

# Left ventricular non-compaction in children and adolescents: Clinical features, treatment and follow-up

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## Abstract

**Background:** *Left ventricular non-compaction (LVNC) is a specific cardiomyopathy that occurs following a disruption of endomyocardial morphogenesis. This study presents clinical findings, diagnostic features, treatment and follow-up of pediatric patients diagnosed with LVNC.*

**Methods:** *Patients with LVNC who were followed from January 2006 to March 2010 were included in this study. Diagnosis was made with the use of characteristic findings of magnetic resonance imaging and echocardiography. Holter electrocardiography and metabolic screening tests were also performed in all patients.*

**Results:** *A total of 24 patients were studied (18 male, six female). Patient age at diagnosis was  $50 \pm 60$  months (eight days to 15 years). Average follow-up period was  $22 \pm 12$  months (four months to four years). Findings at diagnosis were as follows: eight (33%) patients had heart failure, five (20%) had rhythm abnormalities, five (20%) had cardiomegaly, two had murmurs, two had cyanosis, and two presented with fatigue. Ten (41%) patients had been followed previously with other diagnoses. In 21 (87.5%) patients, electrocardiographic abnormalities were noted, especially left ventricular hypertrophy and ST-T changes. Patients had an average ejection fraction of 46% (18–73%) and three of them had additional congenital heart disease (patent ductus arteriosus, aortopulmonary window and complex cyanotic heart disease). Scanning for metabolic diseases revealed fatty acid oxidation disorder in one patient, and mitochondrial disease in another. During follow-up, a permanent pacemaker was implanted in a patient with severe bradycardia and ventricular dysfunction, and three patients died.*

**Conclusion:** *LVNC can be diagnosed at any age from newborn to adolescent and has a variable clinical course. Closer study of patients with cardiomegaly and heart failure can reduce delays in diagnosis of LVNC. (Cardiol J 2011; 18, 2: 176–184)*

**Key words:** left ventricular non-compaction, heart failure, children

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## Introduction

Left ventricular non-compaction (LVNC) is a specific cardiomyopathy (CMP) caused by a disruption in the embryogenesis of the endocardium and myocardium. Formerly known as 'spongy myocardium' it is characterized by trabeculations and deep intertrabecular recesses in the ventricular myocardium [1–3]. Its frequency has increased and it has been reported as comprising 9% of all childhood cardiomyopathies in recent studies [2–4]. It typically affects the left ventricle (LV) but the right ventricle (RV) can be affected as well [2, 5].

The anatomical structure of this cardiomyopathy can be detected at birth, but may appear at any age and have variable clinical presentation. Deterioration of systolic and diastolic functions, congestive heart failure (CHF), thromboembolic events, supraventricular and ventricular arrhythmias are its major clinical features [2–4, 6–13]. In the majority of LVNC patients, presence of dysmorphic facies, growth retardation and neuromuscular anomalies, findings of mitochondrial disease in muscle biopsies and the presence of similar patients in the family history suggest the possibility of metabolic disease [3, 8].

While LVNC is generally diagnosed using certain echocardiographic criteria, cardiac magnetic resonance imaging (MRI) can also be useful in suspected cases of LVNC and may help determine the prognosis by detecting fibrosis [14–16].

In this, the largest study of the pediatric population with LVNC in our country, we present the clinical findings at referral, 24-hour Holter electrocardiographic (ECG) findings, treatment and follow-up of 24 patients with LVNC diagnosed by echocardiography (ECHO) and cardiac MRI. Due to the possible association with metabolic disease, metabolic screening was done in all patients, while muscle biopsy and cranial MR were done where necessary.

## Methods

Twenty-four LVNC patients aged between eight days and 15 years were enrolled in this study between January 2006 and March 2010. Detailed histories, previous diagnoses, physical examinations, associated diseases, 12-lead ECGs, chest X-rays, metabolic disease screenings, 24-hour Holter ECGs, 2-D, M-mode and color Doppler ECHOs and cardiac MRIs of 22 patients were recorded. Clinical follow-up, treatment and invasive procedures were recorded as well.

2-D, M-mode and color Doppler ECHO examinations were evaluated according to the guidelines of the American Echocardiography Association [17, 18]. Trabeculations and deep recesses in the LV myocardium were assessed in the parasternal, apical and subxiphoid views. Left ventricle end-systolic/diastolic diameters and shortening fraction were estimated and structural pathologies were also recorded.

LVNC diagnosis was made after ECHO examination [14] if:

- there was an increase in segmental LV wall thickness, and if thin compact epicardial layer and thick non-compacted endomyocardial layer were present;
- the ratio of end-systolic non-compacted/compacted myocardium was  $> 2$ ;
- there were deep intertrabecular recesses communicating with ventricular cavities and flow was detected with color Doppler ECHO in these areas.

Echocardiographic examinations were done by three different pediatric cardiologists and the affected segments were recorded.

Cardiac MRI was performed using a 1.5 T scanner (Symphony, Siemens Medical Systems, Erlangen, Germany). In the test, the myocardium was divided into nine parts (one apical, four midventricular, four basal) and the diagnosis was made if the ratio of thick non-compacted myocardial layer to thin compacted epicardial myocardium layer was greater than 2.3 at end-diastole.

The study was approved by the local bioethical committee and all patients gave their informed consent.

## Statistical analysis

Statistical Package for the Social Science 13.0 for Windows (SPSS, Chicago, IL, USA) was used for data analysis (reliability, construct validity and internal consistency). The average values and intervals were specified as  $\pm$  SD. Continuous variables were shown as mean, categorical variables were shown as percentage or ratio. Our categorical data was compared with data from other studies using Fisher's exact test and  $\chi^2$  test (Table 1). Continuous variables were not compared due to lack of data in other studies. A  $p < 0.05$  was considered as significant.

## Results

### General findings and demographic data

LVNC was detected in only 24 out of the 20,000 patients examined echocardiographically over a four

**Table 1.** Clinical characteristics of children diagnosed with left ventricular non-compaction.

Characteristics	Chin et al. [7]	Ichida et al. [8]	Pignatelli et al. [2]	Tsai et al. [3]	Wald et al. [4]	Alehan [13]	Present study	P*
Number of patients	8	27	36	46	22	9	24	
Male (%)	63	56	56	50	41	88	75	NS
Age at diagnosis (years)	7	5	0.25	0.44	3.9	7	4.1	
Mean follow-up (years)	≤ 5	6	3.2	1.2	3	≥ 5	≤ 5	
Decreased EF (%)	63	48	83	52	77	66	71	NS
ECG abnormalities (%)	88	88	75	80	100	77	87.5	NS
WPW syndrome (%)	13	15	17	7	9	0	4	NS
Ventricular tachycardia (%)	38	0	3	4	14	0	4	0.039**
Heart failure (%)	63	22	39	54	91	56	33	< 0.001***
Systemic embolic events (%)	38	0	0	2	0	0	0	0.01**
Death (%)	38	7	14	20	14	22	12.5	NS

EF — ejection fraction; WPW — Wolff-Parkinson-White; NS — not significant; \*our own patient group, compared with other groups as binary; \*\*our group of patients, and Chin et al. [7] data are compared; \*\*\*our group of patients, and Wald et al. [4] data are compared

**Table 2.** Signs and symptoms of patients at initial diagnosis.

Signs and symptoms	Number of patients
Congestive heart failure	8
Heart murmur	2
Cyanosis	2
Failure to thrive	2
Cardiomegaly on chest X-ray	5
Rhythm disorders and ECG abnormalities	5

year period. Eighteen (75%) patients who were diagnosed with ECHO and cardiac MR were male, and six (25%) were female. Average age at diagnosis was 50 ± 60 months (eight days to 15 years) and mean follow-up period was 22 ± 12 months (between four months and four years).

**Clinical findings**

Ten (41%) out of the 24 patients with LVNC were less than one year old. Clinical findings of patients before diagnosis are shown in Table 2. The main presentation was signs of CHF, seen in eight (33%) patients. Cyanosis, heart murmurs, fatigue and weakness were seen less frequently. Cardiomegaly on chest X-ray in five patients, and ECG abnormalities in another five, were the main initial findings. Eight patients had more than one finding. Three (12.5%) patients had additional congenital heart disease. One of them had patent ductus arteriosus (PDA) and patent foramen ovale (PFO), another had complex cyanotic congenital heart disease

(tricuspid atresia, atrial septal defect, RV hypoplasia, ventricular septal defect and pulmonary artery hypoplasia), and the third had an aortopulmonary window and severe pulmonary hypertension. One patient underwent PDA coil occlusion, and the patient with complex cyanotic heart disease underwent a Blalock-Taussig shunt operation.

**Associated systemic diseases and metabolic screening**

During the diagnosis and follow-up of patients with LVNC, in nine (37%) of them additional clinical findings were observed. Four (16%) patients had dysmorphic facies, seven (29%) had neurological problems (including epilepsy, hypotonia, myopathy, macrocephaly, hydrocephaly, and mental/motor retardation), two had urinary system anomalies (renal atrophy secondary to horseshoe kidney and vesicoureteral reflux), and one had congenital adrenal hyperplasia. None of them had a family history of LVNC.

Because of the neurological problems and the reported association between LVNC and metabolic diseases [2], metabolic screening was performed in all patients. It included arterial blood gas, blood lactate, pyruvate and ammonia levels, muscle enzymes, amino acid and acylcarnitine profiles by tandem mass spectrofotometry, biotinidase screening and urine examination. Mitochondrial disease was detected in a patient with hypotonia and mental motor retardation, and very long chain fatty acid oxidation deficiency was found in a patient with chronic skeletal muscle myopathy and elevated muscle enzymes. Four patients with dysmorphic facies showed normal results of chromosomal analysis. No other genetic tests were performed.

### Electrocardiographic findings

Twenty-one out of the 24 (87.5%) patients with LVNC showed ECG abnormalities at diagnosis. The most frequent findings were: LV hypertrophy, ST depression in DII, III, aVF and V4–V6 leads, and flattened and inverted T wave. The Wolff-Parkinson-White (WPW) pattern was detected on the standard and Holter ECG of one patient, and hemodynamically significant bradycardia was seen in three patients. On the 24-hour Holter ECG, two patients showed short runs of supraventricular tachycardia (SVT), and a 15 year-old patient complaining of palpitations had 45 beats of ventricular tachycardia (VT). Standard ECG and Holter ECG findings were normal in three (12.5%) patients at diagnosis.

### Echocardiographic and cardiac MR findings

The echocardiographic and cardiac MR findings of patients with LVNC are shown in Table 3. Prominent LV trabeculation and intertrabecular recesses communicating with the ventricular cavity were detected with 2-D echocardiography (Fig. 1) and cardiac MR in all patients. Although it could not be seen with 2-D ECHO, RV involvement was observed with cardiac MR in four (16%) patients. None of our patients had RV involvement solely. Non-compaction was more prominent in the myocardial segment of the LV apex and posterior wall. ECHO showed the average end-systolic LV ratio of non-compacted to compacted myocardium to be 2.5 (2.1–3.5), while cardiac MRI showed the end-diastolic ratio to be 2.8 (2.4–3.5) (Fig. 2). Seventeen (71%) patients had LV dysfunction at diagnosis. Average ejection and shortening fractions were 46% (18–73) and 22% (8–38), respectively. None of the patients had intracardiac thrombi or embolic phenomena at diagnosis or during follow-up, but a 15 year-old patient (patient 15) who was referred to us with palpitations had been on coumadin for intracardiac thrombi for five years.

When we examined our patients retrospectively, we saw that ten of them (41%) were followed up with different diagnoses. Six of these ten were followed for their cardiac conditions and their diagnoses were delayed (patients 8, 12, 14, 18, 22, and 23 in Table 3). This delay in diagnosis may be explained by the similarity between cardiomyopathies and LVNC, and by a lack of experience in the clinician making the diagnosis. Five of these six patients were followed with the diagnosis of dilated cardiomyopathy and one was diagnosed with a double chambered LV.

### Treatment and follow-up

After the diagnosis, CHF was treated as follows: 15 patients were put on digoxin, 12 patients were put on furosemide and spironolactone for the diuretic effect, and 15 patients were put on captopril to reduce the afterload. Two patients with mitochondrial disease and fatty acid oxidation deficiency were treated with a metabolic drug complex (co-enzyme Q, carnitine, thiamine and medium-chain fatty acid diet). For CHF, 12 patients were treated with carvedilol, and an antiaggregant dose of acetylsalicylic acid was started in all patients. None of the patients had thromboembolic events. During follow-up, patient 1 (Table 3) had a permanent pacemaker implanted due to severe bradycardia, exercise intolerance and LV dysfunction, and another patient was treated with amiodarone for VT found on his Holter ECG. The other two patients with hemodynamically significant sinus bradycardia were diagnosed in the neonatal period. They were treated with isoproterenol and, since no further bradycardia episodes were seen, no additional intervention was made.

Depending on their clinical condition, patients were followed-up either every three or six months. In addition to routine ECG and ECHO exams, 24-hour Holter ECG was taken if necessary. In two patients with SVT, and one patient with VT, no relapse was seen after carvedilol and amiodarone+carvedilol treatment, respectively. In two patients with LV dysfunction who underwent treatment with anticongestants and carvedilol, LV ejection fraction rose above 55% after 15 months. In one patient, signs of systolic dysfunction increased, despite treatment. The other 11 patients experienced no improvement in LV function. None of the seven (29%) patients whose LV function was normal at diagnosis developed any ventricular function disorders and none needed drug treatment. No intracardiac thrombi were detected during echocardiographic follow-up in any of the patients.

Average follow-up period was 22 months (between four months and four years). Of the three patients who died, one was a 13 year-old on intense inotropic support who had been diagnosed with LVNC four years previously, had had dilated cardiomyopathy for three years and died of severe CHF and multi-organ failure. A second patient died in the intensive care unit after an adrenal crisis, severe metabolic acidosis, hypoglycemia and severe bradycardia. The third death was of a patient who had pulmonary hypertensive crisis and VT within

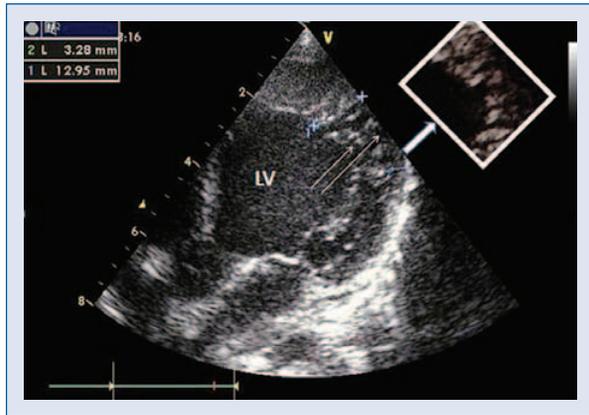
**Table 3.** Echocardiography and cardiac magnetic resonance imaging (MRI) findings at diagnosis\*.

Case no.	LVEDD [mm]	EF (%) (n ≥ 55%)	SF (%) (n = 29–48%)	Non-compacted segment localization	End-systolic NC/C (ECHO)	End-diastolic NC/C (cardiac MRI)	Additional cardiac pathology
1	47 (n ≤ 43)	47	22	LV apex, lateral wall	2.5	3.2	–
2	30 (n ≤ 31)	69	37	LV apex, posterior wall and septum	3.4	3.5	TA + VSD + ASD + RV hypoplasia, pulmonary hypoplasia
3	56 (n ≤ 40)	21	10	LV apex and lateral wall	2.4	2.5	–
4	46 (n ≤ 33)	35	14	LV lateral wall	2.8	3	–
5	30 (n ≤ 31)	67	35	LV apex and posterior wall	2.1	2.4	–
6	25 (n ≤ 30)	70	36	LV posterior wall	2.2	2.5	–
7	51 (n ≤ 37)	21	10	LV posterior and lateral wall	2.5	3	–
8	30 (n ≤ 43)	68	38	LV midventricular segment	2.5	3.4	–
9	52 (n ≤ 34)	23	11	LV apex, inferior ventricular septum	2.5	3	–
10	46 (n ≤ 37)	38	16	LV apex and posterior wall, RV apex	2.4	2.8	–
11	33 (n ≤ 37)	48	24	LV apex and posterior wall	2.4	2.5	PDA, PFO
12	39 (n ≤ 30)	29	14	LV apex and posterior wall	2.3	2.8	–
13	24 (n ≤ 30)	71	36	LV apex	2.2	–	–
14	60 (n ≤ 56)	32	19	LV apex and posterior wall, RV apex	3.4	3.5	–
15	64 (n ≤ 54)	48	26	LV apex	2.5	2.5	–
16	27 (n ≤ 30)	73	38	LV apex and mid ventricular segment	2.2	2.4	–
17	32 (n ≤ 30)	39	14	LV apex and lateral wall	3	3.5	–
18	57 (n ≤ 47)	18	8	LV apex, midventricular and lateral wall, RV apex	2.4	2.5	Pericardial effusion
19	33 (n ≤ 37)	56	29	LV apex and posterior wall	2.2	2.4	–
20	63 (n ≤ 61)	53	26	LV apex and posterior wall	2.4	3	–
21	58 (n ≤ 53)	54	26	LV apex and posterior wall, RV apex	2.3	3.2	Aorticopulmonary window, pulmonary hypertension
22	50 (n ≤ 56)	50	25	LV mid ventricular segment	2.2	2.4	–
23	71 (n ≤ 56)	28	12	LV apex and mid ventricular segment, lateral wall	2.3	3.4	–
24	32 (n ≤ 29)	48	23	LV apex and posterior wall	3.5	–	–

ASD — atrial septal defect; EF — ejection fraction; SF — shortening fraction; LV — left ventricular; LVEDD — left ventricular end-diastolic diameter; n — normal value; NC/C — non-compacted segment/compacted segment ratio; PDA — patent ductus arteriosus; PFO — patent foramen ovale; RV — right ventricle; TA — tricuspid atresia; VSD — ventricular septal defect; \*references [19] and [20] were used to evaluate normal left ventricular measurements.

24 hours of having an angiography (carried out for aortopulmonary window and severe pulmonary hy-

pertension and which revealed biventricular non-compaction).

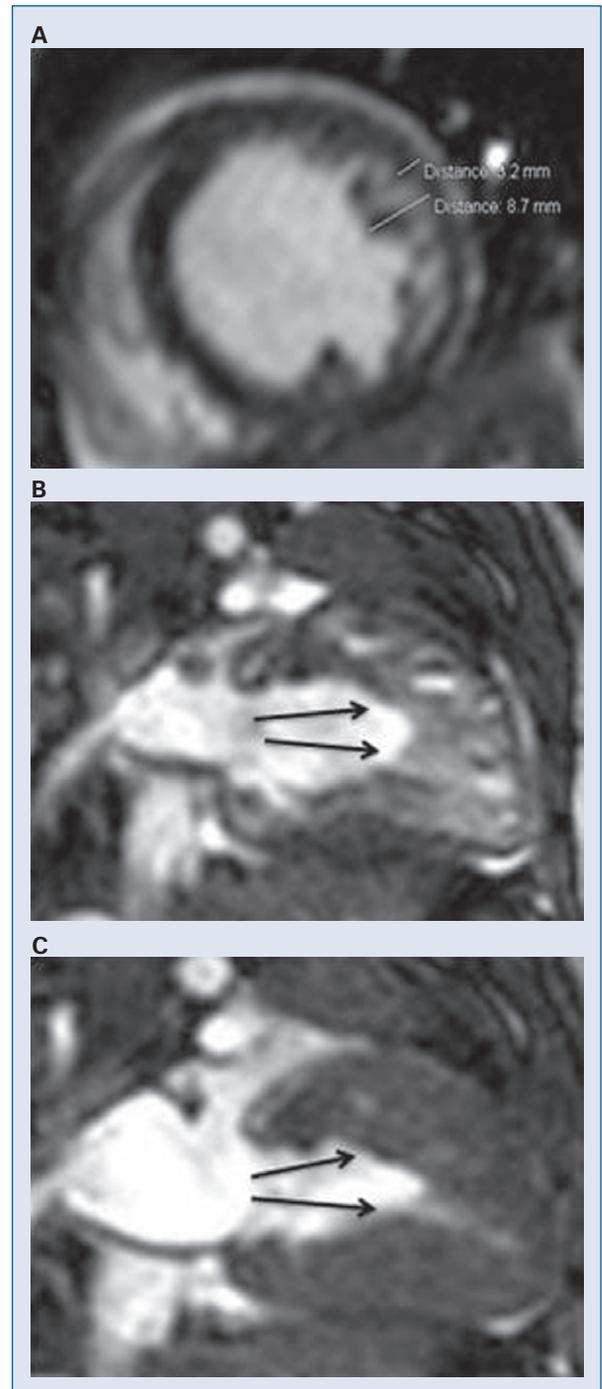


**Figure 1.** Echocardiographic examination. Trabeculations, non-compacted and compacted segments; LV — left ventricle.

## Discussion

Today, thanks to improved awareness and advanced diagnostic tools, LVNC is a congenital cardiomyopathy that is being diagnosed with increasing frequency [3]. The cause of the disease is thought to be a disruption of the endomyocardial morphogenesis at between the fifth and the eighth gestational week [2, 11]. The isolated form of the disease is rare and is classified as a genetic cardiomyopathy by the American Heart Association. It can coexist with congenital heart diseases, particularly during childhood [3, 21]. While pediatric studies report that the most frequently seen concomitant conditions are ventricular septal defect and LV outflow obstructions, LVNC can also be accompanied by tetralogy of Fallot, bicuspid aortic valve, Ebstein anomaly and PDA [3, 22–26]. Three (12.5%) of our patients had concomitant cardiac anomalies and one of the patients was being followed by an outpatient clinic due to LV hypertrophy and double chambered LV caused by mid-cavitary narrowing.

The first choice (and standard procedure) for diagnosing LVNC is 2-D Doppler echocardiography. But computed tomography, MRI and angiography can also be used for diagnosis [2–13]. For an accurate and reliable diagnosis, the physician must be familiar with the condition and must apply very specific diagnostic criteria. Despite this, misdiagnoses may still happen and patients may be followed with inaccurate diagnoses. LVNC is frequently misdiagnosed as dilated cardiomyopathy, hypertrophic cardiomyopathy, restrictive cardiomyopathy, endomyocardial fibroelastosis and myocarditis [8, 11, 13]. In our study group, six (25%) patients had been misdiagnosed. Five had been followed up with a diag-



**Figure 2.** Cardiac magnetic resonance imaging: **A.** Non-compacted and compacted segment in left ventricular short-axis view; **B.** End-diastolic spongeous appearance; **C.** End-systolic appearance.

nosis of dilated cardiomyopathy and one with a diagnosis of hypertrophic cardiomyopathy and double chambered LV. Similarly, Alehan [13] reports that in four (44%) of his patients, LVNC was misdiagnosed as dilated cardiomyopathy.

Even though RV involvement has been reported in patients with LVNC [2, 5, 27], it is clinically insignificant and difficult to diagnose with ECHO. Additional imaging modalities should be used to prevent a delay in diagnosis and the possible misdiagnosis of LVNC, which is a disease with a poor prognosis. Cardiac MRI has a good correlation with ECHO and has a high sensitivity and specificity in detecting non-compacted segments. Thus the chance of misdiagnosis decreases, and the obtained data on RV involvement, fibrosis and segmental analysis may increase [2, 15, 16, 28]. In our study, we performed cardiac MR in 92% of patients, detecting RV involvement in four (overlooked by ECHO).

Whether congenital heart disease is present or not, CHF, arrhythmias and thromboembolic events are the three major clinical presentations of LVNC. Particularly pediatric studies have shown that cardiac failure is the most frequent presentation at diagnosis and follow-up, with a prevalence of between 35% and 91% [2, 3, 5, 7–9, 13, 22] (Table 1). In our study, major clinical manifestations included cardiac shock in two patients, CHF in six and cardiomegaly in five. ECHO revealed LV dysfunction in 71% of patients. The cause of cardiac failure in patients with LVNC is unclear, but possible explanations include a coronary microcirculation disorder leading to subendocardial ischemia in the non-compacted area. Another possible explanation is dependence of the non-compacted area on aerobic oxidation and its sensitivity to hypoxia and the toxic effects of catecholamines [13, 22, 29–31].

Arrhythmias and thromboembolic events are mostly seen in adult patients as complications but may be also seen in childhood. Most of the patients (75–100%) in pediatric studies have ECG abnormalities [2, 3, 5, 7, 8, 13]. Despite an increase in the number of studies, the previously high ventricular tachycardia rate has noticeably fallen. The prevalence of WPW syndrome varies from study to study but its association with Ebstein anomaly is significant [2, 3, 7–13]. In our study, ECG findings were initially abnormal in all but three patients. VT attack and WPW pattern on Holter ECG were detected in one patient each. Three patients had symptomatic bradycardia, and a permanent pacemaker was implanted in one of them. After the implantation, complaints decreased and LV function improved. Systemic emboli are another important complication. Although their prevalence was as high as 38% two decades ago, recent studies report it as now being as low as 0–2% [2, 3, 7, 8, 13]. None of our patients developed systemic emboli; only one patient had been using long-term anticoagulants for

left-sided intracardiac thrombus. This decline in incidence may be the result of early diagnosis, regular and short-interval follow-up and/or antiaggregant or anticoagulant therapy.

Another interesting point is the association of LVNC with dysmorphic features and neuromuscular diseases [2, 7, 32]. Twenty-nine percent of the patients in our study had dysmorphic features and/or neurological findings, which led us to perform metabolic screening of all our patients. Two patients with neurological involvement had fatty acid oxidation disorder and mitochondrial disease, respectively. This suggests that it is only necessary to perform detailed metabolic screening for LVNC patients with dysmorphic features, neurological involvement or metabolic signs. In our study, three patients had dysmorphic features, neuromotor retardation and hydrocephalus, and one of them needed ventriculoperitoneal shunting. Even though previous studies have reported the association of LVNC with neurological signs, no study has reported the association between LVNC and hydrocephalus. Further follow-up and examination is necessary to clarify whether the association is coincidental or not.

Treatment of patients with LVNC should be directed towards the three most important clinical manifestations: CHF, arrhythmias, and systemic embolic events [2, 27–29, 33]. Standard treatment with inotropic support and preload and afterload reducers should be started in patients with systolic and diastolic ventricular dysfunction progressing to CHF [2, 5, 7–13]. In addition to this, patients with decreased systolic functions should be started on beta-blockers (especially carvedilol), which have been shown to improve LV and neurohormonal dysfunction in children [2, 5, 33, 34]. In addition to standard therapy, carvedilol was administered to 12 patients with CHF findings in our study. Continuous Holter ECG should also be performed in all patients due to increased risk of arrhythmias. All patients should be started on aspirin to reduce and prevent the risk of systemic embolic events. No embolic events during follow-up have been reported in patients who were on aspirin and being continuously monitored [2]. Similarly, all our patients were started on aspirin and no thromboembolic events occurred in the two year follow-up period in any of them. Several authors recommend long-term prophylactic anticoagulant therapy to patients with LVNC, regardless of the presence of thrombi, but standard procedure is to use low-molecular-weight heparin or coumadine only if thrombi have been detected [2, 8, 33, 35].

## Limitations of the study

Our study was performed in a tertiary center and so the study group may not accurately represent the general population. The study was retrospective, so one must take into consideration the relative shortness of the follow-up period and the fact that no detailed genetic analysis was performed. Treatment choices were made by the patients' first clinicians so the drug efficacy and the drugs' effect on complications could not be clarified. Long term forward-looking studies with more patients are needed to clarify these effects.

## Conclusions

LVNC is a congenital cardiomyopathy with variable clinical presentation. It can be diagnosed at any point between the neonatal period and adolescence. Although ECG abnormalities are frequent in the pediatric population, arrhythmia and thromboembolic events are rare. If LVNC patients have dysmorphic and abnormal neuromotor signs, detailed neurological examination and metabolic tests should be performed. Echocardiographic examination is the standard tool for diagnosis; however, the physician performing the examination must be familiar with specific findings that point to LVNC, so that any delay in diagnosis can be avoided. Cardiac MR is the diagnostic tool to be used when diagnosis is uncertain. Since LVNC is an important reason for morbidity and mortality, regular long-term follow-up is absolutely required.

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