Family Screening: Who, When, and How

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Key Points

- Hypertrophic cardiomyopathy (HCM) is an autosomal dominant disease.
- HCM has an age-related variable penetrance; cardiac analysis has to be repeated over time.
- Only truly pathogenic mutations can be used for predictive testing in family members.
- The clinical screenings algorithm consists of an ECG and TTE at regular intervals.
- Cardiac events are virtually absent in G+/LVH− subjects with normal ECG.

Introduction

For over 50 years, hypertrophic cardiomyopathy (HCM) has been recognized as an autosomal dominant familial cardiac disease, with a risk for sudden cardiac death (SCD) and progression to advanced heart failure or end-stage disease [1, 2]. With HCM being a familial disease, family screening is important to identify relatives at risk. Guidelines have encouraged family screening by electrocardiogram (ECG) and transthoracic echocardiogram (TTE) since 2003. According to the most recent European clinical guideline on HCM, genetic testing of relatives should precede clinical evaluation in families with a definitive mutation (class I, level of evidence B). In families without a definitive mutation, cardiac evaluation of first-degree relatives should be performed [3].

In this chapter we will focus on the importance of family screening and the genetic – and clinical – aspects of family screening and provide practical tips for the organization of family screening in HCM.

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The Importance of Family Screening

The most devastating presentation of HCM is SCD in a previously asymptomatic and presumed healthy person. HCM is accountable for a significant portion of SCD cases, especially in young persons [4]. Since HCM is an autosomal dominant disease, there is a 50% risk of transmission to first-degree family members. Once the diagnosis of HCM is made, SCD risk can be modified by lifestyle adjustments (especially cessation of intensive physical activity) and by prescription of high doses of beta-blockers in children [5–7]. At adult age, medication does not protect against SCD, but the implantation of an implantable cardioverter-defibrillator can protect against SCD in high-risk patients [8].

The goals of family screening are therefore to identify relatives with unrecognized HCM and to follow at-risk individuals for risk factors of SCD and disease development. Family screening also helps build awareness of the various phenotypes within a given family and the likelihood that multiple family members may be affected despite the lack of overt symptoms.

General Aspects of Family Screening

Proband

Family screening in HCM always starts with the confirmation of the clinical diagnosis of HCM (phenotype) in the proband (the first person of a family presenting with HCM); other causes of left ventricular hypertrophy (LVH), like aortic valve stenosis, hypertension, or storage diseases, should be excluded. After confirmation of the diagnosis, the HCM patient should be informed about the familial character of the disease, the high potential for familial transmission, and the possibility to perform genetic testing. During genetic counseling attention should be given to the risks and possible benefits of genetic testing [2, 3, 9].

In specialized cardio-genetic outpatient clinics, this familial and genetic counseling is performed in close collaboration

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between the cardiologist and the clinical geneticist. The flowchart used at the cardio-genetic outpatient clinic of the Erasmus MC, Rotterdam, the Netherlands, is provided in Fig. 14.1.

The Role of the Clinical Genetics/Genetic Counselor

The cardiac genetic counselor gives information about inheritance risk; provides pre- and posttest counseling; investigates and confirms family history by retrieving medical information of family members with possible HCM (i.e., family members with SCD or heart failure) from general practitioners, cardiologists, and/or pathologists; and discusses worries and fears about the HCM diagnosis for individual patients and their family. During genetic counseling, family members at risk are identified, and first-degree relatives, those sharing 50% of genetic material with the proband, are selected for further analysis. The legal framework for informing relatives varies around the world; in

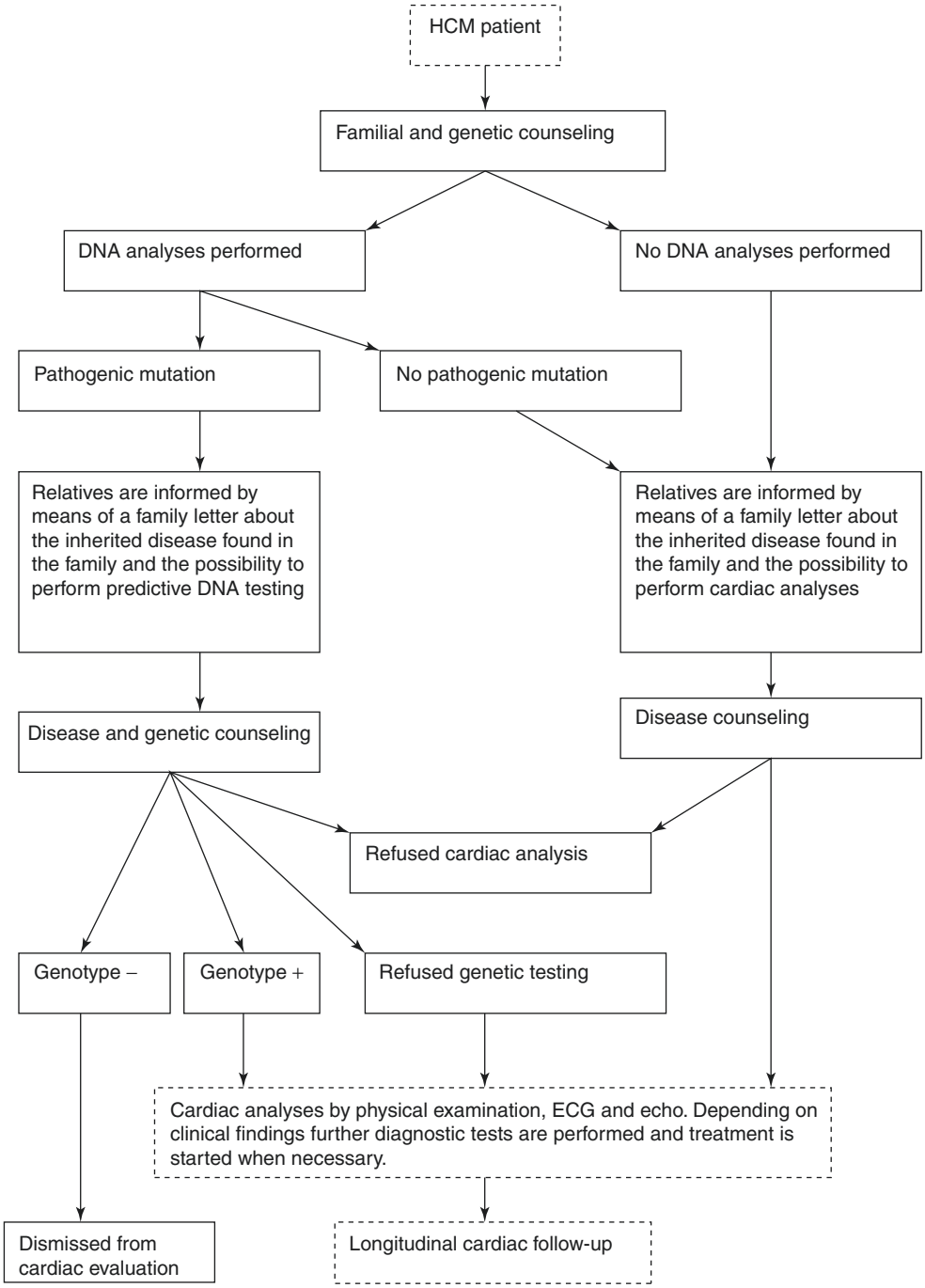

Fig. 14.1 Flowchart used at cardio-genetic outpatient clinic at the Erasmus MC, Rotterdam, the Netherlands. Dashed boxes are taking care of by the cardiologist; solid line boxes are taking care of by the clinical geneticist or genetic counselor. (HCM hypertrophic cardiomyopathy, ECG electrocardiogram, and echo echocardiogram)

most cases first-degree family members are provided with information on HCM through a family letter provided to them via the proband or via direct communication. In the United Kingdom and the Netherlands, direct medical contact, with consent of the proband, has been used for screening of familial hypercholesterolemia. Although family members accept this approach, another study shows that family members prefer indirect cascade screening [10, 11]. Genetic counselors assist in determining the best method of contacting family members, who also may be at some distance or reluctant to learn more.

Genetic Testing of the Proband

After counseling and consent, blood is drawn for DNA analysis. For the proband the potential medical, physiological, financial, and familial implications of genetic testing are minimal, as all these consequences are determined by the phenotype, which is already documented. Since the costs of genetic testing are not covered by general health insurance in all countries, reimbursement of costs may be a problem and may lead to a limited access to genetic testing.

Currently, not all genes causing HCM have been identified, and the likelihood of obtaining a positive genetic test in a proband is about 50–60%. The chance of finding a pathogenic mutation increases in HCM patients with a reverse septal curve morphology, a family history of HCM or SCD, age of HCM diagnosis <45 years, and maximal wall thickness ≥ 20 mm [12]. The relatively low percentage of HCM families in which a mutation is found and the fact that only truly pathogenic mutations can be used for predictive testing in family members exclude a reasonable portion of the HCM families to be screened with genetic testing [9, 13]. Data from population-based exome data are questioning the pathogenicity of previously HCM-associated genetic variants. This reclassification of mutations in HCM patients might lead to misdiagnosis of family members, and this could have potentially devastating clinical consequences. It is therefore crucial that variants being reported as causative of HCM are truly disease causing. The complexity of interpreting genetic test results further warrants close collaboration with clinical geneticists [14].

Predictive Genetic Testing in Family Members at Risk for HCM

Currently, the power of HCM mutational analysis lies most prominently in identifying G+ family members who are at risk for developing disease and excluding unaffected, genotype-negative (G-) relatives of further cardiac evaluation; this is information not achievable otherwise. In Fig. 14.2 a 20-year follow-up of an HCM family is described, in which the advantages of genetic testing are made clear. Predictive genetic testing provides a cost-effective and definitive means of family screening as longitudinal evaluation can be focused on G+ family members because only they are at risk for disease development [15]. The ACCF/AHA guidelines state that genetic testing, preceded by genetic counseling, is reasonable (class IIa) to facilitate the identification of at-risk family members [2]. The latest ESC guidelines on HCM advise to start with genetic testing after pretest counseling in first-degree relatives before cardiac evaluation (class Ib) [3]. Predictive genetic testing can only be offered in HCM families in which a truly pathogenic mutation is identified. In other families, family screening should be offered by cardiac testing of first-degree relatives. It is essential that family members be counseled about the potential medical, physiological (including psychological), financial, and familial implications of genetic and cardiac test results to enable informed decision-making about potential risks and benefits before blood is drawn. If a pathogenic mutation is identified in a family member, this may lead to consequences for employment and insurances, especially life and disability insurances. As much of this testing is performed on a young, asymptomatic population, these concerns are indeed real and must be discussed at length prior to proceeding [2, 3, 14].

The legal implications of genetic testing are dependent on the country of residence; in the United States, the Genetic Information Nondiscrimination Act (GINA), a federal law, prohibits denying or terminating of health insurance, employment, or promotion solely on the presence of a mutation or a family history of genetic disease. However, GINA does not protect against discrimination for disability, life, or long-term care insurance or when there is a documented medical condition [16]. In the Netherlands, the Dutch Medical Examination Act protects unaffected HCM mutation carriers for life insurance below 260,000 euro; above this amount, carriers will have to disclose their HCM risk status, potentially resulting in an increased life insurance premium [17].

G+ family members should subsequently undergo cardiac testing to determine if the HCM phenotype (presence of LVH) is present. Identifying a G+ family member will also lead to extension of the family screening, as the first-degree relatives of the newly diagnosed genotype-positive (G+) subject will be offered genetic testing (so-called cascade screening). This has far-reaching implications to the family as a whole and may allow screening to cross borders including distant countries.

Predictive Genetic Testing in Children

Whether or not to offer predictive genetic testing to children is subject to debate; there may be a good reason to defer testing, including to enhance the opportunity of the child to participate

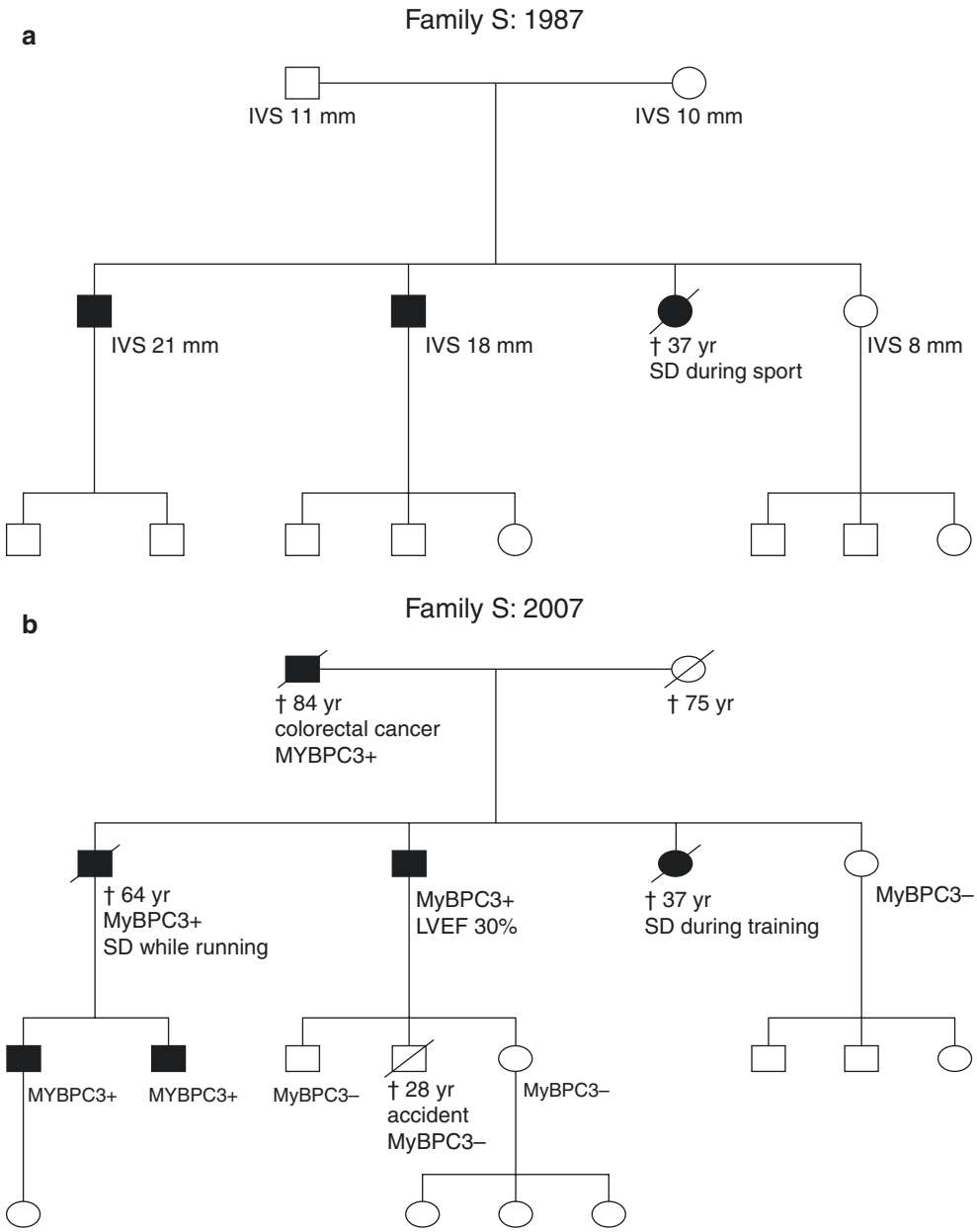

Fig. 14.2 Pedigree of a hypertrophic cardiomyopathy (HCM) family followed at the cardio-genetic outpatient clinic of the Erasmus MC, Rotterdam, the Netherlands. (**a**)**:** Pedigree at presentation in 1987. The proband presented after resuscitation for ventricular fibrillation; she died of severe neurological damage. Her first-degree relatives underwent cardiac evaluation by electrocardiogram and echocardiogram. Her two elderly brothers had HCM; her parents and younger sister had no signs of HCM. (**b**)**:** Pedigree drawn in 2007. Genetic testing revealed a pathogenic mutation in myosin-binding protein C, after which predictive genetic testing was offered to family members. The father was G+/LVH− and died of colorectal cancer. The eldest brother experienced SCD during running; both his sons are G+/LVH−. The other brother developed end-stage HCM; his three children are genotype negative and dismissed from follow-up. The youngest sister is also reassured, since she is genotype negative

in the discussion. However, it is likely that young children are not fully able to comprehend the implications of genetic testing. With the current lack of prognostic value of a pathogenic mutation on disease development and risk, and the possible negative consequences of predictive testing, we are reticent to perform predictive genetic testing routinely in children. An argument in favor of genetic testing of children lies in the fact that knowing that the young child is at risk can be beneficial for advocating and encouraging alternative pastimes [18]. This however can also lead to unnecessary stigmatization and unfounded withdrawal from competitive sports, since cardiovascular events in G+/LVH− subjects are virtually absent. A recent study focusing on follow-up of G+/LVH− children found a very low conversion rate to G+/ LVH+ of 6% in a follow-up period of 12 years; children were in their 20s when HCM was diagnosed, and there were no cardiovascular events in G+/LVH− children [19]. Currently, our HCM program makes decisions on a case-by-case basis after extensive counseling of the family and the child, including psychological support and taking all the above considerations into account. As for cardiac evaluation, genetic testing is normally first offered once the child reaches the age of 10 years or shows signs of puberty [3].

Family Planning in HCM Families

Special attention should be paid to HCM patients and G+/LVH− family members with questions about family planning

regarding the risk of transmission of the disease to their offspring. These aspects should be part of the genetic counseling in subjects in the reproductive age, both male and female. When the underlying mutation is known, prenatal screening or preimplantation genetic testing is theoretically possible. These are not routinely performed due to the variable disease expression, the fact that disease manifestation usually occurs later in life, the fact that there are treatment options available, and the fact that longevity is maintained in these patients when viewed as a group [3, 20].

In both children and adults who have been counseled before they underwent genetic or cardiac testing in screening for HCM, no psychological harm or negative effect on quality of life has been observed [21–23]. Long-term impact on quality of life however requires further research.

Cardiac Evaluation in Family Screening for HCM

Cardiac evaluation should be offered to family members of HCM families in which no pathogenic mutation is found, G+ family members identified during predictive genetic testing, and family members refusing predictive genetic testing. In addition, in cases where the proband has died, and no gene testing was performed, cardiac evaluation is oftentimes the only remaining screening modality prior to the identification of a new proband within the family. It is important that counseling is provided to family members before they undergo cardiac evaluation, since the possible consequences as described before for genetic testing remain for clinical testing.

Because the expression of HCM is highly age dependent, overt cardiac hypertrophy often does not emerge until late adolescence or beyond; guidelines therefore recommend longitudinal screening with variable intervals according to age (Table 14.1). G+/LVH− subjects and family members with unknown genetic status should be evaluated clinically and by ECG and TTE at period intervals of 12–18 months in asymptomatic children and adolescents and about every 5 years in asymptomatic adults (Table 14.1). In case of pre-phenotypic features on TTE and/or ECG, the current ESC guidelines advise to have a repeated cardiac evaluation at 6 to 12 months. In case of new cardiac symptoms, family members should be re-evaluated promptly [3].

The AHA/ACC guidelines advise to start with cardiac evaluation at the age of 12 years (although some advocate for beginning when signs of puberty are noted), while the more recent ESC guideline advises screening from 10 years of age. Screening at even younger ages can be considered in families with a malignant family history, if the child is a competitive athlete, or when there are other signs or symptoms of early HCM [2, 3].

Table 14.1 Proposed clinical screening strategies in family members of HCM patients

Age	History, clinical examination, ECG, and echo
<10 years	Optional unless
	Malignant family history
	Competitive athlete
	Symptoms or signs of possible HCM
10 to 18–21 years	Every 1–2 years
> 18–21 years	At least every 5 years

Based on current guidelines by Gersh et al. [2] and Elliott et. al [3] (*ECG* electrocardiogram, *echo* echocardiogram, and *LVH* left ventricular hypertrophy)

Electrocardiogram

The ECG is abnormal in the vast majority (75–95%) of HCM patients [24, 25]. Abnormalities mainly consist of Q waves, repolarization abnormalities, and isolated voltage criteria for LVH or left atrial enlargement and can be present before there is hypertrophy on TTE [25]. The severity of ECG abnormalities is directly related to both the degree of hypertrophy and the prevalence of fibrosis expressed as late gadolinium enhancement (LGE) on cardiac magnetic resonance imaging (CMR) [24]. The ECG is therefore recommended as a screening tool to raise the suspicion of HCM in family members of HCM patients [2, 3].

In a recent study, the presence of Q waves and/or repolarization abnormalities was highly specific (98%) for the presence of a sarcomeric mutation in family members without LVH; unfortunately ECG abnormalities had a low sensitivity (25%), and therefore a normal ECG is non-informative and does not reliably indicate the absence of a sarcomeric mutation [26, 27]. A normal ECG however excludes severe phenotypic expression of HCM [24]. In G+ individuals without LVH at first evaluation, ECG abnormalities are predictors of developing LVH during follow-up [28].

Transthoracic Echocardiogram

The diagnosis of HCM is conventionally made by cardiac imaging, with at present a TTE most often used. A combination of ECG and TTE is recommended as a clinical screening algorithm in family members of HCM patients [2, 3].

The diagnosis of HCM is typically made when the maximal wall thickness is ≥15 mm; in affected family members with HCM, the degree of hypertrophy may be below this diagnostic threshold, and different criteria combining ECG and echo data have been proposed to diagnose HCM in 50% risk carriers [29]. In the latest ESC guideline, the threshold to diagnose HCM is lowered to ≥13 mm in first-degree relatives [3]. Although HCM is predominantly characterized by the presence of hypertrophy, other features, like mitral valve

or papillary muscle abnormalities or diastolic dysfunction, have been described. Presence of these features in 50% risk carriers should raise the suspicion of an early manifestation of HCM [30–32].

Especially in patients with suboptimal echo windows, TTE can fail to identify focal areas of myocardial hypertrophy, mainly at the inferoseptum, apex, or free wall of the left – or right – ventricle. In these patients other imaging techniques like CMR should be performed [33]. CMR may also show patchy LGE consistent with HCM.

In animal models of HCM, it has been shown that diastolic dysfunction can precede the development of HCM [34]. Tissue Doppler imaging studies in humans revealed differences in different mitral annular velocities; decreased Sm and Em velocities have been described, and one study found increased Am velocities [30–32]. Because of the discrepancies seen in the tissue Doppler imaging and speckle-tracking echocardiography in G+/LVH− subjects, the identification of G+/LVH− family members with echocardiography remains challenging. However, as alluded to above, the presence of diastolic dysfunction in the absence of overt LVH that meets anatomic criteria for HCM may be a sign of preclinical disease.

Cardiac Magnetic Resonance

Although the current clinical guidelines do not mention CMR in the screening algorithm for family members of HCM patients, it can be a useful adjunct in HCM family screening in selected patients. With CMR, the wall thickness of any segment of the ventricle can be accurately assessed, and the use of gadolinium contrast allows tissue characterization, including scar location, distribution, and burden. In a paper by Valente et al., the diagnostic agreement between TTE and CMR was 90%; however CMR detected mild hypertrophy in 10% of patients, which was missed by TTE [33].

CMR studies in G+/LVH− subjects revealed the presence of myocardial crypts, mitral valve abnormalities, and diastolic abnormalities [35, 36]. Myocardial crypts occur particularly in the septum and inferior (posterior) right ventricular insertion point [37]. These crypts are present in a subset of the G+/LVH− subjects, and their presence may be a pre-phenotypic marker of HCM; however their prognostic value needs to be determined [38].

The presence of LGE is extremely rare in G+/LVH− subjects. However, G+/LVH− subjects with LGE on CMR have been described; unfortunately no data on ECG were given in these patients [39]. The presence of an abnormal ECG may raise the suspicion of missed areas of focal hypertrophy or the presence of LGE. The latter is especially important, since sporadic cases of SCD have been described in G+/LVH− patients [40]. In the described patients, the ECG was abnormal, suggesting myocardial abnormalities. LGE is associated with an increased risk of heart failure, and recently special attention has been given to the extent of LGE as a possible risk factor for SCD and end-stage disease (systolic dysfunction) [41, 42].

Accordingly, CMR may especially be useful if TTE images are suboptimal or suggest borderline LVH and if there are unexplained ECG abnormalities or in the case of high-risk situations, i.e., high familial prevalence of SCD or G+/LVH− subjects engaging in competitive sports. Subtle findings on CMR may indicate a likely diagnosis of HCM and prompt more frequent monitoring and lifestyle modification or even solidify a diagnosis through the confluence of evidence, with resultant clinical implications.

Genotype-Positive/Phenotype-Negative Subjects

The penetration of genetic testing in clinical practice has revealed a new subset within the HCM spectrum, the G+/LVH− family members. Although this subset is very important for improving our understanding of how mutations cause disease, the identification of these individuals also leads to clinical decision-making dilemmas. The reported risk of adverse cardiac events in G+/LVH− is very low, and in the largest study thus far, no SCD occurred in mutation carriers without hypertrophy [43].

The precise proportion of the G+/LVH− subjects that will develop overt disease, and when, is still uncertain; this is due to the relatively short period of time that genetic testing has been available in clinical practice, with consequent limited follow-up duration. Disease progression is increasing with age but seems to be slow, both in children and adults [19, 44]. In a recent study, subtle HCM, without cardiac events, developed in 11% of G+/LVH− family members over a period of 6 years [28]. The family described in Fig. 14.2 shows that HCM can be absent until very advanced age.

The current guidelines recommend the intervals for cardiac evaluation as described in Table 14.1 [2, 3]. In G+/LVH− subjects with a family history indicating a high SCD risk, periodic assessment of arrhythmias, by exercise testing and/or Holter monitoring, may be appropriate. Until accurate penetrance data are available, it is prudent to extend standard HCM surveillance with cardiac imaging at least through midlife but perhaps even for the entirety of life.

Diastolic dysfunction, increased collagen synthesis, impaired energetics, expanded myocardial extracellular volume, myocardial crypts, and mitral valve abnormalities have been described in G+/LVH− subjects. These features are very interesting for further unraveling pathophysiology; however their clinical relevance is still unclear [30–33, 35–37, 45].

Whether or not G+/LVH− subjects should be excluded from sports has been subject to debate. At present, the reported

SCD rate in G+/LVH− subjects is extremely low, and therefore both the AHA/ACCF and ESC recommendations do not advise to routinely exclude G+/LVH− subjects from competitive sports [3, 46]. Instead, the G+/ LVH− subjects should be advised on an individual basis taking into account the type of sporting activity, the local legal framework, and the underlying mutation and the results of cardiac evaluation. Based on these recommendations, our HCM program usually allows G+/LVH− subjects to enroll in competitive sport activities but keeps them under close clinical surveillance with cardiac evaluations, including exercise testing and Holter monitoring every year and CMR at first evaluation and when changes in other examinations or symptoms occur.

Future Perspectives

The introduction of next-generation genetic testing with the possibility to test a large number of genes at the same time and the possibility of whole-exome sequencing will also most likely lead to an increased number of pathogenic mutations identified. This will enable predictive testing in a larger portion of the families. It will however also lead to even more complex genetic information to interpret.

Current guidelines suggest a "one-size-fits-all" approach to longitudinal cardiac follow-up for all unaffected family members, both G+ and those with unknown genetic status, regardless of family history. Further studies should aim at developing a more "tailor-made" approach, with intervals possibly based on the presence of pre-phenotypic markers of HCM, confirmed genetic status, and family history. The diagnostic algorithm, now consisting of ECG and TTE in all family members, most likely can also be adjusted to specific situations. Questions of whether or not it is safe to screen family members with ECG alone, as well as if and when to perform CMR, exercise testing, and Holter monitoring, should be answered, i.e., the study by Jensen et al. does not support the current guidelines regarding the short interval of performing serial cardiac evaluation in children [19].

Longitudinal follow-up studies of G+/LVH− subjects are necessary to get robust data on disease penetration, the prognostic value of pre-phenotypic signs, and the risks in these subjects. By studying this subset, we will hopefully be able to unravel the pathophysiology of disease development to the level that drugs to prevent disease development can be developed.

Conclusions

Family screening in HCM is important since HCM is an autosomal dominant disease and SCD can be the first presentation. In both children and adults who have been counseled before they underwent genetic or cardiac testing in screening for HCM, no psychological harm or negative effect on quality of life has been observed [21, 22]. It is important to realize that only truly pathogenic mutations can be used for predictive testing. Challenges of interpretation of genetic results are real and require careful review and are best done in the setting of a multidisciplinary approach to care. When gene testing is not available, or refused, serial cardiac evaluations of family members is the next best approach and likely should continue lifelong for all family members. G+/LVH− subjects are very interesting for research to unravel the pathophysiology of disease development, but the prognostic relevance of so-called signs of pre-phenotypic HCM remains unclear.

Clinical Pearls

- Disease development in G+/LVH− subjects is slow and may reflect the phenotypic variability of this disease even within a given family.
- G+/LVH− subjects should not routinely be denied to enroll in competitive sports, but a CMR to fully exclude the phenotype may be reasonable.
- Ramifications of gene testing, especially with regard to health and life insurance, must be explained to the patient prior to drawing blood for analysis.
- Clinical presentation and treatment in HCM are based on the phenotype, not on the genotype.
- Enabling affected family members to reach the remainder of their family, for example, by use of standardized letters describing the disease, inheritance pattern, and benefits of screening, is oftentimes helpful in raising awareness of HCM and identifying at-risk individuals.

Questions

1. At what age should family screening in hypertrophic cardiomyopathy in first-degree relatives be started?
   A. After birth
   B. At the age of 18 years
   C. At the age of 30 years
   D. At the age of 10 years
   E. At the age of 4 years

The correct answer is D:

Current European guidelines advise to start with family screening at the age of 10, earlier screening is only advised in special circumstances (malignant family history, if the child is a competitive athlete or when there are other signs or symptoms of early HCM).

2. Hypertrophic cardiomyopathy is an inheritable cardiac disease. What is the change of transmission of the disease to offspring?
   A. 10%
   B. 50%
   C. 25%
   D. 5%

The correct answer is B:
Hypertrophic cardiomyopathy is inherited in an autosomal dominant manner, this implicates that every child of a HCM patient has a 50% chance of inheriting the disease.

3. Is repeated cardiac evaluation advised in relatives at risk for HCM?
   A. Yes, cardiac evaluation is recommended with regular intervals until the age of 24 years.
   B. No, one cardiac evaluation is sufficient in adult relatives at risk if there are no abnormalities found.
   C. Yes, "lifelong" cardiac evaluation is recommended in at-risk relatives with regular intervals.
   D. Yes, cardiac evaluation is recommended with regular intervals between the age of 10 and 40 years old.

The correct answer is C:
HCM is characterized by age-related penetrance; this means that cardiac evaluation should be repeated with regular intervals until advanced age.

4. Which examinations are advised in the cardiac evaluation of all at-risk relatives?
   A. Transthoracic echocardiogram and electrocardiogram
   B. Transthoracic echocardiogram, electrocardiogram, and Holter monitoring
   C. Transthoracic echocardiogram and cardiac magnetic resonance imaging
   D. Cardiac magnetic resonance imaging, electrocardiogram, and Holter monitoring

The correct answer is A:
Cardiac evaluation of at-risk relatives starts with an electrocardiogram and echocardiogram; if (subtle) abnormalities are detected, further cardiac evaluation including cardiac magnetic resonance imaging, Holter monitoring, and exercise testing should be done.

5. What should you advise in a genotype-positive/phenotype-negative subject who wants to participate in competitive sport?
   A. Genotype-positive/phenotype-negative subjects should be excluded from all competitive sports.
   B. Genotype-positive/phenotype-negative subjects can only perform low-intensity sporting activities.
   C. Genotype-positive/phenotype-negative subjects can enroll in competitive sports after extensive negative cardiac investigation.

The correct answer is C:
At present, the reported SCD rate in G+/LVH− subjects is extremely low, and therefore both the AHA/ACC and ESC recommendations don't advise to routinely exclude G+/LVH− subjects from competitive sports. If the results of extensive cardiac investigations, including cardiac magnetic resonance imaging, Holter monitoring, and exercise testing are normal, subjects can enroll in competitive sports with regular, i.e., yearly, evaluation.

6. What are the advantages of presymptomatic genetic testing in first-degree relatives of a HCM patient with a definitive mutation?
   A. The advantages of presymptomatic genetic testing are identifying genotype-positive family members at risk of HCM and reassuring genotype-negative relatives.
   B. The advantages of presymptomatic genetic testing are identifying genotype-positive family members and prediction of the disease development and prognosis of HCM.
   C. There are no advantages of presymptomatic genetic testing.

The correct answer is A:
Currently, the power of HCM mutational analysis lies most prominently in identifying G+ family members who are at risk for developing disease and excluding unaffected, genotype-negative (G-) relatives of further cardiac evaluation; this is information not achievable otherwise. Given the extensive clinical heterogeneity of HCM, individual prognostic prediction is mainly based on the phenotype found.

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