Genetic testing in inflammatory cardiomyopathy/myocarditis: a red flag for cardiomyopathy-like histologic findings

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Background: Myocarditis/inflammatory cardiomyopathy is characterized by the presence of an inflammatory infiltrate in the myocardium. Its etiology is heterogeneous, predominantly mediated by viral infection, as well as a wide variety of toxic substances and drugs and systemic immune-mediated diseases. Outcome could vary from a complete recovery to a residual myocardial injury with the subsequent development of dilated cardiomyopathy (DCM). The factors that play a role in the disease progression are not clear, but it has been shown that inflammatory cardiomyopathy complicated by left ventricular dysfunction, heart failure or arrhythmia is associated with a poor prognosis.

Purpose: To characterize the genetic background of inflammatory cardiomyopathy affected patients to determine the prevalence of pathogenic/likely pathogenic (P/LP) variants in cardiomyopathy-related genes and correlate to histopathologic findings in endomyocardial biopsies (EMB).

Methods: Eighty-nine myocarditis-affected patients (mean age 43±14, 55 males) underwent genetic screening of 200 genes related to inherited cardiomyopathies. Definite/moderate gene association with DCM and Arrhythmogenic Cardiomyopathy was based on the ClinGen framework. Variant prioritization was carried out using American College of Medical Genetics and Genomics rules. Correlation with histopathologic findings of the endomyocardial biopsy and family history was appraised.

Results: Twenty of the 89 suspected myocarditis patients (22%) carried a P/LP variant in cardiac-related genes: 8 in Titin, 3 in Myosin Heavy Chain 7, 2 in Desmoplakin, 2 in Lamin A/C; and Troponin T2, Filamin-C, Myosin Binding Protein C3, Desmin and Sodium Voltage-Gated Channel Alpha Subunit 5 carried one variant each. A re-analysis of the EMBs revealed that 82% of patients showed cardiomyopathy-like features at first histologic findings, with fibrosis in the myocardium and DCM-like phenotype at the second EMB. Further, 13 of the genotype-positive patients referred positive family history for cardiomyopathy and/or sudden cardiac death, whereas only 7 genotype-negative patients declared family history, showing a significant difference among both groups (p-value<0.0001).

Conclusion: The prevalence of P/LP variants in inflammatory cardiomyopathy/myocarditis patients is 22%, most of them associated with DCM. Cardiomyopathy-like features were already observed at the first EMB during the histologic re-evaluation in the majority of genotype-positive patients, and among them, high frequency of positive family history was observed. These findings suggest that genotype-positive inflammatory cardiomyopathy/myocarditis affected patients should be deeply clinically evaluated in order to guarantee an appropriate management for them and their families.