Pediatric Cardiomyopathies: Establishing Genotype-Phenotype Relationship as a Determinant in Prognosis and Therapy: A Review of the Literature

Ana Flavia Malheiros Torbey,1,2, a Aurea Lucia Alves de Azevedo Grippa de Souza,1,2,3, a Estela Azeka,4,5, a Maraisa Fachini Spada6

Universidade Federal Fluminense – Hospital Universitário Antônio Pedro – Departamento Materno Infantil,1 Niterói, RJ – Brazil
Programa de Pós Graduação em Ciências Cardiovasculares da Universidade Federal Fluminense,2 Niterói, RJ – Brazil
Complexo Hospitalar de Niterói,1 Niterói, RJ – Brazil
Instituto do Coração do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo,4 São Paulo, SP – Brazil
Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (HCF/UNESP),5 São Paulo, SP – Brazil
Birmingham Women’s and Children’s Hospitals NHS Foundation Trust, Birmingham – United Kingdom

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Mailing Address: Ana Flavia Malheiros Torbey
Universidade Federal Fluminense Hospital Universitário Antônio Pedro – Departamento Materno Infantil – Rua Marques do Paraná, 303. Postal Code 24033-900, Centro, Niterói, RJ – Brazil
E-mail: anaflaviamalheiros@gmail.com
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Abstract
Cardiomyopathies constitute a heterogeneous group of diseases with varying etiologies and clinical presentation. Advances in genetic testing have made it possible to establish genotype-phenotype relationships, determine prognosis, and choose specific treatments in the pediatric population. Therefore, the objective of this review is to assist clinical reasoning and underscore the importance of etiological diagnosis in different disease phenotypes.
Introduction

Pediatric cardiomyopathies constitute a heterogeneous group of alterations in the myocardium with different phenotypes and etiologies. Clinical presentation ranges from asymptomatic individuals to children with heart failure, arrhythmias, and sudden death. It is the main indication for heart transplantation after one year of age.1-3

The etiology may involve secondary causes, for example, infectious, inflammatory, or autoimmune diseases or the use of medications (anthracyclines); however, genetic causes play an important role in pediatric cardiomyopathies. Currently, with the wider availability of genetic tests, the establishment of the genotype-phenotype relationship has made it possible to determine prognosis and provide specific therapies for this group of patients, thus modifying the natural history of the disease.1-3,7

Although rare in pediatrics, cardiomyopathies are accompanied by significant morbidity and mortality, requiring specialized attention to this condition.3,4 Therefore, the objective of this review is to assist clinical reasoning and underscore the importance of seeking etiological diagnosis in different phenotypes of pediatric cardiomyopathy.

Epidemiology

Population studies have estimated an incidence of around 1:100,000 cases per year of cardiomyopathy in children and adolescents. These studies were carried out in Europe, North America, and Australia, and there is still a lack of epidemiological data from Brazil and Latin America.1,5-11 In children under 1 year of age, the diagnosis of cardiomyopathy is more frequent, with an incidence of 8.3 cases per 100,000 children per year; hypertrophic cardiomyopathy (HCM) occurs 3 times more in this age group.1,8,12

These data may possibly be underestimated, given the impact of pediatric heart failure observed in recent years, cardiomyopathies being a common cause of heart failure, along with congenital heart diseases.1,13-16

The main phenotypes (Table 1) in pediatrics are dilated cardiomyopathy (DCM) and HCM, followed by less frequent phenotypes such as non-compaction cardiomyopathy (NCCM), restrictive cardiomyopathy (RCM), and arrhythmogenic cardiomyopathy (ACM).1,3,17

DCM occurs in approximately 50% of patients and HCM is responsible for just over a third of cases in this age group. The annual incidence of these phenotypes is estimated to be between 0.8 and 1 per 100,000 children.1,3,18-20

NCCM is the third most diagnosed among children and adolescents, followed by RCM and ACM. The incidence of NCCM can range from 5% to 10%, as observed in the Australian Registry, and RCM corresponds to approximately 5% of pediatric cardiomyopathies.1,21,22

ACM is a very rare disorder in childhood, with an estimated prevalence of 1:2000 to 1:5000 in adults, in most published series; in pediatrics, however, its real incidence is not known, and studies are limited to case series.20,23,24

The importance of classification

Used to promote understanding and systematic discussion of diseases, classification systems organize cardiomyopathies into logical groups, which share the same morphology, physiology, and biochemistry, also providing standardization of nomenclature.

Among the current classifications, the following stand out: 1) the American Heart Association classification (2006), which divides cardiomyopathies into primary (solely or predominantly confined to the myocardium) and secondary (part of systemic diseases); 2) the European Society of Cardiology classification (2008), based on ventricular morphology and function, subclassifying each phenotype into familial (in the presence of more than one affected family member) and non-familiar (idiopathic and acquired); and 3) the MOGES classification endorsed by the World Heart Federation (2013), which stages cardiomyopathy according to the morphofunctional phenotype (M), organ involvement (O), genetic and familial inheritance (G), etiology (E), and functional status (S).25-28

Clinical-diagnostic reasoning in pediatric cardiomyopathies

The clinical presentation of cardiomyopathies in children and adolescents ranges from asymptomatic individuals to patients with symptoms of heart failure, arrhythmias, precordial pain, syncope, and sudden death. They can manifest from the neonatal period until the end of adolescence, which makes diagnosis challenging.1,17,29

Given that the etiology is highly varied, acquired causes must initially be ruled out. Through personal history, it is possible to identify recent infections that may indicate a condition of myocarditis or even signs and symptoms of autoimmune, inflammatory, and metabolic diseases, directing specific approach and treatments. Past cancer treatment and exposure to cardiotoxic chemotherapy drugs should be investigated. The age of symptom onset is fundamental to investigation of etiology, because infants present with inborn errors of metabolism more frequently than older children.1,13,29,30,31

Family history is essential, and some patients may be diagnosed early thanks to family history, even in the absence of symptoms, due to family screening. The importance of this early diagnosis is due to the possibility of primary prevention of sudden death, which may be the first and only symptom in some cases. Furthermore, family history of at least three generations with the construction of a pedigree is supported by level of evidence A. Obtaining a pedigree makes it possible to observe the pattern of inheritance (autosomal dominant, recessive, or X-linked) and identify which family members are at risk of being affected by the disease.30,32,33

Physical examination should consider alterations beyond the cardiovascular system, since, during childhood, the presence of syndromic causes, inborn errors of metabolism, and neuromuscular diseases are more frequent than in adults.34-36 Thus, developmental delay, hypotonia, hepatoesplenomegaly, and dysmorphisms can assist in the etiological investigation. A multidisciplinary approach with a pediatrician, pediatric neurologist, clinical geneticist, and pediatric cardiologist is often necessary.34-36 Figure 1 displays
<table>
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<th>Phenotype</th>
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<tr>
<td>Dilated</td>
<td>- Genetic mutations&lt;br&gt;- Inborn errors of metabolism&lt;br&gt;- Neuromuscular diseases&lt;br&gt;- Syndromes&lt;br&gt;- Secondary to viral, autoimmune, and inflammatory diseases and medications</td>
<td>- Asymptomatic&lt;br&gt;- Signs and symptoms of decompensated heart failure&lt;br&gt;- Arrhythmias</td>
<td>- Treatment of heart failure&lt;br&gt;- Mechanical circulatory support devices</td>
<td>- Survival at 5 years is 50% to 60%</td>
</tr>
<tr>
<td>Hypertrophic</td>
<td>- Genetic mutations&lt;br&gt;- Inborn errors of metabolism&lt;br&gt;- Glycogen storage diseases or glycogen disorders&lt;br&gt;- Lysosomal storage disorders&lt;br&gt;- Neuromuscular diseases&lt;br&gt;- Syndromes</td>
<td>- Asymptomatic&lt;br&gt;- Progressive heart failure&lt;br&gt;- Sudden death</td>
<td>- Improve left ventricular outflow tract gradient&lt;br&gt;- Decrease risk of sudden death&lt;br&gt;- Surgical reduction of the interventricular septum&lt;br&gt;- Implantable cardioverter-defibrillator</td>
<td>- Survival at 5 years is 95% in sarcomeric hypertrophic cardiomyopathy with clinical presentation after the first year of life and 40% in inborn errors of metabolism</td>
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<tr>
<td>Non-compaction</td>
<td>- Genetic mutations</td>
<td>- Asymptomatic&lt;br&gt;- Signs and symptoms of heart failure&lt;br&gt;- Arrhythmias&lt;br&gt;- Thromboembolism</td>
<td>- Treatment of heart failure&lt;br&gt;- Treatment of arrhythmias&lt;br&gt;- Prevention of thromboembolic events</td>
<td>- Survival at 5 years is around 80%</td>
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<td>Restrictive</td>
<td>- Genetic mutations&lt;br&gt;- Errors of metabolism&lt;br&gt;- Secondary to chemotherapy, radiotherapy, and bone marrow transplantation</td>
<td>- Decompensated heart failure&lt;br&gt;- Arrhythmia&lt;br&gt;- Sudden death</td>
<td>- Treatment of arrhythmia&lt;br&gt;- Decrease the risk of sudden death&lt;br&gt;- Implantable cardioverter-defibrillator</td>
<td>- Limited; heart transplant-free survival at 5 years is around 30%</td>
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<tr>
<td>Arrhythmogenic</td>
<td>- Genetic mutations</td>
<td>- Asymptomatic, with abnormal electrocardiogram findings&lt;br&gt;- Ventricular tachycardia&lt;br&gt;- Sudden death</td>
<td>- Treatment of arrhythmia&lt;br&gt;- Decrease the risk of sudden death&lt;br&gt;- Implantable cardioverter-defibrillator</td>
<td>- Limited; more than 50% of pediatric patients require a transplant within 5 years</td>
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Pediatric Cardiomyopathies: Literature Review

the sequence of clinical reasoning in pediatric patients with cardiomyopathies.

The dosage of biomarkers assists clinical reasoning. Troponin is generally elevated in inflammatory cardiomyopathies, such as myocarditis, and brain natriuretic peptide (BNP) and its precursor (NT-proBNP) indicate evolution to heart failure. Higher levels are associated with worse prognosis.

The morphofunctional phenotype should be determined using available cardiac imaging tools such as electrocardiogram; echocardiogram with color Doppler, tissue Doppler (to assess diastolic dysfunction), and speckle tracking (to assess early systolic dysfunction and subclinical systolic dysfunction); and cardiac magnetic resonance, which characterizes myocardial tissue and detects edema and fibrosis. It is worth noting that the measurements obtained must be expressed in z-scores for proper interpretation.

The search for etiological diagnosis is essential since there are scenarios where specific treatment is available, improving the prognosis. This investigation should be based on the cardiac phenotype and associated systemic changes.

When indicating genetic tests, it is important for the patient and the family to receive adequate counseling carried out by a trained professional, who will explain the possible results that can be found and the impact they could have on the lives of patients and family members.

Dilated cardiomyopathy

DCM is defined by the presence of dilation of the cardiac chambers associated with ventricular dysfunction. It can be classified as primary and secondary. The main primary causes are familial/genetic, mitochondrial diseases, and neuromuscular diseases. Among the genetic causes, genes related to proteins of the sarcomere, cytoskeleton, nuclear membrane, and desmosomes have already been described.

Mutations in LMNA, MYH, TNNT2, SCN5A, and TTN are the most related to the phenotype.

Secondary causes are inflammatory/infectious, toxic, metabolic, storage diseases, nutritional disorders, heart disease, and lung disease.

The clinical picture may vary in DCM, from asymptomatic children and adolescents to the presentation of congestive heart failure or cardiogenic shock requiring ventilatory support, as well as short- or long-term mechanical circulatory assistance.

For diagnostic investigation, the following are recommended: chest radiography, to assess the degree of cardiomegaly; electrocardiogram, which can reveal the degree of left ventricular overload, presence of arrhythmias, and atrioventricular block; echocardiogram with color Doppler that will confirm the degree of dilation of the ventricular chambers, presence of congenital heart disease, and atrioventricular valve insufficiency. Holter can detect episodes of supraventricular and ventricular tachycardia, as well as atrioventricular blocks. Cardiac magnetic resonance imaging assists in the detection of inflammatory processes, edema, and fibrosis and may quantify myocardial impairment and even prognosis when fibrosis is extensive. Tomography angiography assists in the differential diagnosis of anomalous left coronary artery and aortic coarctation when diagnosis is difficult using other imaging methods. Initial laboratory tests in the investigation and evaluation of DCM include evaluation of the exome, electrolytes, BNP, troponin, complete blood count, renal function, hepatic function, thyroid function, and serologies and PCR of cytomegalovirus, toxoplasmosis, Coxsackie A and B, COVID-19, parvovirus-b19, Epstein-Barr, chikungunya, and Chagas. Endomyocardial biopsy is used for diagnostic clarification and is considered the gold standard; however, the patient’s clinical condition must be
evaluated at the moment it is to be performed, as it can lead to deterioration of the clinical condition.  

Treatment depends on the etiology of the DCM and the attempt to improve the patient’s symptoms. In general, patients with congestive heart failure require a multidisciplinary team consisting of physicians, a nutritionist, a physiotherapist, a nurse, a psychologist, and a social worker so that they can provide the necessary support for patients, especially when they are hospitalized, as therapy can be long and require titration of medications in order to obtain adequate success in the evolution.  

In relation to evolution and prognosis, the actuarial survival curve reveals that 50% to 60% of patients are free of heart transplantation and/or death at 5 years. Therefore, DCM is a pathology that requires early diagnosis and therapeutic intervention to improve survival and quality of life.

**Hypertrophic cardiomyopathy**

In the pediatric population, HCM is a heterogeneous group, including etiologies such as classic mutations in sarcomere proteins, inborn errors of metabolism, neuromuscular diseases, and syndromes. The diverse etiologies along with age at presentation explain the vast clinical manifestation, from asymptomatic patients to patients with progressive heart failure and sudden death. In its classic form, which is isolated and not associated with syndromes and other diseases (70% to 75% of cases), the main pathogenesis of HCM is due to mutations in sarcomere proteins. The most common inheritance pattern is autosomal dominant with variable penetrance and expressivity. Pathogenic mutations are identified in half of the cases, and the majority are missense, resulting in functional loss of the protein. Genes commonly involved in the hypertrophic phenotype encode myofilament proteins and include MYH7, MYBPC3, MYL2, MYL3, TNNT2, TNNI3, TPM1, and ACTC1. Recently, similar phenotypes were associated with genes that encode Z-disc proteins and calcium signaling proteins, such as CSRP3, ACTN2, and PLN, thus making the term sarcomeric hypertrophic cardiomyopathy more comprehensive to include these variants.

Non-sarcomeric HCM, also called phenocopies, comprise a group of distinct etiologies, including inborn errors of metabolism, Pompe disease (mutations in the GAA gene), Danon disease (X-linked variant in the LAMP2 gene), PRKAG2 cardiomyopathy (mutations in the PRKAG2 gene), lysosomal storage diseases such as mucopolysaccharidosis (Hurler and Hunter syndromes, both X-linked recessive), Fabry disease (mutations in the GLA gene), neuromuscular diseases such as Friedreich ataxia (mutation in the X25 gene), and syndromic diseases
such as Noonan syndrome (mutations in the PTPN11, SOS1, and RAF1 genes and other RASopathies).1,12,35

Among other causes of myocardial hypertrophy in childhood, HCM secondary to hyperinsulinism stands out, which occurs in neonates with pancreatic adenoma or children of diabetic mothers.1,12,35

In the pediatric age group, the classic sarcomeric form of the disease differs from the other forms by affecting the heart alone, without neurological and/or musculoskeletal involvement. The onset of the condition may occur during fetal life, but diagnosis is commonly made in adolescence or early adulthood. Clinical manifestation ranges from completely asymptomatic patients (who are diagnosed during family screening or investigation for other diseases) to patients with heart murmur, precordial pain, palpitations, syncope, and sudden death (aborted or not).2,3,12,20

Left ventricular hypertrophy leads to diastolic dysfunction responsible for left atrial enlargement and predisposes to tachyarrhythmias. In 5% to 10% of patients, chronic ventricular dysfunction, in later stages of the disease, leads to progressive ventricular dilatation and systolic dysfunction, changing the phenotype to something morphologically similar to DCM, a phenomenon known as burned-out HCM.18,20 Classic signs and symptoms of heart failure, although rarely seen in childhood, can thus be a result of disease progression, and should be evaluated in these cases.

Diseases of the microvasculature, with perfusion disorders and reversible myocardial ischemia, and dynamic obstruction of the left ventricular outflow tract are consequences of myocardial hypertrophy, and they explain symptoms such as precordial pain, dyspnea, pre-syncope, and syncope during exertion, mainly during high-intensity physical activity.20,43

In patients with other types of HCM, however, the clinical presentation tends to be more expressed in the first year of life, allowing for earlier diagnosis.1,3,35,36

In Noonan syndrome, for example, half of the patients are diagnosed up to 6 months of age. Characteristics on physical examination, such as facial dysmorphisms and developmental delay, are warning signs for diagnosis of the syndrome.35,44 Approximately 70% of patients present HCM that may be accompanied by congenital heart disease, such as supraavalvar pulmonary stenosis, mitral valve dysplasia, and interatrial and interventricular communication.1

The clinical manifestation of type II glycogen storage disease, better known as Pompe disease, varies and depends on the age when the condition begins. In infantile Pompe disease, severe myocardial hypertrophy is accompanied by muscle hypotonia and hepatomegaly, which can lead to death in the first year of life if enzyme replacement therapy is not instituted.1,12,34,45

In Danon disease, myocardial hypertrophy is accompanied by intellectual deficit, myopathy, and preexcitation on electrocardiogram. Rapid disease progression and refractory arrhythmias are common.3 The prognosis of HCM in childhood varies, depending on the age of presentation and disease etiology. In general, the 5-year survival rate of patients with sarcomeric HCM who present after the first year of life is around 95%. On the other hand, early clinical presentation (before one year of age) and inborn errors of metabolism are associated with limited prognosis, and it is estimated that only 40% of patients diagnosed with inborn errors of metabolism will be alive and free of heart transplantation in 5 years.1,3,12,20

Heart failure with systolic dysfunction at diagnosis, observed in patients with Noonan syndrome, for example, is also associated with worse prognosis, with mortality of 20% during the first 12 months of life. Other known risk factors are low weight, abnormal left ventricular shortening fraction, and end-diastolic posterior wall thickness.

The main cause of death in this age group is still heart failure, but the risk of sudden death cannot be ruled out. Identifying pediatric patients at high risk of ventricular tachycardia remains a matter of debate, as specific patterns of arrhythmia related to sudden death have not been well described in childhood. Recently, a European group proposed a risk stratification model for sudden death in patients with non-syndromic HCM phenotype between 1 and 16 years of age.46 The parameters associated with an elevated risk of sudden death in 5 years were age, sex, weight, interventricular septal thickness, left atrial diameter, left ventricular outflow tract gradient, non-sustained ventricular tachycardia, and syncope of unknown origin. Subsequently, a group from Canada proposed a similar model and included the presence of a pathogenic or probably pathogenic variant as an important risk factor. Positive genotype almost doubles the risk of sudden death in 5 years.47

The management of HCM is based on controlling the symptoms, improving the left ventricular outflow tract gradient, and reducing the risk of sudden death.

In the classic non-syndromic form of the disease, beta-blockers are the first line of treatment.1,2,12 Decreased heart rate promotes greater ventricular filling during diastole and consequently decreases the dynamic obstruction of the outflow. Moreover, it decreases myocardial oxygen demand. In patients with refractory symptoms and disease of the microvasculature, calcium channel blockers can be associated with betablockers, with significant improvement in precordial pain. Competitive sports and explosive exercise should be avoided.

Cardioverter-defibrillator implantation is recommended as primary prevention in patients with a history of tachyarrhythmia or aborted sudden death. In cases of secondary prevention, the indication of cardioverter-defibrillator implantation in the pediatric population is still a matter of debate, and, in general, two or more risk factors would be necessary. Despite recent advances in the recognition of risk factors for sudden death in childhood, there is still a lack of evidence regarding differences between adult and pediatric populations. The following recently published child risk calculator models can assist clinicians in decision-making: https://pimacycalculator.com and https://hcmriskkids.org.12,46,47
Surgical reduction of the interventricular septum (myomectomy) has demonstrated a significant decrease in the left ventricular outflow tract gradient, and it also has the benefit of decreasing anterior movement of the mitral valve and mitral regurgitation, promoting significant improvement in symptoms.5 20

In HCM associated with inborn errors of metabolism, specific therapies are available. In Pompe disease, for example, enzyme replacement therapy has been shown to be effective in reducing and even reversing the phenotype, if it presents early onset. In mucopolysaccharidoses, enzyme replacement therapy and bone marrow transplantation are also associated with better prognosis.1 4

Non-compaction cardiomyopathy

NCCM is morphologically characterized by a myocardium with trabeculations and deep recesses that communicate with the ventricular cavity. It is most often in the left ventricle, but it also affects the right ventricle. It is believed that a failure in the embryogenesis of compaction of the layers of the myocardium leads to the characteristic phenotype of NCCM. Its etiology is mainly genetic, with alterations found in genes that control functions of the sarcomere, cytoskeleton, and mitochondria. The pattern of inheritance is also diverse (autosomal dominant, X-linked recessive, and mitochondrial).1 2 22

In children, NCCM is usually a mixed phenotype, where there is association with other heart diseases, most commonly DCM and HCM and congenital heart diseases, whereas, in adults, the NCCM phenotype is usually isolated.22

The clinical presentation follows the associated phenotype; thus, signs of heart failure are more common in patients with DCM, whereas asymptomatic children usually have isolated NCCM. Other clinical findings may include precordial pain, syncope, changes in cardiac auscultation, arrhythmias, and thromboembolism, which occur in any age group, including the fetus, making diagnosis by fetal echocardiography possible.1 2 22 48

There has been much discussion about the differential diagnosis between the presence of physiological trabeculations and NCCM. There are different diagnostic criteria for echocardiography and magnetic resonance, the most accepted being the Jenni criteria for echocardiography and the Petersen criteria for cardiac magnetic resonance imaging; the first determines a ratio between non-compacted and compacted myocardium greater than 2 and the second greater than 2.3. Thus, its morphological diagnosis is often a challenge, and the follow-up of the patient’s evolution is important to determine the onset of symptoms, differentiating it from a physiological finding.1 2 22 48

Therapy should focus on clinical presentation, namely, treatment of heart failure, arrhythmias, and prevention of thromboembolic events. There is currently no specific medical or surgical therapy for NCCM.3 22 48

Genetic investigation is recommended, and it is positive in around 45% of cases. The definition of the etiology provides family screening and risk of recurrence among couples who wish to have other children.22 48 Worse prognosis with risk of death or heart transplantation has been observed in patients younger than one year old, with heart failure or ventricular arrhythmias.49 50

Restrictive cardiomyopathy

RCM is characterized by the non-compliance of the ventricles, most frequently the left ventricle, as they resist diastolic filling, leading to diastolic dysfunction, elevated end-diastolic pressure and dilated atria.1 2 51

The epidemiology of this pathology is still unclear, but studies indicate that people of all ages can be affected, and children have worse prognosis. Among this group, female children seem to be more affected. The etiology of RCM is variable. It can be genetic, with involvement of sarcomeric or non-sarcomeric genes, or secondary, caused either by systemic diseases such as amyloidosis and endocardial fibroelastosis.1 2 21 32

RCM can be classified as infiltrative, non-infiltrative, storage disease, and endomyocardial disease.1 22 52

As the ventricles are not dilated and the ventricular thickness is normal, systolic function is preserved in the early stages of the disease, in most cases, and may be reduced in more advanced stages.51

The clinical presentation consists of symptoms that rapidly progress to heart failure, arrhythmia, syncope, and sudden death. The prognosis is limited, and pediatric patients are quickly referred for heart transplantation. It is the cardiomyopathy with the worst prognosis in childhood, where 2 out of 3 children are candidates for heart transplantation.1 2

Arrhythmogenic cardiomyopathy

ACM describes a heterogeneous group, and the complex of genetic and inflammatory disorders are manifested by atrial and/or ventricular arrhythmias, often of a malignant nature, mainly in early childhood.1 53 54 Classically, the most common form is arrhythmogenic right ventricular cardiomyopathy; however, the phenotype with predominance of the left ventricle has recently been described.55 56

Among the genetic causes, alterations in the proteins that encode the cardiac desmosome stand out, and the main genes affected are PKP2, DSP, DSG2, DSP, and JUP. Genetic inheritance is normally autosomal dominant with variable penetrance. Age at presentation and sex seem to have a direct influence, with reduced penetrance in younger patients and a higher incidence in male patients.1 55

Recently, a phenotype that simulates myocarditis has been described, characterized by precordial pain, increased troponin, and changes in cardiac resonance with the presence of delayed enhancement. It is called the hot phase, and its diagnosis should be considered in families with frequent cases of myocarditis. This clinical presentation has a strong genotype-phenotype correlation with the DSP gene.57 58
Diagnosis is made by a combination of criteria based on scientific evidence proposed by the Task Force Working Group of the European Society of Cardiology, including changes in the size and function of the right ventricle confirmed by imaging, presence of fibrosis on myocardial biopsy, alterations on the electrocardiogram (including repolarization disorders, bundle branch block, arrhythmias, frequent extrasystoles), and family history.57

Drug treatment with the use of beta-blockers and other antiarrhythmics has been shown to be fundamental to reduce the risk of cardiac arrest and also for the treatment of heart failure. The use of diuretics and angiotensin-converting enzyme inhibitors can also help control symptoms of heart failure. Lifestyle changes and implantable cardioverter-defibrillator are indicated to decrease the risk of sudden death.55

New therapies

The genotype-phenotype relationship of pediatric cardiomyopathies has provided an understanding of their clinical presentation and prognosis. In children and adolescents, the genetic architecture of cardiomyopathies has its own complex characteristics that differ from the adult population. In recent decades, in an attempt to cure cardiomyopathies and other genetic diseases, new technologies have been developed.59,62 Enzyme replacement therapies available for Pompe and Fabry diseases modify the natural history of the disease, improving the prognosis of these patients.1,3,35,36

Knowledge of molecular alterations has made new therapeutic targets possible. Thus, new classes of drugs that act by modulating cardiac myosin (protein modulators) are also emerging and have already proven effective in alleviating symptoms of heart failure, decreasing arrhythmias, and stabilizing the phenotype.63,64

Several genetic manipulation strategies (gene therapy) have been created, including genome editing, gene replacement, silencing of specific alleles, exon skipping, and spliceosome-mediated RNA trans-splicing. Many of these technologies have already proven effective in animal models, and clinical trials in humans are being conducted successfully.59,61,65

In addition, knowledge of the genotype can stratify the risk of sudden death due to malignant arrhythmias, with early cardioverter-defibrillator implantation indicated for mutations in the FLNC and LMNA genes in ACM.56

Conclusion

Pediatric cardiomyopathies are a heterogeneous group with diverse etiology, clinical presentation, and phenotypes. They can often be diagnosed in asymptomatic individuals during screening tests (echocardiography and electrocardiogram) for sports participation, preoperative exams, and routine pediatric consultation. They should also be a constant concern in the multidisciplinary follow-up of patients with neuromuscular diseases, mitochondrial diseases, inborn errors of metabolism, genetic diseases (mainly RASopathies), and structural heart diseases, even the most common ones. Continuing education for pediatricians (and subspecialists), family physicians, neurologists, pulmonologists, and cardiologists plays an essential role in referring these potential patients to groups specializing in cardiomyopathies at local reference centers.

Detailed clinical investigations focused on each phenotype are necessary to provide specialized clinical care. Considerations regarding family history, especially in relation to sudden cardiac death and non-ischemic cardiomyopathies documented in 2 or 3 parental generations, assist in planning investigation and follow-up. Most cardiomyopathies can manifest at any stage of life; however, some clinical and echocardiographic red flags may allow early identification and therapeutic approach. The timeline of cardiological evaluation for screening should be customized according to the underlying disease, family history, and clinical presentation of each child. The construction of a pedigree during the initial consultations of pediatric evaluation has proven to be an excellent tool for alerting and understanding these pathologies.

Despite the high morbidity and mortality of the disease in childhood, advances in genetic studies, family counseling, and new specialized therapies have shown promise and brought hope to this population.

Author Contributions

Conception and design of the research, Writing of the manuscript and Critical revision of the manuscript for important intellectual content: Torbey AFM, Souza ALAAG, Azeka E, Spada MF.

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Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.
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