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Case report

Phenotypic variability in a series of four pediatric patients with Andersen-Tawil syndrome: A Saudi experience

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ABSTRACT

Andersen-Tawil syndrome (ATS) is a rare genetic disorder characterized by periodic paralysis, ventricular arrhythmia, and dysmorphic features. However, the classical features are not always seen in the syndrome; therefore, the diagnosis can be challenging. We describe our experience with ATS in Riyadh, Saudi Arabia, by presenting a case series involving four patients in the pediatric cardiology clinic confirmed to have ATS. Despite the diversity in phenotypes and clinical course among the four cases, all patients had bidirectional ventricular tachycardia and were confirmed to have ATS by performing genetic testing. In this case series, we identified one novel and three previously described KCNJ2 mutations. We also confirmed the beneficial effect of AAI pacing in one of our patients, together with medical therapy with β-blockers and flecainide. In Saudi Arabia, there is a distinct genetic pool and a high incidence of inherited diseases. Raising awareness about these diseases is crucial, especially in a country such as Saudi Arabia, wherein consanguinity remains a significant factor leading to an increased incidence of inherited diseases. Furthermore, because of the limited information available regarding this rare syndrome, we believe that this case series would offer an opportunity to provide a better understanding of ATS in our local region and worldwide.

1. Introduction

Andersen-Tawil syndrome (ATS) is a rare genetic multisystem disorder with a distinct pattern of features, including periodic paralysis, ventricular dysrhythmias, and dysmorphic features [1]. A diagnosis of ATS should be suspected if two of the following three features are present: (1) periodic paralysis; (2) the presence of electrocardiographic abnormalities (enlarged U-waves, ventricular ectopy, nonsustained ventricular tachycardia [VT], or a prolonged QTc interval); and (3) characteristic physical features (skeletal abnormalities, such as short stature, micrognathia, hypertelorism, low-set ears, clinodactyly, and dental abnormalities) [2,3]. A patient with only one of these criteria may still fit the diagnosis if he/she has one family member with an established diagnosis of ATS [1]. The diagnosis of ATS must be established in a proband who fits either one of the aforementioned criteria and/or by identification of a heterozygous pathogenic variant in *KCNJ2* by performing genetic testing. ATS is an autosomal dominant disorder with variable genetic expressions; however, it can also occur sporadically [4]. (see Table 1)

Owing to the genotypic and phenotypic heterogeneity of this disease, as well as the erratic and paradoxical worsening of symptoms with therapy, management can be difficult. Medications such as tocainide and flecainide have been tried in the past, with variable efficacies, and in some severe cases, implantation of a pacemaker or defibrillator device is required [5].

Approximately two-thirds of patients with ATS have heterozygous loss-of-function mutations in *KCNJ2*, encoding the α-subunit of the potassium channel Kir2.1 [6]. About one-third of patients with clinically confirmed ATS do not have pathogenic variants in *KCNJ2*, and the cause of ATS in such cases remains unknown.

In Saudi Arabia, there is a distinct genetic pool and a high incidence of inherited diseases. Raising awareness about these diseases is crucial, especially in a country such as Saudi Arabia, wherein

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Table 1
Summary of patients with ATS.

Case	Age, y	Sex	Clinical presentation	Physical examination findings	Investigations	ECG study & Holter monitoring findings	Genetic test results	Treatment rendered
1	12	F	Asymptomatic, referred because of an irregular heart rhythm	No dysmorphic features Irregular heartbeats	ECG study, Holter monitoring, genetic testing, and routine laboratory tests	Frequent PVCs, bigeminy, and bidirectional VT	c.412G > A, p. Glu138Lys (heterozygous)	**Propranolol** (2 mg/kg TID) **Flecainide**(150 mg/ m^2/day)
2	10	M	Syncopal attacks and periodic paralysis	Dysmorphic features (short stature, micrognathia, widely spaced eyes) and cognitively normal Irregular heartbeats	ECG study, Holter monitoring, genetic testing, and routine laboratory tests	Frequent PVCs, bigeminy, and bidirectional VT	c.921 G/A p. Met307Ile (heterozygous)	**Nadolol (**1 mg/kg/day) **Flecainide** (150 mg/ m^2/day) **Atrial pacing** **Acetazolamide** (20 mg/kg/day dose divided twice per day)
3	7	F	Asymptomatic, referred because of an irregular heart rhythm	Dysmorphic features (micrognathia, refractive error, and high-pitched voice) Irregular heartbeats	ECG study, Holter monitoring, genetic testing, and routine laboratory tests	Frequent PVCs, bigeminy, and bidirectional VT	**Novel mutation c.366 T/A, p.Cys122Ter (homozygous)**	**Nadolol (**1 mg/kg/day) **Flecainide**(150 mg/ m^2/day)
4	11	F	Syncopal attacks and periodic paralysis	No dysmorphic features Irregular heartbeats	ECG study, Holter monitoring, genetic testing, and routine laboratory tests	Frequent PVCs, bigeminy, and bidirectional VT	c.919 A/G, p.Met307Val (heterozygous)	**Nadolol (**1 mg/kg/day) **Flecainide**(150 mg/ m^2/day) **Acetazolamide** (20 mg/kg/day dose divided twice per day)

F, female; M, male; ECG, electrocardiography; PVCs, premature ventricular contractions; VT, ventricular tachycardia; TID, three times a day.

consanguinity remains a significant factor leading to an increased incidence of inherited diseases [7]. Furthermore, because of the limited information available regarding this rare syndrome, we believe that this case series would offer an opportunity to provide a better understanding of ATS in our local region and worldwide. Therefore, we describe our experience with ATS in Riyadh, Saudi Arabia, by presenting a case series involving four patients in the pediatric cardiology clinic confirmed to have ATS.

2. Patients and methods

2.1. Study design and settings

In this case series, we describe our experience in Riyadh, Saudi Arabia, with four pediatric patients confirmed to be diagnosed with ATS in the pediatric cardiology clinic; they were referred because of ventricular arrhythmias.

2.2. Ethical approval and diagnostic protocol

Demographic data and the following variables were collected: symptoms, developmental history, medical history, family history, school performance, signs upon physical examination, and results of investigations, including electrocardiographic (ECG) studies, laboratory results, and treatment rendered.

After obtaining written informed consent and ethical approval, genetic testing was performed as part of the approved research activities. Whole blood samples were obtained from patients and their family members. Genomic DNA was extracted for each sample by standard salt-precipitation methods. Genomic DNA from affected patients and their parents was amplified by polymerase chain reaction (PCR) using intronic primers designed to flank (50–100 bp) the coding exons of the *KCNJ2* (NM_000891) gene, as defined by the Ensembl Genome Browser. PCR was performed with a final volume of 25 μl containing approximately 10 ng of genomic DNA using standard conditions (primer sequences and conditions are available on request). Purified PCR amplicons covering the entire coding regions of *KCNJ2* were directly sequenced with the dideoxy chain-termination method using an ABI Prism Big Dye Terminator v3.1 Cycle Sequencing Kit (Applied Biosystems, Foster City, CA, USA) following the manufacturer's instructions and processed on an ABI 3730XL capillary sequencer (Applied Biosystems). Sequence analysis was then performed using the SeqMan 6.1 module of the Lasergene software package (DNA Star Inc., Madison, WI, USA), and the results were compared to the reference GenBank sequence. Numbering commenced with the A of the ATG initiation codon as +1.

3. Case descriptions

3.1. Case 1

3.1.1. Patient information

A 12-year-old girl was referred to the pediatric cardiology clinic because of irregular heartbeats. She was asymptomatic and had no history of weakness, fainting, or palpitation. There was no family history of sudden death or similar issues.

3.1.2. Clinical findings

No dysmorphic features were seen. There were irregular heartbeats on auscultation.

3.1.3. Diagnostic assessment

The ECG study and Holter monitoring revealed findings consistent with ATS, with prominent U waves and frequent premature ventricular contractions (PVCs) as well as bidirectional VT (Figs. 1 and 2).

Exercise testing did not provoke the ventricular arrhythmias (as usually expected in patients with catecholamine polymorphic VT and not in ATS). Routine laboratory results and the echocardiogram were normal.

Genetic testing confirmed the diagnosis of ATS. DNA sequence analysis of the coding region of the *KCNJ2* gene identified a heterozygous G > A nucleotide substitution in exon 2 (c.412G > A), resulting in the replacement of glutamic acid at position 138 by lysine (c.412G > A, p.Glu138Lys) (Fig. 3). Genetic samples from the parents were not available for testing. This mutation has been

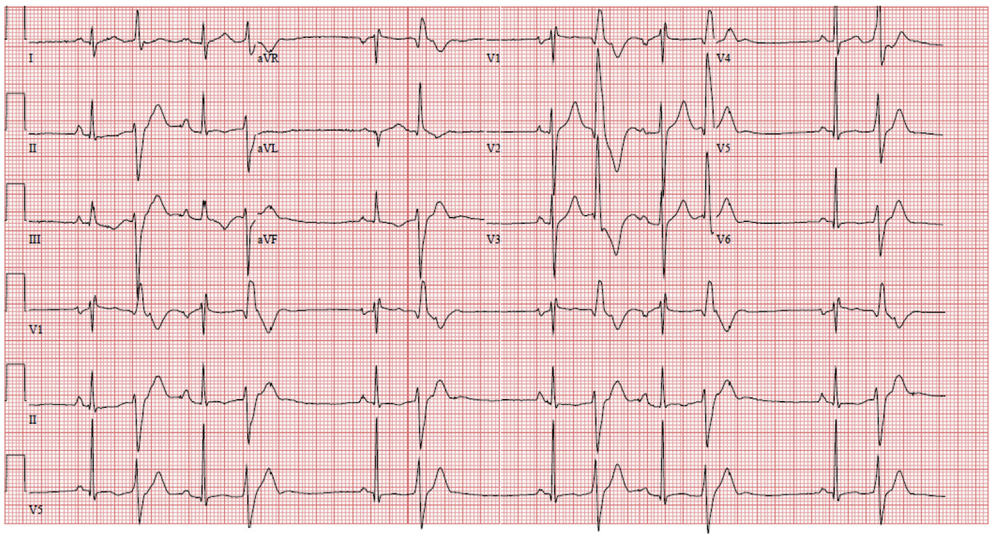

Fig. 1. Twelve-lead electrocardiogram showing frequent premature ventricular contractions in the pattern of ventricular bigeminy (case 1).

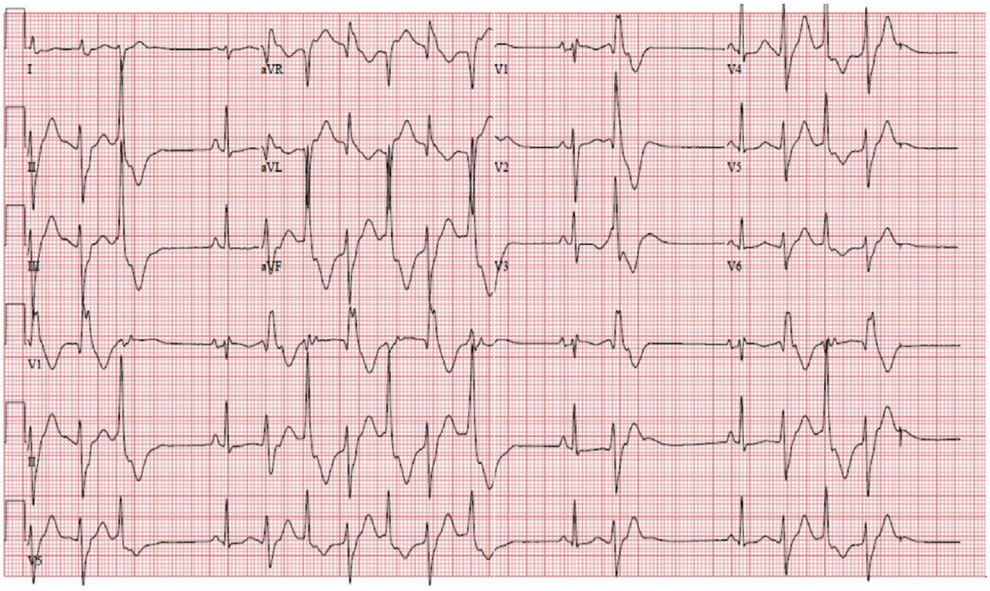

Fig. 2. Electrocardiogram of the same patient (case 1) showing episodes of bidirectional ventricular tachycardia.

previously reported in association with ATS [8].

3.1.4. Therapeutic intervention

We decided to use β-blockers in the patient initially (propranolol three times a day at a dose of 2 mg/kg/day), but the patient's arrhythmia persisted. Therefore, flecainide (150 mg/m^2/day) was added, which showed minimal improvement.

3.1.5. Follow-up and outcome

Because of the absence of symptoms, the patient was noncompliant with her medications, although she continued to be followed-up in the clinic for more than 4 years with no change in her condition.

3.2. Case 2

3.2.1. Patient information

A 10-year-old boy presented with frequent episodes of periodic paralysis involving the whole body, lasting from few hours to few days. These episodes occurred every 2–3 months for 5 years. The patient was born to a consanguineously married couple. However, there was no family history of a similar complaint and no history of sudden death in the family.

The patient denied any other provocative factors preceding the paralysis, such as prolonged fasting or temporal relation to carbohydrate intake. The patient did not complain of muscle pain or cramps.

3.2.2. Clinical findings

He had some dysmorphic features in the form of micrognathia, hypertelorism, and short stature. No finger or toe anomaly was seen. He was cognitively normal and had normal muscle power; however, irregular heartbeats were observed on auscultation.

3.2.3. Diagnostic assessment

Serum electrolyte levels, including potassium (K), were all

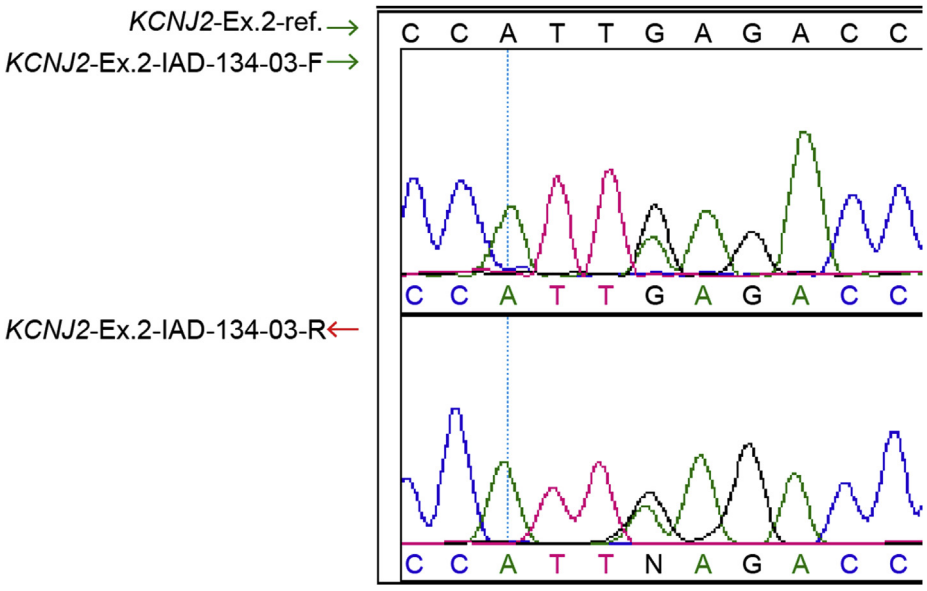

Fig. 3. Mutation identified in case 1.

within normal limits (K: 4.2 mmol/L). The cardiac investigation revealed normal echocardiographic findings with preserved left ventricular function.

The ECG study and Holter monitoring revealed findings consistent with ATS. The corrected QT (QTc) interval was only mildly prolonged (0.45 s). However, he had prominent U waves and frequent PVCs as well as bidirectional VT (Fig. 4).

DNA sequence analysis of the coding region of the *KCNJ2* gene identified a *de novo* heterozygous G > A nucleotide substitution in exon 2 (c.921G > A), resulting in the replacement of methionine at position 307 by isoleucine (c.921G > A, p.Met307Ile) (Fig. 5). The mutation, which was not detected in parents, has been previously reported in association with ATS [9].

3.2.4. Therapeutic intervention

After confirming the diagnosis of ATS and explaining the high risk of cardiac events because of significant PVC and the ventricular burden to his parents, he was started on a β-blocker (nadolol 1 mg/kg/day, once a day for ease of compliance) and flecainide (150 mg/m^2/day). His periodic paralysis continued, and acetazolamide (20 mg/kg/day dose divided twice per day) was added by the neurology team; however, there was no significant improvement in his arrhythmia or paralysis.

The patient underwent implantation of a pacemaker (AAI pacing of the atrium) at a minimum rate of 80 beats/min (Fig. 6) to avoid ventricular arrhythmias.

3.2.5. Follow-up and outcome

The patient was followed up in the cardiology clinic for more than 5 years. The arrhythmia improved as the PVC burden decreased dramatically from 48% to 6%, following AAI pacing. Unfortunately, the periodic episodes of paralysis continued to occur and were refractory to acetazolamide.

3.3. Case 3

3.3.1. Patient information

A 7-year-old girl was referred to the pediatric cardiology clinic because of an irregular heartbeat discovered during a routine examination. The patient was entirely asymptomatic. She belonged to the same tribe as the patient in case 2, but they were not related.

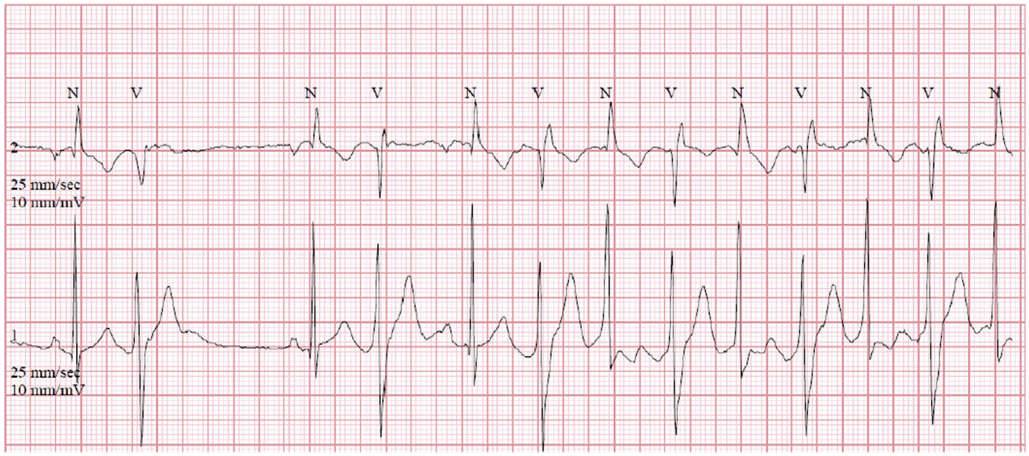

Fig. 4. Bidirectional ventricular tachycardia detected by Holter monitoring (case 2).

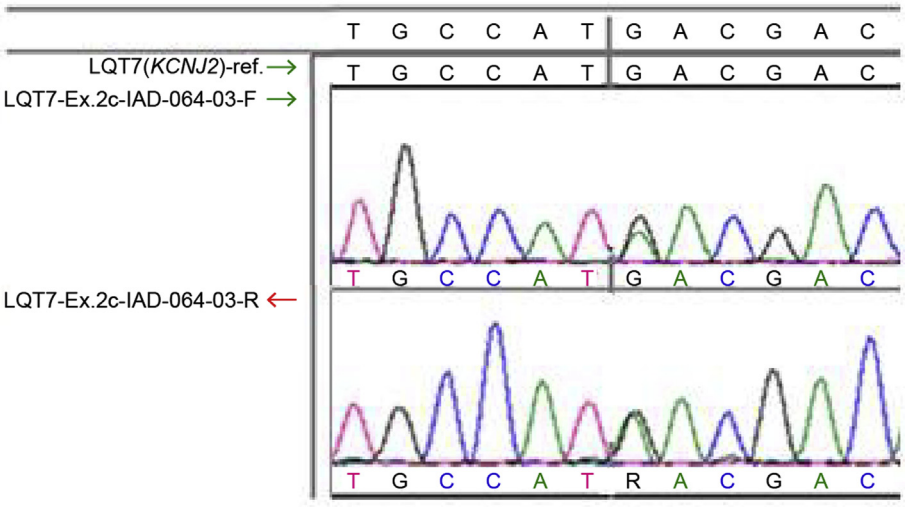

Fig. 5. Mutation identified in case 2.

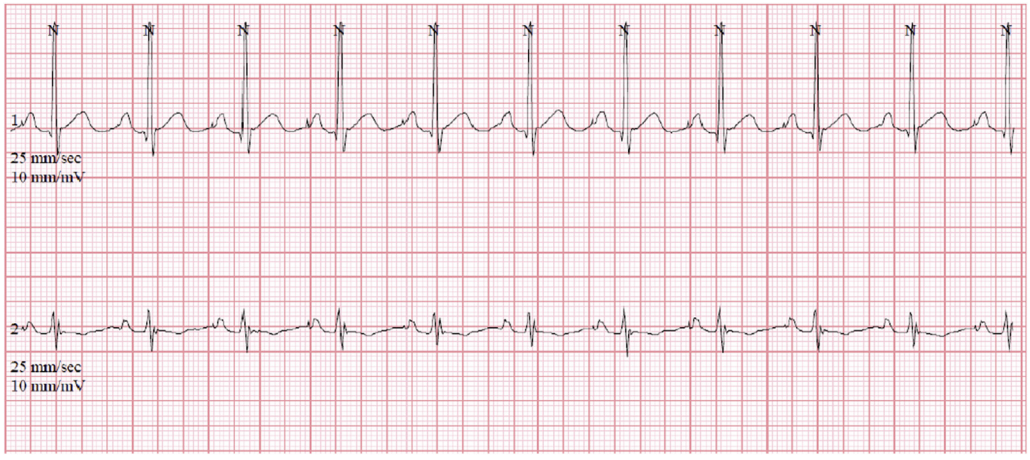

Fig. 6. Stable rhythm after AAI pacing and medication. Note the atrial pacing spike followed by atrial capture and normal conduction through the AV node to the ventricle. No ventricular arrhythmia is seen (case 2).

3.3.2. Clinical findings

The patient had a short stature and dysmorphism (micrognathia, refractive error, and high-pitched voice) and an irregular heartbeat was noted during cardiac auscultation.

3.3.3. Diagnostic assessment

The ECG study and Holter monitoring revealed typical features of ATS, with prominent U waves and frequent PVCs as well as bidirectional VT. Serum electrolyte levels and the echocardiogram were normal.

Genetic testing identified a novel mutation in *KCNJ2,* a homozygous T-to-A nucleotide substitution in exon 2 (c.366T > A), resulting in the replacement of cysteine at position 122 by a termination codon (Fig. 7).

3.3.4. Therapeutic intervention

The patient was started on nadolol (1 mg/kg/day, once a day) and flecainide (150 mg/m^2/day). There was only mild improvement in ventricular arrhythmia.

3.3.5. Follow-up and outcomes

Because of the absence of symptoms, the patient was not compliant with treatment. The patient continued to be followed up in the clinic for more than 4 years, although she did not take any medications and showed no change in her condition.

3.4. Case 4

3.4.1. Patient information

A 11-year-old girl presented to the pediatric cardiology clinic with a history of recurrent episodes of sudden weakness and falls (paralysis attacks) for a few months, involving all four limbs and occurring once every few weeks. There was no family history of a similar complaint and no history of sudden death in the family.

3.4.2. Clinical findings

An irregular heartbeat was found on auscultation. There were no dysmorphic features, and muscle power and tone were normal.

3.4.3. Diagnostic assessment

The patient had normal electrolyte levels and a normal echocardiogram. The ECG study and Holter monitoring revealed rare episodes of slow bidirectional VT. Most of the time, she was in sinus rhythm. She had episodic paralysis several times with normal sinus

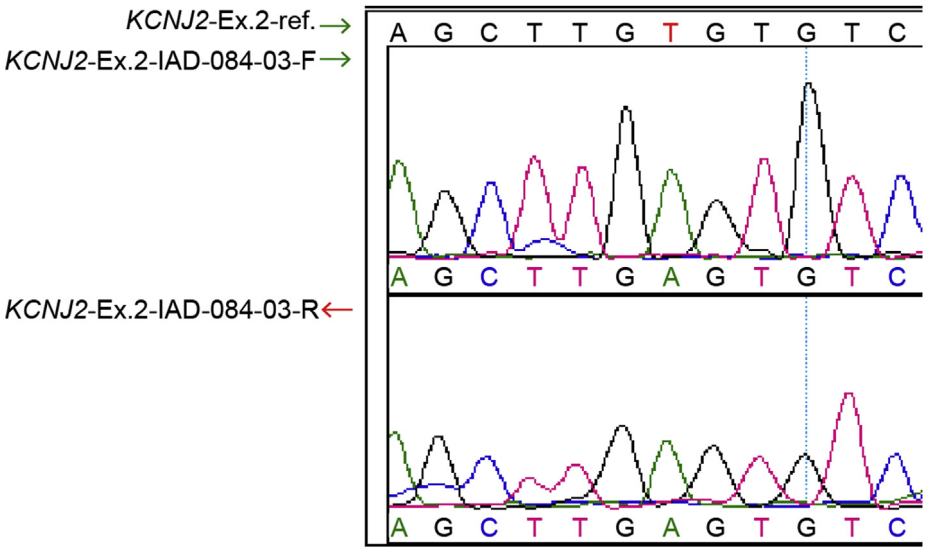

Fig. 7. Mutation identified in case 3.

rhythm seen on Holter monitoring, confirming that the ventricular arrhythmias had nothing to do with the sudden weakness and paralysis (typical in ATS). Genetic testing identified a *de novo* heterozygous A-to-G nucleotide substitution in exon 2 (c.919A > G), resulting in the replacement of methionine at position 307 by valine (c.919A > G, p.Met307Val) (Fig. 8). The parents were tested and were negative. This mutation has been previously reported in association with ATS [10].

3.4.4. Therapeutic intervention

The patient was started on nadolol (1 mg/kg/day, once a day) and flecainide (150 mg/m^2/day). Acetazolamide (20 mg/kg/day dose divided twice per day) was added by the neurology team for the periodic paralysis.

3.4.5. Follow-up and outcome

Unfortunately, there was only mild improvement in her symptoms, despite high compliance with medications, per parental feedback. The patient continued conservative follow-up with medications but without pacing interventions; she has been followed up in the clinic for 8 years.

4. Discussion

When ATS was first described in 1971 by Andersen and colleagues, only periodic paralysis was addressed. Subsequently, the triad of cardinal clinical features (periodic paralysis, cardiac arrhythmias, and dysmorphic features) became universally recognized in the 1990s [2–5]. Dysmorphic features seen in ATS include skeletal and facial abnormalities, including low-set ears, micrognathia, ocular hypertelorism, palatal defects, slight bilateral ptosis, short stature, and fifth digit clinodactyly and syndactyly. These features can provide diagnostic clues, but sometimes they are not easy to identify, as the clinical manifestation is variable, even within the same family [1].

In our case series, we demonstrated great variability in the clinical manifestation of ATS, the presence of dysmorphic features in some patients and absence in others, and the presence of

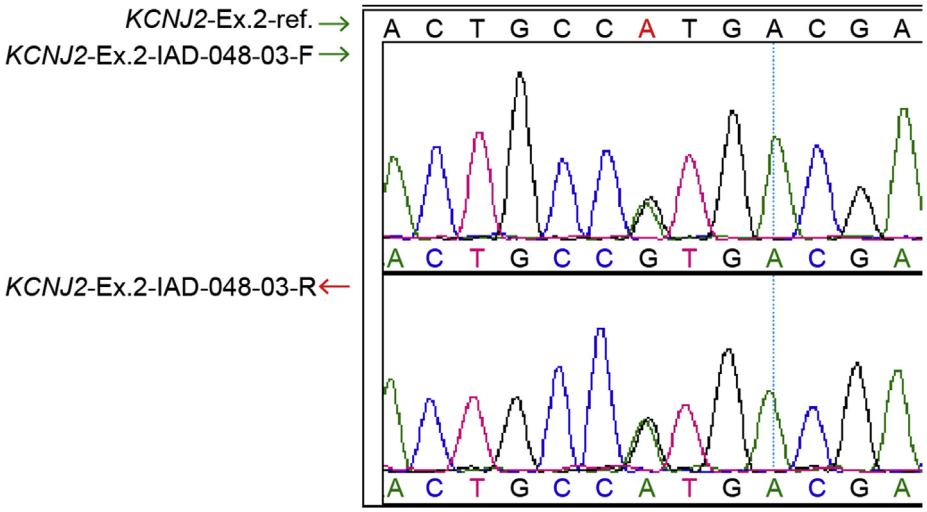

Fig. 8. Mutation identified in case 4.

periodic paralysis in some patients and absence in others. However, they all share the characteristic arrhythmias described in the syndrome, with abnormally prominent U waves and frequent PVCs and bidirectional VT. All diagnoses were confirmed by performing genetic testing. We were able to identify a novel mutation in *KCNJ2,* identified as a homozygous T-to-A nucleotide substitution in exon 2 (c.366T > A), resulting in the replacement of cysteine at position 122 by a termination codon (c.366 T/A, p.Cys122Ter; homozygous). This mutation has not been previously reported and was not detected in 168 ethnically matched controls.

In our patients, response to medical treatment with medications alone was suboptimal; however, the addition of AAI pacing, together with flecainide and a β-blocker, significantly improved the ventricular arrhythmia, which is a risk factor for mortality. The implantation of pacemakers in children carries its own rare, long-term complications, and we believe this intervention should only be undertaken in high-risk patients who are symptomatic and have high-grade ventricular ectopy and bidirectional VT.

4.1. Limitation of the study

The small number of patients in this study makes it difficult to provide treatment recommendations; however, the success of the combination of atrial pacing and medications to control ventricular arrhythmias is a promising treatment option in high-risk patients.

More studies are needed in the future to test other treatment options, including new medications or surgical interventions such as stellate gangliectomy that may treat ventricular arrhythmias caused by inherited disorders such as long QT syndrome or catecholamine polymorphic VT.

5. Conclusions

Through this series, we hope to increase awareness of this rare syndrome and to lend our experience in the treatment of this difficult disease, because making the correct diagnosis helps in proper treatment and prevention of catastrophic effects tremendously. In our country where consanguinity is common [7], the incidence of this autosomal dominant disease could be reduced if proper genetic counseling is provided.

Conflicts of interest

None.

Declarations of interest

None.

Funding

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Ethical statement

This study was conducted as part of the approved projects of the Cardiovascular Genetics Program, with RAC number 2050035.

The samples were obtained for genetic analysis after obtaining the consent from the parents.

Acknowledgments

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