Left ventricular non-compaction with congenital diaphragmatic hernia causing cardiac dextroposition

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Abstract

A 45-year-old man with a 2-month history of breathlessness, fatigue and irregular heart rate was referred to our centre after first-ever cardio-pulmonary decompensation. At presentation he was stable with heart rate of 120/min, blood pressure of 140/90 mmHg, in NYHA class II. 12-lead ECG showed atrial fibrillation, low R-waves voltage and deep S-waves with non-specific ST changes in V1-V6. A posterior-anterior chest X-ray showed an enlarged cardiac silhouette, whereas on lateral picture an unusual structure was identified in the thorax cavity. An echocardiogram showed an enlarged, hypertrophied left ventricle (LV) with severe global systolic impairment. A computed tomography revealed an intestinal loop, characterized as the anterior Morgagni type congenital diaphragm hernia, in the anterior mediastinum resulting in the heart dislocation to the right side. Cardiac magnetic resonance revealed a thinned apex coupled with increased trabeculation at the apex, posterior, lateral and anterior wall. The measurements of double-layered LV wall, confirmed the diagnosis of LV non-compaction (LVNC). This case is an illustrate of a constellation of rare anomalies of LVNC, persistent left superior vena cava with a congenital anterior Morgagni-type diaphragm hernia, causing heart dextroposition. On multidisciplinary team meeting the general decision of conservative treatment was made with typical systolic heart failure pharmacotherapy, restoration of sinus rhythm, considering referral to ICD and/or CRT-D, and regular clinical and echocardiographic follow-up of both patient and patient’s pedigree. JRCD 2012; 1: 18–23

Key words: Cardiac malposition; Dextroposition; Diaphragmatic hernia; Left ventricular non-compaction

Case presentation

Previously fit and well 45-year-old man with 2-month history of gradually increasing breathlessness, fatigue and irregular heart rate was referred from the district hospital after cardio-pulmonary decompensation for the exhaustive cardiological work-up. The patient had typical risk factors of cardiovascular diseases such as hypertension, hyperlipidemia and nicotine abuse, otherwise the medical and family history was unremarkable. At presentation he was stable with an irregular heart rate of 120 beats per minute (bpm), arterial blood pressure of 140/90 mmHg, oxygen saturation of 98%, in New York Heart Association (NYHA) class II. On physical examination he was euvoletic, with normal jugular venous pressure and clear lung fields. Interestingly, heart sounds were more audible at the right side of the chest. Standard 12-lead ECG showed atrial fibrillation, low R-waves voltage and deep S-waves with non-specific ST changes in V1-V6 (Figure 1). However, after electrodes were replaced to the right side of the thorax, ECG revealed prominent R waves in precordial leads (Figure 2). A posterior-anterior chest X-ray showed an enlarged cardiac silhouette, whereas on lateral X-ray an unusual structure was identified in the thorax cavity (Figure 3 and 4, arrows). A transthoracic echocardiogram was of poor quality, nevertheless, revealed enlarged and hypertrophied left ventricle (LV) with severe global systolic impairment (ejection fraction...
of 20%), bi-atrial enlargement with right ventricular systolic pressure up to 40 mmHg. As the results of the examinations were so far rather inconclusive, the patient was scheduled for more advanced imaging studies. Surprisingly, computed tomography (CT) revealed an intestinal loop in the anterior mediastinum resulting in the heart dislocation to the right side. The meticulous analysis of CT scan confirmed the diagnosis of rare form of the diaphragm pathology, namely the anterior Morgagni type congenital diaphragm hernia (Figure 5). Apart from the heart dislocation, the hernia also might had caused the lung compression and impairment of breathing mechanism, however, no functional abnormalities were detected by spirometry. Cardiac magnetic resonance (CMR) repeatedly demonstrated the heart displacement to the right side and confirmed severe systolic dysfunction of the enlarged LV (end-diastolic volume of 197 ml, ejection fraction of 20%). More importantly, a thinned apex (4.5 mm) coupled with increased trabeculation (up to 15 mm) at the apex, posterior, lateral and anterior wall clearly showed double-layered LV structure (Figure 6). Thorough measurements of the LV wall thickness and calculation of compacted and non-compacted layers ratio, confirmed the diagnosis of LV non-compaction (LVNC). Moreover, the CMR examination revealed the persistent left superior vena cava draining to the coronary sinus (Figure 7, arrow). The patient underwent also cardiopulmonary exercise test which revealed moderate exercise capacity impairment with peak oxygen uptake ($\text{VO}_2\text{peak}$) of 18 ml/kg/min (that represents 54% of predicted value), and normal ventilatory equivalent for carbon dioxide ($\text{VE}/\text{VCO}_2$) of 27. On 24-hour ECG monitoring AF was found during whole time with inadequately controlled ventricular rate ($\text{HR}_{\text{max}}$ – 130 bpm; $\text{HR}_{\text{min}}$ – 78 bpm; $\text{HR}_{\text{mean}}$ – 93 bpm), coupled also with numerous supra-ventricular (1500) and ventricular (1200) singular ectopic beats but no serious ventricular arrhythmias. To complete the diagnostic process, the patient underwent also invasive studies. Coronary angiography excluded coronary artery disease and other pathological findings in the coronary bed. Left ventriculogram confirmed global LV systolic dysfunction and two-layered LV structure with deep, blood-filled recesses (Figure 8, arrows). Right heart catherization showed no intra-cardiac shunts, moderately reduced cardiac output of 3.5 l/min, mean pulmonary artery pressure of 25 mm Hg, pulmonary capillary wedge pressure of 12 mm Hg, and pulmonary vascular resistance of 3 Wood units.

### Introduction and classification

Left ventricular non-compaction (LVNC) is a rare congenital cardiomyopathy, which presumably results from the premature arrest of endomyocardial formation during embryogenesis [1]. The hallmark feature of the LVNC is a double-layered LV wall, which is composed of thin, compacted myocardium on the epicardial side and much thicker, trabeculated, non-compacted myocardium on the endocardial side, which forms deep, blood-filled recesses protruding into LV cavity [1,2].

The complexity of LVNC is well reflected with the difficulties to classify this rare condition. According to the current European Society of Cardiology Working Group on Myocardial and Pericardial Diseases guidelines LVNC belongs to the heterogeneous group of unclassified cardiomyopathies [3]. However, American Heart As-
association classified LVNC as primary genetic cardiomyopathy [1]. Although LVNC is recognized as an isolated disease, the non-compaction of the ventricular wall is frequently seen in other conditions, such as congenital right or left outflow tract abnormalities, bicuspid aortic valve, Ebstein’s anomaly, patent ductus arteriosus, or ventricular and atrial septal defects [4]. Additionally, non-compact-ed myocardium was confirmed in other types of cardiomyopathies due to neuromuscular disorders or metabolic diseases [5].

**Epidemiology**

The true epidemiology of LVNC in the general population is unknown. There were only 34 diagnosed cases of LVNC in the referral Swiss echocardiographic laboratory (0.014% of all echocardiograms) during 15 years [6]. This figure is probably an underestimate and with increasing awareness the diagnosis of LVNC is more frequent. In the contemporary registry of systolic heart failure (HF), LVNC was confirmed in 3% of 960 consecutive HF patients [7].
Genetics

As any cardiomyopathy, LVNC may either be sporadic or familial. Detailed history and echocardiographic examinations of relatives showed familial occurrence of LVNC in 12 to 50% of cases [6]. Generally, autosomal dominant inheritance pattern is the most common but X-linked and recessive transmission has also been reported. So far the causative mutations have been identified in nine genes encoding following proteins: tafazzin (TAZ), α-dystrobrevin (DTNA), LIM domain binding protein (LDB3), β-myosin heavy chain (MYH7), α-cardiac actin (ACTC), lamin A/C (LMNA), cardiac troponin T (TNNT2), tropomyosin 1 (TPM1) and (SCN5A) [8]. Strikingly, the same mutations described in LVNC can lead to dilated, hypertrophic or restrictive cardiomyopathy and even in the same family, the same genotype can produce various phenotypes. Therefore, from the genetic point of view, the completely different phenotypes of cardiomyopathies can have the same genetic background, such a phenomenon is termed phenotypic heterogeneity. Therefore, the most exciting and unresolved issue is what factors determine that mutations in the same genes can lead to different myocardial disorders.

The increasing understanding of the genetic nature of cardiomyopathies has prompted the recent European and American guidelines on this issue [9,10]. In contrast to more frequent and better studied cardiomyopathies, the recommendations on the routine genetic evaluation of LVNC are weak and reflect numerous uncertainties and gaps in the understanding of the nature of this condition. Nevertheless, at present a careful, at least three generation family history and clinical and echocardiographic evaluation is advocated [9,10].

Clinical manifestations

Classically, LVNC is characterized by the triad of 1) HF symptoms such as fatigue, dyspne on exertion, lungs or peripheral congestion, etc., 2) arrhythmias and 3) consequences of thrombo-embolic events, including stroke [6,11]. In the historical and widely cited Swiss registry dyspne was reported in 80% of patients, 35% were in NYHA class III or IV, and a quarter had AF [6]. Based on overlapping symptoms and sometimes inconclusive results of examinations, the differential diagnosis of LVNC should include other types of cardiomyopathies such as dilated, hypertrophic particularly apical, infiltrative, as well as a hypertensive heart disease.

The diagnosis of LVNC

The first-line modality for the diagnosis of LVNC is trans-thoracic echocardiography. At present there are three distinct echocardiographic criteria of LVNC, established by Stollberger, Chin, and Jenni [5,12,13]. They differ between each other in the number of ways such as the phase of the cardiac cycle when the measurements are performed, echocardiographic projections, and what cardiac structure is actually assessed. Generally, the criteria are based on the concept of two-layered LV wall, where non-compacted, endocardial layer is much thicker than compacted, thin, external layer. Although such an approach in LVNC reflects the hallmark feature of the disease, serial echocardiographic and CMR studies in the large cohorts of patients, showed that increased LV trabeculation is more common than previously perceived [14]. Therefore, the LVNC diagnosis on the individual basis may be problematic and it looks that it is rather continuum between normal echocardiographic images, thorough various stages of hypertrabeculation to the phenotype of LVNC. Additionally, there is only weak correlation between those three sets of criteria. In the recently published study, Kohli et al. reported that only one-third of patients diagnosed with LVNC
full-field all three criteria and 8% of healthy individuals had at least one criterion of LVNC, especially people of African origin [15].

Because of the frequent over-diagnosis of LVNC with echocardiography, CMR is becoming increasingly important. There are two approaches for the conformation of LVNC with the use of CMR. Criteria published by Petersen et al. utilize the same two-layered LV wall structure as echocardiography [16]. On the other hand, Jacquier et al. advocate different approach. They recommend to measure the mass of LV and also separately mass of trabecule. If the mass of trabecule exceeds the mass of whole LV by 20%, than LVNC can be diagnosed [17].

Newly-developed echocardiographic assessment of LV rotation seems promising as a supportive measurement in LVNC. In healthy subjects and in majority of cardiac conditions, including dilated cardiomyopathy, the opposite direction of rotation between the heart base and apex is observed, where the base rotates clockwise whereas apex counter-clockwise. Interestingly, in LVNC both base and apex rotates in the same direction [18].

Prognosis

Historical studies reported very poor prognosis in patients diagnosed with LVNC with 35% mortality in 4-years observation [6]. However, those reports came mostly from the tertiary centers and severely affected patients, who were not treated with modern pharmacotherapy. More recent studies showed that LVNC is not as malignant condition as previously perceived. In one report of 45 patients with LVNC, the 4-year survival was actually 97% [2].

Management

Due to low prevalence and challenging diagnosis of LVNC, there are no randomized, controlled therapeutic trails and management is mostly based on the analogy with other types of cardiomyopathies and heart failure. Furthermore, there is no specific therapy for LVNC. Generally, when patients presents with HF symptoms and on echocardiogram LV systolic dysfunction (LVSD) is present, than ESC endorsed HF guidelines should apply [19]. Similarly, for asymptomatic LVSD recent ESC-HF guidelines on pharmacotherapy and devices is best what can be offered. Because of an altered LV structure with deep recesses and blood pooling, LVNC patients have increased risk of thrombo-embolic events, particularly when associated with AF. Therefore, rather low threshold for oral anticoagulation is widely accepted. Patients with LVNC are particularly prone to life-threatening ventricular arrhythmias. In one case series in 20% of patients either symptomatic or asymptomatic ventricular tachycardia (VT) was observed in 24-hour ambulatory ECG monitoring [2]. Therefore, regardless of the arrhythmia symptoms, annual Holter monitoring is recommended for all LVNC patients. Indications for implantable cardioverter-defibrillator (ICD) are not different from standard indications in non-ischemic cardiomyopathy. However, as patients with LVNC are probably at higher risk of sudden cardiac death (SCD), the broader use of ICD may be advantageous. Therefore, the widely accepted criteria for the primary prevention of SCD include syncope, non-sustained VT, severe LVSD (EF < 35%) or family history of SCD. Patients with refractory, end-stage HF are candidates for LV assist devices (LVADs) and heart transplantation, and should undergo standard qualification process.

Cardiac malposition in the thorax cavity

Cardiac dextroposition is defined as a displacement of the heart to the right secondary to extra-cardiac causes such as right lung hypoplasia, right pneumonectomy, or diaphragmatic hernia. Mechanical malposition, as in the case of diaphragmatic hernia, usually causes leftward cardiac axis. In contrast, the broad term dextrocardia is a pathological cardiac location in the right hemithorax but is intrinsic to the heart itself and not caused by extra-cardiac abnormalities. In dextrocardia the base-to-apex axis is directed rightward. Dextrocardia accounts for approximately 0.01% of life births, however, the precise epidemiology of dextroposition is not known. There are several types of dextrocardia, which will be briefly reviewed below. The most common is dextrocardia with situs inversus, L-loop ventricles, and inverted great arteries, which is termed mirror-image dextrocardia. In one-quarter of mirror-image dextrocardia cases, occurs Kartagener syndrome (primary ciliary dyskinesis), which is characterized by the triad of situs inversus, parasternal sinusitis, and bronchiectasis. Dextrocardia with situs solitus, D-loop ventricles, and normally positioned great arteries is caused by the lack of the final leftward shift of the heart during embryologic development and is termed dextroversion. In great majority of dextroversion, there are additional cardiac malformations, including spetal defects, tetralogy of Fallot, etc. Less common types of dextrocardia include dextrocardia with situs solitus, D-loop ventricles and congenitally corrected transposition of the great arteries (TGA), dextrocardia with situs inversus, D-loop ventricles, and congenitally corrected TGA, and lastly dextrocardia with the heterotaxy syndromes of asplenia and polysplenia [20,21,22].

In this case, the “extra-cardiac” abnormality, causing dextroposition, was proofed to be an asymptomatic, congenital diaphragmatic hernia. Surprisingly, the base-to-apex axis was rightward, which was caused probably by additional right-sided cardiac rotation along the longitudinal axis during the movement of the heart to the right hemi-thorax.

Congenital diaphragmatic hernia (CDH) occurs in 1 out of every 2000–3000 live births and accounts for 8% of all major congenital anomalies [23]. Anterior Morgagni hernia represents only 2% of all CDH cases [23].

So far, very few cases of LVNC associated with cardiac malposition have been published. In those reports, the reason for cardiac malposition was established to be dextroposition, which is the result of an abnormal heart development [24,25,26]. Despite extensive search of the literature, no report of LVNC with dextroposition has been identified.

Our management strategy This case is an illustrate of a constellation of rare anomalies of LV non-compaction, persistent left superior vena cava with a congenital anterior Morgagni-type diaphragm hernia, resulting in heart displacement to the right side of the tho-
rax, mimicking dextrocardia but in fact is dextroposition. Therefore, the proper management is based rather on expert’s opinions or anecdotal reports, rather randomized studies. Bearing in mind that the diagnosis of LVNC is challenging, the multi-modality imaging with the utilization of CMR is strongly encouraged, especially when echocardiography does not provide equivocal answers. The mean age of the LVNC diagnosis is usually third or forth decade, so our patient has been asymptomatic for a long time. It was believed that the initial hemodynamic compromise was probably the result of new-onset AF. Therefore, after slowing down his ventricular response with beta-blocker to approximately 100 bpm, he felt much better. Patients with LVNC have an increased risk of thrombo-embolic events, especially in the setting of AF. Our patient was initially treated with low molecular weight heparin and after all diagnostics tests, including invasive studies, he was switched to prolong oral anticoagulation with Warfarin. According to the HF guidelines, the patient was prescribed with beta-blocker (Bisoprol 7,5 mg o.d.), angiotensin converting enzyme inhibitor (Ramipril 5 mg b.d.) and aldosterone antagonists (Spironolacton 25 mg o.d.). As no serious ventricular arrhythmias was found on Holter and except for LVSD, the patient had no other major risk factors of SCD, we postponed the decision to perform invasive studies was made to search for possible pathologies in the coronary circulation and to verify the presence of pulmonary hypertension as echocardiogram did not provide clear answer. After four weeks on adequate oral anticoagulation therapy, we performed direct current cardioversion, which restored sinus rhythm of 62 bpm, nevertheless, we decided to continue with Warfarin. After interdisciplinary discussion with lung specialist and cardio-thoracic surgeon, the patient has been disqualified from heart transplantation. Due to good functional status after initiation of HF pharmacotherapy, at present he is not considered for heart transplantation. Careful family history did not reveal a trace of inherited cardiac diseases. Moreover, we performed clinical and echocardiographic examinations of patient’s pedigree, which showed normal left-sided heart position in the thorax cavity and no sings of heart pathology. The patient remains as an outpatient in the heart failure clinic.

Conflict of interest: non declared.

References