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A Review on Wolman Disease

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Abstract: *Wolman disease is an extremely rare genetic disorder cause by increase the level of the LIPA gene into the body. Because LIPA gene is essential for metabolizing the fats in body especially cholesterol &wolman disease cause by increase the level of cholesterol into the identified the disorder in the medical literature in 1956 by Sir Moshe Wolman and these disorder affects equal number of male and female. If both are infected then easily not show any symptoms into the body but only one parent are infected then they show proper symptoms. These disease are found in newborn babies, at the time of 4-week of birth. The main symptoms of these disease is increase the size of liver, it treat by gene transplantation, HSCT (Hematopoietic stem cell transplantation), According to WHO, un till 50 cases are study in medical literature and there is not give any proper treatment on wolman disease. Research on clinical trial are work in progress.*

Keywords: Wolman disease

I. INTRODUCTION

Lysosomal acid lipase is an essential enzyme that hydrolyses cholesteryl esters and triglycerides in human lysosomes, generating free cholesterol and free fatty acids.[1] Lysosomal acid lipase deficiency is an often fatal disease, in which lipids accumulate in different parts of the body, especially in the liver, spleen, lymph nodes, bone marrow[2], and macrophages-interfering with the basic function of these cells, tissues, and organs.[3] Lysosomal acid lipase deficiency is inherited in an autosomal recessive fashion and shows two different phenotypes that lie on a clinical continuum, depending on the amount of functional enzyme that is produced in vivo.[4] Prevalence is estimated to be one in 40,000 to 300, 000 depending on geographical location and ethnic origin, although these figures are undoubtedly low given that lysosomal acid lipase deficiency is often misdiagnosed or undiagnosed.[5]

Wolman's disease can be considered the infantile (i.e., early-onset) form of lysosomal acid lipase deficiency, wherein patients have no or very minimal lysosomal acid lipase activity.[6]These patients rarely survive beyond infancy and often present with hepatomegaly, failure to thrive, diarrhoea, vomiting, malabsorption, and hepatic failure. The exact incidence of this rare form of lysosomal acid lipase deficiency is unknown but is estimated to be around one in 500,000 livebirths.[7]

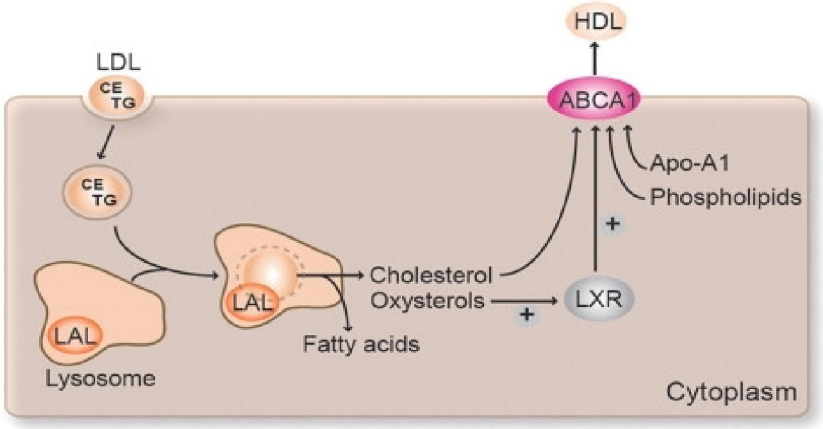

Figure. 1

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1.1 History

A 4-month-old female infant born of second-degreeconsanguineous marriage with a birth weight of 3.2 kg has been diagnosed with cholestasis from 2 weeks of life. She had poor growth, diarrhoea, vomiting, abdominal distension, and worsening jaundice. On physical examination, weight was 4.6 kg (< − 3Z) and she had deep icterus with peripheral stigmas of cirrhosis. She had massive and firm hepatosplenomegaly along with ascites. Hemoglobin was 8.0 g/L, total leukocyte Count 5,050 cells/mm^3, platelet 4,000-16,000 cells/mm^3, bilirubin 180 µmol/L (1–17 µmol/L), aspartate transaminase 431 IU/L (0–40 IU), and alanine transaminase 218 IU/L (0–40 IU). The international normalized ratio was 2.6 and albumin was 20 g/L (35–50 g/L) suggesting synthetic liver failure. Triglyceride was 255 mg/dL (< 150 mg/dL) and cholesterol 75 mg/dL (< 200 mg/dL).

X-ray abdomen showed bilateral adrenal calcifications suggesting WD (Fig. 2A). Ultrasound abdomen was showing hepatomegaly with a coarsened liver echotexture along with splenomegaly and ascites suggestive of cirrhosis with portal hypertension. A liver biopsy was not done as the child had coagulopathy along with ascites, as both factors can result in an intraperitoneal bleed. Bone marrow biopsy showed storage cells (Fig. 2B,2C). Genetic analysis showed homozygous splicing mutation in *LIPA* gene c.676-2A > T disrupting the highly conservative acceptor splice site of exon 7. This confirmed the diagnosis of WD. We counseled the parents on guarded prognosis and explained the possible benefits of various modes of treatments such as enzyme replacement therapy (ERT), liver transplantation, and stem cell transplant. Due to progressive liver failure and worsening pneumonia, the patient died at 4 months and 1 week of age.[8]

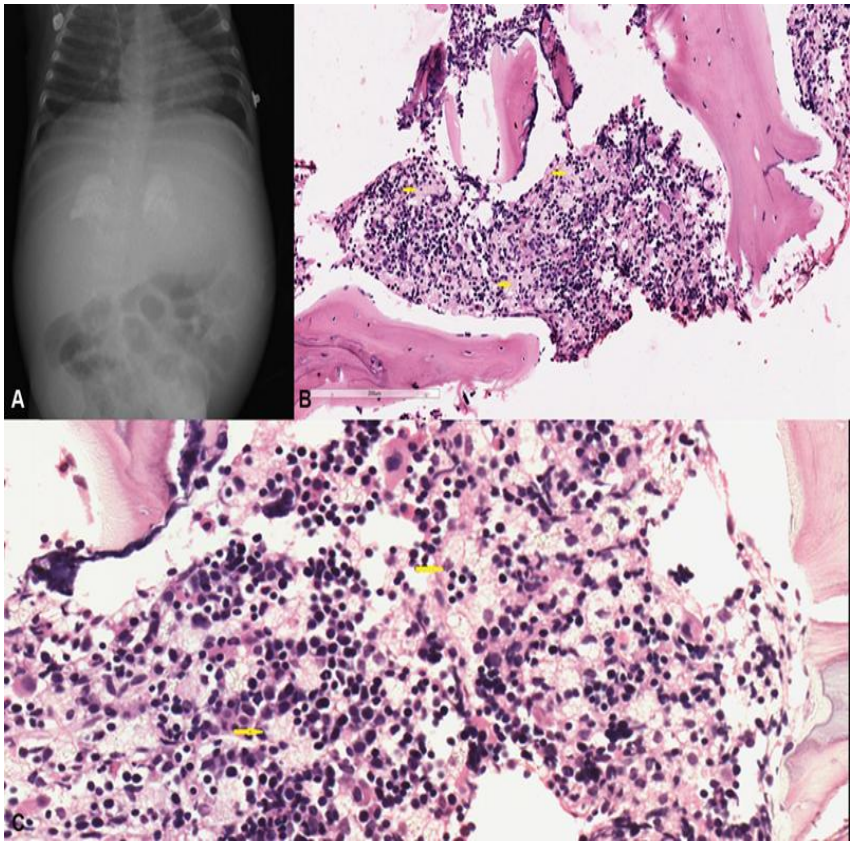

Figure.2 [A, B, C]

X-ray of abdomen showing bilateral enlarged adrenals with dense punctate calcifications with preserved shape of the gland. Massive enlargement of liver can also be visualized. (**B**) Low-power view of bone marrow with multiple foamy histiocytes admixed

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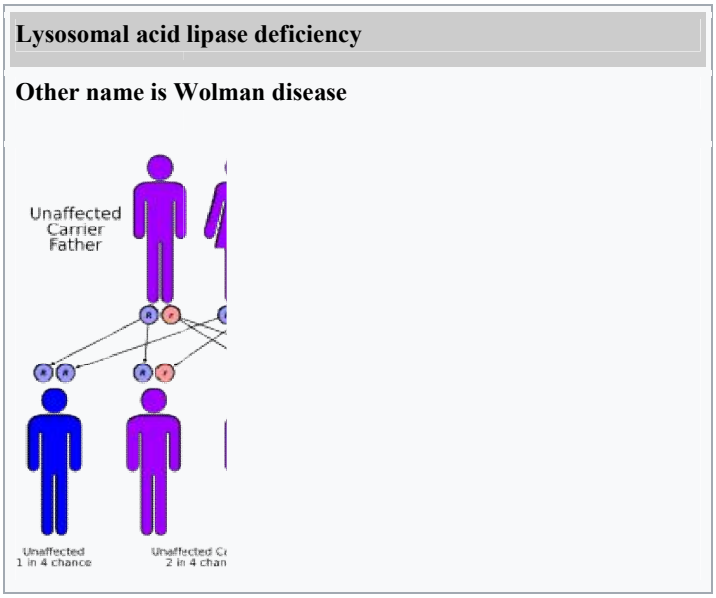

Figure.3

1.2 Pathogenesis

Undetectable or minimal lysosomal acid lipase activity in the liver and spleen of patients with Wolman's disease led to the conclusion that acid esterase deficiency is the causative factor.[9] In the early 1970s, acid lipase deficiency was first identified in fibroblasts from patients.[10] In the early 1980s, the lysosomal acid lipase gene (*LIPA*) was localised to chromosome 10q23·2q23·3.[11] The *LIPA* gene encodes a 46 kDa protein that functions as a cholesteryl ester hydrolase. Human lysosomal acid lipase was purified in small amounts in 1985.[12]

1.3 Radiology

CT scans can be supportive in establishing the diagnosis of adrenal hypertrophy, hepatosplenomegaly, and portal hypertension in patients with lysosomal acid lipase deficiency.[13] High cholesterol can correlate with reduced hepatic density on CT scans, but this observation is neither reliable nor exclusive to patients with lysosomal acid lipase deficiency.[14] MRI is a well-recognised method for measurement of hepatic lipid content. Thelwall and colleaguesused 1H magnetic resonance spectroscopy to measure hepatic triglyceride and cholesteryl ester concentrations in a non-invasive way and reported that 1H signatures can be used to identify abnormal lipid substrate content in the livers of patients with cholesteryl ester storage disorder.[15]

Symptoms of Wolman Disease

Symptoms of this disease may start to appear as a Newborn and as an Infant. The age symptoms may begin to appear differs between diseases. Symptoms may begin in a single age range, or during several age range. The symptoms of some disease may at any age. Knowledge when symptoms may have appeared can help medical provides find the correct diagnosis.[16]

Symptoms:

- Hepatomegaly (enlarged liver)
- Splenomegaly (enlarged liver)
- Failure to thrive

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- Malabsorption
- Jaundice
- Growth retardation
- Vomiting
- Diarrhea
- Difficulty gaining weight
- Lipid-filled macrophages various tissues
- Development
- Progressive liver diseases
- Cardiovascular complication[17]

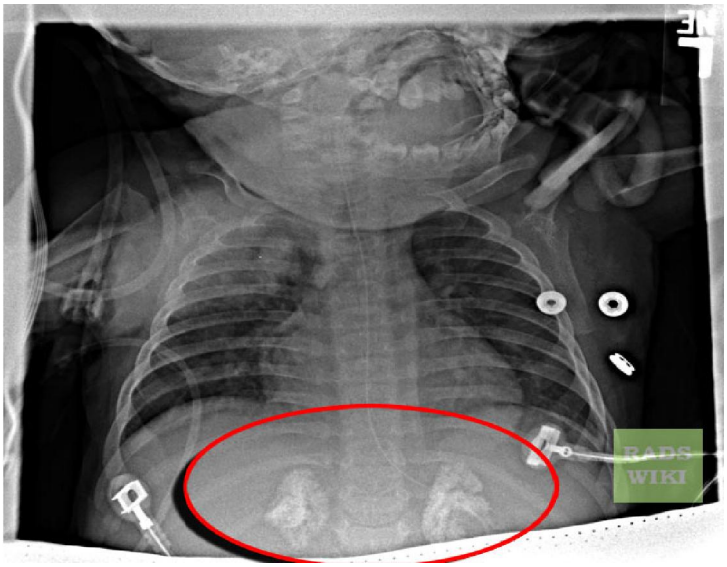

Figure. 4

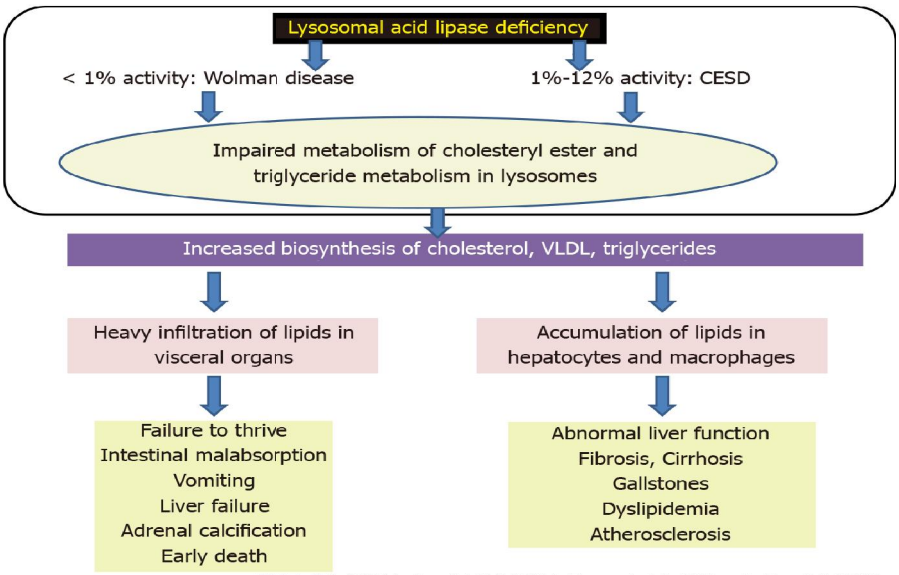

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Figure.5

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Causes of Wolman Disease

1.Wolman disease is caused by mutations in the lysosomal acid lipase (*LIPA*) gene. The *LIPA* gene contains instructions for producing the enzyme lysosomal acid lipase.

2.This enzyme is essential for breaking down (metabolizing) certain fats in the body, especially cholesterol (specifically cholesteryl esters) and to a lesser degree triglycerides.

3.Without proper levels of this enzyme, these fats abnormally accumulate in and damage various tissues and organs of the body.

4.Mutations in the *LIPA* gene that cause Wolman disease result in the lack of production of the LIPA enzyme or production of a defective, inactive form of the LIPA enzyme.

5.Wolman disease is inherited as an autosomal recessive trait. Genetic diseases are determined by the combination of genes for a particular trait that are on the chromosomes received from the father and the mother. [18]

6.Recessive genetic disorders occur when an individual inherits two copies of an abnormal gene for the same trait, one from each parent. If an individual inherits one normal gene and one gene for the disease, the person will be a carrier for the disease but usually will not show symptoms. The risk for two carrier parents to both pass the altered gene and have an affected child is 25% with each pregnancy.[19]

7.The risk to have a child who is a carrier like the parents is 50% with each pregnancy. The chance for a child to receive normal genes from both parents is 25%. The risk is the same for males and females.

8.Parents who are close relatives (consanguineous) have a higher chance than unrelated parents to both carry the same abnormal gene, which increases the risk to have children with a recessive genetic disorder.[20]

Diagnosis of Wolman Disease

A diagnosis of Wolman disease may be suspected in newborn infants based upon identification of characteristic symptoms such as abnormally enlarged liver and gastrointestinal problems. A diagnosis may be confirmed by a thorough clinical evaluation, a detail patient history (including family history) and specialized tests that reveal absence or deficient activity of the enzyme lysosomal lipase acid (LIPA) in certain cells and tissues of the body. Molecular genetic testing for mutations in the *LIPA* gene is also available.[21]

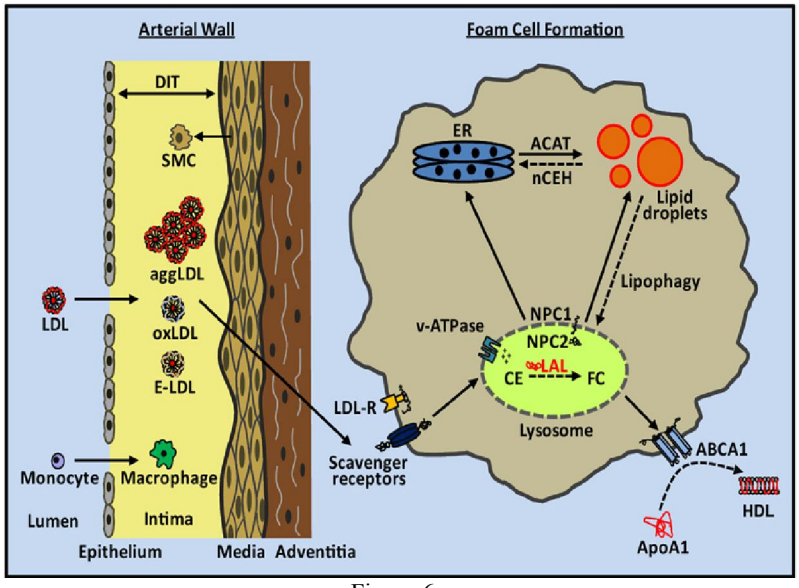

Figure.6

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Treatment of Wolman Disease

STANDARD THERAPIES

Treatment

In December 2015, the U.S. Food and Drug Administration (FDA) approved Kanuma (sebelipase alfa) as the first treatment for people with lysosomal acid lipase (LAL) deficiency.[22]

Other treatment is directed toward the specific symptoms that are apparent in each individual. Treatment may require the coordinated efforts of a team of specialists. Proper nutrition can be maintained intravenously. If the adrenal glands are not functioning properly, medications may be used to supplement the hormones normally produced by these glands.

A team approach for individuals with Wolman disease may be necessary and may include special social support and other medical services. Genetic counseling is recommended for affected individuals and their families.[23]

Clinical Trialof Wolman Disease

In the medical literature, a few children with Wolman disease were treated with hematopoietic stem cell transplantation (HSCT). Hematopoietic stem cells are specialized cells found in the bone marrow (the soft spongy material found in long bones). These blood stem cells grow and eventually develop into one of the three main types of blood cells– red blood cells, white blood cells or platelets.

A transplant is done to replace the bone marrow (and consequently the whole blood system) of an affected individual with marrow from a person who does not have a particular disorder. The healthy cells produced by the new marrow contain sufficient levels of lysosomal acid lipase required to breakdown cholesterol and triglycerides. Individuals with Wolman disease treated with hematopoietic stem cell transplantation have shown dramatic improvement of existing symptoms and avoidance of additional complications such as liver failure.

Researchers speculate that early diagnosis and prompt treatment with a hematopoietic stem cell transplant increases the chances of preserving liver function and preventing cognitive decline. More research is necessary to determine the long-term safety and effectiveness of this potential therapy for infants with Wolman disease. Hematopoietic stem cell transplants are not without drawbacks. The procedure is expensive and carries the risk of serious complications including graft-versus-host disease and other long-term and late effects.

Researchers have been studying enzyme replacement therapy for lysosomal storage diseases such as Wolman disease. Enzyme replacement therapy involves replacing a missing enzyme in individuals who are deficient or lack the particular enzyme in question. Synthetic versions of missing enzymes have been developed and used to treat individuals with certain lysosomal diseases including Hurler syndrome, Fabry syndrome and Gaucher disease.

Gene therapy is also being studied as another possible approach to therapy for some lysosomal storage disorders. In gene therapy, the defective gene present in a patient is replaced with a normal gene to enable the production of active enzyme and prevent the development and progression of the disease in question. Given the permanent transfer of the normal gene, which is able to produce active enzyme at all sites of disease, this form of therapy is theoretically most likely to lead to a “cure.” However, at this time, there are many technical difficulties to resolve before gene therapy can succeed.[24]

Information on current clinical trials is posted on the Internet at www.clinicaltrials.gov . All studies receiving U.S. Government funding, and some supported by private industry, are posted on this government web site.

For information about clinical trials being conducted at the NH Clinical Center in Bethesda, MD, contact the NIH Patient Recruitment Office: Tollfree: (800) 411-1222 TTY: (866) 411-1010 Email: prpl@cc.nh.gov

For information about clinical trials sponsored by private sources,

Contact: www.centerwatch.com

For information about clinical trials conducted in Europe,

contact: https://www.clinicaltrialsregister.eu/[25]

II. CONCLUSION

By these thesis, I would like to conclude thatwolman diseaseis a rare genetic disorder cause by increase the level of LIPA gene(lipase A, lysosomal acid type)into the body because LIPA gene is essential for metabolizing the fats in the body especially cholesterol and wolman disease cause by increase the cholesterol level into the body. It is cause by

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infected parent if one parent is normal and another is infected then easily not show any type of symptoms but both the parent is infected then clearly visible the symptoms into the body. The main symptoms of these disease is inlarge the size of liver and this disease found in newborn babies at the time of 4-week of birth. It treat by HSCT (Hematopoietic stem cell transplantation) but there is no cure or specific treatment for wolman disease. Death usually occurs by the age of six months. According to WHO un till 50 cases are study and research on clinical trial are work in progress.

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