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REVIEW ARTICLE

Cardiac Affection in Lysosomal Storage Disorders: Review Article

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ABSTRACT

Background: A class of illnesses known as lysosomal storage disorders is brought on by deficiencies in membrane transporters, lysosomal enzymes, or other proteins important in lysosomal biology. The diseases are categorized based on the kind of material that builds up; lipid storage disorders, glycoproteinoses, and mucopolysaccharidoses are a few examples of this. In cases of mucopolysaccharidoses, glycosphingolipidoses, and lysosomal glycogen storage diseases, cardiac disease is particularly significant. Valvular disorders and hypertrophic and dilated cardiomyopathy could be seen. Endomyocardial biopsies are crucial for making diagnoses. The diagnosis of these illnesses is aided by microscopic characteristics as well as auxiliary procedures such as ultrastructural studies and specific stains. Further confirmation of the diagnosis is obtained through enzymatic and molecular genetic investigation.

Conclusion: Lysosomal storage diseases frequently cause involvement of the heart muscles. It is advised to use echocardiography for prospective yearly screening, even in cases of moderate affection, in order to supplement dietary therapy and stop life-threatening problems from developing.

Keywords: lysosomal storage disorders, enzyme replacement therapy, mucopolysaccharidosis.

INTRODUCTION

A category of more than 50 illnesses known as lysosomal storage disorders (LSD) are brought on by deficiencies in membrane transporters, lysosomal enzymes, or other proteins essential to lysosomal biology. They are typically brought on by lysosomal dysfunction, which results from a lack of a specific enzyme necessary for the breakdown of fats, glycoproteins (proteins containing sugar), or so-called mucopolysaccharides. With the exception of Anderson-Fabry disease, glycogen storage disease (GSD) type IIb (Danon disease), and mucopolysaccharidosis (MPS) type II (Hunter disease), the prevalent inheritance pattern is autosomal recessive. On their own, LSDs are uncommon. According to estimates, its occurrence ranges from 1 in 7000 to 1 in 8000 live births overall. The majority of LSDs have a progressive course that frequently leads to severe illness symptoms and early mortality **[1].**

De Duve and others found and described the lysosome as a cellular organelle in charge of intracellular digestion and recycling of macromolecules in the late 1950s and early 1960s. These were the scientific discoveries that made it possible to comprehend the physiological underpinnings of LSDs. Membrane-bound vesicles called lysosomes are home to digestive enzymes like sulfatases, proteases, and glucosidases. The endoplasmic reticulum synthesizes the enzymes, which are then sent to the Golgi apparatus and labeled with mannose-6-phosphate to mark them for

lysosomes. Nuclear genes are responsible for controlling lysosomal enzyme synthesis. Various human genetic disorders collectively referred to as lysosomal storage diseases are caused by mutations in the genes **[2].**

Because certain substrates cannot be broken down, they accumulate and cause lysosomal storage diseases. The diseases are categorized based on the kind of material that builds up; lipid storage disorders, mucopolysaccharidosis, and glycoproteinoses are a few examples of this. The lysosomal storage diseases with notable cardiac symptoms are the main topic of this review paper. Cardiovascular illness plays a significant role in mucopolysaccharidosis, and glycosphingolipidoses (Anderson-Fabry disease), as well as lysosomal glycogen storage illnesses (Pompe and Danon disease). Numerous signs and symptoms of the disease can be seen, including as valve disease, coronary artery disease, and hypertrophic and dilated cardiomyopathy. The majority of LSDs are diagnosed primarily by looking for a particular enzyme impairment. Molecular genetic testing (MGT) can improve the enzymatic diagnosis in certain situations. Following the determination of an individual's genotype for LSD, genetic counseling ought should encompass the prediction of potential phenotypes and the identification of carriers within the affected family **[1].**

Glycogen storage diseases:

The liver, skeletal muscle, heart, and occasionally the central nervous system and kidneys are the main organs affected by glycogen storage disorders (GSD). The specific enzyme deficiencies associated with each glycogen storage disorder are used to categorize them. Every one of these enzymes controls the production or breakdown of glycogen. It's interesting to note that even when a certain enzyme is mutated, there is still a lot of variety in phenotype and clinical course. Glycogen storage disease types IIa and IIb (Pompe and Danon disease, respectively) are associated with lysosomal storage and cardiac involvement **[3].**

(1) Pompe disease (Type IIA GSD) (figure 1)

Pompe disease, also known as glycogen storage disease type IIa or acid maltase deficiency, is a lysosomal condition characterized by intralysosomal glycogen accumulations in all tissues, most notably in skeletal muscles, due to abnormalities in the enzyme acid β glucosidase (GAA). Dr. J. C. Pompe initially identified Pompe disease in a girl with cardiomyopathy who was 7 months old. Glycogen accumulated massively in vacuoles across all tissues analyzed. Hugh Gary-Hers, a Belgian biochemist, established the link between lysosomes, the enzyme deficiency, and Pompe syndrome considerably later in 1963. He identified a novel enzyme that underwent acidic pH-dependent glycogen hydrolysis to glucose conversion and showed that Pompe disease patients lacked this enzyme. Dr. Hers discovered that this new enzyme is the only one that breaks down glycogen in the lysosomes and that it is found inside of them **[4].**

Incidence:

Geographical location and ethnicity appear to have an impact on Pompe disease incidence. The estimated frequency of the fast developing infantile-onset variant is 1:138,000 in Caucasian populations, 1:50,000 in Chinese populations, and 1:14,000 in African ancestry populations **[5].**

Clinical manifestations:

Historically, the condition has been classified into three types in the literature according to the intensity and timing of the emergence of clinical symptoms. The degree of enzyme deficiency is correlated with the severity of the condition. Individuals have been divided into three categories: juvenile, adult, and infantile onset**[6]**.

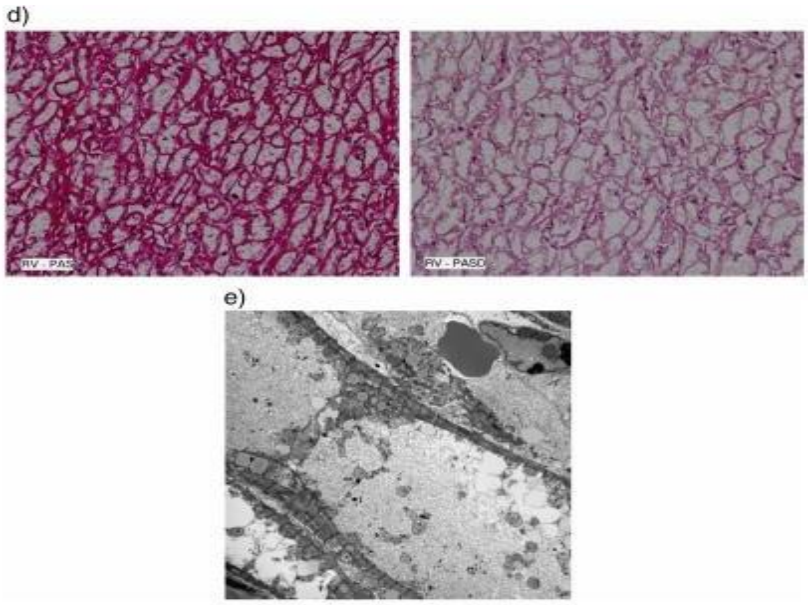


Figure (1): Pompe Disease. (A) Gross image of a heart of a seven monthold child with Pompe Disease shows cardiomegaly with a heart weight of 151 gms(expectedweightof42gms) [9].

Infantile Pompe:

A complete or nearly complete absence of acid α-glucosidase causes the infantile type. The condition typically manifests as severe hypotonia, macroglossia, cardiomegaly, and mild hepatomegaly in the first few months of birth. Heart failure typically manifests between two and six months of age, and always before eighteen months, therefore the age at which symptoms first appear is a diagnostic hint. feeding difficulties, cyanosis, dyspnea, sweating, tachycardia, major heart enlargement, respiratory infection susceptibility, and ultimate congestive failure are among the symptoms that are present.A chest x-ray is routinely ordered since the patients frequently have respiratory illnesses. An X-ray typically shows a significant enlargement of the heart. Although it is an unreliable screening tool, serum CK can be high. A brief PR interval on an ECG is pathognomonic for infantile Pompe illness. The elevated myocardial mass index (beyond the value in the most severe forms of familial hypertrophic cardiomyopathy) is one of the unique features of the echocardiographic results. There is a noticeable abnormal myocardial echogenicity, which is thought to be connected to the infiltrative process **[1].**

Juvenile Pompe:

The onset in the first decade is a characteristic of the juvenile type. The characteristic clinical signs include mild hepatomegaly and skeletal muscular weakness with respiratory muscle involvement. There is also diminished but remaining α-glucosidase activity. Typically, there is no or minimal cardiac involvement, and within a few years, respiratory failure causes death **[6]**.

Adult Pompe:

The disease's adult form is distinguished by its beginning during the third or sixth decade of life. While it is comparable to the juvenile type, it progresses more slowly in terms of skeletal muscle weakening and has larger levels of residual α-glucosidase activity **[1].**

Moleculargenetics:

The lysosomal glycogen storage condition Pompe disease is autosomal recessive and results from a lack of acid β-glucosidase

(GAA). There is a GAA gene on chromosome 17q25. On the GAA gene, more than 250 mutations have been discovered. For the disease to cause a partial or total loss of acid α-glucosidase GAA activity, both copies of the GAA gene must harbor a pathogenic sequence variation. Clinical symptoms are brought on by lysosomal glycogen buildup brought on by a loss of GAA enzyme activity **[7]**.

Pathology:

The heart is noticeably enlarged with Pompe disease. All of the chamber walls—particularly the papillary muscles and the left ventricular free wall—are thicker **(figure 2).** Severe wall thickening in certain people is linked to tiny heart cavities and blockage of the left or right ventricle's outflow. Heart dilatation is evident in other patients. Fatty endocardial thickening affects around 20% of people with Pompe illness. The cytoplasm of cardiac myocytes has a vacuolar alteration and a lacework appearance in histologic sections. Massive glycogen deposits are to blame for this, as they push myofibrils out to the edges of the cells. There is varying degrees of interstitial fibrosis and a scarcity of myofibrils **[8]**.

Periodic Acid Schiff stain shows a modest positive signal in the intracytoplasmic deposits. Following diastase treatment, these deposits are removed. Studies using electron microscopy show that myocytes with a granular or fibrillary appearance and a loss of myofibrils have a free cytoplasmic buildup of glycogen. Large volumes of glycogen accumulate in bodies called glycogenosomes, which are single membrane bound structures, according to ultrastructural research. These have been discovered in striated muscle, liver, kidney, skin, pancreas, brain, and eye in Pompe illness. But a large portion of the glycogen in striated muscle is located outside of lysosomes. It is believed that mechanical pressure from muscular contraction may have caused lysosomal rupture. The simultaneous release of acid hydrolases would account for the electron microscope observations of myelin patterns, cell debris, and defective and necrotic muscle fibers. Glycogen-containing single membrane-bound entities have occasionally been observed in muscle tissues, and not just in cases of Pompe disease **[9]**.

Treatment:

In 2006, enzyme replacement therapy (ERT) received approval for use in humans. The foundation of ERT is the idea that recombinant lysosomal enzymes can be taken up by cells via the mannose-6-phosphate receptor and transported to lysosomes, where they are processed further to take over the role of hydrolases that are defective. Pompe's inclusion in the newborn screening program was of interest because of the availability of a specific treatment. Approved the recommendation in March 2015 by the US Secretary of Health and Human Services to include Pompe illness in the newborn screening program **[10].**

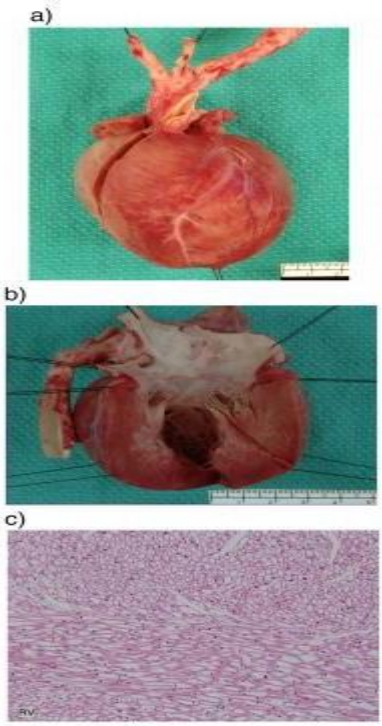


Figure (2): The left ventricle shows concentric hypertrophy with mild endocardial fibrosis (LV wall -16 mm) [9].

(2) Danon disease (GSD Type IIb) (figure 3)

Danon disease (DD) is a rare monogenic metabolic X-linked condition characterized by proximal myopathy, intellectual impairment, and early-onset cardiomyopathy with hypertrophic or dilated phenotype (often leading to fatal end) **[11]**.

IncidenceandPrevalence:

Although the precise frequency of DD is unknown, it has been found in 1-6% of patients with left ventricular hypertrophy (LVH) that cannot be explained and in up to 17% of patients with LVT combined with other characteristics like elevated serum creatine kinase (CK) or Wolff-Parkinson-White (WPW) syndrome **[12]**.

History:

In1981,Two young boys with a clinical trial of myopathy, cardiomyopathy, and intellectual impairment were reported by Danon and colleagues. Vacuolar changes indicative of type II glycogenosis were observed in skeletal muscle biopsies. There was no evidence of a GAA enzyme deficiency. Similar instances have been documented since then, and they are commonly known as "glycogen storage disease without acid maltase deficiency." Later on, it was shown that the primary cause of this illness is a lack of lysosome-associated membrane protein 2 (LAMP2) **[13]**.

Molecular genetics:

LAMP2, which coats the inner surface of the lysosomal membrane and is thought to function as a receptor for proteins to be imported and broken down within lysosomes in chaperone-mediated autophagy, is the major defect that causes Danon disease. The LAMP2 gene is found on Xq24 chromosome. Because men were the primary afflicted party, the illness was thought to be familial and X-linked. Male to male transmission was not seen, and affected moms typically experienced milder and delayed onset cardiac symptoms **[14]**.

Clinical manifestations:

Due to X-linked dominance, clinical manifestations might vary, but they are typically more severe in males. Left ventricular hypertrophy and aberrant EKG results, particularly Wolf-Parkinson's White syndrome with extremely high voltage, are examples of the cardiac symptoms. As extra-cardiac symptoms, these patients may

experience cerebral impairment, skeletal myopathy, and muscle weakness **[15]**.

Pathophysiology:

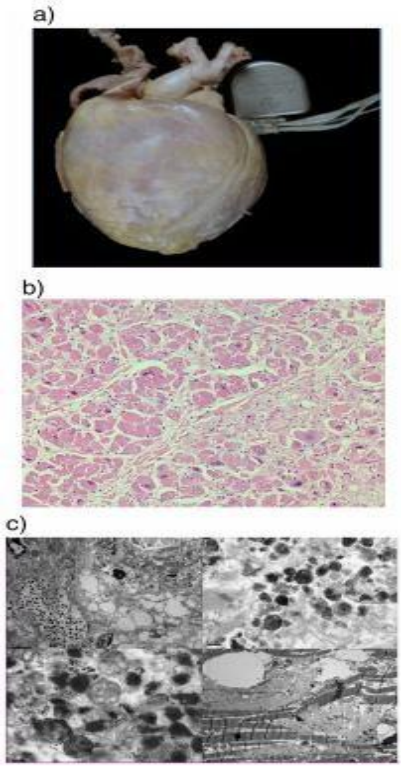
Using lysosomal enzymes, autophagy is a key mechanism in cellular metabolism that allows cells to break down portions of their cytoplasm and organelles. Early autophagic vacuoles must undergo conversion into vacuoles that quickly destroy their contents, which requires LAMP2. This suggests that LAMP2 may play a role in the maturation of autophagolysosomes into actively digesting organelles or in the process of fusing autophagic vacuoles with lysosomes, which supply the acid hydrolases necessary for destruction **[16]**.Disease Biventricular hypertrophy and cardiomegaly are present in the heart in Danon disease. Under a microscope, the cardiac myocytes exhibit widespread hypertrophy and intracytoplasmic vacuoles **[17].**

Pathology:

Periodic Acid Schiff stain shows a modest positive signal in the intracytoplasmic deposits. Following diastase treatment, these deposits are removed. In heart muscle, immunohistochemistry reveals that LAMP2 protein expression is absent. Numerous autophagic vacuoles are visible in electron microscopy, which is consistent with cytoplasmic vacuolization **[17].**

Treatment:

One useful technique for curing Wolff-Parkinson White syndrome is catheter ablation. The implantation of an implantable cardioverter defibrillator, or ICD, is a prophylactic measure for sudden cardiac death. Patients with Danon disease have a far higher chance of survival after heart transplantation. With early morbidity and a short life expectancy (survival beyond 25 years is rare), the prognosis is often poor. Heart failure or sudden cardiac death are the causes of death **[12]**.



Figures (3): Danon Disease [17].

Mucopolysaccharidosis:

A malfunction in the intralysosomal breakdown of glycosaminoglycans (GAGs) results in a broad category of storage illnesses known as mucopolysaccharidosis (MPS). One can distinguish between seven primary forms and several subcategories. MPS I is caused by mutations in the IDUA gene. The IDUA enzyme's function is diminished or eliminated when mutations occur in the IDUA gene. Intracellular GAG buildup occurs as a result of inactive IDUA enzyme, primarily inside lysosomes. Three primary classical clinical entities result from a-IDUA deficiency: the most severe phenotype, Hurler syndrome MPS1H, which manifests in infancy; the intermediately severe phenotype, Hurler–Scheie syndrome MPS1H/S; and the mildest form of MPS I, Scheie syndrome MPS1S. MPS V was the previous term for Scheie syndrome MPS1S. Patients with MPS I, particularly those with the most severe form, have been reported to develop cardiomyopathy and thickening of the heart valves and major arteries **[18].**

The clinical manifestations of these illnesses, such as dysostosis multiplex, coarsening of skin and facial features, and insufficiency of the central nervous system (CNS), respiratory system, and heart, are brought on by accumulation of GAG. In those diseases (MPS I, II, and VI, but not MPS III and IV) where dermatan sulfate catabolism is disrupted, cardiac valve dysfunction seems more likely. According to the majority of research, valvular regurgitation occurs more frequently. The mitral and aortic valves on the left side of the heart are typically more severely afflicted than the tricuspid and pulmonary valves on the right. The mitral valve leaflets have thicker margins and a pronounced cartilage-like appearance. The shorter chordae tendinea and thick papillary muscles developed by the mitral valve's subvalvular apparatus result in dysmorphic and poorly movable leaflets **[19]**.

It is also typical to observe calcific deposits in the mitral annular region. The anatomy and clinical history of increasing valve thickening and failure are comparable in the aortic valve. While cases of coronary artery constriction and/or occlusion have been reported in patients with all forms of MPS, MPS I and II are the most common. High-grade narrowing can result from diffuse intimal proliferation brought on by GAG deposition in big epicardial coronary arteries, which can happen early, particularly in MPS I that is developing quickly. Furthermore, many of the patients also exhibited abnormally large sinotubular and aortic annuli as well as sinotubular junction diameters **[20].**

There is calcification of the mitral valve ring and widespread cardiomegaly at radiographic evaluation. According to reports, the most frequent cause of childhood mitral annulus calcification is mucopolysaccharidosis. There is no discernible electrocardiographic pattern. In addition to cardiac abnormalities, echocardiography may be used to detect valvular abnormalities and calcific deposits **[6]**.

Pathology:

Large, oval or spherical connective tissue cells called Hurler cells are found in the myocardium and blood vessels. These cells are packed with multiple transparent vacuoles that contain acid mucopolysaccharide substances. Furthermore, there are tiny granular cells that contain collagen fibril fragments and membrane-limited, electron-dense material. These cells and an increase in the quantity of fibrous connective tissue are the causes of the tissues' thickening. Patients with Hurler syndrome likely have high levels of collagen in their cardiovascular systems because these cells appear to manufacture collagen abnormally **[20].**

Management:

For the past 30 years, hematopoietic stem cell transplantation (HSCT) has been used to treat MPS disorders by correcting their metabolism (31). The Ross operation, mitral and aortic replacement, and mitral valve repair are surgical procedures. ERT and HSCT are two systemic therapies for mucopolysaccharidosis **[21]**.

Sphingolipidoses:

Fabry, Niemann-Pick, and Gaucher diseases are the three sphingolipidoses with notable cardiac symptoms **[1].**

(1) Gaucher disease (figure 4)

The most prevalent form of sphingolipidosis is Gaucher disease. The most common storage problem was first identified by Philippe Gaucher in 1882 and is known as Gaucher illness. Gaucher disease is brought on by mutations in the GBA gene. The activity of betaglucocerebrosidase is significantly reduced or eliminated when mutations in the GBA gene occur, which causes glucocerebroside to accumulate lysosomally inside macrophages. The reticulo-endothelial system becomes overpopulated with lipid-laden macrophages, or Gaucher cells, which cause hepatosplenomegaly, bone marrow replacement, anemia and thrombocytopenia, as well as anomalies in the skeletal system. With the exception of an uncommon homozygous D409H mutation, cardiac symptoms are uncommon. There have been reports of notable myocardial infiltration by typical Gaucher cells, which results in decreased cardiac output and ventricular compliance. Gaucher cell infiltration into the heart may cause dilated cardiomyopathy with a decreased ejection fraction. There have been reports of pulmonary hypertension and cor pulmonale brought on by bone marrow-derived Gaucher cells obstructing alveolar capillaries. Fewer cases have experienced intrapericardial hemorrhage linked to the bleeding diathesis that is common in Gaucher Disease, which has resulted in constrictive calcific pericarditis. The pathological results of a patient with type III C Gaucher disease with significant cardiac valvular involvement were published by Veinot et al. in 1999. The leaflets of the aortic and mitral valves showed obvious fibrosis and calcifications. Under a microscope, the leaflets' calcification and fibrosis were visible, surrounded by large cells that resembled osteoclasts. Studies using electron microscopy revealed the existence of Gaucher cells

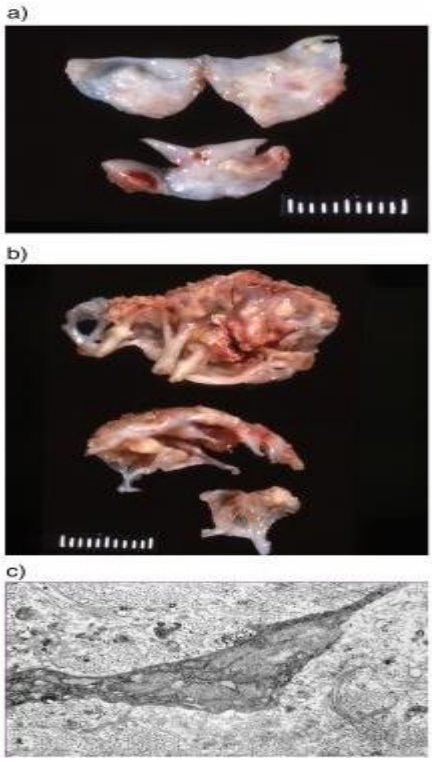


Figure (4): Gaucher disease [22].

(2) Niemann-Pick disease

An acid sphingomyelinase deficit results in Niemann-Pick disease. It is further divided into two subtypes: type B (after development of hepatosplenomegaly, pulmonary involvement, survival into adulthood) and type A (infantile, neurodegenerative). Rarely, there is cardiac involvement, which typically manifests as endocardial fibrosis. Mutations in the SMPD1 gene cause types A and B of Niemann-Pick disease. This gene codes for the production of the enzyme acid sphingomyelinase **[23]**.

(3) Fabry disease (figure 5)

Fabry disease is caused by an X-linked hereditary impairment of lysosomal alpha-galactosidase A (GLA), which leads to a buildup of neutral glycosphingolipids in different organ systems, primarily globotriaosylceramide (Gb3). In 1898, two doctors named William Anderson and Johannes Fabry, who worked independently of one another, published the first descriptions of Fabry disease. In honor of them, the illness is often known as "Anderson-Fabry disease" (AFD) **[1].**

Epidemiology:

For men, the estimated incidence of AFD ranges from 1 in 40,000 to 1 in 117,000 live births. AFD prevalence in hemodialysis patients with end-stage renal disease has been shown to range from 0.2% to 1.2%**[23]**.

Inheritance and Molecular Genetics:

This disorder is X-linked in inheritance. The disease is caused by one mutated copy of the GLA gene per cell in males (who have one X chromosome). Seven exons make up the GLA gene, which is found on the X chromosome's long arm (Xq22.1). In all seven exons, more than 250 alterations have been identified, the most of which are missense point mutations**[24]**.

Clinical manifestations:

Corneal opacities and angiokeratosis are frequent. Heart failure and left ventricular hypertrophy are examples of cardiovascular manifestations. The most common cause of systemic arterial hypertension is renal failure. There could be myocardial infarction and angina pectoris. All cardiac cell types, including fibroblasts, cardiomyocytes, microvascular endothelial and smooth muscle cells, accumulate Gb3. This can cause abnormalities in the heart's valves, myocardial hypertrophy, and myocardial ischemia, which can resemble the clinical and morphological features of hypertrophic cardiomyopathy or unexplained left ventricular hypertrophy. The classic variant and the cardiac variant are the two primary forms of illness symptoms. In the traditional form, males have extremely low or nonexistent α-Gal A activity, leading to significant systemic symptoms that usually start in childhood or adolescence. These symptoms include minor proteinuria, acroparesthesias, angiokeratomas, cornea verticillata, hyperhidrosis, and gastrointestinal issues **[25]**.

Between the ages of 20 and 40 is when cardiac involvement usually manifests itself, and renal involvement usually advances to the point where dialysis or a kidney transplant is necessary. Arrhythmias, myocardial infarction, and heart failure are typically late signs and symptoms. Early stroke, thromboses, and transient ischemic episodes are examples of cerebrovascular symptoms that can cause serious neurological decline and even death **[26]**.

Individuals suffering from the "cardiac variant" of Fabry disease exhibit residual enzyme activity, which ranges from 1 to 5% of typical values. They don't exhibit any other typical Fabry disease symptoms and instead appear in their fifth and sixth decades of life with unexplained left ventricular hypertrophy and conduction disease. individuals with the cardiac variation do not have vascular

endothelial glycosphingolipid deposits, which is a histological difference between them and individuals with conventional Fabry disease. Fabry disease frequently involves the heart. In addition to arrhythmias, valve abnormalities, conduction abnormalities, and left ventricular hypertrophy, patients may also develop coronary heart disease. Heart hypertrophy that is concentric is caused by restrictive pathophysiology brought on by Gb3-mediated infiltration and microvascular impairment in AFD. This is now known to be the main reason why patients with AFD die. The two main characteristics of cardiac involvement in AFD are increasing left ventricular hypertrophy and diastolic failure **[27]**.

Pathology:

Cardiomegaly is evident in the heart, accompanied by either concentric or asymmetric septal hypertrophy. The muscles of the papillaries are visible. Aortic regurgitation, mitral regurgitation, and mitral stenosis are among the disorders of the mitral and aortic valves that are linked. Ceramide trihexoside deposits show up in myocardial histologic sections as vacuoles. They are strongly birefringent, sudanophilic, and PAS positive in frozen sections. These deposits push the contractile components toward the periphery of cardiac muscle cells by occupying the core, perinuclear regions. Histologically, this gives rise to a lacework appearance. The ceramide trihexoside deposits, as revealed by ultrastructural analysis, create intralysosomal aggregates of parallel or concentric lamellae separated by 4 to 5.5 nm. The lamellar deposits in Fabry disease can be distinguished from the irregular arrays of concentric lamellae that are frequently seen as non-specific observations in deteriorated cardiac muscle cells by their birefringence in frozen sections and their highly structured substructure **[8].**

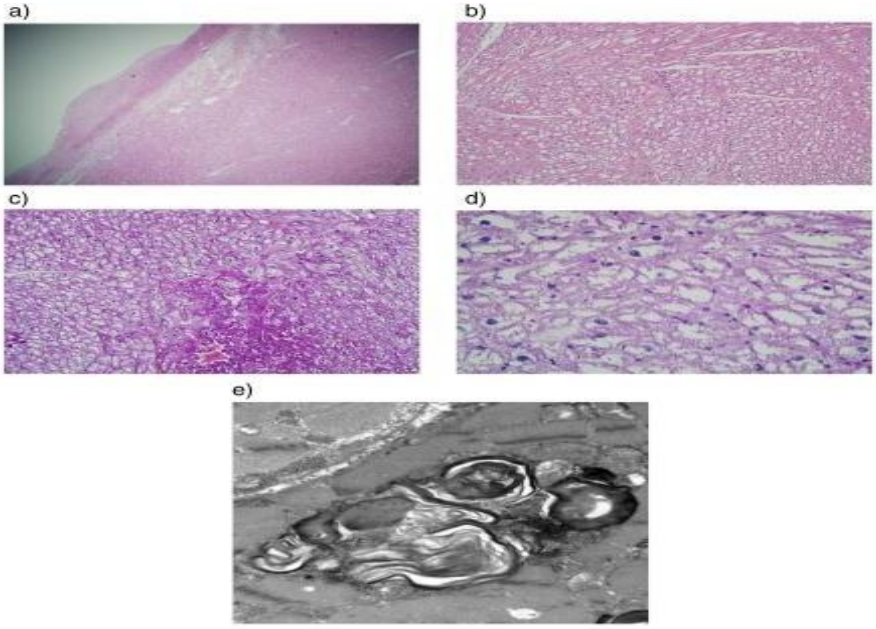


Figure (5): Fabry Disease [8].

CONCLUSION

Lysosomal storage diseases frequently cause involvement of the heart muscles. It is advised to use echocardiography for prospective yearly screening, even in cases of moderate affection, in order to supplement dietary therapy and stop life-threatening problems from developing.

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