Apical hypertrophic cardiomyopathy or left ventricular non-compaction? A difficult differential diagnosis

Paolo Spirito* and Camillo Autore

1 Divisione di Cardiologia, Ospedale Galliera, Via Volta 8, 1628 Genoa, Italy and 2 Divisione di Cardiologia, Ospedale Sant’Andrea, II Facoltà di Medicina, Università ´La Sapienza´, Rome, Italy

This editorial refers to ‘Mutation in the alpha-cardiac actin gene associated with apical hypertrophic cardiomyopathy, left ventricular non-compaction, and septal defects’ by L. Monserrat et al., on page 1953

Hypertrophic cardiomyopathy (HCM) is a familial cardiac disease caused by mutations in one or more of 12 genes encoding protein components of the cardiac sarcomere. The disease is transmitted with an autosomal dominant trait and a variable penetrance. The phenotypic features of HCM may develop at any age from infancy to adulthood, and are characterized by a great heterogeneity in the extent, magnitude, and distribution of left ventricular (LV) hypertrophy. Apical HCM is a relatively rare morphological expression of the disease (<5% of patients), in which LV wall thickening is confined to the most distal portion of the ventricle, below the papillary muscle level. This form of HCM is more frequently sporadic, but may also be encountered in the context of clinical screening of HCM families with more common patterns of distribution of LV hypertrophy. A few families have also been reported with autosomal dominant inheritance of an apical form of HCM. The clinical course of apical HCM appears to be generally benign, without severe symptoms or major cardiac events. Indeed, a particularly low annual cardiovascular mortality rate (0.1%) was reported during a mean follow-up of 9 years in a survey of the largest available cohort of patients with apical HCM (a total of 105 patients).

Non-compaction of LV myocardium is an increasingly recognized but apparently uncommon cardiomyopathy, characterized by a hypertrophied left ventricle with multiple trabeculations and deep intertrabecular recesses communicating with the ventricular cavity. These morphological abnormalities involve predominantly the distal (apical) portion of the left ventricle. Non-compaction can be an isolated finding, or may be associated with other congenital heart anomalies. At present, this disorder is considered to be the result of an arrest of the normal process of intrauterine endomyocardial morphogenesis.

Non-compaction may first become manifest during infancy, usually in association with severe clinical manifestations and an unfavourable natural history. In adults, the clinical course appears to be more variable. A minority of adult patients have mild manifestations of the disease and a relatively favourable clinical course. However, the majority of adults present with LV systolic dysfunction and heart failure, and some may experience arrhythmias, thromboembolic events, or sudden death. Both familial and sporadic cases of LV non-compaction have been described, with the familial forms being reported in ~25% of patients. The disease is more frequently inherited with an autosomal dominant trait, with an X-linked or mitochondrial inheritance being less common. Mutations have been identified in the genes encoding α-dystrobrevin, G4.5 (a member of tafazzin proteins), and LIM domain-binding protein 3 (2,6). In most patients, however, the genetic cause remains undetermined. The clinical phenotype within families, and amongst unrelated individuals with the same mutation, is highly variable, suggesting that additional factors such as modifier genes and the environment may influence the clinical expression of the disease.

Mutations in the alpha-cardiac actin gene have been reported as the cause of HCM in a small minority of patients with heterogeneous clinical presentations, ranging from mild to severe phenotypes. In a recent study, Arad et al. identified a E101K (Glu101Lys) mutation in the alpha-cardiac actin gene as the cause of apical HCM with an autosomal dominant inheritance in two distantly related families, in which all of the 16 mutation carriers had an apical distribution of hypertrophy. A LOD score of >4.5 confirmed the disease-causing role of the mutation. Monserrat et al. have investigated the possibility that the same E101K actin gene mutation could cause a variety of cardiomyopathies. The authors initially screened a large and heterogeneous population for this mutation, including a total of ~250 index patients affected by either HCM, dilated cardiomyopathy, or LV non-compaction. The E101K cardiac actin gene mutation was found in five patients. Four of these patients had been previously diagnosed with predominantly apical HCM and one with LV non-compaction; two of these five patients also belonged to the families previously reported...
by Arad et al. Extensive clinical and genetic screening performed by Monserrat et al. in the relatives of the five index patients with the E101K cardiac actin gene mutation led to the identification of a total of 46 mutation carriers. Penetrance was particularly high, since all the mutation carriers had an abnormal LV phenotype, most patients showing LV trabeculations and intertrabecular recesses. Indeed, 50% of these patients had trabeculations of a magnitude such as to fulfill standard morphological criteria for LV non-compaction. None of the 46 patients showed thickening of the basal interventricular septum, and all patients had the thinnest ventricular segment at the level of the posterior septum. In addition, five of the 46 mutation carriers had an associated atrial septal defect, two had an aneurysm of the atrial septum, and one had a ventricular septal defect. Of note, the family history and/or clinical course in these pedigrees was unfavourable, including four sudden deaths, two cardiac arrests, one heart failure death, and one heart transplantation.

The phenotypic features of the pedigrees with the E101K cardiac actin gene mutation described by Monserrat et al. would not appear to reflect the clinical characteristics of apical HCM. Indeed, prominent trabeculations and deep intertrabecular recesses involving predominantly the LV apex appear to be the most common morphological feature in these families, while only eight patients had a wall thickness ≥15 mm (potentially compatible with HCM) in the compact layer of the LV wall, after excluding the thickness of the trabeculations (Table 1, in Monserrat et al.). Therefore, in most patients, the LV morphology would appear to be consistent with a diagnosis of LV non-compaction rather than apical HCM. The unfavourable natural history in these pedigrees also differs from the benign clinical course generally associated with apical HCM. Finally, congenital heart anomalies were present in ~15% of the carriers of the mutation, a finding which is not uncommon in LV non-compaction, but extremely rare in patients with HCM. Of interest, cardiac actin mutations have also been reported in pedigrees with autosomal dominant inheritance of atrial septal defects.

Independently of which nomenclature is used for the cardiac disease affecting the five families reported by Monserrat et al., either apical HCM or LV non-compaction, the clinical phenotypes in the affected individuals appear to be similar in their genetically programmed morphological abnormalities, and characterized by a uniquely high penetrance. Therefore, the E101K (Glu101Lys) mutation in the alpha-cardiac actin gene would seem to cause a specific and single clinical entity, possibly expressing a disorder of cardiac morphogenesis, which requires genetic screening in order to establish the definitive diagnosis. In recent years, major advances in our understanding of the molecular pathways leading to cardiomyopathies have also increased our appreciation of the frequent similarities in clinical expression of diseases with different aetiologies. The observations of Monserrat et al. show once more that the morphological information derived from cardiac ultrasounds may not always be sufficient to classify the cardiomyopathy affecting some patients. Although the high-resolution images of the heart obtained with magnetic resonance may offer additional help, ever more frequently DNA analysis will become the most definitive method for diagnosis in many patients with cardiomyopathies.

References


