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Clinical predictors of informative genetic testing in hypertrophic cardiomyopathy.

1. Introduction

Hypertrophic cardiomyopathy (HCM) is characterised by unexplained left ventricular hypertrophy in the absence of increased afterload. It is often a result of variants in sarcomeric genes including those that code for the actin and myosin filaments, the z discs and some calcium handling proteins. Mutations in MYBPC3, (affecting the myosin binding protein) MYH7 (affecting the myosin filament) TNNT2 and TNNI3 (affecting the actin filament) have been reported as the most frequent. Non-sarcomeric mutations are less common.

Patients suspected of having HCM can undergo genetic testing. The benefits of testing lie predominantly in using details of a pathogenic mutation to assess risk in other family members, but some mutations can give useful prognostic information.

We reviewed a consecutive series of HCM genetic panels performed across the Merseyside and Cheshire region in the UK and analysed for clinical parameters that predicted an informative result.

2. Aims

To identify clinical parameters that can predict an informative result in patients suspected of having HCM.

3. Methods

A retrospective analysis of 126 consecutive unrelated patients undergoing genetic testing with a confirmed diagnosis of HCM was conducted in a tertiary cardiomyopathy service between January 2014 and June 2016. We used a standard 19-gene panel using next generation sequencing (Oxford molecular genetics laboratory, UK). Informative results included class 4 or 5 variants deemed ‘pathogenic’ or ‘likely pathogenic’.

Cardiac MRI and echocardiography were used to identify left ventricular morphology and measure wall thickness. 12-lead ECG and 24 hour ambulatory ECG monitoring was used to assess for T-wave inversion and non-sustained ventricular tachycardia (NSVT), respectively.

4. Results

The mean age was 57.5 years old. 91 (72%) were male.

44/126 (35%) genetic tests were informative. Patients with informative tests were younger, (median 50.2 years; inter-quartile range [IQR] 34.1-61.8) vs. 58.6 years; IQR 50.0-66.5, p=0.007), were more likely to have a positive family history (FH) of HCM or sudden cardiac death (SCD) (59.1% vs 25.6%, p<0.001) and predominantly had reverse curve morphology of the interventricular septum (64%) (Figure 1.). Twenty-two (50%) patients had a variant in MYBPC3, 11(25%) in MYH7, 3(7%) in TNNI3. GLA, TNNT2, TPM1 had an incidence of 2. The incidence for CSRP3 and PRKAG was 1.

Univariate analysis demonstrated that neither NSVT (p=0.29) or maximum measured wall thickness (p=0.70) predicted an informative test. T wave inversion did not meet the generally accepted statistical cut-off p value of <0.05 (p=0.06). A lower proportion of patients with apical (18%) or sigmoid (19%) morphology had informative genetic testing, compared to 48% of those with reverse curve morphology.

Multivariate analysis demonstrated that a reverse curve morphology (odds ratio (OR) 2.99, CI 1.28-7.01, p=0.012), family history of SCD/HCM (OR 2.91 CI 1.28-6.72, p=0.012) and younger age at time of testing (OR 0.97, CI 0.94-0.99, P=0.008) were predictive of an informative test. A family history of HCM/SCD and reverse curve morphology has a similar OR, 2.99 and 2.91 respectively, whereas younger age had less of an affect with an OR of 0.97. Although there were different OR weightings these 3 factors could then be used in a cumulative manner to predict informative tests. Age was converted from a continuous scale to a binary ≤50 or >50. If none of these factors were present the chance of finding an informative result was 10%. If one factor was present informative results were seen in 28%, 2 factors = 55% and all 3 factors = 77%.

Reverse curve morphology was the most common LV morphology seen with MYBPC3 and MYH7 genetic mutations (77% of informative *MYBPC3* tests and 60% of *MYH7*.) Apical, sigmoid, focal and concentric morphologies did not show any particular trends due to low numbers,

Reverse curve morphology accounted for a greater proportion of patients with informative results (28/44 (64%) patients), than in those with uninformative results (31/82 (38%) patients). It also highlights that more patients with uninformative results had apical or sigmoid morphologies. 24% and 27% of uninformative tests were apical and sigmoid in contrast to 11% for both apical and sigmoid in informative tests.

5. Conclusions

This data illustrates that younger age of diagnosis, FH of SCD or HCM and reverse curve morphology were positive predictors for informative genetic results.

6. References

1. Van Driest SL, Ommen SR, Tajik AJ, Gersh BJ, Ackerman MJ, Yield of genetic testing in hypertrophic cardiomyopathy; Mayo Clinic Proceedings, June 2005

2. Marsiglia JD, Credidio FL, de Oliveira TG, Reis RF, Antunes Mde O, de Araujo AQ, Pedrosa RP, Barbosa-Ferreira JM, Mady C, Krieger JE, Arteaga-Fernandez E, Pereira AC; Clinical predictors of a positive genetic test in hypertrophic cardiomyopathy in the Brazilian population; BMC Cardiovascular disorders; March 2014

3. Bos JM, Will ML, Gersh BJ, Kruisselbrink TM, Ommen SR, Ackerman MJ;

Characterization of a phenotype-based genetic test prediction score for unrelated patients with hypertrophic cardiomyopathy; Mayo Clinic Proceedings, June 2014

4. Ingles J; Sarina T; Yeates L; Hunt L; Macciocca I; McCormack L; Winship I; McGaughran J; Atherton J; Semsarian C; Clinical predictors of genetic testing outcomes in hypertrophic cardiomyopathy; American College of Medical Genetics and Genomics; December 2013

5. Gruner C; Ivanov J; Care M; Williams L; Moravsky G; Yang H; Laczay B; Siminovitch K; Woo A; Rakowski H; Toronto Hypertrophic Cardiomyopathy Genotype Score for Prediction of a Positive Genotype in Hypertrophic Cardiomyopathy; Circulation, Cardiovascular genetics; February 2013

Table 1: a) Univariate analysis showing the relationship between informative tests and phenotypic feature. b) Multivariate regression analysis using pre-defined clinical characteristics. c) The likelihood of informative test using a predictive model.

Univariate analysis			
	Uninformative (n=82)	**Informative (n=44)**	***P* value**
Age at diagnosis (years)	58.6 (50.0, 66.5)	50.2 (34.1, 61.8)	0.007
FH SCD or HCM	21 (25.6)	26 (59.1)	<0.001
TWI	55 (67.1)	22 (50.0)	0.061
NSVT	19 (23.2)	14 (31.8)	0.29
Max width	18 (14, 21)	18 (14, 22)	0.70
Morphology			
Apical	23 (28.1)	5 (11.4)	0.032
Concentric	4 (4.9)	2 (4.6)	>0.99
Focal	2 (2.4)	2 (4.6)	0.61
Reverse Curve	31 (37.8)	29 (65.9)	0.003
Sigmoid	21 (25.6)	5 (11.4)	0.060
Multivariable logistic regression analysis			
	Odds Ratio (95% CI)	***P* value**	
Age at diagnosis (years)	0.97 (0.94, 0.99)	0.008	
Family Hx of SCD or HCM	2.91 (1.26, 6.72)	0.012	
Reverse Curve	2.99 (1.28, 7.01)	0.012	
Likelihood of informative gene test using predictive model Factors: Age <50, FH SCD/HCM, reverse curve septal morphology			
No. Factors	**Likelihood of positive result (%)**		
3/3	77		
2/3	55		
1/3	28		
0/3	10		