Hypertrophic cardiomyopathy: pathological features and molecular pathogenesis

Hipertrofik kardiyomiyopati: patolojik özellikler ve moleküler patogenez

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ABSTRACT

Hypertrophic cardiomyopathy (HCM) is a heterogeneous genetic cardiac disorder with various genotypic and phenotypic manifestations, and is often a diagnostic challenge. Although more than forty years have passed since the first description of HCM, a variety of mutations in genes encoding sarcomeric proteins, that cause the disease have been defined by laboratory and clinical studies over the past few years. The fact that HCM is the most common cause of sudden death in young competitive athletes and that, it is actually an important cause of morbidity and mortality in people of all ages, has made the researchers to concentrate more on the molecular basis and treatment strategies of the disease. This study aims to summarize both pathological features and rapidly evolving molecular genetics of HCM, and so to understand this not infrequently seen, complex disorder better. *(Anadolu Kardiyol Derg 2004; 4: 327-30)*

Key words: Hypertrophic cardiomyopathy, genotype, phenotype

ÖZET

Hipertrofik kardiyomiyopati (HKM), çok çeşitli genotip ve fenotip özellikler gösteren ve bu nedenle sıklıkla tanıda karmaşa oluşabilen heterojen bir genetik kalp hastalığıdır. Hipertrofik ardiyomiyopatinin tanımlanmasının üzerinden kırk yıldan fazla bir zaman geçmiş olmasına rağmen, hastalığa neden olan sarkomer protein genlerindeki mutasyonlar ancak son yıllardaki laboratuvar ve klinik çalışmalarla ortaya konabilmiştir. Hipertrofik kardiyomiyopatinin genç sporcularda ani ölümlerin en sık görülen nedeni ve bütün yaş gruplarında morbidite ve mortalitenin en önemli etkeni olması, araştırıcıların hastalığın moleküler temeli ve tedavisi konusunda yoğunlaşmalarına yol açmıştır. Bu çalışma, HKM'nin patolojik özellikleri ile moleküler genetiğindeki gelişmeleri özetlemeyi ve böylece az sıklıkta gözlenmeyen bu karmaşık hastalığın daha iyi anlaşılmasını amaçlamaktadır. *(Anadolu Kardiyol Derg 2004; 4: 327-30)*

Anahtar kelimeler: Hipertrofik kardiyomiyopati, genotip, fenotip

Introduction

Hypertrophic cardiomyopathy (HCM) is a relatively common genetic cardiac disorder with heterogeneous expression, which primarily affects myocytes. The disease is characterized by myocardial hypertrophy, abnormal diastolic filling, and in about one third of cases, intermittent left ventricular outflow obstruction. The myocardial hypertrophy, which involves left and/or right ventricle, is usually asymmetric, and sometimes includes interventricular septum as well. Impaired diastolic filling, due to the massively hypertrophied left ventricle causes reduced chamber size and poor compliance with reduced stroke volume. In approximately half of patients the disease is familial, and the pattern of inheritance is autosomal dominant with variable expression (1,2). In order to make a definitive diagnosis, diseases, which produce hypertrophy including systemic hypertension, coronary vascular disease, aortic valvular disease, aortic coarctation and congenital heart diseases should be excluded (3).

Morphologic Features

Pathological features of HCM are quite well defined. The most frequently observed, characteristic morphologic abnormality of HCM is massive myocardial hypertrophy, which is more prominent in the left ventricle (LV) rather than the right (2-4). Since left-ventricular cavity usually has reduced or normal size, the increase in LV mass is almost always due to the increase in the wall mass (3,5). The distribution of hypertrophy is characteristically asymmetric, with the anterior septum usually the predominant site, although a few patients may show symmetric (concentric) pattern as well. If hypertrophy is mainly observed in the septum, the condition is termed "asymmetric septal hypertrophy" (ASH) (2,4,6).

The atriums are also dilated and frequently hypertrophic. The causes of changes seen in the atriums are, high resistance and atrioventricular valvular insufficiency, which occurs against ventricular filling due to diastolic dysfunction (4). In addition to these, thickening and stretching of the mitral leaflets, as well

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as fibrous areas in some sections of the LV wall may also be observed (3,5). The distribution and the shape of LV hypertrophy may differ from patient to patient (7). The observed wall thickness of LV is approximately 21-22 mm. The thickness is increased in some patients, and in some, it is within limits observed in any other cardiac patient. The highest value reported until now is 60 mm. This variation in the morphological expression of HCM is seen even in first-degree relatives (5,8,9).

A similar degree of thickening is not observed in all segments of the LV wall. In most patients (55-60%), the hypertrophy is seen in interventricular septum (IVS) and anterior ventricular septum. There is no hypertrophy at the posterior segment (3-5). On cross-section, it is observed that the ventricular cavity has lost its usual round-to-ovoid shape and, due to bulging of the ventricular septum into the lumen, it has compressed into a banana-like configuration (2). Asymmetric LV hypertrophy is not specific only to HCM. Septal hypertrophy may be observed in 5-10 % of patients with congenital or subsequent defects (particularly in patients with increased right ventricular load) (4).

The HCM type, which is characterized by inappropriate myocardial hypertrophy involving the apex of the left ventricle, is called "apical HCM". This condition is mostly seen in Japan and apical HCM is diagnosed in an approximately 25 % of Japanese HCM patients. It is quite rare in other regions. Typical characteristics include a spade-like configuration of the LV during angiography, a giant negative T wave in the precordial electrocardiographic (ECG) leads, absence of intraventricular pressure gradient, and mild symptoms with a generally benign clinical course (4,5).

There are two other HCM types observed particularly in elderly women. "Hypertensive HCM" is related to hypertension as the name implies, and is characterized by severe concentric LV hypertrophy and reduced LV cavity. The most prominent feature of the second type of HCM is reduced LV cavity. Relatively mild hypertrophy, movement of the mitral valve towards the anterior side, broad submitral calcification and LV outflow gradient, contribute to this feature. Symptoms progress in the course of time. In elderly HCM patients there is a septal protrusion localized beneath the aortic valve, in contrast to the young patients (4).

Hypertrophic cardiomyopathy may appear as a congenital heart abnormality as well. A phenotypic appearance like thickness of the LV wall occurs during fetal development. The disease can be observed during or shortly after birth. There are cases of HCM diagnosed infants less than 6 months of age in the literature (10). In infants, severe septal hypertrophy that is mostly concentric, congestive heart failure and outflow obstruction generally contribute to the disease. In serial echocardiographic studies it is observed that LV hypertrophy of HCM after infancy has dynamic nature. The morphological appearance of HCM is not usually completed until adolescence. There is often a spontaneous increase of wall thickness in children, as a consequence of growth and development, and this hypertrophy increases with age. In some children, ECG abnormalities may be the first clinical manifestation of HCM, and may even be observed before the echocardiographic findings. When the development is completed, progression of LV hypertrophy usually seizes (approximately 18 years of age). In adult HCM patients with symptoms, LV hypertrophy is less frequently seen as the age progresses, and it may even regress in the elderly. In patients 60 years or older >25 mm of hypertrophy is rarely seen. Usually, increase in fibrosis contributes to this condition. This inverse relationship between age and hypertrophy is tried to be explained by high early death rates in young patients with severe morphological appearance, or by unknown progressive regression in the amount of hypertrophy (3,5,8).

Many pathologic conditions totally different from HCM may show similar morphological features. This includes; hyperparathyroidism, infants of diabetic mothers, neurofibromatosis, generalized lypodystrophy, lentiginosis, pheochromocytoma, Friedreich's ataxia and Noonan syndrome. Rarely, findings of HCM may be imitated by amyloid, glycogen storage disease or tumor invasion (4).

Histology

Patients with HCM have characteristic microscopic features, as a result of destruction of the myocardial structure (3,5,11,12). Histological features consistent with HCM are as follows: 1) myocyte disarray 2) interstitial fibrosis 3) small intramural coronary artery abnormalities

4) marked myocyte hypertrophy (2,3,7,13,14). Cellular disarray is present in nearly 95% of HCM patients, and may be widely distributed, occupying substantial portions of LV wall

(33% in the septum, 25% in the free wall). In most HCM patients ≥ 5% of the myocardium is affected (3-6,8,15).

In a normal heart, the myocardium consists of bundles of myocytes separated by fibrous bands. Transverse muscle fibers are in the central portion of the ventricle wall, while perpendicular and oblique fibers are in the inner and outer edges. Transverse fibers of the central portion extend into the LV free wall and the ventricular septum, surrounding the LV cavity (12,16). Myocyte disarray may occur also in other forms of hypertrophy and in normal hearts and is not specific to this disorder, but it is generally more extensive (about 30% to 50% of the myocardium) in HCM when compared to regular hypertrophy (13). Transverse diameters of many myocytes of the ventricular septum and LV free wall increase, nearly by 10 to 20 times and the nuclei become hyperchromatic. As a consequence of cellular disarray, multiple intercellular connections cause a chaotic alignment at oblique and perpendicular angles (3,6,8,11). Ultrastructurally, there is distortion of the shapes of myofibrils and myofilaments and they contain disorganized Z bands (17). On superficial sections of hearts of HCM patients, it is observed that the structure between ventricular septum and LV free wall does not extend regularly, instead, a fibril band is found extending from the ventricular septum to the right ventricle (12).

Necropsy studies of HCM patients usually reveal a fibrous tissue in the LV. The distribution and severity of fibrosis is quite variable, and it may extend from the interstitial to the perivascular layer. The amount of fibrosis increases as it reaches the endocardium, and it is more prominent in the IVS rather than the LV free wall. These areas cause stiffening of the ventricles to thus resulting in impaired ventricle relaxation. It is considered that the fibrous tissue formation in HCM patients is a consequence of pre-existing myocardial ischemia or some cardiomyopathic conditions. It is also suggested that the occurrence of fibrosis in the myocardium is related to apoptosis and that, genetically programmed cell death in myocytes causes fibrosis (3,5,12,17,18).

In nearly half of HCM patients, there are abnormal coronary arteries with thickened walls (subsequent to increase in colla-

gen fibers of the intima and the media layers) and narrowed lumens. Abnormal coronary arteries are often located in the ventricular septum. These vessels are usually within the fibrous tissue or in proximity of these areas (4,5,7,8).

Primary structural abnormalities of the mitral valve are characteristic features in most HCM patients. In about 1/3 of the patients there are changes in both the shape and size of the mitral valves, with an increase in the valve area. These changes may occur in both anterior and posterior leaflets or in only one leaflet being asymmetric and segmental. Also, some HCM patients show congenital malformation of the mitral valve. This malformation includes abnormal localization of the papillary muscle towards the anterior mitral leaflet, due to a pause in the embryonic development (5,8).

In some adolescents with the early onset of HCM due to metabolic or mitochondrial diseases, there is a prominent glycogen infiltration in the myocardium, and a number of abnormal mitochondria may also be observed (3,19).

Molecular Genetics

About 55% of HCM cases are familial and 45 % are sporadic. About 75% of the familial form of HCM reveal autosomal dominant pattern of inheritance (7). Until recently, more than 100 mutations in 12 different genes have been identified in HCM patients. Ten of these genes encode protein components of the sarcomere. The recently identified PRKA2 gene encodes the γ2 subunit of protein kinase activated by AMP (AMPK) (20); and MLP gene encodes the major nuclear regulator of myogenic differentiation, which is human muscle LIM protein (21). These all indicate the genetic heterogeneity of HCM.

The other genes, which encode sarcomeric proteins related to the disease are; β-myosin heavy chain (MYH7); α-myosin heavy chain (MYH6); cardiac troponin T (TNNT2); cardiac troponin I (TNNI3); α-tropomyosin (TPM1); myosin binding protein C (MYBPC3); essential myosin light chain (EMLC); regulatory myosin light chain (RMLC); cardiac titin (TTN) and α-cardiac actin (ACTC). In 35% of patients, HCM occurs as a result of mutations in β-MHC gene. MYBPC3, TNNT2 and TPM1 genes also may have mutations and end up with the disease, with a frequency of 20%, 15% and 3%, respectively (22).

Subsequent to mutations in a single gene, diverse phenotypes with various clinical appearances and various degrees of hypertrophy occur. Some mutations in MYH7 gene have poor prognosis, while some have moderate and some have good prognosis. Although mutations in TNNT2 gene usually cause mild hypertrophy they have poor prognosis with a high risk of sudden death. In contrary, some genes and mutations show rather good prognosis. It is possible to determine the mutations in DNA and thus enabling us to diagnose the disease in childhood, even before clinical symptoms occur and to screen nearly all of the mutations, which cause HCM (8). In some patients who have mutations in a single gene, ECG abnormalities may be observed in the absence of echocardiographic findings. These unexplained ECG abnormalities present in the first-degree relatives of HCM patients may indicate a pre-clinical condition or a carrier status.

Hypertrophic cardiomyopathy may also show inheritance similar to mitochondrial diseases which are inherited maternally. The mitochondrial DNA of the mother is transmitted to all children, while the father rarely transmits his mitochondrial DNA. Maternal inheritance often resembles autosomal dominant pattern of inheritance except that sick parents of sick children are the mothers. There are also patients with autosomal recessive pattern of inheritance (3,23).

The exact reason of myocardial hypertrophy in HCM is not known. Many explanations exist to clarify hypertrophy and other histopathological abnormalities. It is suggested that due to increase in the number of calcium channels in the cell wall, inflow of calcium to the cell increases, and the increased intracellular calcium concentration causes hypertrophy and cellular disarray (4).

It has been suggested that, abnormalities in the catecholamine metabolism play an important role in HCM pathogenesis (7). The abnormality of the sympathetic stimulation, due to increased response of heart to catecholamines, overproduction of circulating catecholamines or decreased neural uptake of cardiac norepinephrine may cause hypertrophy. At the same time increase in sensitivity to catecholamines impairs regression of septal hypertrophy, resulting in myocardial fibers disarray in fetal life. As evidence, the Mendelian trait of the disease as well as the myocardial fibers disarray observed in normal hearts of adolescents has been brought up (7).

One of the opinions about the etiology of HCM is that, impaired dilatation of the abnormally thickened intramural coronary arteries may cause myocardial ischemia and subsequently compensatory hypertrophy of the myocardium. Another view is that, subendocardial ischemia due to abnormalities of the microcirculation ends up with diastolic stiffness. Also some structural abnormalities of the septum cause myocardial cellular hypertrophy and disorganization (4).

The pathological conditions of HCM are not only due to influences in sarcomeric proteins, there are abnormalities in the mitral valve, intramural coronary arteries and collagen tissue as well. So, phenotypic expression of HCM is not only explained by mutations in sarcomeric genes. It is suggested that some other genetic factors ("completing" genes) and environmental variables not defined yet, may play a role in the etiology of the disease, and it is expected that within five years, techniques for genetic diagnosis will become more generally available and hence more generally applicable (5,24)

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