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Left ventricular noncompaction associated with hypertrophic cardiomyopathy: Echocardiographic diagnosis and genetic analysis of a new pedigree in China

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ABSTRACT

Background: Hypertrophic cardiomyopathy (HCM) and left ventricular noncompaction (LVNC) are both genetically determined and familial diseases that possess variable but overlapping genetic defects. Previous literature has mostly reported their occurrences as either separate disorders in different members of a family or coexisting entities in sporadic cases rather than familial cases. This study explored the echocardiographic diagnostic values and familial features in a family with coexistence of HCM and LVNC.
Methods: A four-generation family comprised of 30 members was studied; 28 members underwent familial screening by routine transthoracic echocardiography (TTE), contrast echocardiography (CE), and/or cardiac magnetic resonance imaging (cMRI). Echocardiographic and cMRI findings were then compared.
Results: Four members (13.3%) died of sudden death or heart failure. Eleven members (39%) suffered from HCM, LVNC or both. There were 13 left ventricular hypertrophic segments among the echocardiographic images of 9 locally archived patients, including septal, inferior and anterior wall segments (8, 3, 2 respectively) as well as 20 noncompaction segments, including lateral, apical, anterior, antero-septal and inferior wall segments (8, 5, 4, 2, 1 respectively). Left atrial dilatation and diastolic dysfunction were significant in these subjects. Findings from TTE and CE were in accordance with those from cMRI in lesion locations. CE provided more information about noncompaction segments located in the antero-septum and near field than TTE.
Conclusions: HCM and LVNC coexist in one Chinese family, with overlapping phenotypes and different ages, clinical manifestations and multimodality imaging findings. TTE is an excellent tool to diagnose HCM and LVNC with supplementation by CE.

1. Introduction

Left ventricular noncompaction cardiomyopathy (LVNC) and hypertrophic cardiomyopathy (HCM) are primary types of cardiomyopathy with predominant myocardial involvement. Both diseases have been widely accepted as distinct cardiomyopathies and have been classified as genetic cardiomyopathies by the American Heart Association [1]. Recent literature has documented genetic evidence to prove LVNC and HCM as having causative genes which are overlapping [2–4]. Cardiac beta myosin heavy chain defect in two families linking noncompaction cardiomyopathy and hypertrophic cardiomyopathy was reported by Hoedemaekers et al. [3]. Alpha cardiac actin gene mutation, previously known to cause HCM or dilated cardiomyopathy (DCM), was identified in another five families with HCM, LVNC and atrial septal defects [4]. Shared sarcomere defects and the occurrence of HCM & DCM in families with LVNC patients indicated that at least some forms of LVNC are part of a broader cardiomyopathy spectrum [2]. This new insight into the genetic linkage between LVNC and HCM has expanded our knowledge about the heterogeneity of these diseases and demands more attention.

Here, we report the clinical and imaging findings of a multi-generation Chinese family, in whom features of LVNC coexist with features of HCM in some of the kindred. Previous literature has only

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reported HCM & LVNC occurring separately in different members of a family, or both demonstrating aggregation in sporadic cases but not familial. To our knowledge, our study is the first documentation of co-existence of the two types of cardiomyopathies in different members of a large family. We also focus on the role of routine echocardiography, as well as contrast echocardiography (CE), as the initial diagnostic tools in hypertrophic and noncompaction cardiomyopathies family screening.

2. Methods

2.1. Study population

The study was comprised of 30 members (20 males and 10 females) from a single family, identified via the proband — a 48-year-old man with HCM & LVNC. With the exception of 2 undiagnosed deceased kindred, all 28 remaining family members had undergone familial screening through routine TTE and/or CE, and/or cardiac magnetic resonance imaging (cMRI). Nine affected patients were enrolled and archived in our hospital — including 3 adult males, 3 adult females, 2 male children and 1 female child, with ages ranging from 5 to 49 years and a mean age of 28 ± 19 years.

2.2. Routine transthoracic echocardiography (TTE)

All family members were examined by routine TTE, including two-dimensional echocardiography, M-mode, color Doppler imaging and tissue Doppler imaging (TDI). The echocardiographic instrument used was a Philips iE33 (Philips Medical Systems, Andover, MA) equipped with S5-1 and S8-3 probes.

HCM and LVNC segments were localized; hypertrophic myocardial thickness was measured; thickness ratio of noncompaction to compaction myocardium (N/C ratio) was calculated; cardiac function and left ventricular outflow tract (LVOT) pressure gradient were evaluated; and left ventricular outflow tract obstruction (LVOTO) as well as other complications were recorded. The LVOTO was reliably quantified by continuous or pulsed wave Doppler. E & A peak velocities of mitral inflow pulsed wave Doppler were used for diastolic function assessment. When a pseudo-normal left ventricular filling was suspected, TDI was applied to record mitral annulus velocities (e′ & a′ peak) at their septal and lateral areas, and the average values recorded. Ejection fraction (EF) was acquired using the M-mode Teichholz method. These measurements were carried out 3 times, with the mean values recorded.

2.3. Contrast echocardiography (CE)

We performed CE in 4 patients, with left ventricular (LV) opacification mode applied, mechanical index held around 0.2 and real-time imaging of wall motion performed during a SonoVue (Bracco Diagnostics Inc., Milan, Italy) bolus injection to the patient's left antecubital vein. The rate of the bolus injection was 0.5–1.0 ml/s, and after bolus injections (with dose of 1.5–2.0 ml for adults & 0.8 ml for children), a rapid 5 ml saline flush was administered [5,6]. An additional contrast agent dose was administered as required by imaging. Apical 4-, 2- and 3-chamber views and parasternal LV short axis view in different levels were obtained by CE. HCM and LVNC segments were localized, thickness of hypertrophic myocardium was measured, and N/C ratio was calculated.

2.4. Cardiac magnetic resonance imaging (cMRI) & other clinical examinations

Four patients underwent cMRI using a Siemens 1.5 T Magnetom Avanto (Siemens, Germany) instrument. We selected axial, coronal, sagittal, 4-chamber, 2-chamber and short-axis views to optimize imaging. Either electrocardiograms or 24-hour Holter monitoring were performed in 6 patients. Only 1 patient underwent coronary arteriography and left ventriculography.

2.5. Diagnostic criteria

LVNC diagnostic criteria were as follows: (1) an excessively thickened LV myocardium with a two-layered structure consisting of a compacted epicardial layer (C) and a noncompacted endocardial layer (NC) with prominent trabeculations and deep intertrabecular recesses; (2) a maximal end-systolic N/C ratio > 2 in adults, measured at the parasternal short axis; and a N/C ratio > 1.4 in children; (3) color Doppler evidence of deep perfused intertrabecular recesses. And (4) absence of other cardiovascular abnormalities [7,8].

HCM diagnostic criteria were as follows: (1) LV thickness, evaluated at interventricular septum (IVS) and free wall level ≥ 15 mm; (2) Ventricular septal to left ventricular posterior wall thickness ratio > 1.3; (3) Absence of other possible systemic or cardiac causes of LV hypertrophy; (4) hypertrophic obstructive cardiomyopathy (HOCM) with a resting or dynamic LVOT pressure gradient ≥ 30 mm Hg; (5) In the cases involving children, ≥95% confidence interval of the theoretic value diagnostic for HCM [9,10].

3. Results

3.1. Proband's clinical and imaging information

The proband, II_2, first presented clinically in August 2007, with the main complaints of dyspnea, chest tightness, cough and abdominal distension for two weeks. Patient's blood pressure was 92/60 mm Hg, heart rate was 72 beats per minute, and he was classified as NYHA II. He had a history of smoking and alcohol drinking for 30 years. ECG showed sinus rhythm, indeterminate intraventricular block, premature atrial contractions, left atrial (LA) dilatation and ST-T segment changes. Echocardiography revealed the following: non-obstructive HCM, interventricular septal hypertrophy (middle segment thickness of 1.9 cm); LV anterior wall & lateral wall hypertrophy with thickness of 1.6 cm; LA dilatation with antero-posterior diameter (APD) of 5.9 cm; mild to moderate mitral regurgitation; diastolic dysfunction; and normal LV systolic function with ejection fraction (EF) of 60%.

After 10 months, the patient's condition deteriorated with more frequent dyspnea & palpitation; so he necessitated hospitalization. His heart failure classification then was graded as NYHA IV, and 24-hour Holter monitoring showed atrial fibrillation, premature ventricular contractions, ventricular tachycardia, intraventricular block, and ST-T segment change. Echocardiographic findings were similar to those at the initial examination, whereas left atrium (6.5 cm in APD) and right atrium (4.5 cm in left–right diameter) were both dilated, and LV systolic function decreased with EF of 44%. Meanwhile, congestive hepatomegaly was detected by ultrasound.

One week later, the patient was transferred to our hospital for further care. Once again, echocardiography showed similar findings as before except for additional mild pulmonary hypertension. This time, a cardiac MRI showed hypertrophy in the mid IVS, and noncompacted myocardium in the LV anterior and lateral walls (Fig. 1). Thus, our proband was diagnosed as having both HCM and LVNC. Five months later, the patient expired from heart failure at the age of 48.

3.2. Pedigree analysis

In order to explore the spectrum of LVNC and HCM in the proband's family, a pedigree analysis was performed (Fig. 2). Among the 30 familial members, 2 suffered heart failure-related deaths and 2 suffered premature sudden deaths, with a mortality rate of 13.3%. Of the 2 members who did not undergo screening, I_1 was diagnosed with heart failure but not identified as HCM, whereas II_1 suffered from premature sudden death before any cardiac disease was diagnosed. We strongly