Different Clinical Presentation and Tissue Characterization in a Monozygotic Twin Pair with MYH7 Mutation-Related Hypertrophic Cardiomyopathy

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Summary

This case report demonstrates a pair of monozygotic twins with hypertrophic cardiomyopathy (HCM) carrying the same pathogenic mutation of *MYH7* (p.G768R; c.2302G>A), detected by whole exome and Sanger genetic sequencing methods. On multi-modality imaging, they were reported to have similar, but not identical, morphologic expression. Particularly, the clinical presentation and tissue characteristics were not the same. Late gadolinium enhancement (LGE) and T1 mapping of cardiac magnetic resonance showed different extents of myocardial fibrotic characteristics in the twins (twin A: 16.3% LGE and 32.6% extracellular volume [ECV] of the whole left ventricle; twin B: 5.4% LGE and 28.1% ECV of the whole left ventricle). This extraordinary case of HCM provides evidence on the complex pathophysiological mechanisms of HCM and suggests the likely impact of epigenetics and environmental factors on HCM phenotype.

(Int Heart J 2019; 60: 477-481)

Key words: Late gadolinium enhancement, T1 mapping, Cardiac magnetic resonance, Phenotype

Hypertrophic cardiomyopathy (HCM) is an autosomal dominant genetic disease with a prevalence of 1:500 in the general adult population.¹⁾ Approximately 60% of HCM is caused by the genetic variants encoding myocardial sarcomere proteins, in which more than 1000 distinct mutations in 11 genes have been identified.^{2,3)} Of those, β -myosin heavy chain (*MYH7*) is the most commonly affected gene. HCM in monozygotic twins is a rare occurrence. It is interesting to observe HCM in monozygotic twins who share identical genes as it provides a unique opportunity to observe phenotypic differences with the control of genetic heterogeneity and phenotypic diversity can be considered as environmental in origin. HCM is characterized by myocardial fiber disarray and increased extracellular matrix with accumulation of interstitial fibrosis.⁴⁾ Late gadolinium enhancement imaging (LGE) allows for the identification of focal fibrotic areas that are associated with disease progression and portend a worse prognosis.^{5,6)} Extracellular volume fraction (ECV) helps detect diffuse fibrosis in HCM.^{7,8)} Although there are a few reports on the association of genotype and phenotype in patients with HCM,⁹⁻¹²⁾ there are no reports to date on the quantitative assessment of myocardial fibrosis using LGE or ECV in monozygotic twins with HCM. Therefore, in this study, we explored the association of genotype and phenotype in monozygotic twins

with HCM.

Case Report

A 49-year-old female patient (twin B, II3) was admitted to the hospital for syncope. Her monozygotic twin sister (twin A, II2) experiencing symptoms of palpitation and exertional dyspnea had been diagnosed as having HCM and atrial fibrillation (AF) 1 year ago. Blood tests revealed elevated cardiac troponin T (cTnT) level of 19 ng/L (reference range, 0-14 ng/L) and an obviously elevated N-terminal pro-brain natriuretic peptide (NT-pro-BNP) level of 10,214 pg/mL (reference range, 0-88 pg/mL) in twin A and slightly elevated cTnT (18.1 ng/L) and lower level of NT-pro-BNP (1516 pg/mL) in twin B. The twins received a comprehensive evaluation, including electrocardiogram (ECG) and multi-modality imaging, at the same time. ECG revealed AF and left bundle branch block (BBB) in twin A and first-degree atrioventricular block, left anterior hemiblock and right BBB in twin B (Figure 1 A). In addition, twin B was diagnosed as having sick sinus syndrome (SSS) because of frequent sinus arrest, and her maximal RR interval was 3.3 seconds based on 24-hours ambulatory ECG (Figure 2). Echocardiography demonstrated that the twins had both focal ventricular septum hypertrophy and significant bi-atrial enlargement

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This work was supported by the National Natural Science Foundation of China [grant number 81571638 and 81271531].

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Received for publication March 23, 2018. Revised and accepted June 14, 2018.

Released in advance online on J-STAGE February 8, 2019.

doi: 10.1536/ihj.18-167

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Figure 1. Comparison of clinical and multi-modality imaging characteristics in a monozygotic twin pair with hypertrophic cardiomyopathy. (A: electrocardiogram; B: myocardial fibrotic characteristics quantified by late gadolinium enhancement and extracellular volume; C: single-site mutation of *MYH7* [p.G768R, c.2302G > A] gene)

(twin A: left atrium, 48 mm; right atrium, 43 mm; twin B: 47 and 42 mm, respectively). Tissue Doppler examination also showed filling abnormality of the left ventricle (LV) with E/e' (lateral) of 30.4 in twin A and 19.7 in twin B. Cardiac magnetic resonance (CMR) confirmed focal LV hypertrophy mainly located in basal anteroseptum with a maximal thickness of 17 mm in twin A and 16 mm in twin B. In addition, the 3-chambered view revealed no obvious differences in the anterior mitral valve leaflet length (twin A: 29.7 mm; twin B: 30.1 mm) and posterior mitral valve leaflet length (twin A: 16.8 mm; twin B: 18.3 mm). Therefore, the twins were identified to have similar, but not identical, morphologic expression. Interestingly, there were different degrees of fibrotic burden in the monozygotic twins, when quantified either as LGE proportion (LGE defined as 6 standard deviation from normal) or T1 mapping of CMR (twin A: 16.3% LGE and 32.6% extracellular volume [ECV] of the whole LV; twin B: 5.4% and 28.1%, respectively; Figure 1B). In addition, the twins were living far away from each other and therefore, had different living environments and life habits, including diet and exercise.

We conducted whole exome sequencing in the twins. Exon-enriched DNA was sequenced by the Illumina HiSeq 2500 platform following the manufacturer's instructions. Raw image files were processed using BclToFastq (Illumina) for base calling and generating raw data. The low-quality variations were filtered out using a quality score of ≥ 20 (Q20). The sequencing reads were aligned to the NCBI human reference genome (hg19) using BWA.

VarScan and GATK were used to analyze single nucleotide polymorphisms (SNPs) and indel of the sequence. Data analysis was applied as follows: (1) Synonymous changes and SNPs with minor allele frequencies higher than 5% were removed. (2) Nonsynonymous changes were filtered using SIFT software. (3) The function of mutated genes and their association with the disease were analyzed. Genetic results were then confirmed using the Sanger sequencing method. Single site mutation of *MYH7* (p.G768R, c.2302G>A) in twins had been previously reported in HCM¹³⁾ (Figure 1C) and was classified as likely pathogenic based according to the guideline¹⁴⁾ recommendation. In addition, co-segregation with affected family members was demonstrated for at least one patient. Therefore, this genetic variant was considered as a likely pathogenic mutation related to HCM in our study twins. In addition, clinical screening and genetic testing were offered to other relatives (III1, III2, III3, III4, III5, IV1, IV2, IV3, and IV4) of the twins. The pedigree of the twins and other family members is shown in Figure 3. The subjects (III1, III2, III4, and IV1) were also diagnosed as having HCM and identified to be carrying the same p.G768R (c.2302G>A) mutation in the *MYH7* gene. Clinical evaluation and genetic analyses of other family members were normal and considered as being unaffected. Furthermore, cardiac failure in twin A was successfully controlled using beta-adrenergic receptor blockers and diuretics following the diagnosis of HCM. In addition, long-term oral anticoagulation was prescribed for AF. Twin B was recommended a cardioverter-defibrillator (ICD) implantation for

Figure 2. Twenty-four-hour ambulatory electrocardiographic characteristics of twin B.

Figure 3. Pedigree of the family. Squares indicates male relatives; circles, female relatives; y, years; filled symbols, HCM patients; slants, dead members; arrow, proband; ?, the subject died before our investigation and we could not obtain clinical data and confirm his or her genotype and phenotype; SCD, sudden cardiac death; G + , positive genotype; G- , negative genotype; P + , positive phenotype; and P- , negative phenotype.

SSS and a history of syncope.

Discussion

In this study, we reported the case of a monozygotic twin pair with *MYH7* mutation who had variable phenotypic expressions. The findings between the twins are interesting. First, although the single site mutation of *MYH7* has been previously reported in HCM,¹³⁾ we are the first to report the probable association of *MYH7* gene mutation with phenotypic expressivity in monozygotic twins with HCM. Second, the morphologic expression of the twins was similar, but not identical. Third, the monozygotic twins presented different electrocardiographic performances. Furthermore, there were different clinical presentations and different degrees of fibrosis, as quantified by LGE and ECV, between the twins, suggesting that the twins may have different prognosis; however, this needs to be confirmed by further follow-ups.

According to review literatures, phenotypic features of HCM among monozygotic twins have been inconsistent. Maron, *et al.*,¹⁵⁾ Wylie, *et al.*,¹⁶⁾ and Zenovich, *et al.*¹⁷⁾ have reported that identical morphologic expression could be identified in monozygotic twins. In addition, Maron, *et al.* provided an explanation that genetic background is a primary factor determining the morphological expression of HCM, whereas environmental factors may have a limited impact. However, these reports have not explored the change of tissue characteristics in monozygotic twins, and other study results¹⁸⁻²²⁾ have not been consistent with these reports. Palka, *et al.* reported there were different clinical presentations and morphological expressions in monozygotic twins with HCM.¹⁸⁾ Reid, *et al.*¹⁹⁾ and Ko, *et al.*²⁰⁾ found morphological differences in the presence of LV outflow tract obstruction in monozygotic twins. Although various phenotypic features of HCM among monozygotic twins have been previously reported, quantitative assessment of fibrosis characteristics by LGE or ECV among twins has not been reported so far. In our report, although the monozygotic twins had *MYH7* mutation-related HCM phenotype, the clinical presentation and fibrotic characteristics were variable.

Previous studies have suggested that methylation modification²³⁾ may be involved in the phenotypic expression in patients with HCM. In our report, although the monozygotic twins shared an identical mutation, their living environments and life habits were different. Therefore, the possible reason contributing to the phenotypic diversity in the monozygotic twin pair may be environmental factors and methylation modifications. Our report supports the complex pathophysiological mechanisms of HCM, especially in the course of fibrotic natural history, and suggests that epigenetics and environmental factors may affect HCM phenotype.

In conclusion, we reported different clinical presentations and different extents of myocardial fibrotic burden with similar HCM morphologic expression in a pair of monozygotic twins carrying the same *MYH7* gene mutation.

Disclosures

Conflicts of interest: The authors declare no conflicts of interest.

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