or their relatives serum creatine kinase activity remains elevated in absence of other reasons. Cognitive functioning impairment has also been reported in some cases [12].

The syndrome is generally considered as benign, although some cardiac arrhythmias may be hazardous for the patients. Frequency and severity of the paralytic attacks decrease in adulthood. In some patients, weakness and muscle degradation develop with age.

## Diagnosis

The heterogeneous nature of the syndrome is the major difficulty in diagnosis. Phenotypic alterations are the basis for clinical diagnosis. Detection of two of the skeletal, cardiac or developmental abnormalities typical for the Andersen-Tawil syndrome is required for diagnosis of the syndrome. Diagnosis is difficult due to heterogeneity of the syndrome caused by numerous mutations. Manifestation of at least two signs or symptoms representing two phenotypic classes (muscular, skeletal, cardiac or developmental) are required for diagnosis of Andersen-Tawil syndrome. There are however patients with limited symptoms only but confirmed diagnosis with molecular genetic studies [13]. Genetic defect resulting in mutations of Kir 2.1 is shown in 60% of the patients only; thus other molecular causes of the syndrome (e.g. impaired association of the channel proteins) are also possible.

The differential diagnosis includes other forms of periodic paralysis including secondary paralysis due to hyperthyroidism [14].

## Treatment

Management of patients with Anderson-Tawil syndrome is directed toward phenotypic manifestations that occur in the individual. Most of the efforts are associated with episodic muscular weakness and cardiac rhythm disturbances.

The knowledge on the effectiveness of therapy is based on anecdotal reports only because the syndrome is very heterogeneous and rare. Efforts to enhance potassium level are suggested to be a therapeutic option. Such therapies as oral potassium supplementation, sodium restriction, spironolactone or acetazolamide administration are suggested to decrease the severity of muscular symptoms. In female patients, oral contraceptives were reported to be partially successful management.

Cardiac manifestations are another therapeutic target. Unfortunately, there are no controlled trials on the effectiveness of antiarrhythmic drugs. Only anecdotal reports are available. They suggest the effectiveness of calcium channel blockers, amiodarone or beta-blockers or sodium channel blockers (propafenone, flecainide). Radiofrequency catheter ablation or implantation of a cardioverter-defibrillator have also been suggested [15, 16].

## Case report

A 25-year-old male patient was admitted to the Rheumatological Outpatient Clinic in Katowice due to periodic muscular weakness. The weakness was first recognized at the age of 9–11. The weakness was generalized but most significantly affected the lower limbs. It occurred some time (2–3 hrs) after moderate physical exercise. It lasted 2–3 days and sometimes was so severe that the patient had to stay exclusively in bed. There was no seasonal variation of the frequency of weakness episodes or a relationship with exposure to cold. Other medical history was absent but slight symptoms of hay fever were reported in a few recent spring-summer periods.

On physical examination only micrognathia was noted. Muscular force and development were normal. No other abnormal symptoms or signs were shown.

The patient provided medical documentation from his previous hospitalizations. Twice he was admitted to the hospital at the beginning of the weakness. Electromyographic examination revealed signs of muscular damage in the lower limb muscles. Knee jerks were decreased. Serum potassium level was normal and serum myoglobin level and creatine kinase activity were enhanced. These indices were normalized within 3 days of bed rest. Pathological evaluation of the muscle biopsy did not reveal any abnormalities. Myasthenia test was normal. There were no signs or symptoms of metabolic disease. In the stress treadmill test ventricular bigeminy and multiform ventricular extrasystole were found. In contrast to earlier findings, slight elevation of the serum potassium level was noted after the test. No specific treatment was recommended.

It is interesting that the father of the patient was found to have elevated serum creatine phosphate kinase activity. It was discovered incidentally a few years earlier and despite diagnostics there was no detectable cause of this alteration.

Genetic studies were not performed in the patient because he did not admit a second time to the Outpatient Clinic, and did not respond to our calls. Probably he moved abroad.

## Discussion

The final diagnosis in the reported patient remains unknown. Initially, he was suspected to have myopathy but this diagnosis was excluded. Later, periodic hypokalaemic paralysis was suggested. The suspicion of Andersen-Tawil syndrome is based on the clinical picture, exclusion of other causes (myasthenia, myopathy) and co-existence of cardiac abnormalities. Skeletal features were rather mild; only micrognathia was noted. The presence

of elevated creatine kinase activity in the father of the patient is an additional significant suggestion for the diagnosis. A final diagnosis would be possible on the basis of genetic evaluation.

The presented case was described against the background of a literature review to show a rare but probably underdiagnosed cause of muscular weakness due to ion channelopathy [17].

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