Pompe disease NBS: Is early diagnosis a false promise?

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Newborn screening (NBS) programs for lysosomal storage disorders aim to identify affected infants early, allowing for prompt initiation of enzyme replacement therapy (ERT) before irreversible damage occurs. Pompe disease, a severe condition caused by acid alpha-glucosidase (GAA) deficiency, is a prime candidate for such screening. But the presence of pseudodeficiency alleles, which result in reduced GAA enzyme activity without clinical disease, creates a diagnostic challenge for clinicians. This complicates the interpretation of initial screening results and the decision to initiate potentially life-saving treatment.1

KEY TAKEAWAYS

- The Pivot: Newborn screening for Pompe disease identifies infants with GAA deficiency, but the prevalence of pseudodeficiency alleles necessitates careful genetic confirmation.
- The Data: One Japanese infant identified by NBS with IOPD began ERT at 28 days, showing no cardiac hypertrophy at 1 year, unlike a pre-NBS case who started ERT at 100 days and developed cardiomyopathy.
- The Action: Clinicians must pursue rapid genetic confirmation for infants with positive NBS for Pompe disease to differentiate true infantile-onset Pompe disease from pseudodeficiency and initiate ERT promptly.

Infantile-onset Pompe disease (IOPD) represents the most severe manifestation of a lysosomal storage disorder, stemming from a deficiency in acid alpha-glucosidase (GAA). This enzyme is critical for breaking down glycogen, and its absence leads to glycogen accumulation in various tissues, particularly cardiac and skeletal muscle. The rapid progression of IOPD, often leading to death within the first year of life without intervention, underscores the urgency of early diagnosis and treatment.1

Japan initiated a regional enzymatic newborn screening program for Pompe disease in 2013, aiming to identify affected infants before symptom onset and facilitate early enzyme replacement therapy (ERT). Tocan and colleagues reported on the ERT responses of two Japanese IOPD cases: one identified through this NBS program and another diagnosed prior to its implementation. The study, published in Pediatric International, highlights the challenges of timely ERT initiation, particularly concerning the pseudodeficiency problem.1

The Screening Dilemma

Newborn screening for Pompe disease typically relies on measuring GAA enzyme activity in dried blood spots. Low enzyme activity triggers further investigation. But GAA pseudodeficiency alleles, common in some populations, can also result in reduced enzyme activity, leading to false-positive screening results. These individuals do not develop Pompe

disease, but their initial screening results are indistinguishable from those with true GAA deficiency. This creates a significant diagnostic dilemma, as unnecessary follow-up and anxiety for families can result, while delaying ERT for truly affected infants carries severe consequences.1

The Japanese NBS program identified its first IOPD case in 2014. This infant, designated Case 1, showed low GAA activity on initial screening. Subsequent genetic testing confirmed two pathogenic GAA mutations: c.1935C>T (p.Tyr645Ter) and c.2560C>T (p.Arg854Ter). ERT with alglucosidase alfa began at 28 days of age. At 1 year old, the infant showed no cardiac hypertrophy, maintained normal left ventricular ejection fraction (LVEF), and exhibited normal motor development. This outcome contrasts sharply with historical data for untreated IOPD.1

But the path to diagnosis is not always straightforward, even with screening. The authors noted that the time from NBS to confirmed diagnosis and ERT initiation can be prolonged due to the need for confirmatory genetic testing. This delay is precisely where the pseudodeficiency problem introduces friction. Clinicians must balance the urgency of treatment for true IOPD with the need to avoid unnecessary therapy for pseudodeficiency carriers. The complex genetics of newborn screening, particularly for conditions with pseudodeficiency alleles, demands clear communication with parents and rapid access to genetic counseling.1

Comparing Treatment Timelines

The paper presented a compelling comparison between the NBS-identified case and an earlier case (Case 2) diagnosed before the screening program. Case 2, born in 2012, presented with symptoms including poor feeding and muscle weakness at 2 months of age. Diagnosis was confirmed by GAA enzyme activity and genetic testing, revealing the same pathogenic mutations as Case 1. But ERT for Case 2 did not start until 100 days of age.1

The difference in outcomes was stark. Case 2 developed severe cardiac hypertrophy and dilated cardiomyopathy, with an LVEF of 30% at 3 months. Despite ERT, the infant required mechanical ventilation and died at 1 year and 1 month due to cardiorespiratory failure. Case 1, who received ERT 72 days earlier, avoided these severe cardiac complications and achieved normal development at 1 year. This comparison underscores the critical importance of early intervention in IOPD, highlighting that even a delay of a few weeks can have profound clinical consequences.1

"The earliest enzyme replacement for infantile-onset Pompe disease in Japan."Tocan V, Mushimoto Y, Kojima-Ishii K. Pediatr Int 2022.The challenge of pseudodeficiency is not unique to Pompe disease. Other lysosomal storage disorders, such as Fabry disease and Gaucher disease, also have pseudodeficiency alleles that can confound NBS results. This necessitates a robust confirmatory diagnostic pathway, including rapid genetic sequencing, to distinguish true disease from benign carrier states. Without this, the benefits of early screening are diluted by diagnostic uncertainty and potential treatment delays. For a comprehensive understanding of paediatric conditions, the Oxford Handbook of Paediatrics can be a valuable resource.

The Need for Speed

The Japanese experience demonstrates that while NBS successfully identifies infants with IOPD, the time from screening to ERT initiation remains a critical factor. The authors noted that the process of obtaining informed consent for genetic testing, performing the analysis, and securing approval for ERT can introduce delays. These administrative and logistical hurdles must be streamlined to maximize the benefit of NBS. The goal of NBS is not merely identification, but rapid, effective intervention.1

The pseudodeficiency problem adds another layer of complexity. If a positive screen is due to a pseudodeficiency allele, the infant does not need ERT. But if it is true IOPD, every day of delay contributes to irreversible organ damage. This tension demands a system that can quickly and accurately differentiate between these two scenarios. The implications for primary care burnout are also clear; managing these complex genetic results and communicating them effectively to anxious parents adds significant workload.1

The trial was a case report, not a randomized controlled trial, which is the obvious caveat. The small sample size (N=2) limits generalizability, but the stark difference in outcomes between the two cases provides a powerful illustration of the impact of early ERT. The study was also conducted in a specific regional context in Japan, and the prevalence of GAA pseudodeficiency alleles can vary significantly across different ethnic populations. This means that the specific challenges and solutions may differ in other NBS programs globally.1

Still, the paper highlights a fundamental issue in expanding NBS programs for rare genetic diseases: the need for robust, rapid, and accurate confirmatory diagnostics. Without this, the promise of early intervention risks being undermined by diagnostic ambiguity. The next step for NBS programs must involve not just identifying more conditions, but refining the pathways to definitive diagnosis and timely treatment. This includes improving access to genetic counseling and ensuring that genetic testing results are available within days, not weeks. The question remains whether health systems can deliver on this promise, as seen in discussions around Australia's lung cancer screening.1

CLINICAL IMPLICATIONS

The Japanese experience with newborn screening for Pompe disease provides a stark reminder that early identification is only half the battle. The pseudodeficiency problem, where reduced enzyme activity does not equate to clinical disease, forces clinicians into a difficult position. They must navigate the urgency of initiating ERT for true infantile-onset Pompe disease against the risk of overtreating an infant with a benign genetic variant.

This means that a positive newborn screen for Pompe disease should immediately trigger rapid genetic confirmation. Waiting weeks for genetic results, as highlighted by the difference in outcomes between the two cases, is simply not acceptable for a rapidly progressive condition like IOPD. The logistical and administrative hurdles in securing genetic testing and ERT approval must be streamlined to ensure that the window for effective intervention is not missed.

For general practitioners and specialists, this underscores the importance of understanding the nuances of newborn screening results, particularly for conditions with known pseudodeficiency alleles. Communicating these complexities to parents requires a clear, empathetic approach, managing anxiety while emphasizing the need for swift follow-up. The burden of this diagnostic uncertainty often falls on the primary care team, who must coordinate rapid specialist referrals and genetic counseling.

The success of expanded newborn screening programs hinges on the ability of healthcare systems to provide not just screening, but also rapid, definitive diagnosis and immediate access to treatment. Without this integrated approach, the promise of early intervention for rare diseases like Pompe disease will remain partially unfulfilled, leaving clinicians to grapple with the consequences of delayed care.

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