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Andersen Tawil syndrome – a case study

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Abstract

Introduction:

The first case of a patient with periodic paralysis of muscles accompanied by ventricular arrhythmias was described in 1963 by Klein and colleagues [1]. In 1971, the team led by E.D. Andersen published a paper on the familial coexistence of neurological disorders and arrhythmias accompanied by dysmorphic features, suggesting a new, unclassified disease syndrome [2]. Another report, this time by the Tawil team, analyzed 10 cases described up to the time and 4 new diagnosed by him, giving the genetic basis for understanding the mechanisms of the disease inheritance [3]. In 2003, the syndrome described by Tawilla was named after Andersen and Tawill (*Andersen Tawil Syndrome - ATS*).

ATS (syn. long QTc syndrome, type 7, LQTS 7,) is a rare genetic disorder inherited in an autosomal dominant manner. So far around 200 diagnoses of ATS have been made in the world. Mutations in the KCNJ2 gene located on the long arm of chromosome 17, encoding the Kir 2.1 protein, are responsible for the disease subtype 1, which accounts for 60% of the described cases. This protein is a component of the potassium ion channel, and its abnormal structure and function is the cause of repolarization disorders in the cells of the heart and skeletal muscles. However, in 6-20% of patients from families with confirmed presence of KCNJ2 mutations, no clinical symptoms of the syndrome were reported. It proves its differentiated penetration, and the genetic mechanism in the remaining patients remains unknown.

Despite the fact that patients with ATS are a very heterogeneous group in terms of the observed symptoms, this syndrome has a classic triad:

1. changes in the ECG trace of the T wave and the presence of the U wave (extended duration of the descending arm of the T wave, a characteristic wide U wave and a wide combination of T and U waves - these features distinguish ATS from other long QTc syndromes) and arrhythmias in the form of single multifocal premature ventricular beats, polymorphic, bidirectional ventricular tachycardia, which may be asymptomatic or, more often, cause palpitations. Less common manifestations of arrhythmias are fainting, cardiac arrest and sudden cardiac death[4].
2. periodic muscle strength impairment (periodic paralysis) occurring most often after a prolonged period of rest or during rest after intense exercise, accompanied by a decrease in the concentration of potassium in the blood serum; in some cases, there is a constant, albeit slight, weakening of muscle strength
3. typical malformations (dysmorphia), most often including short stature, hypertelorism, small mandible, low-set auricles and abnormalities of curvature within the spine.

In patients with an unconfirmed genetic mutation, the diagnosis of ATS requires at least two of the above-mentioned symptoms. However, in some genetically confirmed cases their expression may be very low[5]

Due to the described dysfunctions in the cognitive sphere, mainly in the field of reading skills and mathematical skills, patients should also be covered by psychological care, and due to behavioral changes, in some cases also psychiatric.

Purpose of work: approximation of the ATS syndrome, case report of a boy with diagnosed ATS.

Materials and methods: physical examination, ECG, 24 hour ECG, echocardiography.

Case report:

An 11-year-old boy was referred to a cardiology clinic due to a burdened family history. The boy's mother, her two sisters, and their father had ECG prolongation of QTc, complex ventricular arrhythmias, loss of consciousness, and presented short stature and some similar dimorphic features. As far as the mother and one of her sister were concerned cardiac arrhythmias increased during clinical observation to haemodynamically unstable ventricular tachycardia, which was ultimately an indication for the implantation of a cardioverter-defibrillator. Despite that treatment the boy's mother died at the age of 25. So far, no genetic diagnosis has been performed in the family. In the immediate postpartum period, the boy had cardiac arrhythmias in the form of sinus arrest, and the ECG showed a tendency to a prolonged QT. Later, he underwent endocrinological examination due to short stature - somatotrophic pituitary insufficiency was excluded.

On physical examination, the boy presented signs of abnormal development and dysmorphism: short stature (height below the 3rd percentile with a body weight of the 10th percentile), small head circumference, microcephaly, triangular face with a wide forehead, micrognathia, low-set auricles, wide-set eyes (hypertelorism), narrow eyelid gaps, thin upper lip, small lower jaw, small hands, clinodactyly of the fifth finger of both hands, small feet. Muscle strength and tone remained within normal limits.

In routine ECG the asymmetry and elongation of the descending arm of the T wave were noticeable, and in the precordial leads, the broad U wave was particularly noticeable in the V2-3. The corrected QT interval was within the normal range. Counted with the U wave in leads V2 and 3, it was a maximum of 670 milliseconds. 24 hour ECG was performed which showed sinus rhythm, QTc measurements technically difficult - a maximum of QTc up to 500 milliseconds, QTUc up to 670 milliseconds. Few monomorphic single premature ventricular beats were recorded. Complex forms of arrhythmias have not been observed. The echocardiographic examination revealed a functional bicuspid aortic valve with no evidence of its dysfunction; besides, the structure and function of the myocardium showed no abnormalities.

A burdened family history, dysmorphism, and changes in the EKG record aroused ATS suspicion. The boy was referred for a neurological and genetic consultations. Standard karyotype test showed normal male karyotype. DNA analysis confirmed the A304D mutation in one allele of the KCNJ2 gene, not yet registered in the HGMD (human gene mutation data) database for the KCNJ2 gene. The PolyPhen technology (Polymorphism Phenotyping v2) and Sift, which predicted whether an amino acid substitution influenced the protein function, classified the change as pathogenic, and the diagnosis of Andersen Tawil syndrome was made on this basis. Metoprolol was included in the treatment at the initial dose of 0.75 mg / kg bw / day with a good drug tolerance. The performed stress test did not increase the arrhythmias. Ultimately, the dose of the drug was increased to 1.2 mg / kg bw / day.

At present, the patient is under multi-specialist care including: cardiological, neurological, psychological, orthopedic and rehabilitation. During the last visits, the patient complained of impaired functions of the lower limbs. Palpitations and fainting have not occurred so far. There are no complex arrhythmias in the 24-hour ECG recordings.

Discussion

The described patient met all clinical, phenotypic and genetic criteria for the diagnosis of ATS. Routine ECG showed a prolonged duration of the descending T-wave, a characteristic broad U wave, and a broad combination of T and U waves.

In their work, Zhang et al. demonstrated a high correlation between the presence of characteristic changes in the T and U waves in the ECG with a mutation in the KCNJ2 gene (91% of patients with ATS and a confirmed mutation had the described changes in the ECG), which were not present any of the patients without mutations in this gene. The duration of the QT interval on a routine ECG is usually normal or slightly prolonged, as in present in our patient. In the study by Zhang et al. cited above, the mean QTc value was 440 ms, only 17% of patients had a QTc prolongation of over 460 ms [6]. These observations are also confirmed by the presented case.

Ventricular arrhythmias found in patients with ATS are usually asymptomatic. According to Zhang et al. single premature ventricular beats occurred in 41% of 96 patients, non-sustained ventricular tachycardia in 23%, and torsade de pointes in 3%. Similar studies conducted by Tristani-Firouzi et al. on a group of 17 patients showed the presence of non-sustained ventricular tachycardia in 65%, torsade de pointes occurred in 2 patients, but no sudden cardiac death was found. [7]. In the described patient, in 24-hour Holter ECG monitoring, only a few single ventricular premature beats, without complex forms, were found.

The presence of a small U wave on the ECG, visible mainly in precordial leads with slow heart rate, is a variant of the norm. A higher U wave may be present in such cases as low concentration of potassium in the blood serum, pheochromocytoma, during the use of certain antiarrhythmic drugs, e.g. class IC or III [8]. Suggested mechanisms that may increase the amplitude of the U wave are ischemia-induced regional inhomogeneity in repolarization, spontaneous Purkinje fiber activity, or the presence of early follow-up depolarizations [9]. In the described patient, the T wave and the U wave remained in correlation to each other in the relation typical for ATS, both during slow and fast heart rate. During the baseline ECG recording, serum potassium was normal and the patient was not taking any medications.

Some reports also emphasize the coexistence of structural abnormalities in echocardiography in patients with ATS in the form of a bicuspid aortic valve, aortic coarctation and pulmonary stenosis, therefore they require echocardiographic control in each case. [10]. The patient we describe was diagnosed with a bicuspid aortic valve.

Another abnormality reported in patients with ATS is dilated cardiomyopathy. Schoonderwoerd reported 3 cases of ATS with the p.Arg218Trp mutation; two of them developed dilated cardiomyopathy [10]. Whether the increased risk of cardiomyopathy in ATS is only related to this particular mutation requires further investigation.

Pharmacological treatment of ATS patients focuses on symptomatic management. Due to the fact that ATS is still a rarely recognized syndrome, there are no studies describing the effectiveness of treatment in large population groups, and most reports are reports of single or family cases. Moreover, the group diagnosed with ATS is also very heterogeneous in terms of the severity of symptoms.

Conclusions

One of the methods of therapeutic interaction is supplementation with potassium preparations, sodium restriction or chronic administration of spironolactone. Such procedures seem to reduce the severity of mainly symptoms of muscle weakness. The management of patients with symptoms of arrhythmia consists in administering beta-blockers, calcium channel blockers or sodium channel blockers (propafenone, flecainide), although there is no evidence on their effectiveness in large population groups. In patients with complex cardiac arrhythmias, chronic use of amiodarone should be considered and a cardioverter-defibrillator should be implanted in case of high risk of sudden arrhythmic death. [9].

References

1. Klein R., Ganelin R., Marks J.F. et al. Periodic paralysis with cardiac arrhythmia. *J Pediatr.* 1963; 62: 371-385
2. Andersen E.D., Krasilnikoff P.A., Overvad H. Intermittent muscular weakness, extrasystoles and multiple developmental anomalies. A new syndrome? *Acta Paediat Scand* 1971; 60: 559-564
3. Tawil R., Ptacek L.J., Paclakis S.G., et al. Andersen's syndrome: potassium-sensitive periodic paralysis, ventricular ectopy, and dysmorphic features. *Ann Neurol.* 1994; 35: 326-330
4. Haruna Y, Kobori A, Makiyama T, Yoshida H, Akao M, Doi T, Tsuji K, Ono S, Nishio Y, Shimizu W, Inoue T, Murakami T, Tsuboi N, Yamanouchi H, Ushinohama H, Nakamura Y, Yoshinaga M, Horigome H, Aizawa Y, Kita T, Horie M. Genotype-phenotype correlations of KCNJ2 mutations in Japanese patients with Andersen-Tawil syndrome. *Hum Mutat.* 2007;28:208.
5. Tristani-Firouzi M, Jensen JL, Donaldson MR, Sansone V, Meola G, Hahn A, Bendahhou S, Kwiecinski H, Fidzianska A, Plaster N, Fu YH, Ptacek LJ, Tawil R. Functional and clinical characterization of KCNJ2 mutations associated with LQT7 (Andersen syndrome). *J Clin Invest.* 2002;110:381-8.
6. Zhang L, Benson DW, Tristani-Firouzi M, Ptacek LJ, Tawil R, Schwartz PJ, George AL, Horie M, Andelfinger G, Snow GL, Fu YH, Ackerman MJ, Vincent GM. Electrocardiographic features in Andersen-Tawil syndrome patients with KCNJ2 mutations: characteristic T-U-wave patterns predict the KCNJ2 genotype. *Circulation.* 2005;111:2720-6.
7. Tristani-Firouzi M, Jensen JL, Donaldson MR, et al. Functional and clinical characterization of KCNJ2 mutations associated with LQT7 (Andersen syndrome). *J Clin Invest* 2002; 110: 381-8.
8. Smith AH, Fish FA, Kannankeril PJ. Andersen-Tawil syndrome. *Indian Pacing Electrophysiol J* 2006; 6: 32-43.
9. Andelfinger G, Tapper AR, Welch RC, et al. KCNJ2 mutation results in Andersen syndrome with sex-specific cardiac and skeletal muscle phenotypes. *Am J Hum Genet* 2002; 71: 663-68.
10. Schoonderwoerd BA, Wiesfeld AC, Wilde AA, van den Heuvel F, Van Tintelen JP, van den Berg MP, Van Veldhuisen DJ, Van Gelder IC. A family with Andersen-Tawil syndrome and dilated cardiomyopathy. *Heart Rhythm.* 2006;3:1346-50.
11. Donaldson MR, Jensen JL, Tristani-Firouzi M, Tawil R, Bendahhou S, Suarez WA, Cobo AM, Poza JJ, Behr E, Wagstaff J, Szepetowski P, Pereira S, Mozaffar T, Escolar DM, Fu YH, Ptácek LJ. PIP2 binding residues of Kir2.1 are common targets of mutations causing Andersen syndrome. *Neurology.* 2003;60:1811-6.