POMPE DISEASE REPORT

Newborn Screening

Overview

Pompe disease is a rare genetic disorder caused by errors in the gene that is responsible for producing the acid alpha-glucosidase enzyme (GAA). The GAA enzyme is important for the breakdown of glycogen, a sugar stored in muscle cells. In people with Pompe, GAA is either missing or non-functional, therefore glycogen is not broken down and begins to accumulate in the muscle cells.

The onset and severity of symptoms are on a spectrum and can vary depending on the amount of functional GAA a person with Pompe has. If a person has no GAA at all, this results in a severe form of the disease that usually present before 6 months of age and may progress rapidly (Infantile Onset Pompe). For those with a small amount of functional GAA, their symptoms will likely present at a later stage in life and may not be as severe (Late-Onset Pompe).

With life changing treatments like Enzyme Replacement Therapy (ERT) currently available for Pompe, newborn screening (NBS) is the most optimal approach for early diagnosis and intervention for Pompe disease. Newborn screening for Pompe involves measuring GAA activity and GAA sequencing using dried blood spots.

Currently, NBS for Pompe is not available in Canada. There are currently numerous pilot NBS in countries around the globe including Taiwan, United States and Australia. These programs have allowed for the appropriate detection and management of babies that receive a positive NBS for Pompe.

Summary

There is an abundance of literature supporting the benefits of newborn screening for Pompe disease as well as testimonials from families that either received a positive screen for Pompe or wished they were given the opportunity to screen for Pompe when they had children. NBS was first implemented in Taiwan in 2005 and as of 2019, it has been implemented in 23 states in the United States and 9 states are actively conducting pilot studies.

The following themes were evident after surveying the literature and family experiences:

1. **Diagnostic Odyssey for Pompe Disease**
2. **Earlier Detection of Late-Onset Pompe Disease (LOPD)**
3. **Higher Prevalence of LOPD than Infantile-Onset Pompe (IOPD)**
4. **Earlier Intervention for Pompe Disease**
5. **Family Planning for Pompe Disease**

Theme 1: Diagnostic Odyssey for Pompe Disease

There is a lengthy diagnostic odyssey for people with Pompe disease particularly caused by poor recognition and underdiagnoses. The diagnostic odyssey stems from a lack of awareness amongst physicians about Pompe disease overall. This is exacerbated by the broad spectrum of non-specific symptoms that can make diagnosis of Pompe difficult.

One parent noticed that their child was displaying unusual symptoms such as failing to reach major motor milestones as a child compared to their siblings, frequent illness and seldom slept for long periods of time. Doctors were quick to dismiss symptoms by saying that ***"All children are different and will do things in their own time".*** A visit to the hospital caused by a respiratory virus prompted further testing, and **three weeks later** the child was diagnosed with IOPD.

The diagnostic delay has been reported to range from **1.4 months to almost 12 years depending on the type of Pompe.** For many people with Pompe, their health and functional status may have already significantly deteriorated at the time of diagnosis. The largest barrier to diagnostic delays is a lack of NBS and limited knowledge of Pompe amongst healthcare professionals. Anecdotally, diagnoses have been reported to frequently come from a major life event such as post child birth, or major surgery.

The differential diagnosis for Pompe disease is wide that confirmation of the diagnosis itself can take several years especially in patients that may present with milder symptoms much later in life. This can be illustrated by one patient's experience with being misdiagnosed: ***"I was diagnosed with Limb Girdle Muscular Dystrophy at age 12. Because I was getting different symptoms I asked my doctor to have me retested. They did muscle testing, bloodwork and it came back as Pompe Disease."*** It is important to consider the cost of unnecessary healthcare visits that these patients may have to endure.

Misdiagnoses of Pompe not only impacts the patient, but further increases costs to the healthcare system due to multiple tests and medications being administered that do not address the underlying cause of symptoms and leaves patients with ongoing uncertainty and a poor quality of life.

Theme 2: Earlier Detection of Late-Onset Pompe Disease (LOPD)

Symptoms of LOPD often present much later in life compared to infantile-onset Pompe disease. Introducing NBS therefore has the potential for identifying children with LOPD while recognizing that the symptoms would not manifest until much later in life. Identifying patients with LOPD through NBS would allow for close monitoring of symptoms in conjunction with appropriate genetic counselling, education and support. The lack of awareness about a rare disease like Pompe among physicians, LOPD diagnosis continues to be a challenge as the rate of poor recognition, under diagnosis and diagnostic delay remain high.

It is important to consider the patient perspective with regards to the advantages of receiving an earlier diagnosis of LOPD through NBS as the diagnostic journey can be significantly shorter. An Australian patient shared their experiences after a 13 year diagnostic journey: ***"There is much that needs to be done to help people with rare diseases, particularly around raising awareness to the public and also medical professionals in order for early diagnosis and also correcting misdiagnosis to occur. Had I been diagnosed even in 1997 when I was 17 and received treatment as soon as it became available perhaps my life would be very different today."****

A study on NBS for Pompe in California showed that out of half a million babies screened within a 1 year period, the birth prevalence was 1 in 25,000. Almost all of the babies that screened positive for Pompe were diagnosed with LOPD and were asymptomatic. This study highlighted that these babies were unlikely to be identified as at risk for Pompe except through NBS. Identifying young candidates for treatment can reduce their chances of living with a long term disability.

NBS for Pompe has had life changing impacts globally as a study in Japan demonstrated the positive outcomes of identifying infants with Pompe and particularly those with LOPD. Identifying the babies with LOPD through screening allowed for them to undergo long term follow-up that enabled ERT to begin before irreversible muscle damage progressed and improved the quality of life for these patients.

*https://www.mdpi.com/2409-515X/6/1/1

Theme 3: Higher Prevalence of Late-Onset Pompe Disease (LOPD)

Newborn screening initiatives across the globe have shown that there is a higher prevalence of LOPD than IOPD. Given that the symptoms of LOPD do not manifest until much later in life, several patients go undetected and are not followed up appropriately until significant damage to the muscles has already been done.

In Illinois, out of 600,000 babies screened within a 5 year period, almost 400 of them screened positive for Pompe disease and **90%** of them were found to have late onset Pompe disease. The patients that were identified through NBS are currently on treatment and have had positive health outcomes as their treatments were initiated prior to the onset of overt symptoms.

A Taiwanese NBS program identified 19 cases of LOPD, 6 of the children had begun ERT between ages 1.5 and 36 months. After follow up at age 81-3, the patients have all met normal motor development milestones. This study emphasized that close monitoring of symptoms, timely treatment initiation, genetic counselling and education support should be key aspects of the long term care of LOPD patients identified through NBS.

Some may question the benefits and consequences of detecting LOPD patients through NBS given the symptoms may present anywhere from infancy to childhood. However, extending the delay in diagnosis can have more deleterious effects with harsher outcomes. Metabolic centers in Pennsylvania closely monitor LOPD patients that were identified via NBS in order to identify early symptoms of the disease that can prompt treatment. The NBS program in Pennsylvania showed that the overall incidence of Pompe was much higher after introducing NBS as more patients with LOPD were being detected.

Theme 4: Earlier Intervention for Pompe Disease

The biggest advantage to introducing NBS for Pompe is arguably the availability of treatment options to improve overall health outcomes in patients. Timely detection of the signs and symptoms of Pompe is imperative as treatment options and timelines will differ for IOPD and LOPD. Patients diagnosed with IOPD benefit the most from receiving an early diagnosis as they are able to begin treatment early on. For instance, a NBS program in Japan identified a patient with IOPD and was able to undergo ERT within the first month of being born before symptoms worsened.

While NBS would allow for patients to receive treatment earlier in life, one family with a history of Pompe diagnoses was the **first to receive in-utero treatment** for Pompe in the world. The patient had normal cardiac function and achieved normal motor milestones postnatally. The key advantage of this treatment as emphasized by one clinician was the timing: ***"We like to treat early, because once you get damage to the muscle of both the heart diaphragm and your skeletal muscle, it's very difficult to reverse that, so you're pretty much just saving what you have."***

Babies that are diagnosed with IOPD through NBS can benefit from the early initiation of therapy. Treatments can begin within the first few weeks of life compared to 4 or 5 months of age when only relying on visible symptoms which result in a diagnosis. One parent shared their frustrations about NBS being unavailable at the time their child who has been diagnosed with Pompe was born: ***"I just wanted to know why when this disease has treatments and gives kids better outcomes, why was it not on our NBS panel. It was really frustrating for me."***

Experiences with NBS in Taiwan has shown that the earlier ERT is initiated, the better the health outcomes. Out of all the patients identified through NBS, **100%** of them were initiated on ERT between 6-34 days and remained ventilator free and were all able to meet age-specific developmental milestones. By comparison, countries that do not have NBS programs report that almost **30-40%** of the children pass away in the first few years of life despite having ERT.

Theme 5: Family Planning for Pompe Disease

Receiving an earlier diagnosis would enable patients and their families to make informed choices around future family planning. A positive NBS result can also help doctors and families assess the reproductive risks before the birth of a second affected child. NBS would offer the families options, access to genetic counselling and knowledge that can equip them to make more informed choices.

Ensuring healthcare providers and GPs are well equipped with information about the genetic patterns and the reproductive consequences of these results can also help parents build a better understanding about their child's screening results. One case report describes an 18-week old infant with IOPD who died before receiving ERT. In this case, the patient's parents had a child previously with Pompe disease, and genetic counselling should have been offered to the parents during the planning of their second pregnancy.

A positive NBS result for Pompe also provides the opportunity for family members to assess their carrier status for the disease. This has implications on their decisions to have more children depending on the result. A study assessing the impacts of NBS on families reported that several families learnt that they were Pompe carriers after receiving a positive NBS result for their children through NBS. This discovery resulted in "cascade testing" within some families who had children with LOPD since Pompe is genetically inherited. Parents felt that knowledge of the diagnosis and would be beneficial should their children choose to have a family of their own.

Recommendations and Considerations

- NBS allows for earlier interventions that are life changing for children diagnosed with Pompe. Treating earlier rather than later has better health outcomes in patients.

- Families who receive positive NBS results should be provided with appropriate education and resources like genetic counselling to help them make informed decisions around treatment and family planning.

- Monitoring and guidance of patients with LOPD that are identified through NBS must improve to minimize exacerbation of life threatening symptoms.

- Healthcare professionals should be equipped with knowledge on rare diseases like Pompe and the appropriate management of patients who receive a positive NBS result.