Genotypic Association with Tachyarrhythmia Occurrence and Sudden Cardiac Death Risk in Hypertrophic Cardiomyopathy

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Introduction: Hypertrophic cardiomyopathy (HCM) is the most commonly inherited form of heart disease, however, genotype-phenotype correlation has thus far been poorly described, especially in terms of atrial and ventricular tachyarrhythmia (ATa and VTa, respectively) and sudden cardiac death (SCD). Therefore, we sought to evaluate its genotypic association with ATa/VTa occurrence and SCD risk according to predefined risk factors.

Methods: We evaluated a total of 23 different types of sarcomeric and non-sarcomeric genetic variations in 89 patients who were first diagnosed with HCM. At the time of diagnosis, patients had undergone baseline echocardiography, heart magnetic resonance imaging (MRI), Holter monitoring, and treadmill test. Structured on the guidelines provided by The AMP and The ACMG, genetic variations were categorized as: pathogenic variant (PV), likely pathogenic variant (LPV), variant of uncertain significance (VUS), likely benign variant (LBV), and benign (BV). These groups were then subdivided into two groups: PV, LPV, and VUS were categorized as the gene detection group (D group), while LBV and BV was categorized as the gene non-detection group (ND group). Additionally, we evaluated SCD risk on the basis of the 2011 ACCF/AHA guideline.

Result: From December 1995 to March 2016, a total of 89 patients were diagnosed with HCM in our hospital. Within this study group, genetic variations were found in 55 patients (sarcomeric n=51, 57.3%, non-sarcomeric n=4, 4.5%), with patients identified as MYBPC3 (n=24, 27.0%), MYH7 (n=11, 12.4%), TNNI3 (n=7, 7.9%), in the respective order of variation frequency. During patient follow-up, AF incidence was reported in 4 patients (16.7%) from the MYBPC3 (+) group and 13 patients (20.0%) from the MYBPC3 (-) group, while VT was reported in 7 (29.2%) and 13 (20.0%) patients, respectively. Statistical analysis results indicated that differences among the two groups were not significant (p=0.959 for AF, p=0.527 for VT), and the presence of genetic variations of the MYH7 and TNNI3 genes was not significantly correlated with the occurrence of AF and VT (MYH7 p=1.000 for AF, p=0.983 for VT, TNNI3 p=0.244 for AF, p=1.000 for VT). In comparing D group and ND group, statistical analysis also showed no significant difference in incidence rates of AF and VT (AF 23.6% vs 11.8%, p=0.268, VT 29.1% vs 11.8%, p=0.101 in D and ND group, respectively). Although data analysis revealed non-significant statistical results, SCD risk was considerably higher in the D group as compared to the ND group (49.1% vs 26.5%, p=0.059).

Conclusion: The correlation between the genetic variation of HCM and incidence of ATa or VTa is
unclear. Nonetheless, in consideration of the multiple risk factors associated with SCD occurrence, patients identified with genetic variations may have a higher chance of requiring subsequent ICD implantation.