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ORIGINAL ARTICLE

A Long Term Follow-up Study of Carriers of Hypertrophic Cardiomyopathy Mutations

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Background Adults who test positive for a mutation associated with the development of hypertrophic cardiomyopathy (HCM) but who have not manifested left ventricular hypertrophy (LVH) at the time of that diagnosis are now commonly identified in the era of genetic testing. There are little published data, however, on the long-term outlook for these phenotypically normal gene carriers.

Methods Fifteen genotype positive/LVH negative patients with HCM were identified, seven of which were children when first diagnosed as gene carriers. Fourteen were followed up with clinical examinations, electrocardiography and echocardiography to determine if their clinical status had changed over time. Measurements included electrocardiographic changes, changes in wall thickness, diastolic function and global longitudinal stain.

Results Ten participants were followed up for a total of 18 years, two for a total of 17 years, one for 11 years and one for 8 years. In addition, magnetic resonance imaging (MRI) studies were performed on 11 participants. Eleven participants carried a mutation for the MYBPC3 gene and three carried a mutation for the MYH7 gene. One patient, an adult at the time of initial investigation, developed phenotypic features of HCM on echocardiography and MRI, one an increase in wall thickness diagnostic for HCM only on MRI and another to be borderline for HCM on MRI.

Conclusion Hypertrophic cardiomyopathy can develop in adult life in carriers who may be negative for LVH at the time of gene diagnosis and warrants periodic supervision of carriers throughout their lives.

Keywords Hypertrophic cardiomyopathy • Carriers • Long-term follow-up • Clinical genetics

Introduction

Familial hypertrophic cardiomyopathy (HCM) is a disorder characterised by excessive myocardial hypertrophy in the absence of an abnormal haemodynamic load, and may be caused by a variety of gene mutations responsible for encoding sarcomeric proteins [1,2]. Mutations in several genes have been described with varying degrees of penetrance in individual families [3–5]. Historical figures suggested the condition affected 1 in 500 adults [6], although more recent estimates suggest that the number may be closer to 1 in 200 [7]. It is a clinically heterogenous condition [7],

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with the majority of patients having a benign course [8,9]. However, approximately 10-20% of people progress to severe heart failure (New York Heart Association (NYHA) functional class III or IV) [10], or, at its most extreme die suddenly, with the overall mortality rate estimated around 0.5-1.5%/year [8,11].

Since the first reports of familial HCM were published in 1960s [12,13], more than 14 individual genes associated with the development of HCM and more than 1,400 mutations have been described to date with varying degrees of penetrance in individual families [1]. However, with the development of cost-effective genetic testing opportunities for HCM and the acceptance that genetic testing is a part of the standard of care [14,15], we have created a new population of patients: patients who are positive for a HCM-causative mutation, but who are phenotype, or specifically left-ventricular hypertrophy (LVH), negative. The risk of developing LVH in this group is uncertain [16] and hence we remain somewhat unsure as to how to appropriately manage them clinically, with a case-by-case basis advocated as our experience of outcomes with these patients is limited [14,15]. Also requiring consideration are the psychological impacts of being predisposed to developing a genetic condition [17,18], although reassuringly, this seems to be minimal, or even improved in HCM gene carriers [19].

Phenotypically normal carriers are common with some HCM-causative mutations and can number up to 45% of all positive cases [20], but there are still varying reports as to the outcomes and progression to overt HCM [21,22]. We identified and studied the clinical course of 14 patients over a 20-year period who are genotype positive for HCM but who were LVH negative for the condition at the time of their gene diagnosis, and report on our findings below.

Methods

Study Cohort

Participants from three families were included in this study (Figure 1). Two of these were part of a genetic study conducted in Tasmania, Australia between 1994 and 1996 [2,20] which included three families. One family was unable to be contacted and has not been included in this study. The third family in this study was subsequently identified through the clinical practice of an investigator (DM) in 1997. Family 1 (F237 in the original study) included 69 family members at risk of HCM from a single family in Northern Tasmania in whom predictive gene testing was conducted [2,20]. This study identified 31 family members who were heterozygous mutation gene carriers for the myosin binding protein C3 gene (MYPBC3 gene) where the change was a heterozygous nonsense mutation Gln969X. Of these 31, 12 were phenotypically normal at the time of the study; four were children. Family 2 (Family F59 in the original study) included 12 family members at risk of HCM, of which eight were found to be carriers of the missense mutation Arg453Cys affecting the β cardiac myosin heavy chain gene (MYH7). Family 2 had a high penetrance rate of

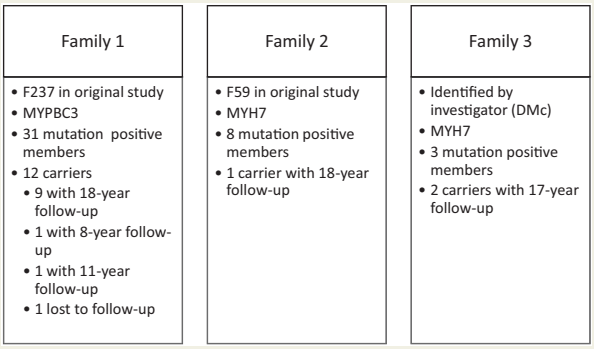

Figure 1 Study cohort.

87.5%, with one unaffected carrier in the cohort of eight (for reasons unknown to us this carrier was not identified in the publication of the original study, however was confirmed to have been screened at this time). Family 3 had two members identified as phenotypically normal carriers when their father, who had phenotypically severe HCM requiring heart transplant, was found to be positive for a pathogenic MYH7 missense gene mutation. At the time of identification in 1997 both participants were children (aged 11 and 12); they had normal echocardiographs.

Overall, 15 potential participants for this study were identified. At baseline (1994-1997), all had no evidence of LVH at echocardiography, which for the purposes of the original study was taken as a measurement of maximum left ventricular wall thickness equal to or greater than 13 mm, or, in the case of children less than 18 years at the time of a genetic diagnosis, a body surface area adjusted maximum wall thickness greater than the mean + 2x standard deviation [14]. Diagnostic criteria for HCM for this follow-up and the original study were the same, given the well-documented positive family history in all three families [15].

Procedures

At the time of their genetic diagnosis, all participants underwent clinical examinations, electrocardiography and echocardiography. The same procedures were followed for this study. All participants were questioned concerning current symptoms, previous cardiac events and current medication. Their blood pressure and pulse rate were recorded and note made of any cardiac murmurs. All participants had initial 2D and M mode echocardiographic measurements and analyses performed at the time of diagnosis and included maximum left ventricular wall thickness and cavity dimensions, structural abnormalities, systolic anterior movement of the mitral leaflets and outflow tract gradients as well as Doppler inflow parameters. At follow-up the same measurements were obtained, but also longitudinal strain measurements, and tissue Doppler velocities at the mitral annulus were included. A Vivid E9 General Electric cardiovascular ultrasound machine with a 2.5Mhz transducer was used for all echocardiographic measurements. The normal average strain for this type of machine has been estimated at -18.6 ± 0.1% [23] with

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