A1427S Missense Mutation in SCN5A Causes Type 1 Brugada Pattern, Recurrent Ventricular Tachyarrhythmias and Right Ventricular Structural Abnormalities

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1. Introduction

Brugada syndrome (BrS) is an ion channelopathy associated with mutations in the SCN5A gene, which encodes for the pore-forming alpha subunit of the cardiac Na\(^+\) channels (1). To date, variants of the gene encoding for Na\(^+\), K\(^+\), Ca\(^{2+}\) and hyperpolarization-activated cyclic nucleotide-gated (HCN) channels have been associated with BrS (2). Structural alterations of these ion channels can lead to characteristic depolarization and repolarization abnormalities observed on the electrocardiogram (ECG) (3-7). These in turn predispose the patient to malignant ventricular tachycardia and fibrillation (VT/VF) and sudden cardiac death (SCD) (8-12).

Brugada patterns can be subdivided to three main types (13, 14). Type 1 pattern has a characteristic coved-shaped ST elevation 2 mm, J-point elevation, a gradually descending ST segment, which terminates with a negative T-wave in the right precordial leads (V1, V2 and V3), with or without a class I anti-arrhythmic drug challenge, such as flecainide (15). Type 2 pattern is described as having saddleback morphology with a minimum 2-mm J-point elevation along with ST elevation of at least 1 mm. Type 3 pattern, the most benign form, is reflected by a narrow ST segment (1 mm) with either coved or saddleback ECG morphology (15). A type 3 pattern can be converted to a type 1 pattern upon pharmacological challenge or other stressors (15). There is significant genetic heterogeneity underlying BrS (16), including loss-of-function mutations in SCN5A, the gene responsible for the a-subunit of the Na\(^+\) channel (17). These mutations can affect different cellular processes, for example, impaired trafficking to the cell membrane, reduced expression and expression of non-functional proteins (18-23). Gating of Na\(^+\) channels can also be altered, as reflected by delayed activation, premature inactivation, enhanced slow inactivation and slower recovery from inactivation (22, 23). Reduced ICa\(_{Na}\) can also arise from mutations in genes encoding for glycerol-3-phosphate dehydrogenase 1-like (GPD1-L) protein (24), MOG1 (25), sarcolemmal membrane-associated protein (SLMAP) (26), desmosomal component plakophilin-2 (27), fibroblast growth factor homologous factor-1 (FGF2) (28) and transcriptional factor HEY2 (29, 30). The consequence is conduction or repolarization abnormalities that produce the characteristic ECG
patterns of right bundle branch block and ST segment elevation primarily observed in the right precordial leads (31). Aside from I_{Na}, reduced I_{Ca} has also been observed in BrS (32). This can arise from genes encoding for different protein subunits, α1 (CACNA1C), β2 (CACNB2), α2 (CACNA2D) and δ (CACNA2D), which make up the L-type Ca\textsuperscript{2+} channel (32, 33). Loss-of-function mutations in these genes can lead to abnormal trafficking, reduced expression or function of the channel (32, 34).

2. Case Presentation

We report a 66-year-old male patient who presented with recurrent syncope and ventricular fibrillation arrest twenty years ago, for which he received an implantable cardioverter defibrillator (ICD). Examination of the ICD records revealed many episodes of arrhythmias, which include one episode of supraventricular tachycardia (SVT), and four episodes of ventricular tachycardia (VT). In response, the patient was placed on chronic quinidine treatment at a dose of 200 mg twice a day to reduce the risk of developing ventricular arrhythmias. No further episodes were observed since the change in medication. Flecaïnide challenge test was also positive, along with a genetic test involving sequence analysis revealing an A1427S missense mutation in the Na\textsuperscript{+} channel gene.

Earlier this year, the shanghai score system for diagnosis of BrS was proposed following the J-wave syndrome consensus conference, stratifying patients into probable/definite BrS, possible BrS and the non-diagnostic category (35). In the latest resting ECG of our patient, the following measures were recorded, a coved-shaped ST elevation ≥ 2 mm, J-point elevation ≥ 2.5 mm and inverted T-waves in the right precordial leads (Figure 1). These findings were accompanied by a prolonged QRS duration (132 ms), a terminal R-wave (rsR') in lead V1 and a slurred S-wave in both leads I and V6. Together with his clinical history of documented VT/VF, these findings are diagnostic of definite BrS, according to the latest criteria (35).

Subsequent cardiovascular magnetic resonance studies demonstrated thinning of the right ventricular myocardium, but without obvious fatty infiltration of the muscle suggestive of arrhythmogenic right ventricular dysplasia (ARVD). Moreover, regional right ventricular (RV) akinesia, dyskinesia or dysynchronous RV contractions and fibro-fatty infiltrations were not observed. Therefore, the patient only partially fulfilled the revised task force criteria for ARVD (36).

3. Discussion

Mutations in SCN5A can cause a number of distinct cardiac diseases, including sick sinus syndrome (SSS), progressive cardiac conduction defect (PCCD, or Lenegre’s disease), long QT syndrome type 3, Brugada syndrome (BrS) and dilated cardiomyopathy (DCM) (37). Brugada syndrome has traditionally been viewed as a primary electrical disorder with little structural abnormalities (38). By contrast, arrhythmogenic right ventricular dysplasia (ARVD) is a cardiomyopathy with prominent structural alterations such as right ventricular (RV) dyskinesia or aneurysms (39). Both are diseases primarily of the RV (40). Although it was initially thought that there is a sharp divide between an electrical disorder and a structural cardiomyopathy, recent evidence shows that this is not the case (37). Thus, myocardial fibrosis is observed in BrS (3); conversely cardiomyopathies have been associated with ion channel abnormalities (41). Indeed, cases of overlapping features between BrS and ARVD have previously been reported (37). Thus, several investigators have suggested that a better classification of cardiomyopathy includes additional subtypes affecting the cytoskeleton, desmosome, sarcomere and ion channels (42).

Our patient had an ECG consistent with Type I Brugada pattern and fulfilled the Shanghai score system for definite BrS. The differential diagnosis was J-wave syndromes (35) and Brugada phenocopy (43). Moreover, our patient was noted to have RV wall thinning on cardiovascular magnetic resonance imaging. Genetic analysis demonstrated an A1427S missense mutation in SCN5A. The same mutation has previously been reported in another case concerning a 56-year-old lady with malignant VT/VF associated with lidocaine use in the context of an acute myocardial infarction (44). Contrastingly to our patient, she did not have ECG features of a Brugada pattern (44). In our case, however, it was not possible to attribute all of the clinical phenotypes to SCN5A, because other genes previously associated with Brugada syndrome were not checked for mutations. Therefore, compound heterozygosity could not be ruled out. Nevertheless, our case illustrates that ion channel mutations can produce not only an arrhythmic disorder but also structural abnormalities that are ordinarily observed as part of a cardiomyopathic process.

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A QRs prolongation (132 ms), a terminal R-wave (rsR’) in lead V1 and a slurred S-wave in both leads I and V6 were observed.

References


