

DILATED CARDIOMYOPATHY- FROM CLINICAL ASPECTS TO PATHOLOGY

Țica Ovidiu^{1,3}, Țica Otilia Anca², Roșca Elena¹, Roșan Larisa², Pantea Vlad³, Ignat Romanul Ioana³, Șandor-Huniadi Anca³, Șandor-Huniadi Mircea³, Popa Anca³, Popescu Mircea-Ioachim^{2,3}.

¹Emergency Clinical County Hospital of Oradea, Pathology Department

²Emergency Clinical County Hospital of Oradea, Cardiology Clinic

³University of Oradea, Faculty of Medicine and Pharmacy

Correspondent author: Țica Otilia Anca, Oradea, nr. 70, Anatole France Str., 410482.

e-mail: otilia_cristea01@yahoo.com

Abstract

Introduction: Dilated cardiomyopathy (DCM) is characterized by a global heart dilation which leads to systolic impairment. More than half of primary DCM are familial in nature. Classic symptoms include paroxysmal nocturnal dyspnea, orthopnea, leg swelling, and shortness of breath. Aim: DCM is one of the most common causes of congestive heart failure with an ominous prognosis. Methods: We performed a retrospective study where we included all deceased patients in our department with diagnosis of DCM (128 patients) during a period of 1 year. We examined medical charts, death certificates, autopsy reports and histopathological reports. Results and Discussions: From the whole cohort, 63 corpses were autopsied and all the organs were examined. Generalized atherosclerosis was documented in 57 patients but the real number is consistently bigger (no documentation of atherosclerosis was made in patients who were exempt of the autopsy). Conclusion: Early detection and proper treatment may improve the quality of life in these patients.

Key words: dilated cardiomyopathy, histopathological, negative prognosis, mortality.

INTRODUCTION

Dilated cardiomyopathy (DCM) is a primary myocardial disease characterized by a global heart dilation which reduces global myocardial contractility, leading to systolic impairment and left ventricular (LV) or biventricular dysfunction. [Longo D.L, et al., 2012] [Mann D.L et al., 2015] [Juneja R, PM Nambiar, 2017]

Cardiomyopathy is divided into two major groups: primary and secondary. The first category includes DCM, obstructive cardiomyopathy, restrictive cardiomyopathy, arrhythmogenic dysplasia of right ventricle and non-compaction of left ventricle. Secondary cardiomyopathies arise in other clinical condition that affects cardiac function. [Suvarna SK, 2013]

More than half of primary DCM are familial in nature (when seen in more than 2 family members), and the rest have genetic etiology. [Apetrei E., 2015]. Idiopathic DCM can be diagnosed after exclusion of identifiable non-genetic causes [Park HY, 2017]

The diagnosis of DCM has been difficult to standardize given the influence of body size, athletic training, and biological heterogeneity on measurements of left ventricular volume and contractile function. [McKenna WJ, BJ Maron, G Thiene, 2017]

Classic symptoms include paroxysmal nocturnal dyspnea, orthopnea, leg swelling, and shortness of breath. Nonspecific symptoms of fatigue, malaise, and weakness also can be present. More severe cases can present with thromboembolic complications, conduction disturbances, arrhythmias or even sudden cardiac death.

Physical examination findings are largely not specific to other causes of cardiomyopathy and consist of typical findings seen with congestive heart failure. Findings include crackles in the lung fields, elevated jugular venous pressures, peripheral oedema, and an S3 gallop. Tricuspid or mitral regurgitation murmurs are not uncommon as a result of ventricular enlargement and annular dilation. [Mahmaljy H1, SS Bhimji, 2017].

DCM presents with decrease in LV ejection fraction (LVEF), congestive heart failure (CHF) and ventricular arrhythmias. Initially, the ventricle dilates to increase the force of contraction and stroke volume (Frank–Starling relationship); however, these compensatory mechanisms gradually fail, progressive ventricular failure ensues and cardiac output (CO) decreases. [Juneja R, PM. Nambiar, 2017], [Mills SE, 2010]

LV chamber dimensions and function, including strain measurements, are also accurately determined by cardiac magnetic resonance (CMR) imaging. Contrast agents, mainly gadolinium, are used to evaluate fibrosis and therefore provide additional information on myocardial tissue quality. In DCM, the degree of fibrosis, marked by delayed gadolinium enhancement, is a predictor of mortality and rehospitalisation. [McNally EM, L Mestroni, 2017]

AIM

DCM is one of the most common causes of congestive heart failure with an ominous prognosis and this study aims to reveal all practical details of this progressive disease.

MATERIAL AND METHOD

We performed a retrospective study in which we included all deceased patients in County Hospital of Oradea with diagnosis of DCM (128 patients) during a period of 1 year (2016), excluding trauma related deaths. We examined medical charts, death certificates, autopsy reports and histopathological reports. According to the law of corpse manipulation all

patients who died in County Hospital of Oradea must be stored in the morgue department of Pathological Laboratory. All bodies were examined externally and all the medical charts were evaluated by the pathologist. Every trauma related death was directed to the forensic department. Afterwards, according to the desire of caregivers and only in cases with diagnosis without doubts, autopsy exemption can be made in compliance to the law. In the rest of cases, we performed necropsy of the corpses. [Law 104/2003].

The data was processed by the MedCalc Software, Maria-kerke, Belgium and SPSS INC, Chicago, IL, USA. Continuous variables were analyzed for normalization and compared using the *t* Student test; they were expressed by mean value \pm standard and median deviation. For comparison of parameter averages in the two groups, the Mann-Whitney U method and the Wilcoxon method W are used. The degree of correlation (*r*) between the studied parameters was evaluated by calculating the correlation coefficient Pearson ($p < 0.05$ was considered significant).

We studied which group was more affected by this disease (sex, age, background), the most important comorbidities (pulmonary, hepatic, atherosclerotic and others) and if DCM was the main cause of death.

Regarding of the autopsy technique we will highlight only the dissection of thoracic organs. After opening the thorax by removing the sternum, the cervico – thoracic organs are taken in one piece. The larynx, trachea and bronchi are dissected using the scissors with a blunt tip. The lungs are sliced separately from the hilum to the periphery. Pericardium is opened using a sharp pointed scissors and the heart is highlighted with the atrial auricles and the base (removing pericardial tissue and fat will expose the great vessels).

The macroscopic features of the heart can be best appreciated with a four-chamber view of the heart, similar to „bread loafing” slicing technique. We trimmed the heart at 1 cm intervals at the apex and continuing to just below the inferior margin of the atrioventricular valve leaflets. Next, we open the atrial and the remaining portions of the ventricular chambers. After removing the vessels and residual post-mortem blood clots the heart is being weighed. [Finkbeiner WE., PC Ursell., RL. Davis, 2009]

Cardiac fragments are harvested, kept in formalin solution for minimum 24 hours necessary for microscopic examination. After trimming and orientation, tissue fragments undergoes processing for paraffin embedding and sectioned at a thickness of 3 to 5 μm using a Leica manual microtome. The sections are displayed on slides, let for drying and de-waxing and stained using classical Hematoxylin-Eosin and then mounting a coverslip. For determine collagen fibres we used Masson's trichrome stain. For microscopic examination we used Leica DM 1000 optical microscope

and the Nikon E600 polarized light microscope. The photos were taken using the camera attached to the microscope.

RESULTS AND DISCUSSION

We included in our study 128 dead patients (71 males and 57 women) with DCM as first and secondary diagnosis of death. No differences were made concerning the background of our patients as seen in *Tabel 1*.

From the whole cohort, 63 corpses were autopsied and all the organs were examined. In 2016, in the emergency room 22 patients died having DCM as a diagnosis and 51 patients admitted in Cardiology clinic died by this disease. Regarding age, the group age between 71 and 80 years old were most affected by DCM.

More than 70 bodies had pulmonary complication (the most frequent was pulmonary oedema) and 40 patients presented hepatic comorbidities. Generalized atherosclerosis was documented in 57 patients but the real number is consistently bigger (no documentation of atherosclerosis was made in patients who were exempt of the autopsy).

Tabel 1

Statistical aspect of DCM in our study			
Criteria		Value (%)	<i>p</i>
Sex (M/F)		55.47 vs 44.53	0.003
Background (U/R)		51.57 vs 48.43	0.08
Age	≤ 40 yo.	2.34	0.009
	41- 50 yo.	6.25	0.024
	51- 60 yo.	9.37	0.012
	61 - 70 yo.	28.12	0.04
	71 - 80 yo.	34.37	0.04
	≥ 81 yo.	19.53	0.07
Autopsy / Exemption of autopsy		49.21 vs 50.78	0.001
Place of death (Hospital/ER)		82.81 vs 17.19	0.001
Primary vs Associate DCM diagnosis		53.91 vs 46.09	0.001

Macroscopy examination reveals increased heart volume with a globular shape and a reduced tonus as seen in Fig. 1. After sectioning, excessive cavity dilatation begins simultaneous with myocardial thinning and may appear as "bovine heart". Endocardium becomes greyish with fibrosis and stiffness. The thin myocardium presents diffuse discolorations, fine whitish streaks, some of which are branched, with lengths of up to 10 mm. Intracavitary we may find thrombi, especially at apical level. Annular dilated atrioventricular valves appear in the final phases of DCM, which confirms valvular regurgitation diagnosed during life.

In microscopy we notice myocyte hypertrophy (enlarged, muscle fibres with hyperchromatic nuclei) and collagenous fibrosis, as seen in Fig.1. Fibrosis may be diffuse or extend into sub-endocardium. Transmural scars may also occur and quantitation of collagen has shown up to 4 times

the normal collagen concentration. Interstitial cellularity is represented by scattered lymphocytes, fibrous cells, fibroblasts. Some myocardial fibres may exhibit degenerative changes and a perinuclear yellow – brown attrition pigment (lipofuscin).



Fig.1 Gross and microscopy aspects in DCM.

Although the onset of the disease occurs with a mean age at presentation at about 50 years, [Dec G, V Fuster, 1994, Underwood JCE et al., 2007] in our study the main age group affected was from 61 to 80 y.o.

Inflammation is an adaptive response to cardiac injury, but the role of an excess or prolonged inflammatory response has been well established as maladaptive and crucial to the pathophysiology of heart failure of all pathogeneses. Evidence for cell-mediated immunity includes involvement of proinflammatory cytokines and lymphocytic infiltration on biopsies in almost half of patients with idiopathic DCM. [Trachtenberg BH, JM Hare, 2017]. Pulmonary and systemic embolism can occur as blood stasis in dilated and hypocontractile cardiac chambers lead to activation of the coagulation cascade. [Davies MR, J.Cousins, 2009] Today the guidelines recommend the use of anticoagulants only in patients with atrial fibrillation, prosthetic heart valves, or known mural thrombus. When there is progressive end-stage heart failure despite maximal medical therapy and the prognosis is deemed poor, one may consider a heart transplant. All patients with DCM must be educated on the disorder and importance of dietary restrictions in sodium and water. Patients with DCM should be referred for cardiac rehabilitation as this has been shown to reduce mortality by 20-30% over 5 years, including improvement in symptoms. [Mahmaljy H, Bhimji SS.,2017] Implantable of cardiac defibrillator reduces cardiovascular mortality and sudden cardiac death in patients with non-ischaemic cardiomyopathy. [Alba AC, et al., 2017] A good correlation has been found between the severity of the condition clinically and the extent and degree of microscopic abnormalities, although the sometimes focal nature of the changes may be misleading. [Rosai J, et al., 2011]

CONCLUSIONS

Without cardio-pulmonary transplant, patients with DCM doesn't have an acceptable 5-year survival rate. Early detection and proper treatment may improve the quality of life in these patients. The unknown etiology of this primary DCM makes it impossible to apply a specific therapeutic strategy. Therefore, the identification of prognostic factors, especially of those modifying, should be performed in these patients.

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