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Benefits and Pitfalls of Genotyping HCM in Cardiomyopathy Clinic

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Background:

Hypertrophic cardiomyopathy (HCM) is a familial disease with autosomal dominant inheritance and age-dependent penetrance, caused by mutations of the sarcomere genes. Clinical utilization of genetic studies in HCM patients is still controversial. We report our experience with the effect of genetic diagnosis on clinical HCM management.

Method:

The decision to perform genetic studies was research-based or patient-driven. Candidate genes were sequenced by Sanger method or using Next Generation Sequencing. Once disease-causing mutation was identified, families underwent genetic counseling and offered genetic testing. The management plan was reevaluated in respect of the disease-causing mutation and the literature.

Result:

We found 10 mutations in 9 pro-bands. Familial disease was present in 6/9. Advanced heart failure of sudden death were the features which prompted genotyping in 8/9 families. There were 2 novel and 8 previously described mutations. In one kindred with severe heart failure due to a hypertrophic/restrictive phenotype a double mutation in TNNI3 and MYBPC3 was found. Of 98 first degree relatives only 54% consented to be tested. Compliance ranged 0-100% per family and was nil is the absence of family history of HCM. In 6 individuals genotyping helped resolve a borderline phenotype. Eight healthy carriers were identified, 19 genotyped negative. Genetic information was also used to prevent transmission to the next generation and played a role in decisions on ICD.

Conclusion:

Genetic studies may improve the diagnosis and prognostic evaluation in HCM because the clinical variability of HCM is related to its genetic heterogeneity. Recurrence of mutations in different families allows application of the information from literature to risk stratification of individual patients. Genotyping helps to diagnose borderline cases but may lead to controversial decisions on reproductive interventions or ICD implantation. We suggest that the clinical context shall determine the indication and the interpretation of the genetic analysis.