Implantable cardioverter-defibrillators in lamin A/C mutation carriers with cardiac conduction disorders

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BACKGROUND Sudden cardiac death is frequent in patients with lamin A/C gene (LMNA) mutations and may be related to ventricular arrhythmias (VA).

OBJECTIVE To evaluate a strategy of prophylactic implantable cardioverter-defibrillator (ICD) implantation in LMNA mutation carriers with significant cardiac conduction disorders.

METHODS Forty-seven consecutive patients (mean age 38 ± 11 years; 26 men) were prospectively enrolled between March 1999 and April 2009. Prophylactic ICD implantation was performed in patients with significant cardiac conduction disorders: patients requiring permanent pacing for bradycardia or already implanted with a pacemaker at the initial presentation, or patients with a PR interval of >0.24 seconds and either complete left bundle branch block or nonsustained ventricular tachycardia.

RESULTS Twenty-one (45%) patients had significant conduction disorders and received a prophylactic ICD. Among ICD recipients, no patient died suddenly and 11 (52%) patients required appropriate ICD therapy during a median follow-up of 62 months. Left ventricular ejection fraction was ≥45% in 9 patients at the time of the event. Among the 10 patients without malignant VA, device memory recorded nonsustained ventricular tachycardia in 8 (80%). The presence of significant conduction disorders was the only factor related to the occurrence of malignant VA (hazard ratio 5.20; 95% confidence interval 1.14–23.53; $P = .03$).

CONCLUSIONS Life-threatening VAs are common in patients with LMNA mutations and significant cardiac conduction disorders, even if left ventricular ejection fraction is preserved. ICD is an effective treatment and should be considered in this patient population.

KEYWORDS Lamin A/C gene; Conduction disturbances; Ventricular arrhythmias; Sudden cardiac death; Implantable cardioverter-defibrillator

ABBREVIATIONS **ATP** = antitachycardia pacing; **AVB** = atrioventricular block; **DCM** = dilated cardiomyopathy; **ICD** = implantable cardioverter-defibrillator; **LBBB** = left bundle branch block; **LMNA** = lamin A/C gene; **LVEF** = left ventricular ejection fraction; **NSVT** = nonsustained ventricular tachycardia; **SCD** = sudden cardiac death; **VA** = ventricular arrhythmias; **VF** = ventricular fibrillation; **VT** = ventricular tachycardia

(Heart Rhythm 2013;10:1492–1498)

Introduction

Lamins A and C, encoded by the lamin A/C gene (LMNA), are major structural components supporting the inner nuclear membrane.[1] LMNA mutations cause a variety of inherited diseases with usually an autosomal dominant pattern of inheritance termed laminopathies, characterized by genetic and phenotypic heterogeneity, including skeletal muscle and cardiac disorders, adipose and neuronal abnormalities, and premature aging.[2–7]

The cardiac phenotype of laminopathies is characterized by conduction disorders, atrial fibrillation, ventricular arrhythmias (VA), and dilated cardiomyopathy (DCM).[6–11] Sudden cardiac death (SCD) can be the first manifestation of the disease[6,8] and may be related to VA, as it occurs even in patients implanted with a pacemaker.[6,9,11] Current SCD risk stratification is based on a few genetic and clinical factors identified in retrospective studies, in which prophylactic implantable cardioverter-defibrillator (ICD) implantation has been shown to be effective in some LMNA mutation carriers,[12,13] particularly in patients with conduction disturbances requiring permanent cardiac pacing.[14] We hypothesized that significant cardiac conduction disorders may help identify a subgroup of LMNA mutation carriers at risk for SCD, and we prospectively evaluated a strategy of primary ICD implantation in these persons.

Methods

Setting and Study Design

This was an observational study performed at the cardiology department of Rouen University Hospital between March

Dr Anselme has received consulting fees from Boston Scientific, Medtronic, Sorin Group, and St Jude Medical and lecture fees from Medtronic and Sorin Group. Dr Moubarak has received lecture fees from the Sorin Group. Dr Savouré has received consulting fees from Medtronic. **Address reprint requests and correspondence**: Dr Frédéric Anselme, Department of Cardiology, Charles Nicolle Hospital, 1 rue de Germont, 76000 Rouen, France. E-mail address: frederic.anselme@chu-rouen.fr.

1547-5271/$-see front matter http://dx.doi.org/10.1016/j.hrthm.2013.06.020

1999 and April 2009. Patients were referred to our tertiary center by their cardiologist or our department of medical genetics. Blood samples were obtained after written informed consent before this study, and sequencing analysis of LMNA gene was performed. Once a pathogenic LMNA mutation was identified, adult first-degree relatives of the mutation carriers were offered mutation screening.

All persons (probands and relatives) were prospectively followed-up and underwent a cardiac checkup every 6 months, including a physical examination, a collection of family history of syncope or SCD, an electrocardiogram, a transthoracic echocardiography, and a 24-hour Holter monitoring. DCM was defined as a left ventricular ejection fraction (LVEF) $<$ 45% and/or a left ventricular end-diastolic diameter $>$ 56 mm. Nonsustained ventricular tachycardia (NSVT) was defined as 3 or more consecutive ventricular beats (but $<$30 seconds) with a rate of $\geq$120/min on Holter monitoring. An electrophysiological study was not performed in all patients owing to uniform findings in the first 20 patients (see Results).

Our strategy was to systematically implant an ICD at any time during follow-up when any of the following prespecified significant conduction disorders was encountered: (1) requirement for permanent ventricular pacing for bradycardia; (2) PR interval $>$ 0.24 seconds and either complete left bundle branch block (LBBB) or NSVT; (3) patients already implanted with a pacemaker at presentation to our center. The choice between single- and dual-chamber ICDs depended on the presence of permanent atrial fibrillation and the type and extent of atrioventricular conduction disorders. Biventricular ICDs were implanted in patients with advanced heart failure, LVEF $\leq$35%, and wide QRS complex. Device programming was standardized with a ventricular tachycardia (VT) zone between 170 and 220 beats/min with 6 antitachycardia pacing (ATP) sequences followed by maximal shocks and with a ventricular fibrillation (VF) zone above 220 beats/min with maximal shocks. The electronic memories of the devices were interrogated at least every 6 months to determine whether VT or VF episodes had occurred. In the case of ATP or shock delivery, event markers and electrogram recordings were analyzed by 2 investigators to verify the appropriateness of the therapies. Malignant VA was defined as appropriate ATP or shock delivery, spontaneous VT or VF requiring ICD implantation as secondary prevention, or SCD.

All patients gave informed consent, and this study was approved by our institution's ethics committee.

Statistical Analysis

Data are expressed as number (percentage) for categorical variables and as mean $\pm$ SD or median (interquartile range) for quantitative variables, as appropriate. Univariate Cox regression analysis was used to identify predictors of occurrence of malignant VA and predictors of inappropriate shocks in ICD recipients. Survival curves free of malignant VA in patients with and without conduction disorders were constructed by using the Kaplan-Meier method and compared with the log-rank test. A 2-sided P value of $<$.05 was considered statistically significant. Statistical analysis was performed by using SPSS software, version 17.0 (SPSS Inc, Chicago, IL).

Results

Population

Between March 1999 and April 2009, 47 consecutive persons (mean age 38 $\pm$ 11 years; 55% men) from 13 families were enrolled. Baseline characteristics including muscular phenotypes and gene mutations are presented in Table 1. Sixteen (35%) patients had a DCM with a mean LVEF of 35% $\pm$ 7% and were older than patients without DCM (49 $\pm$ 10 years vs 40 $\pm$ 12 years; P = .02). Eighteen (38%) patients had isolated skeletal muscular involvement. During a median follow-up of 95 months (interquartile range 54–130 months), 9 patients required cardiac transplantation and 7 patients died.

Electrical Disorders

Thirty-one (66%) patients had sustained supraventricular arrhythmia during follow-up (mean age at first event 42 $\pm$ 9 years;

Table 1 Baseline patient characteristics (n = 47)

Age (y)	38 $\pm$ 11
Sex: male	26 (55%)
Prior syncope	15 (32%)
Family history of sudden death	10 (21%)
Family history of syncope	33 (70%)
Atrial fibrillation or flutter	12 (26%)
Significant conductive disorders	21 (45%)
Nonsustained ventricular tachycardia	31 (66%)
Left ventricular ejection fraction (%)	56 $\pm$ 11
Left ventricular ejection fraction $<$45%	6 (13%)
Left ventricular end-diastolic diameter (mm)	53 $\pm$ 6
Left ventricular end-diastolic diameter $>$56 mm	13 (28%)
Medical treatment	
Beta-blockers	8 (17%)
ACE inhibitors/angiotensin receptor blockers	12 (26%)
Amiodarone	7 (15%)
Class I antiarrhythmic drugs	4 (9%)
Vitamin K antagonists	11 (23%)
Phenotype	
Isolated skeletal muscular involvement	18 (38%)
Dilated cardiomyopathy	16 (34%)
Gene mutation	
Missense mutations	18 (38%)
R377H	4
R482C	1
L530P	1
R482 [R,Q]	1
R335W	4
R377C	4
R50P	1
R249P	1
L379F	1
Non-missense mutations	29 (62%)
Nucleotide A insertion in 444	21
Q6 stop	7
IVS6-1 G -$>$A	1

Data are expressed as mean $\pm$ SD or as n (%).
ACE = angiotensin-converting enzyme.