Effect of the genotype on the outcome in nonischemic cardiomyopathy

Gigli et al (J Am Coll Cardiol 2019;74:1480, PMID 31514951) sought to assess the correlation of the genotype with the outcome in a large group of patients with nonischemic cardiomyopathy (NICM). To accomplish their goal, they evaluated group of patients with NICM who had next generation sequencing genetic testing. All patients had NICM with left ventricular (LV) ejection fraction (LVEF) <50% not associated with other causes of LV dysfunction, such as prior myocardial infarction or sarcoidosis. They likewise excluded all patients with definite, probable, or possible arrhythmogenic right ventricular cardiomyopathy (ARVC) on the basis of current Task Force criteria. Genetic testing was performed looking for pathogenic or likely pathogenic variants in 23 genes known to be causative of NICM. Variants of unknown significance were not included in analyses of the outcome. The genes were assigned to one of several groups for analysis. TTN (titin) and LMNA (lamin) were each considered separately, and the remaining genes were assigned to cytoskeleton, desmosomal, sarcomeric, ion channel, and other groups. Familial cardiomyopathy was defined as 2 or more affected individuals in the same family or unexplained sudden cardiac death (SCD) in the first-degree relative of a patient with NICM on the basis of detailed 3-generation pedigrees (family tree) done on all patients. All other cases were considered sporadic. Outcome measures included (1) all-cause mortality; (2) death from heart failure, cardiac transplantation, or LV assist device (DHF/HTx/LVAD); and (3) SCD, ventricular tachycardia, or ventricular fibrillation (SCD/VT/VF).

Of the 487 patients with NICM included in the study, 178 (37%) had 183 pathogenic or likely pathogenic variants identified. Five patients (1%) had 2 or more variants, and 3 of these patients (60%) had poor outcomes. The prevalence of a genetic abnormality was higher in familial cases than in sporadic cases (43% vs 27%; P < .001). Utilizing the functional groups detailed above and listed in order of incidence, 63% were not gene carriers, 11% were TTN carriers, 10% sarcomeric carriers, 5% cytoskeleton gene carriers, 4% LMNA carriers, 3% desmosomal gene carriers, 2% ion channel gene carriers, and 2% other gene carriers. Of note, desmosomal abnormalities are associated with ARVC, highlighting the overlap between ARVC and NICM. During a mean follow-up of 10.4 years (range 54–185 months), 131 patients (28%) died, 105 (22%) had DHF/HTx/LVAD, and 98 (20%) had SCD/VT/VF events. Overall survival was not different between carriers and noncarriers (P = .99). However, there was a trend toward more DHF/HTx/LVAD (P = .061) and SCD/VT/VF (P = .062) in carriers vs noncarriers, and when assessing the risk of SCD/VT/VF starting from birth rather than from the time of diagnosis, the difference was significant (P = .02) between carriers and noncarriers. Comparing the various carrier groups and noncarriers, it was found that LMNA carriers have a higher incidence of DHF/LVAD and SCD/VT/VF. Desmosomal variant carriers had a higher incidence of SCD/VT/VF than did noncarriers and carriers in other groups. Comparing patients with LVEF <35% with those with ≥35%, it was found that the incidence of arrhythmia occurrence in LMNA and desmosomal variant carriers was independent of LV function. The authors conclude that in patients with NICM, 37% had a defined genetic abnormality and different genotypes have different outcomes including increased risk of SCD/VT/VF in those with desmosomal abnormalities and increased risk of heart failure and arrhythmic outcomes in those with lamin abnormalities.

Precision medicine

According to the National Institutes of Health, precision medicine is “an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person” (https://ghr.nlm.nih.gov/primer/precisionmedicine/definition). While the term precision medicine is frequently assumed to mean the development of a unique therapy for an individual patient, it instead is defined as the use of genetic, imaging, molecular diagnostics, and other information to classify patients in subgroups that can be analyzed to assess the response to treatments or preventive measures. As we better determine who will benefit from a particular treatment, we can concentrate our attention on that group and potentially spare those not likely to benefit the expense and side effects of any given therapy. As the above-mentioned article by Gigli et al points out, we are learning more and more about the genetic underpinnings of NICM and the differences in outcome. This information is adding to our precision in treating those patients.