Lymphocytic Myocarditis

A Genetically Predisposed Disease?

The clinical presentation of myocarditis is extremely heterogeneous, ranging from asymptomatic to overt heart failure (HF). The long-term scenario varies between healing and evolution to dilated cardiomyopathy. A complex interaction between pre-existing genetic background and inflammation might be responsible for this heterogeneity (1). Therefore, we investigated the genetic background of patients with active lymphocytic myocarditis, testing the hypothesis that pathogenic variants in cardiomyopathy-causing genes may give rise to an increased susceptibility to developing left ventricular (LV) dysfunction after myocardial inflammatory stress.

We performed genetic tests in 36 patients (age 46 ± 15 years; 61% males; no relatives included) with biopsy-proven active lymphocytic myocarditis according to Dallas criteria and immunohistochemical analysis. Median duration of symptoms at the time of endomyocardial biopsy (EMB) was 2 months (interquartile range: 1 to 4 months). EMBs were performed from the right or left ventricle, according to operator's choice. Indications to EMB were refractory unexplained HF and LV dysfunction (75%, n = 27), unexplained life-threatening or iterative ventricular arrhythmias (17%, n = 6), or relapsing myocarditis and persistent troponin increase despite normal LV ejection fraction (LVEF) (8%, n = 3). All patients underwent genetic testing using next generation DNA sequencing of multigene panels for dilated, hypertrophic, and arrhythmogenic cardiomyopathies (2). Only pathogenic (P) or likely pathogenic (LP) variants were considered. The study was approved by the institutional ethical board.

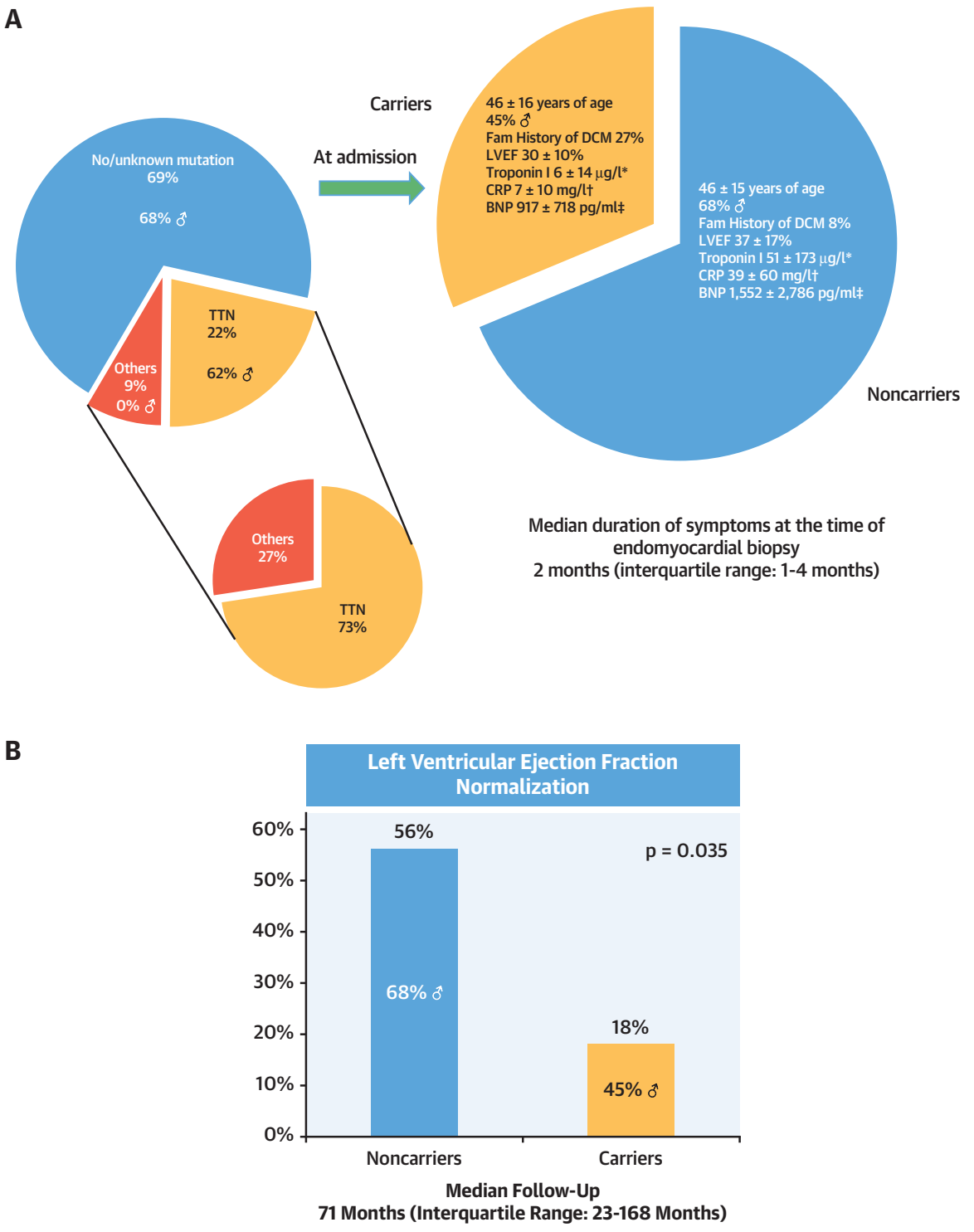
After genetic testing, 11 patients (31%) were found to be variant carriers of P/LP truncating variants (*tv*) in structural cardiomyopathy-related genes: *Titin* (*TTN*) (n = 8, 73%), *Desmoplakin* (*DSP*) (n = 1), *Filamin C* (*FLNC*) (n = 1), and *RNA binding protein 20* (*RBM20*) (n = 1) (**Figure 1A**). Screening of relatives showed that 14% of patients (n = 5), 2 with negative and 3 with positive genetic testing, had a positive family history for dilated cardiomyopathy, unrelated to specific genetic background. When available (in 2 of 3 cases), a segregation study confirmed the pathogenicity of the identified variant. Baseline characteristics according to genotype are reported in **Figure 1A**. Among the 27 patients presenting with HF and LV dysfunction, positive genetic yield was similar to the total cohort (n = 9, 34%; 90% with *TTNtv*). Two of 6 arrhythmic patients (30%) were carriers of variants in arrhythmogenic genes (i.e., *DSP* and *FLNC*), whereas no patients with infarct-like presentation were carriers.

At the last available follow-up (median 71 months [interquartile range: 23 to 168 months]), 16 (44%) of 36 patients presented normal LVEF. Carriers had a lower rate of LVEF normalization compared with noncarriers (18% vs 56%, respectively; p = 0.035). All carriers with normal LVEF during follow-up had a *TTNtv* (**Figure 1B**).

So far, this is the first report investigating the role of genetic background in adult patients with biopsy-proven lymphocytic myocarditis. The genetic yield in this cohort (31%) was higher than other reports addressing this issue in different populations and clinical settings (3,4). Furthermore, the genetic yield found in our population was similar, especially for *TTNtv* prevalence, to a geographically comparable cohort of sporadic dilated cardiomyopathy, recently described (2). This suggests that the inflammatory noxa on the heart might unveil an increased genetic susceptibility to develop overt LV dysfunction or arrhythmogenic phenotypes and is associated with poorer functional recovery over time.

Interestingly, compared with other variants, *TTNtvs* seemed to be important contributing factors in this setting, both for their prevalence and for their association with subsequent recovery. This supports the model whereby inflammation and other environmental factors interact with a patient's genotype to determine cardiac phenotype (5). Furthermore, the distinction between a primary diagnosis of myocarditis and arrhythmogenic cardiomyopathy, especially caused by defects in *DSP*, remains unsolved (4). Despite EMB findings being negative for fibro-fatty replacement, cardiac magnetic resonance data were not systematically available in our patients. Further, larger studies, including recurrences, are required to assess this important issue.

FIGURE 1 Genetic Background of Myocarditis



(A) Genetic landscape and baseline characteristics of patients with biopsy-proven myocarditis according to genotype. **(B)** Association between genetic landscape and normal left ventricular ejection fraction (LVEF) during follow-up. *Reference value <0.06 μg/l. †Reference value <5 mg/l. ‡Reference value <100 pg/ml. BNP = brain natriuretic protein; CRP = C-reactive protein; DCM = dilated cardiomyopathy; *TTN* = Titin.

In conclusion, patients with biopsy-proven myocarditis, especially if presenting with HF and LV dysfunction, are in a non-negligible percentage of cases carrying P or LP variants in cardiomyopathy-causing genes. The present results, despite the small size of the population, claim further research in larger, multicenter studies from different geographical origin to confirm this hypothesis.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate.

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Long-Term Changes in Gut Microbial Metabolite TMAO, CHD Risk, and its Complex Regulatory Network

I read the paper by Heianza et al. (1) with great interest, and congratulate the authors on their excellent work. As the authors correctly state, long-term increases in trimethylamine N-oxide (TMAO) were associated with higher coronary heart disease (CHD) risk (1); however, I would like to call attention to several points. TMAO exhibits complex genetic, dietary, and hormonal factor regulation (2). Research has reported a difference in trimethylamine (TMA) oxidation by flavin monooxygenase family members (FMO) with high FMO3-specific activity and has shown an induced FMO3 expression by dietary bile acids, and a reduced FMO3 expression in male compared with female individuals primarily due to downregulation by androgens (2). Research also has reported different human FMO3 gene polymorphism and different FMO3 individual expression (3), and has demonstrated miR-146a-5p level association with TMAO (4). Research also has identified a novel quantitative trait locus on chromosome 12 for TMAO levels, including 2 genes, *Numb* and *Dlst*, as direct targets of miR-146a and inversely correlated with both miR-146a and TMAO (4), and has postulated that as TMAO levels rise and promote nuclear factor-κB-activated inflammation, miR-146a-5p expression may also increase as a compensatory response to quell the inflammation, suggesting an intricate regulatory network (4). The findings of Heianza et al. (1) add significant information to previously published data, but also evaluating these aspects would be useful for better understanding of the interplay between long-term changes in gut microbial metabolite TMAO and CHD risk.

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