Left ventricular non-compaction: Genetic heterogeneity, diagnosis and clinical course

Gabriella Captur [a,*], Petros Nihoyannopoulos [b]

[a] Department of Cardiology, Mater Dei Hospital, Malta
[b] Hammersmith Hospital, NHLI, Imperial College London, United Kingdom

abstract

Left ventricular non-compaction (LVNC) is a rare disorder that results in multiple deep trabeculations within the left ventricular myocardium. It is thought to be due in part, to an arrest of myocardial development but more recent evidence suggests that some cases may actually be acquired while other isolated cases have regressed with time.

Transthoracic echocardiography remains the imaging modality of choice for LVNC where diagnosis is based on the identification of multiple prominent ventricular trabeculations with intertrabecular spaces communicating with the ventricular cavity.
There is a broad and potentially confusing spectrum of clinical symptomatology in patients with ventricular non-compaction meaning that the primary diagnosis is often missed.

Complications such as potentially malignant arrhythmias, left ventricular failure, and cardioembolic events arising as a result of non-compaction must be treated in an attempt to decrease morbidity and mortality from this disorder. The ultimate outcome for patients remains unclear with some boasting a prolonged asymptomatic course, to others displaying a rapid deterioration of left ventricular systolic function, leading to heart transplantation or death.

In conclusion, LVNC while remaining a rare cardiomyopathy, shall probably be diagnosed with increasing frequency in the coming years because of heightened awareness about its natural history and clinical manifestations and because of the improved modalities available for cardiac imaging.

1. Introduction

Hypertrabeculation of the left ventricle was first recognised in 1932 [1], but left ventricular non-compaction (LVNC) officially described in 1990 [2]. LVNC results in multiple trabeculations in the left ventricular myocardium and is thought to be due, in certain cases but not invariably, to an arrest of myocardial development [3]. The left ventricle generally demonstrates impaired systolic function, with or without dilatation [2,4] and is usually the only site of non-compaction with biventricular involvement occurring in less than 50% of cases [5,6].

Congenital heart disease is absent, by definition, in patients with the isolated form of the disease. LVNC existing in association with congenital heart diseases [7] such as ventricular septal defects, double-orifice mitral valve, [8] Ebstein's anomaly of the tricuspid valve, [9] and bicuspid aortic valve, [10] is referred to as non-isolated left ventricular non-compaction or alternatively as left ventricular non-compaction associated with congenital heart disease.

2. Prevalence

Several landmark case series of LVNC have been published in the literature. Most importantly, the series by Chin et al. [2], El-Menyar et al. [11], Ritter et al. [12], Ichida et al. [3], Oechslin et al. [13], Ross et al. [14], and Stöllberger et al. [15,16] Male subjects tend to predominate among the published cases [17] in human beings, presumably as a consequence of underlying patterns of inheritance and gender-related differences in the prevalence and severity of symptoms which then trigger cardiac investigations. The reported adult prevalence of LVNC in different series ranges between 0.05 and 0.24% [17] with earlier data suggesting that this was an extremely rare condition with an annual pediatric incidence of b0.1 per 100,000 [18].

The reported prevalence of LVNC in two separate centres within the Kingdom of Saudi Arabia and Sudan in 2008 stood at 22 cases per 10,000 echocardiographic studies (0.22%) according to Ali S.K. [19] and this correlates closely to the reported prevalence in an Austrian laboratory presented by Stöllberger et al. also in 2008 (0.27%: 100 diagnosed cases out of 36,933 studied individuals) [20]. The same group had described a prevalence of 0.08% in 2000 (15 cases out of 17,648) [21]. More recent series are in fact proposing a higher prevalence presumably because of heightened awareness about the

disease and improved diagnostic criteria and imaging modalities [13,17].

Ethnic differences in terms of prevalence of LVNC might exist and these differences may be due in part to the condition's genetic basis, and in part to differences in the accessibility to cardiac imaging and uneven thresholds for cardiac investigations between various countries.

Interestingly, Kohli et al. [4] report that out of 5 healthy subjects from a control cohort of 60 (8%) who satisfied echocardiographic criteria for LVNC, as many as 4 of these were of Afro-Caribbean origin. This suggests that racial differences might matter not only in terms of prevalence but also with respect to the specificity of currently available diagnostic criteria.

3. Embryology

Understanding the possible pathogenetic mechanisms that lead up to LVNC necessitates a clear understanding of the developmental sequence of events which take place in the embryonic heart.

The morphogenesis of a four-chambered heart commences with the formation of a linear myocardial tube lined by endocardium. The heart tube comes into existence following the medial migration and later coalescence of cardiogenic primordia arising from the splanch- nopleuric mesoderm. The progenitor cells derived from the first heart- forming field give rise to the primary heart tube, whereas those originating from the secondary heart-forming field give rise to the outflow tracts and inflow tracts.

These precursor cells align themselves in a fixed distribution, with right ventricular progenitors lying anterior to the left ventricular progenitors and future atria.

Looping of the linear heart tube follows (Fig. 1), allowing for the left–right orientation of all cardiac structures and imparting an inner and outward curvature to the heart tube [22]. Cardiac looping is a process consisting sequentially of (1) rightward bending of the initially straight heart tube (dextra-looping) forming a C-shaped tube, (2) transformation of the C-shaped loop into an S-shaped loop and (3) the later morphogenic events which lead to the positional reorienta- tion of the outflow tracts relative to the atria [23].

The heart tube described here, consists initially of two layers: an outer myoepicardial mantle and inner endocardial cell layer separated by an intervening matrix of proteoglycans and glycosaminoglycans referred to as the acellular cardiac jelly. Once looping has taken place trabeculation commences, starting initially along the inner myocardial layers nearer the outer curvature of the looped primitive ventricle. Trabeculations in the embryonic heart are first evident from the end of gestational week 4. Mature trabeculae form later with continued myocyte recruitment or proliferation.

This trabeculated myocardium contains deep recesses which communicate with the blood-filled cavity of the heart tube (Fig. 2). The intertrabecular spaces effectively increase the surface area for gas exchange and blood is allowed to reach the myocardium after percolating through them [24]. This mechanism favors the concomi- tant increase in myocardial mass despite the absence of a distinct epicardial coronary circulation.

Between weeks 5 and 8, and coinciding with the invasion by the developing coronary vasculature from the epicardium, the trabecular myocardium undergoes compaction in its deeper part and gradually turns into the compact muscle constituting the ventricular wall, papillary muscles, interventricular septum and cells of the conductive system. This involution usually proceeds from the epicardial to the endocardial surface and from the basal segments of the ventricle moving towards the apex. Compaction is more pronounced in the left ventricle than in the right ventricle, therefore resulting in a more heavily trabeculated endomyocardial surface within the right ven- tricle. As a result of this compaction process, the intertrabecular

recesses disappear almost entirely leaving a smooth endocardial ventricular surface.

4. Genetics

Over recent years, LVNC was found to harbor a complex and heterogeneous genetic undertone. There is mounting evidence for a role of the following genes in the aetiology of this condition:

1) TAZ/G4.5: Bione et al. [25] identified the tafazzin gene in the q28 region of the X chromosome (TAZ, G4.5) as a disease-causing gene implicated in LVNC in addition to being the culprit gene in a wide spectrum of other severe infantile cardiomyopathies including X- linked endocardial fibroelastosis and dilated cardiomyopathy. The tafazzin gene product plays a role in maintaining cardiolipin levels and exhibits acyltransferase activity within mitochondrial cells. It contributes towards osteoblast and adipocyte maturation while also being expressed at high levels within cardiac and skeletal muscle.

Tafazzin gene mutations are also responsible for Barth syndrome, an X-linked cardioskeletal myopathy seen in infant males which typically demonstrates a dilated cardiomyopathy, abnormal mito- chondria, short stature, low carnitine levels, lactic acidosis and

neutropenia. Barth syndrome was first described by Neustein et al.

[26] and Barth et al. [27]

2. 2) LIM domain binding protein 3: a mutation in the Z-band complex-

encoding gene called Cypher/ZASP (LIM, LDB3) results in zaspo- pathy and also features in LVNC [28]. In both skeletal and cardiac muscle, ZASP is a component of the Z-line, and its deficiency is manifested as a myofibrillar myopathy.

3. 3) Alpha-dystrobrevin: mutation in the autosomal α-dystrobrevin (DNTA) gene has been described in LVNC associated with congenital heart disease. The α-dystrobrevin gene was localized to 18q12.1–q12.2 by in situ hybridization and codes for a cytoskeletal protein which is found in the dystrophin-associated glycoprotein complex. Alpha-dystrobrevin binds dystrophin, syn- trophin and other constituents of this complex permitting plasma membrane stability during muscle contraction and relaxation. Alpha-dystrobrevin also links the dystrophin-associated glycopro- tein complex to the signaling protein, neuronal nitric oxide. Deficiency of α-dystrobrevin has been implicated in several skeletal and cardiac myopathies in mice and in muscular dystrophy in humans.

4) FKBP1A: LVNC was also observed in mice, where the FK506- binding-protein-1A gene (FKBP1A) had been 'knocked out' through embryonic stem cell technology. The FKBP1A gene maps to 20p13 [29].

5) LMNA: mutations in the LMNA gene which encodes two ubiqui- tously expressed nuclear proteins, lamins A and C, were implicated in some cases of hypertrabeculation of the left ventricle. The gene is mapped to human chromosome 1q12.1–q23 and 10. Lamin A

represents an intermediate filament protein making up the lamina

underlying the muscle cell and inner nuclear membrane.
6) 11p15: in 2004, Sasse-Klaassen et al. uncovered a novel gene locus for autosomal dominant LVNC located on human chromosome

11p15 [30].
7) Sarcomere gene proteins: more recently Klaassen et al. conducted

mutational analysis in a cohort of 63 unrelated adult probands with LVNC. Heterozygous mutations were identified in 11 out of 63 samples in sarcomere protein genes encoding β-myosin heavy chain (MYH7), α-cardiac actin (ACTC) gene on chromosome 15q, and cardiac troponin T (TNNT2) [31].

Several other case reports link LVNC with other diverse genetic defects and this profound genetic heterogeneity implies that the pathogenetics behind non-compaction of the ventricular myocardium must be equally diverse, with no single pathological model to fit and suit all cases. Evidence supporting the heterogeneous pathogenetic hypothesis for LVNC stems from the following observations:

1) genetic disorders are identified in only half of the reported cases of non-compaction

2) some case reports suggest that the non-compaction may actually represent an acquired pathology as opposed to a congenital phenomenon

3) regression of non-compaction was observed in a handful of case reports [32]

4) left ventricular non-compaction has an extremely variable clinical presentation and course in different subjects with some remaining relatively asymptomatic [33]

Finsterer J. [33] explains the heterogeneous pathogenesis of LVNC by distinguishing between non-compaction arising as a direct phenotypic expression of a genetic defect which he refers to as Primary Left Ventricular Hypertrabeculation, in contradistinction to Secondary Left Ventricular Hypertrabeculation which carries no underlying genetic cause.

Two hypothesis are proposed to explain Primary (genetic) LVNC:

[33]

A) Non-compaction hypothesis

The non-compaction hypothesis revolves around the notion that compaction of the embryonic, hypertrabeculated myocardium is arrested or impaired because of a primary genetic defect. Supporting this pathogenetic hypothesis, is the fact that most cases of left ventricular non-compaction appear to be present from birth.

B) Compensation hypothesis

The compensation hypothesis suggests that while a genetic defect is indeed present from birth, it is not however directly responsible for disabling the normal embryonic compaction process but rather it impairs ventricular myocardial morphology or function through another mechanism. The non-compaction then arises as an adaptive reaction to compensate for the abnormally contracting myocardium.

Two hypotheses are proposed to account for Secondary (non- genetic) LVNC: [33]

A) Hemodynamic/ischemic hypothesis

It is thought that microcirculatory dysfunction or metabolic disorders give rise to myocardial ischemia or microinfarcts, which then induce a hypertrabeculation reaction [34].

B) Myocarditis hypothesis

The discovery of subendocardial fibrosis on examination of some hearts affected by non-compaction suggested that myocarditis may be responsible for some cases.

5. Presentation

LVNC may present with depressed systolic function of the non- compacted left ventricle resulting in heart failure. The degree of systolic dysfunction is related to the extent of non-compaction. Alternatively it may present with cardiac arrhythmias and conduction defects including atrial fibrillation, ventricular arrhythmias which may sometimes be fatal, atrio-ventricular or bundle-branch blocks and Wolff–Parkinson–White syndrome [11]. In the series by Oechslin et al. [13] ventricular tachycardia was observed in 14 out of 34 patients with LVNC (41%). LVNC has also been known to present with cardioembolic complications, resulting either from atrial fibrillation or clot formation within the myopathic left ventricle. This latter mechanism is supported by necropsy reports of mural thrombi within the deep intertrabecular recesses.

Although LVNC is considered to be a congenital cardiomyopathy in many cases, the clinical manifestations and age at onset of symptoms are highly variable. The clinical spectrum may range from anywhere between the virtually asymptomatic to those afflicted by severe heart failure culminating in heart transplantation or death.

The electrocardiogram (ECG) is usually pathological in both children and adults with LVNC and may show a right or left axis deviation, left or right bundle-branch block, left ventricular hyper- trophy or strain pattern as well as non-specific ST segment and T-wave changes [35]. McCrohon et al. reported a case of LVNC which presented with central chest discomfort, shortness of breath, presyncope and an abnormal ECG. The ECG showed inferolateral Q waves, left ventricular hypertrophy, repolarisation changes in II, III, AVF and V_4–V_6 together with non-specific ST segment elevations in V_1–V_3 [36].

Due to the relatively high incidence of familial recurrence, LVNC is not infrequently an incidental diagnosis made during routine screen- ing of asymptomatic subjects with affected relatives.

Studies in pediatric patients with non-compaction have demon- strated a higher propensity for familial cases, facial dysmorphisms and Wolff–Parkinson–White syndrome in children affected by the dis- order when compared to adults who more commonly exhibited secondary arrhythmias [37].

6. Diagnosis

Various imaging techniques have been employed in the diagnosis of LVNC including, but not limited to, 2-Dimensional transthoracic echocardiography, contrast-enhanced 2-Dimensional echocardiogra- phy, ventriculography, [38] ultrafast computed tomography and Cardiac Magnetic Resonance Imaging. Nevertheless, transthoracic echocardiography supplanted by the use of harmonic imaging and contrast agents in difficult cases, remains the imaging modality of choice for LVNC.

The multiple prominent trabeculations apparent on the 2-Dimen- sional echocardiogram are separated by deep intertrabecular recesses which communicate with the ventricular cavity but which fail to communicate with the coronary circulation [12]. Non-compacted myocardium is most often hypocontractile and focal, usually identified in the apical, mid-lateral and mid-inferior left ventricular segments. Four sets of diagnostic criteria form the basis for identification of LVNC, namely those by Chin et al. [2], Jenni et al. [13,39], Stöllberger et al. [15] and Belanger et al. [40] respectively.

1. The Chin et al. [2] criteria focus on trabeculae at the left ventricular apex on the parasternal long-axis, subcostal and apical views, and on left ventricular free-wall thickness measured at end-diastole. Here LVNC is defined by a ratio of $X/Y \leq 0.5$, where X represents the distance from the epicardial surface to the trough of the trabecular recess, and Y the distance from the epicardial surface to peak of trabeculation. The X/Y ratio progressively decreases from the papillary muscles to the apex.

2. TheJennietal.[13,39]criteriafordiagnosisofLVNCarefoundedon the presence of a two-layer structure, with a thin compacted epicardial layer (C) and a thicker non-compacted endocardial layer (N) measured at end-systole from the parasternal short-axis and apical approaches. LVNC conforms to a ratio of N/CN2 in adults or more than 1.4 in children as suggested by Pignatelli et al. [41]. The Jenni et al. diagnostic criteria may be considered complete after demonstrating the absence of co-existing cardiac structural abnormalities and the presence of numerous excessively promi- nent trabeculations and deep intratrabecular recesses which on colour Doppler, are perfused by intraventricular blood.

3. For Stöllberger et al. [15] the presence of more than three trabeculations protruding from the left ventricular wall, apical to the papillary muscles and visible in a single image plane constitute the echocardiographic hallmarks of LVNC. These trabeculations must move synchronously with the myocardium and must have its same echogenicity. The intertrabecular spaces must be perfused from the ventricular cavity, and visualized on colour Doppler imaging.

4. Belanger et al. [40] describe a modification of the above criteria which demands the presence of prominent apical trabeculations noted in any view where a N/C ratioN2 is not considered to be a prerequisite for diagnosis. Hypertrabeculation must be concentrated in the apex with blood flow demonstrated through the non- compacted segments. The group goes on to devise a system for classifying the severity of non-compaction based on maximal systolic N/C ratios (measured in the apical 4-chamber views) and planimetric area of the non-compacted myocardium.

Of the four published criteria for LVNC available, the Jenni criteria [39] stress the presence of a two-layered structure, whereas the Chin criteria [2] focus on the depth of the recess relative to the height of the trabeculae (Figs. 3 and 4). Obtaining an accurate N/C ratio as advocated by Jenni et al. may be hindered by an altered volume status in the subject or by a failure to locate the maximal site of non- compaction [15].

In a recent study Kohli et al. [4] underscored the limitations of three of the most widely used echocardiographic criteria for LVNC (Chin et al., Jenni et al. and Stöllberger et al.) Among 199 adults with impaired left ventricular systolic function referred to a heart failure clinic as many as 24% of subjects satisfied at least one of the three criteria for LVNC but only 7% fulfilled all three. The poor concordance between the three sets of criteria probably stems from the fact that these differ not only in their definitions of abnormal trabeculation, but also in the echocardiographic planes and phases of the cardiac cycle in which they are applied. In the same study Kohli et al. conclude that current echocardiographic criteria for LVNC might be too sensitive and may be resulting in the over-diagnosis of the condition in patients with left ventricular systolic dysfunction, and particularly in black individuals.

Conversely Belanger et al. [40] suggest that some patients who demonstrate definite hypertrabeculation that falls short of satisfying the conventional diagnostic parameters for LVNC might actually be harboring a milder form of the disease which is remaining undiagnosed.

While there is no singular set of echocardiographic criteria to date, which dominates in the diagnosis of LVNC (Table 1), most authors would recommend employing a combination of the currently available tools, with the Jenni and Stöllberger criteria constituting a reasonable first approach.

Tissue Doppler echocardiography may be useful in the assessment of regional myocardial function and might play an increasingly important role in patient follow-up and diagnosis of LVNC. A recently published pediatric study demonstrated how Tissue Doppler velocities in subjects with LVNC were considerably reduced compared to unaffected children and that decreased lateral mitral annular Tissue Doppler velocities correlated with more adverse outcomes [42]. Due to the regional nature of LVNC, strain and strain rate imaging are also being studied for their role in identifying regional systolic dysfunction within the non-compacted ventricular segments [43].

3-Dimensional echocardiography supersedes its 2-Dimensional counterpart by allowing for more detailed characterization of the left ventricular myocardium and providing pyramid-shaped datasets that may be analyzed in any section and in any angle. Intracavity echodensities that are suspicious for trabeculations can be tracked in multiple directions from base to apex [44].

Contrast echocardiography enhances endocardial border definition after opacification of the left ventricular cavity unmasking the deep intertrabecular recesses and may therefore serve as a valuable adjunct to conventional 2-Dimensional echocardiography in difficult cases [45]. Buss et al. [46] describe a case of LVNC which mimicked an infiltrative myocardial disorder on the routine transthoracic echocar- diogram. The hypertrabeculation became evident only following the use of a left heart contrast agent.

Although multiplane transoesophageal echocardiography is not the method of choice for the diagnosis of LVNC it has several advantages over the transthoracic approach. In particular, it permits excellent views of the left ventricular walls and offers significant diagnostic help in conditions where the left ventricular cavity is abnormal, such as apical hypertrophic or infiltrative cardiomyopathy and apical thrombus [47]. Transoesophageal echocardiography

therefore has a complementary role in the identification of LVNC, particularly in unclear cases and especially in subjects where magnetic resonance imaging cannot be performed.

Magnetic resonance imaging is being increasingly employed in the diagnosis of LVNC, [48] (Fig. 5) but as is the case with echocardio- graphy, the interpretation of findings rests heavily on the experience

of the operator. Cardiovascular magnetic resonance may enhance the detection of more subtle forms of non-compaction that may or may not progress with time and is emerging as a powerful diagnostic tool especially in those patients with poor echocardiographic windows.

The primary diagnosis of LVNC is missed in a large number of cases [49]. This is probably due to unfamiliarity with its diagnostic pattern and to similarities between LVNC and other more common cardio- myopathies. In hypertrophic cardiomyopathy for example, some trabeculae and deep intertrabecular recesses are typically present and may confound the echocardiographer unless the appropriate criteria are diligently applied. Dilated cardiomyopathy may similarly also be accompanied by prominent myocardial trabeculations, but to a lesser extent than in LVNC. Arrhythmogenic right ventricular dysplasia falls into the differential diagnosis of LVNC. The former is character- ized pathologically by right and left ventricular myocardial atrophy and fibrofatty replacement caused by degeneration of right ventri- cular muscle [50].

Finally, the differential diagnosis for non-compaction of the ventricular myocardium during echocardiographic assessment of the heart, also includes prominent normal myocardial trabeculations,

false tendons and aberrant bands, cardiac tumors and left ventricular apical thrombi. Prominent left ventricular trabeculations are always three or fewer in number, and are rarely located in the apical region [51] thereby providing some grounds for distinguishing them from the multiple apical trabeculations present in LVNC. False tendons and apical bands typically cross the left ventricular cavity [52].

Left ventricular thrombi may be falsely diagnosed when non- compaction is confined to the left ventricular apex. However, apical thrombi exhibit a different echogenicity as compared to the surrounding myocardium and should allow for easy discrimination [53]. The echocardiographic examination must be performed with special care to avoid false diagnosis of this disease.

7. Management

Any complication or symptom arising as a result of LVNC must be treated in an attempt to decrease morbidity and mortality from this disorder. Arrhythmias are treated with beta-blockers, calcium channel blockers, amiodarone or other agents depending on the case. In one study by Toyono et al. [34] carvedilol caused a major improvement in a four month old infant with LVNC complicated by congestive heart failure. Carvedilol demonstrated beneficial effects on left ventricular function, mass and scintigraphic findings. The mechanism of these effects is as yet unclear because the exact cause of myocardial failure in patients with LVNC remains poorly understood. Carvedilol reversed ventricular dilatation and hypertrophy in the index case; an effect of the drug which is widely recognised and exploited in the setting of myocardial infarction and idiopathic dilated cardiomyopathy. Inter- estingly it was observed that the reversal of remodeling seemed to occur preferentially in the non-compacted as opposed to the compacted myocardium [34].

Cardioembolic events have been reported in many patients with LVNC but their high prevalence was independent of left ventricular dimensions and function [54]. The endomyocardial morphology in LVNC in truth predisposes to the development of mural thrombi within the deep intertrabecular spaces. Unusual cases of embolic superior mesenteric artery occlusion [55] and another of coronary artery embolism [56] as a direct consequence of underlying isolated ventricular non-compaction have been described in the literature. The overall view is that oral anticoagulation with coumarin drugs should be considered in patients with a prior history of embolic phenomena or in subjects with other indications such as coexistent atrial fibrillation; confirmed left ventricular thrombi or severely impaired left ventricular systolic function, but should not routinely be administered to all those diagnosed with LVNC if asymptomatic [57,58]. Pignatelli et al. [41] however recommend the use of an antiplatelet agent such as aspirin in all patients diagnosed with LVNC following their retrospective review on 36 children diagnosed with LVNC at the Texas Children's Hospital. They reported no subsequent cases of systemic embolisation with this strategy. Still the role of aspirin for primary prevention in LVNC remains a fairly controversial issue [33].

Patients noted to have arrhythmogenic complications warrant a twenty-four-hour ambulatory electrocardiogram. Where serious arrhythmias such as ventricular tachycardias are identified, an automated internal cardioverter defibrillator (ICD) should be implanted. Many authors advocate an aggressive approach in the management of ventricular arrhythmias and they recommend ‘early’ implantation of an ICD, in an attempt to reduce the incidence of premature death in LVNC [59].

8. Prognosis

The ultimate outcome for patients with LVNC remains unclear. The prognosis, as previously stated, may range from a prolonged asymptomatic course to a rapid deterioration in left ventricular

systolic function leading to heart transplantation or death. Generally in both adult and pediatric populations the prognosis is persistently better in asymptomatic subjects. It is fair to say that overall however, the prognosis is poor and in the series by Oechslin et al. 50% of adult patients (6 out of 12) did in fact succumb to sudden cardiac death [13]. Prognosis is worse in patients with heart failure NYHA III–IV, left ventricular end-diastolic diameter exceeding 60 mm, left bundle- branch block and persistent atrial fibrillation. In this subset of patients heart transplantation or implantation of an ICD may improve the long term survival. In view of the possible association with neuromuscular disorders such as mitochondrial myopathies, cardiologists should always consider an early neurological referral in patients with LVNC together with a comprehensive genetic assessment.

Echocardiographic evaluation of family members is strongly recommended because of the high incidence of familial recurrence in LVNC. Unmasking the condition in asymptomatic relatives may allow for closer monitoring over time and possibly primary prevention through implantation of ICDs [60].

9. Conclusion

Non-compaction of the left ventricle belonged to the group of unclassified cardiomyopathies according to the 1995 World Health Organization (WHO)/International Society and Federation of Cardiol- ogy Task Force on the definition and classification of cardiomyopathies [61]. More recently the American Heart Association 2006 Classifica- tion, lists LVNC among the group of Genetic Cardiomyopathies [62].

While remaining a rare condition, the diagnosis of LVNC shall invariably be made with increasing frequency in the coming years because of the improved modalities available for cardiac imaging and because of a heightened awareness amongst cardiologists and echocardiographers about the nature and presentation of this condition. Guided by the evidence published to date we conclude that:

- The pathogenetics underlying LVNC while still unclear are most definitely complex, heterogenous and deserving of all ongoing research efforts.
- Echocardiographers should be made aware of the various diagnostic criteria available for LVNC and the limitations of each, bearing in mind the value of additional imaging modalities such as cardiac MRI in difficult cases.
- Prognosis and clinical course in LVNC is varied but close monitoring by a cardiologist is warranted in all cases.
- Confirmed cases should be offered comprehensive genetic testing, early neurological referral and thorough family screening for first- degree relatives.

Acknowledgements

The authors would like to thank Prof. Peter Buser from the Department of Biomedicine, University Hospital, Basel, Switzerland for kindly providing access to Cardiac Magnetic Resonance images depicting a typical case of left ventricular non-compaction.

The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [63].