`Introduction

The finding of a dilated and diffusely hypokinetic left ventricle occasionally constitutes a challenge in the daily medical practice as far as the identification of the etiology of this finding is concerned ***(Sanbe A., 2013).***

This occurs when the underlying cause cannot be identified, despite a detailed history and a thorough clinical examination, even after cardiac ultrasound. This specific condition of the left ventricle is attributable to two pathological entities: dilated cardiomyopathy, either idiopathic or secondary, i.e. a result of specific pathology but without stenosis of the coronary arteries or ischemic heart disease that is due to severe coronary artery disease ***(Felker GM, et al., 2002).***

Ischemic heart disease is often the long-term result of a clinically obvious coronary artery disease ***(Gersh BJ, et al., 1997).***

However, occasionally the clinical course of the disease is insidious, "silent", and thus indistinguishable from dilated cardiomyopathy ***(Rahko PS, et al., 1988).***

Differential diagnosis between this "silent" ischemic and the non-ischemic cardiomyopathy is required both for therapeutic as well as for prognostic reasons ***(Limongelli G, et al 2010).***

Although prognosis of patients with ischemic cardiomyopathy is poorer than prognosis of patients with non-ischemic cardiomyopathy ***(Bart BA, et al., 1997),*** patients with hibernating myocardium may significantly benefit from myocardial reperfusion ***(André H, et al., 2010).***

The gold standard examination for differential diagnosis in such cases is Coronary arteriography or Multislice computed tomography (CT) angiography. Precisely towards the same direction, many non-invasive techniques have been used, that present, however, variable sensitivity, reduced reproducibility, limited interpretation and sometimes limited availability ***(Franchini M, et al., 2000).***

On the other hand, the extracranial carotid disease is significantly correlated with coronary artery disease and acute coronary syndromes ***(Kallikazaros IE, et al., 1999)*** and vice versa ***(Love BS, et al., 1992).***

Additionally, the coronary and carotid arterial tree share all the factors predisposing to atherosclerosis ***(Hyun S K, et al., 2013).***

The ultrasound examination is reliable and easy to use in order to identify carotid disease.

Stress echocardiography is a well-established method for the identification of stress-induced wall motion abnormality

(WMA) secondary to coronary artery disease. Additionally, the identification of stress-induced WMA may also help differentiate ICMP from NICMP by examination of Dobutamine Stress Echocardiography at high dose. If improvement develops all through the test, it is considered non-ischemic cardiomyopathy. If a biphasic response in any coronary artery territory is recorded, it is considered ischemic cardiomyopathy ***(Miloradović V, et al., 2005)***.

Aim of the Work

1. To study the value of carotid ultra-sonic examination in the differentiation between ischemic and non-ischemic etiology in patients with clinically unexplained dilated myopathic left ventricle.

2. To study the value of dobutamine stress echocardiography examination in the differentiation between ischemic and non-ischemic etiology in patients with clinically unexplained dilated myopathic left ventricle.

3. To evaluate the sensitivity of dobutamine stress echocardiography and carotid artery ultrasound in correlation with coronary angiography in the distinction between ischemic and non-ischemic dilated cardiomyopathy.

Chapter 1

Dilated Cardiomyopathy

Dilated cardiomyopathy (DCM), is the most common amongst cardiomyopathies, is characterized by an increase in both myocardial mass and volume.

The walls become thin and stretched, compromising cardiac contractility and ultimately resulting in poor left ventricular function. DCM may occur at any age, but it is common in males between the ages of 20 and 50 years ***(Schoen F.et al., 2005)***.

Genetically inherited (familial) forms of DCM have been identified in 25–35% of patients presenting with this disease, but many other acquired conditions may result in an identical clinical presentation and pathological function. These conditions include alcohol-induced cardiomyopathy, peripartum cardiomyopathy, haemochromatosis, chronic anemia, non-compaction cardiomyopathy, adriamycin toxicity, sarcoidosis and viral myocarditis ***(Jefries JL, et al., 2010).***

DCM may also occurred secondary to ischemic heart disease, valvular heart disease, hypertension and congenital heart disease ***(Lester WM, et al., 2001).***

In cases where an underlying pathology can't be identified, the patient is diagnosed with an idiopathic dilated cardiomyopathy (IDCM).

The 5 year survival after diagnosis is 50%, as patients often develop progressive congestive heart failure (CHF) and complications such as, thromboembolic conditions and arrhythmias ***(Luk A, et al ., 2009).***

ETIOLOGY

Genetics

Thirty per cent of patients with DCM either have a relative with the disease or show clinical evidence of left ventricular dysfunction or visible enlargement on two-dimensional echocardiography ***(Lakdawala NK, et al., 2012).***

Modes of inheritance include autosomal dominant (AD) with incomplete penetrance due to modifier genes and environmental factors, autosomal recessive (AR), and X-linked. These genes are summarized in table 1***(Towbin JA, et al., 2002).***

Table (1): Identified gene mutations involved in familial dilated cardiomyopathy ***(Towbin JA, et al., 2002).***

Gene	Chromosome location	Additional phenotype
Autosomal dominant		
Cardiac troponin T	1q32	None
β and δ-sarcoglycan	5q33–34	Muscular dystrophy
Cardiac β-myosin HC	14q1	None
Cardiac actin	15q14	None
α-Tropomyosin	15q22.1	None
Lamin A/C	1p1–q21	Conduction system disease
Desmin	2q35	skeletal myopathy
Cardiac ryanodine receptor	1q42–43	ARVC and exercise-induced ventricular tachycardia
Autosomal recessive		
Desmoplakin	6p24	Wooly hair and keratoderma
X-linked		
Dystrophin	Xp21	Skeletal myopathy
Taffazin	Xp28	Short stature and neutropenia

ARVC, arrhythmogenic right ventricle cardiomyopathy; HC, heavy chain.

Other genetic loci have been identified, but the specific genes are not yet known ***(Towbin JA, et al., 2002).***

Certain phenotypes have been identified for specific genes, but there is incomplete penetrance. Mutations inlamin A/ C are often associated with conduction system disease; desmin and dystrophin with askeletal myopathy; desmoplakin and plakoglobin are often associated with wooly hair and keratoderma. Mutations in d-sarcoglycan have been found to cause loss of skeletal muscle and a form of muscular dystrophy.

Patients with a mutation in the tafazzin loci may be neutropenic and short in stature. Lastly, arrhythmogenic right

ventricular diomyopathy (ARVC) and exercise-induced ventricular tachycardia are commonly associated with mutations in the cardiac ryanodine receptor ***(Schonberger J, et al., 2001).***

Environmental

Myocarditis is responsible for a majority of DCM cases diagnosed in North America. Often a secondary complication to viral infections, myocarditis can progress to CHF in children and patients younger than 40 years of age ***(Kawai C., 1999).***

Common causative agents in North America and Europe include enteroviruses, coxsackie virus B3 and adenovirus. Parasitic infections with Trypanosoma cruzi (Chagas disease), which is endemic in South America, can cause DCM ***(Burian J, et al., 2005).***

Other inciting agents include cytomegalovirus, parvovirus, hepatitis C, HIV, Epstein-Barr virus, Chlamydia pneumoniae and Borrelia burgdorferi ***(Burian J, et al., 2005).***

PATHOLOGY

Gross

Hearts of DCM patients often weigh two to three times normal, and in certain cases, may exceed 1000 g, in which case they are known as ‘‘cor bovinum’’ ***(Jefries JL, et al., 2010).***

The heart is enlarged and the muscle fibers hypertrophied, but this may not be evident due to dilatation of the cardiac chambers and when cut in a sagittal section. The heart, if there is biventricular involvement, appears spherical, and the apex rounded rather than pointed. If the disease is predominately left-sided, the interventricular septum may be found bulging into the cavity of the right ventricle, the ventricular walls may also appear thin (fig 1).

Moreover, the mitral and tricuspid valves may show changes consistent with regurgitation, as progressive dilatation stretches the annulus ***(Jefries JL, et al., 2010).***

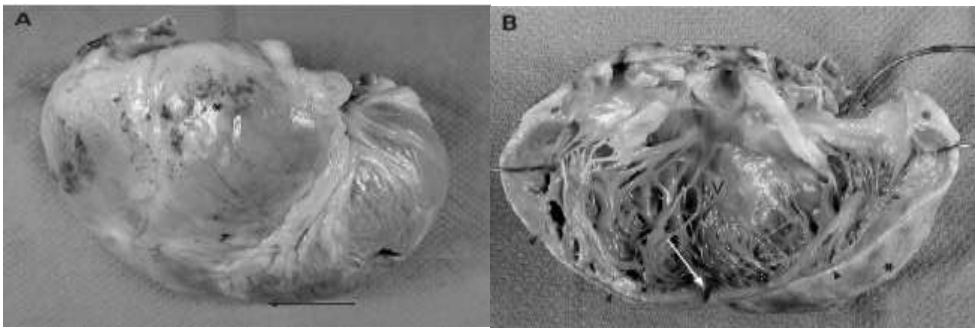

Fig. (1): Explanted heart from a 37-year-old man. (A) Demonstration of gross changes consistent with dilated cardiomyopathy. The heart shows loss of its normal, elongated shape and appears much more spherical due to biventricular hypertrophy and marked dilatation. This is most evident in the apex of the heart (black arrow). There is mild epicardial fibrosis and the subpulmonic region (*) shows petechial haemorrhage. (B) Left atrium and left ventricle (LV) open. The LV is globoid in shape, with rounding of the apex (white arrow). The myocardial walls are thinner than usual (arrowheads). *Patchy white areas of epicardial fibrosis ***(Jefries JL, et al., 2010).***

In cases of IDCM, the coronary arteries are often patent. With progressive dilatation, thinning and consequential fibrosis of the myocardial wall, there is decreased contractility, which is normally most evident in the apical region.

With hemostasis, there is increased incidence of formation of mural thrombi during the terminal stages of the disease, and subsequently can embolism leading to stroke or sudden cardiac death ***(Jefries JL, et al., 2010).***

Histology

Microscopic findings are non-specific and do not necessarily identify the main etiology causing DCM. As the myocardium is hypertrophied and dilated, findings consistent with hypertrophy are evident (fig 2A).

Myocytes may appear thickened with enlarged nuclei, interspersed with these hypertrophied myocytes, others may appear thinned and elongated, with the nucleus occupying the entire width of the myocyte (fig 2B).

The total number of intracellular contractile myofibrils is diminished, and the myocytes may appear empty.

Areas of myocyte death may be evident, which eventually get replaced with collagen and become fibrotic (fig 2C). Degenerative changes responsible for a bundle branch block

pattern on ECG may also be seen on histological examination of dilated hearts (fig 2D) ***(Jefries JL, et al., 2010).***

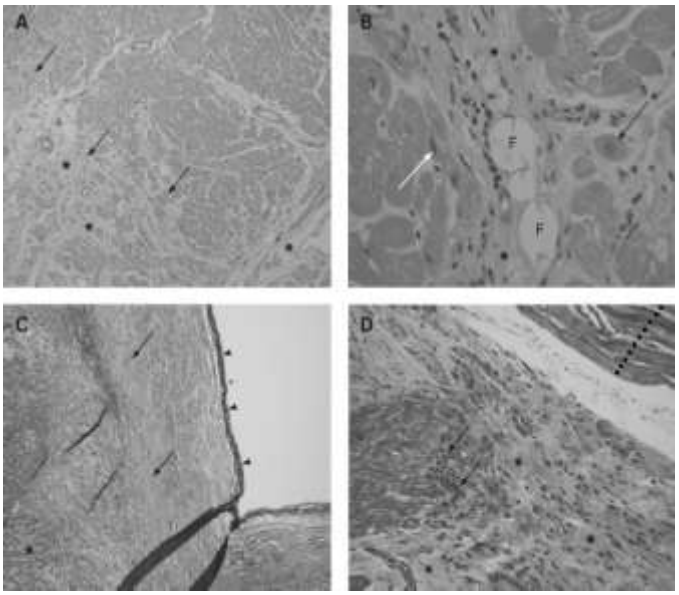

Fig. (2): Microphotographs of the myocardium from a 35-year-old female.

(A) Microphotograph showing evidence of myofibril hypertrophy in a 35-year-old female. Interstitial fibrosis (*) and areas of lymphocytic infiltration (arrows) consistent with resolving myocarditis can be seen (H&E, original magnification 6100). (B) While some myocytes are hypertrophied with enlarged nuclei (black arrow), others are thinned and elongated with nuclei that occupy almost the entire width of the myocyte (white arrow). Some myocytes appear ‘‘empty’’; this is likely to be due to diminished numbers of myofibrils. Areas of interstitial fibrosis (*) and fat infiltration (F) can be seen (H&E, original magnification 6400). (C) Microphotograph showing evidence of interstitial fibrosis (*), sub endocardial fibrosis (arrows) and endocardial fibro elastic changes (arrowheads) (H&E, original magnification 650). (D) Microphotograph of myocardium showing degenerative changes in the left bundle (dotted line). These changes may appear as a bundle branch block on ECG. Areas of interstitial fibrosis (*) and lymphocytic infiltration (arrows) are seen (elastic trichrome stain, original magnification 6400) ***(Jefries JL, et al., 2010).***

Patients with myocarditis may have lymphocytic infiltration surrounding the degenerating myocardial cells (fig 3) ***(Jefries JL, et al., 2010).***

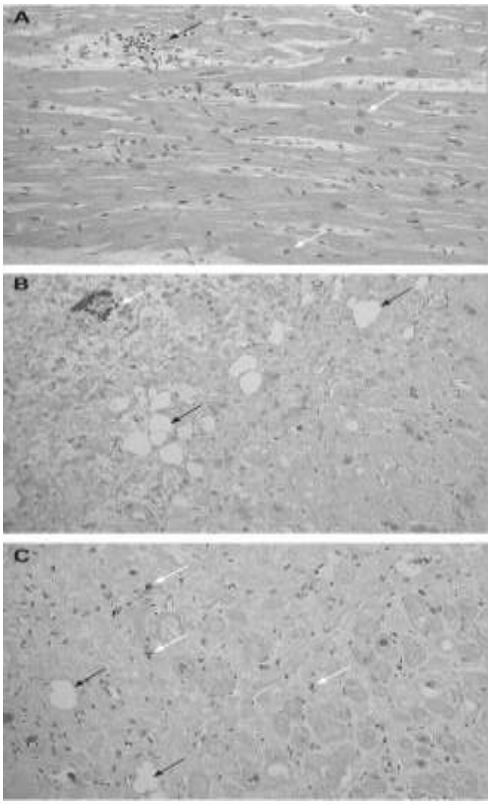

Fig. (3): Microphotographs of myocardium from a 58-year-old male showing evidence of myocarditis. (A) Areas of lymphocyte infiltration (black arrow) are seen. Enlarged nuclei (white arrows) are consistent with myocyte hypertrophy (H&E, original magnification 6200).(B) Specimen is positive for lymphocytic infiltration (white arrow). Areas of fat infiltration are also seen (black arrows) (CD-45 stain, originalmagnification6400). (C) Specimen is positive for macrophage infiltration (white arrows). Areas of fat infiltration are also seen (black arrows) (CD-68 stain, original magnification 6400) ***(Jefries JL, et al., 2010).***

Multi-nucleated giant cells (granulomas) surrounded by a rim of mononuclear cells and macrophages may be found in a patient with sarcoidosis (fig 4) ***(Jefries JL, et al., 2010).***

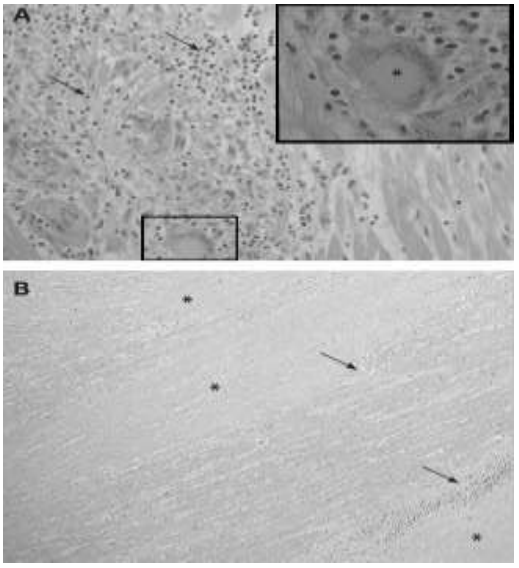

Fig. (4): Microphotograph of myocardium from a 47-year-old male with evidence of cardiac sarcoidosis.

(A) Microphotograph shows non-necrotizing granulomata and diffuse, chronic inflammation (black arrows) (H&E, original magnification6200). Inset, higher magnification of boxed area shows a non-necrotizing granuloma (*) with several multinucleated giant cells (H&E, original magnification 6400). (B) Microphotograph shows extensive fibrosis and scarring (*). Areas such as this are often referred to as ‘‘burnt-out’’, as they used to be sites of active inflammation and granulomas. Patchy areas of active inflammation (arrows) are also seen (H&E, original magnification 650) ***(Jefries JL, et al., 2010).***

An area of intra-myocellular iron-deposition resulting in myocellular degeneration with iron staining is indicative of haemochromatosis. Areas of vacuolization that occur in the perinuclear area and are seen pushing the contractile elements to the periphery of the muscle fibers may be seen in patients with Fabry disease ***(Jefries JL, et al., 2010).***

PATHOPHYSIOLOGY

Genetics

The pathophysiology of DCM has been identified in a majority of the genetic mutations, and may be separated into two categories: defects in force generation and defects in force transmission. The mechanism for DCM from mutations in tafazzin, lamin A/ C and cardiac ryanodine receptor has not been identified ***(McNally EM, et al., 2013).***

Defects in force generation

Defects in generating force are typically due to a loss of integrity of the sarcomere unit. Mutations in the loci coding for b-cardiac myosin heavy chain and cardiac troponin T have been identified to disrupt force generation. Mutations in the b-cardiac myosin heavy chain have been found to disrupt either the site of actin– myosin binding or the site of flexible joints of the myosin

protein that is responsible for its mobility during the contraction process ***(Rayment I, et l., 1993).***

Mutations in cardiac troponin T disrupt the calcium-sensitive troponin C interactions. This interaction is important to generate ATP to drive actin–myosin contraction, and a lack of ATP decreases the amount of force that may be generated by the sarcomere ***(McNally EM, et al., 2013).***

Defects in force transmission

As the actin–myosin contraction is completed, the force is transferred from the sarcomere to the extracellular matrix. This is completed by interactions between the actin subunit and certain cytoskeletal units. Mutations in cardiac actin, at the site of actin–cytoskeleton interaction, have been found to be associated with early disease onset ***(Olson TM, et al., 1998).***

Two mutations coding for the surface of a-tropomyosin have been identified. It is suspected that these areas on the protein are responsible for atropomyosin– actin interactions ***(Olson TM, et al., 1998).***

Mutations in dystrophin, desmin11 and d-sarcoglycan have been found to diminish the maximum force of transmission as well. Plakoglobin and desmoplakin are involved with proper

functioning at the desmosome and adherents junction. Mutations in these genes most likely contribute to impairment in the propagation of force from the sarcomere to the sarcolemma ***(McNally EM, et al., 2013).***

Viral

Despite a number of different viral agents identified in causing cardiac myocarditis, it is hypothesized that these viruses function by directly damaging the myocyte and cleaving dystrophin, acytoskeletal protein that maintains myocyte integrity ***(Badorff C, et al., 1999).***

Loss of this structural component of the myocardium results in a progressively dilated heart. The exact mechanism of how the virus cleaves dystrophin has not been fully elucidated.

CLINICAL PRESENTATION

Patients may present as early as childhood, though most present during the fourth and fifth decades of life. In general, symptoms are manifested when the disease has progressed to end-stage where significant myocardial (interstitial) fibrosis occurs ***(Chen YB, et al., 2009).***

Symptoms related to CHF, such as dyspnea, fatigue, angina, pulmonary congestion and low cardiac output may persist for months to years also, patients may have complications