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Review Article

Isolated Left Ventricular Non-Compaction: A Clinical Update

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Abstract

Isolated LV non-compaction is a rare disorder that can cause sudden cardiac death, heart failure and systematic embolization. Family members of affected patients need to be screened since ILVNC could be inherited in autosomal dominant and autosomal recessive fashion. ILVNC could be part of a broader spectrum of cardiomyopathy, this is supported by common genetic mutations and the finding that family members of ILVNC could have hypertrophic or dilated cardiomyopathy.

Keywords: *Cardiomyopathy; Sudden Cardiac Death; Non-Compaction*

Abbreviations

ILVNC: Isolated Left Ventricular Non-Compaction; LV: Left Ventricle; PET: Positron Emission Tomography; MRI: Magnetic Resonance Imaging; ICD: Implantable Cardioverter Defibrillator; BIV ICD: Biventricular Defibrillator

Introduction

Non-compaction of the left ventricular (LV) myocardium is a rare disorder that occurs in isolation or with other congenital cardiac defects. It is caused by the arrest of compaction of the myocardial fibers, leading to prominent trabeculations. Patients could be asymptomatic and could present with syncope, chest pain, palpitations, shortness of breath and sudden cardiac death. Management of patients with isolated left ventricular non-compaction (ILVNC) involves treating heart failure, protection from sudden cardiac death and anticoagulation to prevent thromboembolic events. Screening of family members is important, since familial involvement is common and usually affected family members are asymptomatic.

Epidemiology

The true prevalence of isolated LV non-compaction is unknown, as most cases are referred to tertiary care centers. In clinical series, the prevalence ranges from 0.05 to 0.25%. The median age at diagnosis ranges from 90 days to 45 years and males are more commonly affected than females [1-4].

Pathology

Non-compaction of the left ventricular myocardium is caused by the arrest of intrauterine compaction of the myocardial fibers, leading to prominent trabeculations giving the myocardium a spongy appearance [5]. It is often associated with other congenital cardiac anomalies, especially obstruction of the right or left ventricular outflow tracts. However, the deep intertrabecular recesses that persist in these cases are in communication with the ventricular cavity and the coronary circulation [2]. In contrast, the intertrabecular recesses in isolated LV non-compaction are in communication with the LV cavity only and not with the coronary circulation. Histologically, there is myocardial thickening as well as interstitial and subendocardial fibrosis [6]. Microcirculatory dysfunction is present in both compacted and noncompacted segments which might explain the subendocarial scar noted on biopsies as well as impaired diastolic filling and wall motion abnormalities noted in imaging modalities [7].

Genetics

Familial involvement was high in initial reports describing isolated LV non-compaction [8]. In later series involving adults, the familial recurrence ranged from 12 to 44%. Some mutations involving the G4.5 gene have X linked Inheritance [9,10]. However, autosomal dominant inheritance was first reported with mutations in chromosome 11p15 [10,11]. Subsequently, sarcomere protein gene defects were also detected in patients with ILVNC and almost half the families screened had autosomal dominant inheritance [12]. Mutations in cipher/ZASP, a gene encoding for the Z-band, can cause dilated cardiomyopathy as well as ILVNC [13]. In a study of 63 unrelated patients with ILVNC, mutations in genes encoding sarcomere proteins were identified in 11 patients. These genes include β myosin heavy chain (MYH7), α-cardiac actin and cardiac troponin T. Similar sarcomere gene mutations, especially in MYH7 are also found in patients with hypertrophic and dilated cardiomyopathies [14]. These sarcomere mutations could account for up to 29% of mutations in ILVNC, but they do not predict clinical outcome [15]. In a study of 58 patients with ILVNC, screening using electrocardiography, echocardiography as well as genetic screening revealed familial involvement in 64% of family members, but these family members did not necessarily have ILVNC, but some had dilated or hypertrophic cardiomyopathy. Furthermore, 63% of recently diagnosed family members were asymptomatic. Genes screened included MYH7, Myosin binding protein C (MYBPC3), Cardiac troponin C (TNNC1), TNNT2, Cardiac troponin I (TNNI3), cardiac regulatory myosin light chain (MYL2), cardiac essential myosin light chain (MYL3) and α tropomyosin (TPM1). The fact that these genetic mutations are also found in Hypertrophic as well as dilated cardiomyopathy underscores the importance of family screening and it is possible that ILVNC can be part of a broader spectrum of cardiomyopathy [12].

Clinical Presentation

Patients with isolated LV non-compaction can be asymptomatic for years and eventually could present with heart failure, arrhythmias, embolic events and sudden cardiac death. The clinical course is variable and depends on symptoms and left ventricular function. Patients who are asymptomatic have a more stable clinical course, while patients presenting with heart failure have a progressive clinical course leading to pump failure and malignant ventricular arrhythmias [16]. Most patients have some degree of LV dysfunction, which has been reported in up to 60% of patients in the four largest reports of LV non-compaction [8,1,2,17]. However, presentation as congestive heart failure with dyspnea on exertion has ranged from 30 to 68%. Patients could have systolic as well as diastolic dysfunction. Microcirculatory dysfunction could lead to ischemia and scar causing impaired diastolic filling, wall motion abnormalities and systolic heart failure. Impaired filling and abnormal relaxation leading to diastolic heart failure could also result from prominent trabeculations [7]. Several arrhythmias have been reported with ILVNC, including atrial fibrillation (5 - 29% in major reports), atrial tachycardia, premature ventricular complexes and ventricular tachycardia (18 - 47% in major reports). Sudden cardiac death accounted for 50% of deaths in ILVNC. Presence of sub-endocardial scar can act as a substrate of reentry in these patients. Embolic complications in ILVNC could be due to thrombus formation in the recesses of the trabeculations, due to stagnant flow from severely depressed LV function or from the presence atrial fibrillation. These emboli can go to the cerebrovascular circulation, peripheral circulation, or even coronary circulation [18,19]. The incidence of embolization has ranged from 21 - 38%. Anticoagulation to prevent thromboembolic complications is very important in ILVNC even in the absence of atrial fibrillation [6].

Electrocardiogram

Abnormalities noted in the electrocardiogram in patients with ILVNC include left bundle branch block, right bundle branch block, left ventricular hypertrophy with repolarization abnormalities, and AV block. Wolff-Parkinson-White syndrome has been described in children with ILVNC. Atrial fibrillation, frequent premature ventricular contractions with sustained and non-sustained ventricular tachycardia could be present and could be the first presentation of the disease. There is a high prevalence of early repolarization in patients with ILVNC, especially in those patients who present with malignant arrhythmias [1,2,20].

Imaging in Isolated Left Ventricular Non-Compaction

Echocardiography

Transthoracic echocardiography is the modality most commonly used to diagnose ILVNC [21]. The most common criteria used for diag-

noses have been proposed by Jenni., *et al*. with a ratio of non-compacted to compacted LV myocardium of 2 to 1 considered diagnostic [22]. This is typically measured at end systole in the parasternal short axis view (Figure 1). Deep intertrabecular recesses that are supplied from the LV cavity and absence of other congenital anomalies are part of Jenni's criteria. However, some experts suggest the ratio of noncompacted to compacted myocardium should be measured but in the parasternal short axis view at end diastole [21]. Chin., *et al*. proposed a measurement of compacted myocardium (C) to the total thickness of both compacted and non-compacted layers (C + NC) at end diastole, with the ratio of C/ (NC+C) of < 0.5 considered diagnostic. However, there is poor agreement between readers when it comes to the ratio of non-compacted to compacted myocardium, with only 74% of agreement noted and there is poor agreement between these two criteria for diagnosis [23]. Jenni's criteria are more specific while Chin's criteria are more sensitive (Table 1). In general, the non-compacted segments most commonly involve the apex more than the base, and are seen mostly in the inferior and lateral walls of the left ventricle [22]. Multiple segments are usually involved (Figure 2). The right ventricle is involved in 40% of the cases [4,23]. Wall motion abnormalities, impaired diastolic filling as measured from mitral inflow velocities are frequently seen. Depressed LV ejection fraction is noted in a lot of patients with LV non-compaction, and patients with severe LV dysfunction have a poor prognosis. It is important to differentiate ILVNC from hypertrophic cardiomyopathy (especially the apical variant), dilated cardiomyopathy, arrhythmogenic right ventricular dysplasia and endocardial fibroelastosis. But in isolated LVNC, perfused recesses and hypokinetic segments are very specific [24], and the wall thickening noted is confined to certain walls of the LV. Visualization of the trabecular recesses could be enhanced using contrast [25]. Transesophageal echocardiography could also be used in diagnoses in patients with difficult windows [26].

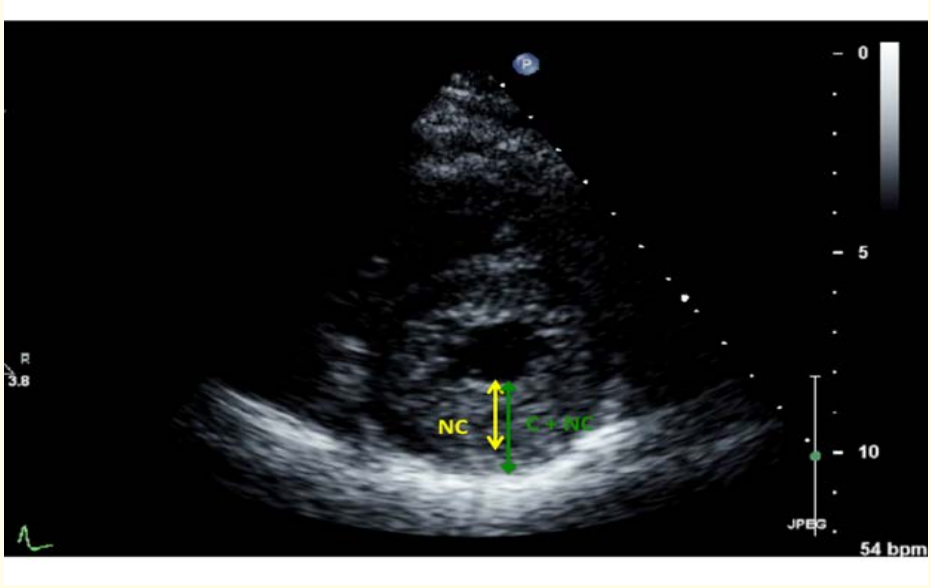

Figure 1: *Parasternal short axis view of the left ventricle in a patient with isolated left ventricular non-compaction taken at end systole. Please note the non-compacted myocardium (NC) in yellow compared to the full thickness of the left ventricle in green. The non-compaction here is seen in the inferior wall. In this patient, the ratio of non-compacted to compacted segments was 3 to 1, confirming the diagnosis.*

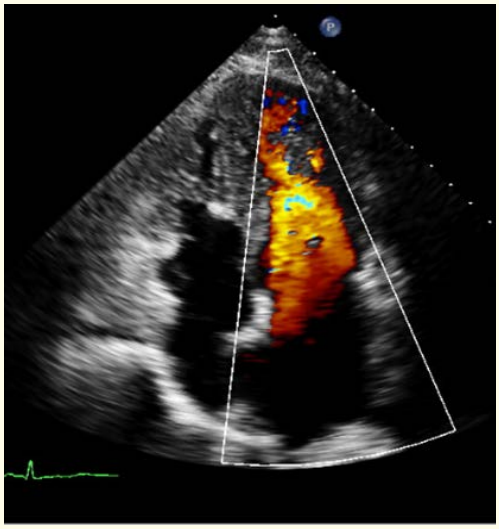

Figure 2: *Apical 4 chamber view of the left ventricle in a patient with isolated left ventricular non-compaction taken at diastole. Please note non-compacted segments in the apex and lateral walls of the left ventricle and the flow between the prominent trabeculations.*

	Jenni Criteria	Chin Criteria
Definition	Bilayered myocardium consisting of a thin C layer and a much thicker NC layer with deep endomyocardial recesses: NC/C > 2	LVNC is defined by ratio of X/Y < 0.5
Predominant location	Mid-lateral, mid-inferior and apex	Trabeculae at the LV apex and LV free wall
Measurement	Acquisition in the short axis with measurement of NC/C ratio at end systole	Parasternal short axis and apical views and on the LV free wall thickness at end diastole
Advantages	More sensitive	More specific

Table 1*: Comparison between Jenni and Chin criteria.*

LVNC: Left Ventricular Non-Compaction; LV: Left Ventricle

Magnetic resonance imaging (MRI)

Magnetic resonance imaging (MRI) has been also used for diagnosis. Delayed gadolinium enhancement has been seen in both compacted and non-compacted myocardium. In compacted myocardium, delayed enhancement correlated well with fibrosis, while in the non-compacted segments, delayed enhancement correlated with fibrosis as well as mucoid degeneration of the endocardium [27]. MRI offers better spatial resolution and can help assess LV and RV functions, wall motion abnormalities, as well as the ratio of compacted and non-compacted segments, which has been shown to be an important predictor of major adverse cardiac events, including heart failure, ventricular arrhythmias and thromboembolism. A ratio of non-compacted to compacted myocardium of > 2.3 at end diastole had the best sensitivity (86%) and specificity (99%) in diagnosing ILVNC [28]. However, 140 patients (43%) of 323 patients in the MESA cohort had at least one area with trabeculated to compact ratio of > 2.3 and the authors advised caution in using these criteria alone for diagnosis of ILVNC [29]. The calculation of trabeculated LV mass using MRI could help also in the diagnosis of ILVNC, with trabeculated LV mass of > 20% of the total LV mass having the highest sensitivity and specificity (93.7%) in diagnosing ILVNC [30].

Other Imaging Modalities

Computed tomography scan could be used to diagnose ILVNC and has high spatial resolution. Prominent trabeculations as well as deep intertrabecular recesses are typically seen [21]. Contrast ventriculography could also be used but is invasive. Positron Emission Tomography (PET) scan could show decreased myocardial flow reserve in non-compacted areas as well as microcirculatory dysfunction in both compacted and non-compacted myocardium but this has limited utility in establishing the diagnosis [7,31]. To date, Echocardiography and MRI remain the most common modalities used for diagnosing ILVNC.

Therapy

Management of patients with ILVNC involves treating heart failure, protection from sudden cardiac death, anticoagulation to prevent thromboembolic events, and screening of family members. β-blockers, angiotensin converting enzyme inhibitors and angtiotensin receptor blockers are used and have been reported to improve symptoms and the LVEF [32]. Anticoagulation with coumadin is recommended in all patients, even if they don't have atrial fibrillation. Electrophysiology testing to predict the risk of sudden cardiac death has not yielded great results. Currently, the decision to implant a defibrillator (ICD) or biventricular defibrillator (BiV ICD) is clear in patients who have survived a cardiac arrest or in patients with LVEF <35% who qualify for an ICD or BiV ICD according to the current guidelines [33]. In a series of 30 patients with ILVNC who received ICDs or BiV ICDs according to the current guidelines, Kobza., *et al*. showed that appropriate ICD therapy (either shocks or anti-tachycardia pacing) occurred in 37% of cases with a mean follow up of 21 ± 16 months. Inappropriate shocks occurred in 13% of cases and were due to SVT or atrial fibrillation. In patients who received ICD therapy for primary prevention, 33% had appropriate ICD therapy with mean follow up of 27 ± 33 months. There were no clinical predictors of appropriate ICD therapy [34].

The prognosis of ILVNC varies. Initial reports were based on the experience in tertiary care centers led to the belief that the prognosis is poor, with progressive heart failure leading to death or transplantation in 47% of adults with ILVNC followed for 44 ± 39 months [6]. However, recent reports challenge this and asymptomatic patients in general have a good prognosis [35]. Certain clinical characteristics are more common in non-survivors compared to survivors, including higher LV end-diastolic diameter, New York Heart Association class III–IV heart failure, left bundle branch block, and persistent atrial fibrillation. Patients with such clinical characteristics need frequent follow up, with strong consideration for more aggressive treatment and possibly referral for heart transplantation [1]. Family screening is important, especially since some of the mutations are autosomal dominant and most of the affected family members are usually asymptomatic. Combining genetic testing with electrocardiographic and echocardiographic screening is currently the best approach. Family members may have other forms of cardiomyopathy, like dilated cardiomyopathy or hypertrophic cardiomyopathy [35].

Conclusion

Isolated LV non-compaction is a rare disorder that can cause sudden cardiac death, heart failure and systematic embolization. Family members of affected patients need to be screened since ILVNC could be inherited in autosomal dominant and autosomal recessive fashion. ILVNC could be part of a broader spectrum of cardiomyopathy, this is supported by common genetic mutations and the finding that family members of ILVNC could have hypertrophic or dilated cardiomyopathy.

Disclosures

None.

Conflicts of Interest

None.

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