What is Infantile Onset Pompe Disease Versus Late Onset Pompe Disease?

Baebies Interviews World-Renowned Expert Dr. Priya Kishnani

In our discussions with state public health laboratories, Baebies has observed confusion and ambiguity on the difference between Infantile Onset Pompe disease and Late Onset Pompe disease. We interviewed world-renowned expert on Pompe disease, Dr. Priya Kishnani, to disseminate insights into the clinical manifestations of Infantile Onset Pompe disease and Late Onset Pompe disease and to elucidate the significance of newborn screening for Pompe disease to public health laboratories who may be interested in adding Pompe disease to their screening panels. Dr. Kishnani is Division Chief of Medical Genetics and Director of the Y.T. and Alice Chen Pediatric Genetics and Genomics Research Center at Duke University Medical Center (DUMC). She also serves as Director of the Lysosomal Storage Disease Program, Biochemical Genetics Training Program and Metabolic Clinic at DUMC.

For over 25 years, Dr. Kishnani has been involved in the care of patients with Pompe disease, from severely affected newborns to mildly affected adults. During this time, she has witnessed the evolution of Pompe disease from the early days before treatment to the new emerging natural history as a result of enzyme replacement therapy (ERT) and newborn screening (NBS). Dr. Kishnani continues to cherish the opportunity she has, to constantly learn from and improve treatment for patients diagnosed with Pompe disease.

Q: Please describe how the natural history of Pompe disease has changed over the years, including the introduction of newborn screening for Pompe.

A: The Pompe disease landscape has drastically evolved over the last 25 years. I have witnessed the natural history progress from the early days before the advent of ERT where Infantile Onset Pompe disease (IOPD) typically resulted in death before a baby's first birthday to a new natural history that is emerging since the introduction of treatment and NBS. Pompe disease is caused by the absence or deficiency of the enzyme acid α-glucosidase (GAA). GAA is responsible for the breakdown of glycogen (sugar that is stored for energy) and its deficiency leads to glycogen accumulation in heart and skeletal muscles.

Babies with classic IOPD develop a hypertrophic cardiomyopathy (enlarged heart), which in the later stages progresses to a dilated cardiomyopathy (decreased ability for the heart to pump blood). These infants also have muscle weakness, significant hypotonia (low muscle tone resulting in a "floppy" appearance) and macroglossia (enlarged tongue). The disease progresses rapidly and by 6-7 months of age babies may be dependent on a ventilator in order to breathe. Without treatment, these babies die of cardiorespiratory failure, which was the unavoidable outcome until 2006.

ERT provided the first treatment for Pompe disease and resulted in significantly longer lifespans and increased quality of life. The FDA approved Myozyme (now marketed as Lumizyme) in 2006 based on positive clinical trial results with

recombinant human GAA (rhGAA). Overall, we learned that there are many factors that affect the treatment outcome with respect to ERT, including the stage of disease and age at initiation of treatment, with improved responses in patients who initiated therapy at a younger age. Through these clinical trials, we also started to understand the true spectrum of IOPD, where some babies have cardiac involvement in the first year of life but the disease progression is less rapid. We also found that some babies had no cardiac involvement; these babies are considered to have non-classical infantile Pompe disease.

The next phase of understanding was investigating the new natural history of babies and children treated with ERT. Enzyme replacement therapy is not a cure. Children with IOPD treated with ERT were found to have residual symptoms including muscle weakness in the form of foot drop (difficulty lifting the front part of the foot) and ptosis (eyelid drooping), hypernasal speech, scoliosis, hearing loss, risk of arrhythmias (abnormal heart rhythms), dysphagia (difficulty swallowing) with risk for aspiration, osteopenia (low bone density) and pulmonary insufficiency. Importantly, ***we started to recognize that earlier treatment means better outcomes for these children*** and that we needed to begin treatment earlier to prevent or reduce symptoms of the disease. Therefore, newborn screening, which allows the identification of babies with all forms of Pompe disease at birth, is vital to allow the earliest possible identification and initiation of treatment.

Lastly, the third phase in understanding the natural history of Pompe disease came from the advent of NBS and lessons learned from classic IOPD. Newborn screening for Pompe disease was first initiated in Taiwan, then implemented in the United States (Missouri, Illinois, Kentucky and New York). ***These newborn screening programs taught us that every day matters! Each day of delay is a day too late for these babies.*** The first glimpse into the necessity for timely interventions came from Taiwan. In their studies, they provided clinical data on babies who were initiated on treatment at 11 days of age versus those on treatment starting at 21 days of age. Biomarkers such as CPK (a muscle enzyme that increases with muscle damage) were more elevated in those that initiated treatment later, and they found that those on treatment at 11 days were walking earlier than those that started at 21 days of age. We now understand that early initiation of treatment leads to a much better clinical outcome.

Q: Can you describe the differences between Classic Infantile Onset Pompe and Late Onset Pompe disease, and elaborate on the clinical manifestations of these ends of the spectrum?

A: The nomenclature for Pompe disease is misleading and often can be confusing. Classic infantile onset Pompe disease, if untreated, results in death within the first two of years of life. The classic form of the disease is characterized by cardiac involvement. Late Onset Pompe disease (LOPD) actually encompasses any patient with Pompe disease, including young children, who do not have all the classic symptoms of IOPD. The term “late onset” may be construed as not having symptoms of Pompe disease until much later in life, which is not always the case. We have seen in our clinic children with Late Onset Pompe who present with the disease in the first year of life. So in reality, ***“Late Onset” is a misnomer because this disease type can present at any time***, just without the typical cardiac involvement seen in the classic infantile form. Patients with LOPD can, however, have some cardiac involvement, especially arrhythmias (disturbances of heart rhythm).

The most common genetic change (pathogenic variant or mutation) in Caucasians with LOPD is the ‘leaky’ c.32-13T>G (or IVS1) splice site mutation. We usually see this variant more in adults

because about 10-20% of the normal amounts of GAA enzyme is produced, which delays onset of symptoms and protects against severe cardiac involvement.

However, at our Genetics and Metabolism clinic at Duke, we are now seeing some children who are diagnosed with LOPD in the first year of life (and not from identification through newborn screening). Some of these children might present with failure to thrive, developmental delays or feeding difficulties, which are not symptoms specific to Pompe disease and therefore makes diagnosis more difficult. Some of these children have the common IVS1 splice site mutation. We've been able to identify these children early enough and start them on ERT between the ages of 18 months to 2 years of age. Even with an increased dosage of ERT, these children are still exhibiting symptoms such as a waddling gait, ptosis, scoliosis etc. ***These patients with early childhood onset of symptoms illustrate that LOPD can and does present within the first year of life.***

The identification of the common IVS1 splice site mutation in a majority of patients diagnosed with Pompe disease via NBS has been an eye opener for me. In these patients with late-onset disease, we have seen a pattern of muscle weakness including hip extensor and abductor weakness, and abdominal oblique muscle weakness, present within the first 6-9 months of life. The question becomes when to start treatment for the LOPD patients, and this is a matter of discussion between families and their physicians. Some families may choose not to start ERT right away to see if some clinical symptoms can be addressed with physical therapy and other interventions before starting their child on life-long ERT.

Q: Pompe Disease was added to the Recommended Uniform Screening Panel (RUSP) in 2015 for newborn screening in the United States. What is the significance of newborn screening for both Infantile Onset and Late Onset Pompe?

A: Studies have been initiated to better understand the burden of knowing or not knowing that a baby has LOPD. Some families would like to know so that they are prepared and know what to expect; others may not want to know because of the misconception that late-onset is not present until adulthood. It all comes down to how the information from newborn screening is presented to families.

Really, it comes down to the cost of not screening. Most adults that were identified clinically as Late Onset Pompe can retrospectively look back and see that they did have symptoms in childhood (trouble walking/in sports/shortness of breath/etc.). However, at that point in their lives, as children, they simply didn't have good explanations for their symptoms. These patients feel that if they had been identified sooner, their outcomes might have been different. Misdiagnosis often occurs throughout childhood. Some children who present with poor feeding, failure to thrive or muscle weakness, may be treated for other suspected conditions by the physician. For example, some patients are misdiagnosed with polymyositis and are treated with steroids. However, when they fail to respond to therapy, further work up is pursued and they are eventually diagnosed with Pompe disease. The diagnostic journey is very long, sometimes as long as 12 years for patients not diagnosed through newborn screening. I recently had an adult patient who developed acute respiratory failure; he was critically ill and on a ventilator. He was diagnosed with Pompe disease by one of our neurologists at Duke through enzyme analysis and then mutation analysis.

Q: What does a public health laboratory need to know about Pompe disease in order to make an informed decision regarding screening?

A: Public health laboratories (PHLs) need to

recognize that Pompe is a continual spectrum of disease. There is more to this disease than just classic infantile and late-onset in adults. There are a large number of LOPD patients that present in the first year of life. Our whole understanding as we know it today is that any delay in diagnosis and treatment results in inadequate or less than optimal clinical outcomes. Clinical outcomes are measured through testing the muscle strength in a 6-minute walk test and lung function tests. In patients with LOPD, we do see muscle damage on a whole body MRI. Clinically, these patients can compensate a lot before they lose their motor abilities or have to go on a ventilator. Just because these patients are ambulatory does not mean that there is not muscle wasting going on. Pompe disease affects many muscles in the body and results in feeding difficulties, respiratory problems, musculoskeletal manifestations, urinary problems, reflux and digestive problems. ***If treatment is delayed or the baby is not identified soon enough, there can be irreparable muscle damage. This is why rapid newborn screening is so important.***

Q: What can PHLs do that would address long-term follow-up of LOPD patients?

A: As we have seen, children with LOPD can present within the first year of life. And as we gain better understanding of the disease, I am sure there will be guidelines that will be developed for systematic follow up of LOPD patients. I encourage PHLs to work together collaboratively to gather necessary information in a systematic way to address long-term follow-up. For the states that are already screening for Pompe, their follow-up programs should share their experiences with states that are considering adding Pompe to their screening programs. PHLs should also discuss long-term follow-up with treating physicians to determine the most effective strategy for following patients identified with LOPD . Physicians will play a vital role in deciding with a family when to start ERT.

Q: What do you see as the greatest challenges and rewards of adding NBS for Pompe disease to state screening panels?

A: The greatest challenge in implementing newborn screening is the steep learning curve and understanding the disease spectrum. We are learning lessons from the Taiwan newborn screening program, but Taiwan is an isolated island with different demographics than the melting pot of the United States. For instance, there have been no reported patients with IVS splice site mutation in Taiwan and babies are all cross reactive immunological material (CRIM) positive. Please remember that CRIM negative status (absence of any protein on a western blot) carries a dire prognosis.

The greatest reward is seeing all of the advancements in what we know about Pompe disease, including the identification, diagnosis and treatment of the disease. All of these come together to enable better outcomes for patients with Pompe, because we know that every day matters!

I am constantly learning from Pompe patients I see. The collective experience of all of us (physicians and newborn screening and follow up personnel) is critical as we move forward with newborn screening. All of us who are physicians are compassionate people, who are willing to learn. We need more insights and research into this to provide the correct information to families. We need to look at musculoskeletal damage and not just cardiac involvement. I predict that in the next 2-3 years, as Pompe screening will become commonplace, we will learn much more about the disease and the need for timely screening.

Dr. Priya Kishnani is compensated as a member of the Baebies Scientific Advisory Board.