

Figure 2. A: Left atrial appendage visualized by endoscopic ultrasound. B: Amplatzer Cardiac Plug release visualized by angiography.

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Available online 15 November 2014

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<http://dx.doi.org/10.1016/j.rec.2014.07.021>

A New Mutation in the Ryanodine Receptor 2 Gene (RYR2 C2277R) as a Cause of Catecholaminergic Polymorphic Ventricular Tachycardia



Una nueva mutación en el gen del receptor de la rianodina (RyR2 C2277R) como causa de taquicardia ventricular polimórfica catecolaminérgica

To the Editor,

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a heritable disease characterized by the appearance of polymorphic ventricular tachycardia during exercise, emotion, or catecholamine perfusion.¹ This cardiopathy is considered a rare disease, with a prevalence of 1/10 000, and is a highly lethal entity (30% of sudden deaths in individuals under 40 years of age who are not undergoing treatment with beta-blockers²). It is usually characterized by autosomal dominant inheritance with 80% penetrance, and by mutations in the ryanodine receptor 2 gene

(RYR2).³ Diagnosis usually requires an exercise stress test (EST) or adrenaline test.⁴⁻⁶

Our objective is to describe a kindred with 19 living members (Figure A), 4 with sudden death and 8 carriers of the new RYR2 C2277R variant (genotype+) (Figure B), 7 of whom exhibit the CPVT phenotype according to EST results (phenotype+).

The proband (II: 1), aged 56, presented with syncope and palpitations. She reported the sudden death of 3 siblings, aged 11 and 15 years (due to physical exercise and an argument) and 1.5 months, and a daughter aged 29 years (while dancing, with previous syncope during exertion), although autopsy was only performed in the latter case, and was inconclusive. We applied the protocol approved by our ethics committee for family studies following sudden death in individuals with unknown cause, and all individuals gave informed consent. In the proband, the electrocardiogram and echocardiogram were normal. Her EST (Bruce protocol) showed ventricular arrhythmias at 100 bpm and above, and was diagnostic of CPVT (Figure C). This diagnosis was defined by the presence of ventricular doublets, sustained ventricular tachycardia, or non-sustained polymorphic ventricular tachycardia or > 10 premature

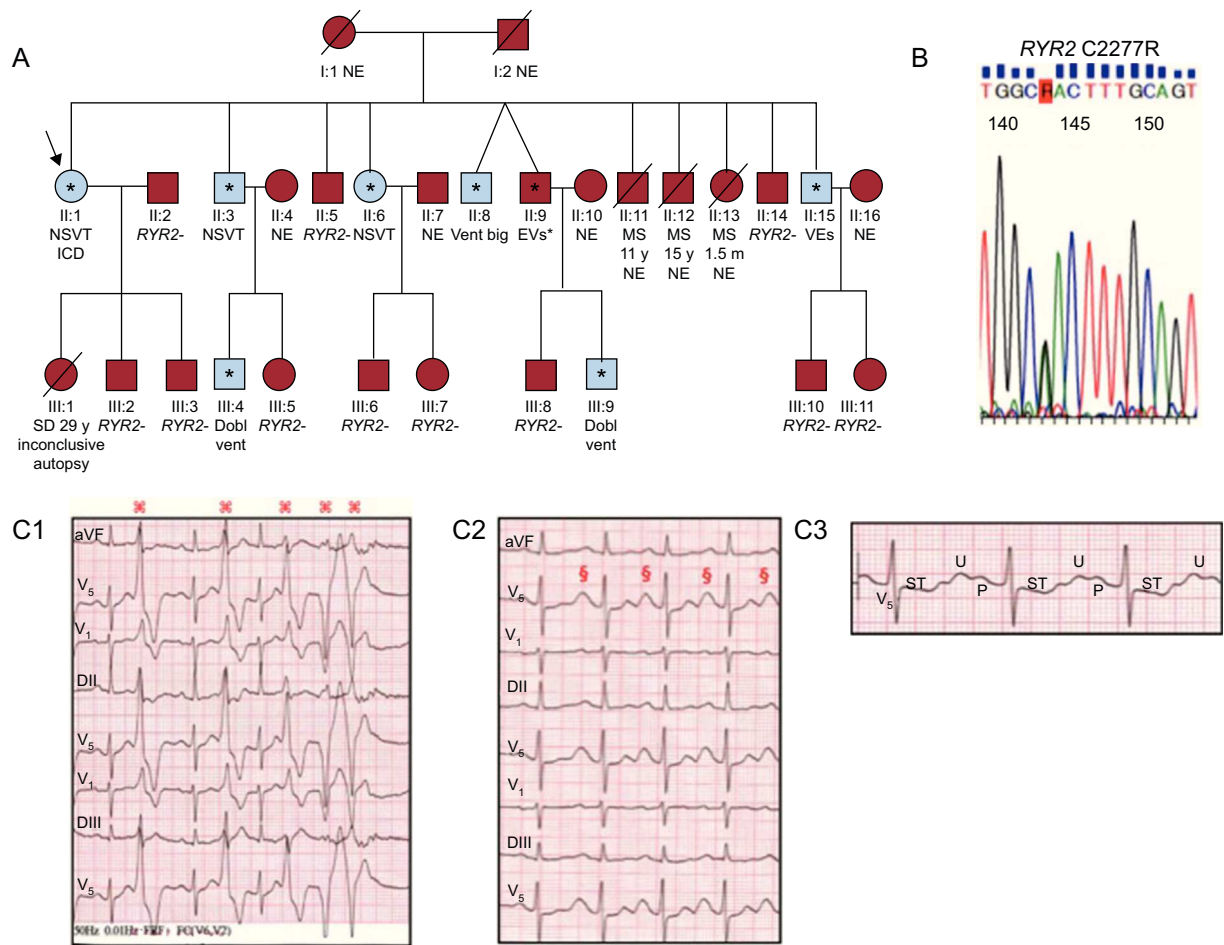


Figure. A: Family tree; the arrow indicates the proband; the blue symbols represent patients with the catecholaminergic polymorphic ventricular tachycardia phenotype, and asterisks indicate heterozygous carriers of the *RYR2* C2277R mutation. B: Electropherogram of the fragment of exon 45 of the *RYR2* gene containing the mutation. C: Consecutive records (C1-C3) of the first minute of recovery following the exercise stress test in the proband, showing polymorphic ventricular arrhythmias (C1, ⚡) and notable merging of the U-wave with the subsequent P wave (C2, §). CD, implantable cardioverter defibrillator; Dobl vent, ventricular doublets; m, month; NE, not evaluated; NSVT, nonsustained ventricular tachycardia; SD, sudden death; Vent big, ventricular bigeminy; Dobl vent, ventricular doublets; VEs, ventricular extrasystoles; y, years.

ventricular contractions/min during the EST or adrenaline test.⁶ Six other members of the 19 tested showed a similar response, with different degrees of complexity of the ventricular arrhythmias (Figure A, Table). Suspecting autosomal dominant CPVT, we

sequenced the 33 most frequently affected exons of the *RYR2* gene in the proband. We identified a previously unreported heterozygous missense variant in exon 45 (C2277R), located in a hot spot encoding part of the calstabin-binding domain, which was classified as a

Table
Clinical Characteristics of the Cohort of Eight Family Members Carrying the Mutation in *RYR2*

Case	Sex	Age at diagnosis, years	Previous symptoms	Baseline ECG	Maximum arrhythmia in the initial EST	Treatment ^a	Events during evolution ^b
II:1 (proband)	F	56	Syncope and palpitations	SB, prominent U	VE, Big, D, NSVT ^c	Nadolol 20 mg/24 h + FI + ICD	Presyncope
II:3	M	53	No	Normal	VE, Big, NSVT	Nadolol 80 mg/24 h + FI	No
II:6	F	43	No	Normal	VE, Big, NSVT	Atenolol 50 mg/12 h + FI	No
II:8	M	55	No	SB	VE, Big, D	Nadolol 80 mg/24 h + FI	No
II:9	M	50	Palpitations	Normal	VE ^d	Atenolol 100 mg/12 h	No
II:15	M	49	No	Normal	VE, Big, Trig	Atenolol 100 mg/12 h + FI	No
III:4	M	35	No	Normal	VE, Big, D	Nadolol 20 mg/24 h + FI	No
III:9	M	27	Syncope and palpitations	SB	VE, Big, D	Nadolol 10 mg/día	No

Big, bigeminy; D, doublets; ECG, electrocardiogram; EST, exercise stress test; F, female; FI, flecainide; ICD, implantable cardioverter defibrillator; M, male; NSVT, nonsustained ventricular tachycardia with 180° change of axis; SB, sinus bradycardia; Trig, trigeminy; VE, ventricular extrasystoles.

^a Treatment at end of follow-up when the manuscript was submitted.

^b Sudden death, arrhythmic symptoms, or appropriate defibrillator discharge. Mean follow-up, 34 months (standard deviation, 4).

^c The initial exercise stress test was carried out while undergoing treatment with beta-blockers.

^d Ventricular extrasystoles not diagnostic of catecholaminergic polymorphic ventricular tachycardia.

mutation that is probably associated with the disease. The mutation cosegregated with the CPVT phenotype, although in 1 person (II: 9), who also underwent an adrenaline test (Mayo Clinic protocol), ventricular arrhythmias did not meet the diagnostic criteria. Thus, we obtained a cohort of 8 carrier subjects, 7 of whom were found by EST to have the CPVT phenotype (87.5% penetrance). Of the carriers, 75% were male, mean age 46 years (SD, 10), 37% reported prior arrhythmic symptoms, and 100% had a normal electrocardiogram at rest (heart rate, 63 [SD,10] bpm, QTc 400 [SD,27] ms). In the initial EST (duration 9 [SD,2] min), the maximum heart rate was 150 [SD,15] bpm, and the diagnosis was established at a heart rate of 132 (SD,11) bpm.

The carriers were treated with beta-blockers at the maximum tolerated dose, and while the ventricular arrhythmias disappeared during the follow-up EST in 3 subjects (37%), in the remaining 5 (63%) the arrhythmic burden (frequent ventricular premature beats, bigeminy, doublets, nonsustained ventricular tachycardia) persisted enough to add flecainide to the treatment regime, as previously proposed¹ (Table). The proband was implanted with a defibrillator due to presyncope with nonsustained ventricular tachycardia during the EST, despite maximum treatment with beta-blockers (before starting the use of the flecainide treatment in this clinical context¹). Finally, at 34 (SD,4) months follow-up, all patients were asymptomatic, without arrhythmia or remarkable clinical events (sudden death, syncope, or appropriate defibrillator discharge).

In summary, for the first time we describe the RYR2 C2277R mutation as a cause of CPVT, in a family with high lethality in younger individuals, with a good diagnostic yield using EST and an excellent response to treatment with beta-blockers, with and without flecainide.

Acknowledgements

We are grateful for the kind cooperation of the patients, and the working group on sudden infantile death of Spanish Association of Pediatrics, and for technical support from the La Fe Biobank (PT13/0010/0026).

FUNDING

This work was funded by the Instituto de Salud Carlos III (PI14/01477 y RD12/0042/0029), Prometeo 2011/027, the Sociedad Española de Cardiología (Pedro Zarco Scholarship) and the Agence Nationale de la Recherche (ANR-13-BSV1-0023-03).

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Available online 27 November 2014

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<http://dx.doi.org/10.1016/j.rec.2014.07.022>

Adherence to the Mediterranean Diet in Patients With Coronary Artery Disease



Adherencia a la dieta mediterránea de los pacientes con cardiopatía isquémica

To the Editor,

Diet is part of the secondary prevention treatment in patients with coronary artery disease (CAD). The guidelines of American societies usually recommend following a diet that is low in saturated fats, whereas European guidelines also include adopting eating habits based on the Mediterranean diet (MedD); however, this diet is only referred to explicitly in the *National Institute for Clinical Excellence* (NICE) guidelines.

Recently, the PREDIMED¹ study, conducted amongst the Spanish population without coronary disease but at high cardiovascular risk, showed the superior efficacy of the MedD supplemented with virgin olive oil or nuts and dried fruit versus a low-fat diet against cardiovascular morbidity and mortality. In this study, the 14-point Mediterranean diet adherence screener (MEDAS-14) was validated, and a good correlation was shown between proper adherence to the diet and its efficacy.² In secondary prevention, the Lyon Diet Heart Study³ demonstrated the benefit of a diet that closely followed the

MedD in reducing reinfarction and clinical manifestations of CAD. Studies conducted in patient cohorts who had suffered acute coronary syndrome observed clinical benefits associated with greater adherence to the MedD, including a reduction in total mortality⁴.

We decided to investigate MedD adherence by CAD patients seen at a primary care center, using the MEDAS-14 screener.

We studied 110 patients selected from the total number of patients seen at the primary care centre, aged between 55 and 80 years, who were diagnosed with CAD, in ascending order starting from the oldest diagnostic coding date. Institutionalised patients and patients with health problems that could shorten their life expectancy or who were incapable of answering a questionnaire were excluded. The patients answered the MEDAS-14 screener and completed the data collection protocol, which included sociodemographic variables, domestic habits, physical activity, cardiovascular risk factors, and prescription of cardioprotective drugs.

Eighty per cent were retired males and 60% performed nonintensive regular exercise 3 or more days per week. The principal characteristics of the series are listed in the Table. The mean score on the screener was 8.9 points (scale from 0 to 14), and ≥ 9 points (acceptable adherence criterion) in 63% (95% confidence interval, 54%-72%). Adherence to each of the 14 points