



Figure 2. Family pedigree. Dark red, noncompaction cardiomyopathy; gray, ASD; green, atrioventricular block. Heterozygotes are indicated by \pm . Echocardiographic images from the 3 probands. ASD, atrial septal defect; SD, sudden death.

Cardiac magnetic resonance examination of the father disclosed no relevant findings. Two uncles were also studied, with negative results. The single positive finding (ECG, imaging) was apical hypertrabeculation in 1 of them (Figure 2).

Cosegregation of the mutation with the phenotype in 4 affected individuals in the family, with variable expressivity and penetrance, provides evidence of its probable pathogenicity. The finding of a carrier without the phenotype is consistent with the incomplete penetrance seen in other *NKX2.5* mutations. In the differential diagnosis of sudden death in the patient's grandfather (subject I-1), it would be pertinent to include other causes, such as ischemic heart disease.

p.Lys183Asn is located in the *NKX2.5* homeobox (amino acids 138-197). A few variants in this region have been associated with the development of ASD and conduction defects, with variable penetrance and expressivity, and most show evidence of cosegregation (eg, p.Leu171Pro³, p.Arg190His³).

Until the description of p.Glu167Lys,¹ the single *NKX2.5* mutation associated with a phenotype comprised of noncompaction, ASD, conduction defects, and sudden death was found in the

homeobox domain of the protein (p.Leu171Argfs*7). This variant, with variable penetrance and expressivity, was described by Ouyang et al.⁴ in a family from the United States. One of the carriers experienced sudden death.

In a European Society of Cardiology congress, Maury et al.⁵ presented a series of 48 patients (18 families), carriers of *NKX2.5* mutations and with 8 sudden deaths. Among the carriers, 75% had ASD and 90% had conduction defects.⁵ Five carriers met the criteria for noncompaction cardiomyopathy.

Our patient underwent implantation of a single-chamber defibrillator for primary prevention. The device recorded recurrent episodes of nonsustained polymorphic ventricular tachycardia and 2 appropriate shocks following degeneration to ventricular fibrillation. Treatment with sotalol was started, and there have been no recurrences in the last 7 months.

The findings in this family, together with those from the family of Bermúdez-Jiménez et al.,¹ suggest that mutations in this region of *NKX2.5* (homeobox) can lead to ASD, conduction defects, and ventricular noncompaction, and are associated with a high risk of sudden death. In contrast to the family reported by

these authors, which showed features consistent with arrhythmogenic cardiomyopathy (carriers of a *DSP* mutation), there was no second mutational event in our patient that could be related to the risk of sudden death and make this association more plausible.

Detection of noncompaction in patients with ASD could alert to the possible presence of this entity, which has a malignant character.

Julián Palomino Doza,* Rafael Salguero-Bodes, María de la Parte, and Fernando Arribas-Ynsaurriaga

Unidad de Cardiopatías Familiares, Hospital Universitario 12 de Octubre, Madrid, Spain

*Corresponding author:

E-mail address: julian.palomino@salud.madrid.org (J. Palomino Doza).

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Diagnostic and Prognostic Findings in Patients With Positive Clinical or ECG Exercise Tests in the Absence of Echocardiographic Abnormalities



Hallazgos diagnósticos y pronósticos en pacientes con prueba de esfuerzo clínica o ECG positivos pero ecocardiografía negativa

To the Editor,

Although normal findings on exercise echocardiography (EE) are considered indicative of a good prognosis,^{1,2} there is little information on the prognosis of patients who have a normal EE together with positive clinical or electrocardiography (ECG) findings. Our aim was to evaluate the prognosis and angiographic results of patients in the following situations: EE (–) in the absence of positive clinical or ECG findings (negative group), EE (–) with

Table
Clinical Characteristics and Exercise Echocardiography Results in 7127 Patients

	All (n = 7127)	Clinical and ECG (–) (n = 6133)	Clinical or ECG (+) (n = 892)	Clinical and ECG (+) (n = 102)	P
<i>Clinical characteristics</i>					
Age, years	61 ± 13	60 ± 13	63 ± 11	63 ± 10	< .001
Women	3393 (48)	2927 (48)	425 (48)	41 (40)	NS
Diabetes mellitus	1141 (16)	949 (15)	163 (18)	29 (28)	< .001
Hypertension	3769 (53)	3200 (52)	507 (57)	62 (61)	.009
Smoking	1559 (22)	1379 (22)	159 (18)	21 (21)	.007
Hypercholesterolemia	3380 (47)	2870 (47)	448 (50)	62 (61)	.004
Atrial fibrillation	326 (5)	282 (5)	38 (4)	6 (6)	NS
ECG nonassessable	1276 (18)	1173 (19)	103 (12)	–	–
History of CAD	971 (14)	796 (13)	143 (16)	32 (31)	< .001
Typical angina	391 (5)	274 (4)	93 (10)	24 (24)	< .001
<i>Medications</i>					
ACEIs/ARBs	2159 (30)	1825 (30)	293 (33)	41 (40)	.02
Nitrites	1307 (18)	1054 (17)	208 (23)	45 (44)	< .001
Calcium channel blockers	632 (9)	520 (8)	95 (11)	17 (17)	.002
Beta blockers*	540 (8)	437 (7)	84 (9)	19 (19)	< .001
Baseline LVEF, %	61 ± 4	61 ± 5	61 ± 4	61 ± 3	NS
<i>Exercise echocardiography</i>					
MET	9.8 ± 3.3	9.8 ± 3.3	9.3 ± 3.1	9.1 ± 2.7	< .001
Submaximal test	1243 (17)	1020 (17)	194 (22)	29 (28)	< .001
Double peak product × 10 ³	25.5 ± 5.9	25.6 ± 5.9	25.1 ± 6.0	24.3 ± 5.5	.004
LVEF peak, %	69 ± 6	69 ± 6	68 ± 5	69 ± 3	< .001
LVEF increase, %	8 ± 3	8 ± 3	8 ± 3	8 ± 2	< .001

ACEIs, angiotensin converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; CAD, coronary arterial disease; ECG, electrocardiogram; LVEF, left ventricular ejection fraction; MET, metabolic equivalents; NS, not significant.

The values express n (%) or mean ± standard deviation.

* At the time of exercise echocardiography.