CASE REPORT

Can flecainide totally eliminate bidirectional ventricular tachycardia in pediatric patients with Andersen-Tawil syndrome?

Flekainid Andersen-Tawil sendromlu pediyatrik hastalarda bidireksiyonel ventriküler taşikardiyi tamamen ortadan kaldırabilir mi?

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Summary– Andersen-Tawil syndrome (ATS) is a disorder that causes episodes of muscle weakness (periodic paralysis), changes in heart rhythm, and developmental abnormalities. QT prolongation and ventricular arrhythmias, including bidirectional ventricular tachycardia (VT) and polymorphic VT, may occur. About 60% of all cases of the disorder are caused by mutations in the KCNJ2 gene. A 13-year-old female patient was referred for frequent premature ventricular contractions. Suspicion of ATS due to dysmorphic findings, electrocardiogram changes, and periodic muscle weakness was genetically confirmed. Beta-blocker therapy was initiated as a first-line treatment for bidirectional VT and frequent polymorphic premature ventricular contractions. Despite proper treatment, the VT attacks were not brought under control. Flecainide was added to the treatment regime. The number of premature ventricular contractions was dramatically reduced with flecainide and the VT attacks completely disappeared. This patient is a rare example of ATS in our country. This article provides a description of successful management of rhythm disturbance in a patient with ATS.

Özet– Andersen-Tawil sendromu (ATS), kas güçsüzlüğü (periyodik paralizi), ritm bozuklukları ve gelişim bozukluklarına neden olan bir hastalıktır. QT uzaması ve bidireksiyonel ventriküler taşikardi (VT) ve polimorfik VT'yi de içeren ventriküler aritmiler ortaya çıkabilir. Tüm olguların yaklaşık %60'ı, KCNJ2 genindeki mutasyonlardan kaynaklanmaktadır. On üç yaşında kız hasta, sık ventriküler erken atımlar nedeniyle hastanemize sevk edildi. Hasta, morfolojik bozuklukları, EKG değişiklikleri ve periyodik kas güçsüzlüğü nedeniyle ATS olarak düşünüldü ve tanı genetik olarak doğrulandı. Bidireksiyonel VT ve sık polimorfik erken ventriküler atımları için ilk basamak tedavi olarak beta bloker başlandı. Ancak tedaviye rağmen, hastanın VT atakları kontrol altına alınamadı. Bunun üzerine Flekainid tedaviye eklendi. Flekainid ile prematüre ventriküler atımların sayısı çarpıcı bir şekilde azaldı. Ayrıca VT atakları tamamen kayboldu. Bu hasta, ülkemizde nadir görülen ATS'li hastalardan biridir. Bu makalede ATS'li bir hastada ritm bozukluğunun başarılı yönetimi anlatılmıştır.

Andersen-Tawil syndrome (ATS) is a very rare disorder that is characterized by ventricular arrhythmias and prolonged QT intervals, periodic flaccid muscle weakness, and anomalies consisting of a small mandible, low-set ears, hypertelorism, syndactyly, clinodactyly, and scoliosis.[1] Mutations in the KCNJ2 gene, which encodes the alpha subunit of the potassium channel Kir2.1, have been identified in 50% of patients with ATS.[1] De novo mutations were observed in the remaining cases.

Cardiac manifestations of ATS include frequent premature ventricular contractions (PVCs), QU interval prolongation, prominence of U waves, and polymorphic ventricular tachycardia (VT) known as bidirectional VT.[2] Despite the high burden of PVCs,

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patients may be asymptomatic. As a result of the low speed, even in cases of bidirectional VT, the occurrence of clinically important events has been reported to be approximately 3%.[2,3] The possibility of life-threatening arrhythmias is relatively low compared with other types of genetic arrhythmia.[3,4] However, a large ventricular arrhythmia burden over a long period can be detrimental to left ventricular function and lead to cardiomyopathy.[4]

Abbreviations:

ATS	*Andersen-Tawil syndrome*
CPVT	*Catecholaminergic polymorphic VT*
ECG	*Electrocardiogram*
ICD	*Implantable cardioverter-defibrillator*
PVC	*Premature ventricular contraction*
QTc	*Corrected QT interval*
RFCA	*Radiofrequency catheter ablation*
VT	*Ventricular tachycardia*

In this article, the case of a 13-year-old girl with frequent polymorphic ventricular premature beats and bidirectional VT is presented. Clinically, the patient was thought to have ATS due to findings of the typical dysmorphic features and episodes of periodic paralysis and ventricular arrhythmias. The clinical diagnosis was confirmed by molecular genetic analysis. Ventricular arrhythmias, which are very resistant to beta-blockers, completely subsided with flecainide treatment. To the best of our knowledge, this is the first presentation of successful treatment of ventricular arrhythmias with flecainide in a pediatric patient with genetically confirmed ATS in Turkey.

CASE REPORT

A 13-year-old female patient visited our clinic for frequent PVCs. Polymorphic PVCs were detected at another center where the patient had initially presented with chest pain. It was learned from her documentation that she had complaints of intermittent palpitations but that she had never fainted. There were no significant features in her medical history other than prematurity and periodic episodes of muscular weakness that repeated every 2 to 3 months and lasted for a week. These episodes were so severe that the patient could not go to school. There was no familial history of sudden death, syncope, or seizures.

A physical examination revealed a syndromic appearance, growth failure with short stature (height: 138 cm [<3rd percentile] and weight 35 kg [<3rd percentile]), microretrognathia, syndactyly between the second and third toes and fingers, a broad forehead, and clinodactyly of the fifth finger of both hands (Fig. 1a-d). Her heart sounds were very arrhythmic, and there were very frequent premature contractions. Her neurological status was consistent with mild cognitive developmental retardation.

Upon admission, a 12-lead electrocardiogram (ECG) showed frequent and bidirectional PVCs (Fig. 2a). At the initial assessment, the bidirectional PVCs were so severe that a corrected QT interval (QTc) could hardly be measured. Although a QTc was measured as 445 milliseconds, prominent U waves and a long TU distance were significant (QTc measurements including U wave were >600 milliseconds). A 24-hour period of Holter monitoring demonstrated frequent polymorphic PVCs, bidirectional VT, and non-sustained polymorphic VT (Fig. 2b). The baseline 24-hour monitoring results demonstrated a very high burden of PVCs — about 28,500 (28%) isolated polymorphic PVCs — with nonsustained VT occurring 4 times during the recording period. Echocardiography revealed mitral valve prolapse with normal left ventricular function.

A treadmill exercise test could not be conducted due to the lower extremity muscle weakness of the patient. However, bidirectional VT was detected at doses of 0.2 microgram/kg/minute infusion during an

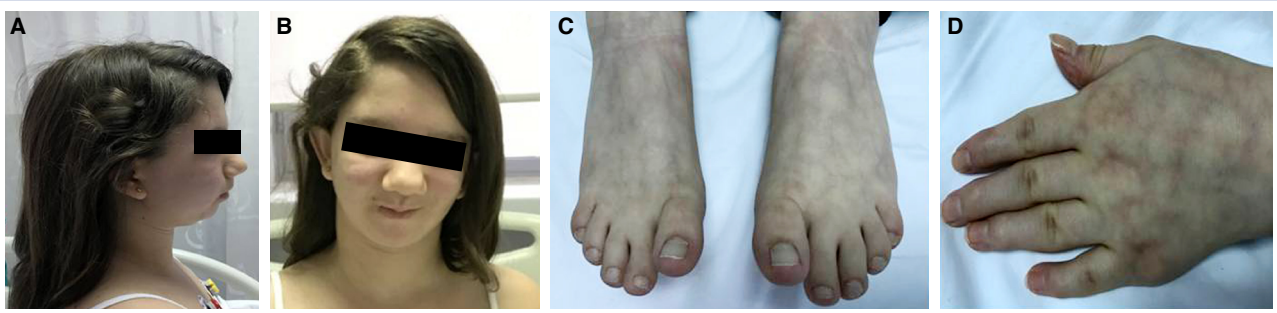

Figure 1. **(A)** Typical dysmorphic facial features of Andersen-Tawil syndrome: microretrognathia, and **(B)** broad forehead; **(C)** Syndactyly between the second and third toes; **(D)** Clinodactyly of the fifth finger.

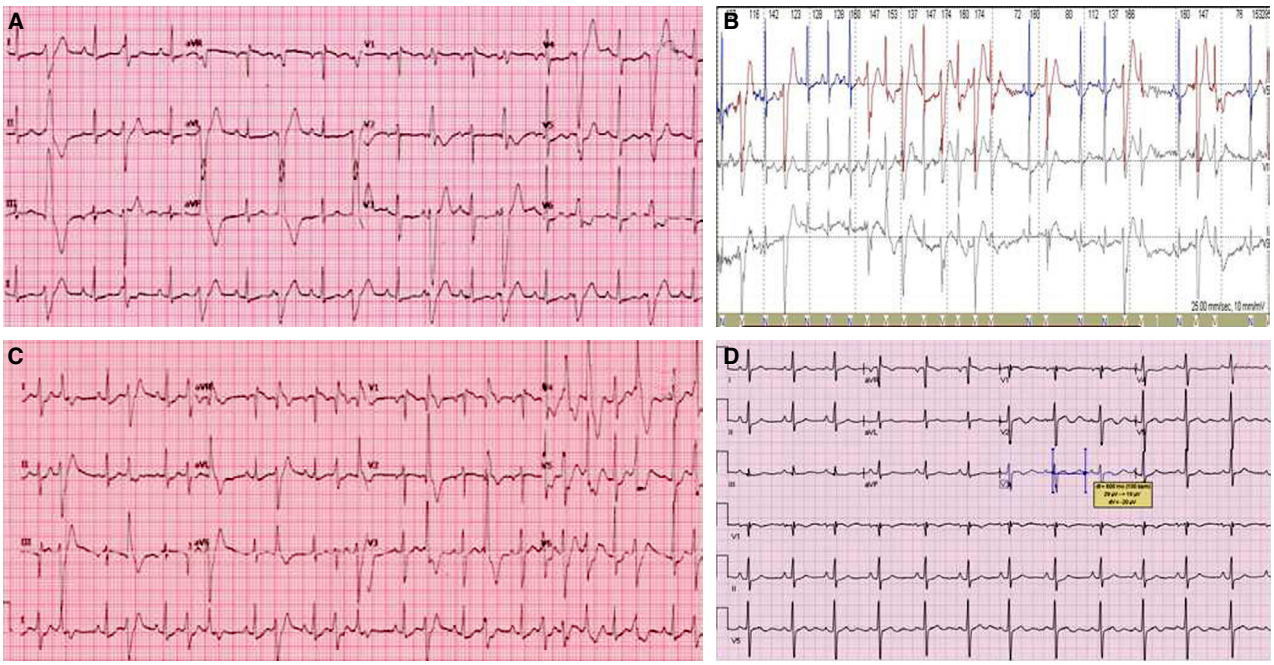

Figure 2. **(A)** Surface electrocardiogram recorded at admission showed bigeminy and bidirectional premature ventricular contractions (PVCs); **(B)** Bidirectional ventricular tachycardia was seen on Holter monitoring; **(C)** Polymorphic PVCs became visible during an adrenaline infusion test; **(D)** After flecainide treatment, there were no PVCs, but prominent U waves persisted.

adrenaline stimulation test (Fig. 2c). The biochemical values, including potassium, were normal. Based on the findings, Anderson-Tawil syndrome was suspected. The diagnosis was confirmed by molecular genetic analysis, which demonstrated a p.V200M (c.598G >A) mutation in the KCNJ2 gene. The patient had no other siblings and her mother's and father's QTc values were normal. Her mother's and father's genetic testing results were still expected at the time of writing.

Beta-blocker therapy (propranolol 4 mg/kg/day) was started after the initial evaluation. Despite appropriate therapy, the PVC burden was not controlled. Thereafter, flecainide treatment (100 mg/m^2/day) was initiated, and the PVC burden immediately decreased dramatically. Within 48 hours after administration of the drug, almost all of the PVCs had disappeared. Flecainide was also very effective in the suppression of bidirectional VT attacks. An implantable cardioverter-defibrillator (ICD) device was not considered because the ventricular arrhythmias were controlled with medical treatment. During a 6-month follow-up period, ECG and 24-hour ambulatory ECG tests were repeated, and a treadmill exercise test was conducted. Two weeks after beginning combination therapy, there was no PVC recorded on a surface ECG. The QT interval shortened to 440 milliseconds, but U waves persisted prominently some precordial leads, especially V2-V3 (Fig. 2d). Diazoxide was added to the antiarrhythmic treatment for the periodic muscular paralysis, and the frequency of episodes of paralysis decreased.

DISCUSSION

ATS is characterized by a triad of episodic flaccid muscle weakness, ventricular arrhythmias, and a prolonged QT interval, as well as anomalies including low-set ears, widely spaced eyes, a small mandible, fifth-digit clinodactyly, syndactyly, short stature, and scoliosis.[1,5] Most patients have a mutation in the KCNJ2 gene, which encodes the inward rectifier K+(IK1) channel.[3–5] This causes prolongation in the terminal phase of the cardiac action potential, producing early afterdepolarization.[6,7] The depressed IK1 function also leads to cellular calcium overload, causing late afterdepolarization and leads to triggered activity.[6,7] These cardiac action potential changes result in a prolonged QT interval, which is originally related to a prolonged QU interval, bidirectional VT, and Torsades de pointes.[3,6] Although the arrhythmia burden is usually high, patients are rarely symptomatic.[4,7] That does not mean that symptoms are never seen,

however. Cardiac arrest occurs in about 3% of patients.[7,8] Although a risk factor for cardiac arrest was not previously identified, one recent study claimed that micrognathia, periodic paralysis, and prolonged Tpeak-Tend time may be associated with a higher risk of arrhythmia, syncope, and cardiac arrest.[9]

The primary cardiac manifestations of ATS include frequent PVCs, QU interval prolongation, prominent U-waves, and a special type of polymorphic VT called bidirectional VT. Bidirectional VT is rarely observed in children, but it is the hallmark of a handful of disease states, including ATS, catecholaminergic polymorphic VT (CPVT), and digitalis toxicity.[1–3] Each of these clinical entities shares a common underlying abnormality in calcium homeostasis that can trigger delayed afterdepolarization-dependent arrhythmias. In ATS, polymorphic VT and/or bidirectional VT is relatively slow, well tolerated, and usually asymptomatic, with a heart rate of about 130 to 150 bpm. Frequent ventricular ectopy at rest is helpful in distinguishing ATS from typical CPVT. In typical CPVT, rapid bidirectional VT is usually associated with exercise. In addition, asymptomatic PVCs are frequently observed in ATS patients, whereas in CPVT patients, PVCs and asymptomatic non-sustained VT are uncommon.[2,8] Finally, dysmorphic facial features and periodic paralysis in ATS patients are very helpful in distinguishing these cases from CPVT.[1–3,5]

The classification of Andersen-Tawil syndrome as a type of long QT interval is still controversial.[7,10] Some authors have emphasized that it should be seen as TU or QU prolongation rather than QT interval.[3,6,7] There is also U wave prominence. But, as opposed to the unaffected population, U waves become more prominent during sympathetic status in patients with ATS.[11]

Beta-blockers are used as a first-line treatment. However, there are many reports about partial efficacy of beta-blockers.[12,13] Therefore, calcium channel blockers, especially verapamil, were of interest.[12] Direct inhibition of cellular calcium overload, which is potentially responsible for arrhythmias, was considered reasonable.[7,12] However, they are only fractionally as successful in preventing life-threatening arrhythmias as beta-blockers.[13] At this point, the superiority of flecainide in ATS should be emphasized. The mechanism by which flecainide suppresses ventricular ectopy and arrhythmias is not fully understood.[14] However, a decrease in sarcoplasmic reticulum calcium overload and sodium currents enhanced by the sodium/calcium exchanger, may explain the antiarrhythmic action of flecainide.[4,7,13] In patients with Andersen-Tawil syndrome, the markedly prolonged QU interval leads to calcium overload. Therefore, intracellular calcium overload and triggered activity may be possible mechanisms for arrhythmias in patients with ATS. Flecainide can change the sodium-calcium exchange, resulting in a decrease in calcium through the exchanger and the calcium content in the sarcoplasmic reticulum.[4,7,13,14] Flecainide has a good safety record and a low incidence of adverse effects, rare reports of end-organ toxicity, and a low risk of ventricular proarrhythmia in children. Potential cardiac adverse effects of flecainide include proarrhythmia (especially atrial flutter with rapid ventricular response, with aberrant conduction and broad QRS complexes), conduction abnormalities, and negative inotropic effects.[15,16] Nonetheless, in children using flecainide, the QRS width should be monitored and patients should be observed for potential proarrhythmic effects.

As in other hereditary primary genetic arrhythmia syndromes, it may seem appropriate to eliminate these arrhythmias by means of radiofrequency catheter ablation (RFCA). To our knowledge, there is no publication of successful RFCA in a case of ATS. Delannoy et al.[3] reported that RFCA was unsuccessful in the 5 cases in which it was attempted.

In ATS patients for whom drug treatment is not effective and who often show bidirectional VT despite treatment or who have had previous cardiac arrest, the use of an ICD may be considered.[17] However, the effectiveness of an ICD in ATS patients without severe cardiac symptoms is controversial. Airey et al.[18] have performed a follow-up study of 16 ATS patients with various cardiac symptoms who underwent ICD implantation. Of these 16 patients, 3 received an ICD for documented VF arrest. Eight patients (50%) received inappropriate shocks, while 4 (25%) had appropriate device intervention. The latter group consisted of 3 patients with an ICD implanted for documented VF arrest and 1 with bidirectional VT and syncope. Given these results, it may be advisable that an ICD is only used when patients are at high risk for cardiac arrest and death.[17,18]

The present case is an example of one of the rarest genetically diagnosed conditions seen in our country.

[19] This is also the first presentation in Turkey of effective suppression of ventricular ectopy and VT via flecainide in a patient with ATS.

In conclusion, ATS should be kept in mind if there is an association between polymorphic PVC, bidirectional VT, and dysmorphic properties. A long QT interval associated with significant U-wave (especially in the V2-V3 leads) on a 12-lead ECG is diagnostic. The use of flecainide in combination with beta-blockers appears to be very effective in the treatment of ventricular arrhythmias in ATS.

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