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INHERITED CARDIOMYOPATHY

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ABSTRACT

During the past two decades, numerous disease-causing genes for different cardiomyopathies have been identified. These discoveries have led to better understanding of disease pathogenesis and initial steps in the application of mutation analysis in the evaluation of affected individuals and their family members. As knowledge of the genetic abnormalities, and insight into cellular and organ biology has grown, so has appreciation of the level of complexity of interaction between genotype and phenotype across disease states. The current state of knowledge with regard to genetics of cardiomyopathy represents a starting point to address the biology of disease, but is not yet developed sufficiently to supplant clinically based classification systems or, in most cases, to guide therapy to any significant extent. Future work will of necessity be directed towards elucidation of the biological mechanisms of both rare and common gene variants and environmental determinants of plasticity in the genotype–phenotype relationship with the ultimate goal of furthering our ability to identify, diagnose, risk stratify, and treat this group of disorders which cause heart failure and sudden death in the young

Keywords: ***Cardiomyopathy, Inherited cardiomyopathy, Types of Cardiomyopathys, Treatments, Conclusion***

INTRODUCTION

CARDIOMYOPATHY

Cardiomyopathy is a chronic disease of the heart muscle, in which the muscle is abnormally enlarged, thickened and stiffened. The weakened heart muscle loses the ability to pump effectively, resulting in irregular heartbeats (arrhythmias) and possibility even heart failure. Cardiomyopathy may be caused by many different factors, including viral infection (e.g, myocarditis), heart attack, alcoholism, long term high blood pressure, genetic

neuromuscular disease (e.g., muscular dystrophies and ataxias), genetic metabolic disorders, complications from AIDS, and other reasons that have not yet been identified idiopathic cardiomyopathy cause by heart attacks (referred to as ischemic cardiomyopathy) results from scarring in the heart muscles. Larger scars or more numerous heart attacks increase the risk that ischemic cardiomyopathy will develop. Alcoholic myopathy usually develop about 10 year after sustained heavy alcohol consumption other toxins that may cause cardiomyopathy include drugs and radiation exposure.[1]

Figure 1: Diseased heart muscles

Inherited cardiomyopathies are major cause of heart disease in all age group, often with an onset in adolescence or early adult life. Not only the patient but also their families can be severity burdened by these illnesses. Inherited cardiomyopathies include hypertrophic cardiomyopathy, dilated cardiomyopathy, arrythmogenic right ventricular cardiomyopathy, left ventricular non compaction, and restrictive cardiomyopathy.. However, locus and allelic heterogeneity are the rule, as are clinical variability and reduced penetrance of disease in carriers of pathogenic variants. These factors combined with genetic and phenotype overlap between different cardiomyopathies, have been made clinical genetic testing a lengthy and costly process, next generation sequencing technologies have removed many limitation such that comprehensive testing is now feasible.[2]

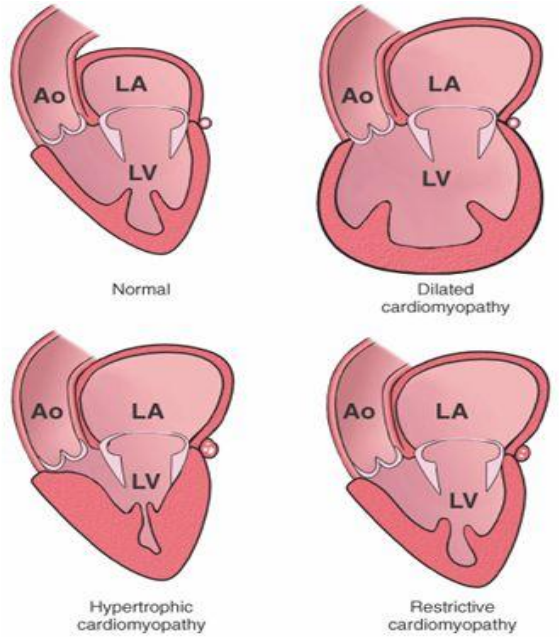


Figure 2: Types of inherited cardiomyopathies

CLASSIFICATION OF INHERITED CARDIOMYOPATHIES

The long standing classification of inherited cardiomyopathies according to functional and morphological features is crude yet clinically useful. Despite considerable heterogeneity within the categories of hyper tropic, dilated, restrictive arrhythmic genic right ventricular and other type of cardiomyopathies, these diagnostic classifications can predict major complications and delineate treatment options for each group. Mutations that affect adjacent amino acid in the beta-myosin heavy chain, for example, cause either hypertrophic cardiomyopathy or dilated myopathy. All the inherited cardiomyopathies are genetically heterogenicity with in each category there are multiple disease gene, and many different genes and many different mutation, each of which is uncommon.[3]

HYPERTROPHIC CARDIOMYOPATHY

Hypertrophic cardiomyopathy is an autosomal disease characterized by unexplained hypertrophy of left ventricles (and sometime of right ventricles), often with predominant involvement of the intra ventricular septum. Hypertrophic cardiomyopathy was a disease of the sarcomere when first three disease genes to be identified were found to encode components of the contractile apparatus of heart muscle. Mutations in nine gene encoding sarcomere protein have now been convincingly shown to cause hypertrophic cardiomyopathy. HCM is characterized by left ventricular hypertrophy (LVH) in the absence of an underlying systemic condition or other cardiac disease, such as valvular heart disease or hypertension.HCM is primarily inherited in an autosomal dominant pattern, although reduced penetrance and clinical variability are common. Clinical manifestations range

from being completely asymptomatic to progressive heart failure and SCD caused by mechanical or electrical defects. HCM is traditionally diagnosed using cardiac imaging modalities, such as echocardiography and cardiacmagnetic resonance imaging, and often presents as asymmetrical septal hypertrophy.[4]

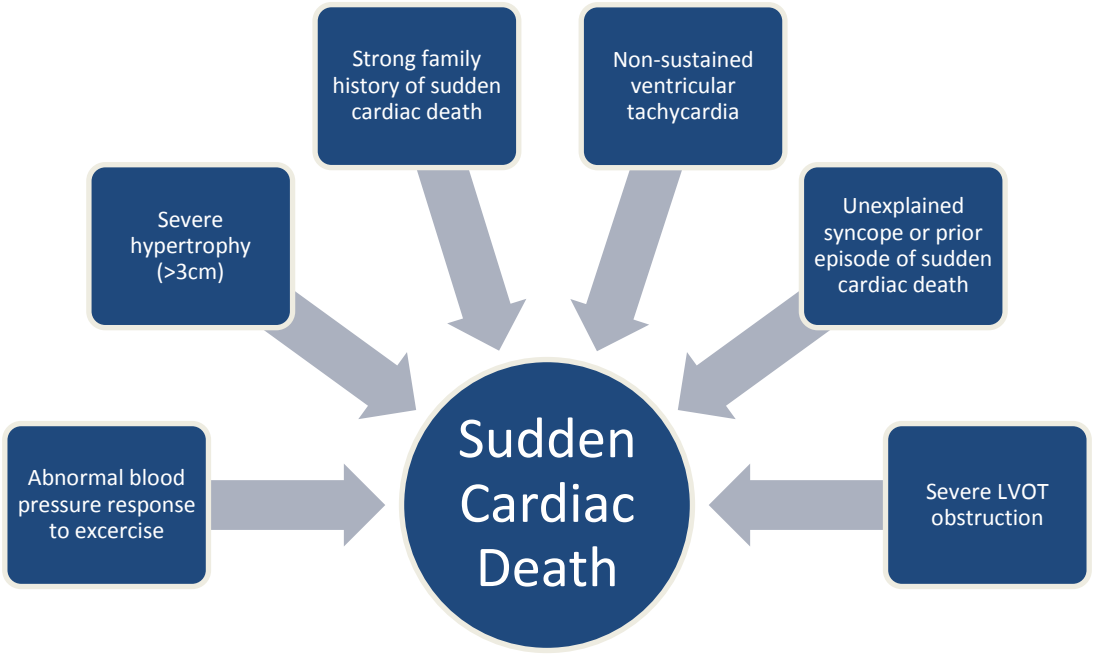


Figure 3: Risk factors for sudden cardiac death in hypertrophic cardiomyopathy

DILATED CARDIOMYOPATHY

Dilated cardiomyopathy (DCM) is defined by left ventricle dilatation and systolic dysfunction (a reduction in myocardial force generation characterized by an ejection fraction of <50%) and is the most common indication for cardiac transplantation. The spectrum of clinical manifestations includes heart failure, thromboembolism and sudden cardiac death (SCD). Dilated cardiomyopathy can also be an end-stage presentation of other diseases or environmental exposures, including myocarditis and alcohol abuse. Idiopathic DCM, which is diagnosed when known systemic or environmental triggers have been excluded, includes genetic DCM. The estimated prevalence of idiopathic DCM is 1 in 2500 individuals, although this maybe an under estimate, and the percentage of idiopathic DCM cases that have a genetic etiology is estimated to be 30% to 50% based on the presence of a family history.

ARRYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is defined by myocyte loss and fibro fatty infiltration of the myocardium, is associated with an increased susceptibility to arrhythmias and sudden death and accounts for a significant portion of sudden deaths in athletes and young adults.Initially thought to affect only the right ventricle, LV

involvement is now becoming increasingly recognized. ARVC is typically inherited in an autosomal dominantpattern with reduced penetrance and variable expressivity and affects men more frequently than women.[6]

LEFT VENTRICULAR NONCOMPACTION

Isolated left ventricular non compaction (LVNC) is characterized by a heavily trabeculated or spongy appearance of the LV myocardium. An arrest of myocardial compaction during the first trimester of embryonic development is widely believed to be a cause although others have proposed that it can be an acquired process based on case observations of LVNC after previous normal echocardiographic findings.

RESTRICTIVE CARDIOMYOPATHY

Restrictive cardiomyopathy (RCM) is characterized by increased stiffness of the ventricular chambers, although ventricular wall thickness and systolic function is generally within normal limits. Most individuals with RCM develop heart failure and succumb to death within a few years.Some reports suggest a clinical overlap between RCM and HCM.Idiopathic RCM is rare, and its genetic etiology is onlybeginning to be defined. Inherited cardiomyopathies have traditionally been defined based solely on clinical features, including ventricular morphology and function**.**

SYMPTOMS

The symptoms of cardiomyopathy vary by type:

- Dilated cardiomyopathy — Symptoms can include:

Shortness of breath, especially during exertion, Fatigue, Difficulty breathing while lying down, Leg swelling, Palpitations, Chest pain

- Hypertrophic cardiomyopathy — Symptoms, when they occur, are usually the same as the symptoms of dilated cardiomyopathy. Sometimes, the first symptom may be fainting or even sudden death. The condition also can cause chest pain, usually during exercise.
- Restrictive cardiomyopathy — Fluid accumulates in the legs and abdomen. This condition also can cause shortness of breath, especially during exertion.[5,6]

DIAGNOSTIC METHOD

The basic evaluation in the proband consists of an accurate family history, physical examination with specific attention to the neuromuscular apparatus, laboratory examination including CPK, chest X-ray, ECG and echocardiogram. In selected cases, an exercise stress test or a pharmacological test, such as dobutamine echocardiography, may be indicated to induce ischemia and unmask an ischemic cardiomyopathy. More specific diagnostic tests include hemodynamic and coronary angiographic study, radionuclide ventriculography and endomyocardial biopsy. Molecular genetic diagnosis should be performed when the test is available and may impact the clinical management. At present, molecular genetic analysis is available for following FDC genes: DES, DMD, LMNA, MYBPC3, MYH7, TAZ, TNNT2, and TMP1.[4,7]

PREVENTION

The best way to prevent cardiomyopathy is to prevent the diseases that cause it. Know the risk factors for coronary artery disease. Modify those risks early in life. One can reduce the risk for coronary artery disease by: keeping blood pressure normal. Eat a diet rich in vegetables and fruits. Take medication as needed. Drinking no more than two alcoholic beverages per day, do not drink alcohol at all if one is at a high risk of dilated cardiomyopathy. If one has any family members with inherited cardiomyopathy, contact the doctor for an evaluation.[2]

TREATMENT

Lifestyle Changes - Doctor may suggest lifestyle changes to manage a condition that is causing cardiomyopathy. These changes can help reduce symptoms. A healthy diet and physical activity are part of a healthy lifestyle Other lifestyle changes - Doctor also may recommend other life style changes, such as:Quitting smoking, losing excess weight, avoiding the use of alcohol and illegal drug, getting enough sleep and rest, reducing stress, treating underlying conditions, such as diabetes and high blood pressure [3, 4].The treatment of cardiomyopathy depends on its cause. Here are some of the more common treatments:

Medications that prolong life in people with dilated cardiomyopathy.

Angiotensin-converting enzyme (ACE) inhibitors, Angiotensin receptor blockers, Beta-blockers, Aldosterone receptor antagonists.

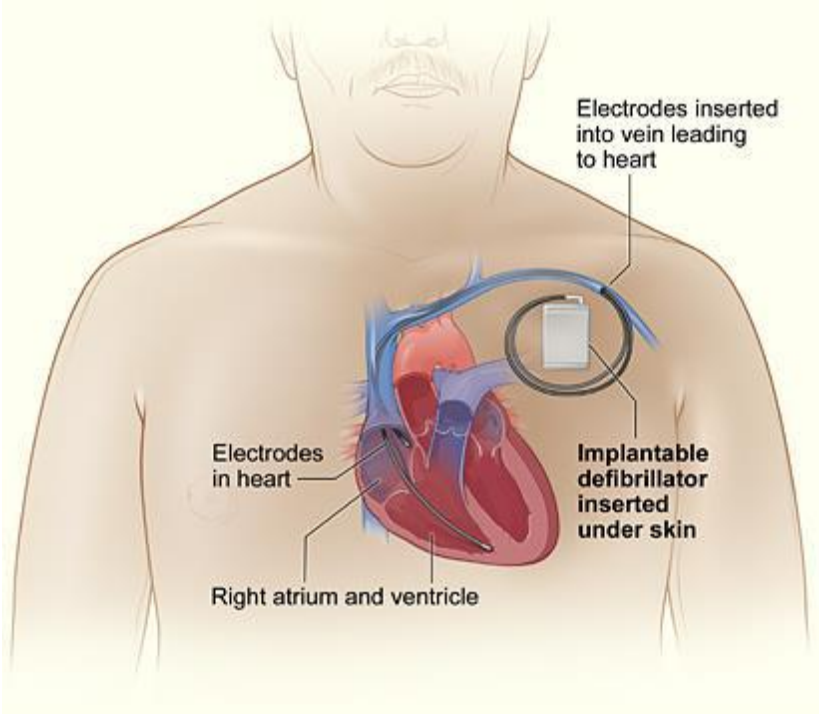
Drugs that improve the symptoms of heart failure in dilated cardiomyopathy.

Diuretics, ACE inhibitors, Angiotensin receptor blockers, Digoxin .Drugs that help to relax the heart muscle in hypertrophic cardiomyopathy. Beta-blockers, Verapamil, a calcium-channel blocker drug, Antiarrhythmic drugs to correct abnormal heart rhythm.

Surgery for Cardiomyopathy

Doctors use several types of surgery to treat cardiomyopathy. They include septalmyectomy, implanted devices to help the heart work better, and heart transplant. SeptalMyectomy- Septalmyectomy is open-heart surgery. It's used for people who have obstructive hyper trophic cardiomyopathy and severe symptoms. This surgery generally is used for younger patients and for people whose medicines aren't working well. During the surgery, a surgeon removes part of the thickened septum that's bulging into the left ventricle. This improves blood flow through the heart and out to the body. The removed tissue doesn't grow back. The surgeon also can repair or replace the mitral valve at the same time (if needed). Septalmyectomy often is successful and allows you to return to a normal life with no symptoms artrhythms.[5]

Surgically Implanted Devices Surgeons can place several types of devices in the heart to help it work better. One example is a pacemaker. This is a small device that's placed under the skin of your chest or abdomen to help control arrhythmias. The device uses electrical pulses to prompt the heart to beat at a normal. Sometimes doctors choose to use a cardiac therapy resynchronizations (DRT) device. A CRT device coordinates contractions between the heart's left and right ventricles. An implantable cardio verter defibrillator (ICD) helps control lifethreatening arrhythmias that may lead to SCA. This small device is implanted in the chest or abdomen and connected to the heart with wires. If an ICD senses a dangerous change in heart rhythm, it will send an electric shock to the heart to restore a normal heartbeat



Location of an implantable defibrillator in the upper chest

ADDITIONAL TREATMENTS

Genetic Testing

Family screening is often missed because the focus is on attending to the child with cardiomyopathy. However, identifying who may be affected is important for family planning as well as assessing the risk to relatives and siblings. Since cardiomyopathy can be inherited and present without any signs or symptoms, it is recommended that all first-degree relatives of a patient (parents, siblings, children) be screened. It is also advisable to screen **20 |** P a g e grandparents, aunts, uncles, and cousins. This is especially the case if there is a family history of sudden infant death or sudden cardiac arrest. Even if there is no evidence of the disease, it is advisable to screen more than once. For children with an affected family member (parent or sibling) but without symptoms, an echocardiogram and ekg should be regularly scheduled every 1 to 3 years prior to age 12 and then more frequently from age 12 to 21. If by early adulthood there is no evidence of cardiomyopathy, it is unlikely that the condition will develop. However, those with a family history of cardiomyopathy may be advised to continue screening every 5 years throughout life even after the age of 21.32 Factors that typically influence the frequency of screening include: Type of cardiomyopathy diagnosed, Family history indicating the likelihood of familial cardiomyopathy and Clinical presentation profile of the affected family member. Alternatively, if a specific genetic diagnosis can be determined (i.e. cardiomyopathy related to another syndrome), other siblings should be genetically tested to see if they are at risk for the disorder and cardiomyopathy. This of testing can lead to a better defined prognosis and more.

CLINICAL COURSE AND MANAGEMENT OF PREGNANT WOMEN WITH INHERETED CARDIOMYPOATHY

Many pregnancy-related problems in women with cardiovascular disease are related to physiological changes in the cardiovascular system. During pregnancy, maternal blood volume increases by 40%, resulting in a 30–50% increase in cardiac output. The increase in cardiac output is achieved by a rise in stroke volume and, later in pregnancy, an increase in heart rate of 10–15 beats per minute. Vasodilation occurs early in pregnancy due to hormonal influences, triggering the increase in plasma volume and cardiac output. In addition, remodeling of placental vessels in the second trimester results in a marked decrease in systemic vascular resistance accompanied by a lowering of the blood pressure by about 10mmHg[2,3,5]. A rise in several blood coagulation factors and a decrease in fibrinolytic activity results in a hyper coagulable state Inlabour, stroke volume is increased due to increased venous return resulting from uterine contractions. Finally, after delivery there is an increase in cardiac output depending on blood loss during labour and auto-transfusion directly after delivery as a result of uterus contraction. All cardiovascular parameters gradually return to pre-pregnancy values a few weeks after delivery. During pregnancy drug absorption

is usually decreased and renal elimination is increased, decreasing the total plasma concentration of the drug. Expansion of the blood volume leads to dilution and a decrease in blood proteins, resulting in higher concentrations of unbound drugs in the blood. Furthermore hepatic metabolism may increase or decrease depending on the isoenzyme involved.

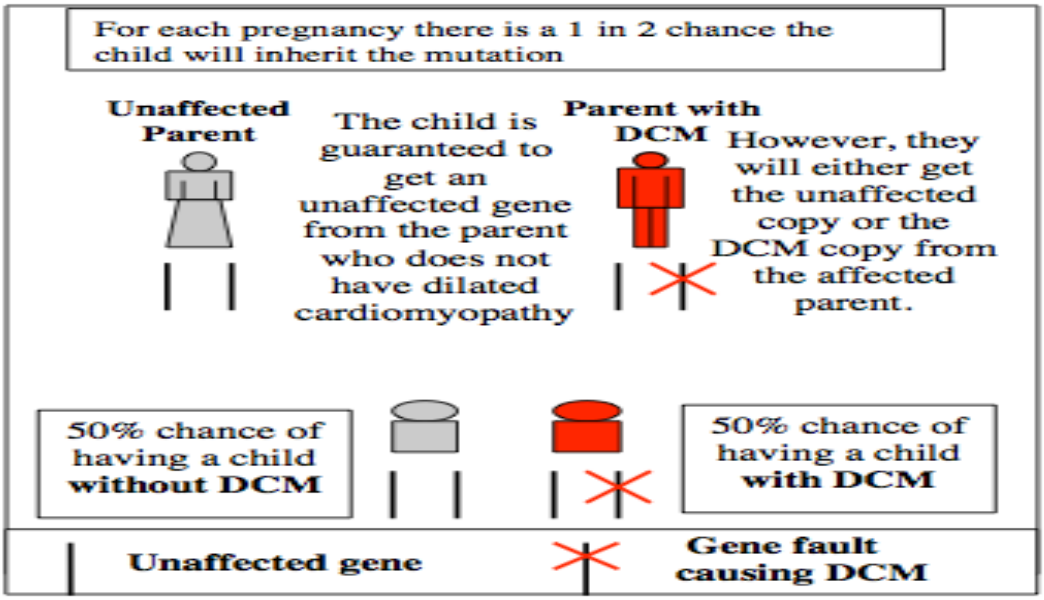


Figure 4: Chances of inheritance

CONCLUSION

Over the last decade, substantial progress has been made in defining single gene mutations that can cause inherited cardiomyopathies. Disease-causing genes have yet to be identified for a number of mapped chromosomal loci, and it is likely that additional loci remain to be discovered.

Pregnancy exposes patients with inherited cardiomyopathies to certain risks, such as arrhythmias and heart failure. Pregnancy is generally well tolerated in asymptomatic patients and is mostly not accompanied by a worsening of the clinical condition postpartum compared with prepartum, but there are exceptions and an adverse clinical course cannot always be avoided despite intensive medical treatment.[1]The chance of maternal cardiac complications increases in the presence of prior cardiac events, poor functional class (NYHA III or IV), severe left ventricular systolic dysfunction, and left outflow tract obstruction in the case of HCM. Early consultation when contemplating pregnancy is an important aspect of managing women with cardiomyopathy. Ongoing efforts to expand our understanding of both pathogenesis of disease and the complex interplay between the factors involved in disease expression will offer continued opportunities for improved care.

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