Current perspectives

The future in hypertrophic cardiomyopathy: important clues and potential advances from an understanding of the genotype phenotype relationship

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Key words:
Hypertrophic cardiomyopathy; Genotype/phenotype relationship; Genetics.

Hypertrophic cardiomyopathy is a familial heart muscle disorder caused by sarcomeric contractile protein gene abnormalities, nine of which have been recognised to date. The condition has been defined clinically and pathologically as a syndrome of unexplained myocardial hypertrophy, which is associated with characteristic pathophysiological (diastolic dysfunction, ischaemia, altered vascular responses) and pathological (myocyte disarray, increased loose connective tissue, small vessel disease) abnormalities. Disease expression is variable. Preliminary observations suggest that the marked clinical and pathological heterogeneity, which has long caused controversy in hypertrophic cardiomyopathy, is at least, in part, a function of the disease-causing gene. The clinical syndrome of hypertrophic cardiomyopathy can then be seen as nine or more different, but related diseases. Greater understanding of these diseases will require broader application of DNA diagnostic testing, as well as careful and accurate evaluation of the clinical/pathological phenotype of hypertrophic cardiomyopathy.

(Ital Heart J 2000; 1 (1): 17-20)

Received December 21, 1999; accepted December 22, 1999.

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Historical perspective

The modern era for hypertrophic cardiomyopathy (HCM) began over 40 years ago with the recognition by astute clinicians and pathologists of the most striking features of the condition asymmetric septal hypertrophy, left ventricular outflow tract obstruction and premature sudden death[1-3]. For the past two decades HCM has been clinically defined by the echocardiographic demonstration of unexplained left ventricular hypertrophy. Disease prevalence using conventional criteria is approximately 1:500 in young adults; HCM is then much more common than is generally recognised[4]. Clinical presentation is with symptoms of chest pain, dyspnoea, palpitation or impaired consciousness; the not infrequent initial presentation with sudden death maintains HCM as one of the leading causes of unexpected sudden death in the young[1,2]. It is probable, however, that many, if not most affected individuals do not experience disease-related symptoms or complications, and go unrecognised throughout their lives. This is supported by the observation that even in referral centres the majority of patients do not experience significant symptoms, and do not have risk markers for sudden death. That said, when exercise capacity is assessed objectively the majority have a peak oxygen consumption of < 70% predicted for gender, age and size[5]. This reflects acceptance and adaptation to limitations that are of gradual onset from a young age, and presumably related to disease expression during adolescence involving both central and peripheral mechanisms.

Prevention of sudden death

The prevention of complications, particularly sudden death, is the most important and neglected challenge of management[6]. Annual mortality rates from sudden death vary from < 0.5 to 6% and are highest in the young. The impact of the potential bias of a literature generated from referral institutions has been highlighted to underscore the fact that most patients with HCM do not experience premature sudden death[7]. Our experience in a HCM referral centre (St. George s Hospital, London, UK) during the

past decade reveals a 1% annual mortality from sudden death in a cohort of 658 patients approximately 25% of whom received amiodarone[8]. This is similar to that of a so-called unselected population seen in Florence (Italy) in which analogous efforts were made to identify and treat high-risk patients, with over 30% receiving amiodarone. Though the mechanism and treatment of obstruction continues to fascinate and pre-occupy perceptions of HCM, sudden death remains the most important clinical aspect of the disease. This is now particularly germane as it is feasible to identify high-risk patients (non-invasive risk stratification) and prevent sudden death (implantable cardioverter-defibrillator, amiodarone) and if the single event or hot phase is survived a normal, or near-normal longevity can reasonably be anticipated[9-11].

Heterogeneity

HCM is a disease which has featured controversy and variable perceptions in relation to pathophysiological and management issues[12]. This is contributed to by the marked heterogeneity of the clinical phenotype. Left ventricular hypertrophy may be absent, mild, severe and confined to the base, apex, specific segments or involve the entire left ventricle. Left ventricular systolic function may be hyperdynamic , normal or impaired. The 10-15% who develop left ventricular failure with wall thinning and cavity enlargement do not resemble the 20% with hyperdynamic systolic function, systolic anterior motion of the mitral valve and outflow tract obstruction, though they may reflect different stages of the same disease. Diastolic abnormalities are common and a key determinant of symptoms and functional limitation but they do not appear to correlate well with the severity of left ventricular hypertrophy or prognosis[13]. Indeed, many patients with familial HCM have mild, or no hypertrophy, but resemble restrictive cardiomyopathy with atrial dilatation, congestion and atrial fibrillation[14]. Other important pathophysiological determinants of symptoms and prognosis, including myocardial ischaemia, altered vascular responses and arrhythmia, also exhibit marked clinical heterogeneity and the presence and severity of these features are not a simple function of morphology and haemodynamics[15]. The pathological phenotype is also characterised by heterogeneity in the severity of the classical triad of histological diagnostic features, myocyte disarray, increased loose connective tissue and small vessel disease. The extent of disarray, the hallmark feature, which may be present in 5-30% of the myocardium, correlates poorly with the severity and distribution of myocardial thickening. Again, families with multiple sudden deaths are recognised in which autopsy examination reveals severe myocyte disarray without increased heart weight or segmental myocardial wall thickness[14,16]. The student of HCM is left with the question What determines the marked clinical and pathological heterogeneity that is a hallmark of the disease? .

Hypertrophic cardiomyopathy a disease of the sarcomere

The past decade has seen the definition of HCM as a disease of the sarcomere as a consequence of gene identification studies in well characterised large families[17]. Mutations in nine different sarcomeric contractile and/or structural protein genes have been identified[17-19]. The gene abnormalities relate to thick filament (b-myosin heavy chain-bMHC, essential and regulatory light chain) and thin filament function (troponin I and T, and tropomyosin) and the scaffolding or structural skeleton of the sarcomere (myosin binding protein C-MyBPC, cardiac actin and titin). The thick and thin filament mutations are predominantly single nucleotide substitutions (missense) which occur at binding sites of the actin-troponin-tropomyosin complex to myosin heavy chain or of bMHC to ATP and which appear to cause disease by a poison polypeptide effect. The MyBPC mutations are predominantly deletions which result in a truncated protein and low levels or the absence of detectable mutant protein in myocardial tissue. The mechanism of disease expression for MyBPC mutations probably relates to protein degradation or impaired synthesis resulting in a lack of protein and impaired filament assembly in the sarcomere[20].

Hypertrophic cardiomyopathy nine different but related diseases

The majority of families with bMHC, MyBPC and troponin T disease have their own private mutation. Gene defects of these three proteins cause approximately 60% of HCM. The relatively small number of genotyped families (< 100 published) and the allelic heterogeneity has limited assessment of the genotype/phenotype relation. Nevertheless, information is accumulating, to indicate that cardiac troponin T and several bMHC mutations (e.g. Arg403Glu, Arg453Cys) are associated with adverse prognosis and premature sudden death while MyBPC mutations typically cause disease in the later decades and not during adolescence[20-22]. The full extent to which the genetic heterogeneity accounts for the clinical and pathological heterogeneity remains to be determined. The emerging information, however, indicates that the heterogeneous clinical syndrome of HCM can be viewed as nine or more different but related disorders of sarcomere function. In the long QT syndrome, which is now recognised to be an ion channel disease, the effect of the specific potassium and sodium channel mutations on the action potential can be examined by microelectrode studies[23]. The measured abnormalities in current flow begin to explain pathogenesis and aspects of the phenotype. The sarcomere cannot be as readily examined as the action potential; in HCM how sarcomeric protein gene defects cause disease is less

well understood. *In vitro* studies of muscle in bMHC patients reveal that myosin generates less force; these data have led to the hypocontractile hypothesis by which the decreased force provides the stimulus for compensatory hypertrophy[24,25]. The studies of muscle function, however, show variable results for the different genes and there is limited pathogenetic information as to how mutations cause disease.

Clinical impact of genetic evaluation

The advent of the molecular genetic era in HCM has increased awareness of the disease, with recognition of its risks and of the familial basis. Genetic counselling with information particularly relating to disease risk for offspring and ECG and echocardiographic evaluation of family members is now accepted routine. Detailed genetic studies of families have also revealed that true sporadic disease is rare (< 10%) and is caused by the same gene defects as familial disease[26]. The clinical implication for the proband is that there is an approximately 90% chance the disease-causing gene was inherited. Recognition of the high probability of disease within families has led to the application of new diagnostic criteria, whereby otherwise unexplained non-specific ECG and echo abnormalities are considered to reflect gene carrier status[27]. Preliminary studies suggest that this proposal/practice is appropriate though the clinical, prognostic and management implications of recognition of early or incomplete disease expression remains to be assessed[28]. Family studies have also documented non-penetrance (i.e. gene carriers who have normal ECG and echo) in up to 25% of some families. Preliminary studies suggest non-penetrance occurs with troponin T and tropomyosin and a small number of the bMHC mutations while limited information is available for the other recognised gene defects[17,20-23]. The preliminary understanding of the genotype/phenotype relation for cardiac troponin T and MyBPC disease is beginning to impact on clinical practice. Recognition that MyBPC mutations cause late-onset disease has altered counselling in the context of documented or apparent adult onset disease development[20]. The application of more sensitive diagnostic criteria is especially relevant in families with troponin T disease where premature sudden death may occur with minimal left ventricular hypertrophy on echo or normal, or near-normal heart weight at autopsy[14,16].

The clinical impact of the molecular genetic advances in HCM, however, will remain limited until DNA diagnostic testing becomes clinically available and not just a spin off of research activities in a few centres. Current methods for genotyping are not practical for service provision but the technology for efficient and accurate genotyping using automated systems (robotics, chips) is on the immediate horizon. The clinical structures to apply genetic diagnosis for HCM, as well as for other inherited cardiovascular diseases however, will need to be developed. The collaboration of cardiovascular physicians, geneticists and counsellors will be required to advise, educate and support patients as a molecular diagnosis will have clinical, prognostic, ethical and other practical (e.g. insurability, employability) implications.

The future

Recognition of the molecular genetic aetiology of HCM raises the spectre of gene therapy . What is the potential for understanding pathogenesis and the development of new treatments, molecular or otherwise? There is emerging precise information for aetiology (the genotypes) and the end product (the phenotypes) but pathogenesis remains speculative. What distinguishes the functional consequences (at the sarcomeric level) of a mild vs severe bMHC mutation? How does cardiac troponin T disease cause extensive myocyte disarray with minimal, or no myocardial hypertrophy? What are the determinants of age-related disease expression in adolescents (bMHC) vs older adults (MyBPC)? The answers will come from understanding pathogenesis but the questions will need to be framed by a detailed knowledge of the genotype/phenotype differences. Currently major efforts are expended on the development of transgenic animals with different disease-causing mutations[29,30]. This will hopefully elucidate the effects of the different mutations on sarcomere function. The use of small transgenic animals to study the phenotype may provide clues in selected circumstances but ultimately, knowledge in man of the phenotypic differences as a consequence of different gene abnormalities will be essential to understanding disease pathogenesis and the determinants of disease expression. This will be essential for the development of treatments which will modify the pathogenetic determinants of disease expression and risk. The discovery of disease-causing genes was an important first step on a much longer trek which to be successful will need to be based on a detailed understanding of the genotype/phenotype relation.

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