Newborn screening for lysosomal storage disorders: what earlier detection changes

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> Lysosomal storage disorders (LSDs) represent a formidable challenge in pediatric medicine, often presenting with insidious, progressive symptoms that lead to irreversible damage before diagnosis. For conditions like Hunter syndrome (mucopolysaccharidosis type II, MPS II) and metachromatic leukodystrophy (MLD), the window for effective intervention is narrow, making early detection paramount. The question for clinicians has long been whether newborn screening can genuinely alter the natural history of these devastating diseases.

KEY TAKEAWAYS

- The Pivot: Newborn screening for lysosomal storage disorders, particularly Hunter syndrome and metachromatic leukodystrophy, enables earlier therapeutic intervention that can mitigate disease progression.
- The Data: Enzyme replacement therapy for Hunter syndrome helps children live longer and healthier lives, while early diagnosis in MLD is critical for accessing emerging gene therapies.
- The Action: Clinicians should advocate for expanded newborn screening panels and understand the implications of early diagnosis for timely access to disease-modifying treatments.

Lysosomal storage disorders are a group of more than 50 rare inherited metabolic diseases, each caused by a deficiency in specific lysosomal enzymes. These enzymes are vital for breaking down waste products within cells. When an enzyme is deficient, these waste products accumulate, leading to progressive cellular damage and a wide range of clinical manifestations affecting multiple organ systems. The insidious onset and variable presentation often delay diagnosis, pushing patients past the point where many therapies can offer maximal benefit.1,2

Hunter syndrome, or mucopolysaccharidosis type II (MPS II), is one such X-linked recessive lysosomal storage disease. It affects the breakdown of glycosaminoglycans (GAGs), complex sugar molecules that are essential components of connective tissues. The deficiency of the iduronate-2-sulfatase (IDS) enzyme leads to the accumulation of dermatan sulfate and heparan sulfate in nearly every cell, tissue, and organ. This accumulation drives a progressive, multisystemic disease that can include skeletal deformities, coarse facial features, hepatosplenomegaly, respiratory issues, cardiac valve disease, and, in severe forms, neurocognitive decline.1

Metachromatic leukodystrophy (MLD) is another severe lysosomal storage disorder, an autosomal recessive condition caused by a deficiency of the arylsulfatase A (ARSA) enzyme. This deficiency results in the accumulation of sulfatides, particularly in the myelin-producing cells of the central and peripheral nervous systems. The progressive demyelination leads to severe neurological impairment, including motor regression, cognitive decline, seizures, and eventually a

vegetative state. MLD typically presents in infantile, juvenile, or adult forms, with the infantile form being the most common and rapidly progressive.2

The Promise of Early Detection

For Hunter syndrome, research has made it possible to reveal the cause of the disease, thus helping diagnose and treating this rare disorder. Enzyme replacement therapy (ERT) with idursulfase (Elaprase) has been available for some time. This therapy aims to replace the deficient IDS enzyme, reducing GAG accumulation and mitigating disease progression. The efficacy of ERT, however, is highly dependent on the timing of initiation. Early intervention, before significant irreversible organ damage or neurocognitive decline occurs, is essential for optimising outcomes.1

A review published in Advances in Neonatal Care in 2018 highlighted the growing consensus that Hunter syndrome should be part of newborn screening panels. Joseph and colleagues argued that the availability of ERT, which can help children live longer and healthier lives, makes early diagnosis through screening a compelling prospect. The review emphasized that identifying affected infants at birth, rather than waiting for the emergence of overt symptoms, could significantly improve the long-term prognosis by allowing for prompt initiation of ERT.1

The challenge with Hunter syndrome, and many other LSDs, is that clinical symptoms are often subtle in infancy and become more pronounced and irreversible over time. By the time a definitive clinical diagnosis is made, often after a protracted diagnostic odyssey, significant damage may have already occurred, limiting the full potential of available therapies. Newborn screening offers a pathway to bypass this diagnostic delay, identifying affected individuals pre-symptomatically.1

Metachromatic Leukodystrophy: A Race Against Time

The situation for metachromatic leukodystrophy mirrors that of Hunter syndrome, but with an even more urgent imperative for early diagnosis due to the rapid and devastating neurological progression. A caregiver survey conducted in the UK and Republic of Ireland, published in Orphanet Journal of Rare Diseases in 2022, highlighted the profound impact of diagnostic delays on families and the potential benefits of newborn screening. Morton and colleagues found that caregivers of individuals with MLD experienced significant delays in diagnosis, often after the onset of irreversible neurological symptoms.2

The survey, which included responses from caregivers of patients with MLD, highlighted the emotional and practical toll of delayed diagnosis. Caregivers reported a median diagnostic delay of 12 months from symptom onset for the late infantile form and 24 months for the juvenile form. This delay meant that by the time a diagnosis was confirmed, many children had already lost significant motor and cognitive function. The survey's qualitative data revealed a strong consensus among caregivers that newborn screening would have been invaluable, providing an earlier opportunity for intervention and potentially preserving neurological function.2

The importance of early diagnosis in MLD has intensified with the advent of gene therapies. Atidarsagene autotemcel (Libmeldy), an autologous CD34+ cell gene therapy, received conditional marketing authorisation in Europe for early-onset MLD. This therapy involves collecting a patient's hematopoietic stem cells, genetically modifying them to express the functional ARSA enzyme, and then reinfusing them. The efficacy of gene therapy is critically dependent on pre-symptomatic or very early symptomatic treatment, before extensive demyelination has occurred. Once neurological

damage is established, gene therapy can halt progression but cannot reverse existing deficits. This makes the timing of diagnosis a matter of preserving function versus merely preventing further decline.2

Implementing Screening: Practical Considerations

Implementing newborn screening for LSDs involves several practical considerations. The screening method typically relies on dried blood spot analysis using tandem mass spectrometry, which can detect enzyme deficiencies or elevated substrate levels. This technology allows for multiplex screening, testing for multiple disorders from a single blood sample. The cost-effectiveness of adding new disorders to existing screening panels is a perennial debate, but the long-term costs of managing advanced LSDs, coupled with the potential for improved quality of life with early treatment, often tip the scales in favor of screening.1

But, the ethical implications of screening for conditions where treatment options are still evolving or carry significant risks also warrant careful consideration. For MLD, the availability of gene therapy makes the case for screening particularly strong, as it offers a disease-modifying intervention. For other LSDs, where therapies may be less effective or still investigational, the decision to screen becomes more complex, requiring robust counselling for parents. This is a challenge that extends beyond LSDs, as our newborn screening coverage has previously explored.

The infrastructure for confirmatory testing and subsequent specialist care must also be robust. A positive screen result requires prompt follow-up with diagnostic tests, such as enzyme assays and genetic sequencing, to confirm the diagnosis. Once confirmed, families need immediate access to specialists in metabolic disorders, genetic counsellors, and, most importantly, the specific therapies. Delays at any stage post-screening can negate the benefits of early detection. The implementation of screening programs, even for common conditions, often reveals systemic gaps.

The open-label design of many early ERT studies for Hunter syndrome is an obvious caveat, as is the relatively small patient numbers in rare disease trials. But, the consistent clinical improvements observed, particularly in non-neurological manifestations, provide compelling evidence for the benefit of early intervention. For MLD, the efficacy of gene therapy in pre-symptomatic patients is a game-changer, but the long-term durability and potential late-onset complications are still being monitored. Clinicians should consult resources like the Oxford Handbook of Paediatrics for up-to-date guidance on managing these complex conditions.

The push for expanded newborn screening panels is not without its critics. Concerns often revolve around the potential for false positives, the anxiety generated for families, and the ethical dilemmas of identifying conditions for which no effective treatment yet exists. But for conditions like Hunter syndrome and MLD, where effective, disease-modifying therapies are available, the argument for screening becomes much stronger. The ability to intervene before irreversible damage occurs fundamentally shifts the prognosis for these children.

The experience of caregivers in the MLD survey highlighted the profound impact of diagnostic delays. Many caregivers reported feeling isolated and frustrated by the lack of awareness among healthcare professionals regarding MLD symptoms. This highlights the need for not only screening but also ongoing education for clinicians to recognise early signs of LSDs, even in the absence of a universal screening program. The diagnostic journey for rare diseases is often protracted, with patients seeing multiple specialists before a correct diagnosis is reached. Newborn screening aims to short-circuit this process, providing a definitive answer much earlier.2

The economic argument for newborn screening is also compelling. While the upfront cost of adding new tests to a screening panel can be substantial, the long-term costs associated with managing advanced disease, including

hospitalisations, specialist care, and supportive therapies, often far outweigh the screening costs. The societal benefits of enabling affected individuals to live healthier, more productive lives are immeasurable. The investment in early detection can lead to significant savings in healthcare expenditure and improved societal well-being.1

Still, the challenge remains in standardising screening panels across different regions and countries. While some European countries have extensive newborn screening programs, others have more limited panels. Harmonisation of screening practices would ensure equitable access to early diagnosis and treatment for all infants at risk of LSDs. The political will and financial commitment are necessary to expand these programs and ensure that every child has the opportunity for the earliest possible intervention.

The next step for these disorders involves not just expanding screening, but also refining the diagnostic algorithms to minimise false positives and ensure rapid, accurate confirmatory testing. Ongoing research into novel therapies, particularly those that can address the neurological manifestations of LSDs more effectively, will continue to strengthen the case for early detection. The ultimate goal is to move from managing symptoms to preventing disease progression altogether.

CLINICAL IMPLICATIONS

The data on Hunter syndrome and metachromatic leukodystrophy makes a clear case: earlier detection through newborn screening is not merely an academic exercise; it is a clinical imperative. For Hunter syndrome, enzyme replacement therapy offers a tangible benefit, but its efficacy diminishes significantly if initiated after substantial organ damage. Screening provides the critical window to maximise this therapy's impact.

For MLD, the stakes are even higher. The emergence of gene therapies like atidarsagene autotemcel means that pre-symptomatic diagnosis is the only real path to preserving neurological function. Waiting for overt symptoms to appear, as the caregiver survey starkly illustrates, means accepting irreversible decline. Clinicians must recognise that for these conditions, time is brain, and time is organ function.

The challenge now lies in expanding and standardising newborn screening panels across Europe. It is not enough to have effective therapies if patients cannot access them early enough. This requires not only technological implementation but also a concerted effort to educate general practitioners and specialists on the early, often subtle, signs of these rare diseases, ensuring that a positive screen leads to rapid, definitive diagnosis and treatment.

The economic and societal benefits of preventing severe, progressive disability far outweigh the costs of screening. This is a clear instance where proactive public health measures directly translate into improved patient outcomes and reduced long-term healthcare burdens. The question is no longer if we should screen, but how quickly we can implement it universally.

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REFERENCES

1. 1. Joseph R, DiCesare EB, Miller A. Hunter Syndrome: Is It Time to Make It Part of Newborn Screening? Adv Neonatal Care. 2018;18(6):467-474. doi:10.1097/ANC.0000000000000552

2. 2. Morton G, Thomas S, Roberts P. The importance of early diagnosis and views on newborn screening in metachromatic leukodystrophy: results of a Caregiver Survey in the UK and Republic of Ireland. Orphanet J Rare Dis. 2022;17(1):398. doi:10.1186/s13023-022-02549-y