Ganesh Elumalai and Emad Abdulrahim Ezzeddin / Elixir Embryology 99 (2016) 43284-43288

Available online at www.elixirpublishers.com (Elixir International Journal)



Embryology



Elixir Embryology 99 (2016) 43284-43288

"THE SUDDEN SOUL REAPER" - HYPERTROPHIC CARDIOMYOPATHY - ITS EMBRYOLOGICAL BASIS

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ARTICLE INFO

ABSTRACT

Article history: Received: 18 September 2016; Received in revised form: 19 October 2016: Accepted: 25 October 2016;

Keywords

Cardiomyopathy, Myocardium, Arrhythmia, Myocardial Infarction, Myocardial Disarray, Hypertrophy,

Hypertrophic Cardiomyopathy is an inherited disorder that affects the muscle of the heart or the Myocardium. This condition results from a mutation to several genes that affects the production of cardiomyocytes proteins and therefore lead to an abnormal thickening and enlargement of the heart walls. That myocardial thickening induces rigidity and stiffness that reduces the heart efficiency of contractility and narrows the capacity of its cavities. Nonetheless it can cause an irreversible damage to the myocardial tissue producing a scar tissue that interferes with the heart electric activity and rhythm which may end with a life-threatening arrhythmia and death.

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Introduction

Cardiomyopathy is an illness that affects the muscle of the heart or the myocardium. Such illness can target all spectrums of people ages from early childhood to elderly [1]. And its signs and symptoms may vary widely from one condition to another, being unnoticeable and benign in many cases to highly morbid or even deadly or mortal in fewer other cases. Cardiomyopathy is mainly categorized into four main types [1], are (i) Dilated cardiomyopathy, (ii) Hypertrophic cardiomyopathy, (iii) Restrictive cardiomyopathy and (iv) Arrhythmogenic right ventricular dysplasia.

The heart muscle (Myocardium) becomes enlarged and thickened [2, 3], sometimes rigid and it loses some or much of its flexibility. The stiffness of the cardiac muscles affects commonly the bottom of the heart and sometimes the septum between the right and left ventricles. That results in the narrowing of the heart chambers especially the left ventricle as in the case of the hypertrophic cardiomyopathy. The heart gradually becomes weaker and less able to pump blood throughout the body, as the heart ventricles wall happens to become rigid and doesn't do sufficient or rather efficient effort to contribute in the propulsion of the blood entity. Also not to forget to mention that a cardiac muscle damage may occur from the abnormal thickening, leading to the formation of scar tissues that eventually replaces the muscles tissue of the heart and lead to even more impairment to the cardiac musculature. As a result the condition worsens and in more advanced situations it leads to an interference with the normal conduction of the heart electric signals [2] which regulates the heart beat ratio, such interference triggers irregular heartbeats that are called Arrhythmia. Those arrhythmias combined with strenuous activities like heavy or competitive sports may lead to a sudden cardiac arrest and death in young athletes or other voung individuals [2, 3].

The Diseases that affect the cardiac muscles or the myocardium often occur because of unknown causes. Yet,

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there are some identified factors that play a clear role in the causality of such type of diseases. Cardiomyopathy diseases can be sourced into two main factors either genetic (or inherited) or acquired from a precursor ailment that in a secondary or a post-traumatic aftermath would develop into the cardiac myopathy. Such an example is Myocardial Infarction [2].

Incidence

The complete literature review surveys were conducted with the pieces of information received nearly from the past twenty-five decades of previous workers [3]. HCM (Hypertrophic Cardio-Myopathy) is a genetic condition in main part of it. It is caused by a mutation to a gene or several genes that are responsible in the production of cardiac muscles proteins [4, 6]. This mutation is passed on through families from parent to offspring. Every child of an HCM suffering person is prone to a 50 per cent chance of inheriting the condition [4]. In a publication that was inducted by the "Hypertrophic Cardiomyopathy Association" in the US, in the 2000's; it indicated that HCM is the most common genetic heart condition (Fig-1), that has afflected more than 1 in a 500 in the population [5]. It showed that there are estimately 700,000 to 725,000 individuals in the United States of America that have this condition [5].

Similarly, in a stated claim by the British Heart Foundation it is mentioned that 1 in 500 of the United Kingdom population suffers from HCM condition. Nevertheless, most people who had it showed a few if not no symptoms [4]. In some more subsequent studies they showed the HCM has a previlance of 1 to 500 in a wide variety of populations including native Americans, rural midwestern US Americans and Chinese and among others.

Looking at the wide population spectrum of HCM incidency and knowing that it complies no relation to a specific age or gender it means that this genetic heart disease is an equal oppurtunity condition [5].

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Figure 1. Shows that the HCM has a greater incidence than other more recognized congenital diseases names.

When looking at the testing results that became available in 2015, cardiac MRI (Magnetic Resonance Imaging) and genetic testing for HCM; they cleared to our view that HCM may be even more common than what has been thought. As the results showed that the number of those with HCM increased to 1 in 200-300 [5]. Therefore, estimated numbers for the presence of HCM is somewhat close to more than 1 million of US population, and 36 million or more worldwide [5].

Normal Embryological Development of the Cardiac Muscle

The heart is consisted primarily of three layers. The first layer is the innermost layer and it is called the Endocardium. This layer is thin and it covers the surface of the inner champers of the heart (atria and ventricles). The second layer is the layer that consists of the heart muscle. It is called the Myocardium and this layer is a thick muscular layer that obtains the ability to contract forcefully and elastically in order to pump the blood all over the body. The third layer is the Epicardium and it is the visceral layer of the pericardial sac which contains a small amount of a lubricating fluid in it that plays a role of protecting and facilitating the heart movement inside the chest cavity while contracting [6].

As the Myocardium (the heart muscle layer) is a part of the heart, and the heart in consequence is a part of the Cardiovascular System, this system originates from the Progenitor Heart Cells that lies in the Epiblast of the Bilaminar Disk embryo in the second week of gestation. Those Progenitor Heart Cells appear immediately adjacent to the cranial end of the primitive streak and then they migrate on the 16^{th} day of gestation from there to the splanchnic layer of the Lateral Mesoderm Plate (Fig-2), as they arrive in the middle of the third week. Those cells arrange in a horseshoeshaped cluster (or blood islands) of cells called the Primary Heart Field cranial to the neural folds [7].



Figure 2. Heart islands position in second week embryo.

A great number of blood islands and cardiac myoblasts develop from the PHF (Primary Heart Field) and they are the precursors that will form the blood cells and the vessels of the cardiovascular system. Their development is induced by the underlying pharyngeal endoderm. This region where the blood islands and Myoblast clusters occupy is hence called the cardiogenic region. In addition to the cardiogenic region a pericardial cavity develops over it from an adjacent part of the intra-embryonic cavity. As time progresses the blood islands start uniting to form a similar horseshoe-shaped endothelial lined tube that is surrounded by the myoblast cells, forming the heart tube [7].

As the embryo starts to fold cephalo-caudally and laterally simultaneously the cardiogenic region that was primarily anterior to the cranial end of the neural fold it starts to reposition towards the cervical then the thoracic region where it settles eventually (Fig-3&4). Upon the closer of the embryonic folds the caudal regions of the paired heart tubes merge while the central part of it expands to make the future outflow and ventricular heart regions. On the 22nd day of gestation the developing heart tube is consisted of an endothelial layer that makes the lining of the tube and a myocardial layer that originates the heart muscular tissue that in the future progresses to structure the Myocardium [7].

The cardiomyocytes (cardiac muscle cells) of the myocardium under a normal genetic development arrange in a regular organization of branched bundles of cells lying in smooth straight lines (Fig-5). Those cardiomyocytes contain serial sets of sarcomeres, which are subunits of striated myofibrils. Those myofibrils are an alteration and interlacing of light microfilaments that are composed of Actin protein and heavy dark microfilaments that are composed of Myosin protein [8].

Congenital Anomalies Correlations of Hypertrophic Cardiomyopathy Condition

The congenital anomalies are the most common causes for the death in infants under one year of age [9, 10, 11, 12, 13]. HCM (Hypertrophic Cardiomyopathy) is in a main aspect a genetic disease. It results from a mutation in one or several genes (1 to 9 genes at least) that are responsible of the synthesis of sarcomere proteins in the cardiomyocytes (heart muscle cells) [14]. A prominent gene mutation (in 45% of cases) is due to a deletion-alteration of the *14qll.2-3* genes that are responsible of the manufacturing of the β -Myosin heavychain, a protein that composes the heavy microfilaments of the sarcomeres inside cardiomyocytes [14].



Figure 3. Cardiogenic Region Repositioning in Third Week Embryo.



Figure 4. Endocardial Tube formation surrounded by the Myocardium.

Mutations to the sarcomere proteins manufacturing genes leads to the disorganization of heart muscle cells and the disruption of their ordinary smooth serial manner causing them to disarrange in a jumbled layers formations [15]. This process is called *Myocardial Disarray* (Fig-6).

When the Myocardial Disarray happens, the muscle walls of the heart become thickened and stiff (Hypertrophy). This stiffness or rigidity may lead later to a scar tissue formation or furthermore to a cardiac electric conduction malfunctioning and therefore arrhythmias. [15] The sites of the myocardial hypertrophy vary according to the pattern that the HCM condition implies as what we will see in the discussion.



Figure 5. Normal Structure of Heart Muscle Cells.



Figure 6. Heart Muscle Cells in Myocardial Disarray. Discussion

A normal heart is developed into several champers that serve as a reservoir and a passageway for the blood to be ejected and then circulated either through the lungs in order to exchange carbon dioxide with oxygen (Pulmonary Circulation) or to provide the whole body with its share of oxygen and nutrients (Systematic Circulation). Those champers are the left and right atria, they work as a recipient of the blood into the heart cavity; and the right and left ventricles, which work as a final destination for the blood to be pumped from the heart outward towards its flow. Between each atrium and ventricle that is situated on their respective side lies a valve that works as a one-way gate that allows the flow only from the atrium towards the ventricle and prevents it from going backwards. It is also worth to mention that between each combination of an atrium and a ventricle on one side there is a Septum that separates them from the other combination of an atrium and a ventricle on the other side (Fig-7) [16].

In order for the heart to pump our blood regularly a synchronized and organized electric activity that is generated by specific specialized heart cells causes its muscle contraction. It all starts from the Sino-Atrial (SA) node, the heart natural pacemaker; it lies in the right atrium. The SA node originates regular electric impulses that propagate through the muscle cells of the atria causing them to contract therefore evacuate their blood contents into the ventricles. Afterwards, the electric impulses reaches to a special center in the heart that works as a junction box called the Atrio-Ventricular (AV) node.

The AV node distributes the impulse through a bundle of muscle fibers called His bundle, which cause the ventricles to contract and pump their blood contents out to its intended destination. The heart muscle contraction rhythm (pulse rate) is basically controlled by the SA node but can be affected by the nervous system through its autonomic system innervations (Fig-8) [16].



Figure 7. Normal Heart.



Figure 8. Normal Electric Impulse Conduction in the Heart.

In HCM (Hypertrophic Cardiomyopathy) certain parts of the Myocardium is thickened and affected within a variation of patterns. Those patterns are categorized into four types: **1) Asymmetrical Septal Hypertrophy without Obstruction**

This type of cardiac hypertrophy pattern is the most common thickening pattern in patients affected with HCM (Hypertrophy Cardiomyopathy). In this pattern the myocardial

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thickening occurs mainly in the septum which separates left side from right side of the heart champers.

The center of the Septum gets enlarged but does not restrict the normal outflow of the blood from the Left Ventricle to the Aortic Valve through the Outflow Tract (the short channel preceding the Aortic Valve). The Mitral Valve in addition is not affected and stays in its normal position; therefore this pattern is known as Asymmetric Septal Hypertrophy (ASH) Without Obstruction (Fig-9) [15].

2) Asymmetrical Septal Hypertrophy with Obstruction

In some other cases, the thickening of the heart Septum is so large that it narrows the outflow tract. The Mitral Valve comes in contact with the wall of the Septum in result leading to a disturbance of blood flow (turbulent flow) which causes a heart murmur (an oscillating deep and unusual heart sound) that can be heard with a stethoscope. Also the narrowing of the Outflow tract below the Aortic Valve reduces the amount of blood that the Left Ventricle can pump out which leads to a Ventricular Outflow obstruction. However, this obstruction may cause the blood to go back towards the left atrium against its natural one-way direction through the Mitral Valve. This unnatural blood flow is named Mitral Regurgitation (Fig-10) [15].



Figure 9. Asymmetric Septal Hypertrophy (ASH) Without Obstruction.



Figure 10. Asymmetrical Septal Hypertrophy With Obstruction.

3) Concentric (Symmetric) Hypertrophy

In this type of cardiac hypertrophy pattern the enlargement and thickening is distributed evenly with equal severity throughout the entire left ventricle including the septum and the lateral ventricular wall along with its apex. This condition is called Concentric or Symmetric Hypertrophic Cardiomyopathy. In such condition the Ventricular Outflow Tract can be obstructed sometimes in addition to reducing the size of the Left Ventricle itself (Fig-11) [15].

4) Apical Hypertrophy:

This condition is present in about 1 in every 10 patients who are affected by HCM (Hypertrophic Cardiomyopathy), as the thickening of the Myocardium happens at the Apex (the bottom tip) of the heart therefore the name Apical Hypertrophic Cardiomyopathy. In this condition usually the Left Ventricular Outflow Tract doesn't get blocked yet the size of the Left Ventricle cavity may reduce in result of the apical enlargement and thickening (Fig-12) [15].



Figure 11. Concentric (Symmetric) Hypertrophy.



Figure 12. Apical Hypertrophy.

Conclusion

Vascular variations are congenital morphological differences that arise in the human body. Although, for the most part, do not cause injury to the individual, may be important in cases where it is necessary a specific access to the vascular system [17]. Congenital myocardial development anomalies in hypertrophic cardiomyopathy condition are closely related to genetic mutation disorders that affect the way that heart muscles operate, arrange and organize. These alterations lead to variable manifestations upon the cardiac musculature which cause the heart to either loses its proper function in pumping blood efficiently or to go out of normal rhythm that may lead in severe cases to a life-threating arrhythmia or cardiac arrest. Therefore, the lifestyle of a (Hypertrophic person who is afflicted by HCM Cardiomyopathy) has to be modified accordingly to be situated with his or her critical heart condition. Despite the fact that most conditions of HCM are not severe or morbid, a sudden cardiac arrest and death of athletes and young members of general population results from this disease. A patient of HCM has to avoid participating in strenuous and highly active sports or heavy manual jobs that need much

physical effort and increase the burden to the heart in order to provide enough blood circulation by increasing its beat rate and contractility.

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In the case of driving vehicles activity, a HCM patient isn't allowed to drive a heavy truck or a public transportation vehicle due to the stress that is experienced in order to administer the needed driving skills in those types of vehicles. Assessment and detection of such inherited heart condition is essential in order to minimize all the symptoms that accompany the disease. HCM clinical diagnoses is provided by checking any medical history of the disease within the family and by examination and testing that the a cardiologist doctor administers including cardiac vital signs reading, listening to heart sounds using his or her stethoscope, taking an ECG (Electro-Cardio Gram) of the heart, providing an Exercise Test to detect any changes in the heart electrical activity rhythm and imaging tests that may include MRI (Magnetic Resonance Imaging), Ultrasound, cardiac CT (Computerized Tomography) scan and Coronary Angiogram (imaging the coronary vessels of the heart). Further detection is provided by taking a sample of the patient's DNA for a genetic testing.

The clinical relevance from this study to create an algorithm or define a set of factors to alert surgeon and anesthetist's to aware of knowledge [18] about the detection of the HCM disease a treatment is provided using a combination of medicine remedies and implantable Pacemakers to control the heart muscle conditions. This pain, as is usually described by the patients, stands in closer sense for complaints [19], the knowledge of such variations may be important for surgeons to reach up to surgical intervention [20] in some cases of obstructive hypertrophy conditions which include myectomy (removing a part of the damaged heart muscle) or Alcohol Septal Ablation (injecting a small amount of alcohol into the branch of coronary artery that supply the thickened part of heart muscle that is causing the obstruction).

The future of diagnosis and treatment of HCM is recently improving by newly developments in faster and cheaper technologies to identify more gene mutations related to the disease and in more advanced and small pacemakers that are inserted to the human body without the need of an invasive approach.

Acknowledgment

I present my gratitude to all the authors of the medical articles from where the reference of this article has been reviewed; for playing a great role in the gathering of related information and understanding the extents of this research. And I am thankful to my faculty teacher for his support and encouragement to accomplish my research within my best effort.

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