



REVIEW ARTICLE

Review of Noncompaction cardiomyopathy in children –an underestimated Incidence

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OPEN ACCESS

PUBLISHED

31 July 2024

CITATION

Karim, T., Islam, MT., Kanti, NT., 2024. Review of Noncompaction cardiomyopathy in children –an underestimated Incidence. Medical Research Archives, [online] 12(7).

<https://doi.org/10.18103/mra.v12i7.5542>

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DOI

<https://doi.org/10.18103/mra.v12i7.5542>

ISSN

2375-1924

ABSTRACT

Noncompaction cardiomyopathy (NCCM) is a heterogenous disorder and third most common cardiomyopathy in children. It is characterized by hyper trabeculation, commonly hypothesized due to an arrest in compaction during fetal development. Since 1984 its first description by Gerecke et al. NCCM has been labeled with several names over 35 years that includes—spongy myocardium, left ventricular noncompaction cardiomyopathy (LVNC), Left ventricular hyper trabeculation (LVHT). In the year 2006, the American Heart Association classified NCCM as a distinct form of cardiomyopathy (CMP). NCCM is a rare cardiac disease with an estimated incidence of 0.12 per 100.000 in children up to the age of 10. In children NCCM is more frequently familial than when diagnosed in adulthood and is associated with other congenital heart diseases (CHDs), other genetic CMPs, and neuromuscular diseases (NMDs). Diagnostic challenges made it underestimated incidence. It may be due to non-uniform diagnostic criteria, unawareness, presumed other CMPs, and presence of CHD. NCCM can be asymptomatic to various presentation like heart failure, arrhythmia thromboembolic events, either as individual or in combination. Specific Treatment strategy has not yet established, nevertheless and, betablocker, ACEI or ARB might lead to remodeling of Left ventricular function (LV). In addition to state-of-the-art review, we discuss the epidemiology, pathogenesis, Phenotypes, aetiology, genetics, clinical presentation, outcome, and advancement in therapeutic options of NCCM in pediatric patients- fetuses to children. Furthermore, we provide a simple classification of different forms of disease. Finally long-term outcomes and future perspective are described.

Keywords: NCCM, Heterogenous cardiomyopathy in children.

Introduction

Non compaction cardiomyopathy is a rare disorder with diverse presentation in paediatric age group. With the advancements in diagnosis and treatment techniques, the detection rate of myocardial insufficiency in children has increased. NCCM is a type of cardiomyopathy classified by an extensive trabeculated myocardium, with two distinct layers composed of compacted and noncompacted myocardium^[1,2]. It as a genetic cardiomyopathy caused by arrested myocardial development classified by The American Heart Association^[2,3]. LVNC can be detected among all ages, ranging from fetuses to nonagenarians, and with normal size and well contractile left ventricles or dilated and poorly contracting LV^[4,5]. Since 1984 its first description by Gerecke et al. NCCM has been labeled with several names over 35 years that includes—spongy myocardium, left ventricular noncompaction cardiomyopathy (LVNC), Left ventricular hyper trabeculation (LVHT)^[6,7]. In recent Australian retrospective studies, the incidence of LVNC in children was reported to be approximately 0.11/100,000^[1].

Even though NCCM is a rare cardiac lesion, it is the third most common cardiomyopathy (CMP) in the pediatric population following DCM and HCM^[7]. NCCM can occur as an isolated or non-isolated phenotype. Non-isolated NCCM may be accompanied by congenital heart diseases (CHDs), features of other CMPs, and/or neuromuscular diseases (NMDs)^[8,9]. The exact pathophysiology of NCCM is poorly understood and are different theories of the extensive trabeculations formation. The Abnormal embryological compaction of the myocardium, leading to a hyper trabeculated honeycomb-like myocardium is one of those theories^[10,11].

However, this does not fit with NCCM diagnosed in adulthood. Many genes have been reported to be associated with NCCM, but none of the proposed pathogenic gene variants or chromosomal defects can directly be linked to a disrupted compaction process in the fetus.

Furthermore, most of the (likely) pathogenic gene variants can lead to different phenotypes^[12].

As it is a rare disorder and the lack of universally accepted diagnostic criteria, and the lack of awareness among the clinicians, knowledge regarding NCCM in children remained little. Fetal NCCM cases are particularly very few in reports^[13,14].

Majority of pediatric patients with NCCM have a poor prognosis, especially those with comorbidities other than cardiomyopathies found in many studies^[15-18]. Morphological characteristics of left ventricle by echocardiography is the most commonly used diagnostic method to detect NCCM now a days. In the past cohort studies, specific echocardiographic criteria were established, including Jenni, Chin and Stollberger^[19-21]. And the widely used LVNC diagnostic criteria are mainly Jenni diagnostic criteria. Mainly in these aspects: (a) it includes dense layer and non-dense layer, and the ratio of the thickness of non-dense layer myocardium to the thickness of dense layer myocardium is more than 2 (children are more than 1.4), so it is necessary to pay attention to the measurement time in systole, (b) the lesion area is generally located at the apex of the heart (>80%), and some patients' lateral walls and inferior walls will be involved, (c) Color Doppler can see that there is blood flow communication, but it should be noted that blood flow is not connected with coronary circulation. It is worth mentioning that, in recent studies, LVNC is not usually recognized and LV hypertrabeculation is perhaps more accurate^[22].

LVNC may be clinically asymptomatic or present with a variety of symptoms such as chest pain, dyspnea, and palpitations; however, three main clinical symptoms require urgent attention^[23-26]. Heart failure, Thromboembolism and arrhythmias are the most common and the most important which causes high clinical concern in patients with LVNC^[27-30]. Additionally, these patients often have a neuromuscular disease and may experience fatigue^[31,32], muscle aches and pains, and elevated creatine kinase levels^[33]. Though it has a grave

outcome, no disease targeted treatment available till date^[34-37].

Some patients with left ventricular noncompaction are asymptomatic from birth to onset, and it is not discovered until they have heart-related symptoms or physical examination. This is called myocardial noncompaction in adults. Therefore, both adults and children with myocardial noncompaction are congenital diseases, but the time of discovery or symptoms is different^[38].

The purpose of the writeup is to give an overview of such heterogenous cardiac disorder in paediatric age group, discuss current advances in the clinical management of the different symptoms of LVNC, facilitate the progress of clinical research, the latest treatment strategy, and to light up the need for future treatment involving genetics.

Prevalence of NCCM in Children:

The exact incidence of paediatric NCCM has not yet been established due to lack of consensus about the diagnostic criteria. The first case of NCCM was probably described by Bellet and Gouley in 1932 as a rare complex congenital myocardial anomaly^[39]. Moreover, recent classification as a distinct form of cardiomyopathy and all these lead to delay or misdiagnosis of NCCM from other form of cardiomyopathy^[40].

The age of presentation of NCCM have been reported includes neonates^[41] and during the prenatal period^[42].

Tian et al.^[42] documented nine cases of LVNC in fetal echocardiography using the criteria proposed by Jenni^[43] and Stollemberg^[44] between 2004 and 2013. NCCM was confirmed in two cases via echocardiography after birth, while the remaining seven pregnancies were terminated, with diagnosis was confirmed during autopsy.

Large-scale studies using echocardiography in both children and adults have estimated the prevalence of so-called non-compaction cardiomyopathy to be between 0.02% and 0.14%^[45-48].

NCCM In the pediatric age group are increasing over the last few decades, possibly due to the improvement of accuracy of imaging methods^[49].

NCCM in children ranks as the third most prevalent cardiomyopathy after dilated cardiomyopathy (DCM) and hypertrophic cardiomyopathy (HCM)^[50] children up to ten years of age the estimated incidence of NCCM is 0.12 per 100.000 in and \leq 0.81 per 100.000 in children up to one year of age^[51].

In addition, similar incidence rates were found in several smaller cohort studies in pediatric patients. An Australian study reported an incidence of 9.2% NCCM in all children diagnosed with a primary CMP under the age of ten between 1987 and 1996^[52]. Nevertheless, the Pediatric Cardiomyopathy Registry (PCMR), a large register including 98 centers from the USA and Canada, 4.8% of all children diagnosed with any form of CMP had an isolated NCCM, over a period of 18 years^[53].

NCCM cases, there was an association with other cardiomyopathies (59% with DCM and 11% with HCM), while 23% presented as an isolated phenotype and 8% as an indeterminate phenotype^[54]. The age of onset was higher for isolated forms of LVNC (average 9.8 years) compared to those associated with other cardiomyopathies (0.4–0.6 years)^[54].

In Denmark from April 2016 to October 2018, Borresen et al.^[41] conducted echocardiograms on 21,133 healthy infants revealing an NCCM prevalence of 0.076%. It was defined on the echocardiogram by the ratio of non-compact (NC) to compact (C) layers thicknesses ($NC/C \geq 2$) in end diastole. However, the absence of a universally accepted standard diagnosing criteria for NCCM renders the incidence and prevalence of this disease uncertain.

Pathogenesis:

Abnormal myocardial embryogenesis may be involved in NCCM. Only two layers of cells, one epithelial and one endothelial layer form the heart as a simple tube with a cardiac substance in between^[55]. As the heart grows in mass, muscle

tissue replaces the cardiac substance^[55]. This newly formed muscle tissue is constructed in a sponge-like structure, enabling the cells to be oxygenated and receive nutrients through the blood flow in the endothelial outlined spaces, because of the absence of the coronary and sinusoidal circulation^[10,11,56].

Normally, compaction of the myocardium occurs between 5–8 weeks of the fetal life, from septal to lateral walls and from basal to apical segments. In congenital NCCM, it is believed that genetic defects or 16 Heart Failure Reviews (2022) 27:15–28 1 3 epigenetic regulation of specific cardiac pathways cause an arrest in the normal process of myocardial compaction resulting in a myocardium consisting of two layers: one compact layer (epicardium) and one honeycomb-like structure with extensive ventricular trabeculation and deep intertrabecular recesses (endocardium)^[10,11,55,56].

With inactivation of the MIB1 gene (known to induce LVNC in humans), LVNC developed due to proliferation (10–15%) of the non-compact myocardium. Luxan et al.^[57] demonstrated that in mice. Normally the compact wall can develop via the suppression of NKX2-5 inducing excessive trabeculation^[58] This suggests that the growth of the compact wall is largely independent of that in the trabecular layer. On the contrary notions suggesting that due to the compaction of pre-existing trabeculations the compact layer forms.

Contemporary observations showed continuous growth of both layers. This evidence conclude that the hyper trabecular phenotype arises from a thickening of the non-compact layer not a failure to compact. In addition, the concept of intrauterine arrest in the process of compaction has been suggested but lacks supporting evidence^[59,60].

LVNC presenting during the neonatal period, can be an acquired phenotype. Increased hemodynamic load on the LV may cause hyper trabeculation, such as pregnancy or physical activity, may lead to the development of LVNC. Paun et al.^[61] demonstrated that the appearance of trabeculations on the LV wall can be considered as

an adaptive response to meet the increased hemodynamic demands of the person, reflecting a relationship between the increase in trabeculations and the increase in stroke volume.

The following features were found on Autopsy of a patient with isolated persisting myocardial sinusoids of both ventricles, to define NCCM:

hyperplastic trabeculae separated by labyrinthic spaces communicating with the ventricular cavity, an extended pericardial sac and thickening of the heart, mostly pronounced in the apical region^[11]. But this bilayer structure of NCCM should be differentiated from normal apical structure of healthy person.

We have to keep in mind, the thickness of the trabecular layer of a healthy individual does not usually exceed the compact layer in size, as in the case in NCCM^[10,11,56]. left ventricle is predominantly affected in NCCM both in the case of children and adults. To date, few cases of biventricular noncompaction in children are reported^[62-67]. Furthermore, in the left ventricular noncompaction (LVNC) apex is predominantly affected.

Paediatric NCCM Phenotype:

NCCM in Pediatric group is typically a non-isolated phenotype which is often associated with concomitant features of other CMPs (DCM & RCM) or in the coexistence of one or more structural CHD(s), malformation syndrome, metabolic disorders, or NMD^[12]. On the other hand, in adult patients the isolated form of NCCM is the most predominant phenotype.

NCCM patients also present with DCM characteristics in 30.4%, 18.7% with HCM characteristics, and 17.9% with both DCM and HCM. Of the pediatric patients, only 32.2% of the pediatric NCCM cases are without any features of another CMP^[52,68-3].

Paediatric group with NCCM concomitantly present with structural CHD^[70-72,74-79]. The exact incidence of CHD in the NCCM population is not known with incidence rates reported varying from 13 to 78%. Ventricular septal defect (VSD; 18.7%),

atrium septum defect (ASD; 10.8%), persistent ductus arteriosus (PDA; 6.3%), and Morbus Ebstein (4.1%) are the most reported forms of CHD in association with NCCM in the pediatric populations^[70-72,74-79].

Neuromuscular disorders (NMD) are more frequently associated with cardiomyopathy populations, which also apply to the NCCM population^[80]. An adult patient with Duchenne muscular dystrophy (DMD) was first described with NCCM^[81]. The incidence of DMD in the pediatric NCCM population is unknown. However, the incidence of NCCM in the DMD population is reported near 20–25%^[82,83]. More research is warranted in the pediatric NCCM population to find out the association of other NMDs.

Fetal NCCM was an arrest in embryonic trabeculation, which should be detected by prenatal echocardiogram. However, only a few cases of fetal NCCM diagnosis have been reported in the literature^[13, 84-87].

Fetal hydrops was present in 33% of these cases and other structural cardiac abnormalities in 60% of patients^[88]. The associated structural cardiac abnormalities most frequently reported in the fetal NCCM were atrioventricular septal defect (33%), double-outlet right ventricle (26%), and left atrial isomerism (24%). Ebstein's anomaly was not reported in this population^[88].

Trend towards a worse survival (37.5%, mean age 26 months) seen in fetal NCCM population. In addition, 9.1% died prenatally, 27.3% died after birth, and in 19.3% the parents decided to terminate the pregnancy. Also, 6.8% was lost to follow-up^[88]. Probably this worse survival of fetal NCCM associated with rareness of the disease, because prenatal echocardiography may only recognize the most severe cases^[89].

Genetics NCCM, like most familial CMPs, is a genetic heterogeneous disease. over 40 monogenetic and chromosomal defects are described in the overall NCCM population, although this is a new field^[90,91]. Different inheritance patterns are described in NCCM^[90-93]

and the exact mechanism of gene mutations involving in NCCM is not known. The same genetic defects have variable penetration, even within the same family. More importantly, a genotype-phenotype correlation has recently been established showing that specific genes may confer risk for overlapping cardiomyopathy phenotypes, like NCCM/DCM and NCCM/HCM within families^[55,91-94]. Various autosomal inherited genetic defects, mostly with dominant inheritance, were associated with NCCM, including pathogenic variants in sarcomere or cytoskeletal genes, and genes encoding ion channels. The sarcomere MYH7 and MYBPC3 genes are most frequently reported to cause NCCM (20–25% and 10%, respectively)^[93]. Certain autosomal defects in other genes encoding proteins such as α -dystrobrevin, α -cardiac actin, and cardiac troponin T are also responsible for DCM and HCM. This implicates a possible similar molecular etiology to various cardiomyopathy phenotypes^[95,96-99]. In NCCM pediatric patients had concomitant congenital heart disease, in a systemic review, most frequent mutations were in MYH7, MIB2, MKX2, NOTC1, NSD1, PTPN2, and a whole range of chromosomal defects^[100]. X-linked the first pathogenic gene variant found to be responsible for NCCM was a genetic variant in the TAZ gene, on locus hydrops was present in 33% of these cases and other structural cardiac abnormalities in 60% of patients^[88]. The concomitant structural cardiac abnormalities most frequently reported in the fetal NCCM population were atrioventricular septal defect (33%), double-outlet right ventricle (26%), and left atrial isomerism (24%). The presence of Ebstein's anomaly was not reported in this population^[88].

Clinical Presentation:

NCCM Clinically symptomatic to asymptomatic in presentation. Isolated NCCM are usually asymptomatic but those with concomitant diseases present with their disease symptoms. Variety of symptoms such as palpitation, chest pain, dyspnea. The most common clinical presentation of isolated NCCM in children is congestive cardiac failure^[52,68-79];

however, three main clinical symptoms require urgent attention^[22–25]. The most common and the most important is heart failure, which is associated with most of the other clinical symptoms^[26–29]. High clinical concern in patients with LVNC are Thromboembolism and arrhythmias. In addition, these patients often have neuromuscular disease and may experience fatigue^[30,31], muscle aches and pains, and elevated creatine kinase levels^[32].

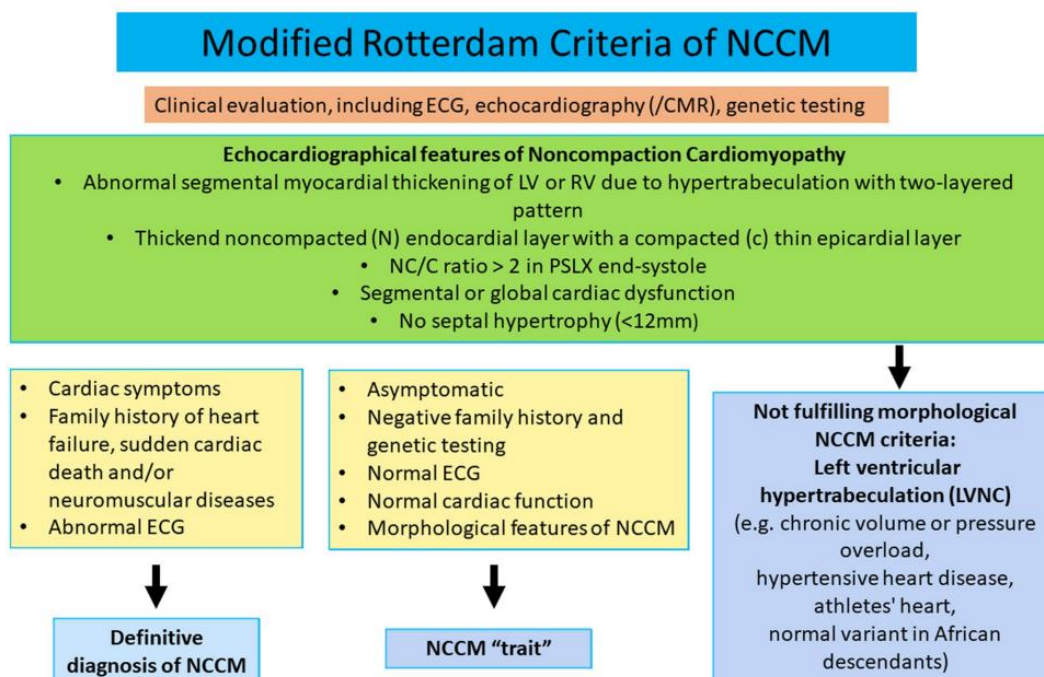
Diagnosis:

The gold standard of diagnosis of NCCM is not yet made. It is usually made through echocardiography or CMR depending on the morphological criteria. To distinguish NCCM from physiological trabeculation and other forms of cardiomyopathy several echocardiographic criteria are proposed in the past 30 years. The two most commonly used echocardiographic criteria are the Jenni criteria^[7], the Chin criteria^[56], and the Stöllberger criteria^[101]. pathoanatomic correlation have poorly tested in most criteria^[7,56,102], and it is important to note that almost a fourth of the heart failure population fulfil one or more of these echocardiographic criteria. This reveals that the current echocardiographic criteria are not enough to distinguish NCCM. Therefore, the Rotterdam criteria, combining both conventional trabeculation criteria (i.e., the “Jenni criteria”) and septal thickness^[40] can be applied. Differentiation between definite NCCM and a normal variant seen in athletes, African descendants, and long-standing hypertension can be made by these criteria^[40]. Concomitant CHD or NMD should not be an exclusion criterion. In case of Uncertainty about the diagnosis of NCCM, CMR, are warranted^[103]. The Petersen criteria are most frequently used in clinical practice for CMR^[104]. NCCM can be distinguished from physiological trabeculation and other CMPs, such as HCM, through CMR, by a noncompacted layer to compact layer ratio of 2.3 (sensitivity of 86%, specificity of 99%) or a trabeculated LV mass ratio of > 20% (sensitivity and specificity of 94%)^[104,105].

Most frequently echocardiography and CMR are used to diagnose NCCM, but no genetic,

histopathological, or imaging diagnostic tool has been developed yet which can distinguish NCCM patients from physiologic hyper trabeculation of the left ventricle. over the past 10 years it has resulted in an exponential growth in the recognition of NCCM. In a large multicenter study in North America, including 98 centers, 217 patients were diagnosed with NCCM between 2000 and 2009, while between 1990 and 1999, only 25 NCCM patients were identified^[68]. This becomes “popular” due to the raised awareness, or the more flexible interpretation of the diagnostic criteria since various other disorders of the myocardium show high similar it used to diagnosis^[106]. Routine genetic testing is currently performed, there are no genes related specifically to NCCM and not even to other cardiomyopathies^[93,94].

Furthermore, the same pathogenic gene variant can cause highly variable phenotypes^[12]. However, a molecular genetic analysis could be useful to identify other affected (asymptomatic) family members (cascade testing) if a family is known to be affected by a certain pathogenic gene variant. Furthermore, for estimation of the chance of re-occurrence genetic analyses should be considered, if the parents wish to have a child. This is especially useful in case of (possible) childhood-onset NCCM, and in complex disorders presenting with NCCM, like in Barth syndrome. Genetic analysis detects genetic cause in approximately 45% of childhood NCCM and may help determine the risk of recurrence and pathophysiology of NCCM^[12].



Treatments option:

NCCM treatment is symptomatic as no specific medical and or surgical strategy has yet been established. However, for remodeling of LV, Beta blockers, ACE I and or ARB may be helpful^[107]. Therapeutic uses of Sacubitril/valsartan combination are not established in Paediatric NCCM. Complications like arrhythmias to be delt with clinical protocols. Uses of ICD therapy needs more evaluation. Despite all medical treatment, if cardiac function deteriorates, heart transplant is warranted. Treatment with mechanical circulatory support for paediatric NCCM management needs more research.

Advances in treatment:

NCCM Patients can present with many symptoms or no symptoms. But can lead to heart failure^[23,29]. However, prevention and treatment of heart failure in children still require improvements. The etiology of heart failure in children is different from that in adults. In former usually caused by congenital heart disease, other is usually ischemic. Therefore, the therapeutic management of heart failure in children also differs from that in adults in some respects.

Two clinical principles of treatment are widely accepted: elimination of the cause and control of symptoms and disease progression^[108,109]. The

primary goal of managing children with heart failure is to closely monitor their general condition and rationally arrange nutritional support. For NCCM, close monitoring of changes in oxygen partial pressure and provide ventilation support if necessary. Additionally, administration of digoxin enhances myocardial contractility in NCCM and left heart systolic dysfunction. Other drugs include β -blockers and those of the ACEI class^[109,110,111]. The selective inhibitor of sinus node is Ivabradine, which can specifically reduce the heart rate, but has no obvious effect on cardiac conduction time, myocardial contractility, and ventricular repolarization^[112]. Clinical studies show that the prognosis of heart failure is significantly related to heart rate, and ivabradine can reduce the hospitalization rate and mortality rate of HF^[113,114,115]. Ivabradine is recommended as promising drugs for HF (chronic heart failure (CHF) in children which is well mentioned in Pediatric heart failure guidelines^[116]. At present, only tablets are approved for adult CHF in China, and the Food and Drug Administration (FDA) has supplemented and approved oral liquid and tablets for children with stable HF caused by DCM for 6 months and above, which provides evidence-based evidence for clinical use in pediatrics. Specific usage and dosage are as follows:

(a) for children over 6 months old and weighing less than <40 kg, the initial dosage is 0.05 mg/kg, twice a day, taken with meals, and the dosage is adjusted every two weeks according to the tolerance to reduce the heart rate by at least 20%; the maximum dose is 0.2 mg/(kg/times) (children aged 6 months to <1 year) or 0.3 mg/(kg/times) (children aged \geq 1 year), and the total dose does not exceed 7.5 mg/time, (b) Children with body weight \geq 40 kg: the initial dose is 2.5 mg, twice a day, and the dose is adjusted every two weeks according to the tolerance to reduce the heart rate by at least 20%, and the maximum dose is 7.5 mg/time^[117].

Safety and efficacy of ivabradine showed in Phase II/III clinical studies that it can reduce the resting heart rate of children, and the left ventricular ejection fraction, clinical cardiac function classification and quality of life have a good improvement trend^[118]. And also, as it is dose-dependent, ivabradine activity depends on the opening and closing of If current channel, which can reach saturation state and prevent infinite decrease of heart rate^[119,120]. It's a new drug treatment idea for children with heart failure who still have symptoms, reduced left ventricular ejection fraction (LVEF), sinus rhythm and resting heart rate of not less than 70 beats/min after using traditional anti-heart failure drugs simultaneously, and can be used as an alternative. At the same time, considering its characteristics of direct action on sinus node and few adverse reactions, it has a good application prospect for the treatment of heart failure in children with sinus tachycardia. Carvedilol can improve the echocardiographic parameters and serum brain natriuretic peptide (BNP) level in children. Studies show that it has only a tendency to improve the prognosis of clinical heart failure^[121-123]. Therefore, there is lack of data to recommend or prevent it for children with congestive HF. Besides, the efficacy of diuretics in pediatric HF population is limited at present, it plays an important role in the acute management of symptomatic HF patients. Data and empirical evidence are enough to prove that routine use of diuretics in the emergency of HF children is

reasonable. Diuretics can reduce the fluid accumulation in children and reduce the burden on the heart^[124]. But it is unknown whether they can improve the condition of patients with LVNC. So, after clinical trials and evaluation, these drugs may be promising^[125,126].

Besides pharmacological therapy there is still a large proportion of children with poor prognosis owing to disease progression or other factors cardiac assist device implantation or even heart transplantation should be considered^[109,127]. The implantation of a left ventricular assist device (LVAD) is a good option when medications fail to improve LV systolic and diastolic function in patients with LVNC^[128]. In an Italian study^[129], researchers concluded that cardiac resynchronization therapy (CRT) was effective in improving LV function in patients with LVNC than in those with DCM alone. The efficacy becomes more evident with a larger area of myocardial densification. Heart transplantation as the ultimate treatment must be beneficial for patients with NCCM or even other cardiomyopathies^[129,130]. First reported case of a 20-yearold LVNC patient who underwent heart transplantation was in Mexico^[131], and the outcome was successful within 15 months with no acute rejection on intramyocardial biopsy. Its long-term prognosis needs further follow-up investigation^[132-135].

Patients with NCCM complicated with Arrhythmias in usually symptomatically manifest as weakness and palpitations^[27,28] which require attention and effective treatment^[34,136]. In a limited pediatric cohort study, of β -blockers was found to be effective in reducing left ventricular ejection fraction and volumes significantly in patients with LVNC^[110,137], with carvedilol having effectively improved left ventricular function; however, the long-term efficacy is not clear^[138,139]. in both adults and pediatrics Sotalol has been proved to be effective in the treatment of ventricular arrhythmia and atrial fibrillation^[138,139]. It is warranted that antiarrhythmic drugs should be used with caution because of their side effects and unknown risks^[110,140,141]. Additionally, the implantable cardiac

defibrillators can effectively prevent ventricular tachycardia and sudden death^[142-144]. Preconditions for Implantation is especially when at least one of the following conditions is met: left ventricular ejection fraction $\leq 35\%$ ^[145], sustained ventricular tachycardia or previous cardiac arrest^[146], presence of comorbidities or family history of genetic disorders^[147]. Risk assessment by analyzing the ECG characteristics of patients with cardiomyopathy has also been performed to determine the risk of ventricular tachycardia^[148] for early detection and prevention, and to provide some guidance for the use of implantable cardiac defibrillators. Catheter radiofrequency ablation is a direct and effective approach for the treatment of arrhythmias^[132,149]. It has the advantages as the procedure is easy to perform, does not cause damage to the heart, and is minimally invasive, while the patient bears minimal pain and recovers quickly. However, some recent investigations have found arrhythmogenic lesions in the epicardial tissue, requiring the endocardium and epicardium to be operated^[33,112,150]. In addition, catheter radiofrequency ablation is contraindicated in patients with wall thrombus in the ventricular cavity, which may lead to dangerous thrombus dislodgement.

Thromboembolism is one of the grave complications of NCCM owing to the presence of myocardial trabecular gap and is a high risk of thrombus formation during blood flushing^(112,151). Patients with LVNC has the risk of thrombosis is about 21%–38%^[126,152]. And can be a fatal threat as it may cause complications such as stroke, pulmonary embolism, and mesenteric ischemia. It is recommended that anticoagulation and thrombolytic therapy are clinically applied for patients with LVNC who have thrombosis. But prophylactic anticoagulation is still controversial. A cohort study including 17 patients taken placed for 30 months with LVNC, Ritter et al. found that the incidence of thromboembolism was approximately 24%; therefore, the researchers concluded that thromboembolism occurs independent of left ventricular function and size, and that LVNC itself is a high-risk factor for it. Ultimately, the

researchers supported anticoagulation for all patients with LVNC^[153]. Anticoagulation is not necessary in asymptomatic patients or those with normal cardiac function. Instead, in more severe cases, other studies found prophylactic anticoagulation in patients with heart failure to increase the risk of bleeding^[154,155]. Nonetheless, when LVNC patients have reduced cardiac systolic function, an ejection fraction below 40%, or thromboembolism or previous atrial fibrillation, anticoagulation is mandatory^[156-158]. Unfortunately, in all anticoagulant therapy strategies, even within the normal treatment range, bleeding is inevitable, which is also a major complication of anticoagulant therapy^[159,160]. When bleeding occurs during anticoagulation, the location, cause and severity of bleeding should be evaluated as quickly and accurately as possible, and specific treatment should be given, including mechanical pressing and lowering the dose of anticoagulant^[161]. When massive bleeding occurs (the standard is that the bleeding is serious enough to require major medical intervention, such as blood transfusion or surgery, and the prognosis is extremely poor^[159,162].

As long as the patient has bleeding or bleeding risk during anticoagulation, it is necessary to closely detect the patient's life state, maintain the patient's body temperature and closely detect the patient's blood gas ion stability. However, if careful anticoagulation is carried out according to the known bleeding risk factors, the risk of bleeding will be greatly reduced^[163]. Therefore, excision of prominent trabeculae may be effective in improving symptoms of LVNC patients^[164-166], which also provides a novel direction for the treatment of LVNC; however, its long-term prognosis still needs further follow-up.

Prospective treatment Gene mutations, such as those involving sarcomere and ion channel genes/proteins, can lead to LVNC^[167]. It has been demonstrated^[168] that LVNC can be induced in the mouse heart using excess All-Trans Retinoic Acid. The successful establishment of this animal model provides a completely new platform for exploring

potential LVNC therapeutic approaches in the future. The implementation of gene editing technologies, including zinc finger nucleases (ZFNs), transcription activator-like effector nucleases (TALENs), and clustered regularly interspaced short palindromic repeats (CRISPR) systems^[169], has made the generation of LVNC cardiomyocytes a reality. Gene editing techniques have been widely utilized in cardiomyopathy research and there have been attempts to explore the role of various genes in the pathogenesis of LVNC^[170,171]. There have been successful experiments using TALENs technology to introduce MYH7 mutated genes into a pig model to obtain a HCM model^[172]. Further, the ability to obtain LVNC animal models provides greater opportunities for treatment experimentations, including the possibility of preventing or eliminating LVNC by means of gene knockout or mutant gene repair, which should be gradually considered^[173]. However, the effectiveness of genetic strategies to treat LVNC and ethical considerations warrant further discussion and reviewing patients with NCCM can be dealt with prevention and restrictions on daily activities in addition to the distinct symptomatic treatment described above. Symptomatic NCCM has much higher mortality and worse prognosis compared to asymptomatic group^[145,174], especially in patients with concomitant heart failure. Although NCCM symptoms' manifestation controlling is impossible, its diagnosis before symptom development can effectively improve quality of life. In Japan a retrospective cohort study conducted^[175] from 2000 to 2017 with 105 pediatric LVNC patients. 44 patients (41.9%) were identified during school screening, and most of these students exhibited abnormal QRS wave segments on the electrocardiogram (ECG). With the detection of ECG abnormalities, school screening may be an important factor in the detection of patients with LVNC in the future. Genetic screening of family's patients with LVNC, may also elucidate whether LVNC is hereditary and determine what changes in their family's related gene is responsible and what effects this change might bring to their relatives,

which could be important for future LVNC eradication and prevention^[34,176]. Statistics showed a good proportion of LVNC patients present with family history. Patients with NCCM can potentially engage in moderate physical activity^[132,177]; which in turn can help prevent cardiovascular disease, as stated in the 2020 ESC Guidelines on sports cardiology and exercise in patients with cardiovascular disease^[178]; the section for patients with LVNC states that only individuals with LVEF >50% and without arrhythmias should engage in high-intensity physical activity as well as competitive sports, and only individuals with LVEF >40% should engage in appropriate physical activity. But the expected outcome requires further research.

Long-term outcome:

Long term prognosis of NCCM is uncertain reflecting from data of different countries. A long-term study from the National Australian childhood cardiomyopathy study showed worse prognosis of NCCM than other series. They found only 45% of subjects alive and transplantation free 15 years after presentation, whereas study from Toronto and Texas^[179,180] revealed 10-year transplantation free survival of 60-86% and study from Japan^[181] showed 93%. Higher mortality in Australian study as study subjects were sick and young at presentation and many of them died within 1 year of presentation. Conversely Study from Japan reflect high proportion of asymptomatic patient as a result of a systematic childhood screening program. A study from China showed patient with no isolated NCCM is more affected by concomitant diseases than isolated NCCM. While analysis of isolated NCCM they found death of 68.1%. their low mortality is due to the fact that they classified LVNC and DCM into non- isolated LVNC, where prognosis is similar to pure DCM^[182].

Future Perspective:

NCCM is a rare entity with lack of gold standard of diagnostic criteria. And no definitive treatment is available for NCCM. So, our focus should be to improve the quality of life through aggressive

symptomatic and preventive treatment. Genetic association with cardiomyopathy^[183-190] was identified in many studies. This information can be employed in genome editing technology^[191]; progressively development of gene therapy with increasing number of tests with the hope for future eradication of NCCM. Researchers are constantly working on refining genomic and proteomic analysis through animal models. This will guide future treatment strategy though the safety and effectiveness of genome editing technology cannot be guaranteed^[192-194].

Challenges are huge but hope is putting light on the way. Although the experimental data are promising, guaranteeing its effectiveness for implication is not possible. The possibility of other mutations or symptoms following gene editing must be considered. So, it will be necessary to ensure its rationality and effectiveness and also ethical proceeding involving multidisciplinary team of professionals to proceed with gene editing treatment strategy.

Conclusion:

NCCM is a rare but heterogenous presentation of cardiomyopathy with potential lists of complications. There is a lack of universal diagnostic criteria and

thus specific treatment. studies conducted showed uncertainty of prognosis. Genetic association detected and noninvasive modalities of diagnosis like ECG, Echocardiography are tools to early detection of disease. So, in conclusion, to deal with disease like NCCM, joint international effort to establish a universally accepted diagnostic criteria and systematic Childhood cardiomyopathy registry along with development of treatment strategy is time demanding. It is recommended that genetic tests of the patient and the immediate family will leave a benchmark in the field of research of NCCM.

Conflict of Interest:

Author declares no conflict of interest.

Funding:

None.

Acknowledgements:

None.

Contribution:

Review theme and write up—Dr Tahmina Karim
Discussion regarding steps of writing –Dr Tahmina Karim, Prof Md. Tariqul Islam
Supporting article collection –Nuzhat Tabassum Kanti

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