Hypertrophic cardiomyopathy: towards an optimal strategy

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Cardiogenetic care in hypertrophic cardiomyopathy

4.2 Quality of life and psychological distress in hypertrophic cardiomyopathy mutation carriers: a cross-sectional cohort study.

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Abstract

Hypertrophic cardiomyopathy (HCM) is a common hereditary heart disease associated with heart failure and sudden death. Quality of life and psychological distress were found to be impaired in HCM patients but have never been assessed in mutation carriers, with or without manifest HCM. We aimed to assess quality of life and psychological distress, using standardized questionnaires, and to identify sociodemographic, clinical, risk and illness perception related predictors thereof in 228 HCM mutation carriers. HCM carriers' overall quality of life and distress scores did not differ from the Dutch population. Quality of life and distress were worst in carriers with manifest HCM before DNA testing and best in predictively tested carriers without HCM. The latter group had even significantly better quality of life than the general population. Substantial determinants of impaired physical quality of life were symptoms (β=5.2, P=0.001) and stronger belief in serious consequences of carriership (β=3.5, P<0.001); determinants of impaired mental quality of life were physical comorbidity (β=3.0, P=0.020) and a higher perceived risk of symptoms (β=0.9, P=0.001). Female gender (β=1.4, P=0.004) and stronger emotional reactions (β=1.2, P=0.002) were associated with more anxiety. Less understanding of carriership (β=0.9, P=0.007) and stronger belief in serious consequences (β=0.8, P=0.008) increased depression. Levels of quality of life and distress were not impaired compared to the Dutch population. Illness and risk perception related variables were major determinants of quality of life and distress. Because these variables can be addressed and adjusted during pre- and post-test counseling, genetic counseling should focus on these determinants.

Introduction

Hypertrophic cardiomyopathy (HCM) is a common autosomal dominant cardiac disease affecting at least 1 in 500 persons worldwide,[1-3] characterized by hypertrophy of the ventricular myocardial wall with variable age at onset. Symptomatic patients may show dyspnea, exertional angina, palpitations and (pre)syncope and sudden cardiac death (SCD) at a young age.[4] The average annual risk of SCD is about 1% in unselected HCM patients.[5] Although HCM is incurable, an effective therapy, the implantation of a cardioverter defibrillator, is available for patients with a high risk of SCD.[6] This risk can be assessed through regular cardiological evaluation. Intense (competitive) sports are discouraged because of the associated risk of SCD.[7]

In specialized cardiogenetics outpatient clinics the aim of so called 'cascade screening' is to detect mutation carriers among relatives of a proven HCM patient (i.e., those with a clinical diagnosis of HCM) with a proven disease causing mutation (proband).[8] Because of the risk of SCD screening is actively offered to all relatives of the proband. Cascade screening followed by regular cardiological evaluations can prevent SCD by detecting mutation carrying relatives with manifest disease and a high risk of SCD. However, it is unclear if early detection of the disease decreases future morbidity, if risk stratification for SCD is efficient in mutation carriers without manifest disease, and if this screening approach including DNA testing is desirable from a psychosocial perspective. Only if the benefits outweigh the disadvantages this screening approach should be continued.[9, 10]

In HCM patients more psychological distress and impaired quality of life compared to the general population have been reported.[11-13] Psychological distress in at risk relatives (not specified if they were mutation carriers) was not significantly different from distress in HCM patients.[14] In relatives at risk for hereditary cardiac diseases emotional distress did not differ from the normal population before and after DNA testing[15] and in relatives from long QT syndrome families predictive testing led to distress, but distress levels normalized within eighteen months.[16] Carriers of a mutation predisposing them to HCM may show similar distress as HCM patients as they face the probability of many high impact events, like the imminent threat of disease and its progression, the threat of SCD and the possibility of having transmitted the disease to offspring. The required adjustment of life style and the occurrence of HCM related events in relatives may add to the distress.

The aim of this study is to assess long-term quality of life and psychological distress in HCM mutation carriers, both with and without manifest disease or symptoms, by comparing these with normative data of the general population. Specifically, we want to assess the effect of DNA testing on quality of life and psychological distress in a cohort of predictively tested relatives, since these individuals only became aware of their disease status because of DNA testing. Our second aim is to identify sociodemographic, clinical and risk and illness perception related factors that are associated with deteriorations in mutation carriers' quality of life and psychological distress.

Materials and methods

Participants

The study was performed at the cardiogenetics outpatient clinic of the Academic Medical Center in Amsterdam. Genetic counseling and identification of a disease causing mutation in the HCM proband is followed by actively offered cascade screening in the proband's

relatives. DNA diagnostics for HCM comprises the MYBPC3, MYH7, TPM1, TNNT2, TNNI3 and GLA genes, while the PRKAG2 and LAMP genes can be tested depending on the phenotype. Counseling sessions combine the consultation of a genetic counselor and a cardiologist and take a minimum of 30 min using adapted Huntington guidelines. Psychosocial care is actively offered but not obligatory before DNA testing.[17]

Study participants were all proven carriers of a pathogenic mutation in one of the genes associated with HCM identified since the start of our clinic in 1996. Disclosure of their DNA test result occurred at least more than 18 months ago. Cardiological evaluation was performed and carriers could be divided in three groups: (1) mutation carriers with manifest HCM before DNA testing (probands and affected relatives), (2) predictively tested relatives with manifest disease detected after DNA testing, and (3) predictively tested relatives still without manifest disease (Figure 1). Participants had to be Dutch speaking and at least 16 years of age. No mutation carriers were excluded because they did not speak Dutch. Fifteen children were excluded because they were aged younger than 16 years. Two hundred sixty-three HCM mutation carriers could be included.

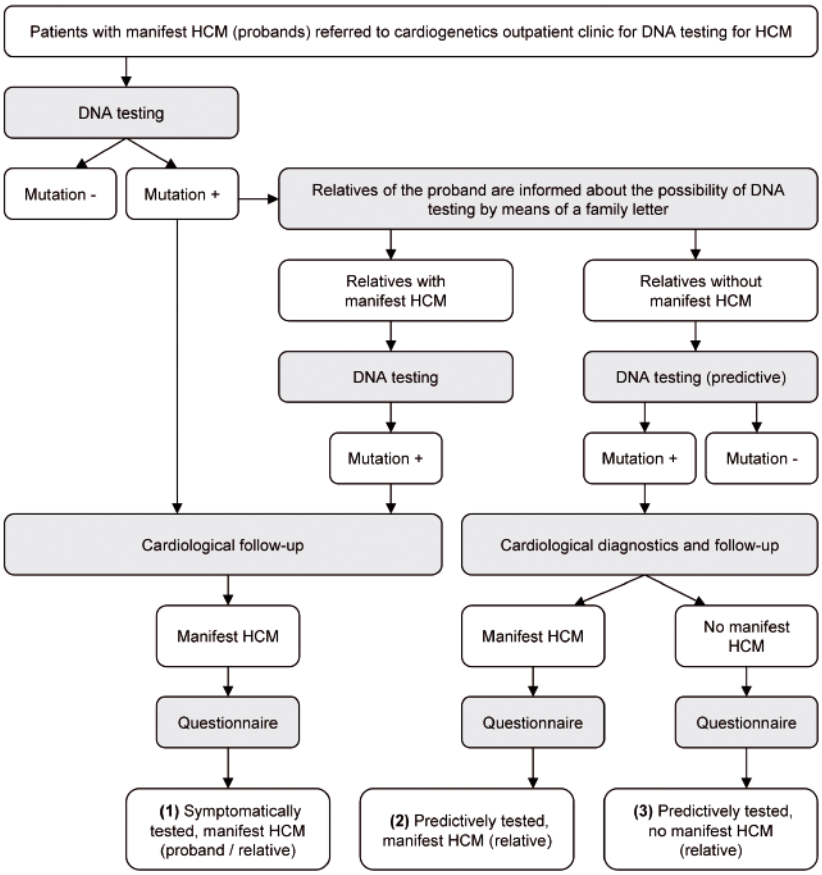

Figure 1. Subgroups of hypertrophic cardiomyopathy mutation carriers in the process of cascade screening for hypertrophic cardiomyopathy.

Each participant was sent a questionnaire, an explanatory letter, and a reply paid envelope. After two weeks a reminder was sent to all participants. The investigation took place from 2007 to 2008.

Outcome variables

Quality of life

Quality of life was assessed using the Short Form 36 Health Survey (SF-36). The SF-36 is a multidimensional measure developed in the Medical Outcomes Study.[18, 19] A Dutch translation has been validated and normative data from the Dutch general population have been published.[20] The SF-36 covers eight dimensions of health-related quality of life: physical functioning, role limitations owing to physical problems, role limitations owing to emotional problems, social functioning, mental health, general health perceptions, vitality and bodily pain. Scores of the eight dimensions were coded, summed, and transformed onto a scale from 0 (worst possible health) to 100 (best possible health). Internal consistency of the eight subscales ranged from 0.83 to 0.94. A summary physical (SF-36PC) and a summary mental component (SF-36MC) of quality of life can be calculated which are standardized for the general population with a mean score of 50 and SD of 10 points.

Psychological distress

Psychological distress was measured using the Hospital Anxiety and Depression Scale (HADS).[21, 22] A Dutch translation and normative data are available.[23] Generalized anxiety (HADS-A) and depression (HADS-D) are each measured with seven items and have Cronbach's alpha's of 0.84 and 0.83 respectively. Response options range from 0 (not at all) to 3 (very much), adding up to a maximum score of 21 for each subscale. A score of ≥8 indicates elevated distress and a score ≥11 indicates potentially clinically significant distress for each of the two subscales separately.[11-13, 22]

Determinants

Demographic and clinical variables

Demographic (age, gender, having a partner, having children) and clinical variables (physical comorbidity, manifest HCM, having symptoms of HCM, SCD in the family) of the participants were collected via the questionnaire. Time since the DNA test result was derived from clinical records.

Perceived risks

The perceived risks of developing (more) symptoms, of SCD, and of developing limitations in daily activities were measured with two items for each event, assessing (1) the risk of that event occurring with 10-point response options ranging from 0% to 100%, and (2) the perceived magnitude of the risk of that event occurring with 10-point response options ranging from 'very small' to 'very large'.[24] For each of the three events a total perceived risk score was calculated by summating the two item scores and dividing this sum by two.

Illness perceptions

To measure carriers' illness perceptions, the revised version of the Illness Perception

Questionnaire (IPQ-R) was used.[25] The IPQ-R provides an assessment of the key components of patients' perceptions of illness based on Leventhal's Self-Regulatory Model and has been used in hereditary diseases before.[26-29] The subscales of the IPQ-R are 'timeline acute/chronic', 'timeline cyclical', 'consequences', 'personal control', 'treatment control', 'illness coherence', and 'emotional representations'. An adjusted mean score (sum of the scale items divided by the number of items) can be calculated, with a possible maximum score of 5 for each subscale. Higher scores on these subscales refer to a stronger belief in a chronic/stable or more changing/episodic time course respectively; a stronger belief in serious consequences of being a mutation carrier; a stronger belief that the illness is controllable either by self-care or medical care; a better understanding of carriership; and stronger emotional reactions triggered by carriership, respectively. The IPQ-R was adapted for use in HCM mutation carriers so that it could be completed by both participants with and without manifest disease. The subscale 'timeline acute/chronic' was removed because it was not possible to adapt the formulation of the items to make them applicable for all mutation carriers (probands and relatives, with and without manifest HCM). The internal consistency of the subscales ranged from 0.67 to 0.84.

Data analysis

Data were analyzed using SPSS (version 15.0) statistical software. Comparison of carriers' quality of life and psychological distress with normative data of the general population was done using t-tests. Comparisons between subgroups of carriers (Figure 1) were made using Wilcoxon-Mann-Whitney tests. Main outcome variables, the summary physical and mental component of the SF-36 and the anxiety and depression subscale of the HADS, were non-normally distributed continuous variables. Univariate associations between dichotomized determinants and outcome measures were examined using Wilcoxon-Mann-Whitney tests and associations between categorical determinants and outcome measures were assessed using Kruskal-Wallis tests. Spearman's rank correlation coefficients (r_s) were used to examine associations between continuous determinants and outcome measures. Associations between determinants and outcome measures were assessed for (1) all mutation carriers (group 1+2+3 in Figure 1) and (2) the predictively tested mutation carriers (group 2+3 in Figure 1). In multiple linear regression analyses determinants were included with P-value <0.1 as threshold. In the regression models of the four different outcome measures multiple members from the same family were included (85 families). To account for the potential correlation between members from the same family generalized estimating equations were created for all linear regression analyses. All models showed correlation coefficients for family as <0.01, indicating that correlation between family members was almost absent. Therefore normal linear regression was performed using a stepwise selection strategy for model-fit with a P-value of 0.05 for entry in the model and 0.1 for removal. Multicollinearity of determinants was checked and no problems were detected.

Results

We retrieved 228 of the 263 (87%) mailed questionnaires. The mean age of responders was 49 (SD 15) years of whom 49% (112) were male. Demographic and clinical characteristics of all responders and of the subgroup of predictively tested carriers (group 2 and 3 from Figure 1) are summarized in Table 1. Twelve mutation carriers reported that they did not know if they

Variable	Group 1+2+3 [a] All carriers n=228		Group 2+3 [a] Predictively tested carriers n=123	
	n	%	n	%
Age (mean(SD; range))	49.0 (15.4; 16-86)		46.8 (16.1; 23-79)	
Male	112	49.1%	52	42.3%
Having children	184	80.7%	94	76.4%
Partner				
- yes, living together	183	80.3%	96	78.0%
- yes, not living together	9	3.9%	8	6.5%
- no	36	15.8%	19	15.4%
Level of education				
- low	71	31.1%	33	26.8%
- medium	102	44.7%	61	49.6%
- high	55	24.1%	29	23.6%
Ethnic background				
- Dutch	224	98.2%	121	98.4%
- other	4	1.8%	2	1.6%
Physical comorbidity	101	44.3%	48	39.0%
Clinical diagnosis of HCM				
- yes	135	59.2%	34	27.6%
- no	81	35.5%	79	64.2%
- does not know	12	5.3%	10	8.1%
Heart complaints	59	25.9%	13	10.6%
SCD in family				
- yes	120	52.6%	70	56.9%
- no	59	25.9%	31	25.2%
- does not know	47	20.6%	20	16.3%
- missing	2	0.9%	2	1.6%
Years since DNA test result (mean (SD))	3.3 (1.4)		3.0 (1.2)	

HCM, hypertrophic cardiomyopathy.
[a] Group numbers as designated in Figure 1

Table 1. Sociodemographic and clinical characteristics of HCM mutation carriers.

had manifest disease despite being seen by a cardiologist after being identified as mutation carrier.

Thirty-seven (17%) of the 224 patients of whom an anxiety score could be calculated, showed signs of anxiety (generalized anxiety score ≥8). Depression (generalized depression score ≥8) was present in 28 (12%) of 227 carriers of whom a depression score could be calculated. Gender, age, and ethnicity were also known from non-responders (n=35). Gender and ethnicity were not different between non-responders and responders, but non-responders were significantly younger (mean age 44 (SD 18) years, P=0.037).

Comparisons with the general Dutch population

Overall, carriers (n=228) had significantly lower general health perceptions, lower vitality and less bodily pain compared to the general Dutch population. However, summary mental and physical quality of life in carriers did not differ significantly from the general Dutch population. With respect to psychological distress, carriers reported significantly less anxiety than the Dutch population. The subgroup of mutation carriers with manifest HCM before DNA testing (n=135, group 1 in Figure 1) scored significantly worse than the general population on four out of eight subscales and on the physical component of the SF-36. Predictively tested carriers (n=123, group 2 and 3 in Figure 1), that is carriers in whom HCM appeared to be manifest after DNA testing (group 2, n=34) and carriers in whom disease was not (yet) manifest (group 3, n=89), did not score worse than the general population. In fact, quality of life scores were

significantly better on five subscales and on the physical component of the SF-36. Predictively tested carriers (group 2 and 3) also had significantly lower levels of generalized anxiety and depression than the general population. These findings were even more explicit in predictively tested carriers without manifest disease (group 3) (Table 2).

Comparisons between subgroups

When comparing the different subgroups from Figure 1, a similar picture arises as in the comparison with the general population. Carriers with HCM already manifest at DNA testing (group 1) have worse quality of life, physical quality of life mainly, and more psychological distress, specifically depression, compared to the predictively tested carriers (group 2 and 3). Moreover, the predictively tested carriers in whom HCM appeared to be manifest after DNA testing (group 2) have in general better quality of life and less psychological distress compared to carriers with manifest disease before DNA testing (group 1) but worse compared to carriers still without manifest disease (group 3). Differences between group 1 and 2 were generally larger than differences between group 2 and 3 (Table 2).

	Group 1+2+3 [a] All carriers (n=209-227)	**Group 1** [a] Symptomatically tested, manifest HCM (n=98-105)	**Group 2+3** [a] Predictively tested (n=116-122)	**Group 2** [a] Predictively tested, manifest HCM (n=32-34)	**Group 3** [a] Predictively tested, no manifest HCM (n=84-89)	Dutch general population (n=1657-1729 SF-36 n=199 HADS)
Subscales of the SF-36 [b]						
Physical functioning	82.4 (23.6)	74.0 (25.1)†**	89.8 (18.4)‡	87.6 (17.2)††	90.7 (18.9)~	83.2 (22.6)
Physical role limitations	81.1 (34.8)	69.1 (41.0)**	90.6 (25.9)‡	88.2 (28.4)#	91.6 (25.0)~	76.6 (36.1)
Emotional role limitations	85.9 (31.3)	79.7 (34.8)**	90.3 (28.1)‡	89.2 (29.3)	90.7 (27.8)~	82.5 (32.8)
Social functioning	84.8 (22.3)	78.7 (25.4)†**	90.2 (17.3)‡	90.1 (14.0)#	90.2 (18.5)~	84.2 (22.3)
Mental well-being	78.5 (15.4)	76.4 (16.1)	80.2 (14.5)	81.2 (14.2)	79.9 (14.6)	76.9 (17.4)
General health perceptions	66.1 (22.2)*	58.5 (22.6)†**	72.3 (19.4)	69.0 (19.2)	73.6 (19.5)	70.9 (20.6)
Vitality	65.4 (31.3)*	59.6 (21.5)†**	70.2 (16.6)	72.5 (14.8)	69.3 (17.3)	68.6 (19.3)
Bodily pain	82.4 (23.3)*	77.5 (25.8)**	87.3 (19.5)‡	81.2 (22.9)#††	89.7 (17.6)~	75.0 (23.3)
Components of the SF-36 [b]						
Physical component	50.4 (10.0)	47.0 (10.5)†**	53.5 (8.1)‡	50.9 (9.0)††	54.5 (7.6)~	50.0 (10.0)
Mental component	50.2 (9.2)	48.9 (9.7)	51.1 (8.7)	52.2 (6.5)	50.7 (9.4)	50.0 (10.0)
Subscales of the HADS [c]						
Anxiety	4.2 (3.8)*	4.6 (3.9)	3.8 (3.6)‡	3.6 (3.6)#	3.8 (3.7)~	5.1 (3.6)
Depression	2.9 (3.5)	3.7 (3.6)**	2.3 (3.1)‡	2.5 (3.1)	2.2 (3.1)~	3.4 (3.3)

Data are presented as mean (SD).
HCM, hypertrophic cardiomyopathy; SF-36, Short Form 36 Health Survey; HADS, Hospital Anxiety and Depression Scale.
[a] Group numbers as designated in Figure 1
[b] SF-36 scores range from 0-100; a higher score represents a better quality of life on that subscale or component
[c] HADS scores range from 0-21; a higher score represents a higher level of depression or anxiety
* Significant difference between group 1+2+3 and Dutch general population, p<0.05
† Significant difference between group 1 and Dutch general population, p<0.05
‡ Significant difference between group 2+3 and Dutch general population, p<0.05
# Significant difference between group 2 and Dutch general population, p<0.05
~ Significant difference between group 3 and Dutch general population, p<0.05
** Significant difference between group 1 and group 2+3, p<0.05
†† Significant difference between group 2 and group 3, p<0.05

Table 2. Quality of life and psychological distress in HCM mutation carriers (SF-36 and HADS).

Determinants of the physical component of quality of life

Multiple regression analyses showed seven determinants to be related to physical quality of life in the entire group of carriers (group 1, 2, and 3), explaining 39% of variance. Variables associated with decreased physical quality of life included: the presence of symptoms, more perceived negative consequences of carriership, the presence of physical comorbidity, the presence of manifest HCM, a belief in a more changing time course of HCM, a higher perceived risk of developing limitations in daily activities and a higher perceived risk of SCD. In the subgroup of predictively tested carriers (group 2 and 3) only two determinants were related to physical quality of life, being the presence of physical comorbidity and more perceived negative consequences of carriership. These two determinants explained 17% of the variance (Table 3).

	All mutation carriers (group 1+2+3)			Predictively tested mutation carriers (group 2+3)		
Determinants	**Estimate (β)**	**SE**	**p-value**	**Estimate (β)**	**SE**	**p-value**
Having symptoms	-5.19	1.56	0.001			
Perceived consequences of carriership	-3.45	0.88	< 0.001	-3.17	1.22	0.011
Physical comorbidity	-2.68	1.24	0.033	-4.64	1.57	0.004
Manifest HCM	-2.43	1.33	0.069			
Perceived more changing time course	-0.80	0.82	0.332			
Perceived risk of limitations in daily activities	-0.34	0.28	0.215			
Perceived risk of SCD	-0.14	0.26	0.598			

HCM, hypertrophic cardiomyopathy; SCD, sudden cardiac death.

Table 3. Linear regression results for variables determining the physical component of quality of life.

Determinants of the mental component of quality of life

The regression model for the mental component of quality of life in all carriers contained three determinants and explained 13% of the variance. Carriers with physical comorbidity, those who had more emotional reactions triggered by their carriership and those who perceived the risk of developing symptoms as higher reported lowest mental quality of life. In the subgroup of predictively tested carriers only the perceived risk of developing symptoms of HCM turned out to be an independent determinant of mental quality of life, explaining 3% of the variance (Table 4).

	All mutation carriers (group 1+2+3)			Predictively tested mutation carriers (group 2+3)		
Determinants	**Estimate (β)**	**SE**	**p-value**	**Estimate (β)**	**SE**	**p-value**
Physical comorbidity	-3.00	1.28	0.020			
Perceived emotional representations of carriership	-1.63	0.92	0.078			
Perceived risk of symptoms	-0.92	0.26	0.001	-0.72	0.34	0.035

Table 4. Linear regression results for variables determining the mental component of quality of life.

Determinants of generalized anxiety

Determinants associated with generalized anxiety in the final regression model explained

24% of the variance in anxiety for the entire group of mutation carriers (group 1, 2, and 3). The level of generalized anxiety was higher in females and in carriers with more emotional reactions triggered by their carriership. A stronger belief in serious consequences of carriership and a higher perceived risk of SCD were also significantly associated with higher levels of generalized anxiety. The same four determinants explained 15% of the variance in anxiety in the predictively tested mutation carriers (Table 5).

	All mutation carriers (group 1+2+3)			Predictively tested mutation carriers (group 2+3)		
Determinants	**Estimate (β)**	**SE**	**p-value**	**Estimate (β)**	**SE**	**p-value**
Male gender	-1.40	0.48	0.004	-1.93	0.65	0.004
Perceived emotional representations of carriership	1.19	0.36	0.001	0.90	0.52	0.088
Perceived consequences of carriership	0.75	0.34	0.030	0.55	0.55	0.321
Perceived risk of SCD	0.33	0.10	0.001	0.31	0.15	0.042

SCD, sudden cardiac death.

Table 5. Linear regression results for variables determining generalized anxiety.

Determinants of generalized depression

The five determinants in the final regression model for generalized depression explained 19% of the variance in depression scores in the entire group of mutation carriers. A lower level of understanding carriership was associated with a higher level of depression, as was a stronger belief in serious consequences of carriership. Other determinants of higher levels of depression were: having symptoms, a higher perceived risk of SCD and a longer time since the DNA test result. In predictively tested carriers only the presence of physical comorbidity was associated with higher levels of depression (Table 6).

	All mutation carriers (group 1+2+3)			Predictively tested mutation carriers (group 2+3)		
Determinants	**Estimate (β)**	**SE**	**p-value**	**Estimate (β)**	**SE**	**p-value**
Understanding of carriership	-0.85	0.31	0.007			
Perceived consequences of carriership	0.84	0.31	0.008			
Having symptoms	0.72	0.59	0.226			
Perceived risk of SCD	0.24	0.10	0.014			
Time since DNA test result	0.03	0.01	0.019			
Physical comorbidity				1.48	0.57	0.010

SCD, sudden cardiac death.

Table 6. Linear regression results for variables determining generalized depression.

Discussion

Quality of life and psychological distress in HCM mutation carriers

We assessed quality of life and psychological distress in a heterogeneous group of HCM mutation carriers and found these to be comparable to scores of the Dutch general population. Hence, HCM carriership does not seem to affect quality of life and psychological distress to a considerable extent. The high response rate in our cohort of mutation carriers indicates a representative sample of HCM mutation carriers. Because there was a difference in age between responders and non-responders, we cannot exclude response bias in other determinants.

Since people attending for genetic counseling are known to be relatively well educated, we checked for any relevant differences in education level and other sociodemographic characteristics between our sample of mutation carriers and the norm populations. Only the proportion of females in our sample was significantly higher than in the SF-36 norm population. However, female gender was not an independent determinant of quality of life in our sample.

Interestingly, in the three subgroups of mutation carriers quality of life and psychological distress were different than in the general Dutch population. In the subgroup of mutation carriers with manifest HCM before DNA testing (group 1) physical quality of life was worse than in the general population and predictively tested carriers (group 2 and 3) surprisingly reported better quality of life and less psychological distress than the general population. This was even clearer in the subgroup of predictively tested carriers without manifest disease (group 3). Considering the impacting issues predictively tested carriers are confronted with, we expected worse or similar levels compared to the general population. We checked for differences in demographic characteristics that could explain our findings. Compared to the SF-36 norm population, carriers without manifest disease were significantly younger. In our mutation carriers a younger age was associated with a better physical quality of life. On the other hand, there was a significant overrepresentation of females in the subgroup of carriers without manifest HCM compared to the norm populations. With female gender being an independent determinant of higher levels of anxiety in our sample, the lower anxiety levels of carriers without manifest disease could not be explained by the difference in gender distribution.

We are not the first to find that patients value their health higher than members of the general public.[30] Stiggelbout and de Vogel-Voogt[31] provided a framework for understanding and studying possible mechanisms that may explain these counterintuitive results. First, this could be due to differences in interpretation; patients answer questions in the light of their experience with the disease, an experience that the general population lacks. In addition, patients often do not value their health with the disease, but their life with the disease. Positive aspects like meaning of life and goals may be more related to well-being than the impact of impairments. Moreover, the judgment of patients' health status might be affected by adaptation to and the ability to anticipate poor health, commonly known as response shift.[31-33] Some of the above mentioned mechanisms might apply to our predictively tested mutation carriers without manifest disease before DNA testing. However, we would expect these mechanisms also to be present in mutation carriers with manifest disease before DNA testing. Therefore these mechanisms are not a likely explanation for the better scores in our subgroup of predictively tested mutation carriers.

The effect of reassurance in predictively tested carriers may provide an additional explanation. Participants come from families with much uncertainty about who is going to be affected and at risk for SCD. Genetic counseling and cardiological diagnostics can take away some of their uncertainties and may provide a greater sense of control. Cardiological evaluations showing the absence of manifest disease or disease in an initial (asymptomatic) phase might also be very reassuring. Several respondents addressed this issue in the free text of the questionnaire, for example, as one respondent wrote: 'I do not worry that much, because I have HCM in my genetic background only.'. Other respondents addressed the benefits of knowing that they are a HCM mutation carrier: 'Since I received my DNA test result, I have found more peace and I am more positive.' and 'I do not feel inferior, I even feel stronger.

Sometimes I think I handle with more sense than others.'.

A second explanation might be that HCM patients and relatives from HCM families with a relatively good quality of life and low levels of psychosocial distress are more inclined to attend the cardiogenetics outpatient clinic for DNA testing. Such a selection bias is difficult to assess, but we do know that only a minority of relatives visit our cardiogenetics outpatient clinic.[17]

Quality of life and psychological distress were worst in carriers with manifest HCM before DNA testing (group 1) and best in the predictively tested carriers without HCM (group 3). Disease duration is probably shorter in predictively tested carriers with manifest HCM -HCM was only detected after DNA testing and fewer years have passed since the DNA testing- compared to the carriers with manifest disease before testing. This suggests that in addition to the presence of manifest HCM, the duration of manifest disease may also affect (physical) quality of life and psychological distress.

Previous studies

Quality of life and psychological distress are only reported on in British HCM patients with manifest disease and in Australian patients and at-risk relatives.[11-14] Although our subgroup of mutation carriers with manifest disease (group 1) most closely resembles the British HCM patients, our carriers score better on all subscales and components of physical quality of life and have less psychological distress.

Signs of anxiety and depression were present in 17% and 12% of our respondents respectively. These proportions are smaller than in British and Australian HCM patients, and also smaller than in patients visiting a general practitioner (a population that closely resembles the general population).[12-14, 34]

Cox et al.[11] measured quality of life and psychological distress using the same questionnaires (SF-36 and HADS) and their HCM patients were approached for participation in a similar way as our mutation carriers. Hence, the similarity in methodology makes this an unlikely cause for the differences in outcomes. Looking at sociodemographic differences only the difference in gender distribution could have shown more favorable results in our carriers with manifest disease. We had more male carriers with male gender being associated with lower levels of anxiety. Differences in counseling procedures may also explain our findings. Only one study involving HCM patients describes counseling.[14] Their cardiac genetic service incorporates a genetic counselor and at risk relatives are cardiologically evaluated. It is unclear if DNA diagnostics is part of risk assessment in relatives. Besides these, differences in disease duration and stage and sociocultural differences might also account for the differences in quality of life and psychological distress between our carriers with manifest HCM and HCM patients reported on in literature.

Determinants of quality of life and psychological distress

As expected, we found the presence of symptoms and physical comorbidity (varying from high blood pressure to cancer) to be associated with worse physical quality of life, the latter also with worse mental quality of life.

In addition, illness and risk perception related variables turned out to be major determinants of both quality of life and psychological distress. The continuous nature of these variables -illness perception scores have a maximum of 5 and risk perceptions range from 0 to 10- makes the effect on the outcome measures larger than that of the dichotomous

variables (being 0 or 1) like the presence of symptoms, even if the beta is lower. Knowledge of determinants of quality of life and psychological distress can be used in genetic counseling. Unlike other determinants as gender and the presence of symptoms, perception related variables are not static. They can be addressed and corrected if needed during pre- and post-test counseling by the genetic counselor, the social worker, and/or cardiologist.[35-38] This may be especially needed if risks and consequences of carriership are perceived as too high or too detrimental.

We expected experience with SCD in the family to be a determinant of psychological distress. Earlier studies in carriers of an hereditary heart diseases found such an association.[16, 39] Likewise, in oncogenetics experience with cancer in the family has been mentioned as a predictor of distress.[40, 41] Although experience with SCD in the family was not an independent determinant of quality of life or psychological distress, the perceived risk of SCD was. This perceived risk of SCD was significantly higher in the carriers who experienced SCD in their family than in carriers who did not (P=0.024).

The effect of DNA testing on quality of life and psychological distress

Because of the cross-sectional nature of this study, relationships between carriers' quality of life and psychological distress and determinants give little information on causation. However, we tried to look at the causal effect of DNA testing on quality of life and psychological distress. One would expect this effect, if present, to be the most apparent in predictively tested relatives who were diagnosed with manifest disease during cardiological diagnostics initiated after DNA testing (group 2), because they are the only subgroup in whom disease status changes as a consequence of DNA testing. In this subgroup, quality of life was better and levels of psychological distress were lower than in the general population. Follow-up studies in other late onset genetic diseases report an increase in psychological distress directly after testing which decreases to baseline within a year.[16, 42-47] We therefore may assume that in HCM, also a late onset genetic disease, long-term quality of life and psychological distress are not impaired by DNA testing. However, studies using a longitudinal design, controlling for baseline levels of quality of life and psychological distress, are needed to draw firm conclusions.

Conclusions and implications for clinical practice

To the best of our knowledge, this is the first study to investigate quality of life and psychological distress in HCM mutation carriers. HCM mutation carriers' quality of life and psychological distress only differed on a minority of subscales from that in the general Dutch population. Therefore we can conclude that HCM carriership does not seem to negatively affect quality of life and psychological distress. The better levels of quality of life and psychological distress in predictively tested carriers with manifest disease being detected after DNA testing suggest no negative effects of DNA testing after on average 3 years after DNA testing.

Not surprisingly, the presence of manifest HCM and HCM related symptoms appeared to be important determinants of impaired physical quality of life. Overall, perceptions of risk and carriership, like the perceived risk of SCD or the belief in serious consequences of carriership, were the main determinants of quality of life and psychological distress. Because perception of risk and disease probably can be addressed and corrected if needed during pre- and post-test counseling, genetic counseling should also focus on these determinants of quality of life and psychological distress. Further studies should be performed to investigate which factors are associated with disease and risk perception in HCM.

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