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Cardiomyopathy in Childhood: Histopathological and Genetic Features

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Abstract: Primary heart muscle disease is a cause of significant morbidity and mortality in childhood. The current WHO classification of cardiomyopathy is based on a combination of clinical features, aetiology and pathology. It is in need of revision because of accumulating genetic information concerning the pathogenesis of cardiomyopathy. It is becoming increasingly obvious that most of the primary heart muscle diseases have a genetic origin. Mutations in the genes encoding the sarcomeric proteins are responsible for hypertrophic cardiomyopathy and some forms of dilated and restrictive cardiomyopathy. Other forms of dilated cardiomyopathy are caused by mutations in genes encoding cytoskeletal proteins. Arrhythmogenic right ventricular cardiomyopathy is now known to be caused by mutations in genes involved in cell cohesion. Gene mutations affecting mitochondrial function can cause cardiomyopathy, either as part of a systemic disorder, or confined to the heart. Gene mutations causing rarer forms of cardiomyopathy associated with abnormalities of cardiac rhythm, such as histiocytoid cardiomyopathy and ventricular non-compaction have also been identified. This review details the pathology of cardiomyopathy and the increasing number of genes involved in its aetiology and pathogenesis. Genetic analysis not only permits diagnosis in many cases but also in an increasing number of the cardiomyopathies provides prognostic information.

Keywords: Cardiomyopathy, heart, dilated, hypertrophic, restrictive, non-compaction,myocardium, arrhythomogenic, mitochondrial, metabolic.

INTRODUCTION

Cardiomyopathy is defined as primary heart muscle disease other than ischaemic. It excludes disease secondary to congenital malformations.

Cardiomyopathy in children is a cause of significant morbidity and mortality, is a cause of sudden unexpected death in this age range and is the commonest indication for paediatric heart transplant. Heart muscle disease associated heart failure in children in the United Kingdom and Ireland has an incidence of 0.87/100,000 of the population less than 16 years of age, with a median age of presentation of 1 year [1]. Although showing a similar spectrum of abnormalities to that found in adults, cardiomyopathy in children presents its own peculiarities; some forms of cardiomyopathy are found exclusively in children, while others are scarcely seen at all.

Clinically, cardiomyopathies are classified into three basic types depending on their pathophysiology:

1. Dilated cardiomyopathy in which the left, or sometimes both, ventricles are dilated and show decreased systolic function as measured by decreased shortening fraction (normal greater than 30%) or decreased ejection fraction (normal greater than 55%) on echocardiography.
2. Hypertrophic cardiomyopathy in which there is abnormal thickening of (principally) the left ventricular myocardium. There may be associated left ventricular outflow tract obstruction. There is disturbed systolic and diastolic myocardial function.
3. Restrictive cardiomyopathy in which there is decreased diastolic ventricular filling often with atrial enlargement. There is abnormal relaxation of the ventricular myocardium with decreased ventricular compliance and consequent restriction of ventricular filling. This causes raised end diastolic pressure with secondary increase in atrial pressure and consequent atrial dilatation.

In addition, cardiomyopathies may be classified according to their specific pathological features, or a combination of pathological and clinical features, or according to their aetiology. The World Health Organisation (WHO) classification attempts a mixture of all [2]. A simplified version of the WHO Classification of cardiomyopathy is given below (Table **1**).

From the point of view of the pathologist, the morphology of the main types of cardiomyopathy tends to be distinctive, but there are areas of overlap; some forms of hypertrophic cardiomyopathy may, late in their course, develop a dilated phenotype and most forms of dilated and restrictive cardiomyopathy will show increased heart weight and histological evidence of myofibre hypertrophy. The aetiology of some cardiomyopathies is known, for example cardiomyopathy secondary to metabolic disorder or in

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Table 1. Classification of Cardiomyopathies

Dilated cardiomyopathy		
Hyertrophic cardiomyopathy		
Restrictive cardiomyopathy		
Arrhythmogenic right ventricular cardiomyopathy		
Unclassified	Non-compacted myocardium	
	Fibroelastosis	
	Mitochondrial	
Specific cardiomyopathies		
Ischaemic cardiomyopathy		
Valvular cardiomyopathy		
Hypertensive cardiomyopathy		
Inflammatory cardiomyopathy		
Metabolic cardiomyopathy		
	Includes:	**Endocrine** e.g. thyrotoxicosis, hypothyroidism, adrenal cortical insufficiency, phaeochromocytoma, acromegaly and diabetes mellitus
		Familial storage disease and infiltrations e.g. haemochromatosis, glycogen storage disease, Hurler's disease, Refsum's syndrome, Niemann-Pick disease, Hand-Schueller-Christian disease Fabry-Anderson disease and Morquio-Ullrich disease.
		Deficiency, e.g., disturbances of potassium metabolism, magnesium deficiency, and nutritional disorders such as kwashiorkor, anaemia, beriberi and selenium deficiency
		Amyloid, e.g. primary, secondary, familial and hereditary cardiac amyloidosis, familial Mediterranean fever, and senile amyloidosis
General system disease		
	Includes:	**connective tissue disorders**, e.g., systemic lupus erythematosus, polyarteritis nodosa, rheumatoid arthritis, scleroderma and dermatomyositis.
		Infiltrations, e.g. sarcoidosis, leukaemia
Muscular dystrophies,		including Duchenne, Becker type and myotonic dystrophy.
Neuromuscular disorders		including Friedreich's ataxia, Noonan syndrome and
		Lentiginosis
Sensitivity and toxic reactions		
		Includes reactions to alcohol, catecholamines, anthracyclinres, irradiation
Peripartal cardiomyopathy		

World Heath Organization/International Society and Federation of Cardiology Task Force on the Definition and Classification of Cardiomyopathies 1995.

association with muscular dystrophy or other skeletal muscle disease. Many forms of cardiomyopathy have a genetic or familial basis, but some forms of heart muscle disease are undoubtedly acquired as a result of exposure of susceptible individuals to infectious agents or toxins. There may be no factor to which the heart muscle disease is as yet attributable - so-called primary or idiopathic cardiomyopathy. The WHO classification is increasingly in need of revision as the genetics and pathology of the underlying diseases are teased out. The American Heart Association (AHA) has offered such a classification. The AHA classification [3] is given below in Table **2**.

HYPERTROPHIC CARDIOMYOPATHY

This refers to disease of the heart muscle where the primary pathology is hypertrophy of the ventricular myocardium in the absence of a predisposing factor such as systemic hypertension or valvar heart disease. Often displaying asymmetrical involvement of the interventricular septum, this form of cardiomyopathy is sometimes associated with obstruction of the left ventricular outflow [4].

Grossly, the heart is enlarged and the heart weight increased. There is hypertrophy of the ventricular myocardium. This may be confined to the septum but usually involves the entire left ventricle (Fig. **1**). Whorling of the hypertrophied myocardium may be evident macroscopically, as may fibrosis. An impact lesion of the left ventricular outflow endocardium, representing an area of white fibrous thickening of the septal endocardium corresponding to the shape of the anterior mitral valve leaflet and caused by abnormal impact of this leaflet on the hypertrophied septum, is commonly seen in adults (Fig. **2**); it is distinctly unusual in children. The histological hallmark of hypertrophic cardiomyopathy is myocyte disarray. Disarray

Table 2. American Heart Association Classification of Cardiomyopathies [3]

Primary Cardiomyopathy
Genetic
Hypertrophic cardiomyopathy
Glycogen storage • PRKAG2 • Danon
Arrhythmogenic right ventricular cardiomyopathy
Left ventricular noncompaction
Conduction system disease
Mitochondrial myopathies
Ion channelopathies • Long QT syndrome • Brugada syndrome • Short QT syndrome • Catecholaminergic polymorphic ventricular tachycardia • Asian SUNDS
Mixed
Dilated cardiomyopathy
Restrictive cardiomyopathy
Acquired
Inflammatory (myocarditis)
Stress provoked (tako-tsubo)
Peripartum
Tachycardia induced
Infants of insulin-dependent diabetic mothers
Secondary Cardiomyopathy
Infiltrative • Amyloidosis • Gaucher disease • Hurler's disease • Hunter's disease
Storage • Haemochromatosis • Fabry's disease • Glycogen storage disease (type II, Pompe) • Niemann-Pick disease
Toxicity • Drugs, heavy metals, chemical agents
Endomyocardial • Endomyocardial fibrosis • Hypereosinophilic syndrome (Loeffler's endocarditis)
Inflammatory (granulomatous) • Sarcoidosis

(Table 2) contd…..

Endocrine • Diabetes mellitus • Hyperthyroidism • Hypothyroidism • Hyperparathyroidism • Phaeochromocytoma • Acromegaly
Cardiofacial • Noonan's syndrome • Lentiginosis
Neuromuscular\Neurological • Friedreich's ataxia • Duchenne-Becker muscular dystrophy • Emily-Dreifuss muscular dystrophy • Myotonic dystrophy • Neurofibromatosis • Tuberous sclerosis
Nutritional deficiencies • Beri-beri, pellagra, scurvy, selenium, carnitine, kwashiorkor
Autoimmune\collagen • Systemic lupus erythematosus • Dermatomyositis • Rheumatoid arthritis • Scleroderma • Polyarteritis nodosa
Electrolyte imbalance
Consequence of cancer therapy • Anthtracyclines • Cyclophosphamide • Radiation

consists of disorganised hypertrophied myocytes that have a splayed appearance. They lack the normal fasicular arrangement and run in various directions, often overlap and may have a whorled appearance (Fig. **3**). Fibrosis is a usual accompaniment (Fig. **4**). There are frequently dysplastic changes in the intramyocardial arteries (Fig. **5**). The disease was originally described in adolescents and was associated with a high frequency of sudden death. In paediatric practice it is an uncommon cause of death. It can occur in neonates and even *in utero*.

A family history of hypertrophic cardiomyopathy is present in about 60% of cases of childhood cardiomyopathy and 53% show sarcomeric protein gene mutations [5]. Most cases of idiopathic hypertrophic cardiomyopathy are now known to be caused by mutations in the genes encoding structural proteins of the contraction apparatus of the cardiac myofibre [6]. To date, mutations in eleven genes coding for cardiac sarcomeric proteins have been found to cause hypertrophic cardiomyopathy [7]. They are listed in Table **3** [8-16].

Among these genes are the genes encoding α and β myosin heavy chains, actin, tropomyosin and cardiac troponins T, C and I. It is also recognised that particular mutations may correlate with a particular phenotype and correspond with, for example, the degree of myofibre hypertrophy or the magnitude of the risk of sudden death [17]. Recently missense mutations causing hypertrophic cardiomyopathy have been described in the gene CSRP3 that encodes for muscle LIM protein that is a component of the cytosol rather than the sarcomere [18]. Affected patients also have mild skeletal muscle disease.

Although myofibre disarray is the histological hallmark of hypertrophic cardiomyopathy, it can occur in other settings. Myofibre disarray occurs in the normal heart at the

junction of the free wall of the ventricles with the interventricular septum. The area involved is small, and disarray should not be seen in the normal heart in the interventricular septum or lateral ventricular walls. Myofibre disarray is present in the hypertrophy accompanying many forms of congenital heart disease, most notably hypoplastic left heart where it is described in up to 80% of cases. Myofibre disarray may also be seen in restrictive cardiomyopathy. The muscle fibre hypertrophy with disarray in hypertrophic cardiomyopathy affects not just the ventricles but can also be found in the atrial myocardium. The identification of hypertrophic cardiomyopathy has important implications for other siblings and family members, and, where, possible genetic material should be obtained at autopsy to permit gene screening, where appropriate.

Fig. (1). Heart from a child with hypertrophic cardiomyopathy. The heart has been cut in a simulated short axis echocardiographic view to demonstrate the concentric hypertrophy of the left ventricular myocardium.

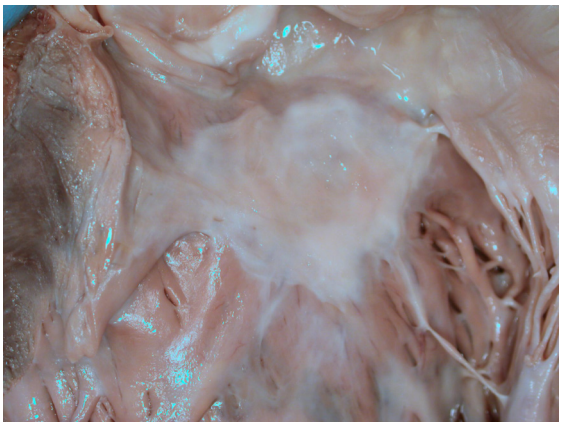

Fig. (2). Heart from a case of hypertrophic cardiomyopathy. The left ventricular outflow tract has been opened to display the septal aspect. There is a plaque of white endocardial thickening corresponding to the shape of the anterior leaflet of the mitral valve. Note the sharp borders of the plaque.

Glycogen Cardiomyopathy

In clinical practice, hypertrophic cardiomyopathy is a phenotype and diseases other than those caused by mutations in sarcomeric protein genes can present with a hypertrophic phenotype. One such disease is the autosomal recessive Pompe disease (glycogen storage disease type II) caused by mutations in the gene for the lysosomal enzyme acid α-glucosidase (acid maltase) on 17q25.2-q25.3. Depending on the severity of the enzyme deficiency, infantile and late-onset variants are described. Severe cardiac involvement occurs predominantly in the infantile form but may be present in the late-onset form. Hypertrophic cardiomyopathy in the infantile form may show subaortic stenosis and endocardial fibroelastosis and is usually fatal in the first year of life. Very rarely glycogen storage disease type III (debrancher enzyme deficiency) may present in infancy with myocardial hypertrophy [19]. The responsible gene is located on chromosome 1p21. In contradistinction to the hypertrophic cardiomyopathy caused by mutations in the sarcomeric protein genes, the cardiomyopathy associated with glycogen storage tends to be associated with abnormal electrophysiology. Histologically, there is vacuolar change in the myocytes with accumulation of glycogen (Figs. **6**, **7**). Myofibre disarray and myocardial fibrosis are not found.

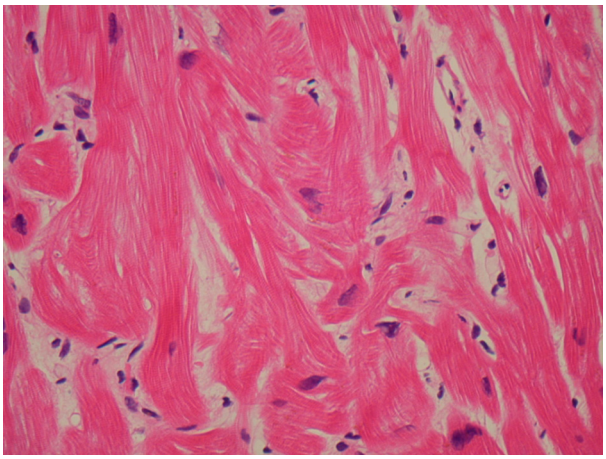

Fig. (3). Hypertrophic cardiomyopathy. A section of the ventricular myocardium displays the broad myocytes that are irregularly disposed - the so-called myocyte disarray. There is a slight increase in interstitial fibrous tissue. (H&E).

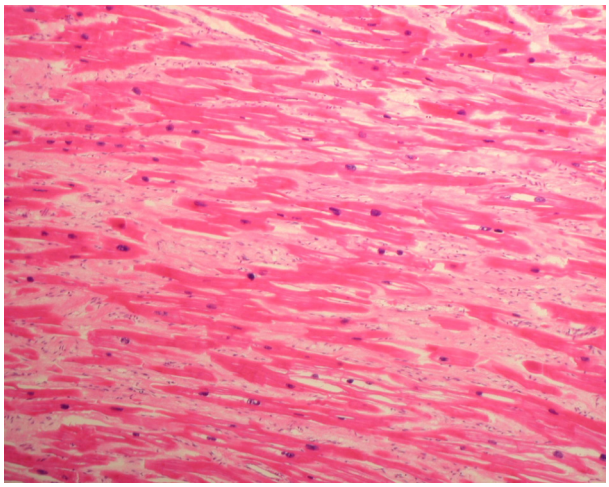

Fig. (4). Hypertrophic cardiomyopathy. A section of the ventricular myocardium shows the enlarged hyperchromatic nuclei of myocyte hypertrophy and also shows myocyte loss with fibrous tissue replacement. (H&E).

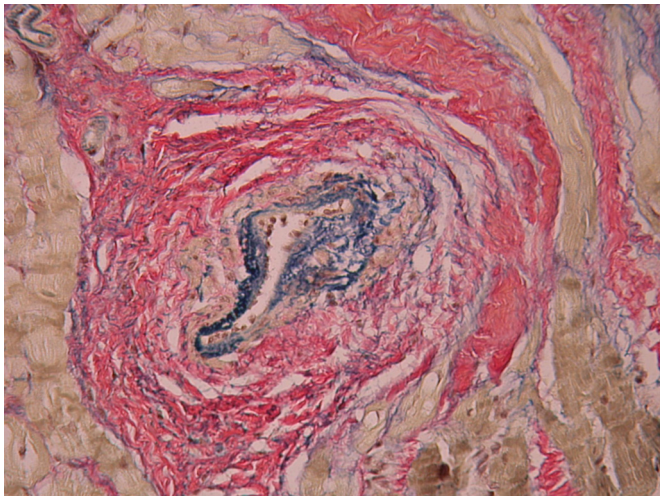

Fig. (5). Hypertrophic cardiomyopathy. A section from the ventricular myocardium shows a small intramyocardial artery with a thick collagenous adventitia an irregularly thinned muscular media and irregular and eccentric proliferation of elastic tissue in media and intima - so-called dysplasia. (EVG).

Table 3. Sarcomeric Protein Genes Mutated in Familial Hypertrophic Cardiomyopathy

Gene	Location	References
β-myosin heavy chain	14q12	[8]
α-myosin heavy chain	14q12	[9]
Cardiac actin	15q14	[10]
α -tropomyosin	15q22	[11]
Cardiac troponin C	3p21	[12]
Cardiac troponin I	19p13	[13]
Cardiac troponin T	1q32	[11]
Cardiac myosin binding protein C	11p11	[14]
Regulatory myosin light chain	12q23	[15]
Essential myosin light chain	3p21	[15]
Titin	2q31	[16]

Danon disease is a systemic disorder caused by mutations in the lysosomal-associated membrane protein 2 (LAMP2) gene on Xp24, and can give rise to a hypertrophic cardiomyopathy with glycogen accumulation. Usually there are other systemic manifestations but these may be sub clinical and hypertrophic cardiomyopathy may be the presenting feature. The disorder is described in (usually male) children as young as 8 years and carries a poor prognosis with progressive heart failure and death [20]. Clinically there is concentric left ventricular hypertrophy that may be severe. Right ventricular involvement is common. Ventricular pre-excitation is usual. Histologically there is prominent myocardial hypertrophy with vacuolation of myocytes. The vacuoles contain glycogen. Ultrastructurally the glycogen is membrane bound.

A similar histological appearance may be seen with mutations the PRKAG2 gene (on 7q36.1) encoding the γ subunit of AMP-activated protein kinase [21]. This produces a hypertrophic phenotype with ventricular pre-excitation and progressive conduction system dysfunction; there is no myofibre disarray or fibrosis, but there is myofibre vacuolation and glycogen accumulation. The glycogen accumulation, in contrast to Pompe and Danon disease is not confined to lysosomes but is present throughout the myocyte [20]. By contrast with the other glycogen storage cardiomyopathies, there are no extra-cardiac manifestations. The disorder is confined to adults.

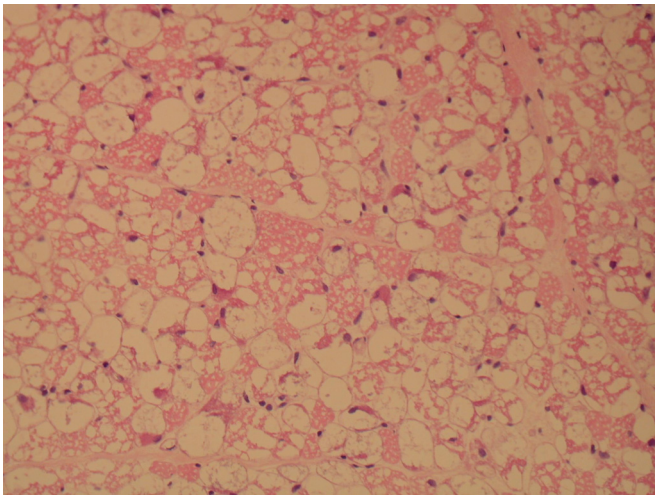

Fig. (6). Pompe disease. A section from the myocardium shows greatly distended myocytes with large empty vacuoles. The less ballooned myocytes also contain smaller vacuoles. (H&E).

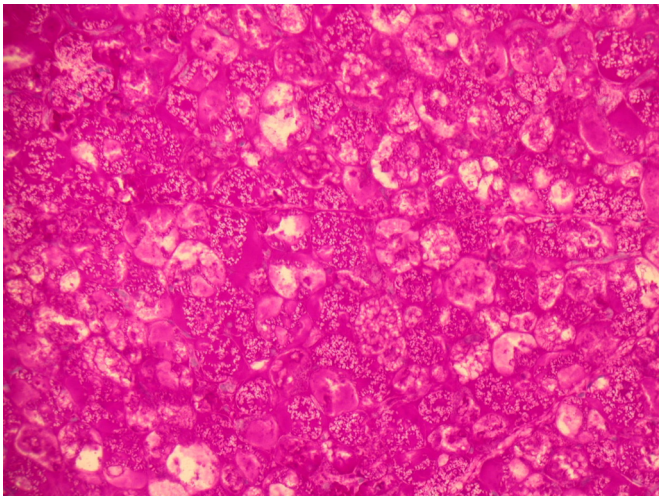

Fig. (7). Pompe disease. A frozen section from the myocardium stained with PAS shows very heavy staining indicating that the vacuolated cells contain large amounts of glycogen. (PAS).

Fabry disease is caused by deficiency of alpha-galactosidase A. Up to 60% of males with classic Fabry disease have cardiac abnormalities, including left ventricular hypertrophy, valvular dysfunction and conduction abnormalities [22].

Other Cardiomyopathies with a Hypertrophic Phenotype

Friedreich's ataxia is a rare autosomal recessive disorder characterised by spinocereballar degeneration. It is caused by an unstable GAA trinucleotide repeat expansion (> 120

repeats) in the first intron of both alleles of the frataxin gene on chromosome 9q13. Most cases that have cardiac involvement demonstrate concentric left ventricular hypertrophy, but dilated cardiomyopathy and electrical disturbance also occur [23]. Pathologically there is myocyte hypertrophy and interstitial fibrosis and deposition of calcium and iron in myocytes is described. The condition tends to remain stable during childhood. The length of the trinucleotide repeats appears not to correlate with the severity of the cardiac disease [24].

Noonan's syndrome is an autosomal dominant disease characterised by short stature, facial dysmorphism and cardiac defects. The most common cardiac defect is pulmonary stenosis occurring in about 50% of cases. Other cardiac defects include polyvalvular dysplasia [25]. About 10% of patients have a hypertrophic cardiomyopathy [26]. Germline mutations in the RAS mitogen activated protein kinase (MAPK) pathway are involved in the pathogenesis of Noonan Syndrome. About 45% of cases of Noonan's syndrome are due to missense mutations in the PTPN11 gene on 12q24.1 [27]. That gene encodes SHP-2, a protein tyrosine kinase that has multiple functions in signal transduction including signalling *via* the RAS-mitogen activated protein kinase (MAPK) pathway. Noonan syndrome-associated PTPN11 mutations are gain-of-function mutations that disrupt the activation-inactivation mechanism of SHP-2. Mutations in the genes encoding for other proteins in the RAS/MAPK pathway have been identified in those cases of Noonan syndrome that do not have PTPN11 mutations, namely SOS1, RAF1, MEK1 and KRAS. Hypertrophic cardiomyopathy is more frequently observed in patients with RAF1 mutations [28].

Infants of diabetic mothers may develop myocardial hypertrophy identical to hypertrophic cardiomyopathy in the neonatal period [29]; this cardiomyopathy is usually transient and resolves spontaneously. Hypertrophic cardiomyopathy is also described in infants who have received steroids for pulmonary immaturity or chronic lung disease [30]; again, this cardiomyopathy tends to be transitory but shows identical echocardiographic appearances and haemodynamics to idiopathic hypertrophic cardiomyopathy.

Mitochondrial cardiomyopathies in infancy frequently display a hypertrophic phenotype (see below).

DILATED CARDIOMYOPATHY

The term denotes the phenotype of bi-ventricular dilatation with atrial dilatation and reduced myocardial contractility. There may be associated conduction system disturbance and in some cases there are extra-cardiac manifestations, most frequently skeletal myopathy, but also skin abnormalities, haematological disorders or hearing loss.

Pathologically there is histological evidence of myocardial hypertrophy and fibrosis [31]. The heart is enlarged, sometimes markedly so, is dilated, has a globular shape and the weight is increased. The muscular trabeculae, including the papillary muscles of the atrioventricular valves, appear stretched and thin. There is associated endocardial fibroelastosis of the left ventricle (Fig. **8**). The affected endocardium is opaque and white and may be up to several millimetres thick. The thickening affects the papillary muscles and extends into the intertrabecular recesses. The right ventricle usually does not show significant endocardial fibrosis. There may be fibrosis of the myocardium - particularly the papillary muscles of the mitral valve. The atria may show endocardial thickening. Histologically, there is myocyte nuclear enlargement and hyperchromasia; the myofibres are stretched and wavy (Fig. **9**). Inflammatory cell infiltration is not usually a prominent feature but scattered lymphocytes may be present. The presence of more than a few inflammatory cells suggests myocarditis and appropriate samples need to be assessed for the presence of viruses. Mast cell numbers (Fig. **10**) are increased in the interstitium [32] The epicardium may show a chronic inflammatory cell infiltrate or fibrosis. Secondary degenerative changes are often present in the valves in the form of thickening of the leaflets. There is usually a considerable degree of interstitial myocardial fibrosis (Fig. **11**). The intramyocardial vessels are usually normal, but in areas of dense scarring they may show intimal fibroelastic thickening. The endocardial fibroelastosis consists of dense laminar fibroelastic tissue that usually does not show increased vascularity or inflammatory cell infiltration. There may be smooth muscle hyperplasia in the endocardium (Fig. **12**).

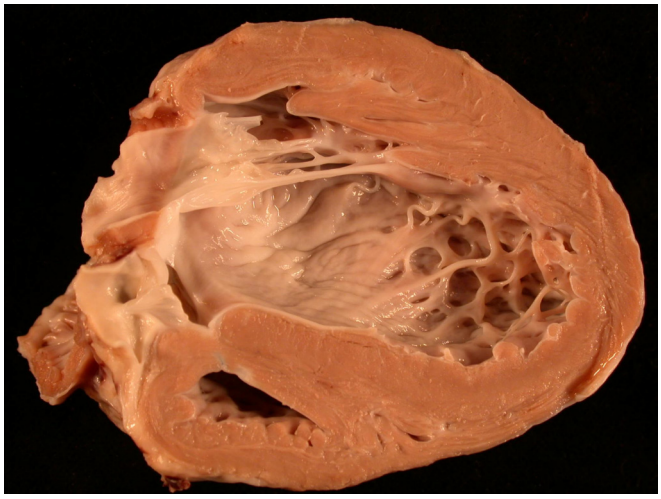

Fig. (8). Explanted heart from a child with idiopathic dilated cardiomyopathy. The heart has been cut in a simulated parasternal long-axis view. The myocardial hypertrophy and left ventricular dilatation are evident. The most striking feature is the opaque white thickening of the left ventricular endocardium.

The dilated form of cardiomyopathy represents a phenotype and it has many causes [33]. About one-third of patients with dilated cardiomyopathy have an affected first-degree relative [34]. The most common mode of transmission of the familial forms is autosomal dominant, but recessive, X-linked and mitochondrial inheritance is also reported. Gene mutations that have been associated with dilated cardiomyopathy are listed in Table **4** [35-51]. There are over twenty genes known to be mutated and they encode for proteins that have a wide range of unrelated functions.

Mutations may occur in genes encoding sarcomeric proteins such as troponins T, C and I, actin, or β-myosin heavy chain [52]. The mutations occur in regions affecting functionally different domains of the molecules from those occurring in hypertrophic cardiomyopathy.

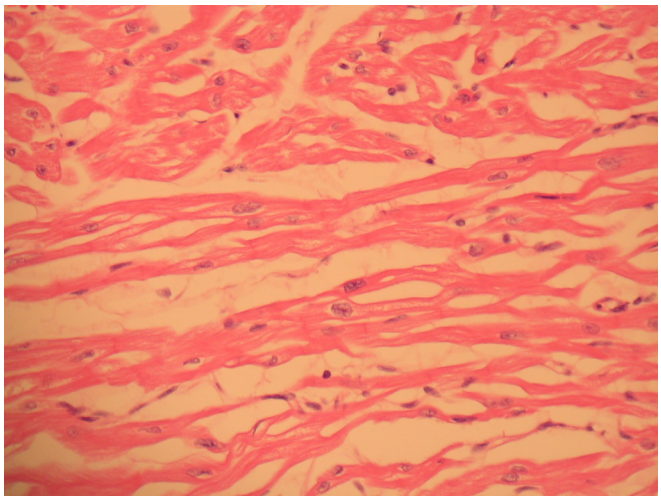

Fig. (9). Idiopathic dilated cardiomyopathy. A section from the left ventricular myocardium to show the stretched and wavy nature of the fibres from the dilated chamber wall. (H&E).

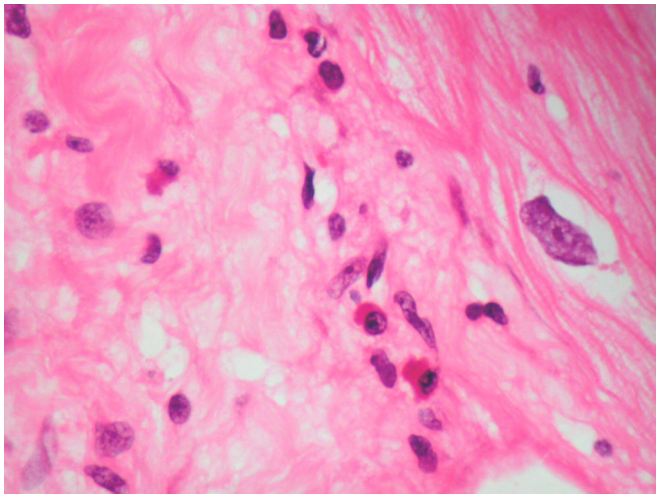

Fig. (10). Idiopathic dilated cardiomyopathy. A high-power view of a fibrotic area of myocardium. At least three mast cells are present in the fibrous tissue. (H&E).

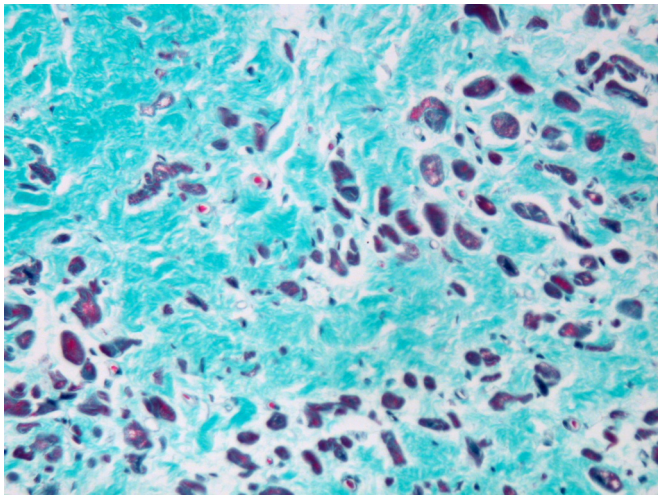

Fig. (11). Idiopathic dilated cardiomyopathy. A section of ventricular myocardium show extensive replacement fibrosis of the myocardium with individual shrunken myocytes surrounded by fibrous tissue (Masson trichrome).

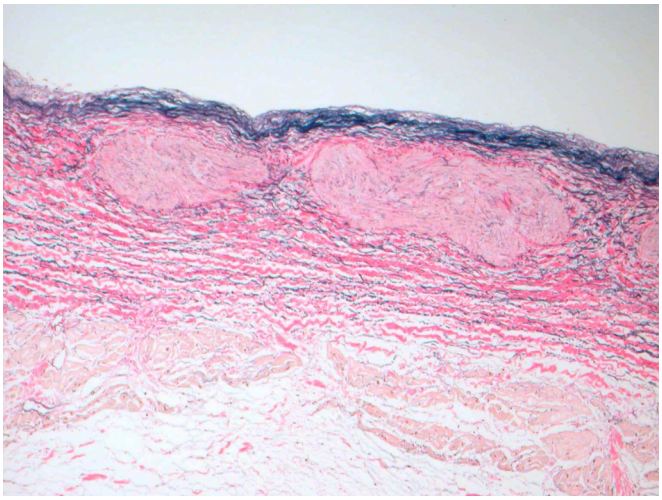

Fig. (12). Idiopathic dilated cardiomyopathy. A section from the left ventricular endocardial surface to demonstrate the fibroelastic thickening of the endocardium. In addition there are rounded bundles of smooth muscle fibres, visible as paler areas within the thickened endocardium (EVG).

Table 4. Proteins whose Genes are Mutated in Dilated Cardiomyopathy

Gene	Location	References
β-myosin heavy chain	14q12	[52]
Cardiac actin	15q14	[38]
Cardiac troponin T	1q32	[35]
Cardiac troponin C	3p21	[36]
Cardiac troponin I	19p13	[37]
Cardiac myosin binding protein C	11p11	[39]
Alpha-tropomyosin	15q22	[40]
Desmin	2q35	[53]
Delta sarcoglycan	5q33	[54]
Dystrophin	Xp21	[55]
Lamin	1q1	[56]
Titin	2q31	[41]
Titin-cap (telethonin)	17q12	[42]
Phospholamban	6q22	[43]
Vinculin (metavinculin)	10q22	[44]
Cardiac muscle LIM protein	11p15	[45]
Alpha actinin-2	1q42	[45]
EYA4	6q223	[46]
Cypher/ZASP	10q22	[47]
Cardiotrophin 1	16p11	[48]
Tafazzin	Xq28	[49]
Cardiac ankyrin repeat protein (CARP)	10q23	[50]
Desmoplakin	6q23	[51]

Mutations may also occur in the myocyte cytoskeleton that connects the sarcomere to the sarcolemma. Such genes include those coding for δ-sarcoglycan [53], desmin [54], dystrophin [55], lamin [56], vinculin [44] telethonin [42] cypher/ZASP [47], cardiac LIM protein [45] and desmoplakin [51]. Such mutations compromise the transmission of contractile force from the sarcomere to the extracellular matrix or impair the normal response of the sarcomere to stretching. Viral myocarditis may progress to dilated cardiomyopathy and some forms of dilated cardiomyopathy yield virus on culture or polymerise chain reaction (PCR). It has been shown that enterovirus proteases cleave dystrophin *in vitro* [57]. Mutations are described also in genes regulating transcription such as EYA4 [46]. Mutations in the phospholamban gene are thought to cause dilated cardiomyopathy by inhibition of calcium uptake in the sarcoplasmic reticulum [43].

Infants of exclusively breast fed mothers may suffer vitamin D deficiency with development of rickets and may present with dilated cardiomyopathy, which, rarely, may be fatal. The condition resolves on administration of vitamin D [58]. Finally, dilated cardiomyopathy may be a feature of the mitochondrial cytopathies [59]. Skeletal myopathy is a feature of mutations in the genes for dystrophin, desmin, lamin, delta-sarcoglycan, telethonin, titin. Tafazzin gene mutations cause Barth syndrome with associated cyclical neutropenia. Mutations in the desmoplakin gene may also cause keratoderma and woolly hair.

RESTRICTIVE CARDIOMYOPATHY

This form of cardiomyopathy has a physiology different from the other two main forms of cardiomyopathy [60]. It accounts for 2-5% of cardiomyopathies in childhood [61]. The defining characteristics are a stiff ventricular myocardium with diastolic dysfunction. This leads to high diastolic pressures and dilatation of the atria. Clinically, restrictive cardiomyopathy mimics constrictive pericarditis [62]. The high left-sided diastolic pressure leads to congestive vasculopathy in the lungs and the development of pulmonary hypertension. Up to one-third of cases show mutations in cardiac sarcomeric protein genes, most notably Troponin-I, Troponin-T and alpha-cardiac-actin [63].

Macroscopically, the atria, particularly the right atrium, are dilated (Fig. **13**). The heart shows thickened ventricular myocardium. Histologically, the myofibres are hypertrophied; there may be myofibre disarray, identical to that in hypertrophic cardiomyopathy, even to the extent of associated small vessel dysplasia. There may be myocyte vacuolation or myocyte inclusions. There is prominent interstitial fibrosis, sometimes with a pericellular distribution. Cardiac involvement by amyloid may give a restrictive cardiomyopathy, but this is very rare in children. Similarly, myofibrillary myopathy - a form of myopathy that shows characteristic myocyte inclusions in association with skeletal myopathy and restrictive cardiomyopathy is rare in children [64]. Glycogen storage disorders and the mucopolysaccharidoses may present as restrictive cardiomyopathy as may primary endocardial fibroelastosis. Secondary endocardial fibroelastosis generally does not.

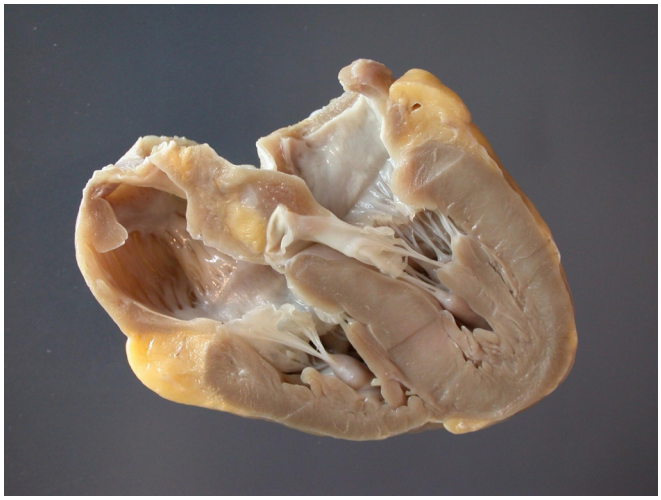

Fig. (13). Explanted heart from a case of restrictive cardiomyopathy. The heart has been sectioned in a simulated echocardiographic four-chamber view. It demonstrates the relatively normal dimensions of the ventricular cavities but the marked atrial dilatation. This is most evident for the right atrium.

EOSINOPHILIC ENDOMYOCARDIAL DISEASE.

Endomyocardial disease with restrictive physiology may develop in patients with hypereosinophilia, whether idiopathic or secondary to leukaemia\lymphoma, vasculitis syndromes or infections [65]. Three stages are described: a necrotic phase characterised by acute eosinophilic myocarditis with diffuse infiltration of eosinophils in endocardium and myocardium with variable necrosis. There is intramural arteritis in some cases. The second phase is a thrombotic phase associated with mural thrombosis along the ventricular inflow tracts. The process begins at the ventricular apex but extends upwards to involve the papillary muscles. Eosinophils are prominent in the thrombus (Fig. **14**). Organisation leads to endocardial thickening. The final phase is the fibrotic phase identical to tropical endomyocardial fibrosis and characterised by thick endocardial fibrous plaques with distinct rolled borders. It is frequently accompanied by atrioventricular valvar regurgitation. There is eventually obliteration of the ventricular cavity. Atrial dilatation is typical, caused by restrictive physiology and atrioventricular valve regurgitation.

MITOCHONDRIAL CARDIOMYOPATHIES

These are disorders of the heart presenting as cardiomyopathy in which the basic defect is mutation of genes of mitochondrial oxidative phosphorylation. These cardiomyopathies are often associated with neurological disorders such as MELAS (myopathy, encephalopathy, lactic acidosis, stroke) [66], or Kearns-Sayre syndrome (ataxia, ophthalmoplegia, pigmentary retinopathy, heart block). The cardiac mitochondria are more numerous than usual and show abnormalities of size or structure with abnormal internal structure [67, 68].

Clinically, infants with mitochondrial cardiomyopathy show failure to thrive, lactic acidosis and cardiomegaly. Hypertrophic cardiomyopathy is commoner in infants than dilated cardiomyopathy (Fig. **15**). There may be associated

conduction abnormalities. Histologically, the myocytes may appear swollen, with perinuclear clearing and replacement of cross striations by fine eosinophilic granules representing increased numbers of mitochondria (Fig. **16**). Staining of frozen sections of myocardium may show reduction in oxidative enzymes and electron microscopy may show abnormal mitochondria [69].

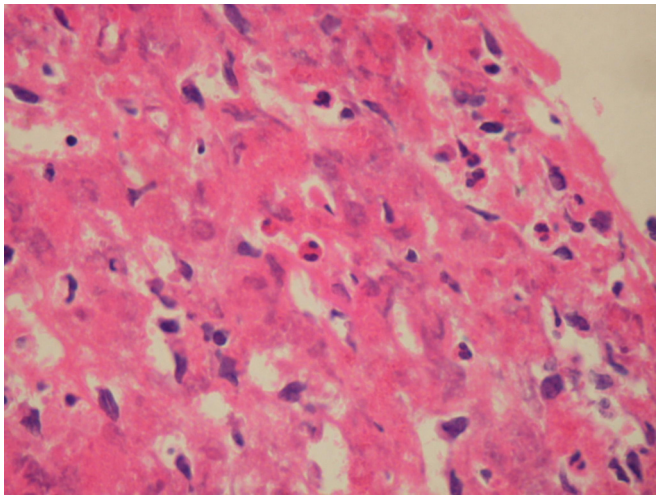

Fig. (14). Eosinophilic endomyocardial disease. Biopsy from the left ventricular endocardium shows organising thrombus with numerous eosinophils (H&E).

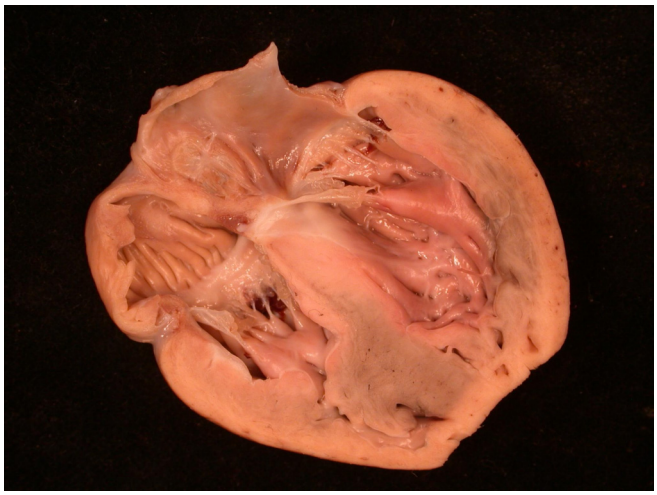

Fig. (15). Mitochondrial cardiomyopathy. Post-mortem heart from an infant who died suddenly and was found to have an enlarged heart at autopsy. There is thickening of the ventricular walls, most marked toward the apex (which had been removed for biochemical analysis). Biochemical investigation showed markedly decrease activity of mitochondrial complex 1.

Mitochondrial cardiomyopathies are caused by defects in specific enzymes of the mitochondrial oxidative phosphorylation system that may affect any of complexes I, II, III, IV and V or affect multiple complexes. Mitochondrial DNA, unlike nuclear DNA, is only maternally inherited, does not show recombination and has a high rate of spontaneous mutation. Mitochondrial DNA encodes for some - but not all - of the proteins of the oxidative phosphorylation complexes. The reminder is encoded in the nuclear DNA. These latter genes are inherited in the usual Mendelian fashion. The majority of the mutations causing mitochondrial cardiomyopathy are mutations in the mitochondrial DNA and are thus maternally inherited. However, mutations are described in nuclear genes involved in mitochondrial DNA replication [70]. Disease may also be caused by mitochondrial DNA depletion in cardiac muscle [71]. The depletion may be confined to the heart.

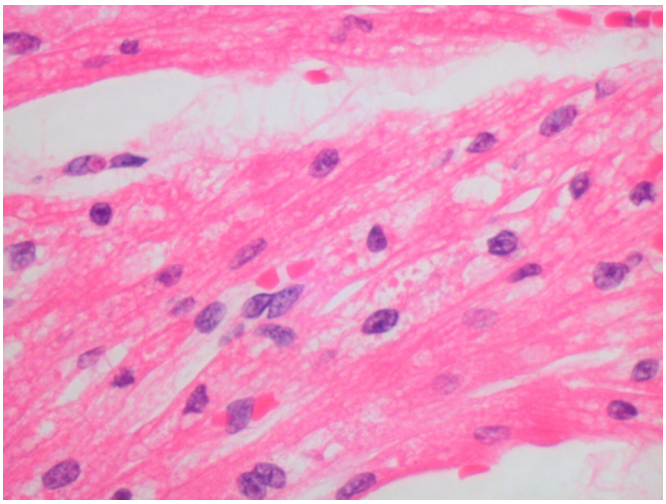

Fig. (16). Mitochondrial cardiomyopathy. A section from the same heart demonstrates vacuolated myocytes with enlarged mitochondria, evident as eosinophilic rounded inclusions in the cytoplasm about one-quarter the size of erythrocytes (H&E).

ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY

A rare inherited disease characterized by right-ventricular dysfunction and ventricular arrhythmias. It may cause sudden death precipitated by physical exercise. Pathologically it is characterised by fatty and fibrous replacement of the right (and sometimes the left) ventricular myocardium [72]. It usually presents in the teenage years or early twenties, but is increasingly being recognised in paediatric practice. It does not occur in the neonatal period, although it does have some phenotypic overlap with Uhl's anomaly. Mutations have been detected in approximately 40% of cases. These occur in the genes encoding the desmosomal junction proteins desmoplakin [73], plakoglobin [74], plakophilin 2 [75], desmocollin 2 [76] and desmoglein 2 [77]. Desmoplakin mutations cause Naxos disease characterised by cardiomyopathy, keratoderma and woolly hair [50].

Macroscopically, there is fatty replacement of the right ventricular myocardium extending from epicardium to endocardium. This fatty infiltration usually affects the so-called "triangle of dysplasia" that encompasses the anterior wall of the right ventricular outflow tract and apex and the posterobasal wall of the right ventricle. There is sparing of the muscular trabeculations. It may affect the left ventricle or interventricular septum. Fibrosis may be obvious macroscopically. There is thinning of the wall, which may bulge to form aneurysm.

Microscopically, it is characterised by fatty and fibrous replacement of the right (and sometimes the left) ventricular myocardium. Myofibre disarray may be seen and there may be a minor lymphocytic infiltrate (Fig. **17**). Fatty

replacement may be seen in the normal right ventricular myocardium particularly in obese subjects. Small collections of adipocytes are a normal finding along the intramural course of the coronary arteries in right and left ventricle in normal subjects, and adipose tissue may even be seen beneath the endocardium in normal hearts. One can see fatty replacement in a variety of pathological condition including dilated cardiomyopathy. Recently, immunohistochemical detection of reduced levels of plakoglobin in endomyocardial biopsies has been postulated as a diagnostic test for the condition [78].

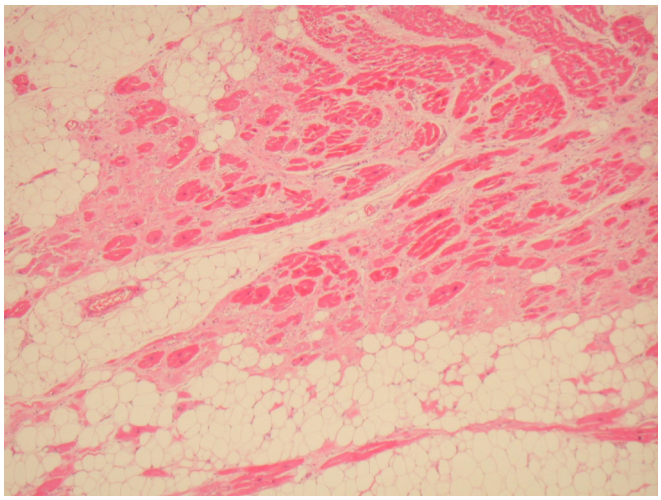

Fig. (17). Arrhythmogenic right ventricular cardiomyopathy. A section of the right ventricular myocardium shows loss of myocytes with replacement fibrosis and fatty infiltration. (H&E).

NON-COMPACTION OF THE VENTRICULAR MYOCARDIUM

This is a form of cardiomyopathy of unknown cause. The clinical presentation is with heart failure and ventricular arrhythmias. There is an increased risk of thromboembolic disease and the pheonotype is particularly severe in infants and young children. It affects predominantly the left ventricular myocardium imparting a spongy appearance [79]. The appearance is reminiscent of the developing embryonic heart. The ventricular cavity extends almost to the epicardial surface among multiple thin muscular trabeculations (Fig. **18**); the normal compact layer separating the muscular trabeculations of the ventricular lining from the epicardium is reduced in thickness. The papillary muscles of the mitral valve are poorly developed. There is quite often prominent endocardial fibroelastosis. Histologically, there are anastomosing endocardial-lined recesses that extend deeply into the myocardium. There may be foci of subendocardial ischaemic necrosis. In children, half the cases show associated cardiac abnormalities such as ventricular septal defect, polyvalvar dysplasia and pulmonary stenosis. The case may present in the neonatal period with cardiac failure or with sudden death, although other cases may not present until later in life. The later-presenting cases tend not to have associated cardiac abnormalities. About 25% of cases are familial [80], usually showing autosomal dominant transmission with incomplete penetrance [81]. X-linked left ventricular noncompaction has been described in Barth syndrome [82], which is associated with mutations in the tafazzin (TAZ) gene at Xq28 [49] that result in cardiolipin deficiency and abnormal mitochondria. Some cases of ventricular noncompaction have been linked to mutations in genes for α-dystrobrevin [83], the Z-line protein Cypher/ZASP [84] and the β-myosin heavy chain [85].

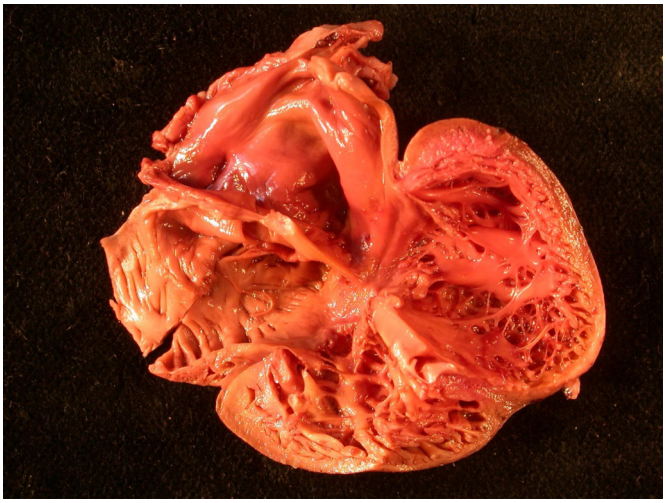

Fig. (18). Ventricular non-compaction. A child with tracheo-oesophageal fistula and oesophageal atresia. The heart is cut in a simulated four-chamber echocardiographic plane and shows an ostium primum atrioventricular septal defect. The ventricular cavities are dilated and the ventricular myocardium shows multiple fine trabeculations with a markedly thinned compact layer.

Syndromes associated with ventricular non-compaction are; Di-George syndrome [86] and Melnick-Needles syndrome [87] an X-linked connective tissue disorder characterised by craniofacial and skeletal abnormalities.

However, the phenotype may be seen in normal adults without evidence of heart failure or arrhythmia [88].

HISTIOCYTOID CARDIOMYOPATHY

This rare, X-linked condition occurs usually in female infants and is characterised by severe, sometimes fatal, arrhythmia. Its histological hallmark is collections of myocytes with vacuolated cytoplasm (Fig. **19**); that resemble histiocytes [89]. Ultrastructurally these cells contain large numbers of mitochondria. Macroscopically, the heart may appear enlarged but otherwise unremarkable or there may be multiple nodules in the myocardium. These nodules, which range in size from a few millimetres to over one centimetre, may be subendocardial or scattered throughout the myocardium and may even occur in the valves. The condition may present in-utero with tachyarrhythmia and heart failure, or presentation may be delayed until after birth to the age of four years when the presenting features may be arrhythmia, seizures, heart failure, cyanosis or sudden death. Structural heart disease such as ventricular septal defect or hypoplastic left heart may be present [90]. The condition is regarded as hamartomatous and of Pukinje cell origin; it is associated with mitochondrial DNA mutations [91, 92]. Histiocytoid cardiomyopathy has been reported in numerous cases of MLS (microphthalmia, linear skin defects) syndrome (also known as MIDAS Syndrome) - a disorder in which where is deletion of the p22 region of the X chromosome [93], suggesting that the gene associated with

histiocytoid cardiomyopathy lies in that region of the X chromosome.

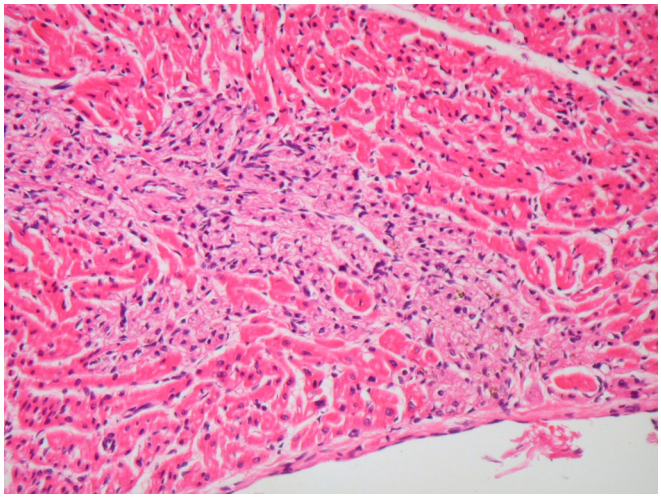

Fig. (19). Histiocytoid cardiomyopathy. This child died suddenly. At post-mortem there was tetralogy of Fallot, but the myocardium appeared otherwise unremarkable. Histologically there were multiple areas similar to that illustrated. There are collections of pale cells among the normal myocytes. These cells are small and have very finely vacuolated cytoplasm, imparting the pale appearance. Note the subendocardial location. (H&E).

OTHER FORMS OF CARDIOMYOPATHY

As the above tables make clear there are many other causes of cardiomyopathy. Some forms of cardiomyopathy with a specific origin such as the cardiomyopathy associated with congenital disorders of glyocosylation do not show specific histological features [94] and the presentation may be as dilated or hypertrophic cardiomyopathy. Endomyocardial biopsy does not permit the specific diagnosis to be made.

CONCLUSION

Recent advances in genetics have revolutionised our understanding of heart muscle disease; how it is should be classified, how it is caused, how it develops and how the normal myocardium works. Genetic testing is now possible for many cardiomyopathies. This allows confirmation of the diagnosis in individuals, screening of families, stratification of risk and appropriate intervention with drugs, lifestyle modification or insertion of implantable cardioversion pacemakers.

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