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REVIEW ARTICLE

POMPE - Most Common Rare Autosomal Recessive Disorder in India

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ABSTRACT
Rare diseases are those that affect only a small percentage of the population. The infrequent incidence of rare diseases in the human population is the common denominator. The World Health Organization (WHO) defines a rare disease as a chronic permanent disease or disorder condition with an incidence of 1 or less per 1000 population. Orphan diseases are often referred to as rare. According to estimates, there are about 365 million people worldwide who suffer from rare diseases. Some of the most common rare diseases in India are: Haemophilia, Thalassemia, Sickle Cell Anaemia, Pompe disease and Cystic Fibrosis. In this article, we discussed a comprehensive review about Pompe disease, medically termed as Glycogen Storage Disease Type II. It is found to be more in people from the south-east Asian areas. The PubMed database was used for article selection, papers were obtained and reviewed. The key terms included: Pompe disease, epidemiology, pathophysiology, etiology, symptoms, diagnosis and management. The accumulation of a complex sugar called glycogen in the body's cells causes Pompe disease, an inherited condition. There is no way to stop it. As opposed to many other diseases that can have serious health effects, it can be effectively treated. Always note, however, that early detection is critical in preventing this genetic condition from being fatal.
Keywords: *Pompe disease, Glycogen, GAA gene, Myozyme, Electromyography.*

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INTRODUCTION

A rare disease is a health condition which has a low prevalence and affects a small number of people. There are a wide variety of rare diseases. Some of them are seasonal and some of them take a long gestational period to start showing symptoms. This makes it extremely hard to find and treat these conditions in a larger population group. There are between 6,000 and 8,000 recognized rare diseases, with 450 of them having been discovered in India. Genetic diseases, rare tumors, infectious tropical diseases, and degenerative diseases are examples of rare diseases. In India, an estimated 70 million people suffer from a rare condition, which equates to one in every 20 Indians. Rare diseases might not be serious conditions. However, the time it takes to get diagnosed makes them extremely fatal. India is a highly populated country, making it really difficult for doctors to identify rare diseases and provide referral to specialists. Pompe disease is a rare autosomal recessive genetic disorder caused by mutations in the GAA gene, which results in a deficiency of the lysosomal hydrolase enzyme GAA. Joannes C. Pompe, a Dutch pathologist, invented the term in 1932. It's a genetic disorder that occurs when the body's cells have too little glycogen, which is a form of sugar.[1]

Types

- ✓ **Classic Infantile-Onset:** This type of Pompe disease is usually seen months after the birth of a kid, characterized by symptoms such as myopathy [2], hypotonia, and an enlarged liver

- ✓ **Non-Classic Infantile Onset:** This type of Pompe disease usually starts around one year after birth. It is characterized by delayed muscle motor skills and progressive weakening of muscles. The disease also results in the development of an abnormally large heart too**. [3]**
- ✓ **Symptoms of late-onset type:** This type may not show until adolescence or adulthood, with some cases occurring as late as age 60. People with the disorder may experience shortness of breath, trouble breathing while sleeping, enlarged liver, stiff joints, weight loss, irregular heartbeat, enlarged heart, muscle pain over a large area, an enlarged tongue that makes it hard to chew and swallow, etc.
- ✓ The accumulation of glycogen in muscle and organ tissues disrupts the normal functioning of these parts, causing complications to the person's overall health.

EPIDEMIOLOGY

Pompe disease affects people of all ages, and the severity of the disease varies. The seriousness of the clinical presentations, tissue involvement, and age of onset normally correlate well with the nature of the mutation and the degree of residual enzyme activity. The disease can present itself in a variety of ways, ranging from severe infantile-onset, [4,5] muscle weakness, hypotonia, and hypertrophic cardiomyopathy to a relatively mild, slowly developing skeletal muscle myopathy in adults [6]. The global prevalence of Pompe disease is estimated to be 5,000 to 10,000 patients, with a cumulative incidence of 1 in 40,000. Some pathogenic forms are more prevalent in certain populations [7].

Etiology

The inheritance of pathogenic recessive mutations in both copies of the GAA[8, 11] gene causes Pompe disease, a rare autosomal recessive genetic disease. This means that to develop this condition, a person must inherit two mutated (flawed) genes, one from each parent.An person can only carry one defective gene and therefore be asymptomatic in some cases. These people, on the other hand, would be disease carriers.

The GAA gene is 18.3 kb long, with 20 exons (coding regions) and non-coding introns[12] interspersed.It can be found at the distal end of chromosome 17's long arm (17q25.2-q25.3). [13,14] The cDNA is more than 3.6 kb long, with a coding sequence of 2859 nucleotides. [15]

Pathophysiology

Glycogen deficiency can have a significant impact on the function of essential muscles such as the heart. The GAA, or Alpha Glucosidase, is unaware or greatly reduced in this disorder.

As a consequence, excess glycogens are not broken down and accumulate in tissues, which should not be the case since it can cause harm. Glycogen storage disease type II, also known as AMD, alpha-1,4-glucosidase deficiency,**[16]** GSD II, or acid maltase deficiency, is a type of glycogen storage disease. As a result, issues with vital body organs such as the heart and lungs arise. The muscles will become weak as a result of this disease. Infants and children are the ones who are most affected. Adults, on the other hand, are not always spared from contracting the disease. Infants and children are the ones who are often diagnosed with this disease disorder.

Symptoms

The signs and symptoms of Pompe disease can differ from person to person. Depending on when the disease first manifests itself, the symptoms can vary.In infants, symptoms include the following were shown in Table 1.

Table 1: Symptoms of pompe disease

Classic type	Non-classic type	Late-onset type, which includes adult-onset
Weak muscles, poor muscle tone and enlarged liver.	Motor skills delayed	Breathing difficulties, an enlarged heart, an erratic pulse, growing trouble walking, and muscle pain over a wide area are all symptoms.
Inability to gain weight and grow at the expected rate.	Muscles get steadily weaker	When a person pushes himself or herself, he or she loses the ability to exercise, falls often, gets regular lung infections, and gets short of breath.
Infections in the respiratory system and trouble breathing.	Abnormally large heart	Headaches in the morning, exhaustion during the day, weight loss, failure to swallow as easily as before, and increased hearing difficulties
Feeding problems and problems with hearing.	Breathing problems	Creatine kinase (CK) levels are higher, which is an enzyme that aids the body's functions and provides energy to cells. [17]

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Diagnosis

The enzymes in the blood are analyzed and counted after a blood sample is taken. Sleep studies, lung ability examinations, and electromyography [18] are among the other tests available. The enzymes in the blood are analyzed and counted after a blood sample is taken. DNA research is used to confirm the findings. There are also the following tests:

- ✓ Obtaining a full patient and family history
- ✓ Breathing tests to assess lung capacity (pulmonary function tests) [19]
- ✓ Electromyography (a test that determines how well the muscles work) and magnetic resonance imaging (MRI)
- ✓ X-rays, electrocardiograms, and echocardiograms for the heart
- ✓ Sleep tests
- ✓ For pregnant women who are at risk, a prenatal diagnosis can be performed.

TREATMENT AND MANAGEMENT

Pompe disease can be lethal if left untreated, and children can die within a year of diagnosis. Children with juvenile Pompe disease have a life expectancy of 30 years or less. A child with classic infantile Pompe disease has a life expectancy of two years or less, while children with the non-classic variety have a life expectancy of early childhood. Early treatment, particularly in children, is the best way to prevent the disease from causing more harm to the body.

Doctors usually prescribe two drugs to replace the protein that has been missing from the body. Both Pompe patients are eligible for enzyme replacement therapy (ERT). ERT may aid in the proper processing of glycogen and the prevention of its accumulation. [20-23] The enzymes used for this therapy are:

Myozyme- is a lysosomal glycogen specific enzyme that is administered and treated for those who are infants or children who have the disease.

Lumizyme- is a genetically modified algluosidase alfa drug that mimics the naturally occurring acid alfa glucosidase enzyme. It is an FDA-approved medication that is used to treat late-onset or non-infantile people who have been diagnosed with this disorder.

Supportive therapy- such as a low-carbohydrate, high-protein diet and aerobic exercise, may help avoid decline by decreasing glycogen storage and increasing fatty acid oxidation, but it won't help with permanent muscle damage. Treatment with a high-protein diet and l-alanine supplementation had no effect on late-onset patients.

Gene therapy- is a new therapeutic choice for a variety of genetic diseases. However, it is still being tested with positive results. Individuals who are affected will also find solace in support groups.

Multidisciplinary Team Approach

A team approach is needed to effectively treat this disease. Speech therapists, genetic counsellors, respiratory therapists, occupational therapists, nutritionists or dieticians, psychosocial therapists, and physical therapists are among the team members.

As opposed to many other diseases that can have serious health effects, Pompe disease can be well treated. Always note, however, that early detection is critical in preventing this genetic condition from being fatal.

CONCLUSION

Pompe disease is a neuromuscular condition that is multisystemic in nature and progresses to death. This can't be stopped right now because it's mostly a genetic disease. New techniques are being developed to increase enzyme distribution through different methods in order to change the disease's natural history. Pompe disease can affect many parts of the body. It is best to do treatment by using a multidisciplinary approach who can help in managing the symptoms. Supportive therapy and care can be done. There is no precise single management, but meticulous therapies can alleviate symptoms and assist patients to live longer.

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CONFLICT OF INTEREST

All authors declare that there is no conflict of interest.

AUTHORS' CONTRIBUTIONS

All the authors contributed equally to the paper.

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