Novel Mutation in the *KCNJ2* Gene Is Associated with a Malignant Arrhythmic Phenotype of Andersen-Tawil Syndrome

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Background: Andersen-Tawil syndrome (ATS) is a rare inherited multisystem disorder associated with mutations in *KCNJ2* and low prevalence of life-threatening ventricular arrhythmias. Our aim was to describe the clinical course of ATS in a family, in which the proband survived aborted cardiac arrest (ACA) and genetic screening revealed a previously unknown mutation (c.271_282del12[p.Ala91_Leu94del]) in the *KCNJ2* gene.

Methods: A cascade family screening was performed in a 5-generation family after identification of the *KCNJ2* mutation in the proband. Subsequently, 10 of 21 screened individuals appeared to be mutation carriers (median age 38 [range 10–75] years, 3 female). Mutation carriers underwent clinical examination including biochemistry panel, cardiac ultrasound, Holter ECG, and exercise stress test.

Results: (1) At baseline, 2 patients had survived ACA, 3 had syncope or presyncopal attacks, and 2 reported palpitations. Exercise-induced nonsustained bidirectional ventricular tachycardia was documented in 4 patients, 2 received implantable cardioverter-defibrillators (ICD) for primary prevention and 2 for secondary prevention. (2) During follow-up, 1 primary prevention and 1 secondary prevention patient received in total 4 adequate ICD shocks. Life-threatening ventricular arrhythmias were documented during childhood in 5 of 10 mutation carriers. (3) All mutation carriers presented with characteristic mild dysmorphic features. Only 1 patient suffered from periodic paralysis. All had normal serum potassium level at repeated assessments and none had any other extracardiac disease manifestation.

Conclusion: Our findings suggest that the novel *KCNJ2* mutation is associated with a predominantly cardiac phenotype of Andersen-Tawil syndrome with high propensity to life-threatening ventricular arrhythmias presenting from childhood and young adulthood.

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Andersen-Tawil syndrome; LQT7; *KCNJ2*; bidirectional ventricular tachycardia; polymorphic ventricular tachycardia; periodic paralysis

Andersen-Tawil syndrome (ATS, LQT7) is a rare multisystem channelopathy with estimated prevalence less than 1:1 000 000, inherited in an autosomal dominant way.^{2,3} LQT7 is caused by mutations in the *KCNJ2* gene located in chromosome 17, encoding for the inward potassium channel protein

Kir 2.1,^{2,3,8,12} and causes prolongation of phase 3 of the action potential. In the presence of low extracellular potassium there can be induction of Na–Ca exchanger dependent delayed after potentials and spontaneous arrhythmias^{8,12} that is distinct from other forms of LQTS.⁸

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ATS affects skeletal and heart muscle but is also known as a neurological disease giving rise to periodic muscle weakness episodes, characteristic dysmorphic features as well as cognitive difficulties and mild mental retardation.^{2,3,10,11}

From the sudden arrhythmic death perspective, ATS has been considered as a relatively benign condition with low propensity to life-threatening ventricular arrhythmias and sudden death.^{3,14} The purpose of the current study was to describe clinical features and propensity to ventricular arrhythmias in an ATS-affected family in which the proband was resuscitated after cardiac arrest.

MATERIAL AND METHODS

Index Case Presentation

The proband (IV:7) is a female who had a near drowning episode at the age of 15. When she was 16 years old she had a syncope triggered by physical exercise during a school gymnastics lesson. The patient regained consciousness after a short period of chest compressions and she was transferred to the hospital where a complex ventricular arrhythmia consisting of bidirectional ventricular premature contractions (VPC), polymorphic VPCs and runs of nonsustained ventricular tachycardia (nsVT) without loss of consciousness were documented. Despite a normal QTc interval at admission, long QT syndrome was suspected and beta-blocker therapy was initiated. Genetic screening focusing on the most common genes associated with LQTS was performed, however no pathogenic mutation was identified in *KCNQ1*, *KCNH2*, or *SCN5A*. Beta-blocker therapy was ineffective in terms of its effect on ventricular arrhythmias and the patient underwent left cervical sympathectomy that did not alter the ventricular arrhythmias. Despite the addition of mexiletine to beta-blockade, the patient continued to have frequent polymorphic and bidirectional ventricular tachycardia (BVT) runs (Fig. 1) for up to 30 seconds at rest without symptoms. The patient was offered ICD-therapy but refused. She had 3 pregnancies without cardiac symptoms but in the second postpartum period at the age of 22 she had a new serious syncope that did not require CPR. However, the patient had residual neurologic symptoms for the first 24 hours. There was no documentation of cardiac rhythm at the time of syncope, however during the hospital stay repeated recordings of nsVT

were observed. At that point, the patient accepted an implantable cardioverter-defibrillator (ICD). At that time, mild facial dysmorphic features were noted and in combination with malignant ventricular arrhythmias and short stature gave rise to clinical suspicion of ATS (Table 1). Targeted questioning revealed subtle muscle weakness that could have been a manifestation of ATS but no signs of periodic paralysis or hypokalemia was found.

KCNJ2 Sequencing

Sequencing of the *KCNJ2* gene located in 17q24.3 was performed and revealed a previously unknown mutation expressed as deletion of 12 base pairs resulting in a deletion of 4 amino acids in the first transmembrane domain of the KCNJ2 protein (c.271_282del12[p.Ala91_Leu94del]). The mutation was considered pathogenic and causal for ATS in this patient.

Cascade Family Screening

Upon diagnosing ATS and identification of a probable disease causing mutation in the proband, cascade family screening was initiated. It included clinical evaluation, control of medical history, review of medical records, physical examination, 12-lead electrocardiogram, echocardiography, Holter monitoring, measurements of S-potassium. Length was plotted in a growth diagram and noted as standard deviation (SD) below the normal values.²² Family members were tested for the presence of the disease-causing mutation identified in the proband. The clinical control was performed prior to the knowledge of the presymptomatic genotyping in all but three family members.

Upon completion of basic clinical and genetic evaluation, the affected family members were followed up for a median of 36 months (range 26–48 months) in order to assess the occurrence of clinically significant events such as syncope, ICD therapies, or death.

RESULTS

Family screening resulted in the construction of a pedigree that covered a 5-generation family (Fig. 2) and included 21 family members. All of them were able to participate in clinical evaluation, while genetic evaluation was not performed in one

Figure 1. Bidirectional VT in IV:7. Note the beat-to-beat alternating electrical polarity of the QRS-axis. This is known in only three conditions; ATS = Andersen-Tawil syndrome, CPVT = catecholaminergic polymorphic tachycardia and digitalis intoxication.

subject (II:2) who died of cancer at the age of 72 years.

Nine of 21 family members were found to be carriers of the ATS-causing mutation (Table 1). The great grandmother (II:2) of the proband did not undergo genetic testing but had clear features of ATS and was clinically diagnosed with the disease. In total, 10 family members (47,6%) were either mutation carriers or had the clinical diagnosis of ATS. The clinical characteristics of the *KCNJ2* mutations carriers are summarized in Table 1.

Cardiac Manifestations

Two females and one male survived aborted cardiac arrest (ACA), four had syncope or near-syncope episodes while the majority ($n = 7$) had palpitation symptoms prior to the diagnosis. The occurrence of potentially life-threatening cardiac

events was confined to the descendants of II:2 while the descendants of II:3 had a more classical form of ATS with frequent VPCs on Holter, but no cardiac symptoms. All four female patients had either syncope or ACA while five of six men had neither of these ($P = 0.047$).

The mutation positive females ($n = 3$) and clinical ATS ($n = 1$) had in total 13 pregnancies. In one woman (III:8) there was a syncope during pregnancy and in another woman (IV:7) a syncope postpartum, both considered arrhythmia-related based on their clinical presentations.

Only two patients (III:8 and IV:7) had intermittent prolongation of the QTc-interval, maximal QTc 450–470 ms, without beta-blocker therapy. Seven patients expressed the characteristic T-U pattern (Fig. 3) earlier described in patients with ATS.¹⁰

Cardiac arrhythmias documented in the screened family members by repeated resting 12-lead ECG and repeated Holter ECG monitoring

Table 1. The Family with ATS, Cardiac and Extra-Cardiac Manifestations

	II:2	II:3	III:1	III:8	III:13	IV:7	IV:9	IV:10	IV:14	V:2
Age at last follow-up	75	70	45	51	44	33	26	21	14	10
Age of dysrhythmia onset	7	7	28-10	7	44	16	20	17	14	No
Gender	Female	Female	Male	Female	Male	Female	Male	Male	Male	Male
Cardiac manifestations:										
Syncope/ ACA/	Syncope	Near-syncope	ACA, Arrhythmia, Other	ACA, Syncope Arrhythmia,	Other	ACA, Syncope Arrhythmia	Arrhythmia	Arrhythmia	No	No
Near-syncope										
Arrhythmia and ECG:										
QTc*, ms	440	420	400	450	400	470	410	430	430	415
VT pattern	BVT	BVT	BVT, PVT	BVT,PVT	None	BVT,PVT	none	BVT,PVT	none	none
Number of VES/24h	500	15500	16000	63000	1700	28000	2600	42000	1800	No
% VES/24h	<1	13	16	30-40	2	25	1,5	36 (ICD)	1,7	<1
Exercice-induced VT	ND	+	+	+	+	+	No	+	+	No
ICD therapy: 1° prevention										
2° prevention				+		+				
Appropriate ICD discharge			+	+		+				
Extra-cardiac manifestations:										
Short stature	-1 SD	-1.5SD	-1 SD	-2.5 SD	-1 SD	-1.5 SD	-1.5 SD	-2.5	-1.75	-2 SD
Skeletal manifestations	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Craniofacial features	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Dental anomalies	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Cleft palate	No	Yes	No	No	Yes	No	No	No	Yes	No
Periodic paralysis	No	No	Yes	No	No	No	No	No	No	No
Renal dysplasia	No	No	Yes	No	No	No	No	No	No	No
Potassium level (plasma)	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal
Genotype	Clin ATS	KCNJ2	KCNJ2	KCNJ2	KCNJ2	KCNJ2	KCNJ2	KCNJ2	KCNJ2	KCNJ2

VT defined as three or more consecutive ventricular beats, bidirectional; VT defined as ventricular extra systoles with beats-to-beat alternating polarity of the electrical QRS-axis, constant RR interval, frequency > 150 bpm.

* = maximal QTc in a QT-prolonging drug-free state; ACA = aborted cardiac arrest; ATS = Andersen-Tawil syndrome; BVT = bidirectional ventricular tachycardia; Clin ATS = clinically ATS diagnosis; ICD = implantable cardioverter defibrillator; NA = not available; PVT = polymorphic ventricular tachycardia; SD = standard deviation; VES = ventricular extra systoles; VT = ventricular tachycardia.

Craniofacial features: broad forehead, hypertelorism, small mandible, low-set ears.

Skeletal manifestations: small hands and feet, V-digit clinodactylia, 2-3 toe syndactylia.

Dental anomalies: missing teeth, enamel hypoplasia.

Figure 2. Pedigree. The family with LQT7. Circles symbols depict female, square symbols depict male individuals.

(Fig. 4) are presented in Table 1. Bidirectional VT (BVT) was documented in six patients while five of them had frequent VPC exceeding 10% of the total number of beats. Exercise test triggered VPCs and BVT in seven patients. Three women (II:2, II:3, and III:8) had complaints of subjective dysrhythmia and frequent VPCs were present in ECGs in childhood, while the men tended to have a later debut of dysrhythmia (Table 1).

Extracardiac Manifestations

All *KCNJ2* affected family members showed dysmorphic features characteristic for ATS. All had short stature (female 149–161 cm, -2.5 to -1 standard deviations (SD) expressed in growth charts,²⁰ male 121–171 cm, -2.5 to -1 SD). Genopositive individuals also had small mandibles, dental engagement with enamel hypoplasia, and were prone to caries. Missing or ectopic teeth were noted in seven of the ten individuals. Cleft palate was found in three. Toe-syndactylia was seen in three of the affected individuals. Digit clinodactylia was seen in all mutation carriers. Muscular weakness was noted in only two members (III:1, IV:7). Only one family member (III:1) had periodic

paralysis triggered by carbohydrate rich ingestion but also by cold weather and stress. Unilateral renal hypoplasia was observed in one male (III:1), this has been described in patients with ATS only once previously. Four patients had delayed speech debut and three required special education support at school.

Management

The two females surviving from ACA were offered ICDs as secondary prevention of sudden death. Three more family members who had $>10\%$ VPCs on Holter ECGs were offered ICD for primary prevention of sudden death, and all but one elderly woman (II:3) accepted ICD. Of the four patients who received ICDs, three received repeated adequate ICD-discharges.

Pharmacological agents used in affected family members in order to suppress ventricular arrhythmias included beta-blockers, mexiletine, verapamil, fenytoin, and sotalol. None of these drugs was judged clinically successful in achieving any marked effect on the occurrence of arrhythmias. Notably, frequent VPCs and nsVT runs up to 30 seconds observed at rest were

Figure 3. ECG. T-U pattern in selected ATS individuals.

completely asymptomatic in all affected subjects. Beta-blockers were well-tolerated by all subjects and this therapy was administered on a life-time basis. Amiodarone was not administered to any patient.

Affected family members were recommended lifestyle modification including avoidance of sudden intense adrenergic stimulation and participation in competitive sports. The patients were counseled in regard to avoidance of weight loss and prevention of hypokalemia. None of our patients had low serum potassium levels. All patients were advised to avoid QT-interval prolonging drugs and drugs that may induce hypokalemia.

Information about ATS was given to the schools to focus on the potential learning disabilities, and to dentists to prevent caries due to hypodontination. As all patients with ATS or LQTS should not swim without supervision and affected family members were advised accordingly.

Clinical Follow-up

The index patient (III:8) suffering from the most complex ventricular arrhythmia had been treated for 17 years in our institution prior to identification of the underlying disease. During the follow-up, the

index case accepted an ICD that delivered adequate ICD-discharge 1.5 and 5 years later triggered by physical exertion. There was a detection of ventricular tachyarrhythmia with cycle length under 200 ms (>300 bpm) corresponding to the ventricular fibrillation detection zone that resulted in immediate ICD discharge and restoration of sinus rhythm. The patient has not received any inadequate ICD-discharge. One patient died from noncardiovascular causes (II:2). Of the remaining nine patients, three (III:1, III:8, and IV:7) experienced syncopal episodes and the same patients (III:1, III:8, and IV:7) received adequate ICD discharges for fast ventricular tachycardia with ventricular rates >200 bpm.

Discussion

In previous reports, the presence of ventricular arrhythmias in ATS patients has been documented^{2,13-15} but it was rarely associated with cardiac arrest (CA). In previous reports CA observed in about 10% of ATS patients,³ and in one publication females appeared to be more affected than males in regard to BVT and periodic paralysis.¹¹

Figure 4. ECG findings, lead II, in some of the ATS individuals. Ventricular extra systoles in biginemia, polymorphic extra systoles, polymorphic nonsustained VT and BVT.

We report a novel familial mutation causing ATS/LQT7. Unlike previous descriptions this new mutation is associated with a malignant cardiac phenotype associated with ACA, repeated syncopal episodes and bidirectional VT. The proband has survived a near drowning episode, a finding previously described in patients with ATS.¹²

In accordance with classical descriptions of ATS phenotypes, dysmorphic features could be recognized from early childhood but the cardiac symptoms did not occur until 7 years of age or later in our material. Male individuals tended to present with later onset of ventricular arrhythmia than females. All affected individuals presented with uniform findings on resting 12-lead ECG consisting of complex ventricular arrhythmias and runs of BVT that

apart from ATS^{2,3,10,19} only have been observed in digitalis intoxication,^{10,19} and catecholaminergic polymorphic tachycardia (CPVT).^{10,18} The observations of BVT might therefore be an important clue to raise a clinical suspicion of ATS.

In this family, cardiac manifestations of the disease were mostly observed in young individuals. With the relatively short follow-up data available, we cannot draw any conclusion whether this finding should be interpreted as an anticipation phenomenon, which has not been reported in LQT7 before,² or whether the arrhythmia burden declines with increasing age.

With knowledge of the condition we could retrospectively find BVT runs in the historical ECGs recorded before the patient received the diagnosis

of ATS. Interestingly, while cardiac rhythm disorders at rest and exercise were observed in all genetically affected family members, the most malignant manifestations that included recurrent syncope and ICD therapies were observed only in one branch of the family while another one had more conventional and benign disease phenotype. It is possible that additional genetic factors play a role in the variation of the ATS phenotype among the members of the same family mutation.

Ventricular arrhythmias are difficult to treat in ATS and the electrical instability of the myocardium is distinct from other forms of LQTS.^{8,10} Notably, one of the most remarkable findings in our patients was that nonsustained ventricular arrhythmias observed at rest or during exercise were completely asymptomatic and their appearance was not affected by antiarrhythmic drugs, which is why beta-blocker therapy was chosen as the least proarrhythmic and the most safe.^{3,8}

CONCLUSION

We present a family with a novel *KCNJ2* mutation with negligible effect on QTc interval duration associated with a highly arrhythmogenic phenotype, with increased risk of ventricular arrhythmic events such as nonsustained bidirectional VT and frequent polymorphic VPCs at rest and exercise, syncope and ICD discharges for fast VT in genetically affected family members.

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