

Age-Dependent Heterogeneity of Familial Hypertrophic Cardiomyopathy Phenotype: A Role of Cardiovascular Magnetic Resonance

Sigita Glaveckaitė¹, Alfredas Rudys¹, Violeta Mikštienė², Nomeda Valevičienė³, Darius Palionis³, Aleksandras Laucevičius¹

¹Department of Cardiovascular Medicine, Vilnius University, ²Department of Human and Medical Genetics, Vilnius University, ³Department of Radiology, Nuclear Medicine and Physics of Medicine, Vilnius University, Lithuania

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Summary. In this case report, we present familial hypertrophic cardiomyopathy with age-dependent heterogeneity of the disease phenotype among the members of one family who carry the same mutation of the myosin-binding protein C gene. Phenotypic heterogeneity is common in patients with familial forms of hypertrophic cardiomyopathy, both in clinical expression and outcome. Compared with other noninvasive cardiac imaging modalities, cardiovascular magnetic resonance provides an opportunity to more accurately characterize the varying phenotypic presentations of hypertrophic cardiomyopathy.

Introduction

Hypertrophic cardiomyopathy (HCM) is a common genetic cardiac disease with a prevalence of about 0.2% in the general population (1, 2). Clinically, HCM is defined by the presence of left ventricular hypertrophy (LVH) unexplained by abnormal loading conditions (1). The natural history of HCM varies from an asymptomatic course to drug refractory angina/dyspnea, sudden cardiac death (SCD), and end-stage heart failure (2). In approximately 60% of cases, HCM is inherited as an autosomal dominant trait caused by mutations in genes coding for cardiac sarcomere proteins (3, 4). The most common mutations are mutations in genes, encoding the cardiac myosin-binding protein C (*MYBPC3*) and the β -myosin heavy chain (*MYH7*). These mutations account for one-quarter to one-third of all HCM cases. Mutations in other HCM-causing genes contribute to less than 5% of all HCM cases for each gene (5). Disease expression in families with HCM related to *MYBPC3* mutations shows marked heterogeneity with incomplete, age-related, and gender-specific penetrance (4).

Thus, the primary aim of this educative case report was to present the age-dependent heterogeneity of disease expression and clinical outcomes in one family with the mutation in *MYBPC3*. The secondary aim of this report was to illustrate an important role of cardiovascular magnetic resonance (CMR) in identifying the varying phenotypic presentations of HCM.

Case Report

A 50-year-old man (an arrow pointing to the index patient in the pedigree chart, Fig. 1) was diagnosed with HCM by transthoracic echocardiography (TTE) at the age of 40 years. He was regularly followed up at our center due to exertional dyspnea. His 28-year-old (indicated as x in Fig. 1) and 17-year-old (indicated as xx in Fig. 1) sons, having no complaints, underwent clinical and genetic screening regarding HCM. The third 25-year-old son, who had a hypertrophic phenotype observed on TTE at the age of 20 years, moved to another country and was lost to genetic and more profound clinical screening. Molecular genetic analysis revealed a mutation in the *MYBPC3* gene causing familial HCM with autosomal dominant inheritance in the index patient and 2 of his sons. No mutation in the *MYH7* gene was found. On TTE, a significant variability of the hypertrophic phenotype without LV outflow tract obstruction was observed in all 3 patients. CMR imaging was performed in order to precisely assess cardiac morphology, function, and myocardial fibrotic changes. The age-dependent intrafamilial heterogeneity of the hypertrophic phenotype was clearly seen on CMR cine images (balanced steady-state free precession sequence) (Fig. 2) with progressing LVH and myocardial fibrotic changes with age. The index patient and his 28-year-old son were scheduled for the implantation of a cardioverter-defibrillator (ICD) because of documented nonsustained ventricular tachycardia (NSVT) during ambulatory electrocardiography (ECG) monitoring and a family history of SCD. Late gadolinium enhancement (LGE) foci con-

Correspondence to S. Glaveckaitė, Department of Cardiovascular Medicine, Vilnius University, Santariškių 2, 08661 Vilnius, Lithuania. E-mail: sigita.glaveckaite@santa.lt

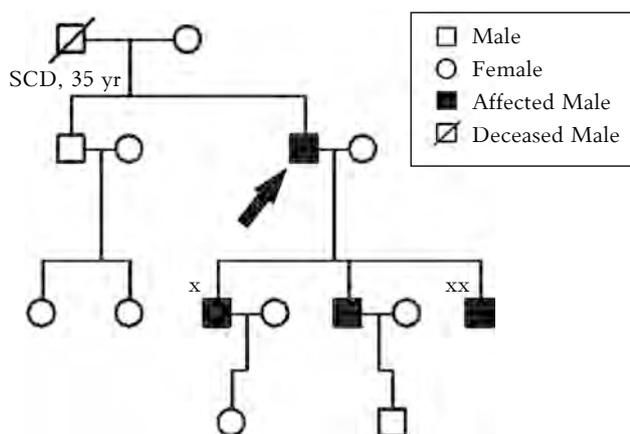


Fig. 1. Pedigree chart representing the phenotypic expression of hypertrophic cardiomyopathy with autosomal dominant inheritance in one family

An arrow indicates the index patient; x, a 28-year-old-son; xx, a 17-year-old son. SCD, sudden cardiac death.

sistent with myocardial fibrosis observed on CMR images (T1 inversion recovery gradient-echo sequence [IR]) (Fig. 2) favored ICD implantation. The 17-year-old son of the index patient was scheduled for further yearly follow-up visits.

Discussion

Like in all other autosomal dominant diseases, a characteristic feature of HCM is the presence of significant variability in its phenotypic expression, such as cardiac hypertrophy and SCD. There can also be large differences among the relatives of the same family (intrafamilial variability), who carry the same mutation. This suggests that additional genetic and possibly environmental mechanisms modulate the phenotype of the disease. Such disease modifiers are not well understood, but some studies have reported an effect of specific genetic polymorphisms (6). In some families, a significant variability in the phenotypic expression of the disease has been explained by the presence of a second causal mutation (6).

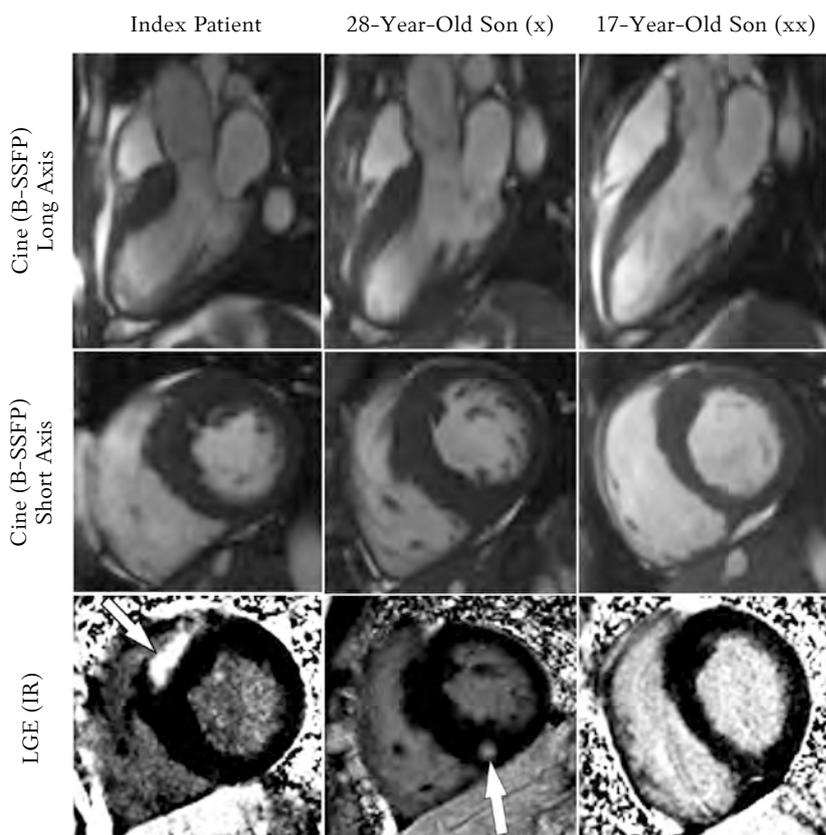


Fig. 2. Cardiac magnetic resonance images representing the phenotype of hypertrophic cardiomyopathy:

3 chamber long-axis (upper row) and short-axis (middle row) cine images and short-axis LGE (bottom row) images

There is a different phenotypic expression of the disease with marked hypertrophy (reaching 22 mm in diastole) of the basal antero-septal and anterior segments in the index patient, hypertrophy of the whole basal and midventricular septum (reaching 19 mm in diastole) in the older son, and lesser-degree hypertrophy (reaching 14 mm in diastole) located only in the basal antero-septum in the younger son. The thickness of the basal inferoseptal wall in diastole was the within reference range in all 3 patients: 8 mm, 7 mm, and 8 mm, respectively. Late gadolinium enhancement foci of different sizes and localizations were observed in the index patient (arrow) and his older son (arrow). B-SSFP, balanced steady-state free precession sequence; LGE, late gadolinium enhancement; IR, T1 inversion recovery gradient-echo sequence.

Like in all other diseases inherited as an autosomal dominant trait, the penetrance of the mutations causing HCM is age dependent. Causal mutations do not lead to hypertrophy and other clinical HCM phenotypes often until the third and fourth decades of life (7, 8). *MYBPC3* mutations have been associated with a cardiomyopathy starting late and evolving slowly but possessing an apparent risk of sudden death similar to that caused by other sarcomeric mutations. All 3 patients presented in our case report have almost the same HCM phenotype: asymmetrical hypertrophy of the LV septum extending to some degree into the anterior wall. We think that the observed heterogeneity of LVH seen in this family is a function of age, i.e., the severity of LVH progresses with age. At a given time point, more profound changes in respect of LVH and myocardial fibrosis are seen in the index patient and his older son, meanwhile the younger son has LVH of a lesser degree without visually detectable myocardial fibrosis.

Compared with other noninvasive cardiac imaging modalities, CMR provides complete tomographic imaging of the entire heart, superior spatial resolution with sharp contrast between the blood and the myocardium, and very accurate and reproducible measurements of cardiac dimensions, volumes, and mass. CMR has incremental utility in atypical cases of HCM (focal segmental LVH limited to the anterolateral free wall, posterior septum, or apex). These areas are technically challenging for TTE due to limited acoustic windows and foreshortening. Additionally, contrast-enhanced CMR offers a unique possibility to visualize LGE foci consistent with myocardial fibrosis using the IR sequence. Due to the abovementioned reasons, CMR now plays an important role in the diagnosis, therapeutic planning, and prognostication of this cardiomyopathy.

Although many patients remain asymptomatic with a benign natural history, SCD might be the initial manifestation in many otherwise asymptomatic or mildly symptomatic young people. Current HCM risk prediction models include previous SCD, ventricular fibrillation, family history of SCD, unexplained syncope, spontaneous sustained ventricular tachycardia, LV thickness of ≥ 30 mm, NSVT on continuous ECG monitoring, and abnormal blood pressure during exercise (2). Published longitudinal studies have emphasized a strong association between LGE and SCD (9–12) and suggested to use LGE detected on CMR as a predictor of SCD in patients with HCM. At the moment, there is insufficient evidence for implanting an ICD based on LGE alone because up to date, there is no large-scale prospective study on how the presence of LGE should be interpreted to alter management (9). Further studies should establish the role of LGE in identifying high-risk patients among those who do

not otherwise qualify for ICD insertion. Taking into account a family history of SCD, NSVT on continuous ECG monitoring, and LGE foci on CMR, the index patient and his oldest son received ICDs for the primary prevention of SCD.

The histological correlate of LGE in HCM seems to be an increased amount of myocardial collagen rather than the disarray of myocardial fibers, which is also observed on the histological specimens of patients having HCM (9). The patterns of LGE in HCM are heterogeneous, may occur commonly in either the ventricular septum or free LV wall, and usually involve myocardial segments that are most hypertrophied. The most common LGE pattern observed in HCM is patchy, multifocal midmyocardial fibrosis. Other patterns include diffuse confluent transmural septal fibrosis and patchy septal fibrosis at right ventricle (RV) insertion points (9). Myocardial fibrosis visually observed on CMR in patients with HCM typically do not conform to particular coronary arterial distributions or subendocardial-to-transmural localizations characteristic of ischemia. An exception to the abovementioned LGE patterns are the areas of burned-out HCM where the LV wall is typically thinned, and full-thickness LGE is present resembling a scar after myocardial infarction (13). The latter condition is mostly seen as an atypical form of HCM – an apical aneurysm. Almost transmural subepicardial fibrosis in the projection of the anteroseptal wall (Fig. 2, index patient) and patchy septal fibrosis at the RV insertion point (Fig. 2, 28-year-old son), which are typical LGE patterns for HCM, were observed in our case.

Histological studies suggest that in HCM, besides focal LGE, increased diffuse myocardial fibrosis can be documented, which that cannot be detected by current LGE imaging techniques. New techniques such as T1 mapping (14) might help quantify the overall extent of diffuse myocardial fibrosis and to identify patients with subclinical HCM.

Conclusions

Hypertrophic cardiomyopathy is a genetic disease with incomplete, age-related expression causing a marked intrafamilial phenotypic but not genotypic variability both in clinical expression and risk of sudden cardiac death. An accurate characterization of the disease is crucial for optimal therapeutic planning and risk stratification. Thus, cardiac magnetic resonance is an excellent tool in clinical practice for the diagnosis of hypertrophic cardiomyopathy and clarification of its phenotype, especially when the phenotype is not adequately defined by means of echocardiography.

Statement of Conflict of Interest

The authors state no conflict of interest.

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