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Dilated Cardiomyopathy in Children: A Review

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Abstract **Review Article**

Dilated cardiomyopathy (DCM) is a heart muscle disorder characterizes by left ventricular (LV) dilatation and systolic dysfunction. It is a frequent cause of heart failure and the primary indication for heart transplantation. DCM is the most prevalent phenotype and is non-specific, which is caused by genetic factors, environmental factors or a combination of both. Research on dilated cardiomyopathy has however focused on the adult populations with fewer dedicated clinical trials investigating pediatric dilated cardiomyopathy. A typical diagnostic work up for a child with DCM also include a number of investigations to identify the specific cause, some of these are expensive and sophisticated. The advance center of the developing country does not have the facilities to do all of these investigations. The results of most of the tests have little impact in the treatment strategies for the child with DCM. The lack of specific clinical management guidelines has influenced the use of general management concepts of LV dysfunction and heart failure, which vary between studies. This paper therefore reviews current evidence on DCM in children to provide a better understanding of its clinical manifestations, etiology, diagnosis and clinical management.

Keywords: Dilated Cardiomyopathy, HEART muscle disorder, Left ventricular.

INTRODUCTION

Dilated cardiomyopathy (DCM) is defined as left ventricular (LV) dilation and systolic dysfunction in the absence of coronary artery disease or abnormal loading conditions proportionate to the degree of LV impairment [1]. Dilated cardiomyopathy is the third most common cause of heart failure and is the commonest type of cardiomyopathy [2]. DCM can develop in people of any age or ethnicity, although it is more common in male than female persons (occurring at a ratio of 3:1 in male to female persons) and typically manifests in the third to fourth decades of life[3, 4]. DCM is the predominant cause of cardiomyopathy in both adult and pediatric populations [2, 4]. In adults, DCM has an estimated prevalence of 1:2500[4]. In contrast, annual incidence in pediatric populations has been reported to be much lower: 1:170 000 in the United States [5] and 1:140 000 in Australia [6]. Although pediatric DCM has a lower annual incidence than adult DCM, the outcome for pediatric DCM patients is particularly severe [7]. DCM is the most frequent cause of heart transplantation (HTx) in pediatric patients [8]. Data from international pediatric DCM registries indicate that the rates of death or HTx over 1 and 5 year periods were 31% and 46%, respectively [2] Conversely, recent data showed that the HTx free survival rate in adult DCM patients receiving optimal treatment is >85% at 8 years [3]. The known causes of DCM include infections, metabolic derangements, hereditary disorders, nutritional deficiencies and exposure to certain drugs and toxins. In spite of the number of etiologies listed the vast majority of patients with DCM are classified as idiopathic because the cause is often not readily identifiable. Recent studies, however, seem to suggest that viral myocarditis may be the initial insult in many patients [9]. It is difficult and sometimes impossible to distinguish myocarditis from cardiomyopathy, particularly in infants and young children and these terms are sometimes interchanged for each other or clubbed together as DCM-myocarditis. The primary purpose of diagnosis of DCM is to identify the etiology of ventricular dysfunction so that an etiology specific treatment can be planned. Current therapy for DCM is mainly based on neurohumoral blockade as for other forms of HF (heart failure) with reduced ejection fraction.[11] In spite of optimal medical therapy, the premature morbidity and mortality rate remains unacceptably high, driving the need for novel and more individualized therapeutic options[12].

Etiologies

The etiology of DCM is extremely heterogeneous. Half (50%) of the cases are idiopathic, caused mainly by inflammatory and immunological processes, while the other half results from a broad spectrum of underlying conditions, which includes peripartum disease, ischemic heart disease, myocarditis and hypertension[13]. Previously, DCM etiology was classified according to the causative agent: genetic/familial, cytotoxic agents, malnutrition, myocarditis/viral and autoimmune disorders. The However, genetic abnormalities identified with familial DCM remains the most dominant etiology accounting for 20-48% of all DCM cases [14]. Most recently, ESC working group on myocardial and pericardial disease categorizes causes of DCM into genetic/familial, drugs/toxins, infection and peripartum[15].

Genetic cause

Genetic etiologies consist of a variety of gene mutations in cytoskeleton, nucleoskeleton or mitochondrial proteins [16]. Between 35% and 40% of genetic DCM cases are thought to be caused by sarcomere gene mutations, with mutations in the giant protein titin estimated to be responsible for about 25% cases [17]. Gene mutations can also affect multiple Z-band proteins, which connect the thin filaments and titin, thereby serving as an important nodal point of mechanosignaling [18]. Mutations in members of the LINC (linker of nucleoskeleton and cytoskeleton) complex, that links the nucleus to the cytoplasm, have been described in pediatric DCM, including the lamin A/C proteins, emerin, and nesprins-1 and -2.[19,20]. Both lamin A/C and emerin-null fibroblasts have altered expression of mechanosensitive genes in response to mechanical stress [20]. Although genotype–phenotype correlations are lacking for most cases of DCM, mutations in genes such as LMNA (and DES) are known to be highly associated with conduction system disease (sinoatrial node disease, atrial arrhythmias, atrioventricular heart block, and ventricular tachyarrhythmias). Thus, the presence of these genes is a risk factor for sudden death [21]. Mutations in dystrophin and the sarcoglycans produce skeletal muscle disease and cardiomyopathy; as such, heart failure in these patients may be further compromised by hypoventilation from respiratory muscle weakness [22].

Non –genetic cause

Drugs/Toxins

The main non-genetic etiologic agents of DCM are drugs (also referred to as toxins), infection and peripartum DCM. Toxins, especially chronic or excessive alcohol consumption, or repeated exposure chemotherapeutic agents can induce DCM [23]. Chronic exposure to some chemotherapeutic agents such as anthracylines can also affect LV function and induce DCM but upon withdrawal, either resolves by itself or persists in subclinical form [15].

Inflammatory

Autoimmune viral infections such as myocarditis cause inflammations to induce DMC in genetically predisposed individuals. In some familial or non-familial patients, infection-negative myocarditis in the absence or presence of DCM phenotype is organ specific autoimmune disorder frequently found in genetically predisposed patients. These patients are asymptomatic but present with organ specific anti-heart antibodies [24]. Anti-heart antibodies have been linked to mild LV abnormalities, which predict DCM progression. In DCM caused by viral infection, if acute inflammation of myocardium stops and the cause resolves, and the disorder is reversible [25].

Table-1: Causes and Agents of DCM [15]

Group	Cause	Etiologic Agents
Genetic/Familial	Main Genes	Titin, lamin A/C, myosin heavy chain, troponin, myosin-binding protein C, RNA-binding Motif-20, Myopalladin, Na+ channel alpha unit and phospholamban
	Neuromuscular Disorders	Duchenne muscular dystrophy, Becker muscular dystrophy, myotonic dystrophy
	Syndromic Disease	Mitochondrial disease, Tafazin
Drugs/ Toxins	Drugs	Antineoplastic/psychiatric drugs
	Toxic Overload	Ethanol, cocaine, amphetamines, ecstasy or iron overload
	Nutritional Deficiency	Selenium, thiamine, zinc/copper and carnitine
	Electrolyte Disturbance	Hypocalcemia, hypophosphatemia
	Endocrinology	Hyper/hypo-thyroidism, Addison disease, phaeocromocytoma, acromegaly, diabetes mellitus
Infection	Auto-immune diseases (myocarditis)	Causes frequent AV-block and ventricular arrhythmias
	Inflammatory DCM	Caused by non-infectious myocarditis
Peripartum	Peripartum cardiomyopathy	Related to during or after pregnancy

Diagnosis

Diagnosis is dependent on patients's history, clinical examination and imaging, i.e echocardiography or magnatic resonace imaging (MRI) features of DCM or heart failure or both. The World Health Organization (WHO) and International Society and Federation of Cardiologists (ISFC), and more recently the ESC working group on myocardial and pericardial diseases developed the criteria for DCM diagnosis as follows:

- Fractional shortening >25% and/or LVEF < 45%;
- LV end-diastolic diameter > 117% corrected for age and body surface area in the exclusion of any known cause of myocardial disease.
- Diagnosis for familial DCM – the presence of more than one relative with DCM fitting the clinical criteria defined above or a relative of patient with DCM-related unexplained sudden death > 30 years[15,26].

However, from a pathology standpoint, the current diagnostic criteria of DCM have important limitations. The criteria establish DCM as a non-specific phenotype resulting from genetic, acquired (environmental), both genetic and acquired or idiopathic etiologies [15].

Clinical manifestations

The clinical presentation of children with DCM ranges from asymptomatic to acute decompensated heart failure and cardiogenic shock [27].

Presenting symptoms can range from mild respiratory or gastrointestinal symptoms to profound cardiac shock [28, 29]. Other common symptoms include fatigue, nausea, vomiting, abdominal pain, chest pain, and diaphoresis. At least one gastrointestinal symptom was evident in over 80% of children in one study [29]. Severe symptoms of poor perfusion and cardiogenic shock are also not uncommon [28].

DCM first presents with signs and symptoms of heart failure (HF) due to high cavitary blood volume or low cardiac output. At diagnosis, the most frequent symptoms are severe impairment of LV ejection function and patients' classification into New York Heart Association (NYHA) functional class III to IV [30]. Patients with neuromuscular disorders, such as Duchenne muscular dystrophy, demonstrate features characteristic of their systemic myopathy [2, 28, 31]. About 20-35% experience angina like chest pains particularly during exercise indicated by ECG pseudoinfarction Q-waves, while 30% feel fatigued. Ventricular arrhythmias may cause palpitations. Although syncope and sudden cardiac death are common clinical outcomes in DCM patients, they do not always presents as the first symptom of DCM. Pulmonary and systemic thromboembolism is usually the first clinical manifestation of DCM [27]. The estimated mortality rate at the third year of the disease ranges between 12% and 20% [32]. There is no known cure for DCM with only cardiac transplantation showing short and long-term favorable prognosis and survival rates [30].

Diagnostic Testing

Laboratory tests provide additional diagnostic information about extra cardiac dysfunctions or disorders such as thyroid disease and diabetes mellitus that may contribute or exacerbate DCM. The test results help in the detection and assessment of secondary cardiac dysfunction, which are non-specific markers of DCM severity especially natriuretic peptides. The ESC recommends laboratory tests for all suspected cases of DCM including creatine phosphokinase (CK), renal function, proteinuria, red/white blood cells counts, serum iron, calcium phosphate and thyroid stimulating hormones. CK tests are diagnostically significant since raised CK is a diagnostic clue for X-linked dystrophin-related DCM. For mitochondrial-related DCM, laboratory test results indicating diagnostic suspicion are lactic acidosis, myoglobinuria and leukocytopenia.[18] Other important laboratory tests based on the suspected etiology include for serum antibodies, suspected infection (HIV, Chagas disease and influenza virus), thiamine for alcohol abuse or nutritional deficiency, and serum angiotensin converting enzyme to test for sarcoidosis[33].

Imaging studies that are indicated for the diagnosis and initial management of patients with DCM include chest radiography, ECG, and echocardiogram. Cardiac magnetic resonance (CMR) imaging is becoming more frequently utilized and may have additional diagnostic and prognostic value [34].

Chest x-rays generally demonstrate cardiomegaly with varying degrees of pulmonary edema. The left mainstem bronchus may be compressed by an enlarged left atrium, resulting in left lower lobe atelectasis [34].

ECGs are usually abnormal in patients with DCM, especially among patients with severe disease. Characteristic ECG abnormalities include LV hypertrophy and ST-segment and T-wave changes [35, 36]. These ECG findings are not specific for DCM; however, certain abnormalities such as conduction disease in DCM are associated with LMNA gene mutations [37]. Patient with myocarditis may present with ECG abnormalities such as tachyarrhythmias, conduction disease, low voltages, ST-segment changes, T-wave abnormalities, and pathologic Q waves [38].

At most institutions, echocardiography is still the imaging modality of choice to establish the diagnosis of DCM, with commonly accepted diagnostic criteria in pediatric patients being a LV end-diastolic dimension >2 standard deviations above normal for

body surface area, in conjunction with depressed systolic function (e.g., shortening fraction/ ejection fraction[39,40].

The ability of cardiac MRI to assess cardiac morphology and functions enables the detection of specific forms of myocardial disease including differential diagnosis of ischemic and non-ischemic cardiomyopathies using late gadolinium-enhanced MRI. It is also able to characterize the presence and location of myocardial abnormalities based on their intrinsic magnetic properties and distribution of MRI contrast agent (gadolinium). The major diagnostic features examined by Cardiac MRI are LV enlargement/LV end-systolic volume, myocardial fat, iron storage, amyloid infiltration and myocardial fibrosis [16]. Various MRI sequences are used in DCM diagnosis. The common sequences include T1- and T2-weighted, T1-inversion recovery, contrast enhanced (late gadolinium), and spectroscopy [41].

Endomyocardial biopsy

Endomyocardial biopsy (EMB) has been used to confirm diagnosis in some forms of DCM although with improved cardiac imaging, EMB is less frequently used. In some settings, for example, iron overload, amyloid, and other infiltrative processes, myocardial biopsy may still be highly useful [42]. The complication rates with EMB range from 1% to 3%, and serious complications including perforation and tamponade occur at 0.5%[42]. EMB has been used to evaluate myocarditis and in the setting of unexplained HF [43].

Family screening

DCM is considered to have a genetic origin after the exclusion of secondary causes of ventricular dysfunction such as hypertension, myocarditis, valvular disease or exposure to toxins or environmental pathogens. Patient/family history provides valuable information for determining genetic origin of DCM.[33] Diagnostic clues suggested for various genetic transmission patterns [33].

In addition to family history, pedigree analysis helps to identify other affected family members and refine diagnosis especially in families with more than one cardiomyopathy phenotypes. However, pedigree analysis does not identify de novo genetic mutation or myocardial disease unrecognized in the family tree [33].

At present, routine genetic testing is only recommended in familial disease ($2 affected family members)[44] where its diagnostic yield is 30% to 35%. Currently, the identification of a causal mutation carries few implications for prognosis or treatment of the index case, and the principal rationale for testing is to allow mutation-specific cascade screening of family members. An exception is LMNA mutations, which are associated with high rates of conduction system disease, ventricular arrhythmias, and sudden cardiac death (SCD) and may consequently lower the threshold for prophylactic implantable cardioverter-defibrillator (ICD) implantation [45].

Table-2: Genetic Transmission Patterns for DCM and Diagnostic Clues [33].

Transmission Patterns	Dia diagnostic Cues
Autosomal Dominant	Male-to-male transmission Affected family members are in every generation Offspring have 50% risk of inheritance of mutated genes If father is affected, autosomal recessive/mitochondrial channels are excluded. If mother is affected, autosomal dominant inheritance is likely after exclusion of mitochondrial disease.
Autosomal Recessive	Suspected when both parents are carriers (not affected). Affects both male and females equally. Offspring have a 25% risk of inheritance
X-linked	Suspected when only/mostly males are affected. Daughters of affected fathers are carriers. No male-to-male transmission. More likely, if one/both parents have symptoms of skeletal muscles disorders.
Matrilineal	Mother transmits gene mutation to offspring Gene mutation usually in mitochondrial DNA. Affects both son/daughter. Suspected with abnormalities in different organs such as lactacidaemia, hypoacusia, encephalopathy

Diffential diagnosis

Differential diagnosis is about distinguishing the cause of disease from others presenting with similar symptoms. It is clinically important in DCM to exclude other etiologies of cardiomyopathy with phenotypic overlap [13]. It is also important to distinguish DCM from secondary causes of ventricular dilation and dysfunction caused by known cardiac or systemic

processes such as ischemia, hypertension, valvular heart disease and myocarditis. Other secondary variants but less common include amyloidosis, sarcoidosis, and toxins such as doxorubicin [26]. In pediatric population, differential diagnosis is important to exclude metabolic cardiomyopathies, which occur at a higher frequency [3].

Management

According to the 2016 AHA recommendations clinical management of DCM lacks specific etiology based therapy [46]. Instead treatment draws upon the general management concepts of LV dysfunction and heart failure therapy. Current therapy includes general measures, conventional pharmacotherapy, mechanical device, and genetic councelling[47].

General measures

General measures target to reduce the exposure to environmental factors that may aggravate DCM phenotype by burdening the susceptible myocardium. General measures frequently prescribed to DCM patients include patient education, restriction on fluids and salt, treating hypertension, stop or limit alcohol consumption, management of body weight, and moderate aerobic exercise [47].

Pharmacotherapy

Pharmacotherapy is not specific to etiopathogenesis but shows favourable prognosis and a reduction in mortality. Specific treatments are not available for most patients with IDC [30].

The objective of drug therapy in DCM is to give supportive relief and maximize cardiac function. There is not as yet a treatment that offers a cure.

Angiotensin converting enzyme inhibitors

Angiotensin converting enzyme (ACE) inhibitors are the mainstays of treatment in patients with IDC, irrespective of the severity of heart failure [48]. Several randomized controlled trials (RCTs) including CONSENSUS, SOLVD and SAVE have demonstrated the prognostic value of Angiotensin Converting Enzyme Inhibitors (ACEI) in reducing the progression, hospitalization and mortality of heart failure. Enalapril maleate was used in these series; there is limited information available on its use in children where captopril is most commonly prescribed. ACE inhibitors are generally well tolerated; their principle side effects include first dose hypotension, non-productive cough, and a risk of hyperkalaemia, especially in patients already on potassium supplements or potassium sparing diuretics [49].

Angiotensin receptor blocker: Angiotensin receptor blockers (ARBs) are the alternative to ACEi that have been primarily used in adults who are intolerant of ace inhibitors. Several studies of ARBs in adult patients with heart failure demonstrated an improvement in survival that is at least as good as ACE inhibitors [50].

Diuretic therapy

Diuretic are important medications for the treatment of congestion in DCM patients. Although these are the most commonly used agents in long term management of heart failure patients, studies demonstrating long term benefits are lacking and higher doses have been associated with increase in the activation of the rennin-angiotensin-aldostrerone system and mortality in adult patients [51, 52].

Digoxin therapy

Digoxin, one of the oldest medications used for treating heart failure symptoms, is still commonly utilized. Digoxin inhibits cardiac Na- K channels in the cardiac myocytes leading to increase contractility [53]. While digoxin is effective in alleviating symptoms of heart failure [54] it has not been shown to improve mortality [55].

Beta –adrenergic blocker

Treatment with B-blockers needs also to be considered. The increased sympathetic drive that occurs as a compensatory mechanism in chronic heart failure appears to have an inverse relationship with prognosis [56]. B-blockers down regulate this sympathetic overdrive [57] and the evidence that they improve outcome in adult patients with chronic heart failure is increasing [58]. RCTs have reported Metoprolol and Bisoprolol reduced in all-cause mortality by 34% and Carvedilol, which has alpha-blocking properties, by 35% for severe heart failure. Beta-blockers begin with lower doses and titrated gradually to the target dose 25 mg or 50 mg twice a day depending on patient weight [48]. However, long-term effect of beta-blocker does not reduce the mortality due to sudden cardiac death [2].

Anticoagulants and antiarrhythmic agents

Anticoagulants and antiarrhythmic agents, particularly amiodarone, are often used in patients with low myocardial contractility and symptomatic arrhythmias, respectively. Results are encouraging. Presence of intracardiac thrombi, symptomatic or not, is another indication for anticoagulant therapy [59].

Disease specific therapies in DCM

If an inborn error of metabolism is diagnosed, treatment strategies can be directed toward the underlying metabolic abnormality and may include dietary management and supplementation to decrease the accumulation of toxic metabolic by-products. Specific management is also directed toward avoiding metabolic or energetic crises [36]. Supplementation with carnitine in primary carnitine deficiency cures DCM, emphasizing the critical need to diagnose this disease promptly [60]. Duchenne muscular dystrophy is one of the rare genetic DCM diseases with a substantial

focus on gene-directed therapies, including viral vector delivery of minigenes, exonskipping approaches, and nonsense suppression therapy [61]. CRISPR/Cas9 technology has been used to remove the mutation in the dystrophin gene and thereby modulates protein expression in mouse models [62]. These approaches may have broader application to other genetic causes of DCM.

Novel potential pharmacological treatments

There are several new medications that hold promise in patients with DCM. Ivabradine, a specific inhibitor of the If current of the sinoatrial node was associated with a decrease in the composite endpoint of cardiovascular death or admission for heart failure in the Systolic Heart Failure Treatment with the If inhibitor ivabradine Trial (SHIFT)[63]. There are limited pediatric data on the medication [64]. A phase II/III study in pediatric DCM patients was recently completed, but the results have not yet been published. Therapies targeting neprilysin are another promising new area of investigation. Neprilysin catalyzes the degradation of multiple substances important in heart failure including natriuretic peptides, angiotensin II, and bradykinin; higher levels of neprilysin are associated with increased cardiovascular morbidity and mortality [65]. Neprilysin inhibition not only increases natriuretic peptides levels but also increases the levels of angiotensin II and bradykinin [66]. As such, it has been combined with an ARB. This combination of an ARB–neprilysin inhibitor was recently found in adult heart failure patients to be associated with decreased overall mortality, decreased cardiovascular mortality, and decreased heart failure hospitalizations when compared to ACE inhibition [67]. For acute heart failure, treatment with serelaxin (recombinant human relaxin-2) was associated with improved dyspnea and 6-month mortality in a prospective randomized trial [68].

Devices

Implantable cardioverter Defibrillator

Implantable mechanical support devices, modified for use in infants and children, have been introduced to support the failing heart until a suitable donor is available for transplantation (bridge to transplant). The Berlin Heart EXOR pediatric has also been successfully used in several centers [68].

Cardiac Resynchronization therapy

Cardiac resynchronization therapy using a biventricular pacemaker has been shown to be effective in adults with DCM. In addition, these devices are available with defibrillator backup for patients at risk for ventricular arrhythmias. They are used in children with DCM with early favorable results [69].

One meta-analysis of ICD therapy in prevention of DCM-related deaths showed ICD therapy either alone or a dual therapy with CRT conveys a protective effect against cardiac death on DCM patients presenting with significantly depressed LV function (LVEF (25%) and symptoms of heart failure [70].

Surgery

Heart transplantation

End stage cardiac failure secondary to DCM has been the most common indication for heart transplantation in children and adolescents [71]. Survival statistics post transplantation is improving. In a series reported from Great Ormond Street, Adwani reported survival for 95% at 1 year and 87% at 3 years, in patients transplanted for dilated cardiomyopathy [72]. Currently the principle limiting factors in paediatric cardiac transplantation is a shortage of donor organs hence the importance of developing a mechanical support system suitable for use in the long term.

Partial Left Ventriculectomy

A second surgical option is the Batista operation where a partial left ventriculectomy is combined with mitral valve repair to restore left ventricular dimensions to normal thus improving pump function. Paediatric experience of this operation is limited but a 55% 2 year survival was reported in adult patients in the US, with most survivors showing symptomatic improvement [73].

Prognosis

The long term outcome of DCM vary depending on the underlying etiology, but overall remain poor.in the paediatric cardiomyopathy registry, the transplant free survival at 5 years was only 50%[2]. Early deaths are principally caused by severe heart failure. Some late deaths are sudden, presumably due to arrhythmia, in children who fail to recover to normal ventricular function. While it is accepted that the risk of mortality is high there is less agreement as to predictors of poor outcome. Failure of improvement or deterioration in shortening fraction, ventricular arrhythmias, detection of mural thrombus, presentation at age >2years, endocardial fibroelastosis and left ventricular end diastolic pressure > 20mmHg have all been put forward as adverse prognostic factor [75].

CONCLUSION

Dilated cardiomyopathy (DCM) is progressive and irreversible heterogenous myocardial disorders characterized by left or bi-ventricular dilatation, impaired ventricular systolic function, myocyte degeneration. Clinically, DCM progress from asymptomatic sub-clinical phase to symptomatic clinical phase. Diagnosis of DCM depends on the detection of structural and functional myocardial abnormalities but in developing country like Bangladesh has limited resources allow for a small number of tests to be performed in a patient. It is a serious disease in children with a guarded prognosis. While some children improve with time and medical therapy, mortality for this condition is unacceptably

high. Pharmacotherapy has shown favorable prognosis in short term basis and heart transplantation and ventricular assist device has shown favorable long term outcome. Ongoing research is needed to continue to advance the care of children with DCM.

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