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Screening for Glycogen Storage Disease Type II in Newborn Babies

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Glycogen storage disease type II, also called pompe disease, is an inherited metabolic disease that was first characterized by Joannes Pompe in 1932 [1]. This metabolic ailment is caused by the lack of an enzyme called α-glucosidase (GAA) or acid maltase. Acid maltase is responsible for breaking down glycogen stores for quick energy. The mutation that causes the lack of acid maltase means that the glycogen accumulates within an intracellular organelle called the lysosome. A lysosome is a membrane bound organelle that contains hydrolytic enzymes in its acidic lumen and functions as the cell's waste disposal system by engulfing unwanted materials by endocytosis. Since in patients with pompe disease acid maltase cannot break down glycogen stores, there is an excessive buildup of glycogen in the cytoplasm and therefore, is engulfed by the lysosome. Tissues that are particularly affected by pompe disease are the muscle and cardiac tissues.

Biochemically, pompe disease is caused by a mutation within the acid maltase gene on the long arm of chromosome 17 - 17q25.2-q25.3 (base pair 75,689,876 to 75,708,272) [2]. The actual acid maltase gene itself is approximately 20 kb in length and contains 20 exons with the first of them being a non-coding exon. The most common mutation that pompe disease arises from is a point mutation from a thymine to a guanine. This pyrimidine to purine transversion is particularly deleterious because it interrupts an RNA splicing site and prevents proper splicing from occurring. This point mutation interrupts the gene coding for acid maltase, which functions as a lysosomal hydrolase – a hydrolytic enzyme that breaks down glycogen within the lumen of lysosomes.

Acid maltase is a very important enzyme due to its crucial enzymatic activity [3]. Glycogen is composed of glucose monomers that are all linked by either an α-1,4-linkage or an α-1,6-linkage. Acid maltase's function is responsible for the degradation of both linkage types of glycogen, maltose, and isomaltose. Acid maltase is also responsible for approximately 1-3% of all cellular glycogen degradation. Mutations within the GAA gene, result in there being accumulation of glycogen in both lysosomal lumen and the cytoplasm. This is particularly damaging to muscle tissue because it can lead to cellular injury by interrupting normal organelle functioning. Skeletal muscle tissue is composed of many bundles of muscle fibers called fascicles. In normal muscle cells, glycogen is normally broken down by acid maltase which prevents the harmful buildup of glycogen in the cells due to a lack of acid maltase. However, in pompe disease, glycogen builds up in the lysosomes and damage the muscle cells. As the condition worsens, the excessive glycogen leaks out of the lysosome damaging the surrounding cells and weakening the the muscle.

Because pompe disease heavily affects the muscular aspect of the body, the main signs and symptoms usually affect the respiratory, musculoskeletal, cardiac, and gastrointestinal (GI) systems [4]. The main respiratory system symptoms are respiratory failure, diaphragm weakness, and sleep-disordered breathing ailments. The main musculoskeletal system symptoms are proximal muscle weakness, muscle pain, and frequent falls. The main cardiac symptoms are irregular heartbeat, elevated creatine kinase (CK) levels, and EKG abnormalities. The main GI system symptoms are difficulty chewing, poor weight gain, and difficulty swallowing or weak tongue muscles.

There are two main types of the clinical presentation [5] of pompe disease that dictate the ploidy of the mutation. If the patient is homozygous for the GAA mutation, then there is no GAA activity

and the mutation is said to be a null mutation because there are no functional copies of the gene. Conversely, if the patient is heterozygous, then there still is some residual GAA activity and the mutation is said to be leaky. The prognosis and acuteness of the symptoms depend heavily on what type of mutation is present within the GAA gene (null or leaky).

Patients who have a null mutation of GAA activity have infantile-onset pompe disease. The infantile-onset pompe disease is a congenital after-birth manifestation that is characterized by progressive muscle weakness and moderate organomegaly of the liver, spleen, and heart. This is the more acute version of the disease and the life expectancy is usually less than 2 years.

Patients with a leaky mutation of GAA activity, have late-onset pompe disease which occurs later in life and is characterized by progressive muscle weakness, hepatomegaly (enlarged liver), no cardiac involvement, and respiratory difficulty. The prognosis for late-onset pompe disease is better than infantile-onset but the life expectancy is also low – usually 20-30 years depending on how aggressive treatment options are.

The mode of inheritance for pompe disease follows the autosomal recessive model of inheritance. It affects 1 in every 140,000 babies per year or 1 in every 60,000 adults per year. It affects all ethnic populations; however, affects Dutch and Chinese populations disproportionally higher than others. Pompe's disease affects 1 in every 40,000 Dutch births and 1 in every 50,000 Chinese births. Having certain ethnic populations more susceptible to pompe's disease implies a founder effect model for the disease. The biochemical interactions that pompe disease causes is evident from the cross-talk that occurs between affected organelles [6]. Initially, there is a deficiency of the GAA gene that codes for a lysosomal hydrolase. This causes there to be excessive levels of glycogen throughout the cell, which specifically accumulates within lysosomes via endocytosis and autophagosomes. This decreases the communication between vitally important waste management organelles such as lysosomes, endosomes, and autophagosomes. The mutation in the GAA gene causes there to be defective acidification within the lumens of the lysosomes, which prevent them from breaking down the glycogen. The glycogen then leaks out of the lysosome due to exceeding the physical limit of the organelle and causes damage to the surrounding tissues and progressive muscular weakness.

There are multiple diagnostic tools that can check if the patient is afflicted with pompe disease depending on the suspicion of the mutation type [7]. If infantile-onset pompe disease is suspected, then a serum creatine kinase test will easily detect elevated CK levels, which are highly indicative of infantile-onset pompe disease. This CK test can also be used to detect late- onset pompe disease but may not be elevated as much and will not give an unequivocal diagnosis. The gold standard diagnostic tool for late-onset pompe disease is to do a GAA assay on skin fibroblasts or a muscle biopsy. There is another GAA assay that is done on leukocytes but is not as popular as on skin fibroblasts because the former gives a false negative approximately 10% of the time. There are other detection methods that are being investigated such as the use of a mass spectrometer [8] (MS) or using fluorometric methods to analyze dried blood spot assays that have specific markers for pompe disease.

The FDA recently approved 2 new enzyme replacement therapies (ERT) for patients with pompe disease [9]. The 2 drugs are called myozyme and lumizyme and are both made by Genzyme. Myozyme is an ERT produced by Duke University researchers and is an IV administered drug. The ERT uses biologically active recombinant human α-glucosidase cells that were produced in Chinese hamster ovary cells. Lumizyme, the analog of myozyme, conatins the same active ingredients but is made with a bigger bioreactor (4000-L vs 160-L). Because the production of these drugs utilizes the latest scientific research and biochemical technologies, the cost for a one-year supply of myozyme or lumizyme is $300,000 and must be taken throughout the patient's life and as a result, insurance refuses to cover these expenses.

The majority of future research deals with better diagnostic tools of pompe disease and how to decrease the uncertainty of diagnosing [10]. The most promising research utilizes ERT as a treatment option but also couples that with using the latest analytical tools for a quicker diagnosis as well. The most compelling research uses a tandem MS-MS experimental design and analyzes GAA activity in dried blood spots (DBS) and contrasts the accurate detection percentage with a competing method – fluorometric assays of DBS with 4-methylumbelliferyl-α-glucoside. The research suggests that the MS-MS method is more of a robust analytical technique and displays a larger analytical range compared to using fluorometry. MS-MS was able to differentiate 96% of the pseudo-deficiency newborns between late-onset and infantile- onset pompe disease compared to only less than 10% by fluorometric assays. As such, there has been increased interest in evaluating various analytical methods as more accurate diagnostic tools for pompe disease with a particular emphasis on tandem MS-MS analyzing GAA activity in DBS.

References

1. Nina Raben, Paul Plotz, Barry J Byrne. Acid a-Glucosidase Deficiency (Glycogenosis Type II, Pompe Disease). Current Molecular Medicine. 2002; 2: 145-166.
2. Chen X, Liu T, Huang M, et al. Clinical and Molecular Characterization of Infantile-Onset Pompe Disease in Mainland Chinese Patients: Identification of Two Common Mutations. Genetic Testing of Molecular Biomarkers. 2017; 6: 391-396.
3. Donald J Voet, Judith G Voet, Charlotte W Pratt. "Additional Pathways in Carbohydrate Metabolism". Principles of Biochemistry, Third edition. 2008; 538.
4. Signs and Symptoms. Pompe Community. Web. DOA: 5/17. https://www.pompe.com/en/patients/signs-symptoms.aspx
5. Van den Hout HMP. The natural course of infantile Pompe's disease: 20 original cases compared with 133 cases from the literature. Pediatr. 2003; 112: 332-340.

6. Jae-Wan Junga, Nguyen-Xuan Huya, Hyo-Boon Kim, et al. Production of recombinant human acid α-glucosidase with high-mannose glycans in gnt1 rice for the treatment of Pompe disease. Journal of Biotechnology. 2017; 10: 42-50.
7. Yijun Li, C Ronald Scott, Nestor A Chamoles, et al. Direct Multiplex Assay of Lysosomal Enzymes in Dried Blood Spots for Newborn Screening. Clinical Chemistry. 2004; 10: 1785-1796.
8. Michael H Gelb, Frantisek Turecek, C Ron Scott, et al. multiplex assay of enzymes in dried blood spots by tandem mass spectrometry for the newborn screening of lysosomal storage disorders. Journal of Inherited Metabolic Disorders. 2006; 3: 397-404.
9. Sechi Annalisa, Salvadego Desey, Alessandro Da Ponte, et al. Investigation on acute effects of enzyme replacement therapy and influence of clinical severity on physiological variables related to exercise tolerance in patients with late onset Pompe disease. Neuromuscular Disorders. 2007; 6: 542-549.
10. Hsuan-Chieh Liao, Min-Ju Chan, Chia-Feng Yang, et al. Gelb. Mass Spectrometry but Not Fluorometry Distinguishes Affected and Pseudodeficiency Patients in Newborn Screening for Pompe Disease. Clinical Chemistry. 2017; 5.