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ELECTROPHYSIOLOGY

CASE REPORT: CLINICAL CASE

Effect of Flecainide on Multifocal Ectopic Purkinje-Related Premature Contractions in an R814W SCN5A Carrier

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ABSTRACT

Multifocal ectopic Purkinje-related premature contraction (MEPPC) is an autosomal dominant *SCN5A* channelopathy characterized by frequent multiform premature ventricular contractions originating from the His-Purkinje system. We present a patient with an MEPPC phenotype whose genetic testing identified a pathogenic *SCN5A* (*HGNC:10593*) variant amenable to precision antiarrhythmic therapy with flecainide. (J Am Coll Cardiol Case Rep 2024;29:102223) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

HISTORY OF PRESENTATION

A 38-year-old female patient (CIII-10 in the family pedigree shown in **Figure 1A**) was referred to the outpatient clinic 2 years previously with a history of palpitations and exertional dyspnea (NYHA functional class II). She had no history of syncope or presyncope. There was a strong family history of sudden cardiac death (SCD). The proband was noted to have an irregular heart rate on initial evaluation, and the rest of the physical examination was unremarkable.

LEARNING OBJECTIVES

- To be able to make a differential diagnosis of cardiomyopathies with multimodality imaging and genotyping.
- To use genotyping data to understand the arrhythmia mechanism and use mutation-guided precision antiarrhythmic therapy.

FAMILY HISTORY

The proband's father (CII-9) and her paternal aunt (CII-8) had a diagnosis of dilated cardiomyopathy (DCM) and died suddenly at the age of 33 years and 43 years, respectively. The proband's father's cousin (CII-11) had received a diagnosis of DCM and severe left ventricular systolic dysfunction and was recommended an implantable cardioverter-defibrillator (ICD). A paternal aunt (CI-5) succumbed to SCD at the age of 30 years.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis included the various subtypes of genetic arrhythmogenic cardiomyopathies resulting from pathogenic variants in the filamin C, lamin A/C, phospholamban, transmembrane protein

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ABBREVIATIONS AND ACRONYMS

DCM = dilated cardiomyopathy

ECG = electrocardiogram

ICD = implantable cardioverter-defibrillator

LBBB = left bundle branch block

LVEF = left ventricular ejection fraction

MEPPC = multifocal ectopic Purkinje-related premature contraction

PVC = premature ventricular contraction

RBBB = right bundle branch block

SCD = sudden cardiac death

SSFP = steady-state free precession

VT = ventricular tachycardia

43, titin, *SCN5A,* and RNA binding motif protein 20 genes.

INVESTIGATIONS

Results of an extensive laboratory panel, including serum electrolytes and thyroid function tests, were normal except for N-terminal pro-B-type natriuretic peptide, which was elevated at 1,800 pg/mL. The patient's baseline 12-lead electrocardiogram (ECG) (**Figures 2A and 2B**) showed sinus rhythm with frequent multiform ventricular premature beats having left bundle branch block (LBBB) and right bundle branch block (RBBB) configurations with an inferior axis, and all showing swift intrinsicoid deflections and a narrow QRS interval width suggesting a possible Purkinje fiber origin. Echocardiography revealed a dilated left ventricle and global hypokinesia (end-diastolic diameter, 57 mm; end-systolic diameter, 44 mm) with a reduced left ventricular ejection fraction (LVEF) (35%). Cardiac magnetic resonance imaging (**Figures 3A to 3C**) showed evidence of mild hypertrabeculation in the left ventricular apical segments and the absence of significant late gadolinium enhancement. A 72-hour Holter monitor showed multifocal premature ventricular contractions (PVCs) and nonsustained ventricular tachycardia (VT)—31% PVC burden; most PVCs had an RBBB configuration with a narrow QRS interval duration and rapid initial deflection suggestive of a Purkinje origin. Multifocal premature atrial complexes were noted, with no sustained atrial arrhythmia. Normal chronotropic competence with usual diurnal variation and a normal relationship of the PR interval with exercise were noted.

In view of an autosomal dominant pattern of a DCM phenotype in the family, genetic testing of the proband by whole exome sequencing established the presence of a pathogenic heterozygous missense variant in exon 16 of the *SCN5A* gene c.2440C>T (p. Arg814Trp; R814W), that resulted in the amino acid substitution of tryptophan for arginine at codon 814 and was subsequently validated by Sanger sequencing (**Figure 1B**). The R814W variant is a gain of function mutation at exon 16 of the *SCN5A* gene.[1]

MANAGEMENT

Because of the high SCD risk, the patient subsequently underwent single-chamber ICD insertion for the primary prevention of SCD, and antiarrhythmic drugs were initiated along with other guideline-directed medical therapy. Despite the use of multiple antiarrhythmic drugs, including amiodarone and sotalol, in varying doses, follow-up visits revealed incessant episodes of nonsustained VT during device interrogations with a persistently low LVEF (35%).

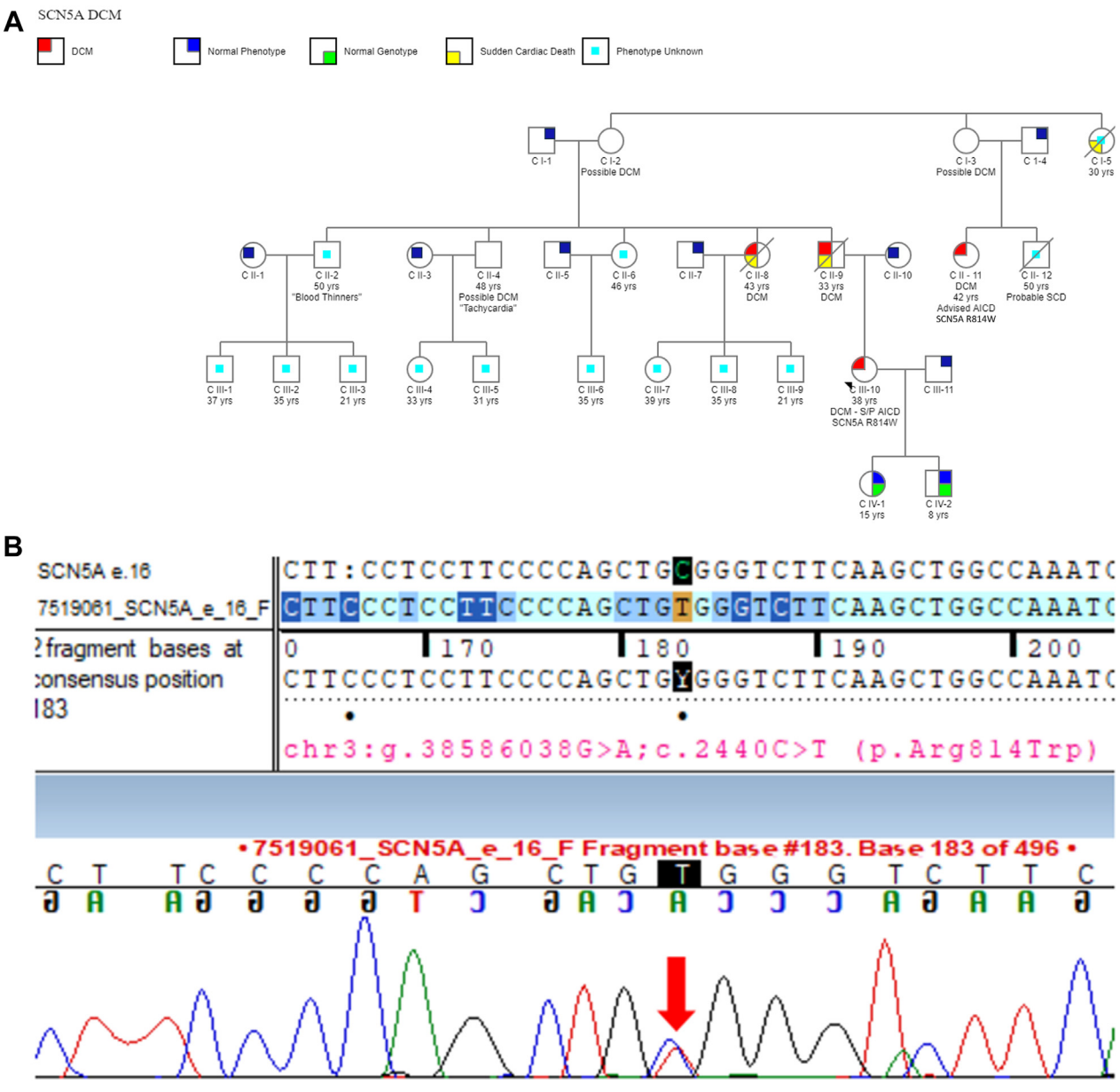
The presence of multifocal PVCs of likely Purkinje origin, a DCM phenotype with autosomal dominant mode of inheritance, and the detection of a pathogenic heterozygous missense variant in the *SCN5A* gene (p. Arg814Trp; R814W) led to a diagnosis of the *SCN5A* channelopathy multifocal ectopic Purkinje-related premature contraction (MEPPC). Because the R814W mutation is a gain of function variant that can potentially be responsible for the hyperexcitability of the His-Purkinje fibers, the patient was switched over to flecainide in a starting dose of 50 mg twice a day, which was gradually increased to 100 mg twice a day.

DISCUSSION

SCN5A variants (likely pathogenic/pathogenic variants) are detected in nearly 2% of DCM cases.[2] Rare *SCN5A* variants may lead to unique biophysical phenotypes, providing the substrate for progressive conduction system disease. The MEPPC phenotype was first described by Laurent et al,[3] who reported that a novel autosomal dominant form (exon 6; *SCN5A* - c.665G>A; R222Q) of cardiac arrhythmia characterized by frequent multiform PVCs originating from the His Purkinje system was associated with a DCM phenotype and a history of SCD.

The *SCN5A* R222Q variant is the most common variant described in a patient with the MEPPC phenotype.[1] Other rare *SCN5A* variants that have been reported to cause the MEPPC phenotype are *SCN5A* R814W, *SCN5A* A204E, and *SCN5A* L828F.[4,5] The patient we report here has the *SCN5A* R814W pathogenic variant, and there have been very few reports describing this variant in association with the MEPPC syndrome in the literature.[6] Functional studies performed by Nguyen et al[1] have shown that the R814W variant results in a hyperpolarized shift of the conductance-voltage relationship, leading to altered voltage dependence of the Nav1.5 channel. Therefore, the R814W variant is a gain of function variant that leads to hyperexcitability of the fascicular-Purkinje system, resulting in incomplete repolarization of the Purkinje cells and manifesting as a chaotic rhythm characterized by frequent ventricular premature complexes. The DCM phenotype in these patients is

FIGURE 1 **Pedigree Chart and Sanger Sequencing**

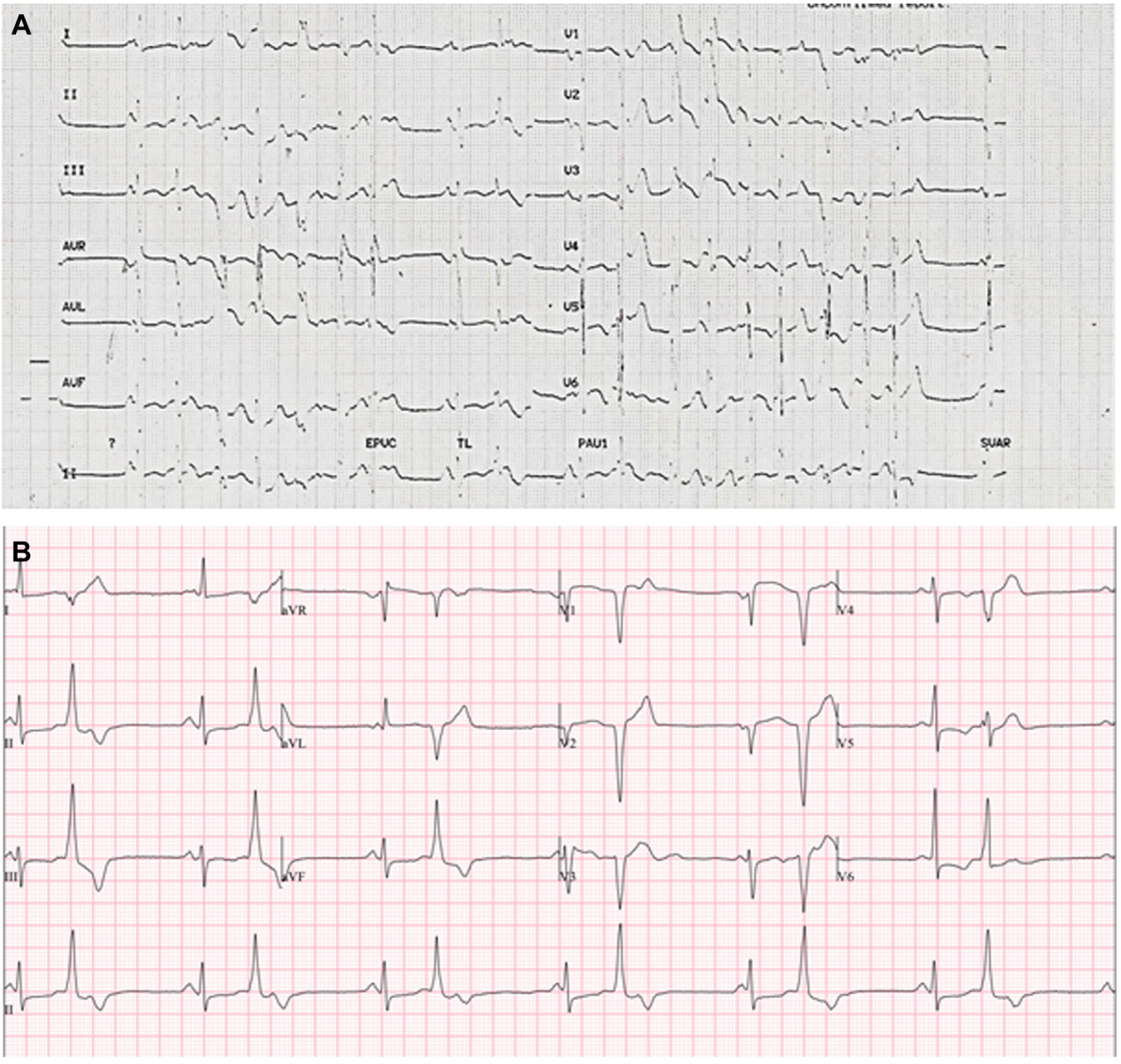


(A) A multigeneration pedigree chart showing an autosomal dominant inheritance pattern. (B) Sanger sequencing validation of the *SCN5A* variant (p.Arg814Trp). AICD = automated implantable cardioverter-defibrillator; DCM = dilated cardiomyopathy; SCD = sudden cardiac death; S/P = after (status post).

likely a consequence of a high burden of ventricular arrhythmia.

In patients with the MEPPC syndrome, reports have shown that therapy with appropriate sodium-channel blocking antiarrhythmic drugs (flecainide, quinidine, mexiletine) has successfully reduced the PVC burden and led to a restoration of left ventricular systolic function.[6,7] In our patient, there was a rapid and effective response to flecainide therapy in as little as 4 weeks after treatment initiation. Although the current guidelines do not advocate the use of Class I drugs (flecainide, quinidine) for the treatment of multifocal PVCs in patients with DCM, recognition of an MEPPC phenotype in a patient with DCM along with genetic confirmation of a gain of function *SCN5A* variant can potentially lead to Class

FIGURE 2 12-Lead Electrocardiograms



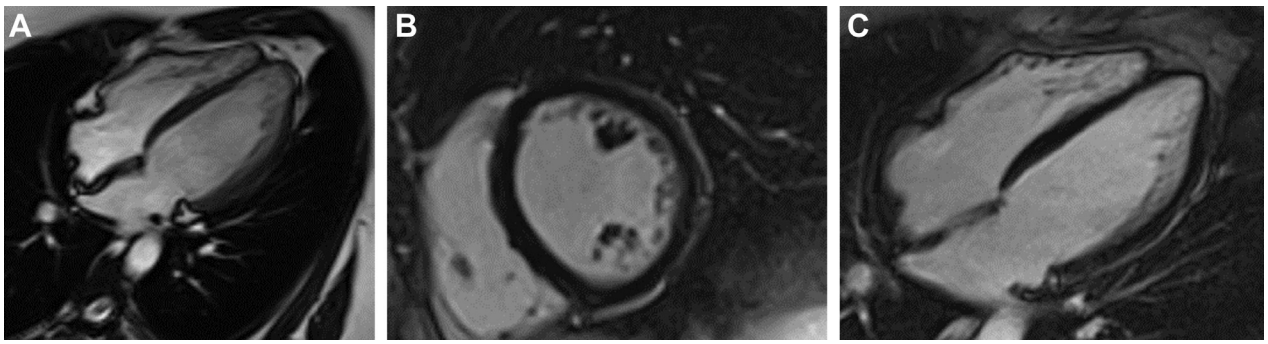
(A and B) Sinus rhythm with frequent multiform ventricular premature beats having left and right bundle branch block configurations with an inferior axis, and all showing swift intrinsicoid deflections and a narrow QRS interval duration. EPVC = ectopic premature ventricular contraction; PAU1 = pause of 1 missed beat; SVAR = supra-ventricular atrial rhythm; TL = Learned T wave.

I agents being used with therapeutic success in these patients.[8]

FOLLOW-UP

A 72-hour ambulatory ECG monitoring protocol 8 weeks after flecainide initiation showed a marked reduction in the VPC burden from 31% to 3%. There was PR interval shortening with exercise both before and after flecainide initiation. There was mild QRS interval prolongation (<10%) with flecainide at rest and during heart rate increases on follow-up Holter monitoring. The QTc interval was within the normal range before and after the administration of flecainide despite a <10% increase in QRS interval duration post flecainide initiation. A

FIGURE 3 Cardiac Magnetic Resonance



(A) Mild hypertrabeculation in the left ventricular apical segments (steady-state free precession). (B and C) Late gadolinium enhancement imaging (phase-sensitive inversion recovery with appropriate inversion time done after 10 minutes) showed an absence of significant subepicardial, midmyocardial, or subendocardial late gadolinium enhancement.

repeat echocardiogram (Videos 1 to 3) at the end of 8 weeks revealed a near normalization of left ventricular systolic function (LVEF, 55%). The left ventricular global longitudinal strain after marked suppression of PVCs was −19. The rapid and sustained response to therapy with a type Ic antiarrhythmic agent such as flecainide is an additional layer of evidence supporting the diagnosis of the *SCN5A* MEPPC syndrome. At the last follow-up visit, 4 months after initiating flecainide, the patient was asymptomatic, with a resting ECG demonstrating the absence of ventricular premature complexes, and flecainide continues to be well tolerated.

CONCLUSIONS

The MEPPC syndrome should be suspected in the presence of incessant polymorphic ventricular premature complexes with a narrow QRS interval width, indicating a possible origin from the His-Purkinje system. Patients with DCM and MEPPC should be tested for pathogenic *SCN5A* variants, potentially leading to mutation-guided precision antiarrhythmic therapy.

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REFERENCES

1. Nguyen TP, Wang DW, Rhodes TH, George AL. Divergent biophysical defects caused by mutant sodium channels in dilated cardiomyopathy with arrhythmia. *Circ Res*. 2008;102(3):364-371.

2. Cohen SA, Barchi RL. Cardiac sodium channel structure and function. *Trends Cardiovasc Med*. 1992;2(4):133-140.

3. Laurent G, Saal S, Amarouch MY, et al. Multifocal ectopic Purkinje-related premature contractions: a new SCN5A related cardiac channelopathy. *J Am Coll Cardiol*. 2012;60(2):144-156.

4. Beckermann TM, McLeod K, Murday V, Potet F, George AL. Novel SCN5A mutation in amiodarone-responsive multifocal ventricular ectopy-associated cardiomyopathy. *Heart Rhythm*. 2014;11(8):1446.

5. McNair WP, Ku L, Taylor MRG, et al. SCN5A mutation associated with dilated cardiomyopathy, conduction disorder, and arrhythmia. *Circulation*. 2004;110(15):2163-2167.

6. Chen H, Liu J, Dai D, Yang J, Shi H. An unusual incessant narrow-wide complex polymorphic tachycardia: electrophysiological phenotype due to an allelic variant. *Jam Coll Cardiol EP*. 2022;8(10):1337-1339.

7. Leventopoulos G, Perperis A, Karelas D, Almpanis G. You cannot ablate the Lernaean Hydra: SCN5A mutation in a patient with multifocal ectopic Purkinje-related premature contractions syndrome treated with Flecainide and an implant of a subcutaneous defibrillator-a case report. *Eur Heart J Case Rep*. 2021;5(4):ytab158.

8. Towbin JA, McKenna WJ, Abrams DJ, et al. 2019 HRS expert consensus statement on evaluation, risk stratification, and management of arrhythmogenic cardiomyopathy. *Heart Rhythm*. 2019;16(11):e301-e372. https://doi.org/10.1016/j.hrthm.2019.05.007

KEY WORDS arrhythmogenic cardiomyopathy, cardiomyopathy, dilated cardiomyopathy, mutation, *SCN5A* channelopathy

APPENDIX For supplemental videos, please see the online version of this paper.