

Commentary

Genetic counselling for hypertrophic cardiomyopathy: are we ready for it?

Hans-Peter Vosberg

Max-Planck-Institute for Physiological and Clinical Research, Bad Nauheim, Germany

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Abstract

Hypertrophic cardiomyopathy (HCM) is a dominant genetic disorder of the myocardium associated with dysfunctional contractile proteins. The major risk of HCM is sudden cardiac death, which may occur even in asymptomatic carriers. Causes are highly heterogeneous. Over 140 different mutations in nine sarcomeric genes have been described to date. The majority of cases (80% or more) may eventually be traced to one of these genes. Although genetic counselling is suggested even if mutations are not known, molecular diagnosis implies new options such as carrier identification or – theoretically – preclinical risk stratification. A scheme according to which cardiologists and clinical and molecular geneticists could cooperate in counselling patients and managing HCM clinically is proposed.

Keywords: Genetic counselling, hypertrophic cardiomyopathy, risk stratification, sarcomeric genes, sudden cardiac death.

Introduction

A young boy of 13 collapsed while running after the schoolbus. He could be resuscitated, but at the price of crippling brain damage. Clinical and genetic analysis subsequently revealed that he and his father were predisposed to hypertrophic cardiomyopathy (HCM): they were carriers of a missense mutation in the α -tropomyosin gene. The boy had no symptoms before he collapsed, whereas his father (in his early forties) had borderline myocardial hypertrophy in the interventricular septum associated with mild symptoms of cardiac disease. A daughter, age 11, also carried the mutation, but she was entirely asymptomatic. On average, penetrance of the disease gene was incomplete in this family. The boy's collapse was presum-

ably due to an episode of extreme ventricular tachycardia. Although the familial character of the disorder was suspected for some time prior to this event, genetic counselling had not been considered before the boy experienced cardiac arrest.

In a second family the disease was associated with a high frequency of cardiac death. Three documented cases of premature sudden death in two generations, two of them in young adults, and numerous relatives being clinically affected imposed a heavy burden on the family. Early onset of the disease, syncopes, chest pain and progression to heart failure with no, or inconspicuous, hypertrophy were encountered. A few patients were only mildly

affected. A mutation in the cardiac troponin T gene was identified by genetic analysis. All first-degree relatives of the patients were seeking counselling and asked for a DNA test. They were aware that this test offered a 50% chance of excluding the carrier status for those who were asymptomatic, in particular for children of parents at risk. Hence, parents also asked on behalf of their children.

These are two different disease phenotypes randomly picked from numerous published or unpublished case reports of familial HCM. This is a heavily investigated disorder for which we have ample knowledge about causes and – to a lesser degree – about mechanisms. It is autosomal dominant and known to exist worldwide with a prevalence possibly as high as 1:500 in the general population [1]. It may occur sporadically, but in the majority of cases it is a familial condition. Onset of symptoms is normally encountered during adolescence or in young adults, but first appearances may also be experienced in later decades of life. Symptoms are usually unspecific at first, and may include breathlessness, chest pain, syncope and others. The diagnosis is confirmed by echocardiographic demonstration of myocardial hypertrophy, most frequently in the interventricular septum. Diagnostic criteria for the assessment of the disease in members of families at risk have been proposed [2].

Causes and mechanisms

A major dysfunction in cardiac performance is impaired relaxation during diastole. Systolic functions are (at least in the beginning) not affected [3]. The most serious complication of HCM is ventricular fibrillation, which may cause sudden cardiac death.

A typical problem is the extensive clinical variability of HCM, even within families where all patients have the same mutational background. The spectrum ranges from very mild or even asymptomatic to malignant courses. A multitude of causes has been identified. More than 100 different mutations (mostly missense mutations leading to amino acid exchanges in respective proteins) have been reported [4,5]. These mutations are in nine genes, all coding for contractile proteins – cardiac motor proteins and their control components. HCM was, therefore, defined as a disease of the sarcomere [6]. The most frequently affected genes, accounting for more than 50% of all cases, coded for β -myosin heavy chain, cardiac troponin T and myosin binding protein-C. Mutational hot spots are rare and contribute only a few percent of the total genetic load of HCM.

The mechanisms responsible for cardiac dysfunction and disease are not fully understood. Altered kinetics of cross-bridge cycling of myosin and actin filaments are probably involved [7]. Increased (or decreased) sensitivity of force development in response to calcium may be a critical

parameter [8,9]. Other calcium-dependent mechanisms influencing gene expression rather than contraction have also been discussed [10].

Diagnosis and repercussions

Since HCM is inherited, a major question bears on genetic counselling. Is it available and what will it offer to whom? The goals of counselling are, in general, the assessment of causes, which requires genetic testing of probands and family members, the determination of recurrence risks, communication about reproductive options and prenatal diagnosis, if suggested or requested.

The clinical diagnosis of HCM is made by the cardiologist who might then refer patients and families to the geneticist. Genetic tests are performed in specialised labs (of which only a few exist). The estimate of recurrence risks is easy in most instances, because the usual mode of transmission is known to be dominant. Dominant transmission (when only one parent is a carrier of the condition) means the parent has a 50% chance of transmitting the mutation to their offspring. Recessive transmission (with both parents being carriers) is extremely rare. More challenging, but also rather infrequent, are asymptomatic parents with one affected child, a condition indicative of a new, or *de novo*, mutation which originated in a single parental gamete [11,12]. Such a mutation has a negligible chance of re-occurring in siblings, but it can be passed to the next generation by carriers.

HCM is in many cases not a devastating condition and usually it does not produce symptoms in children, unlike Duchenne muscular dystrophy or cystic fibrosis. Many gene carriers have a reasonable chance of getting away with minor symptoms and normal life expectancy (see eg [13,14]); in some, however, quality of life and longevity may be severely affected. Families have been described where only 50% of gene carriers lived beyond the age of 45 years [15]. Although underlying mutations in these families are statistically characterised as malignant, it is difficult (if not impossible) to assign individual risks on the basis of a DNA test alone. Thus, in most cases of a positive HCM family history, reproductive decisions are normally not affected.

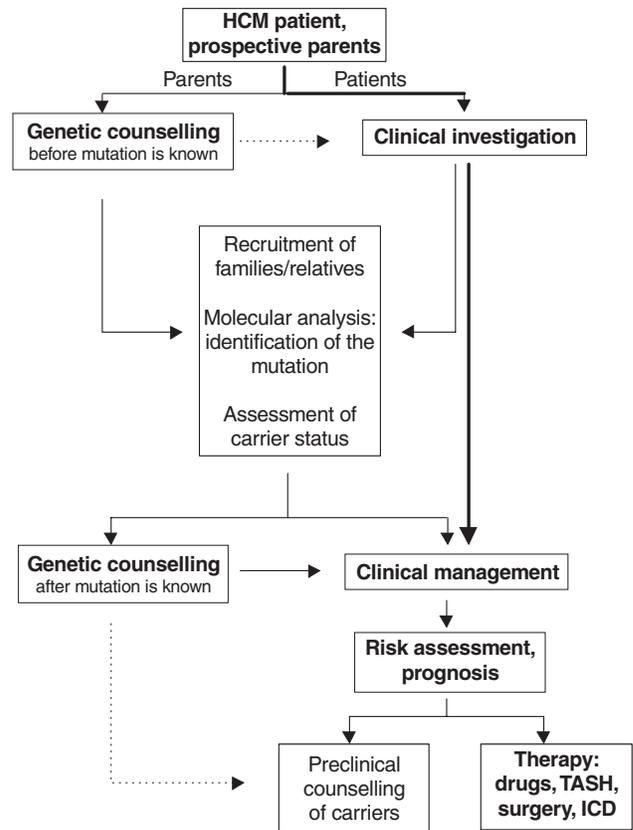
Occasionally it may happen that premature sudden death is a frequent event imposing an unusually high psychosocial and medical burden on a family. In these cases prospective parents may wish to prevent passing the mutation to their offspring and, hence, ask for a prenatal DNA test with the option to terminate a 'carrier' pregnancy. The test depends on knowledge of the mutation. If that information is not available, testing will normally be futile because of the current slow speed of screening genes for unidentified DNA changes. If the mutation is known, a preimplantation diagnosis after *in*

vitro fertilisation may be considered as an alternative to prenatal testing [16].

In addition to professional counselling by geneticists, a practice of informal communication developed in some institutions since the main reference person for HCM patients and their families is the cardiologist whom they see on a regular basis to control the progression of the disease and the efficacy of therapy. Diagnostic efforts require informed consent by the patient; this consent frequently covers the submission of blood samples to a specialised molecular lab for a DNA test, as part of a new clinical routine which should, but which frequently does not, include genetic counsel. This practice of quasi automatic DNA testing may not be the same in all countries, but at least in some places the geneticist is not regularly consulted. The reason is simply that it is the cardiologist, not the clinical geneticist, who has the main responsibility for the patient. The recognition that a patient is at high risk depends on identification of clinical markers such as excessive hypertrophy [17] or nonsustained ventricular tachycardia [18] rather than on the demonstration of a particular mutation.

The lack of appropriate counselling has, however, certain drawbacks. Normally it is the genetic counsellor, not the clinician, who is trained to explain the meaning of genetic risks in terms understandable to patients. The burden of the disease must be clearly communicated and reproductive options have to be discussed. Reassurance should be given to those who worry about the consequences of their genetic status. It may be added that these discussions should also cover health and life insurance problems which will probably become relevant in the future, in particular for those who have no symptoms but who are at risk to be gene carriers. Potential gene carriers with no symptoms may increasingly tend to refuse participation in familial screening to avoid unfavourable terms of insurance, a conflict to which young adults in their early career stages are exposed more than others. (The strategy of avoiding knowledge about genetic risks would, however, only work in the absence of compulsory testing.). A serious question is whether DNA tests should be applied in children. They usually have no symptoms, and the test may therefore stigmatise them as gene carriers – in the absence of efficient prevention ([19], but see [20]). One should realise, however, that careful investigation of the preclinical stages of HCM will eventually help to advance knowledge of the natural history of the disease – a prerequisite to the development of improved protocols for prevention and therapy of this disorder. At present, in the absence of formal constraints to apply DNA tests to entire families, it can be foreseen and it seems inevitable that in a growing number of families all gene carriers will become known. As a rule (with occasional exceptions), both cardiologists and parents want to know. Appropriate communication with genetic

Figure 1



A scheme for cooperative interaction between cardiologists, clinical and molecular geneticists and those affected by HCM. Note: Prenatal diagnosis is not usually involved. TASH, transcatheter ablation of septum hypertrophy (by alcohol); ICD, implantable cardioverter defibrillator.

counsellors should help to alleviate psychosocial and emotional problems associated with the assessment of the carrier status, in particular in the young. A scheme according to which cardiologists, clinical and molecular geneticists could cooperate in both aspects, counselling patients and managing HCM clinically, is presented in Fig. 1. This scheme emphasises the different branches involved in management and counselling of HCM, with a predominance on the side of clinical activities. Prenatal diagnosis – which in our experience is almost never requested – has not been considered in this scheme as a major topic.

Conclusion

A DNA test can confirm the diagnosis; however, in most cases, a sarcomeric mutation does not by itself fully explain the pathogenic character of the disease. For one, many families have their own 'private' mutation, and for another, evidence is accumulating that other components, for example genetic polymorphisms, which contribute to cardiovascular performance without being bona fide disease genes, also affect penetrance and severity of the disease. It

is likely that non-Mendelian, multifactorial conditions modify the natural history of HCM [21] which otherwise is, by definition, a Mendelian disorder. The difficulties of drawing firm conclusions from knowledge of a mutation in a distinct disease-related gene should not excuse a lack of competent genetic counselling. Counselling is more than mutation detection. Appropriate activities depend on the existence of an organisation comprising cardiologists, a molecular laboratory, and clinical geneticists, as shown in the flow diagram of Fig. 1. Such an organization is not everywhere at hand. Since, however, knowledge and tools are in principle available, the appropriate answer to the initial question of whether to provide genetic counselling “ready or not” is that there is no good reason not to be ready.

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Author affiliation: Max-Planck-Institute for Physiological and Clinical Research, Bad Nauheim, Germany

Correspondence: Prof. Dr. med. Hans-Peter Vosberg, Max-Planck-Institute for Physiological and Clinical Research, Department of Experimental Cardiology, Benekestr. 2, D-61231 Bad Nauheim, Germany. Tel: (+49) 6032 705 455; fax: (+49) 6032 705 458; e-mail: hvosberg@kerckhoff.mpg.de