

Evaluation for the Current Management of Pompe Disease

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ABSTRACT

Pompe disease is an autosomal recessive condition characterised by deficiency of the enzyme acid α -glucosidase. This causes accumulation of glycogen in muscles, significantly in the heart. The affect is a progressive muscle dysfunction, leading to profound generalised weakness and hypertrophic cardiomyopathy. Recent trials of enzyme replacement therapy have shown some promising results that could help people with the disease, however some have not responded to the treatment. Physical therapy is another method of treatment applied to help enhance movement and delay the associated weakness. However this type of therapy could be contra indicatory in light of the pathology of the disease. This report reviews current knowledge regarding the pathology behind Pompe disease and how treatment options work with this, to conclude if they really are beneficial and if so, to what extent can they be of benefit.

Keywords: pompe, enzyme, cardiomyopathy, therapy, disease

1 INTRODUCTION

Pompe disease is also known as Glycogen storage disease type II or acid maltase deficiency. It is a progressive autosomal recessive condition that leads to a deficiency of acid α -glucosidase (GAA). GAA is a lysosomal enzyme that degrades glycogen, a deficiency in this leads to the accumulation of glycogen in many tissues, especially muscle. [1, 2]

The disease was first described by a Dutch pathologist called Johannes C. Pompe, who experienced the death of a 7 year old infant that died of idiopathic hypertrophy of the heart. Furthermore to the cardiac problems, the infant had generalized muscle weakness. The crucial observation was made that these problems were all linked with the accumulation of glycogen in virtually all tissues, especially that of the heart. Further to this, in 1955 Christian DeDuve, a Nobel Prize winner discovered an intracellular figure where things were broken down, he named this 'lysosome'. Eight years later (1963), Prof. H.G. Hers discovered that the glycogen storage in Pompe disease is caused by the deficiency of the lysosomal enzyme 'acid α -glucosidase'. This was the first discovery of a lysosomal enzyme deficiency and opened the doorway to the concept of lysosomal deficiency diseases.

2 DISEASE PATHOLOGY AND PRESENTATION

Pompe disease is an extremely variable disorder that differs according to age at onset, rate of disease progression and extent of organ involvement. Symptoms can present during the first months of life or at any time, during adolescence or adulthood. Cases have also been reported of symptoms appearing as late as the sixth decade of life. Muscle weakness is a prominent feature in all forms of Pompe disease [1].

The disease can be classified into two broad categories – infantile onset and late onset patients.

Patients affected with the infantile form of the disease typically present with symptoms within the first 12 months of life. The infantile-onset form produces massive deposition of glycogen in the heart, liver, and skeletal muscle resulting in rapidly progressive cardiomyopathy, hepatomegaly, generalized muscle weakness, hypotonia, and motor delay. Death from cardiac and/or respiratory failure generally occurs before the end of the first year [1].

A subset of patients with infantile-onset Pompe disease has been described by Slonim et al.[3] The clinical course of these patients was characterized by a slower progression of cardiomyopathy and longer survival, generally developing cardio respiratory failure between 1 and 2 years of age. Although several of these patients die before the age of 1, others may survive beyond 2 years.

late-onset Pompe disease appears during childhood to adulthood. The main feature of this type is a slow progressive proximal myopathy with minimal cardiac involvement. Death normally results from respiratory failure [1]. The classification of Pompe disease phenotypes can be unclear as they range in a clinical spectrum extended throughout different ages of onset, degrees of organ involvement and rates of progression [1].

This clinical spectrum is emphasized in Figure 1 where an infantile onset (green line) of the disease shows a steeper progression to increased cardiomyopathy, and death, the graph also emphasizes the link between reduced levels of GAA activity and disease progression. As we can see in late onset disease (blue line), progression is slower, people live longer and there is a slightly increased GAA activity which is the reason why deterioration takes longer.

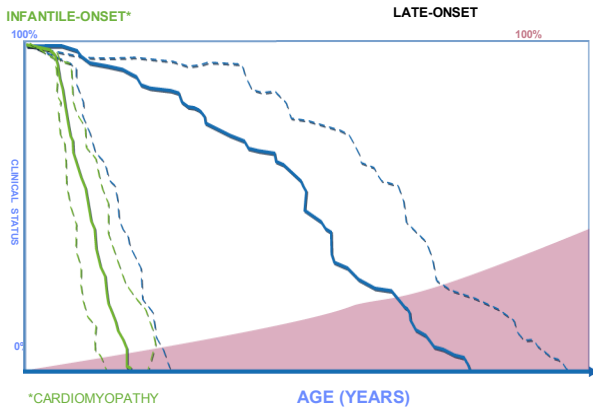


Figure 1: A graph showing the spectrum of affect for Pompe Disease

Figure 2 shows that Acid alpha-glucosidase (GAA) is the only pathway for glycogen breakdown in the lysosome. Without it, massive accumulation of glycogen occurs leading to lysosomal distention [4]. Glycogen accumulation inside the lysosome is followed by leakage or rupture, this leakage or rupture also releases hydrolytic enzymes which have a role in muscle destruction [5].

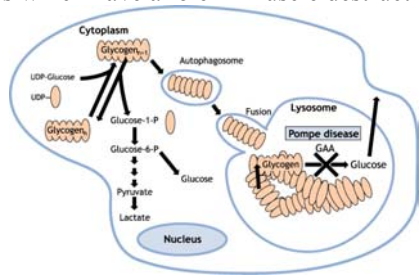


Figure 2: Cellular Pathogenesis

3 AVAILABLE TREATMENT MODALITIES

Genetic counselling is important for families with a history of Pompe disease, and prenatal screening can be carried out to identify a foetus at risk of Pompe disease. Respiratory therapy can help to ameliorate the respiratory insufficiency caused by weakening of the diaphragm and other respiratory muscles. It may be particularly useful in overcoming the respiratory decompensation during active respiratory tract infections [1].

Patients may also benefit from physical therapy, this may help to maintain a range of motion and muscle strength, from the use of assistive devices (eg, orthotics, cane, walker, or wheelchair), which may be necessary for ambulation. Nutritional and dietary therapies, such as a high-protein, low-carbohydrate diet or, alternatively, a diet rich in amino acids may be of benefit for some patients. Speech and occupational therapy may be useful for children with Pompe disease, and psychosocial therapy may be helpful for both patients and their families [1].

3.1 PHYSICAL THERAPY

Physical therapy management aims to prolong the onset of muscle problems by stressing the muscles by exercise. Muscle involvement begins with the enlargement of muscle fibres as glycogen accumulates in the lysosomes, later followed by muscle wasting. A mechanism for the destruction could be the leakage of hydrolytic enzymes from the lysosomes into the surrounding cells and tissue [6].

Because of the course of the destruction, physical management could be more so disadvantageous than good. Continuous contraction of muscles may further enhance the leakage or the rupture of lysosomes leading to further muscle damage [6]. The extent to how much destruction will be caused by the exercise depends on how vigorous it is. If someone with the disease is made to do a lot of strenuous anaerobic exercise, it will have a more adverse affect, however trying to reduce the exercise to an aerobic level, with sub maximal excursion is believed to be important [6].

Even with an exercise regime where maximum efficiency of aerobic respiration is being met, there could still be a slight increase in the leakage of enzymes from the lysosomes compared to if no physical activity was induced. The extent to which minimal activity provides benefit compared to muscle destruction needs to be weighted to see if this really does help. Because if destruction of fibres is an irreversible process then physical therapy can be questioned. Even though there is hypertrophy of existing fibres to compensate for the destruction, this advantage could be short lived with a 'catching up' affect of slow destruction.

Studies of the affect of strengthening in individuals with Pompe disease have been few, with small numbers, limited to late onset form, reporting that sub-maximal exercise 'may' stimulate the degradation of some of the glycogen that accumulates in the cytosol [7].

3.2 Enzyme Replacement Therapy

Enzyme replacement therapy involves the use of recombinant human α – glucosidase (rhAGLU) enzyme created by rabbits, or other non human vectors. One study looked at the use of human α – glucosidase produced by transgenic rabbits by the epithelial cells of the mammary gland. The human gene that codes for the enzyme is spliced into the pronucleus of fertilized rabbit oocytes and then these are planted into the womb. Newborns carrying the transgene are selected by southern blot analysis; those that transmit the transgene are used for breeding [8].

Four patients with infantile onset Pompe disease were reviewed for 36 weeks who were given the rhAGLU intravenously and the advantages noted. Factors such as a reduction in the accumulation of glycogen in lysosomes, cardiomyopathy and the affect on movement were assessments for the success of treatment. Quadriceps muscle biopsy was taken to assess the reduction in glycogen store [8].

All patients had a severe deficiency of α – glucosidase activity in muscle ranging from 1 to 2% of the normal value (normal is 8-40 nmol/h per mg). A second biopsy was taken after 12 weeks that showed a 7 – 30 fold increase in enzyme activity, showing the target tissue was being reached. However this was still below normal and so the dose was increased. Twelve weeks after, another biopsy was taken that showed all patients had acquired normal levels, this is seen in table 1 [8].

Patient	Activity (nmol/h per mg)		
	Muscle <i>t=0</i> ^b	Muscle <i>t=1</i> ^b	Muscle <i>t=2</i> ^b
Patient 1	0.15	4.9	27
Patient 2	0.27	2.7	8
Patient 3	0.2	2.1	13
Patient 4	0.37	2.7	16

^a Normal α -glucosidase activity 8-40 nmol/h per mg (*n*=29)
^b *t*=0, baseline; *t*=1, 12 weeks after start of treatment with 15 or 20 mg/kg; *t*=2, 12 weeks after dose adaptation to 40 mg/kg

Table 1: The affects of enzyme replacement therapy [8]

Enzyme replacement therapy in this trial can be seen to have helped considerably. However still the therapy has its drawbacks [8]. all four patients still showed infusion reactions, these were all managed by reducing the infusion rate.. It takes a long time for the enzyme to be taken up, a total of 24 weeks of therapy was required until required enzyme levels were reached. All patients benefited to different degrees, showing the variability of treatment. The contribution of lysosomal versus cytoplasmic glycogen to the total content of muscle is unknown. Maybe the enzyme replacement is not the only way to tackle the problem; the physical therapy could have a role in reducing the cytoplasmic storage of glycogen.

A study in America that used eight participants has shown a different outcome. Figure 7 shows a light microscopic examination of the quadriceps muscle biopsy of two patients who received the treatment. In patient 1, the glycogen accumulation has been cleared in them majority of myocytes after 52 weeks, however, a rare myocyte is still completely replaced by glycogen and seems to be unaffected by ERT (marked with an asterisk in box b). Patient 2 demonstrates a heavy glycogen load present at 3 weeks as seen in box c and marked by the red arrow. After 52 weeks of ERT there has been little glycogen clearance and myocytes appear completely replaced by glycogen, similar to the appearance of the isolated cell in patient 1 [9].

These differences in the follow up of ERT could emphasise different things. This could show the variability of the disease itself, in progression as well as response to treatment. In patient two, the results could mean ERT actually speeding up disease progression, but it could also just be the case of ERT not working and the disease taking its natural course. Patient one has shown proof of myocytes that are resistant to the uptake of recombinant enzyme, this could possibly mean within the problem of reduced enzyme activity in Pompe disease, maybe there is a secondary problem in intracellular transport, making it an even more complicated pathology.

It may be that the type of myocyte in patient one is one that is expressed at different amounts in different patients. A higher resistant myocyte expression could be in those of a more rapidly progressive disease, such as that shown in patient 2.

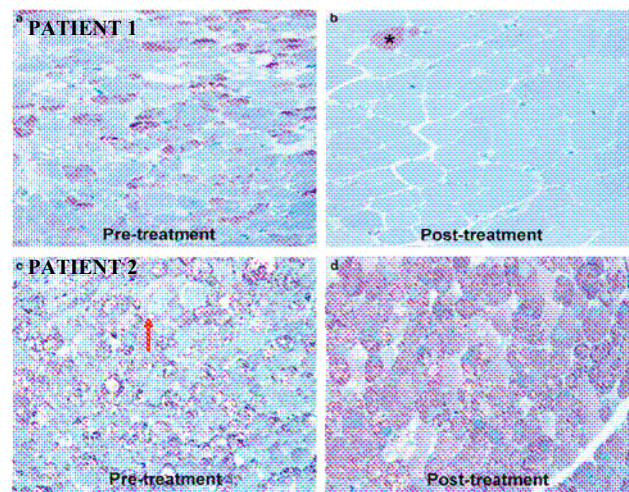


Figure 7: - Light microscopic examination of muscle tissue showing glycogen stores post therapy [9]

muscle specific promoter has also increased the amount of enzyme taken up by cells. Chemical chaperones have been used to modulate the uptake of enzyme into cells.

However all these techniques have only been tried in rats. They may react differently in humans or show an increase rate of uptake. An increased rate of uptake is advantageous in speeding up the therapy, but this may only work in some patients and not others. A modulator is required to overcome those cells that are resistant to ERT such as that in Figure 7 [9].

4 CONCLUSION

Enzyme replacement therapy and physical therapy are both two management options that are integrated into the multidisciplinary approach for treatment of Pompe disease. Both treatments have their advantages and disadvantages.

With regards to ERT, it has been seen that it is possible for individuals not to benefit at all, and the disease to progress. A patient showed cells that had no response to ERT whereas another has shown a mixture where most cells did and one did not. Further research is required to identify the cause of specific cells that do not take up ERT and the reason for this. The question of if ERT could speed up disease progression should also be studied. The main drive towards that question was the patient who did not respond to the ERT and progressively got worst. It is not known if the reason for this was the natural route of the disease or the treatment being administered.

Research has shown other ways to increase and speed up the transfer of ERT using an adjuvant such as chemical chaperones, however this research has only involved animals. Administration of adjuvant is required in humans to see if there is benefit, especially in the cells that have shown resistance to the uptake. If a combination of administration can be found to alter the uptake to an extent where the time of treatment is reduced it will be a more practical approach. Nanotechnology could be promising to achieve such a goal and a more efficient enzyme administration. Furthermore it may be the same chemical adjuvants that are being used to speed up the uptake of ERT as well as increase the intracellular concentration may help suppress the problem of resistant cells.

Physical therapy may be of benefit to sufferers of the disease, but a tight regime is required over the type of activity and to exclude a level where lysosomal leakage is more than the advantage gained. This in itself requires research and a proposed method could be to check levels of lactic acid after an exercise regime to see how much stress is induced on the muscles. In concordance with this the level of lysosomal leakage will also need assessment; a possible means could be by muscle biopsy. After monitoring both these aspects a link could be established between the level of exercise and muscle destruction. Further to this an advantageous regime can be administered.

Muscle biopsy of patients on ERT has shown an increase in enzyme within the lysosomes in some, this has led to the breakdown of glycogen within the lysosome. However there has not been a significant reduction in the extracellular glycogen within the muscle tissue. This is where physical therapy may act as an advantage. The physical activity could increase the requirement of energy and lead to the uptake and breakdown of this extracellular glycogen store.

Two controlled trials are needed one with ERT and physical therapy in combination. Here an assessment of intracellular and extracellular glycogen store is required with an objective assessment of motor improvement. The same trial with just ERT therapy is needed to compare the two and see if physical therapy really does improve motor status when used in conjunction with ERT, or is it just the ERT that improves movement and physical therapy is not required.

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