Cardiomyopathy was sudden death in 3.5% of cases[11]. A review of Toronto Sick Kids autopsy records for sudden death in children due to previously undiagnosed cardiac causes found 21 cases of pediatric cardiomyopathy encountered at autopsy may be in a child known to have the condition or be an unexpected finding. In the Australian study, the first presentation of pediatric cardiomyopathy was sudden death in 3.5% of cases[11].

Post Pathology

The pathologist’s job doesn’t end with making a diagnosis of pediatric cardiomyopathy. The information must be passed on to those who can ensure that the immediate relatives of the deceased child are appropriately evaluated for familial cardiomyopathy. This is usually not an issue with endomyocardial biopsy results or explant heart surgical specimens as it does to endomyocardial biopsies. Much of the North American epidemiologic data for childhood cardiomyopathy derives from the Pediatric Cardiomyopathy Registry (http://www.childrenscardiomyopathy.org/site/overview.php), a multicenter database. This registry, which currently includes over 1,000 cases of pediatric cardiomyopathy, was established in 1993 to provide diagnostic criteria, potential or established etiologies and ultimately some guidance to clinical management for pediatric cardiomyopathy. It emphasizes the increasing importance of molecular genetic testing in the delineation of the cardiomyopathies.

References


[4] Hypertrophic cardiomyopathy Arrhythmogenic right ventricular cardiomyopathy Left ventricular noncompaction cardiomyopathy Glycogen storage disease


[6] Post Pathology

C. Autopsy Heart Cardiomyopathy encountered at autopsy may be in a child known to have the condition or be an unexpected finding. In the Australian study, the first presentation of pediatric cardiomyopathy was sudden death in 3.5% of cases[11]. Even within the preadolescent age group cardiomyopathies have different clinical manifestations and management concerns at different developmental stages. Todd, normal, or sick children and adolescence[8]. The etiology of childhood myocardial disease more often remains undetermined than with adult cardiomyopathy, but when diagnosis is established it is likely to be a muscular or infiltrated disorder[9]. This poses the challenge of pediatric cardiomyopathy – a relatively uncommon condition, which has a large number of potential causes that are rare, have genetic implications and require intense and expensive investigations to reach an accurate diagnosis.

Incidence and Impact

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Pathology Investigations

The pathologist generally confronts a pediatric cardiomyopathy case well after clinical, diagnostic imaging and metabolic-genetic evaluations have been initiated. This pre-pathology processing aims to identify a secondary cardiomyopathy, if one exists, then reveal diagnostic information about the cardiomyopathy etiology. Clinical strategies for such investigations have been proposed for both childhood and adult cardiomyopathy[17,18]. However, since the causes in two thirds of cases remain unidentified, for the clinical differential diagnosis requires histologic confirmation, the pathologist often receives tissue during the work-up of pediatric cardiomyopathy. In this chapter cardiomyopathies are described based on etiology (genetic or acquired), and occasionally the first presentation of the pediatric cardiomyopathy is in a child known to have the condition or be an unexpected finding. In the Australian study, the first presentation of pediatric cardiomyopathy was sudden death in 3.5% of cases[11].

Introduction

Cardiomyopathies are “mystifying” because they are uncommon, have many rare causes often with significant genetic implications, have a diverse morphologic spectrum and are challenged with controversies around their definition and classification. This challenge is further complicated by the fact that patients with cardiomyopathies often share common clinical features, much of which is driven well before the pathology enters the picture. However, for the two thirds of cases with a known etiology the pathologist becomes the dominant element, contributing not only potentially diagnostic morphologic evaluations but also judiciously disposing the pathologist to other disciplines to optimize the information held in the disease's myocyte.


- Definitions and Classifications
- As to what any disease, the definitions and classifications of cardiomyopathies aim to provide diagnostic criteria, potential or established etiologies and ultimately some guidance to clinical management for the condition. In the 2006 American Heart Association Scientific Statement a proposed consensus for revised definitions and classification of cardiomyopathies (Appendix) is proposed to replace the 1995 Nomenclature Committee for the definition and classification of cardiomyopathy. As such, these disorders that widely or predominantly affect the heart, called “primary”, from those that have myocardial involvement as a concomitant or unrelated manifestation, called “secondary”. Consequently, the new AHA classification aligns with and promotes the multidiagnostic approach required for the investigations, diagnosis and management of pediatric cardiomyopathies. It emphasizes the increasing importance of molecular genetic testing in the delineation of the cardiomyopathies.

- Acquired
- Dilated cardiomyopathy Restrictive (nonhypertrophied) cardiomyopathy

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- Primary Cardiomyopathies
- Genetic

- Cardiomyopathy

- Post Pathology

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and in Sprague-Dawley strains. GATA-4 cardiogenic activity reflects in activation of cardiac growth factors like BMP-4 in as well as other TFs required for heart formation. Thus, GATA-4 is a central player of self-renewing feedback loop of the normal and altered development.

As development proceeds, the primitive heart tube undergoes a series of complex events which include chamber specification, septation and subcavitation, to form the four-chambered heart. Defects in cardiogenesis and proper communication between the heart chambers account for the majority of the heart structural defects. The T-box family of transcription factors were originally isolated by virtue of their binding to A/T rich elements of promoters and are known to regulate heart development. Although the molecular mechanisms underlying cardiac morphogenesis remain largely enigmatic, the production of six gene expression domains is associated with the formation of the six gene expression domains (Hand, Mef2, Tbx5) which are associated with left and right heart field, respectively. Inactivation of the T-box gene in mice results in embryonic lethality at the loop stage, and the loss of the heart tube destined to form the right ventricle, is absent. Loss of Hand1 results in severe underdevelopment of the right ventricle due to placental defects. Thus, Hand1 and Hand2 are essential for normal cardiac development. Finally, one member of the growing family of T-box factors, Hand2, is essential for cardiac formation. Interestingly, Hand2 is a gene mutated in Holt-Oram syndrome (edited here).

In addition to heart tube defects, the myocardium contains myocardial defects and the left heart field (LHF), which are essential for normal left and right heart field specification. Cells from the LHF are incorporated into the growing heart tube during the loop stage at the ventral midline. Recently, it was shown that the myocardial defects of the right ventricle are derived from the AHF, further understanding the differences between the two ventricular compartments. Thus, myocardial cells appear to derive from two embryologically distinct mesodermal layers. This knowledge is important in understanding the molecular basis of disease.

II. Cardiac transcription: a multi-partner affair

The complex morphological and molecular changes that occur during heart formation are accompanied by a wide range of gene expression changes that are essential for dynamic and spatially complex patterns of gene expression.

Hand2 transcription: a multi-partner affair

In addition, in vivo and in vitro studies have shown that Hand2 expression is regulated by the T-box family of transcription factors, such as T-box 5 (Tbx5). Tbx5 is essential for atrial formation. Thus, loss of Tbx5 results in abnormal atrial development and atrial septal defects. Tbx5 expression is regulated by Hand2, which is essential for normal atrial development. Finally, one member of the growing family of T-box factors, Hand2, is essential for cardiac formation. Interestingly, Hand2 is a gene mutated in Holt-Oram syndrome (edited here).

The GATA family. The GATA family consists of a number of TFs that are essential for normal heart development. GATA-4, GATA-5, and GATA-6 are essential for normal heart development. GATA-4 is a central player of self-renewing feedback loop of the normal and altered development.

The GATA family: gene expression.

GATA-4 is expressed in the precardiac mesoderm as well as in non-cardiac precursors and is essential for normal heart development. GATA-4 cardiogenic activity reflects in its activation of cardiac growth factors like BMP-4 in as well as other TFs required for heart formation. Thus, GATA-4 is a central player of self-renewing feedback loop of the normal and altered development.

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syndrome, which is characterized by heart and limb malformations and the demonstration that a
dominant negative Tbx protein interferes with Xenopus heart development.


Combinatorial interactions. The spatio-temporal complexity of gene expression during heart
development would necessitate a very large number of regulators which need to be finely regulated
temporally. Even then, since few cardiac genes are coordinately regulated at any given
developmental stage, this would be virtually impossible to achieve if complex regulation were
only to be achieved through combinatorial interactions of multiple genes, as was first demonstrated
by the interaction between Xenopus Nkx2.5 and drosophila Nkx2.5 in vivo. This, and our own
studies of Tbx5 and Tbx6, have demonstrated that the same gene can lead to different malformations
and how the same malformations can be caused by different genes.


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I. Shunt lesions

A. Ostium secundum atrial septal defect
1. Size and direction of shunt determined by defect size and relative ventricular compliance
2. Large defects typically present with heart failure from large left-to-right shunt in infancy (1-3 mos)
3. Complete septum may begin to develop pulmonary vascular disease as early as 2 years of age resulting in cyanosis only in adulthood
4. Common in older adults
5. Many small to become large over time
6. Present little risk of heart failure or pulmonary vascular disease but are the most likely congenital heart defect to develop bacterial endocarditis
7. Spontaneous closure in early childhood is common but can probably occur throughout period of growth

B. Partial anomalous pulmonary venous connection
1. If isolated, usually asymptomatic and incidental finding with small left-to-right shunt
2. Frequently associated with sinus venous type atrial septal defect with clinical findings and physiology similar to ostium secundum atrial septal defect above
3. However, unlike ostium secundum ASD, sinus venous ASD requires surgical repair in order to redirect anomalous pulmonary venous return

C. Incomplete common atrioventricular canal
1. Also known as “double inlet atrial septal defect,” in which both AV valves have similar or identical orifices
2. Always has associated ventricular valve abnormalities – so-called “left predominant” or “right predominant”
3. Many develop left-sided atrioventricular valve regurgitation, which exaggerates the left-to-right shunt through the atrial septal defect
4. Abnormal atrioventricular valve substitutes the left ventricle into inflow and outflow portions (not present in the normal left ventricle); hence, left ventricular outflow tract at common AV valve is inherently small

D. Ventricular septal defect
1. Hypoplastic left heart syndrome
2. Heterotaxy syndrome with functional single ventricle – typically unbalanced common atrioventricular canal with hypoplasia or absence of one ventricle usually the left

IV. Systemic right ventricles (in a two-ventricle system)

A. Transposition of the great arteries
1. Morphologic right ventricle connects to both atria and systemic arteries, with the great arteries arising from the right heart
2. Frequent associated by other anomalies: septal defects, Ebstein anomaly of the tricuspid valve
3. Many develop left-sided atrioventricular valve regurgitation, which exaggerates the left-to-right shunt through the atrial septal defect
4. Systemic output is usually maintained at normal levels (by systemic pulmonary surgical shunt), increased systemic vascular resistance (e.g., with exercise, after feeding, fever, general anesthesia)
5. Repair involves patch closure of VSD so that aorta is baffled entirely to left ventricle, and right ventricular outflow tract is arterialized – muscle resection and/or patch enlargement
6. In some cases patch enlargement of pulmonary valve annulus is necessary, resulting in pulmonary regurgitation and potential in right ventricular dilation and failure in adulthood

B. D-Transposition of the great arteries
1. Morphologic right atrium connects to morphologic right ventricle, to aorta, left atrium to left ventricle to pulmonary artery
2. Separately systemic and pulmonary circulations; cyanosis is related to degree of mixing rather than amount of pulmonary blood flow (as in tetralogy)
3. When isolated virtually always repaired in infancy (infancy has been demonstrated to be safe and effective) since 1980s or early childhood (atrial inversion prior to 1980s)
4. About 1/5 have more complex disease: VSD with or without aortic or pulmonary outflow obstruction – surgery without repair is mandatory

III. Functional single ventricles

A. Only one substantial ventricle – must become the systemic ventricle
1. Generally morphologic left ventricle makes better systemic ventricle than morphologic right ventricle
2. Typically patients with single ventricle physiology can live into the 4th decade as they do not have excessive or inadequate pulmonary blood flow
3. To aortic outflow obstruction, must convert pulmonary valve to be systemic ventricular valve
4. Fontan operation uses principle that with one good ventricle and unobstructed pulmonary circulation (atrietes, arterioes, veins), blood flow directly from ventricle to pulmonary arteries (surgically anastomosed) to pulmonary arteries without an intervening atrium

B. Functional single left ventricles

IV. Pathophysiology of Adult Congenital Heart

A. Ostium secundum atrial septal defect
1. Morphologic right ventricle connects to both atria and systemic arteries, with the great arteries arising from the right heart
2. Frequent associated by other anomalies: septal defects, Ebstein anomaly of the tricuspid valve
3. Many develop left-sided atrioventricular valve regurgitation, which exaggerates the left-to-right shunt through the atrial septal defect
4. Systemic output is usually maintained at normal levels (by systemic pulmonary surgical shunt), increased systemic vascular resistance (e.g., with exercise, after feeding, fever, general anesthesia)
5. Repair involves patch closure of VSD so that aorta is baffled entirely to left ventricle, and right ventricular outflow tract is arterialized – muscle resection and/or patch enlargement
6. In some cases patch enlargement of pulmonary valve annulus is necessary, resulting in pulmonary regurgitation and potential in right ventricular dilation and failure in adulthood
Pediatric mechanical assist device

Mechanical circulatory support as a bridge to either recovery or transplantation has become an established therapy in pediatric cardiac surgery and is currently used in over 200 cases in the world. The most widely used systems include the Impella 2.5 (Abiomed) and the HeartMate II (Thoratec), which are the only devices approved by the US Food and Drug Administration for pediatric use. The Impella 2.5 system is a percutaneous ventricular assist device that can be inserted through the femoral artery and is suitable for a wide range of pediatric patients. The HeartMate II system is a continuous-flow left ventricular assist device that can be implanted surgically or percutaneously and is suitable for patients with severe heart failure of different etiologies, including cardiomyopathy, myocarditis, and congenital heart disease and is available in sizes to accommodate patients ranging from infants to adults. Several improvements in device design along with management of anticoagulation and clinical decision making have resulted in a significant increase in durability and function of the device in the past decade, with less than one year of use. Pediatric patients are typically supported for periods of 7–8 weeks with early withdrawal and mobilization within the hospital setting. However, some children have been supported for over one year and can be discharged from hospital while waiting for a surgical donor organ or the natural disease progression. Some children undergoing mechanical support for right heart failure who received a biventricular assist device, (Bivacor or HeartMate II) have demonstrated that such a group would otherwise likely face mortality rates in excess of 90%.

Antierteral valve assessment by 3D echocardiography

Normal antierteral valve function is complex and dependent on leaflet morphology, supporting apparatus, as well as annular dynamics which are directly influenced by valvular redundancy. Detection of any of these, either in disease or in individuals with congenital heart defects, can result in valve dysfunction. Although two-dimensional echocardiography provides useful information about antierteral valve morphology and function, it is not adequate to understand the most subtle annular alterations that result in valvular regurgitation. Three-dimensional echocardiography provides a more detailed understanding of valve structure and function and provides information that is particularly useful in the preoperative planning of antierteral repair as well as the evaluation of potential complications related to antierteral surgery. It is also preferable to identify the involved antierteral regurgitation causative reganal artery, intravalve maneuvers, and valve replacement in terms of optimality and feasibility. The exact morphology and function of the annulus in the presence of redundant leaflets and annulus is even more important in an adult, growing patient in whom valve replacement may require lifting, suture, or annuloplasty procedures with mixed outcomes or severe regurgitation. The ability to accurately assess the precise cause of valve regurgitation preoperatively and carefully plan surgical repair entails the entire time of the operating room likely increases the probability of achieving a successful valvular reconstruction.

Introduction

Pediatric heart tumors are comprised of non-neoplastic-hamartomatic lesions. These inclusions are found in various organ derivations, namely rhabdomyoma and histiocytoid cardiomyopathy (henceforth designated Pediatric Cellulare Hypertrophy). Cardiac tumors are the most common solid tumor in children and can be defined as tumors that arise from specialized cardiac cells and extend into the cardiac chambers, atrial, or venous outflows. Cardiac tumors are typically small and often benign, but may result in morbidity and mortality.

Cardiac fibroma

Cardiac fibroma is a benign neoplasm that may result in syncope, myocardial infarction, and sudden death. Fibromas are typically small and often are discovered incidentally. These are slow-growing neoplasms that can be associated with structural cardiac defects and often present as subaortic obstruction or hypoplastic left heart syndrome. They can be associated with structural cardiac defects.

Histiocytoid cardiomyopathy

Histiocytoid cardiomyopathy is a rare, arrhythmogenic disorder caused by multifocal infiltrations of cardiomyocytes with oncocytic features. The female:male ratio is 3:1. Approximately 5% of infants show symptoms in the first year of age, with the remaining patients presenting later in childhood. Histiocytoid cardiomyopathy is characterized by cardiac dysfunction and arrhythmia. The histologic findings are pathognomonic, with nests of foamy-appearing myocytes resembling macrophages. The clinical presentation includes failure to thrive, cardiomegaly, and signs of left-sided heart failure. The management of histiocytoid cardiomyopathy involves targeted therapy with cardiac drugs and may require heart transplantation.

Cardiac rhabdomyoma

Cardiac rhabdomyomas are well-differentiated nodules of striated cardiac myocytes with clear cytoplasm. In some tumors, remnants of eosinophilic cytoplasm extend from a central vacuole to the cell membranes giving rise to cells that resemble a "spindled" cell spike. The majority of cells show vacuolization with sparse myofilaments. There is a strong reaction with periodic acid-Schiff, reflecting the glycogen content of rhabdomyoblasts.

Inflammatory myofibroblastic tumor

Inflammatory myofibroblastic tumors (IMFTs) are proliferations of uncertain differentiation, which may arise from inflammatory, reactive opposing, or tumor-forming processes. They can be seen in various organ derivations, including the lung, skin, gastrointestinal tract, and heart. IMFTs are most commonly seen in the lung and have a lower incidence in other organs. They are characterized by a proliferation of spindle cells with inflammatory cells, including lymphocytes, histiocytes, and plasma cells. The molecular basis of IMFTs is not fully understood, but recent studies have identified potential drivers of tumor growth and differentiation.

References:


