LEFT VENTRICULAR NONCOMPACTION CARDIOMYOPATHY: A SCOPING REVIEW

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ABSTRACT

Introduction: **There has been an upsurge in the reporting of cases of Left Ventricular Noncompaction (LVNC) cardiomyopathy in medical literature in the last 35 years due to advances in medical imaging.**

The condition was first described in 1926 and the first reported case by echocardiography was in 1984. The American Heart Association considers LVNC a primary cardiomyopathy of genetic origin, while the European Society of Cardiology and the World Health Organization grouped it as an unclassified cardiomyopathy. Its variability in terms of genetic profile, phenotypic expression, clinical presentation, and histopathological findings makes it somewhat a variant of other cardiomyopathies.

Case presentation: **Patients with LVNC cardiomyopathy may not have any symptoms or may present with ventricular arrhythmias, heart failure, thromboembolism, or sudden death. LVNC cardiomyopathy diagnosis is typically made by echocardiography, although there are higher resolution cardiac imaging techniques. Management will depend on the patient's clinical presentation. Due to its genetic association, there is a need to screen living relatives once the diagnosis is made in an individual.**

Conclusion: **The aim of this paper is to review current knowledge on this condition.**

Keyword: Non-compaction, Cardiomyopathy, Genetics, Echocardiography

INTRODUCTION

Left Ventricular Noncompaction (LVNC) cardiomyopathy, also known as "spongy myocardium" or "zaspopathy," is a congenital defect in which there is a developmental arrest of the normal compaction process of the myocardium during the first trimester.[1] This leads to the formation of two layers of myocardium: the compacted and noncompacted layer.[2] There are three prominent features in LVNC: left ventricular trabeculations, deep intertrabecular recesses communicating with the ventricular cavity and a thin compacted epicardial layer. Together, these impair the heart's ability to pump blood around the body leading to cardiomyopathy.[3–5] The morphological changes are typically seen around the apex and the lateral walls of the myocardium. LVNC can occur as part of a syndromic congenital anomaly[6–8] and can also occur in isolation from other congenital abnormalities.[4,9–11] The disease is associated with high morbidity and mortality due to thromboembolic events, arrhythmias and heart failure.[4,12] In this paper we review current knowledge on this condition.

HISTORICAL PERSPECTIVE

In the past, newborns with spongy myocardium were usually found with other congenital cardiac anomalies.[13,14] In 1984, due to the advent of better imaging modalities such as echocardiography, the first published case of spongy myocardium without associated cardiac anomalies was documented.[15] In this article, it was called "persistence of isolated myocardial sinusoids," and this term was used for other subsequent cases.[16] Thereafter, Chin *et al.* proposed the term "isolated non-compaction of the left ventricular myocardium."[17] Since then, many terms have been used to describe LVNC, including spongy myocardium, honeycomb myocardium, fetal myocardium, noncompaction cardiomyopathy, hypertrabeculation syndrome and left ventricular noncompaction cardiomyopathy. A graphic representation of the history of LVNC is shown in Figure 1.

EPIDEMIOLOGY

There appears to be an increasing prevalence of LVNC; however, this could be attributed to the

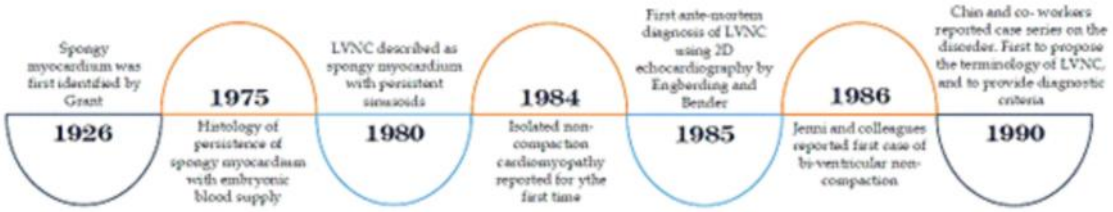

Figure 1: Historical timeline of LVNC

emergence of better imaging modalities.[12] The true prevalence of LVNC cannot be estimated as results vary greatly depending on the imaging modality used and the population studied. In a 2020 meta-analysis, the prevalence was found to be 1.28% among the population studied using echocardiography, while it was 14.79% among the population assessed with cardiac magnetic resonance imaging.[18] In the pediatric population, a prevalence of 0.14-1.3% has been documented using echocardiography. A US study found the prevalence of LVNC to be 9.5% in children while 9.2% was documented in Australia.[19] The prevalence of LVNC is estimated to be between 0.01% and 0.27% of all adult patients referred for echocardiography.[2,20–22] In the general populace, it is between 0.05% and 0.25% per year.[23,24] In the sporadic form, there is no significant difference in the prevalence of LVNC between both sexes.[25] LVNC is not very common among whites.[26] There seems to be a higher prevalence (about 30%) among black patients presenting with heart failure. A study among African athletes found that up to 15% almost fulfilled the echocardiographic criteria for LVNC.[27,28] Few cases of LVNC in some sub-Saharan African countries such as Djibouti[29], South Africa[30,31], Gabon[32], Cote d'Ivoire[33], and Nigeria[34,35], have been reported in literature. The epidemiology of LVNC is summarized in Table 1.[27,36,37]

EMBRYOLOGY

The first functional organ to develop in humans is the heart. It starts to develop by the third week of intrauterine life, and by the seventh week, a four-chambered heart has been formed.[38] The development of the myocardium evolves through four distinct phases. (i) Formation of early heart tube: Heart morphogenesis begins with the migration of cardiac progenitor cells to the ventral midline, where the embryonic endoderm induces the adjacent mesoderm to develop into a tubular heart structure, made up of a monolayered myocardium and endocardium lining the inner wall and an extracellular matrix between them.[39] (ii) Emergence of trabeculations: As the myocardial cells begin to proliferate, the endocardial cells invaginate, and the inner layer of myocardial cells begins to form projections into the heart lumen, known as trabeculations. These trabeculations create an increased surface area for diffusion of nutrients from the blood to the heart as, at this stage, the coronary vessels have not developed. (iii) Trabecular remodeling: At around 5-8 weeks, the formation of the coronary plexus increases blood flow to the myocardial cells, and the trabeculations begin to collapse, giving rise to a compact ventricular wall. This compaction process starts from the base of the heart and proceeds toward the apex.[40] (iv) Development of a multilayered spiral structure: The myocardium develops into a multilayers

Table 1: Summary of the prevalence of LVNC cardiomyopathy in adults

Based on Echocardiography		
Population	Prevalence (%)	95% CI
Pooled prevalence	1.28%	0.95-1.64
Apparently healthy persons	1.05	0.00-7.88
Athletes	3.16	0.26-8.84
Pregnant women (Primigravida)	18.63	
Cardiac patients	0.90	0.64-1.20
Non-cardiac patients	2.21	0.24-5.46
Based on Cardiac Magnetic Resonance Imaging		
Population	Prevalence (%)	95% CI
Pooled Prevalence	14.79	8.85-21.85
Apparently healthy persons	15.03	8.94-22.24
Athletes	27.29	13.58-43.27
General Population	19.72	11.64-29.28
Cardiac patients	9.76	4.59-16.56
Non-cardiac patients	36.21	23.64-49.72

structure and the heart develops into a spiral organ. A balance in ventricular trabeculation and compaction is needed for normal heart structure and function.[41] LVNC occurs due to an early arrest in the compaction process. Because the normal compaction proceeds towards the apex, non-compaction more commonly occurs at the apex.[36]

PATHOGENESIS

The precise mechanism by which LVNC occurs is unknown, but studies suggest that this normal compaction process does not occur in patients with LVNC, leading to a loose myocardial meshwork (Fig 2).[27] A defect in the compaction process of the trabeculae is the proposed mechanism for ventricular noncompaction. Therefore, ventricular noncompaction is sometimes called hypertrabeculation, although it has been found that hypertrabeculation is not seen in all cases of noncompaction in mouse models.[42] Newer studies have proposed that LVNC is not due to an arrest of the compaction process but, rather, an ingrowing of the compacted myocardium into the ventricular lumen in a trabecular fashion.[43]

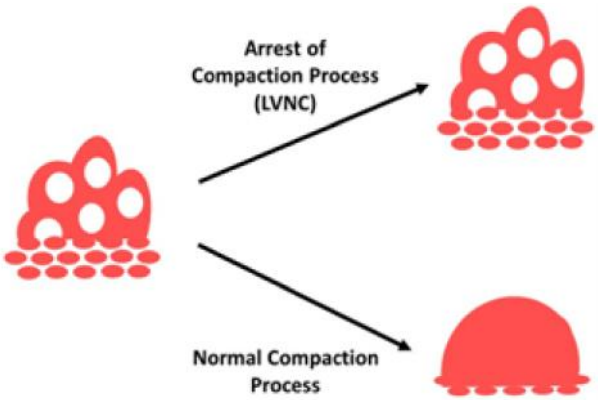

Figure 2: Embryological basis of LVNC

Table 2: Genes associated with LVNC and their location

Genes associated with LVNC		Chromosome number
TTN	Titin	2q31
HCN4	Hyperpolarization activated cyclic nucleotide gated potassium channel 4	15
MYH7	Myosin heavy chain 7	14
RYR2	Ryanodine receptor 2	1q43
SCN5A	Sodium voltage-gated channel alpha subunit 5	3p21
DTNA	Dystrobrevin alpha	18q12
LMNA	Lamin A/C	1q11-23
TAZ-G4.5	Tafazzin	Xq28
LDP3	LIM Domain-binding protein 3	1q23
TPM1	Tropomyosin 1	15q22

Table 3: Clinical conditions and genetic syndromes associated with LVNC

Associated Clinical Conditions	Congenital heart defects
	Ebstein anomaly (with or without gene mutations
	Familial cardiomyopathy
Associated Genetic Syndromes	Barth syndrome
	Noonan syndrome
	Roifman syndrome
	X-linked disorder with cyclic neutropenia
	Skeletal myopathy
	Mitochondrial functional impairment
	3-methyl-glutamic aciduria
	Lactic acidosis
	Growth deficiency
	Cardiolipin deficiency
	1p36 gene deletion syndrome
	Holt-Oram syndrome
	Sengers syndrome
	Kearns-Sayre syndrome

GENETICS

Various genetic defects have been associated with the pathogenesis of LVNC. The genetic defects are often limited and show heterogenicity[44]. Mutations associated with LVNC include TTN, HCN4, MYH7, RYR2, SCN5A, alpha-dystrobrevin (DTNA), lamin A/C (LMNA), tafazzin (TAZ-G4.5), sarcomere protein genes and LIM domain-binding protein 3 (ZASP/LDP3)[27,43–49] as shown in table 2. LVNC can be sporadic or familial. In patients with the familial form of LVNC, the mode of inheritance could be X-linked, autosomal-dominant or mitochondrial inheritance patterns[6,45,50]. Robust reviews on the molecular basis of LVNC has been described extensively in literature[51,52]

Left ventricular noncompaction has also been found to be associated with syndromes such as Barth, Roifman and Noonan syndromes[6–8]. Other clinical conditions associated with LVNC are summarized in Table 3.

HISTOLOGY

The patterns of left ventricular non-compaction cardiomyopathy identified at autopsy include broad trabeculae, coarse trabeculae and sponge-like interlacing small muscle bundles. The best histological clue for diagnosing LVNC is the presence of papillary muscles that are not well-formed.[53]

CLINICAL PRESENTATION

The clinical presentation of patients with left ventricular non compaction is variable; ranging from asymptomatic disease to congestive heart failure, cardiac arrhythmias, thromboembolic phenomena, and sudden cardiac death.[54,55] It is said to take approximately 3.5 years to diagnose LVNC from the time of initial presentation due to similarities in symptomatology with other cardiomyopathies.[21,56].

Congestive Heart Failure

Congestive heart failure is the most common form of presentation in patients with LVNC. They present with typical symptoms of heart failure, including worsening exertional dyspnoea, orthopnoea, and lower extremity edema. Tachypnoea is the most common presentation. Diastolic dysfunction is often due to abnormal relaxation and restrictive filling caused by numerous prominent trabeculae while systolic dysfunction is usually from sub-endocardial hypoperfusion and microcirculation dysfunction.[27,57–59]

Cardiac Arrhythmias

The type of arrhythmia caused by LVNC may be age-dependent, with Wolff-Parkinson-White syndrome and ventricular tachycardia being more common in children while atrial fibrillation and ventricular arrhythmias are typically seen in adults.[21,60] The other associated electrocardiographic features include paroxysmal supraventricular tachycardia, left bundle branch block, fascicular block, atrioventricular block and T-wave inversions.[4,61]

Thromboembolism

Thromboembolism is often due to impaired LV function, presence of atrial fibrillation and abnormal myocardial trabecular that predispose patients to stroke, mesenteric ischaemia, systemic arterial emboli, pulmonary embolism and isolated RV thrombi, although rarely.[57]

Sudden cardiac death

Patients with LVNC may present with sudden death due to heart failure, arrhythmias, or thromboembolic phenomena[62].

DIAGNOSIS

Diagnosis of LVNC is mainly by echocardiographic findings, although other imaging modalities such as computed tomography, angiography and magnetic resonance imaging can be used. LVNC is diagnosed by imaging the LV and comparing the trabeculation thickness with the thickness of the compacted myocardial wall. Further evaluation can be done with contrast-enhanced CT scan and contrast left ventriculography (LVG). LVNC changes are more pronounced around the apex and lateral walls of the myocardium. This typically occurs in the absence of any coexisting congenital lesion. Further review of the images may show LV systolic dysfunction with depressed ejection fraction and regional wall motion abnormalities involving the noncompacted area.[53]

Echocardiography Criteria

There are three non-standardized sets of criteria to diagnose LVNC by echocardiography[63] as shown in Table 4.

Chin *et al.* first proposed that when the ratio of the distance between the epicardium and the trough of the trabeculation recess to the distance between the epicardium and the peak of the trabeculation is less than 0.5 at end-diastole, then it is diagnostic of LVNC.[17] It is not used in clinical practice.

The criteria by Jenni and colleagues is the most acceptable and widely used in clinical practice. It proposes the maximum ratio of the noncompacted to compacted myocardial wall > 2 at end of systole, presence of characteristic trabeculations with deep recesses between them, evidence of blood flow in the

Table 4: Echocardiographic criteria for LVNC cardiomyopathy

Author	Chin *et al.*[17]	Jenni *et al.*[16]	Stollberger *et al.*[22]
Year	1990	2001	2013
Criteria	Ratio of X to Y taken at mitral valve, papillary muscles and apex is less than 0.5 Where X is distance from epicardium to trough of intertrabecular recesses Where Y is distance from epicardium to peak of trabeculations	Ratio of noncompacted to compacted myocardium at thickest part of myocardium > 2 Presence of characteristic trabeculations Deep recesses between trabeculations Evidence of blood flow in recesses Absence of coexisting cardiac abnormality	>3 trabeculations from LV wall Trabeculations form noncompacted part of bilayered myocardium Perfusion of intertrabecular recesses Trabeculations move with compacted myocardium
Cardiac Phase	End-diastole	End-systole	Trabeculations – End-diastole 2-layered myocardium – End systole Perfusion of recesses – End diastole

LV: Left Ventricular

recesses and absence of coexisting cardiac abnormalities.[64]

Stöllberger and colleagues[65] suggested that the number of trabeculations visible in the apical view of the left ventricle during end-diastole should be used in diagnosing LVNC. It made use of four criteria to make a diagnosis of LVNC: (a) More than 3 trabeculations protruding from LV wall in end-diastole; (b) Perfusion of intertrabecular recesses from ventricular cavity at end-diastole seen on color doppler or contrast echocardiography; (c) Trabeculae form the noncompacted part of a bilayered myocardium in end-systole; and (d) Trabeculae move with compacted myocardium.

Other echocardiographic modalities like speckle tracking and strain rate imaging can be used to identify characteristic pattern of myocardial texture. They are especially useful in differentiating LVNC from similar cardiac conditions such as dilated cardiomyopathy and hypertrophic cardiomyopathy, in order to avoid overdiagnosis of the disease.[66,67] The use of echocardiography for the diagnosis of LVNC is not without its limitations. The operator-dependent nature of echocardiography and the difficulty that can be experienced with visualizing the apex and trabeculations are some of the limitations. However, the diagnostic yield can be improved by the use of contrast medium.[68]

Table 5: Cardiac magnetic resonance imaging criteria for LVNC cardiomyopathy

Author	Petersen *et al.*
Year	2005
Criteria	Ratio of noncompacted to compacted myocardial segment with most prominent trabeculations > 2.3
Cardiac Phase	End-diastole

Cardiac Magnetic Resonance Imaging (MRI) Criteria

The most sensitive method of diagnosing LVNC is through the use of Cardiac MRI, using the noncompacted/compacted wall ratio in end-diastole.[69] It is useful when the apex cannot be visualized with echocardiography.[4] It can also identify two-layered structures in segments like anterior, inferior, anterolateral and inferolateral better than echocardiography[70]. To diagnose LVNC on cardiac MRI, one takes three diastolic long axis views and choose the myocardial segment with the most prominent myocardial trabeculations to measure the NC/C ratio at the end of diastole. Diagnosis is made when NC/C ratio is >2.3. One of the limitations to the use of MRI in diagnosing LVNC is its high cost, which is marked in regions where health insurance is inadequate.[68]

Left Ventriculography

Left ventricular ventriculography (LVG) is an invasive procedure and it is indicated in patients with non-obstructive coronary artery disease, reduced LV function and a decreased ejection fraction. It is not done routinely.[23]

MANAGEMENT

There is no specific management guideline for LVNC. Management is guided by the symptomatology of the patients, although some patients receive cardiac transplant.[71] Treatment of heart failure usually requires the use of a combination of beta-blockers, ACE inhibitors/ARB, diuretics, medications and aldosterone antagonists.[27] Heart failure can also be managed by using cardiac resynchronization which could improve left ventricular function when the indication is fulfilled.[72] Symptomatic ventricular arrhythmias with impaired systolic function should be treated with electrical or chemical defibrillation especially in patients with EF<35%. WPW syndrome or other types of AV nodal reentrant tachycardia should be managed with radiofrequency ablation.[55] Chronic warfarin therapy is indicated in patients with a history of thromboembolism, atrial fibrillation, and/or an LVEF <40% due to the risk of thrombus formation within intratrabecular recesses.[27] LV remodeling surgery is effective in managing LVNC associated with large LV dimension and depressed ejection fraction.[73] If there are associated conditions as in syndromic LVNC, management will also include the treatment for the associated conditions such as in congenital heart disease.

SCREENING

Echocardiographic screening of family members of patients with LVNC is suggested in literature.[74,75] Patients with LVNC are also encouraged to undergo timed neurological evaluations whether they manifest symptoms or not.[76] This may also include genetic screening.

PROGNOSIS

Recent advances in medicine, especially in the management of arrhythmia have led to improved prognosis in patients with LVNC. Early age at presentation and increased end-diastolic diameter have been associated with a poor prognosis[77]. The condition is also associated with an increased risk of adverse cardiovascular events[78].

CONCLUSION

LVNC remains a major cause of morbidity and mortality by predisposing patients to other cardiovascular diseases. With the advent of newer imaging techniques, and the presence of widely accepted diagnostic criteria, this condition is becoming more demystified. The management is symptomatic and case-specific, although cardiac transplant remains the definitive treatment. Screening with echocardiography is advisable in individuals with a family history of the disease.

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