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CLINICAL OVERVIEW

Dilated cardiomyopathy in children

Miocardiopatía dilatada en el niño

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What do we know about the subject matter of this study?

Dilated cardiomyopathy is a myocardial disease that affects ventricular systolic function. With multiple etiologies, in children is an important cause of heart failure. Prognostic factors are not completely clear, and treatment is focused on management of heart failure.

What does this study contribute to what is already known?

An updated revision of the subject, incorporating changes in nomenclature and classification, with emphasis on physiopathological mechanisms and etiologies. Prognostic determinants are reviewed as well as a therapeutic approach focused on heart failure management based on updated evidence and expert recommendations.

Abstract

Pediatric cardiomyopathies are infrequent diseases of the cardiac muscle, with an annual incidence of 1.1 to 1.2 per 100,000 children. Dilated cardiomyopathy (DCM) is the predominant form, characterized by ventricular dilatation and systolic dysfunction. Etiologies are multiple, with at least 50%-70% of cases being idiopathic. When assessing a child with DCM, secondary potentially reversible causes must be ruled out. The main diagnostic tool is the echocardiogram which allows the identification of cardiac phenotype, to establish the degree of functional compromise, and response to medical therapy. Prognosis is limited but more favorable in infants younger than 1 year at the onset, post myocarditis, or with a lesser degree of ventricular dysfunction. At least 20% of patients may recover ventricular function in the first 2 years after the onset and 40%-50% may die or need heart transplant in the first 5 years. Medical therapy is mainly based on adult experience with limited scientific evidence in children. Heart transplant is the therapy of choice in patients with end-stage disease, with excellent short- and medium-term survival. A significant proportion of patients may require stabilization on the waiting list, including the use of mechanical circulatory support as a bridge to transplantation. The purpose of this revision is to update the available information on etiology, physiopathological mechanisms, prognostic factors, and management of DCM in children.

Keywords:
Heart Diseases;
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Introduction

Cardiomyopathies (CM) in children are a group of rare diseases that affect the myocardium and manifest with altered systolic and/or diastolic function, which may involve one or both ventricles. After congenital heart diseases, CM are the main cause of heart failure in children and are associated with significant morbidity and mortality.

After the first classification in 1980, subsequent reclassifications have added new morphologies and advances in etiology[1-4]. In 2019, the American Heart Association (AHA) adopted a classification based primarily on morphofunctional characteristics (phenotype), and secondarily on causes or subtypes (genetic and non-genetic)[5] (table 1). According to several population studies, dilated cardiomyopathy (DCM) is the main phenotype, occurring in up to 50% of total cases, followed by hypertrophic cardiomyopathy (HCM) in 35% to 50%, left ventricular non-compaction (LVNC) in 5%, and restrictive cardiomyopathy (RCM) in 4% to 5%[5,6]. There is also a mixed category in which different phenotypes may overlap (e.g., LVNC/HCM, LVNC/DCM)[8].

The purpose of this article is to update available information on etiology, physiopathological mechanisms, prognostic factors, and treatment of DCM in children.

Dilated Cardiomyopathy

DCM is the main form of CM, and the predominant reason for requiring a heart transplant (HT) in both children and adults. It is characterized by dilation of the left ventricle (LV) and systolic dysfunction, with normal or decreased thickness of ventricular walls. It is important to rule out a cause that may explain both ventricular dilation and dysfunction, such as anatomical (with abnormal preload or afterload, such as mitral insufficiency or coarctation of the aorta), or ischemic (e.g., coronary artery anomalies). If the morphofunctional phenotype persists after normalizing hemodynamic and/or anatomical conditions, it may be possible to conclude that it is a DCM[9].

Epidemiology and etiology

CM have an annual incidence of 1.1-1.2 cases per 100,000 children from birth to 18 years of age[5-7]. The incidence of DCM is 0.57 cases per 100,000 children, which is higher in men (0.66 vs 0.47 cases per 100,000), in black people (0.98 vs 0.46 cases per 100,000), and infants compared with those over 1 year of age (4.4 vs 0.34 cases per 100,000) (3.10). In Chile, there are no population studies on pediatric CM; however, according to the reported experience of HT in children, the most common diagnosis was DCM[11].

There are multiple causes of DCM, which are classified as primary and secondary (table 2). Primary DCMs are mainly idiopathic or genetic. Secondary DCMs are characterized by having a potentially treatable cause and by involving multiple organs and systems, not just the heart. On the other hand, in order to classify a DCM as primary, secondary causes must be ruled out[12].

The diagnosis of idiopathic DCM is by exclusion, and it is estimated that it may occur in 50% to 70% of cases; this proportion diminishes as some may be reclassified as familial-genetic. No morphological or functional characteristic are useful in order to differentiate idiopathic from familial forms[10]. Also, in pediatric patients survival is similar in both types of DCM. Genetic study is important in the evaluation of all children with CM, since 42%-50% of cases may have a genetic background, understood as the presence of an affected first-degree family member, or a positive test in a genetic panel[9,13,14].

Table 1. Classification of Cardiomyopathies (CM)
Phenotypes
Dilated cardiomyopathy (DCM)
Hypertrophic cardiomyopathy (HCM)
Restrictive cardiomyopathy (RCM)
Arrhythmogenic cardiomyopathy (ACM)
Non classified: Left ventricular non-compaction cardiomyopathy (LVNC)
Subtypes
Genetic and non-genetic

Table 2. Causes of dilated cardiomyopathy (DCM)
Primary DCM
Familial/genetic
Sarcomeric
Neuromuscular diseases
Mitochondrial disease
Laminopathies
Secondary DCM
Inflammatory
Toxins
Metabolic diseases
Nutritional diseases
Structural heart diseases

DCM: dilated cardiomyopathy.

Familial DCM occurs in 30% to 48% of cases[15,16], is predominantly of autosomal dominant inheritance, with other forms of inheritance being autosomal recessive, X-linked, and mitochondrial[6]. The genes involved encode two major protein subgroups: cytoskeletal and sarcomeric proteins[17]. Cytoskeletal proteins identified include dystrophin, desmin, lamin A/C, δ-sarcoglycan, β-sarcoglycan, titin, and meta-vinculin. The same genes responsible for HCM may be involved in sarcomeric proteins, including myosin heavy chain, myosin-binding protein C, actin, α-tropomyosin, and troponin T and C. A new group of sarcomeric genes has been identified, which encode Z-disk and ion channel proteins[18]. Dilated cardiomyopathies associated with sarcomeric mutations account for 10%-20% of the inheritable DCMs and result in an inability to generate myocyte contractile force. In general, the interaction between genetic, environmental, and other potential modifying factors in pediatric CM is not completely clear.

In patients with neuromuscular diseases, CMs cause significant morbidity and mortality, especially Duchenne (DMD) and Becker (BMD) muscular dystrophies. BMD is a less severe myopathy than DMD, with a greater chance of deambulation after adolescence. About 60%-75% of patients with BMD develop DCM after the age of 20, where the cardiac disease is the main cause of death in these patients[19]. Both conditions affect the dystrophin gene (dystrophinopathies) located in the short arm of the X chromosome; inheritance is X-linked recessive type. Barth syndrome is a disease that affects the mitochondria due to a defect in cardiolipin. It typically occurs in male infants with neutropenia, acidosis, heart failure, and arrhythmias. It is caused by mutations in the TAZ gene and is associated with different CM, including DCM, HCM, and LVNC[20]. Emery-Dreifuss muscular dystrophy is caused by a mutation in the LMNA gene (laminopathy) and presents as a myopathy associated with DCM[20].

Inflammatory causes can be either infectious or non-infectious, where the latter are very rare. In children, viral myocarditis is the main cause of inflammatory DCM. Different viruses may be identified as responsible of myocardial inflammation either by PCR of the viral genome in blood, respiratory secretions, or by myocardial biopsy. Currently, common viruses related to myocarditis are adenovirus, enterovirus, parvovirus, human herpesvirus 6, influenza A and B, varicella-zoster virus, cytomegalovirus, and Epstein-Barr virus. The diagnosis of myocarditis requires a complete diagnostic study that includes, in addition to an electrocardiogram (ECG) and echocardiogram, confirmation of inflammation and myocardial damage, and being able to attribute the inflammatory process to a suspected viral infection. This would require a myocardial biopsy, a method not free of risks in patients with acute heart failure, with also false negatives due to regional inflammation. Currently, cardiac MRI is an alternative method, based on Lake Louise criteria for myocarditis[21]. The identification by PCR of viral particles in blood or respiratory secretions supports the diagnosis when all other clinical information is concordant. Elevation of plasma troponin is a useful complementary test.

Another cause of DCM to consider is cardiotoxicity in children who survive cancer treatments, either by the use of anthracyclines and/or radiotherapy, especially at higher cumulative doses and at younger ages[22].

Physiopathology

In DCM, myocardial damage is accompanied by ventricular systolic dysfunction, dilation of cardiac chambers, cardiac remodeling, and often, mitral insufficiency. Unlike adults, in children, there may also be biventricular involvement[5]. Hemodynamic changes are associated with activation of the neurohormonal system (sympathetic nervous system and renin-angiotensin-aldosterone pathway) as an adaptive mechanism. Changes in the loading conditions are beneficial in the short term, but over time they determine greater cardiac remodeling and deterioration in ventricular function. These may lead to the appearance of symptoms and signs characteristic of the syndrome known as congestive heart failure (CHF)[23].

Clinical presentation and diagnostic evaluation

In children with CM clinical presentation is variable depending on the specific subtype and on the degree of myocardial involvement, with a predominance of signs and symptoms of CHF[6,7]. In patients with DCM, up to 75% to 80% may have clinical features of CHF, many of which can be mistaken for common childhood pathologies such as asthma, feeding difficulty, vomiting, poor weight gain, and hepatomegaly, especially in infants and young children[6]. Older children may present dyspnea and abdominal pain, along with hepatomegaly and evidence of decreased cardiac output. The spectrum of clinical presentation may vary from asymptomatic patients to acute heart failure and cardiogenic shock. A significant number of patients require hospitalization at the time of diagnosis for stabilization and treatment of CHF. Unlike adults, the need for hospitalization in children due to DCM and CHF is associated with increased morbidity and mortality, and with the use of advanced cardiac therapy, including vasoactive drugs, mechanical ventilation, and occasionally mechanical circulatory assist devices[24]. Common tests such as a chest x-ray and ECG may advance a possible diagnosis of DCM. The x-ray can typically show cardiomegaly and signs of pulmonary venous congestion, including pulmonary edema in some patients. The ECG is nonspecific, but sinus tachycardia and changes in QRS complex voltage may appear; some patients may present with arrhythmias such as supraventricular or ventricular tachycardia, or atrioventricular conduction abnormalities. When ischemic changes are present, including deep Q waves in leads I, aVL, and ST and T-wave changes in precordial leads, coronary anomalies must be ruled out.

In the evaluation of a child with CHF and suspected CM, the main diagnostic tool is echocardiography, since it allows to establish a specific cardiac phenotype, the degree of severity of functional compromise, and response to medical treatment. In patients with DCM, the degree of ventricular dilatation and dysfunction may be an important prognostic indicator towards an increased risk of death or the need for HT[25]. The characteristic phenotype is dilation of left heart chambers and systolic ventricular dysfunction (dilated-hypokinetic). In children measured heart chambers need to be adjusted to body surface. Dilation is defined as the presence of left ventricular end-diastolic diameter or volume (LVDD) and left ventricular end-systolic diameter or volume (LVSD) above two standard deviations from average normal adjusted to body surface area (> 2 Z-values). The most commonly used parameters of systolic function are fractional shortening (% FS, normal range 28%-38%), and ejection fraction (% EF, normal > 55%). In every first diagnosis of DCM, especially in infants, it is essential to rule out potentially treatable causes, such as anomalies of coronary arteries (for example, anomalous left coronary artery from the pulmonary artery or ALCAPA), and obstructive lesions (especially coarctation of the aorta). When left ventricular dilation is significant, it may be accompanied by mitral valve dilation, resulting in mitral insufficiency and left atrial enlargement.

Prognosis

Children with DCM have a poor prognosis. Using mortality or HT as a clinical variable, about 40%-50% of patients diagnosed with DCM either die or need to be transplanted at 5 years, and in most cases adverse events occur in the first 2 years after presentation[10]. The probability of dying or requiring a HT varies according to individual patient characteristics; however, there are no risk stratification studies in children. Some series have identified three factors of good prognosis: younger age, higher % FS or % EF at presentation, and past history of myocarditis[25]. Similarly, factors of poor prognosis are presentation with CHF, age older than 1 year at presentation, and a greater degree of LV dilation with worse systolic function[10]. In patients who present with CHF, the risk of dying can be as high as 34% at one year[26]. According to etiology, patients with muscular diseases have the worst prognosis and the least probability of receiving a transplant. Between 27%-33% of patients may show normalization of ventricular function within 3-15 years after diagnosis[27]. The risk of sudden death (SD) in children with DCM is 2%-3% within the first 5 years after diagnosis[28].

Medical Management

Management strategies for DCM focus on relieving symptoms and preventing hemodynamic alterations that are the cause of potential maintenance of CHF as a chronic disease. The number of controlled prospective studies evaluating the efficacy and safety of CHF therapy in children are very limited, and much of the available information comes from extrapolation of therapies in adults. Available guidelines for the management of CHF in children include a four-stage classification according to clinical condition (A-D) (table 3)[29].

Therapy according to CHF stages

Stage A: This stage includes children at risk of developing CHF, as can occur in cancer survivors exposed to cardiotoxic therapy (anthracycline and/or radiation therapy), and in children with DMD. There is no available information to support the prophylactic use of angiotensin-converting enzyme ACE inhibitors in children who received cardiotoxic therapy with normal heart function. A few small randomized studies support the use of ACE inhibitors (such as perindopril) in children with DMD[30].

Stages B and C: Medical treatment of patients with chronic CHF includes a combination of ACE inhibi-

Table 3. Stages of Heart Failure (HF)

Stage	Interpretation
A	Patients at risk of HF, with normal cardiac function
B	Asymptomatic patients with normal cardiac function
C	Patients with abnormal cardiac function, with prior or current history of symptoms
D	Patients with refractory or end-stage HF requiring continuous infusión of inotrpes, mechanical circulatory support, or HT

HF: heart failure; HT: heart transplant.

tors, β-blockers, diuretics, aldosterone antagonists, and digoxin. ACE inhibitors are used as vasodilators to decrease the elevated post ejection after activation of the renin-angiotensin-aldosterone system. The utility of these drugs is widely established in adults (with level of evidence A), which supports an improvement in the survival of patients with CHF[31]. In children, although there are few studies which are inconclusive[32], the use of these drugs (captopril, enalapril) is considered a first-line treatment and is incorporated into the guidelines of CHF management (level of evidence B)[29]. β-blockers antagonize the deleterious effect of chronic sympathetic activation on the myocardium; carvedilol also has vasodilatory properties due to its α-blocker effect. In adults, the use of carvedilol has shown to improve survival and decrease morbidity in patients with advanced CHF[33]. In children, results have been contradictory, with retrospective and prospective studies that support an improvement in ventricular function and clinical condition[34-36]. Currently, their incorporation is recommended (evidence level B). Loop diuretics (furosemide), are used for symptomatic relief in patients with congestive signs and symptoms (evidence level C). The use of aldosterone antagonists is well established in adults with CHF due to systolic dysfunction, for their effect on mortality and also anti-fibrotic and myocardial remodeling properties[37]. In children, the use of spironolactone in the treatment of patients with symptomatic CHF, associated with ACE inhibitors and β-blockers is recommended (evidence level C). Historically, digoxin has been used in children with CHF. Its utility is based on potential inotropic effects, attenuation of neurohormonal response, and heart rate control in adult patients. In symptomatic children, its use is recommended at low doses (5-8 μg/kg per day) with an ideal plasma concentration range of 0.5-0.8 ng/mL[38] (evidence level C). Based on experience in adults, a few pediatric patients with ventricular systolic dysfunction (EF < 35%), complete left bundle branch block, and/or wide QRS complexes may be candidates for cardiac resynchronization therapy[39] (evidence level B).

Stage D: In this stage are found symptomatic patients with CHF refractory to optimized oral therapy, which frequently require in-hospital management, including vasoactive drugs (especially milrinone), and sometimes mechanical ventilation. In general, hospitalization may be due to decompensation associated with comorbidities (such as infections, anemia, feeding problems, hydroelectrolytic alterations), or compromise in cardiac output and/or volume overload. In some cases, frequent decompensation reflects progression to a terminal stage of the disease, in which long-term survival depends on mechanical circulatory assistance, or HT. Circulatory support devices are used in patients with decompensated CHF in which medical therapy alone is not enough to maintain organ and systemic perfusion. They have the potential to improve the patient's general conditions while waiting for a HT and, in many cases, to reverse secondary compromise (renal and/or hepatic failure). However, their benefit must be weighed against the risk of thromboembolic and hemorrhagic complications[40]. HT is the therapy of choice in patients with refractory end-stage CHF (evidence level B), and in some patients with symptomatic stage C CHF, with complex arrhythmias and high risk of SD, or with reversible pulmonary hypertension (evidence level C)[29]. Survival at 1 year in transplanted children is about 92%, 80% at 5 years, and 72% at 10 years[41]. This survival compares favorably with the high mortality reported in natural history studies in children with DCM, with 1-year survival at 70% and 5-year survival at 58%[42]. However, mortality on the waiting list is significant, which is high in centers with low transplant volume (close to 30%), and low in high-volume centers (5%-10%)[43]. In our experience, the waiting list mortality has been 33%, with an average waiting time of 199 days; in addition, 30% of the patients on the waiting list have required mechanical circulatory assistance, reflecting the complexity and severity of enlisted patients[8]. HT is a therapeutic option not free of problems, including a limited donor pool, high waiting list mortality, rejection, and the need for lifelong immunosuppression.

Conclusions

Although rare, DCM is the main form of CM in children and a major cause of CHF. Its etiology is multifactorial, with idiopathic or family-genetic predominance, and is characterized by ventricular dilation and systolic dysfunction. Prognosis is limited, with a 40%-50% risk of death or requiring a HT at 5 years. Lower risk factors are age under 1 year, higher % FS or % EF at presentation, and history of myocarditis. Treatment is aimed at relieving symptoms and avoiding chronic hemodynamic changes; clinical management is based on information from adult studies. In patients with advanced or terminal CHF, the definitive treatment is HT.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

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