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ORIGINAL INVESTIGATIONS

Prognostic Relevance of Gene-Environment Interactions in Patients With Dilated Cardiomyopathy

Applying the MOGE(S) Classification

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ABSTRACT

BACKGROUND The multifactorial pathogenesis leading to dilated cardiomyopathy (DCM) makes stratification difficult. The recent MOGE(S) (morphofunctional, organ involvement, genetic or familial, etiology, stage) classification addresses this issue.

OBJECTIVES The purpose of this study was to investigate the applicability and prognostic relevance of the MOGE(S) classification in patients with DCM.

METHODS This study used patients from the Maastricht Cardiomyopathy Registry in the Netherlands and excluded patients with ischemic, valvular, hypertensive, and congenital heart disease. All other patients underwent a complete diagnostic work-up, including genetic evaluation and endomyocardial biopsy.

RESULTS A total of 213 consecutive patients with DCM were included: organ involvement was demonstrated in 35 (16%) and genetic or familial DCM in 70 (33%) patients, including 16 (8%) patients with a pathogenic mutation. At least 1 cause was found in 155 (73%) patients, of whom 48 (23%) had more than 1 possible cause. Left ventricular reverse remodeling was more common in patients with nongenetic or nonfamilial DCM than in patients with genetic or familial DCM (40% vs. 25%; $p = 0.04$). After a median follow-up of 47 months, organ involvement and higher New York Heart Association functional class were associated with adverse outcome ($p < 0.001$ and $p = 0.02$, respectively). Genetic or familial DCM per se was of no prognostic significance, but when it was accompanied by additional etiologic-environmental factors such as significant viral load, immune-mediated factors, rhythm disturbances, or toxic triggers, a worse outcome was revealed ($p = 0.03$). A higher presence of MOGE(S) attributes (≥2 vs. ≤1 attributes) showed an adverse outcome ($p = 0.007$).

CONCLUSIONS The MOGE(S) classification in DCM is applicable, and each attribute or the gene-environment interaction is associated with outcome. Importantly, the presence of multiple attributes was a strong predictor of adverse outcome. Finally, adaptation of the MOGE(S) involving multiple possible etiologies is recommended.
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ABBREVIATIONS AND ACRONYMS

CAD = coronary artery disease

DCM = dilated cardiomyopathy

EMB = endomyocardial biopsy

HF = heart failure

HTx = heart transplantation

LV = left ventricular

LVEDDI = indexed left ventricular end-diastolic diameter

LVEF = left ventricular ejection fraction

LVRR = left ventricular reverse remodeling

MOGE(S) = morphofunctional, organ involvement, genetic or familial, etiology, stage

NYHA = New York Heart Association

PCR = polymerase chain reaction

Classification of cardiomyopathies has been subject to revisions for more than 60 years (1). To date, classification remains difficult because of incomplete knowledge about the mechanisms of the disease, its heterogeneous clinical presentation, and overlapping clinical and molecular findings (1,2). Dilated cardiomyopathy (DCM) is a myocardial disease characterized by left ventricular (LV) dilation and systolic dysfunction (2). DCM is assumed

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to be the end stage of multifactorial pathogenesis with common terminal pathophysiology. After exclusion of prevalent causes (e.g., coronary artery disease [CAD], valvular disease, congenital disease, hypertension) (2), DCM comprises poorly defined subgroups of cardiac inflammation with or without an infectious agent (3), cytotoxic medication or drugs (4,5), rhythm disturbances (6,7), and genetic mutations (8). Nevertheless, only some persons who are exposed to these triggers develop DCM. Additionally, in up to 50% of patients, the cause of DCM remains unknown (4,5).

The hypothesis is that gene-environment interactions (i.e., exposure to an environmental trigger in addition to an "underlying genetic background") may lead to DCM, but a family history of DCM is present in only 20% to 35% of patients with predominantly autosomal dominant inheritance (1,8). The genetic knowledge of cardiomyopathies has evolved exponentially (1,8), and in view of these developments, the World Heart Federation published a new classification scheme for cardiomyopathies, called MOGE(S) (morphofunctional, organ involvement, genetic or familial, etiology, stage) (1). In the MOGE(S) classification, a combination of phenotype, genetic variation, and etiologic annotation has been proposed, but studies investigating the applicability and prognostic value of this new classification are lacking. The routine use of endomyocardial biopsy (EMB), the referral of all patients with DCM to our specialized cardiogenetics unit, and long-term follow-up allowed us to evaluate gene-environment interactions in a large, well-characterized population with DCM.

METHODS

STUDY DESIGN. Between 2004 and 2014, 394 consecutive patients with unexplained heart failure (HF) caused by DCM were enrolled in the Maastricht Cardiomyopathy Registry. A complete diagnostic work-up was performed in 213 index patients by using medical history, 12-lead electrocardiogram, echocardiography, Holter monitoring, EMB, and genetic evaluation (Online Figure 1). Excluded patients with DCM (n = 181) had incomplete diagnostic work-ups and did not demonstrate significant differences in baseline characteristics (Online Table 1, Online Figure 2). The protocol was approved by the local ethics committee. All patients gave written informed consent.

Inclusion criteria were as follows: 1) left ventricular ejection fraction (LVEF) <50% and indexed left ventricular end-diastolic diameter (LVEDDI) >33 mm/m^2 (men) or >32 mm/m^2 (women) (9); 2) EMB performed; 3) genetic evaluation, including counseling, pedigree analysis, and genetic testing in index patients; and 4) age ≥18 years.

Exclusion criteria included the following: the presence of a previous history of myocardial infarction or significant CAD (stenosis >50%) determined by coronary angiography; primary valvular disease (mitral regurgitation grade ≥3, aortic regurgitation grade ≥2, or aortic stenosis <1 cm^2); hypertensive heart disease; congenital heart disease; (suspected) acute myocarditis; and (likely) diagnosis of arrhythmogenic right ventricular dysplasia.

Echocardiographic measurements were performed in the standard parasternal, apical, and subxiphoid views (10). Left ventricular reverse remodeling (LVRR) was defined as an absolute increase in LVEF of ≥10% or an LVEF ≥50% in addition to a decrease in LVEDDI of ≥10% or an LVEDDI ≤33 mm/m^2 (11).

Six EMB samples were taken from the right ventricle. Two to 3 specimens were used for immunohistological analysis and 3 for the detection of viral genomes by using polymerase chain reaction (PCR)

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