Challenges of lysosomal storage disorders need not dishearten the nonspecialist

An interview with Raymond Y. Wang, MD

By Theodore Bosworth

On paper, the diagnosis of a lysosomal storage disease (LSD) appears daunting: Almost 50 of these rare diseases have been identified, onset can occur at any age, and symptoms can vary markedly, even among patients with the same LSD diagnosis. The catch, however, is to first consider the *possibility* of an LSD; ultimately, the diagnosis is relatively easy to confirm.

"LSDs are part of the larger world of rare genetically linked neurologic disorders, and most of them can now be identified with genetic testing. Clinicians need to keep these disorders in mind, ordering the diagnostic tests or referring the patient to a geneticist when there is any suspicion," said Raymond Y. Wang, MD, director of the multidisciplinary lysosomal storage disorder program at Children's Hospital of Orange County, Orange, Calif.

Different cell types, different organ systems affected

Pathobiologically related, LSDs are inherited in an autosomal-recessive manner. The underlying genetic defect results in impairment of enzymatic function in cell lysosomes, where unneeded substrates are broken down and expelled in a normal process of housekeeping in the cell. Absent this process, accumulation or storage of macromolecules within the lysosome ultimately impairs cell activity. It is specific enzyme deficiencies that differentiate LSD pathologies, which vary in the substances accumulated and the cells in which accumulation takes place.

Any single LSD is, by itself, rare; most LSDs occur in fewer than 1 of every 100,000 live births. Collectively, the rate rises to approximately 1 case in every 7,000 to 8,000 births, according to data in a review and guidelines article published 10 years ago, for which Dr. Wang was lead author.[1] In that article, written for the American College of Medical Genetics, the authors explain that prevalence climbs even higher for some specific LSDs in specific populations, such as Tay-Sachs disease among Ashkenazi Jews.

The many types of LSDs affect different cells in different organ systems, which explains the variability in symptoms across these diseases; furthermore, signs and symptoms of the same LSD can vary from one patient to the next. One reason for this interpatient variability is that the degree of impairment in enzymatic function can differ. Modest relative impairment in enzyme function, for example, might delay age of onset or lead to slower progression. Heterogeneity of clinical expression is also a consequence of individual differences in disease modifiers or the downstream impact of macromolecule accumulation.

Raymond Y. Wang, MD

"Our patients have not necessarily read the textbooks, so the textbook descriptions are not always reliable," Dr. Wang said. "It is not uncommon to see children who do not follow the usual age of onset, severity, or speed of progression. If only these standard criteria are used, an LSD diagnosis may be missed in the children who present differently."

Some LSDs are apparent at birth; in others, symptoms might not emerge or bring the patient in for a diagnosis until adulthood. It is likely that many patients with a mild expression of an LSD are never given an accurate diagnosis. Some presenting symptoms, such as a seizure disorder, are difficult to ignore, while the onset of others, such as muscle weakness, can be subtle.

"It is particularly important to be concerned in a child that has had normal development but then begins to lose skills or milestones," Dr. Wang said. Although many of the more severe LSDs manifest early in childhood, there is, he emphasized, no peak age that would lead one to think of an underlying diagnosis of LSD.

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Diagnostic precision, not a 'diagnostic odyssey'

Based on his experience, Dr. Wang explained, a parent's perception of a change or reversal in their child's development must be taken seriously to avoid what he calls "the diagnostic odyssey" that sends many families to multiple physicians and specialists. If a patient has an LSD, a definitive diagnosis will be the key, in many cases, to preventing or attenuating irreversible disease progression.

"Parents are the first to know when something is not right," Dr. Wang said. In cases of unexplained functional loss, he strongly advises against a wait-and-see approach. LSDs are rare, but if there is suspicion when other explanations do not fit, genetic testing is specific and can now be performed at reasonable cost. Genetic testing confirms or rules out not only LSDs, Dr. Wang noted, but a much longer list of other rare inherited diseases.

"With next-generation sequencing, we can screen for a broad array of inherited diseases," Dr. Wang said. "Even if testing reveals a disease for which there are no current therapies, it can end the search for families anxious for answers."

Whole-genome sequencing is possible, Dr. Wang explained, but gene panels that are guided by signs and symptoms narrow the focus. These include panels of 200 genes or more to test for causes of such symptoms as epilepsy and altered neuromuscular function. Compared with qualitative or cumbersome testing that was once required – such as thin layer chromatography or sequencing one gene at a time – current genetic testing for rare inherited neurological disorders provides an answer quickly, reducing delay in beginning treatment when treatment exists.

"We do not have effective therapies for many of these diseases, but we do for some," Dr. Wang said. This is an important message: He believes that the mistaken impression that few, if any, of these disorders are treatable might underlie the lack of urgency sometimes seen in establishing a diagnosis. Even if no treatment exists for a specific LSD, management of symptoms, such as epilepsy, or supportive care for cognitive deficits or neuromuscular weakness can offer benefit.

The therapeutic landscape

Treatment has, for decades, been available for a handful of LSDs.

Stem-cell transplantation. Reports that hematopoietic stem-cell transplantation is beneficial in mucopolysaccharidosis (MPS) type I, known as Hurler's disease, date back more than 30 years.[2] The procedure presents significant risk and usually is not curative, but sustained response has been reported in long-term follow-up.[3]

Enzyme replacement therapy. Although now being expanded as an option for an increasing number of LSDs, enzyme replacement therapy (ERT) was first described in 1974, when benefit was demonstrated in 12 patients with Gaucher disease.[4] There is now ERT, offering variable degrees of benefit, for approximately 15 LSDs – nearly one-third of all known types. Many patients with Gaucher disease now lead a normal life on maintenance ERT, although the quality of the response in this disease is not necessarily shared by all other LSDs for which ERT has been developed.[5]

In Pompe disease, for example, ERT initiated in infancy improves survival but does not prevent disease progression. Available ERT does not cross the blood-brain barrier, so benefits are minimal for symptoms that arise from cells affected in the CNS. About 25% of Pompe patients do not respond at all to ERT.[5]

In MPS type II and Fabry disease, results of long-term follow-up with ERT have also been mixed. In MPS II, a study associated ERT with longer survival (33 years, compared with 21.2 years without ERT), but substantial rates of persistent morbidity question the quality of life achieved during this extended survival.[6] In Fabry disease, as well as in MPS II, ERT does not appear to reverse existing organ damage or protect against CNS deficits.

"ERT has improved outcomes for many patients with LSD, but the inability of most forms of ERT to cross the blood–brain barrier has been an issue for CNS symptoms," Dr. Wang said. "Also, for those who require ERT infusions every week, some of which can take several hours, treatment does require time and [causes] inconvenience."

Still, ERT has offered hope for improving the lives of LSD patients where there was once little hope. This includes CLN2 disease (a ceroid lipofuscinosis, neuronal, also known as Batten disease), which typically develops in infancy after a period of normal development. This once invariably fatal LSD is also characterized by CNS involvement, but intracerebroventricular infusion of cerliponase alfa, an ERT, recently became the first approved treatment for this LSD type.[7]

"We had nothing to offer patients with CLN2 and many of the other LSDs when I started, and it was one of the reasons I got involved in this field," Dr. Wang recalled. "A diagnosis of CLN2 was heartbreaking because we had to tell parents that their child had a progressive and fatal disease for which we could do nothing. Obviously, the treatment for CLN2 along with the promise of many therapies on the horizon has been very exciting."

Gene therapy. Substantial hope for treating LSD is pinned on gene therapies and gene editing. Unlike ERT, which is not curative but must be administered lifelong, gene-based therapy, whether through exogenous delivery or in vivo gene editing to regain function, offers the chance to restore normal enzymatic activity to cure underlying LSD.

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Supporting patients and families affected by Niemann-Pick Disease

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The **National Niemann-Pick Disease Foundation, Inc.** is a non-profit patient advocacy and family support organization dedicated to supporting and empowering patients and families affected by Niemann-Pick disease through education, collaboration and research. NNPDF serves families throughout the nation at all stages of their Niemann-Pick journey. Our goal is to provide information, support, and programs to help reduce the challenges and burden of Niemann-Pick disease on affected individuals and families.

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"There are more than 10 gene therapies in clinical trials for various LSDs. Basically, these provide the genetic information to produce the deficient enzyme," Dr. Wang explained. "The premise is that this will be a one-time treatment, although we do not yet know for certain whether the effect will persist indefinitely."

Several strategies for delivering genes are being pursued: in particular, viral vectors, as well as novel nonviral approaches using nanoparticles, polymer-DNA complexes, and naked plasmid DNA delivered by electroporation or hydrodynamic injection.[8] Clinical trials have been promising, but safety is not fully established.

"We are seeing patients expressing the proteins they were missing, which provides a proof of principle, but the field remains investigational," Dr. Wang said. Risks, he explained, such as the potential for foreign DNA to activate proto-oncogenes, require evaluation of more patients over a lon- ger period. However, based on progress with gene therapy in LSD and other areas of medicine, such as spinal muscular atrophy, cystic fibrosis, and familial hypercholesterolemia, Dr. Wang is optimistic.

Gene editing. Identifying and correcting defective genes "has a longer way to go," Dr. Wang acknowledged, before the technology reaches the clinical setting, but it is also intriguing for its potential to cure, not just treat, LSDs. Using CRISPR-Cas9 and other gene-editing tools, the theory is that the inherited defect can be fixed, restoring normal enzymatic function.

Screening, testing, referral

With progress in controlling LSDs, newborn screening of these diseases, particularly among babies with a family history, will become increasingly attractive. For diseases that can be treated with ERT or for which gene therapies are yet to be developed, identifying LSD prior to symptoms not only circumvents the diagnostic odyssey experienced by many patients who have a rare disease but also permits treatment to begin in advance of expression of pathology. Dr. Wang believes that this approach is increasingly feasible.

"With just a drop of blood, there is the potential to look for an array of LSDs, as well as other inherited genetic diseases, at the time of birth. If the LSD is treatable, these patients could lead normal lives."

The burden of early detection and early treatment of LSD rests on the ability of primary care physicians to consider these rare disorders and then order genetic testing when first-line diagnostic studies fail to provide answers. According toDr. Wang, these referrals play a critical role in bringing patients to specialized centers where treatment can be optimized.

"For LSD, it makes sense to consider a specialist center where there are resources to consider the available and investigational treatment strategies," Dr. Wang said. He described how, at his center (the multidisciplinary lysosomal storage disorder program at Children's Hospital of Orange County), referral of two siblings with CLN2 disease led to the opening of a clinic dedicated to this disease. With nine cases being treated, "we now have the biggest CLN-2 program in the U.S.," he said – a footnote to just how rare these diseases are.

Still, genetic testing "has taken the pressure off clinicians," including neurologists and primary care physicians, Dr. Wang said in conclusion. It is less crucial to recognize which one specific disorder of the large array of inherited neurologic conditions a patient might have; rather, it is important to have a high index of suspicion – especially in context of significant parental concerns – and consider genetic testing for children and adults with symptoms that are consistent with these progressive disorders. ■

Resources

Lysosomal Storage Disorders Support Society
www.lsdss.org

Lysosomal Disease Network Centers of Excellence
https://lysosomaldiseasenetwork.org

National Organization for Rare Disorders
https://rarediseases.org/rare-diseases/lysosomal-storage-disorders

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