Instituto Nacional Cardiovascular
Archivos Peruanos de Cardiología y Cirugía Cardiovascular
Arch Peru Cardiol Cir Cardiovasc. 2024;5(3). doi: 10.47487/apcyccv.v5i3.378.
Sociedad Científica de Medicina Cardiovascular del Perú

Case Report

Andersen-Tawil Syndrome, a differential of bidirectional ventricular tachycardia: a case report

Miguel J. Tejeda-Camargo[1,2,a], **Paula N. Vanegas-Rincón**[1,b], **Luis E. Villamil-Ramírez**[1,c], **Julio C. Rojas-Rojas**[1,d], **Richard Soto Becerra**[3,a]

Received: April 28, 2024
Accepted: July 08, 2024
Online: July 26, 2024

Authors' affiliation
[1] Angiografía de Colombia, Clínica Cardiovascular; Villavicencio, Meta, Colombia.
[2] Cardiometa, Villavicencio, Meta, Colombia.
[3] Facultad de Medicina, Universidad Nacional Mayor de San Marcos, Lima, Peru.
[a] Cardiovascular electrophysiology physician.
[b] General practitioner, hospital-based electrophysiology.
[c] General practitioner, hospital-based hemodynamics.
[d] Specialist in Internal Medicine and Intensive Care.

Correspondence
Miguel J Tejeda-Camargo
Angiografía de Colombia, Clínica Cardiovascular; Carrera 40#33–08. Villavicencio, Meta, Colombia.
057+ 3152003191

E-mail
migueljosetejeda@hotmail.com

Funding
None.

Conflicts of interest
The authors declare no conflicts of interest.

Cite as
Tejeda-Camargo MJ, Vanegas-Rincón PN, Villamil-Ramírez LE, Rojas-Rojas JC, Soto Becerra R. Andersen-Tawil Syndrome, a differential of bidirectional ventricular tachycardia: a case report. Arch Peru Cardiol Cir Cardiovasc. 2024;5(3). doi: 10.47487/apcyccv.v5i3.378.

ABSTRACT

We present the case of a patient with Andersen-Tawil syndrome (ATS), a rare genetic disorder characterized by ventricular arrhythmias, dysmorphic features at the skeletal level and periodic muscle paralysis. The diagnosis was delayed due to the non-simultaneous presentation of symptoms. This case underscores the importance of investigating neurological symptoms in patients with unexplained ventricular arrhythmias, as well as considering cardiac symptoms in those with periodic paralysis. The diagnosis was confirmed through the identification of a mutation in the KCNJ2 gene (c.224C>T(p.Thr75Met)); which has not been reported in the gnomAD database, suggesting a minor allele frequency (MAF) of less than 1%. The patient is currently being managed pharmacologically with a beta-blocker and remains free of arrhythmias episodes.

Keywords: Andersen Syndrome; Long QT Syndrome; Tachycardia, Ventricular; Mutation (Source: MeSH-NLM).

RESUMEN

Se presenta el caso de una paciente con síndrome de Andersen-Tawil (SAT) una entidad genética rara que se caracteriza por la presencia de arritmias ventriculares, rasgos dismórficos a nivel esquelético y parálisis muscular periódica, con un diagnóstico tardío dada la no simultaneidad de la presentación de los síntomas. Se resalta la importancia de buscar síntomas neurológicos ante la presencia de arritmias ventriculares de origen no claro o síntomas cardiacos en pacientes con parálisis periódica. El diagnóstico se confirmó por la mutación del gen KCNJ2 (c.224C>T(p.Thr75Met)); dicha mutación no se encuentra reportada en gnomAD, por lo cual se presume una frecuencia alélica (MAF) menor del 1%. Actualmente en manejo farmacológico con betabloqueador y sin arritmias.

Palabras clave: Síndrome de Andersen; Síndrome de QT Prolongado; Taquicardia Ventricular; Mutación (Fuente: DeCS-Bireme)

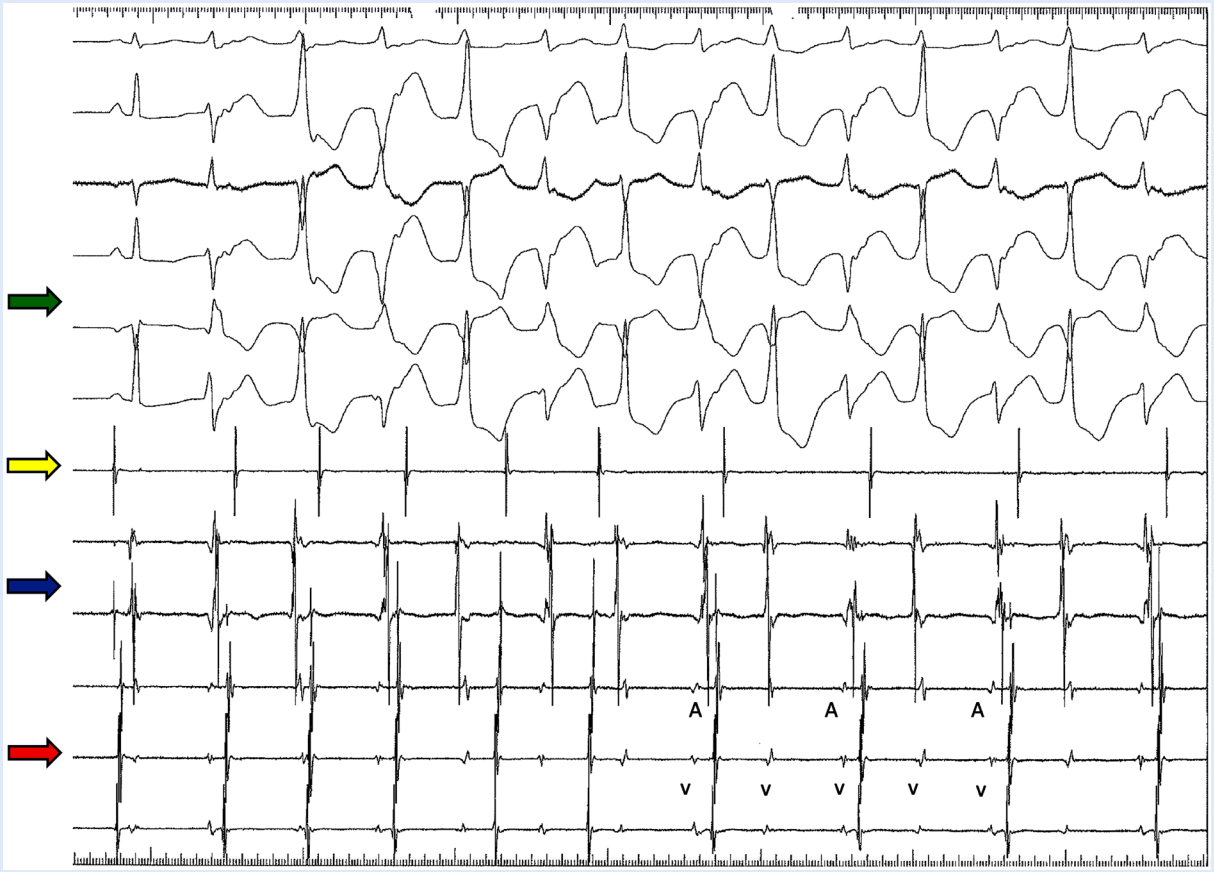
Introduction

Andersen-Tawil syndrome (ATS) is a rare genetic condition characterized by ventricular arrhythmias, skeletal dysmorphic features, and periodic muscle paralysis. Diagnosis is often delayed due to the intermittent presentation of symptoms [1]. Genetic support is crucial [2], and treatment includes managing periodic paralysis, antiarrhythmic medications, and the use of devices to prevent sudden death. The following case is presented as relevant due to the syndrome's prevalence, the delayed diagnosis, and the rarity of the mutation type involved.

Case report

The case of a 33-year-old female physician from Villavicencio (Meta, Colombia), is reported. She presented with shock-like sensations from an implanted cardioverter-defibrillator (ICD). She has a history of catecholaminergic polymorphic ventricular tachycardia (CPVT), diagnosed during an electrophysiological study in 2010. This diagnosis was prompted by the presence of palpitations, frequent ventricular extrasystoles, and a sensation of near-syncope episodes. Two stress tests showed chronotropic incompetence criteria, but no induction of ventricular arrhythmias. A cardiac MRI revealed thinning of the free wall towards the apex, with a wall thickness of 1 mm, making it difficult to assess for fat infiltration. Tests for Chagas disease were negative, and an electrophysiological study induced bidirectional ventricular tachycardia (using a protocol with eight baseline train beats at 400 ms, with 2 extra stimuli at 300 ms and 280 ms, followed by a sinus beat and sustained bidirectional ventricular tachycardia (VT) **(Figure 1)**. No adrenergic agonists were used during the study.

Due to the presence of sinus node dysfunction and the risk of sudden death, a dual-chamber ICD was implanted as a secondary preventive measure. In 2015, the device's battery depleted, leading to a generator replacement. In 2018, due to inappropriate shocks caused by noise in the right ventricular lead, the lead was



Green arrow: indicates the surface electrocardiogram in descending order (DI, DII, AVL, AVF, V1, and V6), initially showing a sinus beat followed by bidirectional ventricular tachycardia. Yellow arrow: atrial electrogram (catheter in the atrium) where atrioventricular (AV) dissociation is evident. Blue arrow: catheter positioned in the tricuspid annulus region with AV dissociation. Red arrow: catheter located in the coronary sinus (V: ventricular electrogram and A: atrial electrogram) with AV dissociation.

Figure 1. Electrophysiological study. A beat-to-beat shift in the QRS axis is observed, indicative of bidirectional ventricular tachycardia. The coronary sinus shows clear atrioventricular dissociation.

abandoned, and a new high-voltage lead was implanted. By the last follow-up in 2022, the device was functioning normally. The patient was undergoing pharmacological management with bisoprolol. Physical examination and laboratory tests revealed no abnormalities. Device telemetry showed noise in the ventricular, which resulted in inappropriate shocks. The patient was informed of the need to implant a new lead, but declined further intervention.

During this hospitalization, the electrocardiogram (ECG) documented alternating sinus rhythm with pacing rhythm. Given that the patient had not experienced ventricular arrhythmias in over 13 years of follow-up, her refusal to undergo new surgical interventions, and the proper functioning of the device in terms of pacing, a decision was made in consultation with the institutional board to deactivate the high-voltage therapies.

During follow-up, a new evaluation revealed periodic episodes of muscle paralysis triggered by intense exercise, along with physical features such as clinodactyly, a prominent forehead, micrognathia, and low-set ears **(Figure 2)**. Previous ECG records (2010) documented prominent U waves **(Figure 3)**, raising suspicion of ATS.

Currently, one year into follow-up, the patient remains asymptomatic. The genetic test report indicates a heterozygous variant in the KCNJ2 gene (c.224C>T(p.Thr75Met)), a finding consistent with ATS.

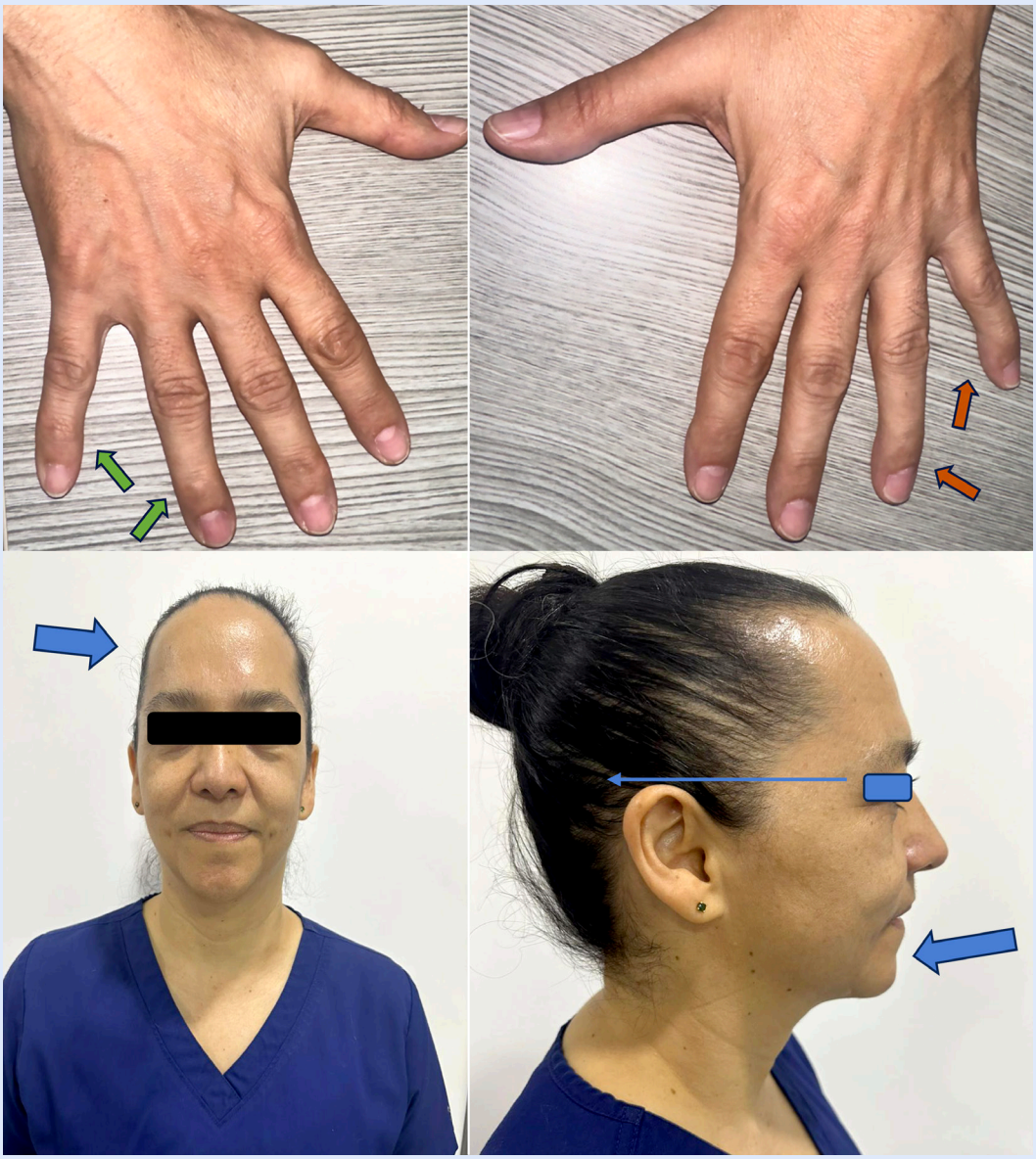


Figure 2. Clinodactyly in the right hand (green arrow) and left hand (orange arrow). In the lower part of the image, other physical features are identified (blue arrow), such as a prominent forehead, low-set ears, and micrognathia.

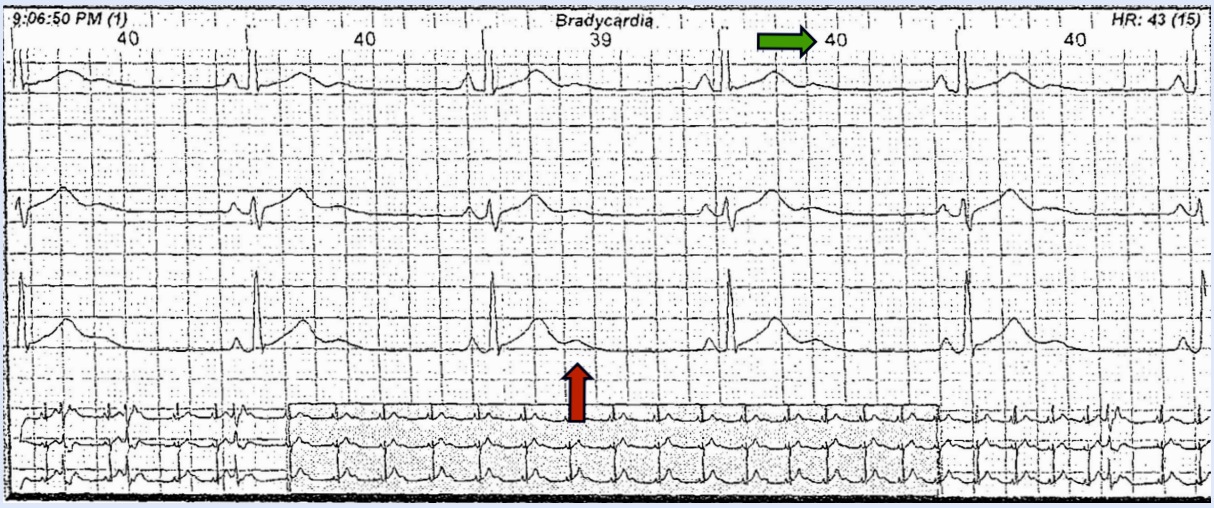


Figure 3. Holter from 2010. Sinus bradycardia (green arrow, patient at 40 beats per minute) with characteristic giant U waves (orange arrow) indicative of ATS.

Discussion

Sudden arrhythmic death secondary to channelopathies continues to have a significant clinical impact due to delayed diagnosis [1], thereby requiring a high index of suspicion, and ATS is not exempt from this phenomenon. The actual prevalence of this condition is unknown, but it is estimated to affect approximately 1 in 1,000,000 people [2]. The diagnosis of the ATS is based on the presence of a clinical triad **(Table 1)**, supported by the presence of a related mutation (the mutation is confirmed in 70% of cases, classifying ATS as type 1 when present and as type 2 when absent; the penetrance of the pathological mutation varies from 80% to 95%) [3]. However, it is important to emphasize that the diagnosis of this condition is primarily clinical [4]. In our case report, the patient met the diagnostic criteria based on the presence of periodic muscular paralysis and ventricular arrhythmia. Although the presence of bidirectional VT is characteristic of CPVT, it is not exclusive to this condition **(Table 2)** [5]. In this case, physical stress did not induce the arrhythmia, and the identified mutation is consistent with ATS [6].

Table 1. Disease characteristics

Definition	Epidemiology	Clinical	Diagnosis	Treatment
It is an arrhythmic syndrome with a genetic substrate, characterized by the presence of ventricular arrhythmias (polymorphic VT, bidirectional VT, ventricular extrasystoles), dysmorphic skeletal features, and periodic muscle paralysis. Type 1 (with documented mutation) Type 2 (without demonstrated mutation)	Estimated prevalence: 1 in 1,000,000 Mutation in 70% Autosomal dominant inheritance Penetrance varies from 80% to 95%	Different presentations: - Asymptomatic - Palpitations - Syncope and presyncope - Electrical storm - Sudden death - Periodic muscle paralysis - Physical changes (clinodactyly, scoliosis, hypertelorism, dental anomalies, etc.)	Criterios clínicos Mutación del gen KCNJ2 o KCNJ5 Niveles de potasio (normales, bajos o altos durante los episodios de debilidad) Hormonas tiroideas normales Estudios de conducción nerviosa normales usualmente Electrocardiograma y holter con arritmia ventricular Ecocardiograma normal	Multidisciplinary Potassium replenishment during episodes of muscle paralysis Avoid known triggers (lifestyle changes) Potassium-sparing diuretics or carbonic anhydrase inhibitors ICD in patients with syncope or aborted sudden death Flecainide Beta-blockers Avoid QT-prolonging medications Genetic counseling

Table 2. Causes of Bidirectional Ventricular Tachycardia

Etiology	Possible mechanism
CPVT	Intracellular calcium overload
Acute ischemia	Delayed afterdepolarizations
Ischemic heart disease	Dual reentry or single reentry with dual exit
Digoxin toxicity	Intracellular calcium overload
Sarcoidosis	Delayed afterdepolarizations
Andersen-Tawil syndrome	Delayed afterdepolarizations
Myocarditis	Delayed afterdepolarizations
Familial hypokalemic paralysis	Potassium current imbalance
Cardiac neoplasms	Dual reentry or single reentry with dual exit
Sobredosis de cafeína	Delayed afterdepolarizations
Coronary allograft vasculopathy	Two parasystolic foci

Adapted from reference (1). CPVT: catecholaminergic polymorphic ventricular tachycardia.

Furthermore, it is important to note that symptoms may be intermittent and not present simultaneously at the time of consultation, which poses a diagnostic challenge. A thorough evaluation for neurological symptoms in the presence of unexplained ventricular arrhythmias, or for cardiac symptoms in patients with periodic paralysis, is imperative [7]. Moreover, patients should be assessed for minor genetic anomalies such as clinodactyly, scoliosis, or low-set eyes, among others. In the case of our patient, there was a diagnostic delay of more than 10 years, due to the absence of an active search for neurological symptoms, and the presence of minor skeletal anomalies was also overlooked.

In all patients suspected of having ATS, it is recommended to measure potassium levels (both baseline and during episodes of weakness, which may be normal, low, or high), thyroid hormone levels, and perform nerve conduction studies (usually normal). A study of 11 patients found an abnormal post-exercise response [1] in 82% of cases. The mutation in the potassium channel (70%, KCNJ2 or KCNJ5) is the distinctive genetic anomaly. In our patient, a missense mutation was found, where cytosine was replaced by thymine at codon 224 of the KCNJ2 gene. This mutation leads to the substitution of the amino acid threonine with methionine at position 75 of the protein, altering its physicochemical properties. The KCNJ2 variant (NM_000891.3) .224C>T; p.Thr75Met is absent from general population databases (https://gnomad.broadinstitute.org/variant/rs104894585) (PM2_Sup).

The significance of these findings is pathogenic, and nine cases of this specific mutation have been described in the literature [2-4]. It is not reported in gnomAD, indicating a minor allele frequency (MAF) of less than 1%. This variant has been documented in multiple patients with ATS, showing variable phenotypes. Dysmorphic features were observed in all patients and there was high penetrance of periodic paralysis in males (PMIDs: 15911703, 16217063, 17341397, 17582433, 18452873). Moreover, this variant has been associated with a high risk of cardiac events in one report (PMID: 24861851). The KCNJ2 gene is definitively associated with ATS (OMIM#70390) under an autosomal dominant inheritance pattern. Based on ACMG criteria, the variant is classified as pathogenic. Treatment [5] for these patients is multidisciplinary **(Table 1)** and should focus on the management and prevention of episodes of muscle weakness, risk stratification for sudden death, avoiding medications that prolong the QT interval, providing a genetic counseling (for children and family members), and regular follow-up [6]. Currently, a clinical trial is underway to compare pharmacological strategies, including beta-blockers, calcium channel blockers, and flecainide, aimed at reducing arrhythmic burden (NCT06205550).

In conclusion, the diagnosis of this condition requires a high index of suspicion. A detailed clinical history is essential, and genetic testing is crucial for the comprehensive diagnostic approach in these patients.

Ethical considerations

The publication of the photographs was authorized by the patient and also approved by the institution.

Author contributions

MJTC: Conceptualization, writing - review & editing and supervision. PNVR: investigation, writing - original draft. LEVR: project administration, investigation. JCR: resources, writing - review & editing. RSB: Visualization and writing - review & editing.

Acknowledgments

To Yesid Pino, manager of the Angiografía de Colombia clinic, for providing opportunities for the academic and research development of his team. To Leidy Mancipe, nursing leader in the electrophysiology department, for her dedication and commitment to patient care, and for assisting in the collection of the necessary information for this publication.

References

1. Weir RA, Petrie CJ, Murday V, Findlay IN. Andersen-Tawil syndrome. Int J Cardiol. 2011;148(1):e13-5. doi: 10.1016/j.ijcard.2009.01.057.
2. de Vera McMullan P, Corella Aznar E, Granados Ruiz MÁ. Andersen-Tawil syndrome: A long QT syndrome with variable expression. Med Clin (Barc). 2024;162(6):309-311. English, Spanish. doi: 10.1016/j.medcli.2023.10.021.
3. Rocha-Arrieta MC, Arias-Díaz A, Quiróz-Romero CA, Rocha-Arrieta Y. [Catecholaminergic polymorphic ventricular tachycardia in adolescents: a clinical, electrocardiographic and genetic diagnosis]. Arch Peru Cardiol Cir Cardiovasc. 2021;2(3):205-210. Spanish. doi: 10.47487/apcyccv.v2i3.151.
4. Pérez-Riera AR, Barbosa-Barros R, Samesina N, Pastore CA, Scanavacca M, Daminello-Raimundo R, et al. Andersen-Tawil Syndrome: A Comprehensive Review. Cardiol Rev. 2021;29(4):165-177. doi: 10.1097/CRD.0000000000000326.
5. Donaldson MR, Jensen JL, Tristani-Firouzi M, Tawil R, Bendahhou S, Suarez WA, *et al*. PIP2 binding residues of Kir2.1 are common targets of mutations causing Andersen syndrome. Neurology. 2003;60(11):1811-6. doi: 10.1212/01.wnl.0000072261.14060.47.
6. Statland JM, Fontaine B, Hanna MG, Johnson NE, Kissel JT, Sansone VA, *et al*. Review of the Diagnosis and Treatment of Periodic Paralysis. Muscle Nerve. 2018;57(4):522-530. doi: 10.1002/mus.26009.
7. Almarzuqi A, Kimber S, Quadros K, Senaratne J. Bidirectional Ventricular Tachycardia: Challenges and Solutions. Vasc Health Risk Manag. 2022;18:397-406. doi: 10.2147/VHRM.S274857.
8. Gutiérrez LK, Moreno-Manuel AI, Jalife J. Kir2.1-NaV1.5 channelosome and its role in arrhythmias in inheritable cardiac diseases. Heart Rhythm. 2024;21(5):630-646. doi: 10.1016/j.hrthm.2024.01.017.
9. Vivekanandam V, Jayaseelan D, Hanna MG. Muscle channelopathies. Handb Clin Neurol. 2023;195:521-532. doi: 10.1016/B978-0-323-98818-6.00006-6.
10. Tan SV, Matthews E, Barber M, Burge JA, Rajakulendran S, Fialho D, *et al*. Refined exercise testing can aid DNA-based diagnosis in muscle channelopathies. Ann Neurol. 2011;69(2):328-40. doi: 10.1002/ana.22238.
11. Kostera-Pruszczyk A, Potulska-Chromik A, Pruszczyk P, Bieganowska K, Miszczak-Knecht M, Bienias P, *et al*. Andersen-Tawil syndrome: report of 3 novel mutations and high risk of symptomatic cardiac involvement. Muscle Nerve. 2015;51(2):192-6. doi: 10.1002/mus.24293.
12. Johnson JN, Tester DJ, Perry J, Salisbury BA, Reed CR, Ackerman MJ. Prevalence of early-onset atrial fibrillation in congenital long QT syndrome. Heart Rhythm. 2008;5(5):704-9. doi: 10.1016/j.hrthm.2008.02.007.
13. Zhang L, Benson DW, Tristani-Firouzi M, Ptacek LJ, Tawil R, Schwartz PJ, et al. lectrocardiographic features in Andersen-Tawil syndrome patients with KCNJ2 mutations: characteristic T-U-wave patterns predict the KCNJ2 genotype. Circulation. 2005;111(21):2720-6. doi: 10.1161/CIRCULATIONAHA.104.472498.
14. Davies NP, Imbrici P, Fialho D, Herd C, Bilsland LG, Weber A, *et al*. Andersen-Tawil syndrome: new potassium channel mutations and possible phenotypic variation. Neurology. 2005;65(7):1083-9. doi: 10.1212/01.wnl.0000178888.03767.74.
15. Eckhardt LL, Farley AL, Rodriguez E, Ruwaldt K, ,Hammill D, Tester DJ, et al. KCNJ2 mutations in arrhythmia patients referred for LQT testing: a mutation T305A with novel effect on rectification properties. Heart Rhythm. 2007;4(3):323-9. doi: 10.1016/j.hrthm.2006.10.025.
16. Tani Y, Miura D, Kurokawa J, Nakamura K, Ouchida M, Shimizu K, et al. T75M-KCNJ2 mutation causing Andersen-Tawil syndrome enhances inward rectification by changing Mg2+ sensitivity. J Mol Cell Cardiol. 2007;43(2):187-96. doi: 10.1016/j.yjmcc.2007.05.005.
17. Wu L, Fang Y, Zhang BR. World J Emerg Med. 2020;11(4):267-269. doi: 10.5847/wjem.j.1920-8642.2020.04.012.
18. Maffè S, Paffoni P, Bergamasco L, Dellavesa P, Zenone F, Baduena L, *et al*. Therapeutic management of ventricular arrhythmias in Andersen-Tawil syndrome. J Electrocardiol. 2020;58:37-42. doi: 10.1016/j.jelectrocard.2019.10.009.
19. ClinicalTrials.gov [Internet]. N-of-1 in ATS and MEPPC. Identifier: NCT06205550. Bethesda, MD: NIH; 2024 [cited March 9, 2024]. Available from: https://clinicaltrials.gov/study/NCT06205550?viewType=Table&page=11&rank=102