Relationship between high-risk electrocardiogram, mortality and genotype in a geographical cohort with childhood hypertrophic cardiomyopathy

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INTRODUCTION: An ECG risk score has been described, scoring amplitudes and morphological abnormalities, which predicts a very high relative risk of sudden death if the point score is >5. The genotype-phenotype relationships, and correlation with sudden death, have been studied in a geographical cohort of patients diagnosed with HCM <19 yrs of age in the West Götaland Region, Sweden.

METHODS: Diagnosis was established with echocardiography, and ECG risk score was quantified from a 12-lead ECG according to Eur.Heart J 2010;31:439. DNA was analysed at international laboratories.

RESULTS: 69 patients with childhood presentation had ECG and echocardiographic data, 64% male. 46 (67%) had familial disease, and 12 Noonan-spectrum dysmorphology. Based on ECG-risk score 29 patients were high-risk (>5 points), and 40 low-risk (<6 points). The risk score correlated with death (correlation coefficient 0.57, p<0.0001); there were 8 sudden deaths in the high-risk group and none in the low risk group (p=0.003). There were also two heart failure deaths in the high-risk ECG group. Familial disease was more common in the low-risk (85%) than in the high-risk group (37%). 57 of the patients had genotyping performed, 23 in the high risk group, and 34 in the group with low risk ECG. In the former a very high proportion of pathogenic mutations were found, 86%, versus 66.7% in the latter. However, both groups had significantly higher proportion of causative mutations found than 83 patients with adult disease-presentation from the same geographical area, where only 45% of patients had clearly pathogenic mutations (p=0.0019), and 21% had variants of unknown significance. The spectrum of mutations varied strikingly between groups, MYH7-mutations were prominent in the high-risk group (26.1%) but not in low-risk paediatric group (16.7%), or adult group (12.1%) with corresponding figures for MYBPC3 being 26.1%, 33.3% and 26.5% respectively. Noonan-spectrum dysmorphology appeared in both ECG groups, and were associated with RAF1 or PTNP11 mutations. Further genes affected in the high-risk group were ACTC, MYL and LAMP2.

CONCLUSIONS: The simple inexpensive ECG risk score effectively pinpoints high-risk individuals who require urgent full risk assessment, and where the yield of genetic testing is particularly high.