

Clinical presentation and outcomes in paediatric hypertrophic cardiomyopathy patients with compound sarcomeric gene mutations or additional genetic variants

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Introduction:

Genetic panel testing of paediatric patients with hypertrophic cardiomyopathy (HCM) enables better understanding of causes of disease in individuals presenting with the condition at an early age. We aimed to examine clinical features of patients carrying multiple pathogenic mutations or with pathogenic mutations in combination with genetic variants of uncertain significance (VUS), in order to explore the significance of these combined genetic factors.

Methods:

Between 2015 and 2017, thirty-three paediatric patients with a diagnosis of HCM underwent genetic panel testing at our centre. All genetic tests were processed and reported by the Health-in-Code laboratory in Spain. Test results and clinical records of patients were reviewed and information relating to cardiac phenotype was collated.

Results:

Three proband children were found to carry two mutations in MYBPC3. In two of these, cascade screening revealed that one mutation was inherited from each (clinically unaffected) parent. All three had severe hypertrophy, and two had significant history of arrhythmia: one presenting with an out-of-hospital VF arrest aged three years and the other with repeated episodes of non-sustained VT on ambulatory monitoring.

Eleven patients had potentially relevant VUSs in addition to a pathogenic mutation. Variants were found in ten genes: MYBPC3, MYH7, ANKRD1, CSRP3, DES, DSP, FHOD3, FLNC, MYL3 and PKP2. Five of these children were family probands with severe disease. Their phenotypes included two with VF arrests, one requiring cardiac transplantation aged twelve and one presenting at seven years old with complete heart block requiring pacemaker implantation. In six patients with an additional VUS there was family history of HCM; one of these had a VF arrest aged fourteen. Maximal LV wall thickness and diastolic function appeared similar in patients with single mutations compared to those with additional VUSs.

Conclusions:

In three cases, patients carried multiple MYBPC3 mutations, which appeared to correlate with a severe phenotype associated with increased risk of ventricular arrhythmia. In paediatric probands with a VUS detected in addition to a pathogenic mutation, disease also appeared more aggressive with an increased risk of ventricular arrhythmia, although detailed comparison to outcomes in single mutation carriers without additional variants will improve understanding of this apparent correlation.