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A SYSTEMIC REVIEW HYPOKINETIC NONDILATED CARDIOMYOPATHY, AN UNDER DIAGNOSED, UNDER ESTIMATED SUBCATEGORY OF DILATED CARDIOMYOPATHY: NEEDS REDRESSAL

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ABSTRACT
Hypokinetic non-dilated cardiomyopathy (HNDC) is a subtype of DCM, characterised by LV dysfunction, despite absence of LV dilatation. It is most often underdiagnosed and undertreated by physicians due to presence of subclinical symptoms and signs along with subtle radiological and electrocardiographic manifestations. However, a proportion of patients with specific characteristics may develop end stage disease and life-threatening arrhythmia with grievous outcomes. Therefore a systemic qualitative analytic study conducted collecting and compiling all the literatures and guidelines related to HNDC and its related groups to find out high risk groups of patients in terms of arrhythmogenicity or progression of disease. An attempt was also initiated to derive a solution about early accurate diagnosis of patients with HNDC and its related groups. During analysis we obtained useful information's as described below. Family history with genetic association is an important prognostic marker with poor outcomes. Elicitation of family history and pre-degree analysis also help early diagnosis and prevention of progression of disease in relatives. Red flag approach to detect specific clinical, electrocardiographic, radiological signs and laboratory findings can help to detect familial disease with poor outcomes. Screening echocardiography single most important tool to confirm the diagnosis at an earlier stage and prognostication of patients. Speckle tracking is a higher modality of echocardiographic tool,that has greater sensitivity to detect subtle abnormalities of systolic function at an earlier stage. Biomarkers like NT-probnp can have a role in suspecting heart failure in patients without significant cardiomegaly. High risk group of patients can be detected at an earlier stage by stratifying patients as per their family history, genotype, electrocardiographic, echocardiographic, radiologic findings and biomarkers value, so that appropriate measures can be taken at an earlier stage .

Key words: Family history, High risk group, HNDC, Red flag approach, screening echocardiography,

Introduction

Hypokinetic non-dilated cardiomyopathy (HNDC) is a subtype of DCM, characterised by LV dysfunction, despite absence of LV dilatation.[1] It is most often underdiagnosed and undertreated by physicians due to presence of subclinical signs, symptoms along with subtle radiological and electrocardiographic manifestations. Clinical outcomes of patients is highly variable and can be influenced by multiple factors. Patient with HNDC and related group most often remain asymptomatic with subclinical diseases. [2-5] However, a proportion of patients with specific characteristics may develop end stage disease with grievous outcomes.[6-10] Secondly Patients with HNDC with specific genetic mutation are susceptible for life threatening arrhythmia and sudden cardiac death irrespective of LV function.[11] Prevalence of such sub-type is high, contributing 1/3rd population of DCM, that can't be ignored.[8] Therefore a systemic approach during evaluation of patients with HNDC is extremely essential to find out high risk group of patients to avoid dreadful complications like dreadful

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arrhythmia and end stage heart failure e.t.c. At the same time early diagnosis of subclinical cases is extremely important for prevention of clinical progression of disease at an earlier stage. Therefore a systemic review of available literatures conducted with following objectives

1. To stratify high risk groups among patients with HNDC to prevent life threatening arrhythmia, sudden cardiac death and prevent progression of disease at an early stage.
2. To find out a solution for early and accurate diagnosis of subclinical cases of HNDC

Methodology: As the terminology HNDC was recently proposed by ESC in 2016 [1], therefore literatures related to HNDC is very limited.[1,6,11-13] However the concept of HNDC i.e. "LV dysfunction without significant LV dilatation " is pretty old. Over a period of last three decades different authors already had been worked on the same concept, but with different terminologies like Mildly dilated Congestive cardiomyopathy, Mildly dilated Cardiomyopathy, Non dilated cardiomyopathy etc.[2-10] Therefore all the literatures and guidelines related to HNDC and its related groups were collected and compiled and a systemic qualitative analytic study conducted to find out high risk groups of patients in terms of arrhythmogenicity or progression of disease. At the same time an attempt was initiated to derive a solution about early accurate diagnosis of patients with HNDC and its related groups to prevent life threatening arrhythmias and progression of disease in patients with subclinical features.

Historical prospective: About three decades ago (1990) an eminent pioneer of cardiology Keren et.al noticed a category of dilated cardiomyopathy i.e. mildly dilated congestive cardiomyopathy having severe LV dysfunction without significant LV dilatation in patients with congestive cardiac failure.[10] However his nomenclature didn't get enough recognition, as it deserve. Over a period of times, different authors realised importance of such category of DCM with LV dysfunction without LV dilation and defined different nomenclatures like minimally dilated cardiomyopathy, non-dilated cardiomyopathy, mildly dilated cardiomyopathy for the same.[2-9] However these attempts became non effective due lack of uniformity among their studies while defining the disease subtype. Different nomenclatures, parameters, criteria's for the same disease subtype created complexity during diagnosis.[2-10] So it became difficult in the part of physicians to choose a criteria for the diagnosis of disease subtype. In 2016 for the first time, European society of cardiology (ESC) coined a universal, univocal terminology hypokinetic non-dilated cardiomyopathy (HNDC) and proposed a criteria, for early diagnosis and prevention of progression of disease subtype.[1] New ESC criteria excluded hypertension, coronary artery disease while defining HNDC and placed arrhythmic cardiomyopathy in a separate subgroup.[1] It firmly fixed the cut off value for EF at 45% to maintain uniformity and advised to utilise normogram for LV end diastolic dimensions as per age, sex and body surface area.[1] Esc also represented DCM as a broad continuous phenotypic spectrum consisting two phases i.e. preclinical phase (genetic mutation carrier without cardiac expression, isolated LV dilatation or arrhythmic cardiomyopathy) and clinical phase (HNDC, DCM) (Figure I).[1] It conveyed a message that HNDC, a subtype of DCM , that can present persistently with overt clinical phase with LV dysfunction despite absence of LV dilatation or can progress later to dilated phase as an intermediate phenotype of DCM.[1]

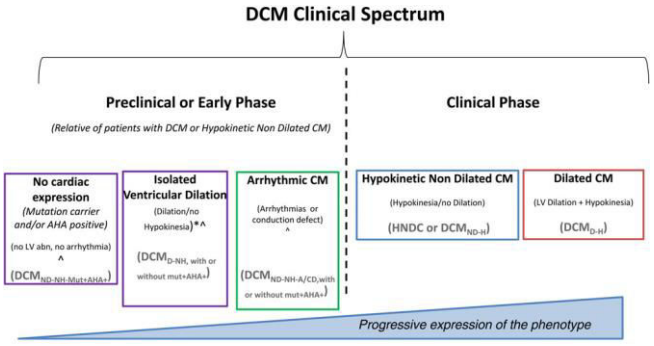

Figure I.Description of the clinical spectrum of DCM (Adapted from reference no. 1)

[LV abn-left ventricle abnormality. DCM can be further classified as ND or D (nondilation/dilation) or NH or H (non-hypokinetic/hypokinetic) or mut+ (mutation carrier) or AHA+ (anti-heart autoantibody positive) or A/CD (arrhythmia/conduction defect]

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Definitions As definitions of HNDC and other older terminologies (table I) were derived from the same concept, therefore these terminologies can be defined as HNDC related groups.

Table.I: Definition of HNDC and its related group with authors contributions

Author	year	Terminology	Definitions
Keren et.al[10]	1990	Mildly dilated Congestive cardiomyopathy	Mildly dilated congestive cardiomyopathy as end-stage heart failure of unknown aetiology (New York Heart Association class IV, left ventricular ejection fraction less than 30%), occurring with neither typical hemodynamic signs of restrictive myopathy nor significant ventricular dilatation (less than 15% above normal range).
Lida et.al [4]	1990	Mildly dilated Cardiomyopathy (MDCM)	MDCM defined as conditions with: 1) left ventricular end-diastolic dimension between 55 and 65 mm and 2) left ventricular fractional shortening between 10 and 25%.
Gavazzi et.al [7]	1993	Mildly dilated Cardiomyopathy (MDCM)	MDCM defined as LV dysfunction along with left ventricular end-diastolic diameter index < or = 15%.
Kitaoka et.al [9]	2002	Mildly dilated Cardiomyopathy (MDCM)	MDCM defined as LV ejection fraction (LVEF) ≤40% with a LV end-diastolic volume ≤120ml/m2 on left ventriculography and the absence of a dip-and-plateau right ventricular pressure caused by a restrictive cardiomyopathy.
Giovanni et.al [2]	2005	Non dilated cardiomyopathy (NDCM)	NDCM defined as an ejection fraction (EF) ≤ 40% with LV end-diastolic volume (LVEDV) ≤78 mL/m2 and the absence of the typical features referring to hypertrophic or restrictive CMP.
Trimothy et.al [5]	2009	Non dilated cardiomyopathy (NDCM)	NDCM defined as an ejection fraction (EF) ≤ 45% with end diastolic dimension (EDD) ≤ 56mm in the absence of congenital, coronary and valvular disease.
Doumas et.al [3]	2010	Non dilated cardiomyopathy (NDCM)	NDCM defined as an ejection fraction (EF) ≤ 45% with end diastolic dimension (EDD) ≤ 56mm in the absence of congenital, coronary and valvular disease.
Gigli et.al **8**	2016	Mildly dilated Cardiomyopathy (MDCM)	MDCM was defined as LVEF <45% and LV end-diastolic volume index (LVEDVI) ≤70 mL/m2 in women and ≤89 mL/m2 in men
Pinto et.al [1] (ESC)	2016	Hypokinetic non dilated cardiomyopathy (HNDC)	HNDC defined as left ventricular or biventricular global systolic dysfunction without dilatation (defined as LVEF, 45%), not explained by abnormal loading conditions (history of severe hypertension, valvular heart disease or congenital heart disease) or coronary artery disease. Systolic dysfunction is defined by abnormal LV ejection fraction, measured using any modality and shown either by two independent imaging modalities or on two distinct occasions by the same technique, preferably echocardiography or CMR. Left ventricular dilatation is defined by LV end-diastolic (ED) volumes or diameters >2SD from normal according to normograms (Z scores > 2 standard deviations) corrected by body surface area (BSA) and age, or BSA and gender

Epidemiology: HNDC stands as a dominant subcategory of DCM, contributing to 1/3rd its population.[8] Prevalence of such subtype is very high among general population i.e. ranging from 0.9%

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to 1.9%, which can't be ignored. HNDC is most common in age group of 35 to 45 years in both sexes.[12] As age increases, the prevalence decreases from 2.9% in 35–45 year group to 0.9% in >65 year group.[12] Prevalence of disease subtype in females is slightly higher than that of males (i.e.2.0% vs. 1.7%), without any statistical significance.[12] A total of 1 of 4 elderly patients with systolic HF had a non-dilated left ventricle.[2]

Family history; Prevalence of family history in HNDC related group is 23%, which is higher than that of DCM (i.e.18%).[8] Family history of disease among patients with congestive cardiac failure is as high as 50% ,which can't be ignored.[10] Family history in relatives is an important prognostic marker implying worse prognosis in patients with HNDC.[11] At the same time, it provide an opportunity to detect asymptomatic subclinical disease in relatives with genetic mutation.[14,15] Therefore pre-degree analysis of the patients extremely essential to diagnose new cases with subtle symptoms and signs.[16] Predigree analysis is also a most important genetic tool to find out the type of genetic transmission and evaluate genetic disease associated with DCM and HNDC.[17] Heart Rhythm Society (HRS) recommended Family screening of at least three generations is in order to detect the potential heritability of the disease.[18] ESC also suggested to provide utmost importance for elicitation of family history in patients with HNDC and DCM through pre-degree analysis to detect the disease subtype at an earlier stage.[1] It also provides a criteria to diagnose familial HNDC/DCM to detect the disease in family members, so that disease can be prevented from the progression at an earlier stage.[1]

Genotype: Besides family history with pre-degree analysis, genotyping has an important role in prognosticating patients. Genetic testing is recommended in the presence of a familial forms or in sporadic DCM or HNDC with clinical clues suggestive of a particular/rare genetic disease (such as atrio-ventricular block or creatinine kinase elevation).[1] Genetic disease in DCM and it subtype HNDC inherit in the family in multiple patterns of transmissions like autosomal dominant(most common), X-linked and autosomal-recessive ,maternal inheritance etc. Familial DCM and HNDC associated with mutation of multiple genes (Figure II) like Titin (TTN),Lamin A/C (LMNA),Myosin heavy chain (MYH7),Troponin T (TNNT2),Myosin-binding protein C (MYBPC3),Sodium channel alpha unit (SCN5A),Phospholamban (PLN),Duchenne muscular dystrophy (DMD),Becker muscular dystrophy (BMD),Myotonic dystrophy or Steinert (MD),Mitochondrial diseases, Tafazin (TAZ/G4.5) etc [19], out of which Titin is the most common genetic mutation seen in 20-25% cases followed by laminin mutation in 6% cases of familial DCM .[20-22] Patients with titin mutation have better prognosis as compared to laminin mutation in terms of response to medical therapy.[11] But paradoxically patients with such genetic mutation are more prone to arrhythmias, which can predispose patients to sudden cardiac death.[11] Patients with desmin mutation can have restrictive filling pattern in patients with HNDC with grievous outcomes.[8,23-24] Patients with laminin mutation worst outcome as compared to other types of genetic mutation.[25]

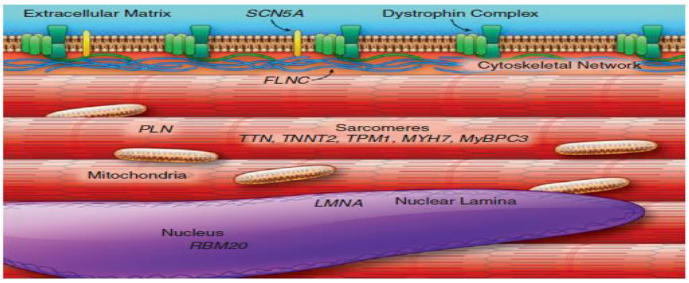

Figure.II : Cardiomyocyte compartments contributing to genetically mediated dilated cardiomyopathy and its subgroups HNDC. (Adapted from reference no.19)

Clinical examination-As around 4/5th patients with HNDC most often remains asymptomatic or mildly symptomatic, therefore patients most often remain subclinical till they develop advanced form of disease. [3,6] Apart from absence of symptoms, subtle clinical signs likes S3, severe MR are less common in patients with HNDC as compared to DCM counterpart.[2,8,27] Important clinical and radiological sign to suspect cardiac disease i.e. cardiomegaly not observed in patients with HNDC even in advanced stage . Other clinical signs of heart failure like elevated JVP, pedal oedema can provide clue towards suspecting heart disease in patients, more specifically in advanced stage of disease. However in early stage of disease, it is difficult in the part of physicians to diagnose the disease subtype. Other investigations X-ray, ECG, Echocardiography, cardiac biomarker can have a role for diagnosis of disease.

As familial inheritance is common in patients with HNDC, therefore red flag approach to find out specific clinical features,that can help in evaluation of specific syndromic disorders with genetic aetiologies.[26] Clinical features like sensorineural deafness , inter actual disability, visual impairment

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due to sub capsular cataract, palpebral ptosis, pigmentation of skin, keratoderma, dysmorphic facies, gait disturbances can provide a clue for familial cause for cardiomyopathy with poor outcome.[25,26]

X-ray finding: Patients with HNDC most often missed by primary contact physician due to absence of cardiomegaly in chest X -ray. Therefore meticulous examination other radiological findings can provide a clue for suspicion of heart failure. Radiological signs of pulmonary artery hypertension (like enlargement of the main pulmonary artery , peripheral pruning of distal pulmonary vessels, right ventricular dilatation e.t.c) [28],pulmonary venous hypertension(like Kerley lines, Perihilar peribronchial cuffing , Bat wing edema e.t.c) [29] can provide clue towards evaluation of heart disease in the absence of cardiomegaly.

Electrocardiographic findings: Electrocardiography is an important tool to suspect cardiac disease in patient with heart failure. However electrocardiographic signs like LBBB, LVH, LAE, which are typical and more prevalent in idiopathic DCM, are less prevalently observed HNDC and its related group. [6-8, 25] Therefore it becomes a challenge in the part of physician to suspect heart disease from electrocardiographic or radiological finding.

Besides diagnosis, some electrocardiographic signs also have prognostic value. LBBB is an important prognostic maker with poor outcome [30,31], observed in 1/4th patients with HNDC related group.[8] LAE is also a poor prognostic sign of cardiomyopathy indicating increased LV end diastolic pressure.[32,33] Low voltage QRS complex, intraventricular conduction defect, bundle branch block in ECG leads is a marker of advanced diseases in cardiomyopathy. Fragmented QRS and T wave alternans is an important prognostic marker of disease.[34] Besides typical ECG finding brady or tachyarrhythmia are common in cardiomyopathy. Ventricular ectopics, non-sustained VT and supraventricular tachycardia can have arrhythmogenic substrate involving genetic mutation like laminin, titin, SCN 5A etc.[35] Non sustained VT, ≥1000 Ventricular ectopic beats/24 h, or ≥50 ventricular couplets/ 24 h are associated with a higher incidence of SCD, sustained VT, or ventricular fibrillation, though arrhythmic cardiomyopathy can be an important differential diagnosis in above cases.[35] Bundle branch re -entrant VT with LBBB morphology is the most common form ventricular tachycardia with grave prognosis.[35] Tachy-arrhythmia like atrial fibrillation also more common in patients with LV dysfunction without LV dilation.[3,5,7] Patients with atrial fibrillation have better prognosis in comparison to patients without atrial fibrillation.[3,5,37] LV function improves partially or completely in most of the patients after control of rate or rhythm by antiarrhythmic drug.[37]

Besides diagnostic and prognostic importance, some atypical red flag ECG signs can help to provide a clue to evaluate aetiology of disease subtype. Brady-arrhythmia and conduction abnormality like high grade AV block can provide a clue towards familial cardiomyopathy with laminin or dystrophin mutation.[38-39, 26] Patients with onset of AV conduction defects in middle age or earlier should be evaluated for inflammatory or familial cardiomyopathy. Presence of pseudonecrosis can represent dystrophinopathy.[39, 26] Extremely low voltage QRS complexes can indicate towards phopolamban mutation.[26] Atrial stand still and low voltage P wave can indicate Emery Dreifuss syndrome. [26]

Sometimes typical pathognomic electrocardiographic signs helps to exclude other cardiac diseases, which can mimic HNDC .Right bundle branch along with low voltage complex and inferolateral T wave inversion helps to exclude left dominant arrhythmogenic cardiomyopathy.[40] Sinus tachycardia, ST wave and T wave abnormalities , PR depression and diffuse ST segment elevation ,widened QRS and Q waves can help to exclude myocarditis.[41] Electrocardiographic findings like RBBB with AV block , which can help in exclusion of sarcoidosis .[42]

ECHOCARDIOGRAPHY; Echocardiography is the most important tool to confirm LV dysfunction, when electrocardiographic and radiological findings are subclinical.[43] Global hypokinesia with normal end diastolic LV dimension is typical echocardiographic feature of HNDC, though regional wall motion abnormalities with akinesis or dyskinesis may be noticed, mostly at LV septum or apex with better contractility in the posterior and lateral walls.[36] Previously it was presumed that LV dilation representing increased LV end diastolic dimension is an important predictor of clinical outcome and mortality.[2] However many studies confirmed that LV dimension has no role in prognosticating patients with DCM.[10,26] Rather ejection fraction is an important predictor of mortality and hospitalisation irrespective of LV end diastolic diameter.[44] It was observed that, average mean EF in patients with HNDC related groups is higher as compared to DCM.[2,7] Presence of restrictive filling (RPF) pattern is also an important predictor of worse progression of disease indicating desmin mutation.[23,24] Prevalence of RPF observed in patients with HNDC related group is 20%, which is lower as compared to idiopathic DCM (i.e. 35%).[8] In addition left atrial enlargement ,severity of MR and RV dysfunction were also significant predictors of poor outcome in patients.[7,45-47] Prevalence of moderate to severe MR in patients with HNDC is 20% ,which is comparatively low as compared to DCM (49%).[8] Prevalence of RV dysfunction in HNDC is as high as 47.3% as per a recent study.[13]

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Speckle tracking is a higher modality of echocardiographic tool in prognosticating patients with HNDC.[6] It has greater sensitivity to detect subtle abnormalities of systolic function than EF, so that disease progression can be prevented at an earlier stage.[48] Global circumferential strain, longitudinal circumferential strain, mechanical dispersion, twist are the important parameters of measurements, out of which global circumferential strain is most important tool for discriminating HNDC and idiopathic DCM.[6] HNDC patients tends to have lower positive circumferential strain and mechanical dispersion in comparison to idiopathic DCM.[6] Global circumferential strain is a sign of advanced intrinsic myocardial systolic dysfunction, whereas mechanical dispersion is an important predisposing sign of arrhythmogenecity of myocardium.[6] To summarise echocardiographic findings, higher ejection fraction, smaller left atrial area, lower rate severe MR , restrictive filling, lower GCS score were more common in HNDC related groups in comparison to DCM.

Cardiac MRI: It is very essential for prognostication and evaluation of etiology. Late gadolinium enhancement (LGE) is an important finding in MRI, that implies the area with replacement fibrosis or scarring.[49] LGE is as an important predictor of mortality, hospitalization, and sudden cardiac death.[50] Distinctive LGE patterns provides clue for evaluation of different etiologies. Patchy midwall LGE may occur in dystrophin mutation. Presence of focal LGE involving the subepicardium and midwall myocardium can represent myocarditis. LGE involving the basal LV segments of the heart or submitral area can help to exclude other etiology like sarcoidosis.[49]

Laboratory investigation: Bimarker like NT probnp, troponin I can have both diagnostic and prognostic value in patients with suspected heart failure. Higher level NT probnp is a prognostic marker of heart failure.[51-52] Troponin I may be raised in acute myocarditis [53], ischemic cardiomyopathy with heart failure. Serum galectin-3 is a marker of cardiac fibrosis with adverse outcome. [52] Elevated C-reactive protein, erythrocyte sedimentation rate and leucocyte count are non-specific markers in patients with suspected myocarditis. Increased creatine kinase can provide a clue to evaluate genetic mutations like Dystrophinopathies, Laminopathies, Myotonicdystrophy ,Desminopathies. [26] Hyperferritinaemia can be observed in hemochromatosis.[26] Lactic acidosis, myoglobinuria can provide a clue about mitochochondrial cardiomyopathy.[26]

Endomyocardial biopsy: Endomyocardial biopsy (EMB) is a gold standard investigation to exclude myocarditis.[54] Other cause of cardiomyopathy like sarcoidosis, infiltrative cardiomyopathies, and hypereosinophilic syndromes can be excluded by EBM. [54]

Electron microscopy: Absence of myofibrillar loss is the most common finding in patients with HNDC in contrast to DCM.[55] Myofibrillar loss correlates more with heart size than with ejection fraction. [55] Thumbprint appearance of stacked mitochondrial cristae is pathognomic of familial cardiomyopathy.[56]

Electrophysiological study (EPS): Syncope in patients with suspected arrhythmic origin should be evaluated is with EPS according to the latest ACC/AHA guidelines.[57] Programmed ventricular stimulation can be useful in detecting HNDC cases with high arrhythmic burden.[58]

Coronary angiography : Patients with HNDC with age more than 35 years of age should undergo coronary angiography to exclude ischemic cardiomyopathy. However in patients with age less than 35 years, coronary angiography indicated, if there are significant personal coronary artery disease (CAD) risk factors or a family history of early CAD.[1]

Differential diagnosis;

Arrhythmic cardiomyopathy: Patients with chronic arrhythmia like AF, multiple VPC,NSVT can progress tachy-cardiomyopathy, which can mimics features of HNDC. However EF improves and completely or partially normalises after rhythm or rate control. [36,37] Previous investigatory reports (ECG, echocardiography) of isolated arrhythmia without LV dysfunction sometimes provide a clue for differentiating arrhythmic cardiomyopathy from HNDC.

Myocarditis: Myocarditis can mimic echocardiographic feature of HNDC. However recent history of fever can provide a clue towards viral myocarditis leading LV dysfunction. Secondly echocardiographic feature of regional wall motion abnormality in non-coronary artery distribution indicates myocarditis.[36] However myocarditis can present with global hypokinesia mimicking DCM or DCM subtype. In the above circumstances myocardial biopsy is the important tool to differentiate from HNDC.

Ischaemic Cardiomyopathy; History of angina, previous history of coronary artery disease can provide a clue for suspecting ischemic cardiomyopathy. Echocardiocardiographicaly patients usually presents with regional wall motion abnormality in a defined coronary artery territory.[36] However patient with CAD with triple vessel disease can present with global hypokinesia mimicking HNDC.in above cases coronary angiography is a the usual methods to exclude CAD.[1]

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Hypertensive cardiomyopathy; Patients with persistent hypertension can present with echocardiographic feature of HNDC. However history of previous persistent grade 2 hypertension provides a clue about hypertensive cardiomyopathy.LV function improves and reverses completely after control of hypertension.[59] These group of patients usually have better prognosis as compared to HNDC.[59]

Restrictive cardiomyopathy: Patients with HNDC restrictive filling can mimics restrictive cardiomyopathy. However early diastolic dip and plateau pressure patterns or equalization of right and left ventricular diastolic pressures typical of restrictive cardiomyopathy.[36]

Advanced HCM: Patients with HCM in advanced stage can present with global hypokinesia with LV dysfunction. LVOT gradients can be decreased towards normalisation due to decreased myocardial contractility. Associated significant asymmetrical LV hypertrophy can help to differentiate HCM with LV dysfunction from HNDC. [36]

Arrythmogenic RV cardiomyopathy with biventricular involvement: Echocardiographic features can mimic features of HNDC with RV dysfunction. However disproportionately significant RV dilatation and dysfunction along with typical electrocardiographic sign ARVC differentiate from HNDC.[36]

Clinical outcomes: Most of the patients usually have class I or II symptoms.[3,6] These groups of patients have better survival rate as compared to idiopathic DCM.[2-5] Marta etal noticed that 15% patients with HNDC group either died or underwent heart transplant as compared to 30% patients in DCM group.[8] Around 1/4th of patients with HNDC group evolved into dilated cardiomyopathy over a period of two years.[8] Patients with HNDC, they evolved in to dilated form had similar clinical outcome and prognosis as that of idiopathic DCM.[8] 1/6th patients regress back to normal LV function.[7] However outcomes of patients with congestive cardiac features have grievous prognosis. As per keren etal 2/3rd patients with congestive cardiomyopathy without any significant LV dilation die despite medical therapy over 20±8 months.[10] Patients with HNDC can develop arrhythmia like VT,VF and sudden cardiac death, irrespective status of LV ejection function.[11]

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Prognosis:

Table II. Poor prognostic signs and markers in patients with HNDC and its related groups

Findings	Poor prognostic signs and markers in HNDC and its related groups.
Family history	Positive family history bad prognostic indicator of HNDC [11]
Associated comorbidities	Association of diabetes, chronic kidney disease, obesity, metabolic syndrome can have worse prognosis.[60]
Genotype	Laminin, Titin and SCN 5A mutation are the important predisposing factor for arrhythmia in patients.[11,25]
	Laminin mutation also associated with rapid progression of disease and heart failure [25]
	Desmin mutation associated with restrictive filling pattern on echocardiography with poor outcome [8,23-24]
Clinical findings	Features of congestive cardiac failure (S3,elevated JVP, pedal oedema)[10] ,moderate to severe MR[45]
	Sensorineural deafness , inter actual disability, visual impairment due to sub capsular cataract, palpebral ptosis, pigmentation of skin, keratoderma indicate familial form of cardiomyopathy with poor outcome [25,26]
X –ray findings	Radiological signs of pulmonary venous hypertension (like Kerley lines, perihilar Peribronchial cuffing , Bat wing oedema etc.) [29]
	Radiological signs of pulmonary artery hypertension (like enlargement of the main pulmonary artery , peripheral pruning of distal pulmonary vessels, right ventricular dilatation etc.) [28]
Electrocardiographic findings	Low voltage QRS complex, intra-ventricular conduction defect , left bundle branch block, left atrial enlargement in ECG leads is a marker of advanced diseases in cardiomyopathy. [30-33]
	NSVT, ≥1000 VEB/24 h, or ≥50 ventricular couplets/ 24 h, was associated with a higher incidence of SCD. Previous history of cardiac arrest or sustained VT is a important prognostic indicator of poor outcome.[35]
	Depolarization abnormalities (fragmented QRS, intra-ventricular delay, signal-averaged ECG),repolarization abnormalities (T wave alternans) [34]
	Red flag electrocardiographic signs like high grade AV block, low voltage P wave, atrial stand still can be associated with genetic disorder with bad prognosis. [26,37-38]
Echocardiographic abnormality	Echocardiographic abnormality low basal EF, higher positive GCS score in speckle tracking, restrictive filling pattern, RV dysfunction, moderate to severe functional MR are the negative prognostic marker in HNDC.[6,23-24,44-48]
Haemodynamic parameter	increased left atrial pressure, left ventricular end-diastolic pressure and mean pulmonary artery pressure also indicates poor outcome in patients. [7,9]
Autonomic parameter	heart rate variability, baroreflex sensitivity, heart rate turbulence [34]
Laboratory parameter	Higher level NT probnp is a prognostic marker of heart failure.[52]
	Serum galectin-3 is a marker of cardiac fibrosis with adverse outcome.[52]
	Increased creatine kinase can provide a clue to evaluate genetic mutations like Dystrophinopathies, Laminopathies, Myotonic dystrophy,Desminopathies .Hyperferritinaemia can be observed in hemochromatosis. Lactic acidosis, myoglobinuria can provide a clue about mitochochondrial cardiomyopathy.[26]
MRI findings	LGE as an important predictor of mortality, hospitalization, and sudden cardiac death. It implies the area with replacement fibrosis or scarring [49-50]
Electrophysiological study (EPS)	Induced ventricular arrhythmia on programed ventricular stimulation is a bad prognostic sign.[58]

Conclusion: Patients with HNDC and its related groups most often remains asymptomatic or mildly symptomatic. Clinical, electrocardiographic, radiological manifestations most often remains subtle. Therefore chances of missing diagnosis from routine check-up is high in patients with HNDC. Screening echocardiography single most important tool to confirm the diagnosis at an earlier stage. Speckle tracking is a higher modality of echocardiographic tool, that has greater sensitivity to detect subtle abnormalities of systolic function at an earlier stage. Biomarkers like NT-probnp can have role in suspecting heart failure in patients without significant cardiomegaly. Patients with HNDC have better clinical outcome and prognosis as compared to DCM counterpart. However a proportion (1/4th)

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of patients progress to dilated form, can have adverse outcomes equivalent to DCM. Family history along with genetic association is an important prognostic factor for adverse clinical outcomes in terms of susceptibility for life threatening arrhythmia, sudden cardiac death and progression of disease towards end stage heart failure. Elicitation of family history and pre-degree analysis is also an important part for early diagnosis and prevention of progression of disease in relatives. Red flag approach to detect specific clinical, electrocardiographic, radiological signs and laboratory findings can help to detect familial disease with poor outcomes .High risk group of patients can be detected at an earlier stage by stratifying patients as per their family history, genotype, electrocardiographic, echocardiographic, radiologic finding and biomarker value, so that appropriate measures can be taken at an earlier stage.

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