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Needles in haystacs: the challenges of rare diseases

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Abstract

Rare diseases are always a real challenge. The first test is to remember the myriads of often obscure but frequently tell-tale clinical signs that lead to suspicion for a specific disease. The next is to recognize these signs in the clinic, something that is not easy unless you are looking for them. Then there is the difficulty of figuring out the appropriate diagnostic work-up. Getting samples to the right diagnostic centers often presents a logistical problem, and when the results return, how to manage the condition. Comprehensive care is particularly challenging, due to frequently hidden comorbidities. So how are these challenges to be handled for more than 3000 rare diseases?

The article by McCarthy et al.,1 together with similar recent articles,2, 3 all on Lesch-Nyhan disease (LND), provide some valuable lessons applicable to rare diseases in general. LND is a developmental disorder distinguished by overproduction of uric acid and a characteristic neurobehavioral syndrome. The excess uric acid leads to hyperuricemia, nephrolithiasis, and gout. The neurobehavioral syndrome includes motor disability dominated by dystonia, cognitive impairment, and peculiar self-injurious behaviors. The classic syndrome is easy to recognize when full-blown, but there are attenuated variants where some of these features are lacking or sufficiently mild that they are overlooked.2, 4 LND and its variants are caused by mutations in the HPRT1 gene, which encodes the purine salvage enzyme, hypoxanthine-guanine phosphoribosyltransferase.5

The tell-tale clinical signs leading to suspicion for LND include self-injurious behavior and hyperuricemia. The appearance of either is highly suspicious, and often triggers the right diagnostic work-up. But even these telltale signs are not foolproof. Self-injurious behavior may be absent or delayed until adulthood,2 and serum uric acid levels may be normal or only slightly elevated.1 Patients presenting in clinic don’t often appear with the classic and complete phenotypic syndromes described in textbooks, so it is important to avoid dismissing diagnoses when a specific feature is absent. These lessons are true of many rare diseases. Many have tell-tale clinical signs that together paint a picture for specific syndrome, but incomplete syndromes may be more common than complete ones. What do you do if you find an odd clinical sign and you are not sure which rare disease it might point to? Google it. You will be surprised at how fast this can start a list for differential diagnosis.

Regarding the diagnostic work-up, there now are many online resources to lessen the challenge. Some resources catalog many rare diseases, such as the National Institutes of Health Office of Rare Diseases Research (rarediseases.info.nih.gov) or the National Organization for Rare Disorders (www.rarediseases.org). Others are more disease-specific, such as the Lesch-Nyhan Disease International Study Group (www.lesch-nyhan.org). Often these sites include contacts for more information, and most experts working in rare diseases

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are readily willing to help because they understand the difficulties involved. For some disorders, diagnostic studies can be obtained free of charge, either as a philanthropic service or as part of a research program aimed at learning more about the condition.

Similar assistance is available for clinical management. When evidence-based medicine is lacking, the opinions of experienced providers and comprehensive care centers becomes particularly valuable. For example, self-injurious biting in LND is extremely difficult to control, and often leads to the desperate proposal that teeth be removed to stop it. The decision to proceed with such an outrageous suggestion becomes much less horrifying to patients and families when they learn that more than half of all patients with LND (in some of the best treatment centers) ultimately must have their teeth removed, and later are happy with the decision.1

Finally, the enormous challenges faced by providers dealing with rare diseases are tiny in comparison to the challenges faced by the patient and family. It is essential that patients and their families be directed to support groups and online resources devoted to the disease. These directions can be extremely useful, as it is not uncommon for patients and their families to become the best teachers of the providers who return their care.

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