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Brugada syndrome & AKAP9: Reconciling clinical findings with diagnostic uncertainty

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ABSTRACT

Introduction: Brugada Syndrome typically presents with sudden nocturnal arrhythmias. Diagnosis may be challenging due to variable and transient electrocardiogram patterns and nondiagnostic provocation studies. Genetic testing can establish the etiology, but results may be inconclusive with variants of uncertain significance.
Case: A 24-year-old male with family history of sudden cardiac death was found unresponsive due to seizure. He was hemodynamically stable. ECG showed saddle-back ST elevations in V1 and V2. Procainamide challenge was negative. We subsequently performed genetic testing, which demonstrated *AKAP9* variant.
Discussion: AKAP9 is a scaffolding protein that facilitates phosphorylation of delayed-rectifier potassium channels. The *AKAP9* variant alters potassium current causing disordered repolarization and ventricular reentry. It has been previously linked to other channelopathies, but its pathogenicity is fully undetermined.
Conclusion: Genetic testing is a useful tool to determine the origin of channelopathy, but inconclusive results with variants of uncertain significance should be clinically correlated.

Introduction

Brugada Syndrome (BrS) is a channelopathy characterized by unprecipitated ventricular fibrillation in structurally normal hearts with ECG patterns of right precordial ST-segment elevations [1]. While it often causes sudden cardiac death (SCD), many patients have variable history and clinical findings [2,3]. Genetic testing is useful to elucidate the etiology of suspected channelopathies, but results may be equivocal due to the vast number of implicated genes with variants of questionable clinical significance [4,5].

Case

A 24-year-old male was found in his bed unresponsive and cyanotic with foam and blood at the mouth. He was intubated in the field for hypoxic respiratory failure. He was hemodynamically stable with sinus tachycardia of 110 bpm. ECG changes demonstrated dynamic changes with approximately 1–2 mm J-point elevations in V1 – V3 with saddle-back morphology most prominent in V1 and V2 without reciprocal changes (Fig. 1). Initial arterial blood gas showed hypoxic, hypercapnic respiratory failure with increased anion gap metabolic acidosis and elevated lactic acid. Urine toxicology and alcohol level were negative. Total creatinine kinase peaked at 7435 U/L. Troponin on admission was 0.203 ng/mL and peaked at 0.984 ng/mL. Transthoracic echocardiogram showed normal ejection fraction without wall motion abnormalities and normal wall thickness. Further history was obtained after extubation one day later. Patient reportedly went to bed around 11 pm in his usual state of health. He denied any history of chest pain, palpitations, shortness of breath, or dizziness. He had no prior episodes of syncope or seizures, or prior hospitalizations. He did not take any medications. No history of substance abuse. His mother had recently passed away from SCD. She had a witnessed seizure prior to cardiac arrest which was precipitated by refractory ventricular fibrillation and followed by PEA. No autopsy or genetic testing was performed. These findings were suspicious of inherited channelopathy. Patient underwent electrophysiology study with procainamide provocation, which failed to induce type 1 ECG changes. Cardiac MRI was unremarkable without delayed gadolinium enhancement, dyskinesia, infiltration, or fibrosis of the myocardium. Given the inconclusive workup, the etiology of the suspected channelopathy was unclear. Consequently, we performed genetic testing with the *Invitae arrhythmia and*

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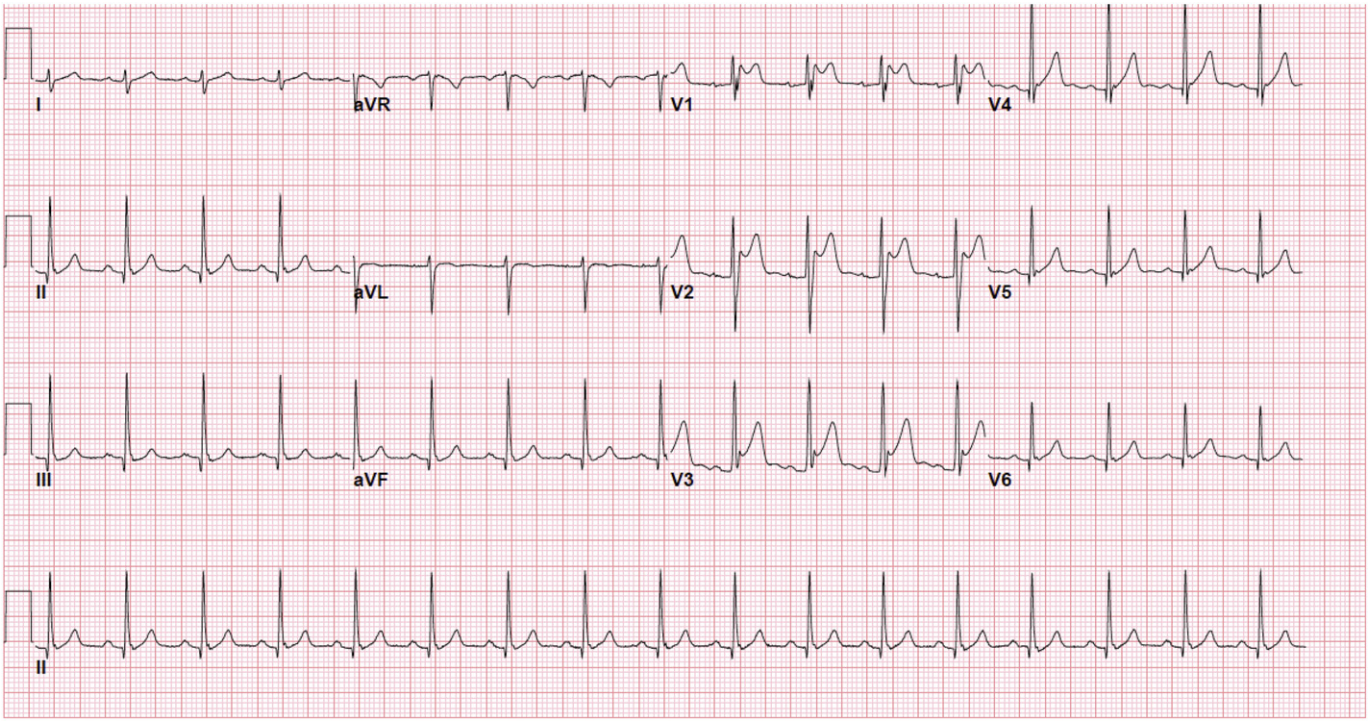

Fig. 1. ECG demonstrates 1–2 mm J-point elevations in V1 – V3 with saddle-back morphology most prominent in V1 and V2 without reciprocal changes, consistent with Type 2 Brugada pattern.

cardiomyopathy comprehensive panel (with add-ons) that sequenced 149 genes. It was positive for *AKAP9* variant of uncertain significance. Patient was counseled for ICD placement in consideration of his clinical presentation and family history.

Discussion

BrS accounts for 12% of all SCD, but the pathophysiological mechanisms are still not fully understood [4]. Arrhythmogenic events commonly occur during vagal predominance, presenting as nocturnal death, seizure, or agonal breathing [1,6]. The conduction abnormalities are theorized to have a predilection for the right ventricular (RV) due to the distinct electrical and structural features of the RV subepicardium [7]. It is suggested that discordant currents result in loss of the action potential dome with early repolarization of the RV epicardium. The resultant gradient between the RV epicardium and endocardium produce down-sloping ST-segment elevations with a prolonged action potential that is demonstrated by T-wave inversions in the right precordial leads [7,8]. Lead V1 typically shows the most prominent ST-segment elevations with varying degrees among V2 – V3 that are not accompanied by reciprocal ST changes. The ST morphology may be coved (diagnostic) or saddle back (nondiagnostic) [8]. Ventricular arrhythmias can occur due to the heterogeneity of repolarization where late potentials cause preexcitation in the epicardium and induce phase 2 reentry [5,8]. Literature has also described structural changes among BrS, such as myocardial atrophy with infiltration and fibrosis of the RV, but this is unproven [7,8].

Definitive diagnosis of BrS may be challenging. ECG changes are often dynamic and variable, and while provocation tests with sodium blocking agents may unmask them, nearly 25% are falsely negative [1]. In the setting of clinical suspicion and diagnostic uncertainties, genetic testing can delineate the etiology of channelopathies [5]. Approximately 25 genes are currently linked to BrS with loss of function mutations that occur in cardiac sodium or calcium channels, or gain of function mutations in potassium channels [3,9]. Yet, genetic screening fails to diagnose 80% of phenotypic BrS [9]. This may be attributable to single nucleotide polymorphisms that occur in exomes and non-coding regions of DNA that were not formerly recognized by conventional DNA analysis [2]. The advent of Sanger whole-genome sequencing has expanded genetic testing from single-gene analysis to multi-gene panels. This spurred genome-wide association studies, identifying patterns of variants, defined as nucleotide changes that occur in the general population. When these variants are identified repeatedly among individuals that share pathogenic phenotypes, they may serve as markers of disease [3,10]. These variants are cautiously being linked to inheritable channelopathies among individuals without identifiable mutations in gene-coding loci [2]. They may induce functional change when occurring on or near genes, or alter gene modifiers, which are proteins involved in trafficking, regulation, growth, function, transcription, and structural support [3,6,9]. More than 300 pathogenic variants have been linked to BrS with many more of undetermined significance [4,9]. Prior cohort studies have discovered rare variants among 64% of patients with BrS phenotypes and 50% of patients who suffered sudden nocturnal death [6,11].

Variants of *AKAP9*, also called *Yotiao*, are implicated in Long QT syndrome [6,12,13]. *Yotiao* is a scaffolding protein that binds KCNQ1 and creates a macromolecule complex with enzymes that regulate cardiac delayed-rectifier potassium channels (I_{Ks}) that are critical for action potential repolarization. Yotiao facilitates protein kinase A (PKA) mediated phosphorylation and protein phosphatase 1 (PPI) dephosphorylation of the I_{Ks} channel. It also intercepts adenylyl cyclase and phosphodiesterase (PDE) activity that balance cAMP levels [12–14]. While AKAP9 variants have been associated with loss of function mutations in LQT-1 and LQT-11, polymorphisms that hinder PPI or PDE activity could theoretically cause gain of function [14]. Whether AKAP9 plays a structural-regulatory role in other cardiac channels is unknown, but other AKAP subtypes have been observed among cardiac ryanodine receptors and L-type calcium channels [13,15]. Literature has demonstrated very few cases of AKAP9 variants among BrS phenotypes and sudden nocturnal death [6,11,16,17]. Our patient demonstrated a heterozygous AKAP9 variant on chromosome 7, Exon 8, c.2239G > A (p.Glu 747Lys). The ExAC population frequency is $8.475e^{6}$ and gnomAD frequency is

4.35e^{6}. The predicted *in silico* missense mutation algorithms are inconsistent (SIFT: "tolerated"; PolyPhen-2: "probably damaging"; Align-GVGD: "Class C0"). The ClinVar classification is of "uncertain significance," (accession VCV000582369.1, variation ID 582369, allele ID 564452).

The pathogenicity of indeterminant polymorphisms should be interpreted cautiously in the context of clinical findings [1,4,5]. Initial evaluation should exclude conditions that mimic Brugada ECG patterns, such as arrhythmogenic cardiomyopathy, early repolarization syndrome, RV infarct, or pulmonary embolism [1,8]. Precipitating factors, such as fever, hyperkalemia, cocaine, and medications (antidepressants, antihistamine, Propofol) should also be identified [1]. An inherited channelopathy should be strongly considered when unprovoked electrical instability occurs among patients with structurally normal hearts who have 1st degree relatives with history of SCD [11].

Conclusion

Advances in genetic testing have enhanced the diagnostic capabilities of assessing for inherited channelopathies. Consequentially, this has uncovered variants of uncertain pathogenic significance, which has complicated clinical interpretation of these results. We present a suspected case of BrS with a rare variant of AKAP9 of unclear pathogenicity. While AKAP9 is associated with long QT syndromes, its role in other channelopathies is unknown.

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