Pompe Disease: A Rare Disease of Glycogen Storage

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ABSTRACT

Pompe Disease, a glycogen storage (most notably in skeletal muscle) disease type II is an autosomal recessive disorder caused by deficiency of acid α-glucosidase (the lysosomal enzyme). It occurs due to mutation in acid α-glucosidase gene which is located on chromosome 17q25.3. It has two types; classic form (Infantile form) and late onset form (Juvenile form). It is a rare disease (estimated frequency 1:40,000) with common symptoms like cardiomegaly, congestive heart failure, enlargement of liver, impaired alerntness and limb-girdle weakness. It is diagnosed by muscle biopsy, urine analysis, chest X-ray, echocardiography, measurement of α-glucosidase activity in tissues etc. Enzyme replacement therapy by Alglucosidase alfa (an enzyme by recombinant DNA technology) is very effective and substantially improves the prospects for patients. Recently, several therapies are also as add on therapy with enzyme replacement therapy. This review gives an overview of different complications of Pompe Disease and approaches towards the treatment of this disease.

Keyword: Pompe, Enzyme Replacement, Blood Spot, acid α-glucosidase

INTRODUCTION

Pompe Disease (glycogen storage disease type II) is an autosomal recessive disorder associated with acid maltase (alpha 1-4 glucosidase) which is characterized by accumulation of glycogen in various tissues, including skeleton muscle, heart and cells of the central nervous system. Pompe Disease is rare, progressive and at some instance it is fatal.1

Pathophysiology

Accumulation of lysosomal glycogen starts when the acid α-glucosidase activity decreases below critical. In knockout mouse models of Pompe Disease with complete enzyme deficiency, storage was seen in almost every tissue and cell type. Lysosomal glycogen storage was also identified in the organ of Corti, inner and outer hair cells, and spiral ganglia of knockout mice when investigating by analogy the cause of hearing deficit of some infants with Pompe Disease. Hypertrophic cardiomyopathy is a typical sign of classic infantile Pompe Disease in which no residual acid α-glucosidase activity is present. Pathological changes in skeletal muscle, on the other hand, are prominent throughout the entire clinical spectrum. The process by which skeletal muscle function is eventually lost is also intriguing. Investigator noted an order of events by comparing pathological changes in muscle in various stages of disease in knockout mice and patients. When the disease advances, the lysosomes expand, become many, and fuse to form larger structures that interfere with the architecture of the fibre. Additionally, regions develop with lipofuscin deposits; cellular debris surrounded by membranes and freely dispersed cytoplasmic glycogen. The increase noted in the amount of titin and desmin in the mouse muscle points to the generation of mechanical stress by these inclusions. In work addressing pathological changes in muscles of a knockout mouse model of Pompe Disease, both mobility of storage vesicles and communication between autophagosomes, endosomes, and lysosomes decreased with disease progression.2,29

CLASSIFICATION

Early Onset of Pompe Disease

The symptoms of early onset of Pompe Disease may be present at the time of birth or appear within the first few months.

The general symptoms include: cardiomegaly, hypotonia, rapidly progressive muscular weakness, in conjunction with delayed motor milestones, cardio-respiratory failure, by age 1year, impairment of respiratory muscles (including abdominal and intercostal muscles and the diaphragm) and rapid-onset respiratory insufficiency, difficulty in Swallowing, malnutrition, aspiration pneumonia, and respiratory tract infections, other common findings include macroglossia, hepatomegaly, hearing loss, osteopenia, and scoliosis.

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Patients with early onset of Pompe Disease develop secondary cardiomyopathy due to the massive accumulation of glycogen within the cardiac muscles. In this, laboratory examination usually reveals cardiomegaly on thoracic radiography; electrocardiogram changes, with a high-voltage QRS complex and short PR interval; elevated serum creatine-kinase, CKMB isoenzyme, alanine amino-transferase, and aspartate amino-transferase levels; and increases in the level of enzyme origin, which is more evident with progression of the disorder.1,4

Late Onset of Pompe Disease

The late onset of Pompe Disease is milder than the infantile form, and heart is usually is not affected. Because of only partial deficiency of acid α-glucosidase, the general symptoms of late onset of Pompe Disease may occur any time after the first year of life up to the sixth decade of life. Disease progression is slower than in infants but is still progressive. The paraspinal muscles and lower limb proximal muscles are the firstly affected which leads to motor impairment and difficulty performing daily activities, and scoliosis, kyphosis. Diaphragm impairment and auxiliary respiratory muscles causes chronic respiratory failure with fatigue, carbon dioxide retention, respiratory insufficiency and sleep apnea. Repeated aspiration pneumonia is common. Other findings include; macroGLOSSIA, palpebralptosis, cerebral aneurism, hyporeflexia, osteopenia and muscular weakness is the most prominent and detectable in cases of the disease. Respiratory problems also appear as the first symptom in few cases. Laboratory findings include increased creatine-kinase, aspartate amino-transferase, and alanine amino-transferase values and spirometric parameters indicating altered respiratory assessment capacity, including forced expiratory volume in 1 second and forced vital capacity in erect and supine positions with a normal electrocardiogram.5,6

ANIMAL MODELS FOR POMPE DISEASE

In order to design and evaluate different treatments, approaches of animal modeling is essential. Naturally occurring animal models of Pompe disease include Brahman and Shorthorn cattle, Lapland dog, cats, sheep and a strain of Japanese quail which are less suitable for Pompe Disease research due to long generation time and small litter size (cattle), or evolutionary distance from human. Therefore, five mouse models have been developed. The first knockout mouse model was generated by targeted disruption of exon 6. Soon after birth, these mice developed generalized and progressive glycogen accumulation in lysosomes of liver, heart and skeletal muscle cells. This model is representative for the infantile form. These mice are remained phenotypically normal which might be partially due to their genetic background.

The exon 6 of the acid α-glucosidase gene was replaced by a cassette containing a neomycin resistance gene into exon 6 flanked by LoxP sites (6neo/6neo) to generated second knockout mouse model with both the adult and infantile phenotypes feature of Pompe disease. Acid α-glucosidase activity measurements confirmed the absence of functional enzyme in several tissues.

A third mutant mouse model was created by exon 6 of the acid α-glucosidase gene and the neomycin resistance gene of 6neo/6neo mice were removed (D6/D6) which is resulted by mating 6neo/6neo mice to cre-producing mice. This model is similar to second model with regard to acid α-glucosidase activity measurements in tissues and tail. In both models, abnormal lysosomal glycogen storage in heart which is more marked than skeletal muscle is observed.

Raben et al. created a similar mouse model by targeting exon 14 of the acid α-glucosidase gene (D14neo/D14neo) which is comparable to the 6neo/6neo mouse model with regard to clinical course.

Two other models were generated because sequential administration of acid α-glucosidase results in the development of an immune response. In which the exon 6 knockout mouse model therefore was further improved to generate tolerant knockout mice which express low levels of human acid α-glucosidase in the liver, but still retain the disease phenotype which are immunological tolerant to injected recombinant enzyme.

To avoid production of anti-human acid α-glucosidase antibodies after enzyme administration the fifth animal model was developed. Due to lack of anti-human acid α-glucosidase antibodies increased enzymatic activity and decreased glycogen accumulation was observed in liver, heart and other organs were detected after expression of human acid α-glucosidase.7-8

DIAGNOSIS

The diagnosis of Pompe disease is done by the presence of clinical symptoms which demonstrate the deficiency of acid α-glucosidase. Generally infants with Pompe disease possess acid α-glucosidase activities in muscle tissue and skin fibroblasts that are less than 1% then that of in normal controls. In older children and adults, activity of acid α-glucosidase reduces but is higher in infants. Acid α-glucosidase activity assays can be used to diagnose Pompe disease, and a second test should be performed to confirm the diagnosis.

Assays of acid α-glucosidase activity in samples without maltaseglucoamylase

Acid α-glucosidase activity can be measured in muscle biopsy, fibroblasts cultured from skin biopsy and purified lymphocytes using either the glycogen (natural substrate) or
4-methylumbelliferyl-a-D-glucoside the (synthetic substrate). Muscle biopsies are used for the histology in patients with muscle weakness and to measure acid α-glucosidase activity which is a particular risk for infants with Pompe Disease. Estimation of acid α-glucosidase in muscle tissue can be problematic because loss of acid α-glucosidase activity during sample transport and processing and glycogen accumulation in the muscles of patients varies with biopsy site, so the lack of glycogen accumulation does not exclude the diagnosis of Pompe Disease. The muscle biopsy is not enough for diagnosis of Pompe Diseases assay using cultured fibroblasts is currently considered as the fibroblasts do not contain maltaseglucoamylase. However the extraction of fibroblast from skin biopsy is time consuming. Acid α-glucosidase activity cannot be assayed specifically in mixed leukocytes because the neutrophils are present in mixed leukocytes contain maltaseglucoamylase, which leads to false-negative results. Acid α-glucosidase activity can be diagnosed in purified lymphocytes (free from neutrophils) but it is difficult when blood sample is not fresh and leads to false results.

New assays of acid α-glucosidase activity in samples containing maltaseglucoamylase

To measure the acid α-glucosidase activity in the presence of maltaseglucoamylase two techniques have been developed. They are immunocapture and competitive inhibition.

Immunocapture circumvents isoenzyme interference but requires antibodies which are not commercially available and this method leads to the loss of activity of acid α-glucosidase during the assay. Competitive inhibition of maltaseglucoamylase by maltose and acarbose was demonstrated in acid α-glucosidase assays in dried blood spots.

Acarbose performed better when the two inhibitors were compared. Dry blood sample are easy to obtain and useful for rapid diagnosis in newborns and children. Dried blood spots are stable during shipping, which permits easy transport to specialized laboratories for diagnosis. Acid α-glucosidase activity can be assayed selectively in mixed leukocytes by inhibiting neutrophil maltaseglucoamylase by acarbose. The addition of acarbose to assays using purified lymphocytes prevents false-negative results. With the competitive inhibition acid α-glucosidase assays using blood samples can now be considered the method of choice for the enzymatic diagnosis of Pompe disease because they are reliable, less invasive, more convenient, and faster.

Optimizing acid α-glucosidase assay techniques

Assessment of acid α-glucosidase activity requires at least two assays: the selective acid α-glucosidase assay, and the assay of a reference enzyme to confirm the quality of the sample.

The selective acid α-glucosidase assay is performed under acidic conditions (pH 3.8–4.0) using up to 2 mM of 4-MUG or glycogen (50 mg/mL), in the presence of acarbose. Acarbose completely inhibits maltaseglucoamylase activity at acidic pH without affecting the acid α-glucosidase activity of 4-MUG (substrate) concentrations up to 2 mM, in mixed leukocytes, lymphocytes, and dried blood spot. Higher concentrations of acarbose, inhibit acid α-glucosidase and by varying the concentration of 4-MUG it can affect the results and also the required concentration of acarbose. The synthetic substrate 4-MUG is easy in the assay, but the better results can be achieved with the natural substrate glycogen.

Other lysosomal enzymes which could be used as a reference activity are β-galactosidase or β-hexosaminidase. A poor quality sample often has low acid α-glucosidase activity, which could lead to a false positive diagnosis of Pompe disease. Low activity of the reference lysosomal enzyme will reveal a poor sample. Sample collection and enzyme assays should be performed in accordance with standard laboratory guidelines.

Some Other Diagnostic Parameters

Muscle Biopsy

Muscle biopsies reveal vacuolar glycogen storage. The glycogen contained in the vacuoles can be visualized with Periodic Acid Schiff staining and by the staining of acid phosphatase, indicating an increased lysosomal compartment. The intracellular accumulation of glycogen causes displacement or compression of normal cellular organelles, leading to damage of muscle fibers. Ultimately lead to replacement of muscle fibers by connective tissue and fat. In the classic infantile form vacuolization is eventually present in all muscle fibers. In the non-classic phenotype muscles are involved more heterogeneously. In about 20% of patients with non-classic Pompe disease, muscle biopsy shows neither glycogen accumulation nor other morphologic abnormalities.

Urine Analysis

A common biochemical characteristic in Pompe disease is the presence of a tetrasaccharide in urine on thin layer chromatography. The origin of this tetrasaccharide band is unknown. It is suggested that undegraded glycogen is released into the circulation and degraded by serum amylase to the oligosaccharide present in urine.

There are some other diagnosis methods such as; chest radiography, electrocardiography, echocardiography, bone densitometry etc. B-type natriuretic peptide can also be utilized for surveillance of cardiac functions. Trends in mineral density and architecture over a long period of observation can be measured by high-resolution peripheral quantitative computed tomography and may be an early
indicator of the response to interventional therapies. In addition, a combination of decreased loading forces due to decreased mobility likely contributes to the compromise of bone integrity in Pompe disease. These trends can be reversed by applying increased loading forces such as vibration therapy and maintaining weight-bearing and mobility. This technique can serve as a valuable tool to monitor bone health in patients with Pompe disease.  

MANAGEMENT

Enzyme Replacement Therapy

The early attempts of enzyme replacement therapy treatment were for gaucher disease by β-glucosidase which was firstly purified from placenta in 1974. Physical therapy is an important component of management. Recently, the recombinant acid α-glucosidase purified from mice milk was internalized via the mannose 6-phosphate receptor and corrected the enzyme deficiency in fibroblasts from patients. The pre-clinical studies also disclosed one truth that high doses of the recombinant enzyme were required for the positive response. For example, the effect of high-dose treatment was much better than low-dose treatment.

There are also some disadvantages of this therapy such as; development of nephrotic syndrome, anaphylactic reactions including anaphylactic shock, antibody development in treated patients within the first 3 months of treatment. Recent studies have shown that high antibody titers can occur in patients receiving enzyme replacement therapy and counteract the effect of treatment. Human cell products will be better than animal cell products which can be the part of recent development and this development need to overcome other difficulties especially in targeting the enzyme.  

For example, conjugation of mannose 6-phosphate-containing oligosaccharides to acid α-glucosidase improves the delivery to muscles and the clearance of glycogen in Pompe mice. Also, a tag with an acidic oligopeptide may enhance drug delivery to bone, and a phosphorylated rhGALNS can be delivered to multiple tissues, including bone, implying a potential enzyme replacement treatment for mucopolysaccharidosis type IVA.  

remodelling the carbohydrate of recombinant human acid α-glucosidase to improve its affinity for the cation-independent mannose 6-phosphate receptor represents a feasible approach to enhance the efficacy of enzyme replacement therapy for Pompe disease.  

But there are many other complications which are associated with human recombinant acid α-glucosidase such as less effective for skeletal muscle.  

Gene Therapy

The gene therapy concept for lysosomal storage disease was borne out because it lies in the category of genetic disease because a single gene is responsible for all primary disease manifestations. It is an important concept of adjunctive therapy for Pompe disease used in the current clinical study of recombinant adeno-associated virus mediated gene therapy. In clinical trial the Gene therapy in cardiac cell reveal the efficacy of systemically delivered adeno associated virus–acid α-glucosidase shows high-level transduction in cardiac tissue leading to the reduction of glycogen content and restoration of cardiac morphology and function. The recombinant adeno-associated virus has been shown to be capable of efficiently transducing neural tissue either by direct administration or via retrograde transport of vector after intramuscular delivery. In preclinical studies direct administration of recombinant adeno-associated virus to the diaphragm in animal model lead with increased efferent phrenic nerve activity which suggested that recombinant adeno-associated virus mediated gene therapy induced a tolerance to introduced acid α-glucosidase, and this strategy could enhance the efficacy of enzyme replacement therapy in cross-reacting immunologic material negative patients with Pompe disease and in patients with other lysosomal storage diseases.  

Adjunctive β2-agonist treatment increased cation independent mannose-6-phosphate receptor expression and enhanced efficacy from gene therapy in Pompe disease, which has implications for other lysosomal storage disorders.  

NADH–dehydrogenase subunit 5 gene shows deleterious effect on m.12908T>A (Mutation in acid α-glucosidase gene).  

Substrate replacement therapy

The substrate reduction therapy is a combined synergistic therapy that aims at reducing glycogen accumulation in muscles. The approach should make to target on enzyme involved in muscle glycogen biosynthesis pathway and regulation meanwhile preserving the hepatic glycogen storage to prevent glucose homeostasis disturbance. Some study shows that modulation in glycogen synthesis provides a novel therapeutic option in Pompe Disease. Glycogen synthase is negatively regulated by phosphorylation by different kinases. So glycogen synthase can partially be regulated by mTOR (a mammalian target of rapamycin). It is serine/threonine kinase which is part of different multiprotein complexes such as (mTORC1 and mTORC2). Recently, it has been demonstrated that acid α-glucosidase knockout mice treated with rapamycin (an inhibitor of mTORC1) significant decreased muscular glycogen storage due to the phosphorylation-mediated inhibition of Glycogen synthase and also demonstrated that the mTORC1 pathway regulates the muscular glycogen synthesis without affecting the liver glycogen synthesis.
Treatment of Pregnant Patient

Weida J. et al (2012) describe the complication of Pompe in pregnant patient which suggest that recent developments in diagnosis and treatment of Pompe disease have allowed more women to reach reproductive age. The obstetricians must monitored for respiratory complications, metabolic derangements, and worsening functional status during pregnancy. Pregnant patient of Pompe Disease are often treated by giving a high-protein diet to avoid muscle wasting and Supplements like coenzyme Q and L-carnitine to increase the metabolism of fat as an energy source and to decrease protein degradation and preserve muscle integrity. Ephedrine is also used to stimulate the degradation of glycogen, and thus decrease toxic accumulation in lysosome and decrease muscle damage during stress. Furthermore pregnant Pompe disease patient deliver a healthy baby but they have to significantly decline in their muscle strength during the pregnancy because it cannot be recovered through enzyme replacement and supportive nutritional therapy. Expertise in neuromuscular disease, maternal-fetal medicine, biochemical genetics, pulmonology, anaesthesia, and dietetics are some approaches which requires in management therapy. Although during pregnancy, the continuous use of enzyme replacement therapy has been reported but the initiation of enzyme replacement therapy during pregnancy has not.46

Role of Stem Cells

A study is done which had successfully made induced pluripotent stem cells for Pompe Disease patients. In which they made induced pluripotent stem cells which are specific to Pompe disease and demonstrate that these cells possess human embryonic stem cell characteristics and pluripotent developmental propensity. They also demonstrated that these induced pluripotent stem cells differentiate to cardiomyocytes and exhibit the pathological characteristics of Pompe disease. The potential of lentiviral vector–mediated expression of human acid α-glucosidase in hematopoietic stem cells is also recently explored in a Pompe mouse model. Current study reveals that hematopoietic stem cells have proven the prominent and sustained therapeutic efficacy, especially in cardiac and respiratory functional impairments and also in complete clearance of glycogen in liver and spleen.41-42

Other Approaches Towards The Treatment

Role of Hyaluronidase

In order to enhance acid α-glucosidase activity into the muscle in Pompe Disease, matalon et al. 2006 examined the efficacy of hyaluronidase in the heart, quadriceps, diaphragm, kidney, and brain of mouse model of Pompe disease. These studies suggest that hyaluronidase enhances penetration of enzyme into the tissues including muscle during enzyme replacement therapy and therefore hyaluronidase pre-treatment may be important in treating Pompe disease.43

Role of c.546G>T Mutation

Mutant acid α-glucosidase in patient fibroblasts carrying c.546G>T mutation is stabilized without cytotoxic effect by treatment with proteasome inhibitor as well as pharmacological chaperon N-butyl-deoxynojirimycin. In this study, researchers characterized the effect of two proteasome inhibitors, bortezomib and MG132, on maturation, sub cellular localization and residual activity of mutant acid α-glucosidase in the patient fibroblasts carrying c.546G>T mutation. These studies indicate that proteasome inhibitor may be a novel drug as potential pharmacological chaperone therapy for Pompe disease patient carrying chaperon-responsive mutation.44

Role of Angiotensinogen Converting Enzyme

In a study researcher reveals the role of angiotensinogen converting enzyme in early symptoms of Pompe Disease and also severe motor dysfunction in patient. According to a research angiotensinogen converting enzyme have three genotypes DD, ID, II out of which DD alleles encode for angiotensinogen converting enzyme influence. Patient with D allele had increase action of angiotensinogen converting enzyme it decrease half-life of bradykinin and increase level of angiotensinogen II that is vasoconstriction. The angiotensinogen converting enzyme genotype work in place of angiotensinogen converting enzyme in early symptoms of Pompe Disease and therefore hyaluronidase pre-treatment may be important in treating Pompe disease.45

Role of BMN-701

A new molecule BMN-701 which is a fusion protein of insulin-like growth factor 2 and acid α-glucosidase for the treatment of late-onset Pompe disease is in clinical trial. The results show improvement on maximal inspiratory pressure and also maximal inspiratory pressure which are the important parameter of respiratory muscle function. The clinical trials are proceed for the entity BMN-701 and will replace with alglucosidase alfa used now days.46

Role of Cancer Drugs

Immune response against enzyme replacement therapy is treated with a cocktail preparation of chemotherapy drugs rituximab and methotrexate, plus the intravenous gamma globulin immune booster to prevent the immune response to the enzyme replacement therapy.47
Role of Targeting Intercellular Adhesion Molecule-1

Targeting intercellular adhesion molecule-1, a protein involved in inflammation and over expressed on most cells under pathological conditions, provides broad bio distribution and lysosomal transport of therapeutic cargoes. Delivery of this is improved by coupling acid α-glucosidase to polymer nanocarriers coated with an antibody specific to intercellular adhesion molecule-1. Radioisotope tracing in mice demonstrated enhanced acid α-glucosidase accumulation in all organs, including Pompe targets. Along with improved delivery of Niemann-Pick and Fabry enzymes, previously described, these results indicate that intercellular adhesion molecule-1 targeting holds promise as a broad platform for lysosomal enzyme delivery.  

CONCLUSION

Pompe Disease is a rare disease which may be fatal several times. It is of two type late onset and early onset. It can be treated by enzyme replacement therapy, by gene therapy, by using cancer drugs cocktail and some new molecules are also involved in its treatment. Pompe Disease can be treated effectively even during pregnancy. Stem cells also play a new role in treatment with enzyme replacement therapy. Due to its rarity the necessary systematic clinical studies and establishment of minimal standard clinical care are hindered. To provide constant improvement in both technology and in health care provision, continuous medical education is necessary, especially in diagnosing and treating this rare disorder. It is all depends upon awareness towards rare diseases.

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