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Descriptive cohort study of patients with dilated cardiomyopathy enrolled to SU-Sahlgrenska from June 2018 to June 2020 within the framework of Sahlgrenska Cardiomyopathy Project (SCMPC)

DEGREE PROJECT IN MEDICINE

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Abbreviations

ACE- Angiotensin-converting enzyme

ARB- Angiotensin receptor blocker

ARNI- Angiotensin receptor neprilysin inhibitor

BMI - Body mass index

CMP- Cardiomyopathies

CRT- Cardiac resynchronization therapy

DCM- Dilated cardiomyopathy

ESC- European Society of Cardiology

HCM- Hypertrophic cardiomyopathy

HF- Heart failure

ICD- Implantable cardioverter defibrillator

IHD- Ischemic heart disease

LV- Left ventricle

LVEF- Left ventricle ejection fraction

LVEDD - Left Ventricle end diastolic volume

MRA- Mineralocorticoid receptor antagonists

MRI- Magnetic resonance imaging

NYHA - New York Heart Association

RV- Right ventricle

SCMPC - Sahlgrenska cardiomyopathy project

UCG- Ultrasound cardiography

Abstract

Introduction and Aims: Cardiomyopathies (CMP) is a heterogeneous group of disorders associated with different types of myocardial dysfunction or ventricular arrhythmia, which may lead to premature death. In early stages, CMP may be asymptomatic or present with few symptoms which most often explains the difficulty of early diagnosis. As the CMP disease progresses, heart contractility gets affected and most often leads to heart failure (HF) or arrhythmias. The purpose of the study was to describe baseline characteristics, initial symptoms and medical treatment in patients with dilated cardiomyopathy (DCM).

Method: **This is a retrospective descriptive** cohort study with a total of 89 patients with a DCM diagnosis within the Sahlgrenska cardiomyopathy project (SCMPC). The patients were enrolled between June 2018 and June 2020. Data from medical records were collected and analyzed. Variables obtained were baseline characteristics (age, sex, BMI), age at onset and type of earliest symptoms, New York heart association (NYHA) class, and treatment.

Results: Mean age at symptom debut was 45.7 (15.2 SD). Men were overrepresented with 75.2% of the patients. DCM patients had a BMI of 26.2 (5 SD) which is classified as overweight. Amongst DCM patients, 43.5% presented with NYHA class 3, followed by NYHA class2 (26%), NYHA class 1 (16%), and NYHA class 4 14%. Dyspnea was the most common initial symptom (67.4%) followed by fatigue (55.1%). Beta blockers were the most frequently used medical therapy (93.3%), followed by ACE-inhibitors (79.8%), spironolactone (66.3%) and loop diuretics (57.3%).

Conclusion: Dyspnoea was the most common symptom at disease presentation. Men in their forties with overweight were over represented in DCM patients, which should raise awareness of DCM as a differential diagnosis even in relatively young men with dyspnoea.

Key words: Cardiomyopathy, Dilated Cardiomyopathy, Baseline characteristics, Initial symptoms, Treatment.

Introduction

Cardiomyopathy (CMP) is a heterogeneous class of heart muscle diseases. CMP is defined by structural and functional abnormalities in the ventricular myocardium which is not explained by loading abnormalities such as hypertension, valve disease and myocardial structural defects, pericardial and endomyocardial pathologies, high output states and volume overload or coronary artery disease (1). Cardiomyopathies represent a significant health burden and can cause premature death from progressive heart failure (HF) and arrythmia. (2-4, 5-9).

Since the 1960s, several international CMP classifications have been released. One of the latter was developed by a working group of the European Society of Cardiology (ESC) and is based on the patient's clinical picture and ultrasound findings (1). This classification is currently used in Sweden. The ESC classification system is based on specific functional and morphological criteria which then are divided into genetic/familial and non-genetic/non-familial (1). The five main groups according to the ESC classification are dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM), arrhythmogenic right ventricular cardiomyopathy (ARVC), restrictive cardiomyopathy (RCM), and unclassified cardiomyopathies. The two unclassified cardiomyopathies are left ventricular (LV) non-compaction cardiomyopathy (LVNC) and takotsubo or stress-induced cardiomyopathy (SIC; often referred to as "broken heart syndrome"; 1, 5).

Etiology

Cardiomyopathies are idiopathic in most cases but there are several known distinct etiological factors. CMPs could be inherited with a defined genetic origin. The degree of heredity varies and is highest among HCM (10). There are several known disease-causing gene mutations, some of which are inherited in an autosomal dominant pattern. Genetic testing is usually performed in patients and first-degree relatives with HCM and ARVC and may be considered in DCM if there is a family history of DCM. However, the majority of these patients today have no known hereditary cause and for most, the cause is idiopathic. A few of the forms are relatively common at a cardiology clinic, while others are rare. CMPs can also be acquired by excessive consumption of alcohol or drug abuse, toxins, bacteria, and viruses (1,11). In early stages, CMP may be asymptomatic or present with only few symptoms which explains the difficulty of early diagnosis. In this study, the focus will be on DCM.

The ability to detect and diagnose CMP has gradually improved as non-invasive methods (cardiac ultrasound, magnetic camera, etc.) for imaging of the heart have been developed and made generally available. The treatment of CMP is mainly focused on symptomatic treatment of HF and arrhythmias, since there is no treatment that cure the underlying pathology. Several treatment options are both symptomatic and have a positive effect on prognosis. Treatment options may be pharmacological, implantable devices, surgical procedures, and as a last alternative heart transplantation (1).

Heart failure definition

HF is defined as a clinical syndrome presenting with typical symptoms (such as dyspnea, fatigue, and ankle swelling) and objective signs of a structural and/or functional cardiac abnormality which results in a reduced cardiac output and/or elevated intracardiac pressures during stress or rest (23), usually applying ultrasound (UCG, also echocardiography) and blood analysis (NT-pro-BNP). On physical examination, HF may be accompanied by signs such as pulmonary crackles, distended jugular veins, and peripheral edema. HF occurs because the heart cannot contract or relax enough. In both cases, it leads to reduced cardiac output (CO), but with reduced (contraction defect / systolic) or preserved (relaxation defect / diastolic) ejection fraction (EF) {Vasan, 2003 #138}. The EF is a measurement of the amount of blood the LV pumps out in a contraction (stroke volume), it equals the blood volume ejected from the LV divided by the total LV end diastolic volume (LVEDD) (23).

Diagnostic criteria for heart failure and classification of severity

HF is often categorized by the measurement of the LVEF and is divided according to the ESC diagnostic criteria into HF with normal LVEF ≥50%; HF with preserved EF (HFpEF), HF with reduced EF (HFrEF) <40%. Patients with LVEF of 40-49% are said as having HF with a midrange EF (HFmrEF) as they represent a "grey area".

HF can also be divided into left-sided and right-sided HF. Left-side HF is the most common type. It occurs when the LV and cardiac output (CO) fails and no longer pumps enough blood to the body; also referred to as forward failure. The amount of blood ejected from the LV over one minute is called CO; CO = stroke volume x heart rate. As a result of LV failure, the filling pressure increases and there is a backward stasis of blood into the left atrium, pulmonary veins, and pulmonary capillaries. This will cause accumulation of the blood and

increase the backward pressure in pulmonary capillaries and can cause edema. This causes dyspnea (shortness of breath), orthopnea (dyspnea with decubitus position) and paroxysmal nocturnal dyspnea (sudden shortness of breath during sleep). (23). {King, 2012 #146}.

Left-sided HF often leads to and is the most common cause of right-sided heart failure. Pulmonary diseases such as chronic obstructive pulmonary disease (COPD) and pulmonary arterial hypertension (PAH) can also result in right-sided HF. Right-sided HF occurs when the right ventricle becomes weak and lose its ability to contract effectively and pump enough blood through the lungs and to the left side of the heart. The blood backs up into the right atrium and the peripheral venous circulation which causes increased pressure and venous congestion. The result is jugular venous distension as well as accumulation of fluid (edema) in the legs and abdominal organs. (23).

Systolic HF is when the heart loses its ability to pump enough blood during systole and diastolic HF is when the filling ability is disturbed during diastole. Systolic HF is also referred to as HFrEF and diastolic HF as HFpEF. (23). Table 1 illustrates diagnostic criteria of HFrEF, HFmrEF and HFpEF according to ESC guidelines. (23).

Table 1 diagnostic criteria in HFrEF, HFmrEF and HFpEF verified by ESC guidelines. (23)

Type pf HF	HFrEF	HFmrEF	HFpEF
	Symptoms +/ - Signs	Symptoms +/ - Signs	Symptoms +/ - Signs
	LVEF <40%	LVEF 40-49%	LVEF > 50%
		1, Elevated levels of natriuretic peptides 2, At least one additional criteria: a, relevant structural heart disease. Diastolic dysfunction	1, Elevated levels of natriuretic peptides 2, At least one additional criteria: a, relevant structural heart disease. Diastolic dysfunction

NYHA functional class (New York Heart Association) is a classification used to describe the severity of symptoms. (23) Table 2 illustrates NYHA Classification. (23).

Table 2 New York Heart Association NYHA classification. (24, 25).

NYHA Class 1	No limitation in normal physical activity
NYHA Class 2	Mild HF, shortness of breath and fatigue only in normal physical activity.
NYHA Class 3	Moderate HF, shortness of breath and fatigue with light to moderate physical activity. The class is divided into IIIa and IIIb depending on whether the patient is able to walk> 200 m
NYHA Class 4	Severe HF with shortness of breath and fatigue even rest.

Echocardiography

Echocardiography is the most commonly used tool to diagnose HF and should be performed at least once on HF patients according to ECS guidelines. (23){Zarrinkoub, 2013 #142} To diagnose HF using echocardiography focuses on EF, diastolic function, structural heart disease and valvular disease, and atrial filling / pulmonary hypertension (23){Marwick, 2015 #143}. However, echocardiography is user dependent and may be difficult to access which is a limitation. {Tait, 2012 #144}.

NT-proBNP

NT-proBNP can be used as an initial diagnostic test and is measured from a venous blood sample {Kelder, 2011 #139}, (23). NT-proBNP is excreted from the LV wall upon increase in wall tension. Elevated levels support a HF diagnosis and lead to further cardiac investigation. BNP is rapidly degraded in plasma, which is why NT-proBNP is most often used in measurement.

A high value can have several different causes, such as aging, acute cardiac ischemia, atrial fibrillation, renal failure, pulmonary embolism, inflammation (23) {Tait, 2012 #140}{Jernberg, 2006 #141}. NT-proBNP often rises in eldery, which may be due to an increased incidence of kidney and heart diseases, which leads to reduced excretion of substances as well as increased formation of substances. (23) {Tait, 2012 #140}{Jernberg, 2006 #141}. NT-proBNP should never be used alone as a diagnostic method in HF as the lab result may be influenced by many other factors, but combined with the other methods

{Jernberg, 2006 #141}. NT-proBNP is a good tool for monitoring the progression of heart failure and deciding whether to proceed with echocardiography. A value below the limit is strongly against HF and does not require further investigation with echocardiography (23)

Electrocardiogram (ECG)

In HF, the ECG is rarely normal and an abnormal ECG increases the suspicion of HF (23). ECG can be used to identify the cause of symptoms as well as the etiology of heart failure. Findings that can be seen include signs of LV hypertrophy, a prior myocardial infarction, stress signs, arrhythmias, and conduction disturbances {Henes, 2016 #145}.

Magnetic resonance imaging, chest X-ray, and coronary angiography

Magnetic Resonance Imaging (MRI) gives similar information as echocardiography but in addition an opportunity to study tissue characteristics in the myocardium. (MRI) is used as a complement to echocardiography and gives important information on LV mass, volume and function. Findings include enlargement of the chambers, elevated systolic and end diastolic volumes, ejection fractions, valve insufficiency as well as information of the myocardial metabolism. Abnormal myocardial delayed enhancement (delayed enhancement occurs when gadolinium contrast is taken up into necrotic, inflammatory or fibrotic myocardial tissue) can help to differentiate between ischemic and non-ischemic DCM enhancement pattern. (43). (44).

Chest X-rays gives information of cardiac enlargement or pulmonary stasis and pulmonary diseases. Coronary angiography is used to prove or exclude ischemic heart disease (IHD) which is the most common cause of HF (1), and also shows the possibilities of coronary revascularization

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Dilated cardiomyopathy

DCM is the third most common cause of HF after IHD and hypertension. (1). DCM is characterized by an enlarged LV with decreased contractility. DCM is thus an example of systolic HF or HFrEF. In contrast to ischemic cardiomyopathy LV dysfunction is general rather than regional. The degree of LV dysfunction varies in DCM and is often progressive (1, 13). DCM can be caused by genetic or non-genetic causes including inflammatory/infectious causes, toxins, drugs and alcohol. DCM is idiopathic in 50% of the cases and between 20-35% of the cases may be due to inherited gene defects (14-15).

Diagnosis

Before making a final diagnosis, it is important to rule out HF secondary to potentially treatable causes such as IHD, hypertension, atrial fibrillation, systemic diseases, pericardial disease, congenital heart disease or pulmonary hypertension. DCM is thus an exclusion diagnosis without specific objective signs or tests.

Echocardiography is the first line imaging examination in DCM. It provides important information for diagnosis, risk stratification, and guides the treatment. Echocardiogram shows dilated cardiac chambers, most common a globally dilated left ventricle with reduced mechanical function, and secondary mitral valve insufficiency due to the dilatation of the LV. Echocardiography is also used in family member screening. Diagnostic criteria include ejection fraction <45% and/or fractional shortening of <25% and LV dilatation >117% of the normal value of the LVEDD corrected for body surface area and age (normal value + 2SD +5%; 42).

MRI is used as a complement to echocardiography and gives important information on LV mass, volume and function. Findings include enlargement of the chambers, elevated systolic and end diastolic volumes, EFs, valve insufficiency as well as information of the myocardial structure. Abnormal myocardial delayed enhancement (delayed enhancement occurs when gadolinium contrast is taken up into necrotic, inflammatory or fibrotic myocardial tissue) can help to differentiate between ischemic and non-ischemic DCM enhancement pattern. Enhancement pattern typical for DCM is mid-wall and curvilinear most often seen in the septum in approximately 28-37% of DCM patients (43). (44).

Chest X-rays gives information of cardiac enlargement or pulmonary stasis. Coronary angiography examination is used to exclude ischemic heart disease (IHD. (1).

In severe cases of HF, where cardiac transplantation is an option, patients may undergo right heart catherization that gives detailed information on end-diastolic pressure, pulmonary vascular resistance, cardiac output/cardiac index etc. Most often in unclear cases of HF a right sided heart biopsy is part of the diagnostic algorithms to exclude possible 2nd causes to the HF symptoms.

Clinical manifestation

DCM may affect children and eldery but are most commonly seen between the ages of 20 and 50 years. (13, 16, 17). A recent study reported a median age of 46 years at onset of symptom in DCM. (18). DCM have heterogeneous clinical manifestations. Generally, clinical manifestation ranges from dyspnea, edema, fatigue, chest pain, arrhythmias, acute decompensation to cardiogenic shock (19). However, HF is the most common initial manifestation and is seen in 75-85% of the patients (11, 13, 17, 20-22).
There are different HF clinical manifestations between men and women. In the Euro Heart Survey, systolic HF was developed in men whereas preserved ejection fraction and diastolic HF were seen in women. (26, 27).

Treatment

Treatment is primarily aimed to reduce HF symptoms and improve cardiac function (45). Conventional HF treatment has a satisfactory effect in most cases of DCM. A considerable percentage of patients included in HF studies have been diagnosed with DCM. Thus, the effect of conventional treatment in this group is well studied (23, 45). All patients have an indication for angiotensin-converting enzyme inhibitor (ACE) or angiotensin receptor blockers (ARBs) and beta-blockers. Mineralocorticoid receptor antagonists (MRA) is given to patients with persisting symptoms and EF <35%. The mentioned medications have shown to reduce mortality, morbidity and hospitalization for HF (12, 46-50) Loop diuretics such as furosemide is an important symptomatic treatment and reduce signs of congestion but lack prognostic effect on the disease (23, 45, 51). Table 3 illustrated

treatment strategy according to HF symptoms and EF% reduction according to ESC guidelines (23).

Table 3 – Treatment strategy according to HF symptoms and EF% reduction.

1st line treatment	- **All patients receive therapy with ACE inhibitors or ARB and Beta blockers.**
2nd line treatment	- In cases where symptoms still appear and LVEF <35%, MRA such as spironolactone or eplerenon will be added.
3rd line treatment	- Angiotensin receptor neprilysin inhibitor (ARNI) can replace ACE inhibitors/ARB. - Cardiac Resynchronization therapy (CRT) is a pacemaker that synchronizes the right and left ventricle contraction which may be indicated in patients with QRS duration complex above 130 ms for example in patient with left bundle branch block. - Ivabradine may be given to patients with sinus rhythm and heart frequency above 70 bpm.

Advanced therapy may be required in patients with refractory HF including cardiac resynchronization therapy (CRT) by bi-ventricular pacing, LV assist devices (pumps) or cardiac transplant (23, 45). Patients in class 2 and 3 who are not responding to optimal medical therapy should switch from ACE inhibitors and ARB to angiotensin receptor-neprilysin inhibitor according to the updated ESC guidelines (23, 49). The above treatments may be combined. In cases of resistant symptoms, digoxin (specially in the presence of atrial fibrillation), CRT, LV assist device (LVAD) or heart transplantation should be considered. (23). Patients that have reached the end stage of HF may be considered for a heart transplantation. (45) (23).

Prognosis

DCM is progressive and leads in most of the cases to chronic HF with high mortality rate. However, a recent study demonstrated that the long-term prognosis of patients with DCM has improved during the past 30 years. Evidence based pharmacological treatment, implantable devices and heart transplantation has improved the prognosis. (52, 53)

Study project

Background and aim

Cohort studies have presented the natural history of cardiomyopathies from a small number of specialized centers, but there is a lack of data describing baseline characteristics and initial symptoms of the disease. Sahlgrenska cardiomyopathy project (SCMPC) is a huge project including all cardiomyopathies; Figure 1. Due to the vast number of existing cardiomyopathies a decision was made to target those with DCM. The main focus for this study was to describe patients' baseline characteristics and initial symptoms who had received a diagnosis of DCM by the physician in charge. Both women and men were included. Patients with different degrees in severity according to the NYHA classification were also included in the study

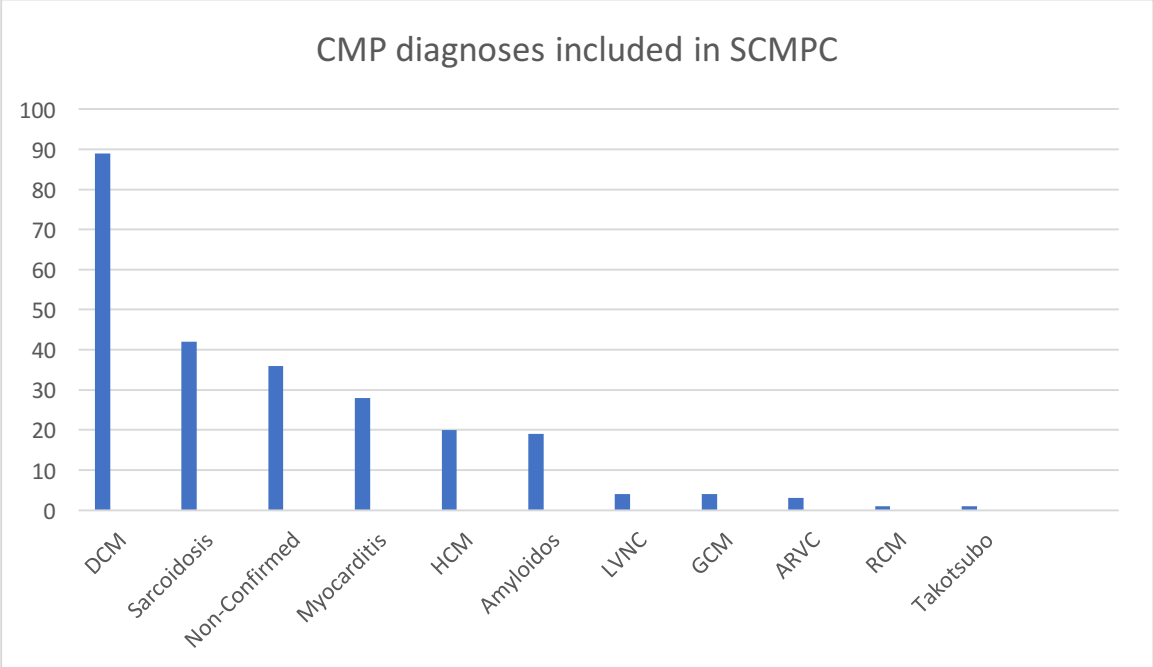

Figure 1. Frequency histogram showing the number of patients in the SCMPC at the time for the study divided by diagnoses. For abbreviations see text and list.

Objective

1. Describe the baseline characteristics and symptoms at onset patients with DCM enrolled to Sahlgrenska cardiomyopathy project during June 2018 to July 2020.
2. What kind of pharmacological treatment was prescribed in patients with DCM and which of them is most common?

Method

This study is a retrospective descriptive cohort study. The cohort consists of 89 patients with DCM out of 244 patients with different CMPs enrolled in The Sahlgrenska Cardiomyopathy Project (SCMPC) during the study period of approximately two years year from June 2018 to July 2020. SCMPC is a prospective research database and was started in June 2018 and is still ongoing and aims to include all CMP patients who are being investigated or treated for a cardiomyopathy at Sahlgrenska University Hospital/Sahlgrenska. The Patients were included consecutively in connection with inpatient care and out-patients visits. In connection with the clinical visit, informed consent was obtained from the patients.

Data collection procedure

A database was created to enter data from included patients and analyze these on the basis of the scientific issues.

Data was collected retrospectively from the patients' medical records, compiled in a customized database, and analyzed by the author. Sahlgrenska University Hospital use a medical record system called Melior. Nurses and doctors at the cardiology clinic filled in data obtained from the patients in Melior. Blood pressure were taken by the doctors and nurses both manually using a cuff and by blood pressure monitor when the patients had rested for 10 minutes. Patients height and weight were measured at the clinic by the nurses body mass index (BMI) was calculated as the person's weight in kilograms divided by the patient's height in meters squared. BMI is then used to characterize patients as underweight <18.5, normal weight 18.5-24.9, overweight >25 and obese >30. With regards to symptoms at onset , the patients reported their first symptom to the responsible doctor who registered the information in Melior. NYHA class was described by the responsible doctor based on the

patients' symptoms and following the NYHA classification. All patients included in the study had an echocardiography. Basic blood test was taken including NT-proBNP, hemoglobin and creatinine; troponin was taken in some cases. Some patients had further investigations such as MRI, PET-CT, cardiac catherization, and coronary angiography in order to rule out other causes for HF as DCM is mainly an exclusion diagnosis. Each individual investigation and final diagnosis is based on the assessment of the responsible doctor. Data from the medical records was stored in the research database. Variables obtained were age, gender, BMI, NYHA classification and onset of symptoms.

Statistical Method

Variables were collected from the database and registered in an Excel file. The Excel file was converted to the statistics program SPSS statistics, where all data was analyzed.

The first step was investigating whether the quantitative variables; Age at onset of symptoms, BMI, SBP and DBP were normally distributed (which they were).

Since the data was not from a randomized sample but a particular cohort, descriptive statistics were used and no hypothesis tests were performed. In category variables (nominal-scaled), the number and percentage were calculated, and for numerical variables (quota-scaled), the mean and standard deviation (SD).

In the NYHA classes, each category is reported, and the proportion of all individuals was calculated after patients with missing data had been excluded.

Sex is reported as the proportion of men and women respectively.

Ethics

For protection of the patients' integrity all patient data is encrypted, and the code key is not stored where other patient data is stored. All work is done on password-protected computers and journal processing takes place only within locked rooms at Sahlgrenska University Hospital. Written informed consent was obtained from all patients before the study. The study was approved by the Ethical Board in Gothenburg, Sweden (DNR: 935-17, 2018).

Results

Over the period 2018-2020, a total of 89 patients with DCM in Västra Götalands region were registered in the Sahlgrenska cardiomyopathy project. The patients were diagnosed at Sahlgrenska university hospital. Table 4 displays baseline characteristics of the study group. The mean age at symptom debut was 45.7 years (15.2 SD), the majority were men (75.2%), and their average BMI was 26.2 (5 SD). New York heart association (NYHA) class was formally documented in 62 patients (69.7), 36 of them (58.1) were in NYHA functional class 3-4 at enrollment.

Ten symptoms were identified. Dyspnea was the most common initial symptom at disease presentation in DCM patients (67.4%), followed by fatigue (55.1%). Syncope (6.7%) was the least common symptom at disease presentation. Five patients (5.6%) had survived cardiac arrest. Initial symptoms are shown in table 5 together with information about recorded arrhythmia.

A total of 83 (93.3% of the patients) had prescription of beta blockers which was the most frequently prescribed medication, followed by ACE inhibitors (79.8%), spironolactone (66.3%) and diuretics (57.3%). The least commonly prescribed medication was positive inotropic drugs (3.4%). Medical treatment is shown in table 6.

Table 4 Baseline characteristics of patients with dilated cardiomyopathy at enrollment to cardiology clinic

Variable	All patients n=89
Age at symptom debut, years [mean (SD)]	45.7 (15.2)
BMI [mean (SD)]	26.2 (5)
Men [n(%)]	67 (75.2)
Systolic blood pressure, mmHg [mean (SD)]	119 (21.5)
Diastolic blood pressure, mmHg [mean (SD)]	76 (14.9)
NYHA	
class 1 [n(%)]	10 (16.1)
class 2 [n(%)]	16 (25.8)
class 3 [n(%)]	27 (43.5)
class 4 [n(%)]	9 (14.5)

Table 5 Initial symptoms at presentation in patients with dilated cardiomyopathy

Variable	All patients n=89
Dyspnea [n(%)]	60 (67.4)
Fatigue [n(%)]	49 (55.1)
Edema [n(%)]	15 (16.9)
Atrial fibrillation [n(%)]	11 (12.4)
Chest pain [n(%)]	9 (10.1)
Multiple VES (PVC) [n(%)]	9 (10.1)
VT* [n(%)]	8 (11.6)
Syncope [n(%)]	6 (6.7)
Cardiac arrest [n(%)]	5 (5.6)
Bradycardia [n(%)]	3 (3.4)

Table 6 Medical treatment prescribed to patients with dilated cardiomyopathy

Variable	All patients n=89
Beta blockers [n(%)]	83 (93.3)
ACE/ARB [n(%)]	71 (79.8)
MRA [n(%)]	59 (66.3)
Loop diuretics [n(%)]	51 (57.3)
Anticoagulants [n(%)]	39 (43.8)
ARNI [n(%)]	11 (12.4)
Antiarrythmic [n(%)]	11 (12.4)
Immunosuppressive [n(%)]	11 (12.4)
Positive inotropic [n(%)]	3 (3.4)

Discussion

In this study, the objective was to describe patients with DCM included in the Sahlgrenska cardiomyopathy project regarding baseline characteristics such as age, sex, BMI and initial symptoms at disease presentation, and treatment. The present data confirmed that DCM was more common in men than in women in line with previous research (52-56). The disease presentation is earlier in men than in women, although the mechanism for this finding remains unexplained (56). Sex differences in the cardiovascular system are largely attributed to the sex hormones testosterone and estrogen. During HF, estrogen have an effect on the cardiovascular system which include reduced vessel wall- response to injury, rapid vasodilation, reduced development of atherosclerosis and apoptosis prevention in cardiac myocytes. (57-59). Testosterone may contribute to inflammatory mechanisms by activating factor-kB and inversely influence myocardial remodeling after myocardial infarction and impair cardiac function (60-62).

In this study, the mean age at symptom debut was 45.7 (15.2 SD) years. Recently, Elliot et al examined the characteristics of four CMP phenotypes including DCM. The study included a total of 346 DCM patients and showed that the mean age at enrollment was 52.6 (14.65 SD), slightly higher than in our study. (18). A possible explanation for this difference may be the lower number of patients included in our study. Certain studies have previously demonstrated that the age at symptom debut varies from 20 to 50 but that the range is wide and DCM can affect both children and elderly (16, 17). The wide age span for symptoms debut can possibly be explained by the different pathophysiological causes of DCM, such as inflammatory/infectious causes, toxins, drugs and alcohol. (1, 11, 14, 15). However, since DCM is idiopathic in most of the cases, factors affecting the time to debut symptoms remain to be investigated.

The most common symptom in this cohort of DCM patients was dyspnea which was reported by 67.4% of the patients, followed by fatigue (55.1%), and edema (16.9%). These three symptoms are typical of congestive HF, and this finding broadly supports the work of other studies in this area linking HF symptoms in patients with DCM. (17, 20, 21) (13). (11). (22). Five patients (5.6%) had cardiac arrest as initial of symptom of the disease. Elliot et al found cardiac arrest in 11% of the patients with DCM. (18).

This study shows that 58.1 % of DCM patients are in NYHA class 3-4 at first evaluation. This proportion was lower than that in a study from 1992 which found that 90% of the patients had symptoms typical of NYHA class 3-4 at the time of diagnosis. There could be several explanations for a difference. The previous study was published 29 years ago and probably performed earlier than that. Early diagnosis of the disease was maybe not possible if imaging techniques was not as readily available as today, and therefore patients might have presented with more severe symptoms at diagnosis. (21). NYHA class 2 was seen in 26 % of the patients. This percentage are similar with those obtained by Elliot et al who found that approximately 30 % of the patients presented with NYHA class 2. (18).
A recent study in Sweden found a strong association between high BMI and some cardiomyopathies specially DCM, and among younger patients also an elevated risk of developing cardiomyopathy in those with high BMI. (40). The mean BMI in patients with DCM were 26.2 in this cohort which is classified as overweight but far from obesity. This finding strengthens the association between high BMI and DCM as observed in previous studies. However, right sided HF and edema both can affect the appetite and absorption from

the intestine, therefore it is difficult to know if these patients' BMIs represent a risk association.

A possible explanation for the association between high BMI and HF may be due to the increase in blood volume and cardiac output due to overweight leading to ventricular dilatation, compensatory LV hypertrophy and LV diastolic dysfunction. However, according to a study made by Folkhälsomyndigeten in Sweden, the BMI in Sweden is high and classified as overweight in 51% of the population. This may indicate that patients with DCM is not more overweight than the general population in Sweden, as 51% of the population is classified as overweight. High BMI may be seen as a risk factor and is modifiable even if this study did not focus on identifying risk factors. Further studies are required in order to study the relationship between high BMI and CMP.

Drug therapy is often required to improve symptoms and prognosis in patients with CMP. Reflecting current guidelines for DCM, beta blockers were the most frequently used drug in this cohort and were prescribed in 93.3% of the patients. ACE inhibitors were prescribed in 79.8%, while 66.3% had prescription of MRA. These results are in agreement with those obtained by Elliot et al which demonstrated high use of beta blockers with 88% and 73% with ACE inhibitors in DCM. (18,23). Studies have shown that these medications have positive prognostic effects. (12,22). Loop diuretics were prescribed in 57.3%. They are prescribed to patients with congestive HF, due to their ability to greatly improve the symptoms. (23,51,61). Oral anticoagulants were prescribed in 43.8%, probably reflecting the incidence of thromboembolism and arrythmia in this group. (64).

Limitations

This study has some limitations. The small sample size is a major limitation. Most of the patients included were from Sahlgrenska University Hospital in Gothenburg and do not represent all DCM patients in Region Västra Götaland. As Sahlgrenska University hospital is a highly specialized tertiary center, only the sickest patients may be referred which may lead to an over-representation of patients with more severe clinical characteristics. This was a retrospective study of medical records and some information was missing e.g. NYHA class was not formally documented in 30% of the patients. It requires further studies with more included patients in order to confirm the findings. Finally, because DCM is a diagnosis based on exclusion of specific etiologies the cohort might be less homogenous than intended. Atrial fibrillation was present in 11 and multiple ventricular extra systole (VES) in 9 and these arrhythmias might be both a cause and a consequence of HFrEF as seen in DCM.

Conclusion and Clinical implications

Acknowledging that the current study is based on a small sample of participants, the characteristics of these DCM patients agree with those of earlier studies. The study set out to identify certain patterns in DCM. Dyspnoea was a common symptom at disease presentation, this is something clinicians should be aware of. Many DCM patients have a high BMI, which is something that may increase the risk of developing the disease, therefore it is important to recommend lifestyle measures at an early stage to prevent disease development. Two unchangeable factors were age and sex. Men were over represented in this group. Therefore, DCM should be considered as a differential diagnosis in men presenting/seeking medical care with dyspnea and an are overweight.

Medical treatment in DCM reflects the current guidelines, beta blockers, ACE inhibitors, spironolactone, and diuretics were the most frequently used medications.

Early detection of the disease with early treatment provides better prognosis. However, there were few patients included and no comparison with other HF patients with different etiologies and therefore not possible to draw any conclusion in this aspect. Additional studies are required to develop a full picture of CMPs in general and DCM in particular including diagnosis, lab results, hereditary history, comorbidities, interventions and prognosis.

Populärvetenskaplig sammanfattning på svenska

Kardiomyopatier är en heterogen grupp av hjärtmuskelsjukdomar. Kardiomyopati påverkar hjärtmuskeln och leder till att den blir strukturellt eller funktionellt förändrad vilket i sin tur leder till nedsatt pumpförmåga och risk för att hjärtat slår oregelbundet. Kardiomyopati kan leda till hjärtsvikt med symptom i form av andfåddhet, trötthet samt vätskeansamling i kroppen etc. Hjärtsvikt är ett allvarligt tillstånd och har generellt dålig prognos. För att förbättra prognos och livskvalité är det viktigt att tidigt sätta in behandling. Det finns flera viktiga faktorer att tänka på innan hjärtsviktsdiagnos sätts, såväl diagnostisk metod som tolkning av erhållna resultat är viktiga. Det finns olika typer av kardiomyopatier och dessa kan manifestera sig kliniskt olika. I detta arbete fokuserade författaren på typen dilaterad kardiomyopati förkortad DCM. Orsaken till DCM är inte helt klarlagd, det kan röra sig om genetisk sjukdom samtidigt som sjukdomen kan vara helt idiopatisk (okänd orsak) eller förvärvad.
Kardiomyopaticentrum på Sahlgrenska bildades för att systematiskt handlägga och kartlägga patienter med kardiomyopati. Sjukdomsgruppen har ofta dålig prognos vilket gör att forskning inom denna sjukdomsgrupp är angelägen. Patienter med bekräftad DCM registreras i en databas för att beskriva baslinje karaktäristiken dvs ålder, kön, BMI, debutsymtom och behandling.

I examensarbetet inkluderades 89 patienter med DCM där bakgrundsfaktorer och sjukdomspresentation kartlades. Dessa patienter inkluderades i Sahlgrenska kardiomyopati projektet från 2018 till 2020. I detta arbete kunde vi identifiera vissa karakteristika. I denna studie kunde man se att medelåldern vid insjuknandet var 46 år och att majoriteten av patienterna var män. Andningssvårigheter var ett vanligt debutsymtom bland patienterna. Ett medelvärde på BMI var 26, vilket innebär att patienterna var något överviktiga. Betablockerare och ACE hämmare var förskrivet till de flesta patienterna. Dock var det få personer inkluderade och inga jämförelser med hjärtsviktspatienter med t.ex. kranskärlssjukdom eller hypertoni genomfördes och därför kan man inte dra säkra slutsatser om vad som är speciellt hos patienter med hjärtsvikt och diagnosen DCM. Detta arbete är hypotesgenererande, men fler och större studier behövs för att kunna bekräfta fynden och öka förståelsen för DCM.

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