Coll. Antropol. **33** (2009) 4: 1415–1419
Case report

Isolated Left Ventricular Non-Compaction Cardiomyopathy Associated with Ventricular Preexcitation: A Case Report

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A B S T R A C T

Isolated left ventricular non-compaction (ILVNC) is one of the most misclassified cardiomyopathies. It is caused by failure of normal embryonic development of the myocardium from loosely arranged muscle fibers to the mature compacted form of myocardium, but it seems that etiology is not exclusively congenital. Diagnosis of ILVNC is mostly missed because of lack of awareness and knowledge. The recognition of the disease is mandatory, because of its high mortality and morbidity due to the progressive heart failure, thromboembolic events and lethal arrhythmias. We report of a family in which two adult members were found to have ILVNC. A literature review about ILVNC pathogenesis, diagnosing, and treatment was discussed.

Key words: *cardiomyopathy, echocardiography, left ventricular non-compaction*

Introduction

Isolated left ventricular non-compaction (ILVNC) is a congenital cardiomyopathy caused by arrest of normal embryogenesis of endocardium and myocardium, characterized by multiple prominent myocardial trabeculations and deep intertrabecular recesses communicating with the left ventricular cavity[1]. Although clear diagnostic criteria have been established, ILVNC is not widely known yet, and as a consequence, its diagnosis is frequently missed[1]. Therefore, it could be speculated that frequency of ILVNC in the general population may have been underestimated. The recognition of the disease is mandatory, because of its high mortality and morbidity due to the progressive heart failure, thromboembolic events and lethal arrhythmias[2–4]. The most common findings in the ILVNC patients are nonspecific abnormalities of the resting electrocardiography (ECG)[1,3]. We present a family in which ILVNC was revealed in two adult members by ECG changes.

Case Report

A 26-year-old man was referred to the cardiologist because of an abnormal ECG, detected in the regular medical checking. ECG documented a sinus rhythm (80/min), with ventricular preexcitation evidenced by a short PR interval, a δ wave and repolarization changes (Figure 1). The patient was asymptomatic, with no history of cardiovascular risk factors or previous heart disease. A physical examination was unremarkable as well as there no abnormalities in results of chest radiography and routine hematological and biochemical parameters. Transthoracic echocardiography (TTE) in apical 4-chamber view showed prominent left ventricular trabeculations with deep intertrabecular recesses in the lateral wall and apex of the left ventricle (Figure 2a). Parasternal short axis view showed a honeycomb-like appearance typical for ILVNC. The ratio of non-compacted to compacted myocardial layers at the site of maximal wall thickness was 2.7. The color Doppler study showed blood flow from the

Received for publication November 6, 2008

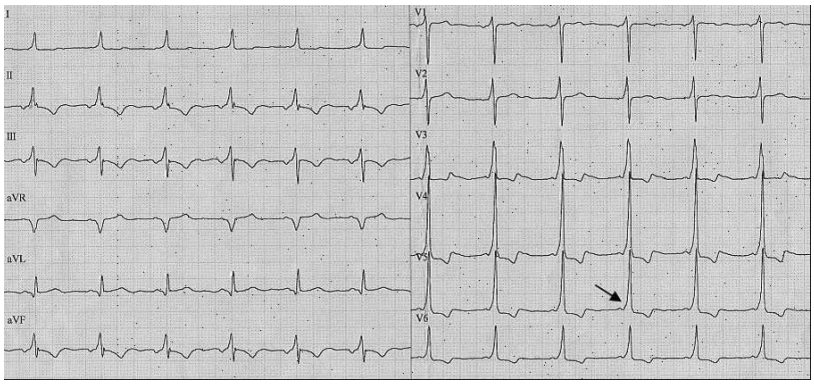

Fig. 1. Typical electrocardiographic preexcitation pattern with short PR interval, δ wave, and repolarization changes. Arrow indicate δ wave.

ventricular cavity into the spaces between the prominent trabeculations throughout the cardiac cycle (Figure 2b). There was no abnormality in the left ventricular regional contractility. Cavities size and left ventricular function, as well as function of the valves were normal. There was no pericardial effusion. Echocardiographic examination was interpreted as an ILVNC. Exercise stress imaging with thallium 201 revealed homogenous uptake of the radiopharmaceutical throughout the myocardium and has been described as normal. Holter recordings yielded no significant arrhythmia. Coronary angiography and electrophysiological study with eventual radiofrequency ablation were not considered due to lack of the manifest clinical indications. Because of echocardiographic presentation with dense and extensive ILVNC, despite sinus rhythm and normal left ventricular systolic function, a chronic anticoagulant therapy with warfarin was initiated with a target INR within the therapeutic range of 2.0–3.0.

Screening over three generations of family members abnormalities are demonstrated in the patient's father only. This 60-year old man has been treated due to dilated cardiomyopathy, with highly reduced left ventricular systolic function (ejection fraction 30%) for 15 years. His ECG demonstrated atrial fibrillation and left bundle branch block. Although there were no echocardiographic abnormalities typical for ILVNC, our opinion is that dilated cardiomyopathy in these patient is in the close etiopathogenic relationship with ILVNC. He had experienced an ischemic stroke seven years ago, and after that he received permanent anticoagulation. Beside that, there were no other abnormal neurological findings among ours cases.

Discussion

ILVNC is a congenital unclassified cardiomyopathy characterized by multiple prominent myocardial trabeculations and deep intertrabecular recesses communicating with the left ventricular cavity[1]. ILVNC was initially described in children, but recent studies have characterized this disease in adult populations in whom it may be missed because of lack of awareness and knowledge[4]. It

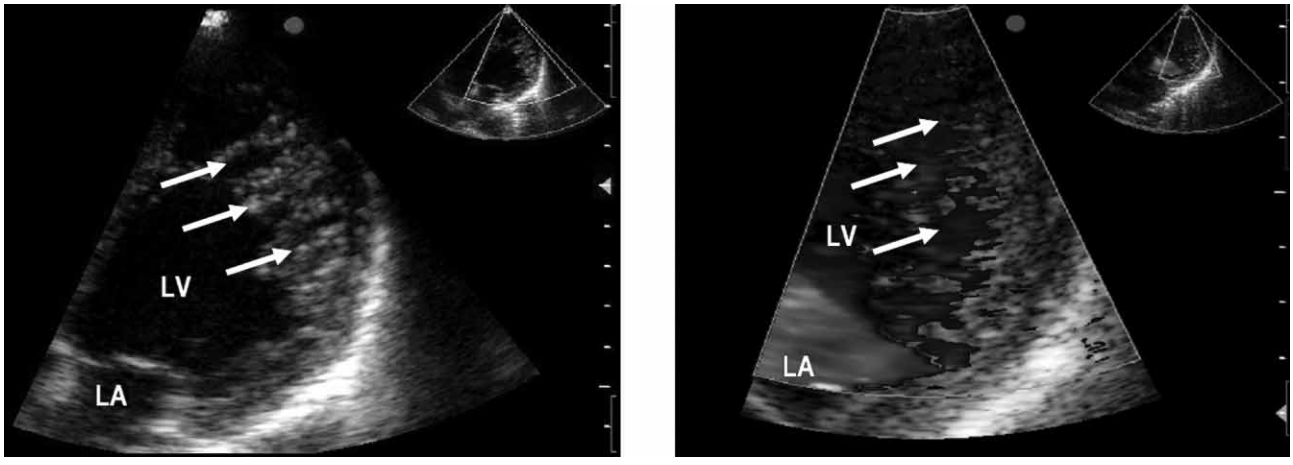

Fig. 2. a) Apical 4-chamber view, shows dense left ventricular trabeculations with deep intertrabecular recesses. b) Color-flow imaging shows communication between intertrabecular spaces and the left ventricular cavity. LV – left ventricle, LA – left atria, arrows indicate non-compacted left ventricle.

seems that etiology is not exclusively congenital: there is several case reports indicating that noncompaction may develop or disappear during lifetime[5]. According to some speculations in adults the prevalence of ILVNC is 0.014% to 0.25% *per* year[3,4]. However, the real prevalence of ILVNC among the general population is unknown since no investigations have been carried out thus far. It is possible that for that reason, as well as frequently asymptomatic course of the disease, ILVNC in adults is underappreciated in prevalence.

ILVNC is most frequently attributed to an arrest of the physiologic intrauterine compaction process during embryonic heart development[6]. During fetal ontogenesis the developing myocardium gradually condenses and large intertrabecular spaces transform into capillaries as the process of compaction occurs from epicardium to endocardium and from base toward the apex of the heart, with trabecular compaction being more complete in the left ventricular than in the right ventricular myocardium[6]. The coronary circulation develops concurrently during this process and the intertrabecular recesses are reduced to capillaries[6]. In the abnormal condition, the compaction process arrests at an early stage, resulted with deep recesses communicate only with the ventricular cavity, not the coronary circulation. Abnormal compaction process in ILVNC has a segmental distribution typically affecting apex, lateral and inferior wall of the left ventricle[3,7].

Failure of left ventricular compaction process is possible caused by mutations in the genes encoding ∝-dystrobrevin and Cypher/ZASP, integral parts of the complex which links the extracellular matrix of the myocardial cell to the cytoskeleton[8]. This mutation is also common in the patients with dilated cardiomyopathy and may explain frequently development of left ventricular dilatation and systolic impairment in patients with ILVNC, as well as the frequently occurrence of dilative cardiomyopathy and left ventricular enlargement without ILVNC in relatives of ILVNC patients[8]. Coronary microcirculatory abnormalities play an important role in ILVNC pathophysiology. Subendocardial perfusion abnormalities cause ischemia even in the absence of epicardial coronary disease and may be reason for microscopic necrosis in the subendocardial area and within trabeculations which have been documented in histological specimens during postmortem analysis of ILVNC patients[9]. Subendocardial ischemia in ILVNC could be attributed to isometric contraction of the endothelium and myocardium within deep intratrabecular recesses[9]. The underlying mechanism may be failure of the coronary microcirculation to grow with the increase in ventricular mass, or compression of the intramural coronary vascular bed by the hypertrophied myocardium, or a combination of both mechanisms[9]. Observed left ventricular systolic with or without diastolic dysfunction, arrhythmogenesis and hypokinesis of the left ventricle may also be consequence of the microcirculatory dysfunction[9].

Clinical manifestations of ILVNC are highly variable, ranging from no symptoms to disabling congestive heart failure, arrhythmias, and systemic thromboembolism[1–4]. The most common findings in the IVNC patients are nonspecific abnormalities of the resting ECG including left ventricular hypertrophy, inverted T waves, ST segment changes, axis shifts, intraventricular and atrioventricular conduction abnormalities[1–4]. Oechslin and al reported that abnormal ECGs were seen in 94% of adults, and 56% of them showed ventricular conduction defect[3]. Atrioventricular by-pass tract, like in our patient, has been reported in 13–15% of pediatric ILVNC patients, but it was not observed in the large observational studies of adults with ILVNC[3]. An extensive MEDLINE search revealed only few relevant reports of preexcitation in adult patients with ILVNC[10,11]. Conduction abnormalities are possible results of the progressive endomyocardial fibrosis in ILVNC and reasonable they are observed much more frequently in the adult population because the fibrotic change develops gradually[12]. Possible causal link between atrioventricular by-pass tract and ILVNC is unclear. The WPW syndrome is thought to arise from a failed regression of developmental embryologic atrioventricular anatomical and electrical continuity attributable to abnormal embryologic persistence of atrioventricular muscular continuity, which can also be seen in the failing regression of noncompacted myocardium in ILVNC[13]. The final separation of the right atrium from the right ventricle is part of the normal postnatal development, and it has been hypothesized that, as like as a normal process of compaction, the normal process of development of the annulus fibrosus after birth is also arrested[13]. ILVNC are also frequently associated with extra-cardiac manifestations in particular neuromuscular diseases, so it seems that is necessary extensive neurological and genetic testing, even in asymptomatic cases[5].

TTE is the gold standard for ILVNC diagnosis[1,7]. Four clear-cut echocardiographic diagnostic criteria have been established: 1) absence of coexisting cardiac abnormalities; 2) a 2-layered structure of the left ventricular wall, with the end systolic ratio of noncompacted to compacted layer >2; 3) finding this structure predominantly in the apical and mid-ventricular areas; and 4) blood flow directly from the ventricular cavity into the deep intertrabecular recesses as assessed by Doppler echocardiography[1,7]. Different echocardiographic diagnostic criteria also exist and overdiagnosis as well as missing of the diagnosis occurs[5]. Other modalities including transesophageal echocardiography (TEE), contrast ventriculography, computed tomography (CT) and cardiac magnetic resonance (CMR) may be also helpful, but no diagnostic criteria for these modalities have yet been proposed. CT and CMR guarantees more operator independency and might be superior to echocardiography in cases of an impaired echocardiographic imaging quality[14]. However, it should be kept in mind that both techniques also claim experienced operators and there are no comparison studies between these techniques and echocardiography, as well as the lack of large studies comparing pathoanatomic with echocardiographic or other imaging studies. Because myo-

cardial perfusion and coronary flow reserve in areas of ILVNC are impaired, CMR, PET and thallium-201 scintigraphy may be helpful in detection of subendocardial perfusion defects in these patients[13]. Although PET, CMR, echocardiography and ventriculography are reliable imaging modalities to diagnose ILVNC, only PET provides data to quantify the extent of the myocardial ischemia[15].

Treatment of ILVNC patients can be divided into the two categories regarding to clinical presentation and left ventricle function. In symptomatic ILVNC patients or in the patients with asymptomatic left ventricular dysfunction, treatment should consider for three major clinical manifestations: heart failure, arrhythmias and embolic events[3,4]. Treatment strategies for symptomatic ventricular arrhythmias in ILVNC are comparable to those currently recommended in cardiomyopathies, with special attention to proarrhythmic drug effects. In most severe cases, those with documented sustained ventricular arrhythmias, in NYHA classes III and IV, and/or severely dilated left ventricles, treatment of choice are implantation of automated cardioverter defibrillator or heart transplantation[3,4]. On the other hand, management of the asymptomatic ILVNC patients with preserved left ventricular function and no standard thromboembolic risk factors (e.g. atrial fibrillation, prior embolic event, age >75 year, diabetes) is more difficult. Despite an increasing interest in this disorder until to date there have not been clinical studies to show potential differences in outcome in this group of ILVNC patients treated with anticoagulants, ACE-inhibitors, beta-blockers or amiodarone. Therefore, there are no clear recommendations about necessity of medical treatment for asymptomatic ILVNC patients with preserved left ventricular function. However, it has been reported that the majority of ILVNC patients who were asymptomatic at presentation developed left ventricular dysfunction within 6 years of diagnosis[3]. Although, it has been reported beneficial effect of carvedilol in infants with ILVNC on left ventricular function, mass and both metabolic and adrenergic abnormalities[16], there are no effectiveness data of early carvedilol treatment in adult ILVNC patients with preserved left ventricular function. Indeed, there is no uniform opinion about necessity of preventive permanent anticoagulation. Contrary to opinion that even ILVNC patients with sinus rhythm and normal left ventricular systolic function should be anticoagulated[3,4,17], some authors suggests that thrombus-formation is a rare event in patients with ILVNC, and that ILVNC by itself does not seem to be an embolic risk factor[18]. However, thromboembolic events have been observed in young patients with sinus rhythm and normal left ventricular function[19]. Therefore, treatment for asymptomatic ILVNC patients with preserved left ventricular function should be individualized. In that context, we stress potential role of echocardiography in decision making of necessity for permanent anticoagulation and treatment with ACE--inhibitor and carvedilol[20]. By our opinion, ILVNC patients with dense and extensive hypertrabeculations, even in the case of preserved ventricular function and no additionally embolic risk factors should be anticoagulated. Contrary, ILVNC patients with similar clinical characteristics, but with a rare trabeculations and capacious intertrabecular spaces, may be treated with low-dose aspirin (≤325 mg/day). Also, echocardiographic documented ILVNC is a reliable reason for initiating therapy with carvedilol and ACE-inhibitor titrating up to maximal tolerable doses[20].

Conclusively, we recommend that in patients with non-specific ECG abnormalities ILVNC should be considered. Echocardiography is mandatory in the ILVNC patients' first-degree relatives due to frequent findings of ILVNC, dilated cardiomyopathy, and left ventricular enlargement. Due to high possibility of left ventricular dysfunction development, initiating carvedilol and ACE-inhibitor are recommended.

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IZOLIRANA NEKOMPAKTNA KARDIOMIOPATIJA LIJEVE KLIJETKE S PREEKSCITACIJOM – PRIKAZ SLUČAJA

S A Ž E T A K

Izolirana nekompaktna kardiomiopatija lijeve klijetke jedna je od najčešće neprepoznatih kardiomiopatija. Posljedica je zastoja u normalnom embrionalnom razvoju miokarda tijekom kojeg iz neorganiziranih mišićnih vlakana nastaje zreli kompaktni miokard. Ova kardiomiopatija se često previđa zbog nedostatnog poznavanja ovog entiteta. Dijagnosticiranje je osobito značajno zbog visokog pobola i smrtnosti, kojima su uzroci progresivno zatajenje srca, tromboembolijski incidenti i maligne aritmije. U radu je prikazana obitelj, u kojoj je dijagnosticirana izolirana nekompaktna kardiomiopatija lijeve klijetke u dva odrasla člana. Također se iznose trenutne spoznaje u svezi s patogenezom, dijagnostikom i liječenjem bolesnika s izoliranom nekompaktnom kardiomiopatijom lijeve klijetke.