HYPERTROPHIC CARDIOMYOPATHY

Hypertrophic cardiomyopathy: an introduction to pathology and pathogenesis

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Hypertrophic cardiomyopathy is defined as myocardial hypertrophy for which no cause, such as hypertension or valve disease, is present. By implication the abnormality lies within the myocardium itself. Many conditions broadly fall within this classification (fig 1), but central to current thinking is a familial genetic form about which a great deal is now known. Much of this section of the supplement is concerned with the recent advances in knowledge of the genetic mechanisms and treatment of familial hypertrophic cardiomyopathy. A complete understanding of this familial disease, now known to be caused by at least four genes (fig 1), may help to elucidate the other forms of hypertrophic myocardial response.

By producing septal hypertrophy some diseases mimic hypertrophic cardiomyopathy, particularly on echocardiographic examination, without having any mechanistic association with true hypertrophic cardiomyopathy.

The phenotypic expression of other genetic familial diseases in the heart can resemble familial cardiomyopathy. The gene responsible for Friedreich's ataxia lies on chromosome 9 and must therefore be totally unrelated to the genes so far identified that produce familial hypertrophic cardiomyopathy. The gene for Noonan's syndrome has

been tentatively placed on chromosome 15 and could therefore share a gene abnormality with one form of familial hypertrophic cardiomyopathy.

Some people, for example athletes, develop an exaggerated hypertrophic response that can be difficult to distinguish from familial hypertrophic cardiomyopathy. So far little is known about the genes that control the normal hypertrophic response in the myocardium but polymorphisms in the angiotensin converting enzyme gene may be involved.

Familial hypertrophic cardiomyopathy

Since Teare first described this disease in 1958 knowledge about it has grown rapidly. Contrast the view of the disease held in the 1960s with that held today. The disease was first recognised as being asymmetrical and septal and this is reflected in the names used at the time. Today the phenotypic expression is recognised to be bewilderingly large. Such knowledge largely comes from studies of whole families, and it is clear that an identical gene abnormality can produce very diverse effects even in siblings brought up in the same household.

Range of phenotypic expression

The disease is often asymmetrical and it can affect different regions of the left ventricle. The septum is most commonly affected, with or without involvement of either the anterior wall or posterior wall in continuity. Any segment of the left ventricular free wall can be involved. The right ventricular anterior wall is often affected when there is septal involvement. Symmetrical involvement of the left ventricle is common. A particular form of regional involvement affects the apex but spares the upper portion of the septum. Reported frequencies of these different forms vary widely depending on whether a series is dominated by clinical or by pathological cases.

The most confusing aspect is that the phenotype can change with time. Hypertrophy that is recognised as wall thickening on echocardiography develops in the adolescent growth phase and usually persists throughout adult life. In some patients, however, the septum later thins and the left ventricle

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Figure 1 Classification of the causes of myocardial hypertrophy that can be confused with or may be related to familial hypertrophic cardiomyopathy.

Figure 2 Myocardium stained to show myofibrillary organisation. In the central area myofibrils cross each other in a disorganised manner. In the adjacent areas on each side the appearance is more normal with parallel arrays of myofibrils. (PTAH stain; original magnification, $\times 240$.)

becomes more like that seen in dilated cardiomyopathy. A major factor in this development is the replacement of muscle by fibrous tissue, possibly because the small intramyocardial arteries are obliterated. The small number of cases with no increase in left ventricular mass or wall thickness despite a histological appearance of hypertrophic cardiomyopathy are another cause of confusion.

Histological characteristics

The typical case does have readily identifiable abnormal features (fig 2). These occur at three levels. Within the myocyte the myofibrillary arrangement itself may be abnormal with loss of the usual parallel arrays. This change, though it is very sensitive for the diagnosis, is of low specificity. The second level is at the myocyte to myocyte arrangement. In hypertrophic cardiomyopathy the individual cells are misshapen and the lateral connections to adjacent myocytes are increased. This change leads to circular

arrays of myocytes around central foci of connective tissue and is the most sensitive and specific change. Finally there may be the abnormal arrangement of large muscle bundles crossing each other. This change is of low specificity, being found, for example, in the outflow tract of the right ventricle in tetralogy of Fallot.

The sensitivity and specificity of all these changes taken together have been evaluated in necropsy material. Hearts from control cases—that is, hypertrophy with a known cause—and normal hearts do show individual foci of disarray. Such foci are particularly common in the areas where the right ventricle is attached to the septum. They can usually be encompassed within a single low power microscopic field. If disarray is present in more than 20% of the area of the myocardial slice specificity is excellent. Diagnosis based on a biopsy sample is unreliable because too little tissue is available to quantify and to be certain of the extent of disarray.

Pathogenesis

This supplement reviews the new data on the genetic abnormalities of myofibrillary proteins in hypertrophic cardiomyopathy. The data on abnormalities of heavy chain myosin are clear cut: the abnormal protein causes the disease and is not simply a concomitant phenomenon. How could such an abnormality explain the morphological features? One explanation is that the abnormal myosin interferes with the normal spatial arrangement of the myofibrils. This in turn leads to bizarre misshapen myocytes with an abnormal cell to cell arrangement. The concept that hypertrophic cardiomyopathy is a “myofibrillary dysgenesis” is enhanced by the recent discovery that two of the other genes responsible for familial hypertrophic cardiomyopathy also encode for contractile proteins. We are, however, left with a fascinating puzzle: what other factors control the phenotypic expression to produce such a diversity of disease within a family with the same abnormality of the same gene? This diversity complicates clinical management.