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ARRHYTHMIC RISK AND GENETIC VARIATIONS IN DILATED CARDIOMYOPATHY PATIENTS

Elisabete Martins[1], Alexandra Sousa[1], Paulo Canedo[2], Manuel Campelo[3], Brenda Moura[4], Sérgio Leite[3], Adriana Belo[5], Francisco Rocha Gonçalves[1], José Carlos Machado[2], José Silva-Cardoso[3]

[1] Faculty of Medicine, University of Porto, Porto

[2] Institute of Molecular Pathology and Immunology, University of Porto, Porto

[3] São João Hospital, Porto

[4] Regional Military Hospital nº1, Porto

[5] Portuguese Society of Cardiology, Lisboa

elisabetemartins09@gmail.com

Introduction: Dilated cardiomyopathy (DCM), characterized by left ventricle (LV) enlargement and contractile dysfunction, is associated with high risk of arrhythmic sudden cardiac death (SCD) in a subgroup of patients. Until now, risk stratification has been based on the individual arrhythmic profile and LV ejection fraction (EF), even though SD may occur with EF>35%. Family history of unexplained SD, especially in the young, is a raising concern, taking into account potential inheritable risk factors. Currently, with rare exceptions of lamina A/C mutations carriers, it remains unknown how genetic factors and respective tests can be used in clinical practice for SD prediction. We intend to assess the relation between the arrhythmic risk and genetic variations in dilated cardiomyopathy patients, to evaluate the potential role of genetic tests in clinical practice.

Methods: In this work we included idiopathic DCM patients (age ≤ 50 years) and familial DCM patients (irrespective of the age), and compared the presence of genetic variants between two subgroups with a priori distinct SD risk: those with family history of SD and/or previous implantable cardioverter-defibrillator (ICD) for primary or secondary prevention, versus those without any of the conditions. Molecular analysis included the search of mutations in *LMNA/C*, *MYH7*, *MYBPC3*, *TNNT2*, *ACTC1*, *TPM1*, *CSRP3*, *TCAP*, *SGCD*, *PLN*, *MYL2*, *MYL3*, *TNNI3*, *TAZ* and *LBD3* genes using PCR technique with direct-sequencing (next-generation sequencing with at least a 30- fold coverage combined with Sanger sequencing). Pathogenicity was assessed by comparisons with mutations previously described, functional tests and segregations studies.

Results : We studied 112 patients, 46.4% with familial DCM; 58.3% males, mean age 47±12 years, with mean age at diagnosis of 38±13 years. Mean left ventricle ejection fraction was 32±12% and LV end-diastolic diameter 64±9 mm, and 37.4% of them presented left bundle branch block. Twelve (10.7%) patients had family history of unexplained SCD, 21 (18.8%) patients had implanted an ICD device and 3 patients (2.7%) presented both conditions.

A total of 35 genetic variants were found in 29 (25.6%) patients. These mutations occurred in different genes: 10 in *MYBPC3*, 6 in *TNNT2* and in *LMNA*, 3 in *MYH7*, in *PLN*, in *TCAP* and in *LBD3*, and one in *TPM1* gene, with their relative distributions being similar between both groups (30.6% versus 23.7% in patients with and without family history of SCD/ICD, respectively; p=0.438).

Conclusion: In our DCM patients, family history and previous ICD implantation decision could not predict the genetic results. Follow-up of DCM patients with distinct genetic mutations is necessary to clarify how the genetic profile can be integrated in algorithms for SCD primary prevention.