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Familal left ventricular hypertrabeculation (noncompaction) is myopathic ☆,☆☆,★

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ABSTRACT

Background: Left-ventricular hypertrabeculation/noncompaction(LVHT) is a cardiac abnormality of unknown aetiology, frequently associated with arrhythmias, heart failure, and embolism. In most cases LVHT is associated with neuromuscular disorders (NMDs) or other rare non-neuromuscular genetic syndromes. Occasionally, LVHT occurs familiarly.
Methods and results: Invited for a cardiologic investigation were all first-degree relatives of index patients with LVHT who attended the cardiologic department. Altogether 25 relatives of 15 index patients from 15 families were investigated. Three members each were investigated in 3 families, 2 patients each in 4 families and 1 member each in 8 families. Among the 25 relatives from the 15 families, LVHT was found in 4 of them. Accordingly, familial LVHT was detected in 4 of the 15 investigated families (27%). Among the 4 relatives with LVHT, extension and morphology were similar to the appropriate index patient in 2 families. A NMD was diagnosed in three of the four relatives (75%) with familial LVHT. One relative without LVHT presented with a history of Fallot's tetralogy, and two relatives each presented with thickening of the left-ventricular myocardium.
Conclusions: LVHT is familial in at least 27% of the patients with LVHT. LVHT may differ between relatives in some of the patients with familial LVHT. Familial LVHT is associated with a NMD in the majority of the cases. Relatives of LVHT patients may present with cardiac abnormalities other than LVHT.

1. Introduction

Left ventricular hypertrabeculation (LVHT), also known as non-compaction, is an increasingly diagnosed myocardial abnormality [1,2], frequently associated with neuromuscular disorders (NMDs) if appropriately looked for [3]. Since the vast majority of the patients with LVHT carry mutations in genes encoding components of the skeletal muscle or the myocardium [4], it is quite likely that LVHT is also an inherited condition. This study aimed to investigate how often first degree family members of a propositus also exhibit the abnormality, if LVHT differs between multiple carriers within a family concerning morphology, complications, or outcome, how often familial LVHT is associated with a NMD, and which other cardiac or neurological abnormalities can be found in other family members.

2. Materials and methods

2.1. Inclusion criteria

Included were first degree family members (children, siblings, and parents) of patients with LVHT, diagnosed between 1995 and 2010, who attended the cardiologic department. All eligible family members were invited by their propositus to undergo a cardiologic and neurologic investigation, including echocardiography, to screen for neurological abnormalities or the presence of LVHT or other cardiac abnormalities.

2.2. Cardiologic investigations

Cardiologic investigations included the cardiovascular history, physical examination, 12-lead electrocardiogram (ECG), and transthoracic echocardiography in all included patients. In single patients, cardiac magnetic resonance imaging (cMRI) or 24-hour ECG were carried out. All basic cardiac examinations were performed during one visit by the same investigator (CS). In each participant blood pressure was measured. A 12-lead ECG was registered and evaluated for predefined abnormalities [5]. Transthoracic echocardiography by M-mode, 2-D, pulsed, continuous-wave Doppler and color-flow mapping were carried out with a Vingmed System Five with 2.5 to 3.6-MHz transducers. Patients were examined from parasternal, apical and subcostal views. Standard parameters were evaluated. The investigation was documented electronically as cine-loops.

LVHT was diagnosed if there were >3 trabeculations protruding from the left ventricular wall, apically to the papillary muscles, visible in one image plane, at end-diastole, if there was a two-layered composition of the left ventricular myocardium at end-systole with a thinner, compacted epicardial layer and a thicker spongy endocardial layer, and if perfusion of the intertrabecular spaces was visible on colour Doppler imaging at end-diastole [Stöllberger, submitted]. Trabeculations needed

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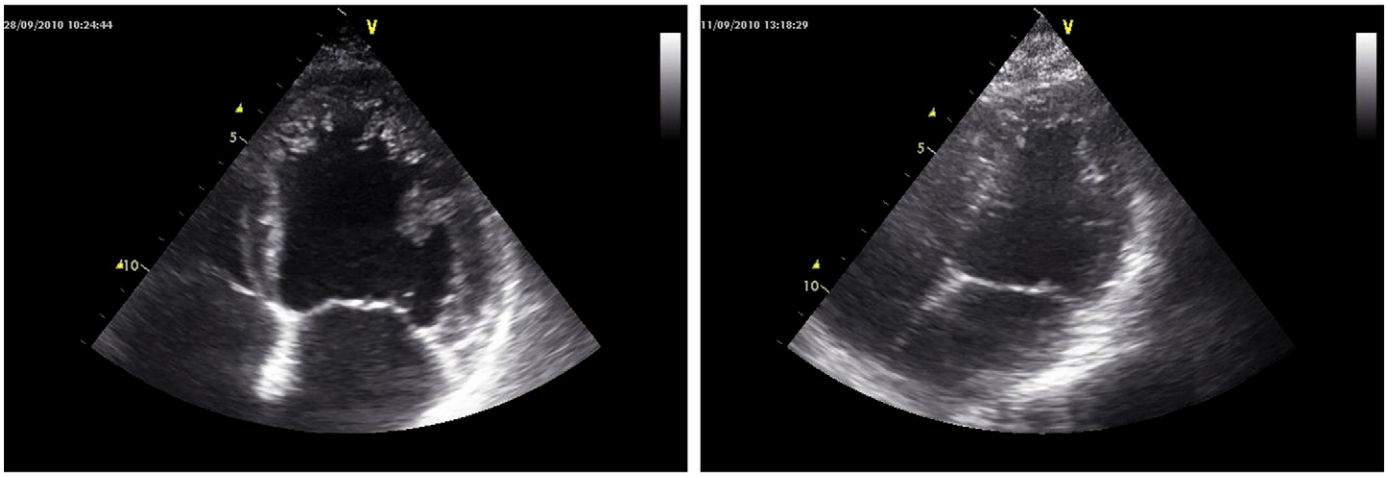

Fig. 1. Left: Echocardiographic apical four-chamber view showing left ventricular hypertrabeculation/noncompaction affecting the apical and lateral region of the left ventricle. The left ventricle is dilated and has a reduced systolic function. Right: Echocardiographic apical four-chamber view of the daughter of the patient on the left, showing left ventricular hypertrabeculation/noncompaction affecting the apical region of the left ventricle. The left ventricle is not dilated and shows a normal systolic function.

to have the same echogenicity as the myocardium, and needed to move synchronously with the ventricular contractions [3]. In order to differentiate between trabeculations, false tendons, and aberrant bands, and to delineate the compacted from the foamy layer, the transducer was angulated and pictures in atypical views were obtained. The location of the trabeculations was determined and the ratio of compacted to noncompacted myocardium was calculated [6]. To improve visualization of the left ventricular apex, LVHT was assessed from all obtainable echocardiographic views by adapting the focus. In order to validate the diagnosis of LVHT, a second experienced investigator from the same department (ES), reviewed all video-tapes blinded to the first investigator's diagnosis. In case of discrepancies about presence or absence of LVHT, a third experienced observer from another institution (GB) reviewed the recordings. cMRI was performed if the left ventricular apex could not or only poorly be visualized on echocardiography or in questionable cases. cMRI was applied since it has been shown to excellently visualize the apex and to contribute to the correct diagnosis of LVHT [7,8]. All patients reporting palpitations and those with LVHT were referred for a 24 h ECG.

2.3. Neurological investigations

Each relative with or without LVHT was invited for a neurological investigation, comprising history, clinical exam, blood chemical investigations at rest or under stress, nerve conduction studies, electromyography, and, if indicated, genetic studies. History and clinical exam were always carried out by the same investigator (JF). The neurological history was taken with particular regard to symptoms of a NMD and if any of the predecessors had already complained about such symptoms. The clinical exam was comprehensive and focused on peripheral nervous system abnormalities. If history or clinical neurological exam indicated a NMD, muscle enzymes were determined at rest or under physical or metabolic stress. If history, clinical neurological investigations, or blood chemical investigations indicated a NMD, nerve conduction studies of motor or sensory nerves and electromyography of apparently affected muscles were carried out. If history, clinical exam, blood chemical investigations, or electrophysiological investigations suggested polyneuropathy or motor neuron disease, an appropriate standard screening was carried out. If history, clinical exam, muscle enzymes, or electromyography suggested myopathy, muscle biopsy and eventually biochemical investigations were carried out. In case muscle biopsy allowed to establish the diagnosis or in case of a known mutation in the propositus, genetic studies were initiated.

3. Results

Between 1995 and 2010 LVHT was diagnosed in 162 patients. By the end of 2010 44 of these patients had died. Of the remaining 118 patients 17 could not attend the hospital because they or their relatives were living abroad (n = 11), in Austria but outside Vienna (n = 5), or were bed-ridden (n = 1). In four families 2 family members each were investigated. Among the remaining 97 patients those attending the cardiologic or neurologic ambulatory unit during 2010 were asked to send their first degree relatives to assess if and how many of them may also present with LVHT. From those invited, 25 from 15 families followed the invitation (Table 1). Three family members each were investigated in 3 families, 2 members each in 4 families, and 1 member each in 8 families. In four families more than one patient presented with LVHT (Table 1). In none of the families more than two family members presented with LVHT (Table 1). Since altogether 15 families were investigated, familial LVHT occurred in 27% of the families.

LVHT did not differ significantly between family members with regard to morphology, complications, or outcome in two families. In family 5 LVHT was restricted to the apex in both brothers. In family 6 both father and daughter had LVHT in the apex and the lateral wall. When comparing the other four patients of whom 2 each were related, it turned out that in family 9 the propositus presented with LVHT in the apex and the lateral wall, whereas his daughter had LVHT only at the apex (Fig. 1). In family 12 the mother had LVHT only in the apex whereas the son had developed it also at the lateral wall.

Of the 19 patients with LVHT and the 21 relatives from the fifteen families, 33 were seen by the neurologist (Table 2). None of the two patients from family 6 were seen by the neurologist. In the remaining 14 families a neurological diagnosis was established in at least the propositus (Table 2). Metabolic myopathy was diagnosed in four of these patients, myotonic dystrophy-1 in 2 patients, and myopathy of unknown etiology in 3 patients. In one patient each, Becker muscular

Table 1
Cardiac findings in the investigated families.

Family	NIFM	LVHT	OCA	PIL	OFML	OIFM
1B	2	1	0	BH	None	Son
2C	2	1	0	CW	None	Son
3D'O	2	1	0	DC	None	Brother
4F	3	1	0	FT	None	Father, mother
5I	2	2	0	IE	Brother	Brother
6Lo	2	2	0	LJ	Daughter	Daughter
7Lö	4	1	0	LM	None	Father, mother, brother
8 Pe	2	1	0	PH	None	Daughter
9 Pr	3	2	0	PJ	Daughter	Daughter, son
10Schu	2	1	0	SR	None	Mother
11U	4	1	0	UU	None	Father, mother, sister
12V*	3	2	Fallot	VC	Son	Daughter, son
13K	4	1	LVT	KA	None	Father, mother, sister
14W	3	1	LVT	WE	None	2 sons
15 Schm	2	1	0	SII	None	Sister

NIFM: number of investigated family members, LVHT: number of patients with LVHT, OCA: other cardiac abnormalities, PIL: patient initially diagnosed with LVHT, OFML: family member with LVHT, OIFM: other investigated family members, Fallot: Fallot's tetralogy, LVT: left ventricular thickening, *: previously reported [63].