

Review Article

Dilated Cardiomyopathy in Paediatric Population: A Review

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Abstract:

Key Words:

Dilated cardiomyopathy, Genetic, Echocardiography

Dilated cardiomyopathy (DCM) is a common cardiac diagnosis in children that may result as a consequence of diverse genetic and environmental insults. The differential diagnosis remains quite broad and as a result the approach to diagnosis and management may, at times, be quite difficult. A rigorous work-up can exclude alternative causes of left ventricular (LV) dilation and dysfunction, identify etiologies that may respond to specific treatments, and guide family screening. Assessment of myocardial detection of pre-clinical DCM could significantly reduce morbidity and mortality by allowing early instigation of cardio protective therapy. This review article discusses genetic and acquired causes of DCM, diagnostic modalities and therapeutic implications in the hope of informing physicians of a clinical entity that afflicts a substantial number of children worldwide.

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Definition:

Dilated cardiomyopathy (DCM) is a myocardial disorder characterized by a dilated left ventricle (LV) and systolic dysfunction that commonly results in congestive heart failure (CHF).^{1, 2} It is the most common form of cardiomyopathy and cause of cardiac transplantation in adults and children. In some cases, right ventricular dysfunction is also noted and may add to the severity of disease.³

Epidemiology:

Pediatric cardiomyopathy has an annual incidence of 1.1 to 1.5 per 100,000 in children <18 years old.⁴ Dilated cardiomyopathy (DCM) and hypertrophic cardiomyopathy (HCM) are the most common phenotypes with an annual incidence of 0.57 and 0.47 per 100, 000 children.^{1,4} Restrictive cardiomyopathy (RCM) has an incidence of 0.03 to 0.04 per 100,000 children and accounts for only 4.5% of pediatric cardiomyopathies with about 30% of patients having a mixed phenotype.⁵

Classification of Pediatric Cardiomyopathies:

In 1949, Evans⁶ reported on families with unexplained cardiomegaly, and in 1957, Brigden⁷

first used the term cardiomyopathy (non-coronary cardiomyopathies) to describe patients with idiopathic myocardial disease, several of whom had familial disease. Twenty three years later, a task force of the World Health Organization (WHO), chaired by John Goodwin (Figure 1), presented the first classification of the cardiomyopathies which was based on the predominant structural and hemodynamic phenotype that is dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy, and restrictive cardiomyopathy (Fig 2). The 1995 WHO classifications were based on a combination of morphological (dilated and



Fig-1: John F. Goodwin (1918–2001).

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hypertrophic), physiological (restrictive), and etiologic (causes extrinsic to the myocardium, such as infection, were excluded) characteristics.⁸

The American College of Cardiology/American Heart Association classification (Figure 3) and European Society of Cardiology Classification of Cardiomyopathies (Figure 4) are shown below.^{9,10}

DCM-dilated cardiomyopathy, HCM-hypertrophic cardiomyopathy, ARVC-Arrhythmogenic right ventricular cardiomyopathy, LVNC-Left ventricular non-compaction cardiomyopathy, LQTS-Long Q-T syndrome, SQTS-Short Q-T syndrome, CVPT-Catecholaminergic polymorphic ventricular tachycardia, SUNDS- Sudden unexpected nocturnal death syndrome.

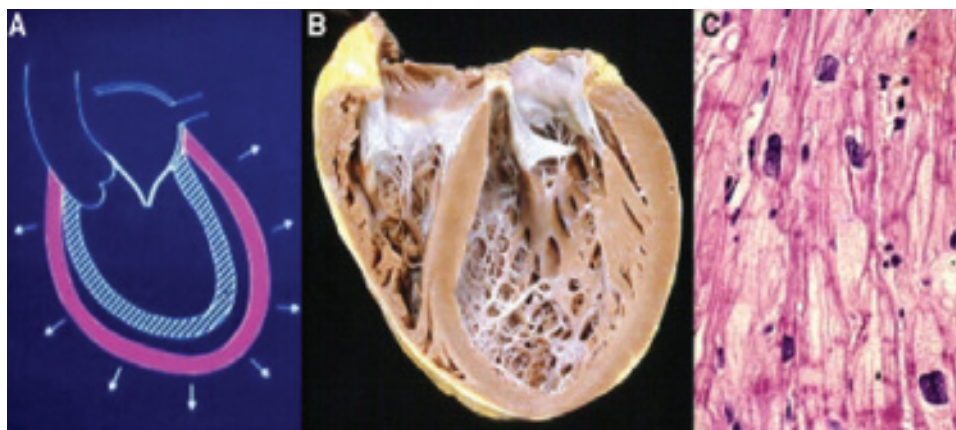


Fig.-2: Dilated cardiomyopathy. A. Schematic of dilated left ventricle, in the absence of valve disease. The blue area represents a normal left ventricle. The red area represents a dilated ventricle. B. Four-chamber view of a heart specimen with dilated ventricular cavities (first case of cardiac transplantation in Italy). C. Histology of the myocardium: myocytolysis with abnormal nuclei and no inflammatory infiltrates. Haematoxylin–Eosin stain.

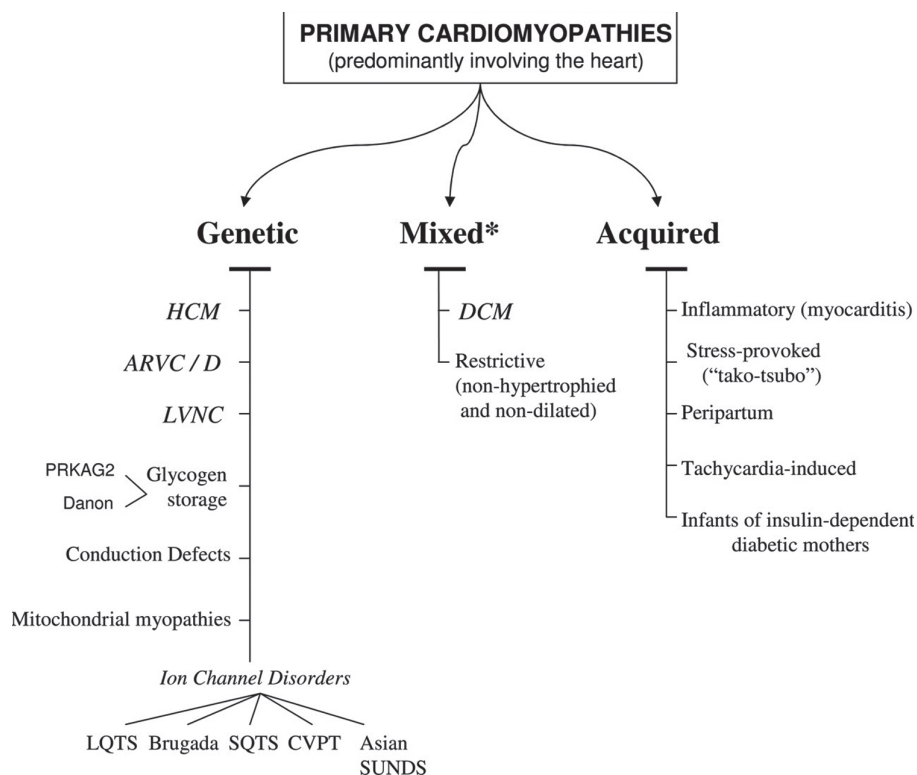


Fig.-3: American Heart Association Classification of Cardiomyopathies.

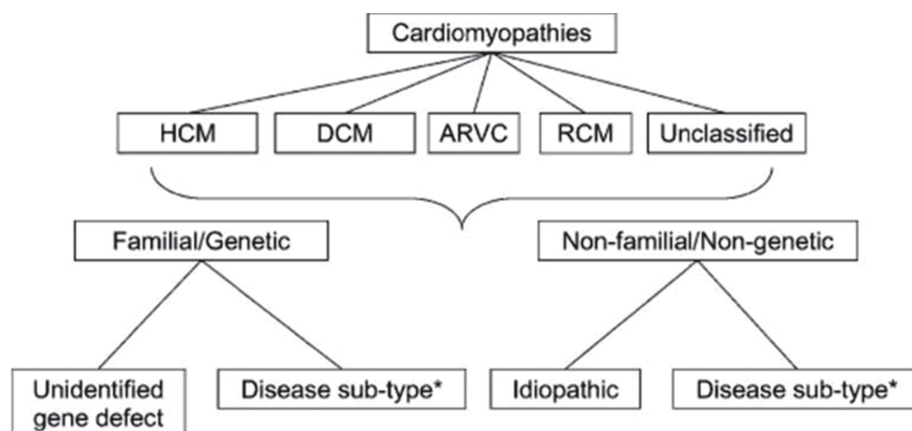


Fig.-4: *European Society of Cardiology Classification of Cardiomyopathies.*

Causes of DCM:

The most common causes of DCM are myocarditis and neuromuscular disease. Specific viral association with neuromuscular disorders (Duchene or Becker muscular dystrophy) was known in very few cases. Because the accuracy and availability of genetic testing has increased, the importance of genetic mutations in the development of pediatric cardiomyopathies has become apparent. The study of pediatric cardiomyopathies offers important insights into the pathogenesis of myocardial dysfunction in the absence of confounding comorbidities common in adults, such as atherosclerosis, hypertension, renal dysfunction, and diabetes mellitus. Pediatric cardiomyopathies can result from coronary artery abnormalities, tachyarrhythmia, exposure to infection or toxins, or secondary to other underlying disorders.¹⁰

DCM Genetics:

The majority of genetic DCM is inherited in an autosomal dominant pattern with variable expressivity and penetrance, although specific forms of autosomal recessive, X-linked recessive, and mitochondrial inheritance can occur.^{11,12} De novo mutations also contribute to genetic cardiomyopathy and are defined when neither of the biological parents carries the offspring's mutation which is exceedingly rare.^{13,14} Genetic mutations in the dystrophin gene have been demonstrated in Duchene muscular dystrophy and other X-linked forms of DCM, creating a link between the acquired and genetic forms of DCM.^{15,16}

Inflammatory Causes of DCM:

Evidence of viral myocarditis is common in children with DCM. From registry data, between 35% and 48% of children with DCM who undergo endomyocardial biopsy have evidence of myocarditis.^{17,18} Parvovirus B19, influenza, Epstein–Barr, HIV, coxsackie virus, herpes, and adenovirus have all been identified.^{19,20}

Toxic Causes of DCM:

Pediatric DCM can occur after exposure to toxins, such as anthracycline exposure during chemotherapy. The mechanism of anthracycline-induced injury is incompletely understood, but oxidative stress and reactive oxygen species activation may play a key role in cell damage.²¹ Radiation exposure and genetic polymorphisms have been associated with a higher frequency of anthracycline toxicity.²²

Neurohormonal Activation in DCM:

The role of neurohormonal activation in the pathophysiology of chronic heart failure in adults is well described. The neurohormonal derangements in pediatric DCM are described in small series and include elevations in circulating norepinephrine,²³ and activation of the renin-angiotensin system, decreased aldosterone, and sympathetic nervous system activation with carvedilol treatment. There is some evidence that the cardiac molecular response to stress in pediatric DCM is distinct from adult DCM.²⁴

Signs and symptoms of DCM:

Dilated cardiomyopathy can appear along a spectrum of no symptoms, subtle symptoms or, in

more severe cases, congestive heart failure (CHF), which occurs when the heart is unable to pump blood well enough to meet the body's needs for oxygen and nutrients. When only subtle symptoms exist, infants and young children are sometimes diagnosed with a viral upper respiratory tract infection or recurrent "pneumonia" without realizing that a heart problem is the basis for these symptoms. Older children and adolescents are less likely to be diagnosed with viral syndromes and more likely to present with decreased exercise capacity or easy fatigability.²⁵

With CHF, babies and young children will usually have more noticeable clinical changes such as irritability, failure to thrive, increased sweating especially with physical activities, pale color, faster breathing and/or wheezing. In older children, congestive heart failure can manifest as difficulty in breathing and/or coughing, pale color, decreased urine output and swelling of body, excessive sweating, and fatigue with minimal activities. Some patients with DCM caused by viral myocarditis can have a rapid increase in the number and severity of CHF symptoms such that within 24–48 hours the child can become very ill requiring emergency hospitalization, and occasionally, advanced life support. Symptoms due to heart rhythm problems (or arrhythmias, which means irregular, fast or slow

heart rates) can also be either the first symptom or a symptom that appears after other symptoms that led to a diagnosis of DCM.^{26,27}

Clinical Diagnosis of DCM:

DCM has been defined by the presence of (1) fractional shortening $<25\%$ (>2 SD) or ejection fraction $<45\%$ (>2 SD), and LV end-diastolic diameter $>117\%$ (>2 SD of the predicted value of 112% corrected for age and body surface area), excluding any known cause of myocardial disease.²⁷ In the context of a familial DCM, these criteria are used to diagnose the proband in a family.²⁸ Familial DCM is defined by the presence of (1) ≥ 2 affected relatives with DCM meeting the above criteria, or (2) a relative of a DCM patient with unexplained sudden death before the age of 35 years.²⁶ Interestingly, myocarditis and peripartum cardiomyopathy can occur in a familial setting and are believed to have a genetic component.²⁸

Diagnosis of DCM:

Chest X-ray

The chest X-ray typically shows cardiac enlargement and features of pulmonary venous congestion. Rib notching in an older child with suspected cardiomyopathy is more likely to be associated with Takayasu's arteritis rather than with coarctation.²⁹

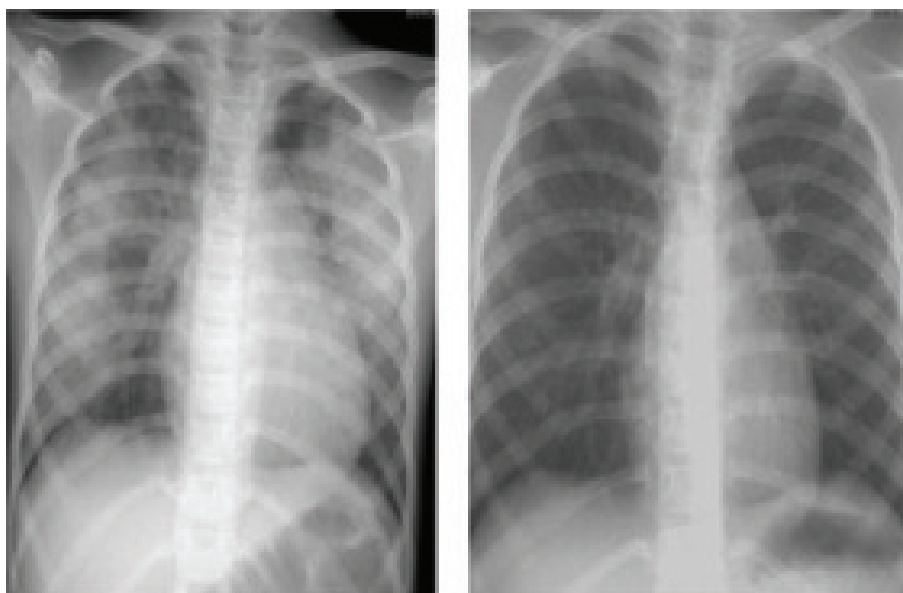


Fig 5: The chest X-ray on the left shows pulmonary edema with characteristic 'bat-wing' opacities in both lung fields. The X-ray on the right was obtained 4 hours later after diuresis. Note the absence of significant cardiac enlargement.

Electrocardiography

The electrocardiography (ECG) may yield several useful clues. The presence of an anomalous coronary artery from the pulmonary artery may be suspected if prominent Q waves are seen in V4–6 and aVL. Often this is associated with ST segment elevation and T wave inversion. A careful evaluation of rhythm and P wave morphology is a must in every patient with suspected cardiomyopathy. Any longstanding tachyarrhythmia can be associated with ventricular dysfunction (tachycardiomyopathy). Typical examples include ectopic atrial tachycardia (EAT) and permanent junctional reentrant. ²⁹

Imaging: Echocardiography

To diagnose DCM, LV measurements can be determined using multiple imaging modalities. M-mode and 2-dimensional echocardiography are frequently used to determine LV internal dimensions in systole and diastole (Fig 7). It was originally thought that LV dilatation occurs in response to reduced function. However, in genetic DCM, where genetic markers make it feasible to monitor LV dimensions for many years, increased LV dimensions typically precede detectable reduction in function. This state of LV enlargement is recognized as a prodrome to DCM. ³⁰

Imaging: Cardiac Magnetic Resonance

LV chamber dimensions and function, including strain measurements, are also accurately determined by cardiac magnetic resonance (CMR) imaging. Contrast agents, mainly gadolinium, are used to evaluate fibrosis and therefore provide additional information on myocardial tissue quality. In DCM, the degree of fibrosis, marked by delayed gadolinium enhancement, is a predictor of all cause mortality and need for future hospitalization. ³¹

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. The complication rates with EMB include perforation and tamponade at 0.5% cases. EMB has been used to evaluate myocarditis and in the setting of unexplained HF. ^{32,33}

Noninvasive Arrhythmia Monitoring

DCM is associated with an increased risk for cardiac arrhythmias and sudden cardiac death (SCD), and specific genetic DCM subtypes are especially prone to arrhythmias. ³⁴ Because of increased risk for

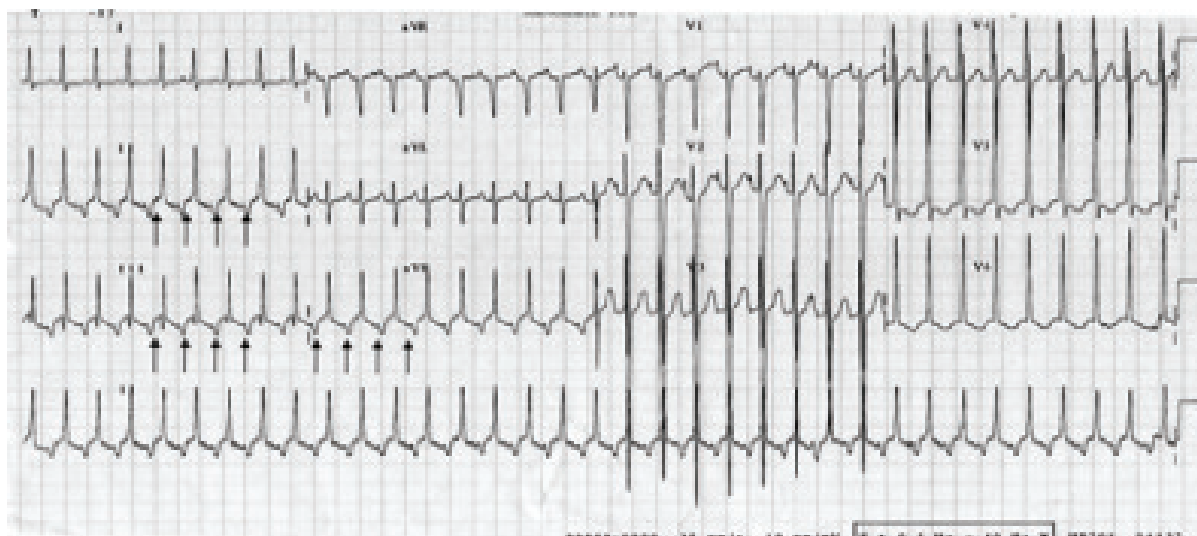


Fig.-6: This electrocardiogram is from a 2-year-old child with severe left ventricular dysfunction, who was suspected of having dilated cardiomyopathy. The clue to the presence of tachycardia-related cardiomyopathy is the presence of inverted P waves in leads II, III, and aVF (arrows). This is an example of permanent junctional re-entrant tachycardia. The ventricular dysfunction completely improved after successful radiofrequency ablation.

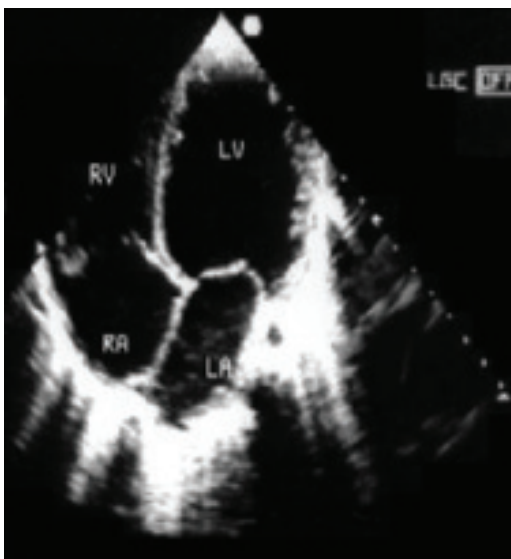


Fig.-7: *Echocardiogram obtained from apical 4-chamber view revealing a dilated left ventricle in a child with idiopathic dilated cardiomyopathy.*

SCD, there is need for arrhythmia surveillance to more appropriately deploy device management, including pacemakers and implantable cardioverter defibrillators (ICDs). Symptomatic and even life-threatening bradycardia and tachycardia may occur in genetic DCM. Personal history of syncope or near syncope should be ascertained, and patient education to increase awareness of symptoms is needed. Holter monitoring, for its ease, remains a mainstay using 24- to 48-hour sampling.³⁵

Metabolic and Genetic Work-up

The large number of possible metabolic conditions that could result in cardiomyopathy intimidates most pediatric cardiologists. These conditions are thought to be very rare, and the tests required to identify them with a high level of specificity are thought to be limited and expensive. But a lot of useful information can be obtained from basic biochemical tests that could serve as good screening tests. Blood tests for glucose, lactate, calcium, blood urea nitrogen, creatinine, and electrolytes are useful screening tests. A baseline blood gas analysis should be obtained to determine the acid–base status, and the urine should be tested for ketones. Serum ammonia levels could serve as a screening test for certain forms of metabolic myopathies. Serum carnitine levels and urinary carnitine excretion should be performed if facilities exist.^{3,12} Urine for

organic acids and amino acids is useful if Barth syndrome is suspected clinically.³⁶

Muscle and Cardiac Enzyme Assays

Creatine phosphokinase (CPK) levels are typically elevated in dystrophin defect-related DCM. The diagnosis of dystrophin defect-related DCM is important for patients and families, especially for carrier detection. Molecular analysis for dystrophin mutations and G 4.5 mutations is diagnostic, but the test is not universally available.^{37,38} In suspected cases of myocarditis, troponin I and CKMB estimation are useful.

Viral Studies

Viral culture from blood, urine, or stool has a very poor diagnostic yield. Similarly, serial antibody titers are also quite nonspecific.⁶ A positive viral culture from the myocardium is the diagnostic standard, but this too has very low sensitivity. Polymerase chain reaction (PCR) used in conjunction with standard endomyocardial biopsy appears to enhance the likelihood of detecting viral genome in the myocardium of patients with clinical evidence of myocarditis. Detection of the viral genome often does not alter the treatment plan. It is therefore difficult to justify doing this test routinely for children with DCM.³⁹

Screening Family Members

With the growing interest for this problem and the evolution of molecular genetic techniques, prospective, controlled studies have been performed by using a systematic screening of the families of DCM patients regardless of family history. With this approach, the occurrence of a genetic transmission can be detected in 20–30% of patients with DCM. Screening of family members either by clinical means or by echocardiography is not always performed. Careful screening of first-degree relatives of all children with DCM may identify genes that are specific for our population.^{40,41}

Treatment of Dilated Cardiomyopathy in children:

Treatment of DCM in children involves supportive management of the congestive heart failure and etiology-specific treatment. Once end-stage heart failure sets in, options are limited and cardiac transplantation can be considered if resources permit.²⁹

Management of extreme heart failure and cardiogenic shock

A proportion of patients with myocarditis present with cardiogenic shock and are often brought in an extremely sick state. Cardiogenic shock is an emergency. The clinician must initiate therapy before shock irreversibly damages vital organs. Major objectives in the management are rapid recognition of shock state and resuscitation, protection, support, and maintenance of vital organ function, etiology-specific management, identification, and correction of aggravating factors and monitoring of cardiovascular and hemodynamic response.⁴²

Supportive Treatment Digoxin and Diuretics

The use of digoxin in symptomatic childhood DCM has not been disputed. This is generally safe even in the presence of myocarditis. Frusemide (0.5–3 mg/Kg/day in 1–3 divided doses) is included as initial diuretic therapy in almost all symptomatic patients with DCM because of its efficacy in alleviating symptoms that result from systemic and pulmonary venous congestion.^{29,43}

Intravenous Inotropes and Vasodilators

Intravenous inotropic support is used to improve cardiac function and output during episodes of decompensation. The mainstays of therapy have been dobutamine and dopamine.^{29,43}

Angiotensin-converting Enzyme Inhibitors

The rationale for the use of angiotensin-converting enzyme (ACE) inhibitors in children with DCM is reduction of systemic vascular resistance (SVR), thereby improving LV performance. A reduction of SVR and increase in cardiac output after administration of captopril has been shown in children with DCM. However, unlike in adults, carefully conducted randomized controlled trials evaluating long-term survival are not available for children with ventricular dysfunction. Both captopril and enalapril are used. The latter has the advantage of requiring twice-daily dosing. The dose of captopril varies from 1–4 mg/Kg/day and the dose of enalapril varies from 0.5–2 mg/Kg/day. Impressive hemodynamic benefits have been demonstrated with doses as low as 0.5 mg/Kg of captopril.^{29,43}

Beta-blockers and Carvedilol

The use of β -blockers for DCM is counterintuitive because it could further reduce the already

diminished ventricular function. However, β -blockers have been shown to have several beneficial effects on the failing myocardium. They increase the β -receptor density of the myocardial cells and may protect against tachyarrhythmias. Selective β -blockers such as metoprolol have been used in children in small studies with documentation of their feasibility, safety, and efficacy.⁴⁴ Carvedilol is a new β -blocker with vasodilatory effects as well. Impressive symptom benefits have been demonstrated with carvedilol in the adult population. The dosing, efficacy, and side effects of carvedilol for the management of heart failure in children were recently evaluated in a multicenter study. The average initial dose was 0.08 mg/Kg, up titrated over a mean of 11.3 weeks to an average maintenance dose of 0.46 mg/Kg.⁴⁵

The authors concluded that carvedilol does not significantly improve clinical heart failure outcomes in children and adolescents with symptomatic systolic heart failure. Careful dose titration over several weeks is often done to avoid adverse effects. Typically, initiation of treatment requires hospitalization. Side effects, mainly dizziness, hypotension, and headache, occurred in 54% of patients but were well tolerated. The authors concluded that carvedilol as an adjunct to standard therapy for pediatric heart failure improves symptoms and LV function. Careful dose titration over several weeks is often done to avoid adverse effects. Typically, initiation of treatment requires hospitalization.⁴⁶

Anticoagulation and Aspirin

The rationale for administration of anticoagulation is to prevent the development of new LV clots or progression of existing LV clots. Children with DCM are prone to develop clots in their ventricles because of stasis of blood in a dilated ventricle. These clots can embolize and result in strokes. Oral anticoagulants are effective, but requirements for frequent blood sampling for prothrombin time/international normalized ratio (INR) estimation and limitations in the availability of reliable facilities for accurate determination of INR have prevented their universal use. Practices vary from use of aspirin in all, oral anticoagulants like warfarin for only those with demonstrable LV clot, and oral anticoagulants for LV ejection fractions below arbitrary cutoffs. Warfarin interferes with hepatic

synthesis of vitamin K-dependent coagulation factors. It prevents thrombus formation within cardiac chambers and the venous circulation. A common practice is to administer modest doses of anticoagulation to keep INR levels in the 1.5–2 range.²⁹

‘Etiology-specific’ Treatment: L-carnitine and Thiamine

The significance of L-carnitine lies in its primary role of shuttling fatty acids across the mitochondrial membrane, delivering them for β -oxidation and the production of energy (ATP).⁴⁷ Deficiency of L-carnitine, depending on severity, results in the accumulation of lipid in muscle, muscle myopathy, and weakness and can involve the myocardium. Carnitine deficiency can be primary, resulting from a recessively inherited defect in muscle transport of carnitine, or secondary to decreased availability of free carnitine with many causes. These secondary deficiencies can result from decreased dietary intake (as with total parenteral nutrition [TPN]), decreased absorption (as with cystic fibrosis), increased loss (as with dialysis or renal Fanconi syndrome and increased use), and excretion of esterified (acyl) carnitine (as with organic aciduria). Primary or secondary carnitine deficiency syndrome as the only concomitant entity accompanying DCM is rare. The drug is expensive, and life-long administration would require a stronger basis, preferably through prospective randomized controlled studies.⁴⁸

Thiamine deficiency was, at one time, widespread in the developing world as a result of the exclusive use of polished rice as a staple diet in many Asian countries. Until recently, thiamine deficiency was considered to be a disease of historical importance only in the developed world. However, it is now realized that a large number of certain populations may be at high risk for developing this deficiency, including CHF; therefore, the interest in thiamine and thiamine deficiency has recently been reemerging. A number of case reports presented different cases with CHF secondary to idiopathic dilated cardiomyopathy, which, despite the optimal medical management, was progressively worsening, but dramatically improved after Thiamine supplementation.^{49,50}

Immunoglobulin

The potential utility of immunoglobulin (Ig) in myocarditis/DCM was suggested in one uncontrolled

multicenter study.⁵¹ This evidence has not been compelling enough for most practicing pediatric cardiologists to routinely administer this expensive agent. However, IgG apheresis was documented as a safe and effective method for managing DCM patients.⁵²

Immunosuppressive Treatment

While the myocarditis treatment trial conclusively showed no benefit in the adult population, two small studies in children have suggested significant benefit. Because of the potential toxicity of immunosuppressive treatment, a large controlled trial of immunosuppression in children with DCM is warranted. Until clear evidence is available, immunosuppressive treatment is not generally recommended.^{53,54}

Surgical Options for the Treatment of End-stage Heart Disease Reduction Cardiomyoplasty

Reduction ventriculoplasty or the Batista operation involves partial left ventricle resection and is aimed at improving the ejection efficiency of the heart by reducing the ventricular volume and wall stress.⁵⁵ International pediatric experience is rather limited. This procedure may delay the need for transplantation in selected cases. Because of its limited long-term benefit, it cannot be generally recommended for children with DCM.⁵⁶

Assist Devices and Artificial Heart

These are useful options as a ‘bridge to transplantation procedure’. However, they are prohibitively expensive.²⁹

Transplantation

Cardiac transplantation is considered the final treatment for the symptomatic child with DCM and severe LV dysfunction that shows no signs of improvement. Five year survival after cardiac transplantation varies from 50% to 70%.⁵⁷ Most children experience significant improvement in their lifestyle limiting symptoms. Lifelong surveillance is required to monitor occurrence of rejection and infections from immunosuppression and long-term complications that include cancer (lymphoma) and coronary artery disease in the transplanted donor heart.⁵⁸

Prognosis of Dilated Cardiomyopathy in children:

Unlike adults with DCM, a significant proportion of children with DCM may show significant

improvement with complete clinical and echocardiographic resolution in a small proportion of patients. In previous studies, mortality from pediatric DCM at 5 years after presentation is 33%–67%.^{1,59} found in a study done at the All India Institute of Medical Sciences. Female sex was the only multivariate predictor of death in a recent report of eleven patients with acute fulminant myocarditis, Aggressive symptomatic management is warranted, and heart transplantation should be considered only when maximal supportive therapy does not lead to improvement. The highest-risk period for children with DCM is in the first year after diagnosis, with 26% of patients achieving the end point of death or transplantation compared with ~1% per year in subsequent years. Survival is worse for subjects diagnosed at <4 weeks and >5 years of age, those with familial cardiomyopathy.^{60,61}

DCM: Perspective in Bangladesh:

The department of Pediatric Cardiology in CMH Dhaka, Bangladesh has been treating critically ill children with different spectrum of cardiac problems since 1998. A lot of DCM cases (around 300 cases) were managed here very successfully within this period.

Most of the cases were of idiopathic origin but other causes were detected as secondary to congenital heart disease like anomalous left coronary artery from the pulmonary artery (ALCAPA), critical aortic stenosis (AS), coarctation of aorta (CoA) and thiamine and carnitine deficiency. A strong correlation of DCM was found with neonatal supraventricular tachycardia (SVT) and these cases are not very uncommon in neonatal ICUs. Majority of the cases were due to myocarditis and relation with Cocksackie virus was also identified in few cases. Several cases were dramatically improved after introduction of IVIG and Thiamine. Experience in this institute instills the importance on etiology oriented management for better outcome in DCM cases.

Conclusions:

In children, DCM is a diverse disorder with outcomes that depend largely on cause, age, and heart failure status at presentation. Most children do not have a known cause of DCM, which limits the potential for disease-specific therapies. Management of children with dilated cardiomyopathy remains difficult but

recent advances including early introduction of ACE inhibitors and β -blockers may improve. Early identification of detectable causes and prompt management accordingly can save lives of many debilitated children. In the future implantable left ventricular assist devices may provide interim mechanical support, but referral for transplantation remains the cornerstone of treatment.

Conflict of Interest - None.

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