JPPT | Case Report

Bidirectional Ventricular Tachycardia and Prominent U Waves: Look at Fingers and Muscles and Use Flecainide

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We present a case of bidirectional ventricular tachycardia in a 15-year-old boy asymptomatic for arrhythmias, whose major complaint was muscle weakness. At our first evaluation he was receiving sotalol for his ventricular arrhythmias. In addition to bidirectional tachycardia, electrocardiogram during sinus rhythm showed prominent U waves and prolonged QT-U interval. These electrocardiographic signs, along with the evidence of clinodactyly and mild hypertelorism, led us to the diagnosis of Andersen-Tawil syndrome, confirmed by genetic analysis that revealed a "*de novo*" missense mutation of KCNJ2 gene. Monotherapy with flecainide was rapidly effective and almost eliminated ventricular arrhythmias. After a 4-year follow-up there were no adverse events, flecainide has been well tolerated without significant modification of the QRS or repolarization, and ventricular arrhythmias have not been relapsed to date. The case highlights the importance of a correct clinical diagnosis, which is crucial for the optimal selection of the most appropriate drug therapy, which is expected not to be harmful, before being beneficial.

ABBREVIATIONS ECG, electrocardiogram; VEB, ventricular ectopic beat; VT, ventricular tachycardia

KEYWORDS Andersen-Tawil syndrome; bidirectional tachycardia; flecainide; U-waves

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Case Report

A 15-year-old white boy (weight 50 kg) with history of muscle weakness was referred to our outpatient pediatric cardiology service for the occasional finding of ventricular ectopic beats (VEBs) during his workup for the assessment of suspected myopathy, requiring muscular biopsy. He was completely asymptomatic for arrhythmias and had no family history of sudden death or congenital heart disease.

Cardiovascular examination was unremarkable, except for the sudden onset of tachycardia during auscultation. Electrocardiogram showed a ventricular bidirectional tachycardia (Figure 1A) alternating with atrial rhythm with frequent polymorphic VEBs (Figure 1B). The patient was already on sotalol 120 mg/day divided 2 times a day at that time (2.4 mg/kg/day; recommended dosage, 2–8 mg/kg/day[1] up to a maximum dose of 320 mg/day), for the purpose of performing cardiac magnetic resonance for suspected cardiomyopathy, but the therapy was not effective after 3 weeks.

He was then admitted to our hospital for a better characterization of the rhythm disturbance.

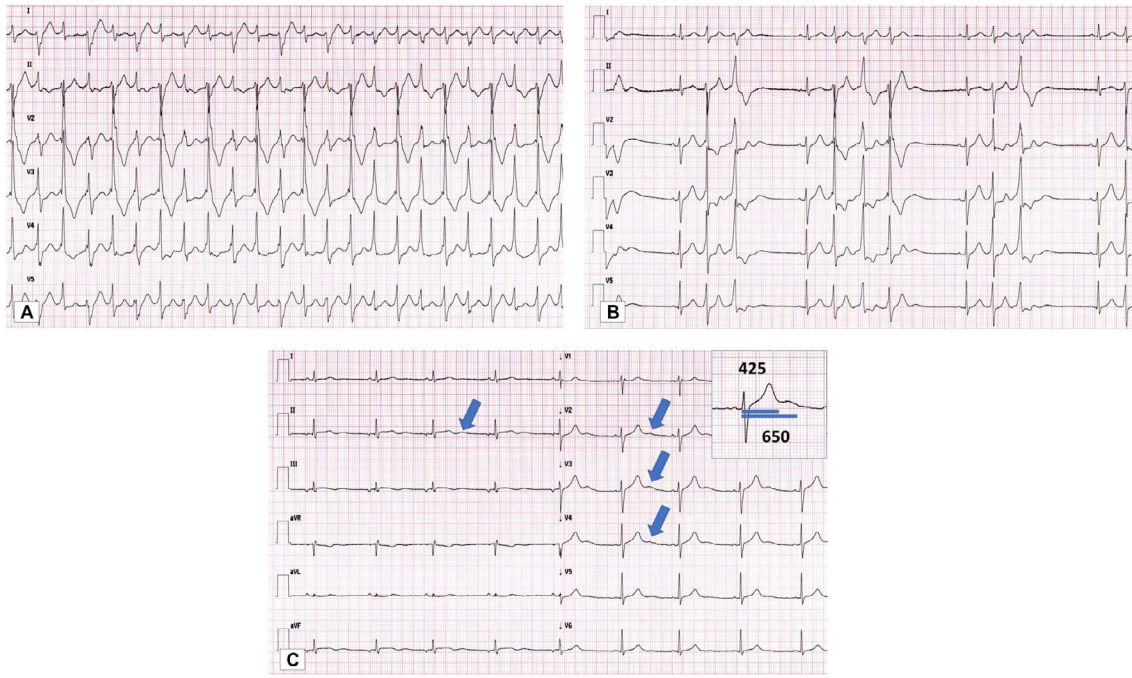
Holter monitoring documented a VEB burden of 9.8%, with frequent episodes of sustained bidirectional ventricular tachycardia (VT). Surprisingly, the patient was completely asymptomatic and ventricular function on echocardiography was normal. Baseline electrocardiogram (ECG) free from arrhythmias (Figure 1C) was characterized by low atrial ectopic rhythm (P axis, −15°) with normal atrioventricular conduction (P-R interval, 120 msec) and incomplete right bundle branch block (QRS width 90 msec). Prominent U waves were present in almost all precordial and inferior leads. Mean QT corrected interval was 425 msec, whereas the mean corrected QT-U interval was extremely prolonged, calculated as 650 msec. A typical sign was also noticed on the Holter recording, because prominent U waves had longer duration and higher amplitude during normal sinus rhythm (Figure 2A) but showed increased amplitude with faster heart rates, generating the so-called U-on-P sign (Figure 2B) when the P wave during sinus tachycardia was inscribed within the U wave of the preceding beat, resembling high-voltage P waves.

Treadmill exercise testing documented significant suppression of arrhythmias during exercise, with ventricular bigeminy only at the peak of exertion. This behavior ruled out suspicion of cathecolaminergic polymorphic VT.

Sotalol was then replaced with propranolol 120 mg/day (2.4 mg/kg; recommended dosage, 1–3 mg/kg/day)[1] divided 3 times a day for 1 month, and then by nadolol 40 mg/day. However, after a few days the patient complained of profound asthenia, along with there being a completely absent effect of any drugs on arrhythmias.

Meanwhile, muscular biopsy documented a vacuolar autophagic myopathy, and muscular weakness was

Figure 1. (A) Bidirectional ventricular tachycardia at heart rate of 140 bpm. (B) Sinus rhythm with frequent premature bidirectional ventricular ectopic beats, in couples and triplets. (C) A 12-lead electrocardiogram with atrial rhythm, narrow QRS, and prominent U waves (arrows). Particular of V1 is shown in the box, showing a normal corrected QTc interval and prolonged QT-U interval.



better characterized as periodic paralysis. Genetic evaluation based on periodic paralysis, prominent U waves on ECG, and ventricular arrhythmias led to evidence of mild hypertelorism and clinodactyly (Figure 2C), suggesting together a diagnosis of Andersen-Tawil syndrome, also referred to as Long QT Syndrome 7, caused by mutations of the gene encoding for potassium channel proteins (KCNJ2).

The patient was then started on flecainide 200 mg/day divided 2 times a day (4 mg/kg/day; recommended dosage, 2–7 mg/kg/day),[1] and shortly after the burden of ventricular arrhythmias on Holter ECG was reduced from 9.8% to 0.5% (Figure 2D). The patient has been regularly followed up for 4 years, without any adverse event; flecainide has been well tolerated without significant modification of the QRS or repolarization; and ventricular arrhythmias have not been relapsed to date.

Genetic characterization revealed a missense mutation in heterozygosity of KCNJ2 gene (variant NM_000891.2(KCNJ2):c.[914C>T];[=] (p.[Thr305Ile)];[=]). The patient's family also was screened, although the mutation was not found in the mother or the father.

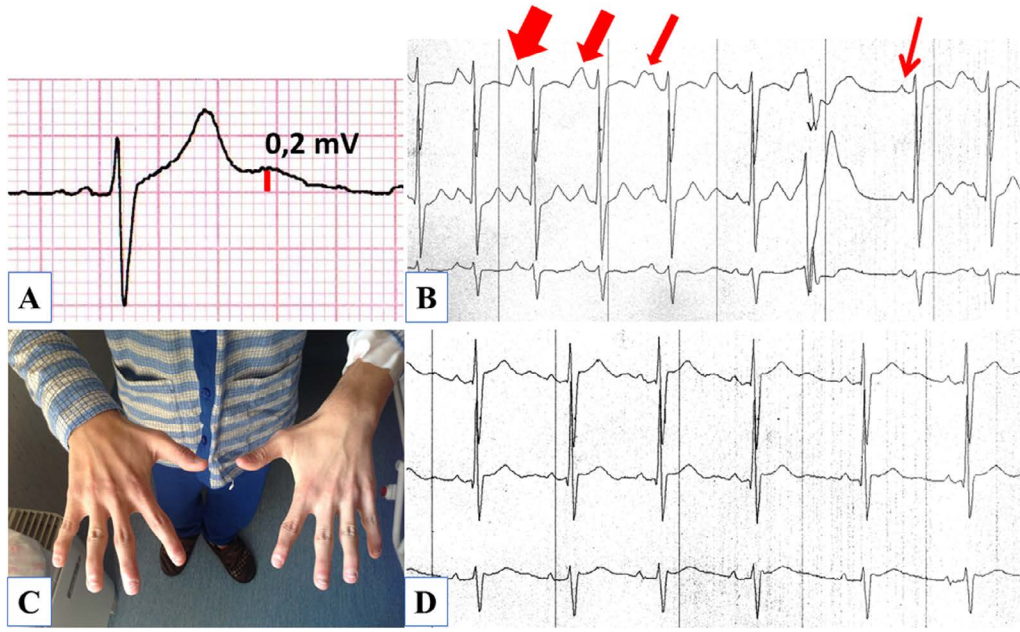
Discussion

Clinical signs and symptoms are very typical in Andersen-Tawil syndrome, and they include bidirectional VT, prominent U waves on sinus rhythm electrocardiogram, QT-U interval prolongation despite normal QTc interval, clinodactyly, and periodic paralysis. These signs and symptoms themselves should immediately lead the clinician to a prompt suspicion of the syndrome, which will then need a genetic study to be confirmed.[2,3]

Our case aims to draw attention to the importance of a correct clinical diagnosis, based on signs and symptoms, which has profound implications for the drug choice, because inappropriate drugs in this setting may also have detrimental effects, rather than simply being ineffective. As already reported,[4–6] our case confirms that monotherapy with flecainide can be rapidly effective in the long-term management of ventricular arrhythmias, whereas β-blockers are not.

The syndrome is very rare (nearly 1 individual per 1 million),[7] caused by a loss-of-function mutation of the KCNJ2 gene, and arrhythmias are often clinically silent, although sometimes they may lead to fatal complications, like syncope or sudden death. Bidirectional VT is the hallmark of the syndrome, and it claims for a differential diagnosis with 2 principal other causes, namely catecholaminergic polymorphic VT and digitalis toxicity, whose mechanism is mediated by intracellular calcium overload, potentiating delayed afterdepolarization and triggered activity.[8]

Figure 2. Prominent U waves, with longer duration and low amplitude during normal sinus rhythm (A), showing increased amplitude with faster heart rates, generating the so-called U-on-P sign (B) when the P wave during sinus tachycardia is inscribed within the U wave of the preceding beat (arrows), resembling high-voltage P waves. (C) Clinodactyly of the fifth finger. (D) Sinus rhythm on Holter recording, free from arrhythmias, without significant modification of QRS and T waves induced by flecainide.



KCNJ2 gene encodes the α subunit of the potassium channel Kir2.1, a transmembrane protein that regulates the inward potassium rectifying current, stabilizing resting potential during repolarization.[9]

We know from experimental models that the inhibition of the delayed rectifier potassium current in Andersen-Tawil syndrome is associated with increased duration of ventricular action potential, leading to increased calcium influx. Consequent calcium overload facilitates delayed afterdepolarizations, which may be responsible for ventricular arrhythmias.[10]

In addition, elevated intracellular calcium is not the only determinant of arrhythmias, because cytosolic sodium entry and its modulation on intracellular calcium has proved to be necessary for arrhythmogenesis.[10] Although the mechanisms of calcium-mediated arrhythmias exacerbated by the sodium current remain unclear, some have advocated for the role of the sodium-calcium exchange. Specifically, inhibiting sodium entry might decrease diastolic intracellular calcium accumulation and thereby reduce arrhythmia propensity.[11]

In fact, recent studies in a drug-induced Andersen-Tawil syndrome animal model demonstrated that selective and nonselective sodium channel inhibition reduced the incidence of calcium-mediated arrhythmias.[10]

Based on the above considerations, the characteristic ECG manifestations in Andersen-Tawil syndrome, either the prominent U waves during sinus rhythm or the bidirectional VT, can be attributed to delayed afterdepolarization and triggered activity, and therefore it is easy to understand the central role of class IC antiarrhythmic drugs, like flecainide, for the treatment of ventricular ectopy in Andersen-Tawil syndrome.[6]

Flecainide presents some advantages for patients (once Brugada pattern has been ruled out, it is relatively safe and easy to use, with a good tolerability profile) as well as for clinicians (for its modest effect on QTc interval, in the setting of a reduced reserve of repolarization and potentially associated hypokalemia).

Calcium antagonists, like verapamil, also have proved to be equally useful in this setting, even if they may not be effective in monotherapy, as described by Janson et al,[11] who obtained arrhythmia suppression through the combined use of verapamil and flecainide.

As a class of agents, β-blockers are not involved in this calcium-mediated type of arrhythmia, and therefore are not reported to be effective in Andersen-Tawil syndrome, as occurred in our patient. Even if no detrimental effects are expected with β-blockers, in our case the patient complained of worsening asthenia with the use of nadolol, probably due to the cumulating effect of bradycardia and muscle weakness. Nonetheless, β-blockers have been used in Andersen-Tawil syndrome, probably because of the initial experience that considered it as a variant of Long QT Syndrome (type 7) and, for this reason, sensitive to antiadrenergic agents.

Regarding class III antiarrhythmic agents, based on their potassium-blocking effect they should not be indicated in a disease characterized by a loss of function of potassium channel. In fact, sotalol proved to be unable to modify the arrhythmia burden in our patient.

When the patient came to our attention, he was already receiving sotalol, aimed at reducing the arrhythmic burden to allow a cardiac magnetic resonance, because his major complaint was muscle weakness and he was suspected to have a myopathy with associated cardiomyopathy. Other reports pointed out detrimental effects of amiodarone on similar occasions,[7] particularly if used in association with other QTc-prolonging agents, which may further reduce the reserve of repolarization.[12] It is worth noting that ventricular arrhythmias in patients with suspected cardiomyopathy may easily induce unaware clinicians toward the inappropriate use of amiodarone.

In this regard, some studies have underlined that disappearance of arrhythmias may not be sufficient by itself to protect the patient from adverse events. Mazzanti et al[7] have proposed three major risk factors leading to higher risk of adverse events in patients with Andersen-Tawil syndrome: history of syncope, documented sustained ventricular arrhythmias and treatment with amiodarone, due to its potentially proarrhythmic effects.

We do not know if sotalol may have facilitated the episodes of biventricular tachycardia, at the time of our first evaluation. Either way, although our first concern was catecholaminergic polymorphic VT, we were immediately able to rule out that diagnosis by the exercise test and by the identification of typical U waves on ECG.

In our patient, the diagnosis was confirmed by the sequence analysis of KCNJ2 gene, which revealed a "*de novo*" missense variant in heterozygosity; in fact, mother and father did not show any mutation of the gene.

In this case, the threonine amino acid at codon 305 is replaced by an isoleucine (p.Thr305Ile). This substitution has been reported only in 1 other case report,[13] and it is not been registered in ClinVar or dbSNP, nor it is present on the gnomAD browser, the population frequency database. This variant is predicted to be probably damaging by the bioinformatic tool PolyPhen-2. Moreover, the amino acid substitution takes place in a well-preserved residue located in C-terminal domain, which probably has a role in the protein architecture. In the same position, pathogenic or likely pathogenic variants (p.Thr305Ala and Thr305Pro) have also been reported in association with Andersen-Tawil syndrome.

This case highlights the importance of a correct diagnosis of Andersen-Tawil syndrome, which is a very rare disease and for this reason it may be underrecognized for many years, because its clinical expression may initially concern only the neurologic aspect, whereas dysmorphic features and arrhythmias can easily be overlooked, particularly in the pediatric ages. We based our diagnosis on the typical electrocardiographic signs, namely bidirectional VT and prominent U waves, along with the observation of clinodactyly and mild hypertelorism; diagnosis was then confirmed by genetic analysis. Dealing with ventricular arrhythmias and suspecting cardiomyopathy, particularly in the presence of reduced ventricular function, cardiologists may be induced to administer potentially adverse antiarrhythmic drugs, like amiodarone. There is evidence that the combination of calcium channel blockers with class Ic antiarrhythmics is effective in suppressing arrhythmias in many patients with Andersen-Tawil syndrome.[10,13–15] However, monotherapy with flecainide at the dosage of 4 mg/kg/day can be effective, as in our case, even in the long-term control of arrhythmias.

Article Information

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Ethical Approval and Informed Consent. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation and have been approved by the appropriate committees at our institution (University of Messina). However, given the nature of this study, informed consent was not required by our institution.

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