Dilated Cardiomyopathy

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Abstract

Dilated cardiomyopathy (DCM) is a heart disease that enlarges the heart muscle and reduces its function, leading to heart failure, arrhythmia, and sudden cardiac death. The causes of DCM are not always clear, but may include genetic mutations, viral infections, alcohol abuse, and certain medications. Common symptoms include shortness of breath, fatigue, swelling, and irregular heartbeats. Diagnosis involves physical exams, ECGs, echocardiograms, and additional tests to identify underlying causes. Treatment includes medication, such as ACE inhibitors and beta blockers, to improve heart function, diuretics to reduce fluid buildup, and anticoagulants to prevent blood clots. Surgery or implantable devices, like pacemakers or defibrillators, may be necessary. Early diagnosis and treatment are crucial for managing DCM, and many individuals with DCM can lead full and active lives with proper treatment and lifestyle changes.

Introduction

Dilated cardiomyopathy is a myocardial disorder characterized by progressive ventricular dilatation and myocardial stretching, impairing systolic function. This, along with valvular regurgitation, gives rise to congestive heart failure (1).

DCM constitutes 90% of all cardiomyopathies. 25-30% of DCM can be identified as familial (2), however the recent increase in incidence rates in the younger population is suggestive of non-genetic factors contributing to the development of the disease in predisposed individuals (3). Apart from genetic predisposition, the etiology also includes malnutrition, cytotoxic agents such as anthracycline derivatives, viral myocarditis and autoimmune disease (4).

The diagnosis of idiopathic DCM is based on:

1) a left ventricular ejection fraction of less than 45% and/or fractional shortening less than 25% and
2) end-diastolic diameter greater than 117% of the predicted value based on age and body surface area.

Familial DCM is diagnosed if there are two or more affected relatives or by the sudden death of a first-degree relative before reaching the age of 35 (5).

Mild cases of DCM can be totally asymptomatic but undiagnosed, it may become symptomatic, or even fatal (6). Symptoms of DCM are due to cardiac inadequacy – angina, lethargy, dyspnoea and oedema as a result of congestive heart failure (7). The prognosis of DCM is dependent on a multitude of factors, namely the cause, degree of disease and functional impairment and comorbidities. In the United States, it accounts for approximately 46,000 hospitalisations and 10/000 deaths annually (8). Moreover, a recent study showed that 8% of Sudden Cardiac Deaths are caused by DCM (9).

The aim of this review is to give a brief overview of the pathophysiology, detection and management this devastating disorder, which can be screened for and essentially prophylactically managed, minimising its adverse outcomes.

Causes

Genetic

Genetic mutations in genes encoding for sarcomere, cytoskeletal and envelope proteins account for 20-48% of cases (10).

Z-discs are the basic contractile unit of the cardiomyocyte, approximating when there is cardiac muscle contraction. Along with the cytoskeleton, they are vital for the structural integrity, contraction and mechano-sensing transductions of the cardiomyocyte. Titin is an elastic protein anchored in the Z-disc. It is passively stretched in diastole, returning to its original size once contraction has occurred. It is coded for by the gene *TTN*, present on chromosome 2. Non-sense or frameshift mutations in the *TTN* gene, cause truncation of the protein, interfering with its elasticity. Such mutations are responsible for up to 25% of DCM cases, with an even higher prevalence in patients over 40 (11). Formatting...

Mutations in the *DES* gene, which encodes for desmin, a cytoskeletal protein forming muscle-specific intermediate filaments account for 1-2% of dilated cardiomyopathies (12).Formatting...

Dystrophin, encoded for by the *DMD* gene on the X chromosome, is important in the transmission of force of contraction, being the mechanical link between the intracellular cytoskeleton of all muscles and the extracellular matrix. DCM arising from *DMD* mutations were linked to 90% of Duchenne's muscle dystrophy cases and 70% of Becker's muscular dystrophy cases. However, isolated DCM can exist without signs of muscular dystrophy (13).

Desmosomes hold myocardial cells together, ensuring the mechanical and electrical integrity of the heart. An autosomal dominant pattern of inheritance of desmosomal genes has been noted in patients suffering from DCM. The *DSP* gene encodes for the desmoplankin protein, an intracellular component of desmosomes. *DSP* gene mutations result in DCM associated with left ventricular fibrosis and ventricular arrythmias (14).

The sarcomere is the functional unit of the cardiac muscle consisting of thin actin and thick myosin filaments. Mutations in the genes encoding for these proteins give rise to 10% of cases of familial DCM while

mutations in *MYH7* gene, encoding for the myosin heavy chain beta subunit are associated with 4-6% of familial DCM cases.

Acquired

Acquired forms of DCM may result from; myocarditis, sarcoidosis, toxins like alcohol and drugs, endocrine and metabolic disturbances and pregnancy.

Myocarditis damages the heart muscle by scarring, limiting its ability to contract. It is brought about by acute phase viral inflammation where exposure of intracellular antigens leads to a T-lymphocyte-mediated inflammatory response which may persistent in some patients with with poor immune response. Around 20% of myocarditis patients develop chronic DCM (6).

In sarcoidosis, granulomas form in heart muscle tissue as a response to inflammation, possibly causing fibrosis, restricting the elasticity of the heart muscle, leading to left ventricular dilatation and loss of contractile power. The papillary muscle and mitral valve function may also be affected. Heart blocks and tachyarrhythmias commonly arise from the disease due to interference with the conduction pathway of the heart (15).

36% of DCM cases in the West are associated with alcohol abuse. It causes tachycardia and vasodilation and cardiac muscle hypoperfusion, weakening its contractility. Alcohol is pro-arrhythmic. By causing electrolyte abnormalities it affects the heart rate variability and the QT interval (16). Cocaine stimulates the sympathetic system, increasing myocardial oxygen demand and causing coronary vasospasm, leading to coronary micro-ischaemia and scarring. Therapeutic drugs such as doxorubicin, used in chemotherapy are possible culprits (17).

In hemochromatosis, iron is deposited in organs, causing damage and dysfunction. In the heart, it deposits in the ventricle initially, causing DCM, reducing the ejection fraction, and giving rise to arrythmias. Hemochromatosis is not entirely acquired since it can be caused by a mutation in the HFE gene which controls absorption of iron in the small intestine (18).

Peripartum cardiomyopathy is DCM in pregnancy. Although the underlying causes are still unclear, it is thought that it may be a result of a previous abnormal immune response or viral illness. It can be difficult to detect as its symptoms may be attributed to usual third trimester physiology such as lower limb oedema and slight dyspnoea. It is diagnosed when heart failure develops in the last month of pregnancy or within 5 months of delivery with no other possible cause and when the ejection fraction is decreased to less than 45% (6).

Pathophysiology

Ventricular remodeling is brought about by cardiomyocyte hypertrophy and apoptosis, proliferation of myofibroblasts and interstitial fibrosis. In DCM, this occurs because of myocardial injury, increased left ventricular stress and haemodynamic disruption, bringing about an increase in oxidative stress, endothelin and pro-inflammatory cytokines, upregulation of the renin-angiotensin-aldosterone system (RAAS) and the adrenergic nervous system. This results in pathological left ventricular remodeling, giving the ventricle a spherical shape (19).

Left ventricular function changes in conjunction with the alteration in shape and size. Though there is an increase in end-diastolic volume and preload, the stroke volume and cardiac output are reduced because the alteration of the extracellular matrix of the ventricles disturbs the excitation-contraction coupling, making it stiff. This ventricular stiffness also prevents complete relaxation of the ventricles during diastole, impeding ventricular filling (7).

$$\text{tension} = \text{pressure x } \frac{\text{radius}}{\text{wall thickness}}$$

In, DCM, according to the Law of LaPlace, the pressure in the left ventricle increases, increasing the wall tension. A larger force is needed to push the blood out of the heart. Repressed contractility reduces the force produced, resulting in a decrease in stroke volume, leading to organ hypoperfusion, including the heart itself. Insufficient energy supply causes deterioration of the cardiac myocytes, worsening the degree of heart failure, and creating a vicious cycle. Cardiac inefficiency can be calculated by measuring the myocardial oxygen consumption (19). Formatting...

To compensate for the reduced cardiac output, the sympathetic nervous system is upregulated and vagal stimulation of the heart is diminished. The levels of circulating catecholamines and ADH increase and there is activation of the RAAS. These together, bring about tachycardia, increased fluid retention and afterload which in turn elevate the wall stress and the myocardial oxygen demand further (6). The increase in wall tension is compensated for by muscular hypertrophy (19).

Congestive heart failure occurs as the atria push blood into the relatively overfilled ventricles. The cardiac output is decreased, and the heart cannot keep up with the body's demands. Due to ventricular over-filling, the ventricular walls cannot be approximated and complete closure of the atrio-ventricular valves is prevented, resulting in regurgitation (17).

The enlargement of the left ventricle displaces the papillary muscles and causes dilatation of the mitral annulus. The leaflets of the mitral valve retract towards the apex and the mitral valve fails to close, leading to mitral regurgitation (20). The backflow of blood into the atrium along with the poor ventricular function increases left-sided pressure which causes further dilation and remodelling of the left ventricle, decreasing the stroke volume and leading to further deterioration (21).

The conduction pathway in the heart muscle is disturbed by the alteration in the structure of the myocardium, the electrical activity responsible for keeping the heart beating normally is stopped or slowed considerably, resulting in a varying degree of heart block. The "irritable focus" giving rise to the arrhythmia can be a result of myocardial fibre stretching and fibrosis (22). Most of the ion channel dysfunction giving rise to the arrhythmias is within the sarcolemma and occurs due disruption of the sarcolemma-sarcomere link. The ion channel dysfunction can otherwise be due to a gene mutation giving rise to a dysfunctional cytoskeletal protein binding, impairing contractility. 25-30% of DCM patients have LBBB (23). The occurrence of supraventricular arrhythmias should prompt investigation for familial DCM (24). 40% of patients have non-

sustained ventricular arrhythmias – this gives a higher risk of Sudden Cardiac Death [25].

Thrombotic complications are commonly seen in DCM. Cardiac thrombus formation would be expected to be more frequent in the left ventricle, but not exclusively. The underlying cause is the diminished ventricular contractility, wall motion abnormalities and a blood flow disorder within the heart itself, markedly at the left ventricular apex (26). DCM gives rise of heart failure, which is prothrombotic in itself – there is more platelet activation, increased mean platelet volume, higher levels of fibrinogen and D-dimer and reduced levels of ADAMTS-13, which cleaves Von Willebrand Factor (27). Embolisation of the LV thrombi can result in stroke and peripheral emboli while embolisation of right-ventricular thrombi, can result in pulmonary embolism.

Clinical Presentation

The majority present between 20-60 years of age, usually after a lengthy latent period. Eventually, they present with symptoms of LV dysfunction and congestive HF (28). One of the earliest symptoms of DCM is dyspnoea, due to organ under-perfusion and subsequent hypoxia due to pump failure. Orthopnoea may interfere with sleep. This, in combination with the decreased energy production, makes the patient lethargic. Poor exercise tolerance and weakness are non-specific but common symptoms. Syncope and light-headedness can be due to an under-perfused brain, or arrhythmias (6).

Signs of HF can be detected on examination. Jugular vein distension with a hepatojugular reflux, hepatomegaly and pitting oedema of the lower limbs is indicative of right-sided HF (7). Chest auscultation could also reveal pulmonary crackles. A holosystolic murmur would be indicative of mitral and tricuspid regurgitation and an additional S3 gallop would be indicative of blood flowing into the ventricles in diastole (7).

Thrombosis presents according to the affected organ. In stoke, there would be localizing signs depending on the part of the brain affected. In pulmonary embolism there is acute shortness of breath and chest pain. Echocardiography is the most sensitive and specific tool to detect of thrombosis in cardiomyopathies (29).

SCD accounts for 30% of DCM mortality. Although the morality is higher in NYHA functional class IV, due to progressive heart failure, the rates of sudden death is higher in classes I and II. SCD is rarely the initial presentation of DCM. It generally follows the clinical presentation of HF when there is an improvement in the symptoms and is usually due to an arrhythmia (30).

Investigations

Cardiac MRI

Cardiac MRI is the gold standard in identifying both the cause and for monitoring the response to treatment, allowing quantification of ventricular mass, volume and function. Its primary role is differentiation of ischaemic and non-ischaemic cardiomyopathy (31). It also detects thrombi and gives the prognosis of the DCM. Cardiac morphology is assessed by black blood imaging, cardiac function by bright blood imaging, myocardial fat infiltration is assessed by fat saturation

imaging, blood flow is measured by velocity encoding mapping and vascularity by perfusion imaging while vasculature is assessed by gadolinium-enhanced angiography (32).

Echocardiography

An echocardiogram shows the degree of left ventricular dilation, the stage of the disease and the severity of the systolic dysfunction. It also allows measuring of heart size and the visualization of mitral or tricuspid regurgitation, its advantage is that it is not invasive and more easily available (33).

In DCM, LV diameter would be enlarged while the wall thickness would be reduced. The long axis/short axis ratio of the LV, is also reduced as the ventricle adopts a more spherical shape, as seen in Figures 1 and 2. Echocardiography allows calculation of the ejection fraction, which would be reduced to less than 45%. This is due to impaired contractility (34). Mitral regurgitation could be seen by colour flow Doppler echocardiography, as seen in Figure 4. The mitral regurgitation causes the left atrium to dilate, as seen in Figure 4.

3D echocardiography provides a better visualisation of the heart. Tissue Doppler imaging is used to evaluate myocardial diastolic and systolic function, both on a global and regional level. Speckle-tracking echocardiography is a technique used to measure the level of myocardial deformation (35).

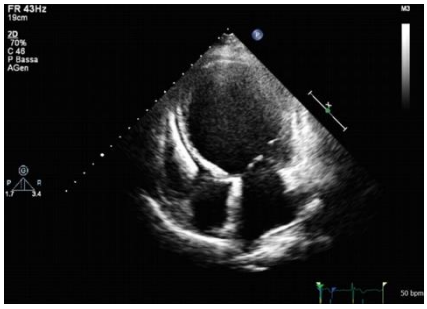

Figure 1: apical 4-chamber view of DCM, showing increased left ventricular sphericity and an implantable defibrillator lead on the right side of the heart. Retrieved from Gil *et al.*, 2016.

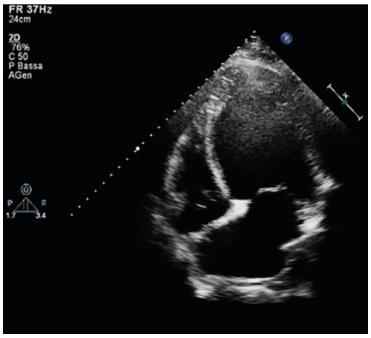

Figure 2: transthoracic echo in apical 4-chamber view, showing extreme remodelling of the heart chambers. Retrieved from Gil et al., 2016.

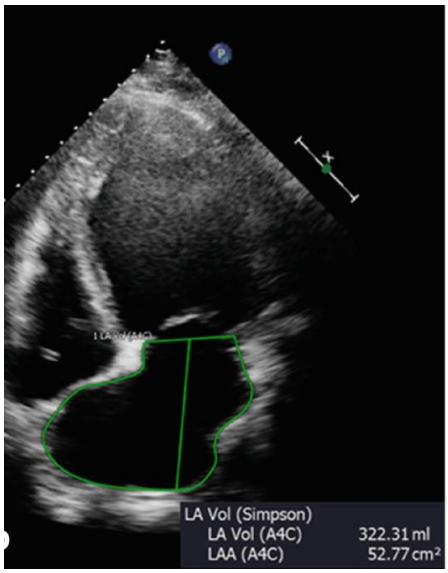

Figure 3: transthoracic echo in apical 4-chamber view, showing severe left atrial enlargement. Retrieved from Gil *et al.,* 2016.

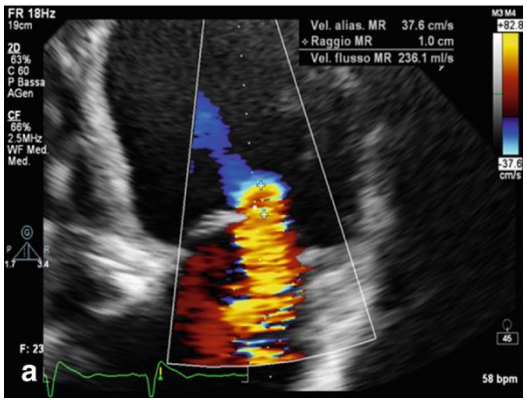

Figure 4: transthoracic echo of DCM with severe mitral regurgitation. Retrieved from Gil et al., 2016.

Plain X-ray

A plain chest x-ray, would show cardiomegaly and in the case of congestive heart failure, signs of pulmonary oedema – batwing hila, Kerley B lines, upper lobe venous distension, increased lung markings, interstitial oedema, and pleural effusion, seen as blunting of the costophrenic angles (36).

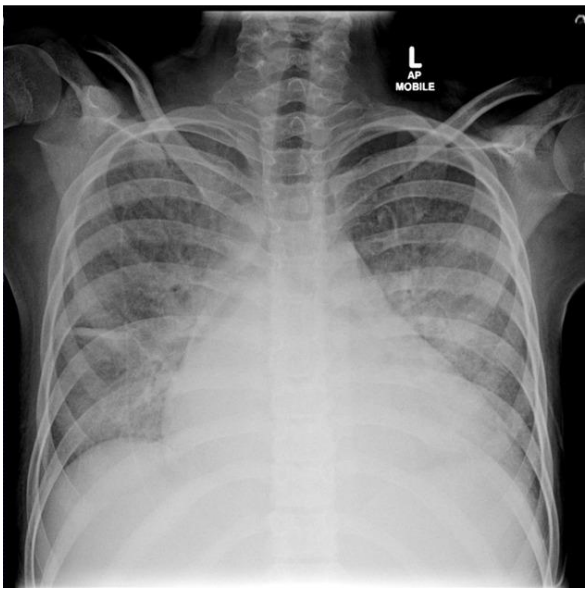

Figure 5: radiographical signs of congestive HF in a young patient, showing cardiomegaly, Kerley B lines, thickening of the interlobar fissures and interstitial oedema. Retrieved from Masarone *et al.*, 2018.

Electrocardiography

Different arrythmias arising from DCM include atrial fibrillation, ventricular ectopic beats, ventricular tachycardia and ventricular fibrillation. Left bundle branch block, may also be seen on the ECG.

Endomyocardial Biopsy

This is an invasive technique which is sometimes used to confirm DCM. It can be useful in cases of iron overload, amyloidosis and other infiltrative diseases but it carries a complication rate of 1-3% (37).

Management and Treatment

Pharmacotherapy aimed at improving the prognosis is required in symptomatic disease, and in asymptomatic left ventricular systolic dysfunction. In both, the onset of heart failure should be prevented by controlling hypertension and increasing the ejection fraction. ACEi, ARBs or ARNI are the preferred drugs to use. Beta-blockers are another possibility (38).

The most obvious and primary intervention would be lifestyle modification to minimize the factors interfering with the cardiac function, such as hypertension and ischaemic heart disease, so maintaining a healthy body weight, cessation of smoking, avoiding

alcohol, reducing sodium intake and restricting fluid intake (39).

Pharmacologic Treatment

The therapeutic algorithm has been proposed by the current European guidelines for patients showing symptoms of heart failure. ACEi (40) are the most effective drugs, replaced by ARBs in case of side effects (41). Beta-blockers are used in concomitance. Incorporation of a mineralocorticoid receptor antagonist would be considered with the dual therapy in persistent heart failure symptoms (42). All three drugs inhibit the sympathetic nervous system, reducing the workload of the heart, hence preserving it. Blocking of the RAAS and the beta-adrenergic system was found to reverse LV remodeling in patients with heart failure and severe LV dilation (19). Several clinical trials conveyed successful outcomes in morbidity and mortality when using the three drugs together.

More recently introduced drugs, ARNI and ivabradine – a hyperpolarization-activated cyclic nucleotide-gated channel blocker, have been added to the recommended list of drugs (39). By inhibiting neprilysin, ARNI inhibits ANP breakdown, hence increasing water loss by the kidney and reducing congestion. Ivabradine is used in patients whose sinus rhythm is over 70bpm at rest whilst on beta-blocker therapy (43). Both drugs were shown to minimize mortality and hospitalization rate of HF patients (44).

Diuretics also decrease symptoms of congestion, but no clinical trials were able to prove its effectiveness in improving mortality and morbidity of heart failure patients (39).

Since dilated cardiomyopathy may give rise to arrythmias, methods of controlling heart rhythm are considered. For ventricular arrythmias, amiodarone is the preferred major anti-arrhythmic agent, especially when the ventricular function is severely depressed. Sotalol is given to treat arrythmias in compensated HF (45).Formatting...

Anticoagulation may be used to prevent the formation of cardiac thrombi, pulmonary and peripheral embolisms [26]. Their use is especially recommended in patients with comorbid atrial fibrillation, history of mural thrombi and artificial valves (28).

Percutaneous Therapies

Catheter ablation can be considered for drug-resistant symptomatic AF and sustained monomorphic ventricular tachycardia (46), whereby heart tissue giving rise to the abnormal electrical activity generating the arrythmia is destroyed via extreme cold or heat. This is carried out by the introduction of catheters through a vein or artery in the groin which are threaded to the heart. This, however, is limited in patients with coronary artery disease.

In chronic heart failure with left ventricular impairment and functional mitral regurgitation, the MitraClip® is used as an alternative option for valve replacement in patients who are surgically high-risk. By preventing the leakage of blood back into the left atrium, it minimises symptoms of heart failure (47).

Device Therapies

An implantable cardioverter-defibrillator is recommended for patient with non-ischaemic DCM, symptomatic heart failure and in instances of a very low ejection fraction. However, it has proven to be more beneficial for patients with ischaemic heart disease than for patients with other HF causes. (39). All candidates for pacemaker implantation should be considered for ICD, even in the absence of LV dysfunction and ventricular tachyarrhythmias (48).

Cardiac resynchronization therapy is recommended by all guidelines for symptomatic HF, especially in non-ischaemic DMC. Despite this, the great majority of patients are non-responders. To minimize the rate of non-response, multimodal cardiac imaging is being used to refine the selection criteria and implantation techniques. Apical rocking seen on apical four-chamber view echocardiogram and myocardial asynchronism seen on cardiac MRI are positive predictors of CRT effectiveness (49).

Operative Treatment

The frequent complication of LV dysfunction in DCM by a regurgitant mitral valve necessitates its treatment. Mitral valve repair by undersized ring annuloplasty is a widely used option that leads to reversal of LV remodeling, and improves morbidity. It improves mortality in patients with moderate to severe mitral regurgitation secondary to idiopathic or ischemic DCM. However, it is limited by residual and recurrent mitral regurgitation in functional mitral regurgitation. To prevent recurrent or persistent mitral insufficiency, mitral valve replacement is preferred, especially in the presence of predictors of repair failure in the pre-operative echocardiogram (50).

Patients whose conditions are not improved by medical therapy develop chronic heart failure. For these patients, mechanical circulatory support (MCS) devices are necessary to unload the failing ventricle and improve organ perfusion. Short-term MCSs stabilise the haemodynamics and help recovery of patients with acute heart failure or cardiogenic shock until a more permanent solution is decided (45).

A left-ventricular assist device (LVAD) may be used to assist the left ventricle of the heart in pumping blood to the rest of the body. It is a battery-operated mechanical pump used in patients at end-stage heart failure. The LVAD has proved to be a successful alternative to a heart transplant, which is limited by donor availability. A heart transplant increases greatly the quality of life of patients with chronic heart failure who have no alternative choices (45).

Preventing Sudden Cardiac Death

Cardiac MRI and Holter monitoring are used to monitor risk stratification of HF progression and SCD (51). In LV dysfunction, with an EF of 35% of less, ICD reduces SCD by 80%. As a result, ICD is also being considered in familial cardiomyopathy with SCD, impaired LV function without HF symptoms and DCM with sustained ventricular tachycardia or syncope (52). Prior to consideration of ICD therapy, the HF has to be optimally controlled for 6 months and reassessment of LV function recovery has to be carried out beforehand, unless there is a significant risk such as familial DCM with ventricular arrythmias (30).

Familial Screening

Echocardiography and electrocardiogram should be used to screen all first-degree family members of affected patients. extensive family members should only be considered for testing if they have a high-risk occupation. Genetic testing is carried out depending on the clinical features of the presenting disease. Genetic testing offers an opportunity for early identification and intervention to stop or reverse the disease progression (5). Although seemingly beneficial, screening has its repercussions as well – detection of familial DCM with reduced penetrance, meaning that the individuals will not exhibit the signs of disease would mean unnecessary worry and treatment. To prevent this, only the clinically affected family members should receive pharmacological treatment based on their symptoms and their severity while a follow-up cardiac screening approach should be adopted for asymptomatic relatives, with ECG and echocardiography to detect even minor changes (53).

A Multidisciplinary Approach

This approach needs to be taken both to determine the cause of the disease and because several systems may be affected, either by the complications of the disease itself or else by the primary cause. In addition to the cardiac electrophysiologists, heart failure specialists and radiologists, which you would expect to be involved in all cases of DCM, the involvement of other specialist physicians would be specific to each case. For instance, DCM arising from sarcoidosis would most likely require the input from a respiratory physician as the lung is more commonly affected than the heart, in autoimmune disease, rheumatologist input would be required, neurologist involvement in neuromuscular disease, hematologists in DCM arising from iron overload and oncologists when arising from cytotoxic complications of chemotherapy (54). The management of the outcomes of the disease also calls for a multidisciplinary approach. In familial DCM, there is geneticist involvement to tackle the risk of relatives, as well as determining the type, risk of SCD and possibly guiding the management. Considering that congestive heart failure increases the risk for kidney disease, owing to congestion and hypoxia from hypoperfusion, which impairs urine output and exacerbates the HF, nephrologist involvement might be beneficial (55). If the patient is an athlete, consultation with a sports physician would be ideal.

Introducing the patient to a heart failure clinic which personalizes a management plan encourages the patient to have an active role in managing the disease. This programme would involve nurses, physicians and the appropriate specialist input as well as the patients themselves. Heart failure clinics educate the patient on how to adequately manage the disease through appropriate lifestyle modifications, exercise and medication while offering regular follow-up and close monitoring of the disease progression and response to treatment.

Conclusion

In essence, the diagnosis of DCM can be easily made by the use of appropriate investigations, most notably the cardiac MRI and the echo. The management is broad, and highly specific to each case but essentially, its aim is to optimise the cardiovascular health and to minimise symptoms and complications

of the disease, one of the most important being heart failure. Despite the multiple forms of treatment and prophylactic approaches previously mentioned, many patients still develop heart failure and as much as 50% die within 5 years (28).

Declarations

Conflict of interest: N.A.

Ethical statement: N.A.

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