Hypertrophic cardiomyopathy. An historical and anatomopathological review

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Abstract

Hypertrophic cardiomyopathy (HCM) is characterized by the presence of an abnormal hypertrophy of the left ventricle (LV), without dilation, and in the absence of any condition or another cardiac or systemic disease capable of inducing such hypertrophy. This primary or idiopathic hypertrophy can occur with or without dynamic obstruction (induced by exercise) of the LV outflow tract, so in its natural history two fundamental aspects are highlighted: the production of symptoms by blocking the LV outflow tract and the occurrence of sudden cardiac death secondary to ventricular arrhythmias. This revision includes the work of different Iberoamerican investigators, who contributed in an important way to lay the groundwork of what we know nowadays as HCM. It also includes the main anatomopathological characteristics, from its initial description to the new perspective we have concerning the myofiber disarray as the main histopathologic feature. (Gac Med Mex. 2016;152:624-8)

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Background

Hypertrophic cardiomyopathy (HCM) is a disease of the myocardium which main characteristic is an abnormal ventricular hypertrophy, not related to other causes (i.e. intense physical exercise or heart diseases) known to induce hypertrophy (Fig. 1)1. Most cases of HCM are hereditary but 1) not all family members inherit the disease and 2) phenotypical expression in those affected is variable2. The entity we now refer to as HCM was described in 1907 by Schmincke as “muscular stenosis of the left outflow tract”, who published the first autopsy cases of idiopathic muscular hypertrophy in two females3. It is accepted that it corresponds to Sir Russell Brock, 50 years later, the merit for this entity to be currently better known, since he described the first series of patients with dynamic obstruction of the left ventricle (LV) outflow tract. He named it “acquired subvalvular aortic stenosis”4. Since then, this condition has received different names, including “hypertrophy of unknown cause”5, “pseudo-aortic stenosis”6 to indicate that, clinically, it mimics aortic stenosis, “asymmetric hypertrophy” to indicate that the septum is more hypertrophied than the LV free wall7, among other denominations. Although Braunwald, et al. introduced the term “idiopathic hypertrophic subaortic stenosis”8, the term that finally gain acceptance and the one we use nowadays (HCM) was coined by Cohen, et al.9.
In Mexico, the first publication on this disease was made by Fishleder, et al.\textsuperscript{10} whom, in 1962, two years before the now considered classical works by Braunwald and Cohen, reported 6 cases of HCM under the denomination of “dynamic subaortic stenosis”. With this name they want to emphasize the hemodynamical behavior (“stenosis”), its location (“subaortic”), as well as its functional nature (“dynamic”). Since current medical literature is based on English language journals, some relevant articles on HCM published in Spanish language journals before 1975 are described in table 1 as a recognition for such pioneer work on the field\textsuperscript{10-17}.

**Incidence and prevalence**

Our understanding of HCM has dramatically increased thanks to many medical advances, but mainly due to increased clinical use of genetic molecular studies and advances on imaging techniques, both in echocardiography and magnetic resonance imaging, which have considerably increased the number of diagnosed cases\textsuperscript{18}. The prevalence of HCM in Europe is estimated to be 0.33\% (166,000 patients were diagnosed in 2011). Although there are no national statistics available in Mexico, a diagnosis of HCM was confirmed in 136 patients at the Ignacio Chávez National Institute of Cardiology between 2000 and 2014, out of a total of 81,460 individuals attended for a prevalence of 0.16\% (data not published). In the same period, 467 autopsies were practiced, out of which only one case corresponded to HCM. This is not surprising; for example, in Italy, out of 54 autopsies of individuals younger than 40 years of age with sudden cardiac death (SCD) performed between 1993 and 2012, no one corresponded to HCM\textsuperscript{19}. There are several explanations for these reduced numbers of HCM findings in autopsies; one of them might be that affected subjects die outside the hospital; another, that they die of heart failure after developing dilatation and the condition being catalogued as dilated cardiomyopathy. Finally, another possibility is that SCD can be the first manifestation of the disease\textsuperscript{20}.

In countries with appropriate statistics available on SCD, HCM is one of the main causes of SCD in young subjects. Corrado, et al.\textsuperscript{21} studied the cause of SCD in individuals younger than 35 years in Italy. They found that HCM was the cause of SCD in 6.3\%, with a marked difference between athletes (2\%) and young subjects who were not athletes (7.3\%). As previously mentioned, one of the most concerning aspects both for doctors and for those who are diagnosed with the disease and their families, is the fact that SCD can be the first manifestation of the disease, even with mild exercise, not necessarily with extenuating sports activity.

**Figure 1.** A: anatomical pathology specimen of a heart with HCM showing interventricular septum significant thickening. B: interventricular septum histological slice of figure 1 A specimen, showing fiber disarray at the periphery and a fibrosis zone in the center.
Table 1. Articles on HCM published in Ibero-American journals prior to 1975

<table>
<thead>
<tr>
<th>Author</th>
<th>Date</th>
<th>Number of cases</th>
<th>Males/Females n (%)</th>
<th>Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fishleder</td>
<td>1962</td>
<td>6</td>
<td>5/1</td>
<td>Clinical (systolic murmur of low localization, without thrill or radiation to the neck, its left behavior with the Valsalva maneuver, etc.) and phonocardiographic manifestations are described, as well as the carotid sphygmogram characteristics.</td>
</tr>
<tr>
<td>Bonetti</td>
<td>1965</td>
<td>3 Males</td>
<td></td>
<td>Hemodynamic and angiocardiographic findings are described. The article points out that the left ventricular infundibulum abnormal contraction site can be visualized with cineangiography.</td>
</tr>
<tr>
<td>Glenny</td>
<td>1965</td>
<td>16 N/S</td>
<td></td>
<td>Clinical and phonocardiographic study.</td>
</tr>
<tr>
<td>Rotberg</td>
<td>1969</td>
<td>1 Female</td>
<td></td>
<td>A case is presented of double infundibular stenosis: aortic and pulmonary.</td>
</tr>
<tr>
<td>Vidne</td>
<td>1970</td>
<td>9 N/S</td>
<td></td>
<td>Surgical results with myotomy (only two linear incisions) are described in two cases, as well as resection of a portion of the hypertrophic septal mass in seven.</td>
</tr>
<tr>
<td>Skromne</td>
<td>1972</td>
<td>1 Male</td>
<td></td>
<td>Report on a 2-year 4-month old boy with Ebstein disease in whom the postmortem study also demonstrated interventricular hypertrophy (14 mm), with no apparent cause. Histopathological data consistent with HCM.</td>
</tr>
<tr>
<td>Salazar</td>
<td>1973</td>
<td>26</td>
<td>20/6</td>
<td>A series of cases with ages ranging from 3 to 67 years, with an average of 31, is described. Two families with HCM and sudden death are described.</td>
</tr>
<tr>
<td>Cueto</td>
<td>1974</td>
<td>1 Female</td>
<td></td>
<td>The case presented was a newborn clinically diagnosed with myocarditis; the necropsy confirmed obstructive HCM.</td>
</tr>
<tr>
<td>Vallés Belsué</td>
<td>1974</td>
<td>23</td>
<td>14/9</td>
<td>Left ventricle cineangiographic findings in 23 obstructive HCM cases are presented.</td>
</tr>
</tbody>
</table>

Anatomical and histopathological changes

It is generally accepted that the first who describe the histopathological features was Teare, who reported 8 cases with a “disorganized and bizarre arrangement of muscle bundles associated with hypertrophy of individual muscle fibers and their nuclei”. Since then, the literature generally emphasizes that HCM has three histopathological features (none is pathognomonic nor should be considered as gold standard): myocyte hypertrophy, myofibre disarrangement or disarray (in some areas of the heart) and interstitial and replacement fibrosis (plexiform). There are two relevant additional characteristics: The presence of abnormal intramural (intramyocardial) coronary arteries with thickened walls due to proliferation of smooth muscle and collagen in both, intima and media tunicas. This thickening reduces the lumen and could explain some exercise-related deaths. The second characteristic corresponds to structural changes of the mitral valve apparatus: (1) Anomalous...
Figure 2. Interventricular septum histological slices from figure 1 A specimen. A: with 10x enlargement, myocardial fibers disarray is shown (hematoxylin-eosin staining, 10x). B: with higher enlargement, cardiac myocytes with signs of hypertrophy are observed (hematoxylin-eosin staining, 20x).

insertions of the papillary muscle into the anterior leaflet favoring anterior displacement of the mitral valve and obstruction of the LV outflow tract\textsuperscript{26}. (2) Mitral valve elongation and thickening have been also reported. The pathologic myocardium is thought to produce an excess of paracrine growth factors, which drives this valvular growth\textsuperscript{27}. It is highly unlikely that these anomalies are secondary to mechanical or acquired factors, suggesting that HCM is not confined to cardiac muscle\textsuperscript{28}.

Hypertrophy and myofiber disarray are not uniform, they are not observed in the entire heart, and are found only in certain areas. In the interventricular septum, alterations predominate in the middle region, in comparison with right and left ventricular sides of the septum\textsuperscript{29}. For this reason, endomyocardial biopsy is not 100% sensitive, since the representative zone may not be sampled. Nunoda, et al.\textsuperscript{30} found HCM characteristic changes in 71% of their cases.

Specifically, myofiber disarray, which has been considered as a pathognomonic finding, is now questioned regarding its diagnostic value in HCM, since it has been also observed in many congenital heart diseases and also in normal hearts\textsuperscript{2} (specifically, in the septum and some small areas of the LV). It is also known that, in some areas, a disorganized histological appearance of fibers can be obtained by varying the orientation of the same tissue block with slices in parallel or cross-sectional to the heart’s axis\textsuperscript{31}.

Attempts have been made to correlate genotype with histology; for example: patients with HCM and troponin T gene mutations have more myofiber disarray and, in spite of having less fibrosis and hypertrophy than those with an unknown genotype, they were more prone to SCD\textsuperscript{32}. With the use of confocal microscopy, intercalated discs structural alterations have been found, specifically of desmosomes and gap junctions, as it was expected\textsuperscript{33}. The remodeling of gap junctions, which are in charge of electrical impulse transmission, might be the substrate to generate and maintain ventricular arrhythmias in these patients.

HCM has been known since long to be able to evolve to dilated cardiomyopathy. Hina, et al.\textsuperscript{34}, in a 6.5-year follow-up of 51 patients with HCM classical criteria, observed that LV was dilated and LV ejection fraction decreased in 8 of them (15.7%). At HCM advanced stages, large amounts of fibrous tissue appear on the LV together with thinning of the wall and dilatation of cavities. Coppini, et al.\textsuperscript{35} reported that mutations on genes that encode for thin filaments (tropomyosin, troponin, actin) are associated with greater systolic dysfunction than those affecting thick filaments (myosin).

The presence of myocardial bridges has been reported in up to 40% of cases with HCM. Although in a first report the presence of this anomaly in children was significantly associated with SCD\textsuperscript{26}, other groups have not confirmed this finding in children\textsuperscript{37} or adults\textsuperscript{38,39}.

The myocardial bridge probably represents only another phenotypical expression of this disease.

In summary, HCM is a disease that has drawn the attention of many researchers since its original description. Although most texts generally focus on Anglo-Saxon investigators’ initial contributions, here is shown that there were also important contributions of Ibero-American authors since the beginning. Clinically, this condition manifests itself in different ways, with SCD as the worst outcome. Histopathologically, in addition to the three classical features (myocyte hypertrophy, myofibre disarray and fibrosis), there are underrecognized findings that can be characteristic of the disease, such as coronary and mitral valve apparatus anomalies, which may have relevant clinical significance.
Conclusion

Hypertrophic cardiomyopathy is a disease that has drawn the attention of clinicians, surgeons and pathologists in the past. It has several anatomopathological characteristics of its own. Beyond left ventricular hypertrophy, myofiber disarray should be considered a quantitative rather than a qualitative marker for HCM. The genotype-phenotype correlation regarding different structural alterations and its clinical significance is currently being studied.

References


