New Aspects of LSD: Pathophysiology, Diagnosis, and Treatment

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Recent progress in revealing the complex pathomechanisms of lysosomal storage disorders (LSD) and the development of new ways for treatment have awaked interest in these diseases not only in geneticists and biochemists but also in physicians who are experienced in metabolic disorders. As it can be assumed that knowledge in this fast growing area is important for both, scientists and physicians, the editorial board of *Journal of Inborn Errors of Metabolism and Screening* has decided to launch a special issue of the journal that is dedicated to all aspects of lysosomes and LSD, including pathophysiology, new diagnostic procedures, and recent therapeutic options.

After the description of the lysosome by de Duve in the 1950s, this cellular organelle has been regarded as a trash disposal unit that is simply responsible for the degradation of macromolecules. However, as Matte and Pasqualim point out in their article, lysosomes must now be recognized as the central regulator of cell homeostasis that has several functions besides the degradation of large molecules in cellular processes such as signal transduction and immune response. The role of lysosomes in inflammation and immunity is depicted extensively by Simonaro. In her chapter, she describes how autophagy, one of the most important functions of the lysosomes, and disturbances of sphingolipid metabolism can lead to inflammatory changes and autoimmune diseases. Gaucher disease, Fabry disease, and Faber disease are excellent examples for the association of LSD and inflammation.

After the surprising realization that the incidence of Parkinson disease in patients with type I Gaucher was higher than expected, one has become aware that LSD and frequent neurodegenerative conditions such as Alzheimer and Parkinson diseases have many clinical and pathophysiological aspects in common, as is illustrated in chapter 4.

In spite of many attempts to increase awareness of LSD, the diagnosis of these diseases is often made very late. Hence, new diagnostic procedures such as newborn screening become necessary to improve this situation because a treatment must start as early as possible to show optimal efficacy. Multiplex tandem mass spectrometry seems to be a very useful method for newborn screening as it is described in the article of Schmitt Ribas and coworkers.

Komlosi and coauthors describe in their contribution how by using cutting-edge genetic techniques, such as whole exome sequencing, an unexpected new clinical manifestation (osteolysis of the bones of extremities) of a rare lysosomal storage disorder (Farber disease) has been identified.

For decades, there was a hope that gene therapy may become a therapeutic option for LSD, and nowadays, the dream has become a reality to be explored. After innumerable animal studies, gene therapy treatment by using gene transfer with the aid of viral vectors has reached the clinical development stage, as Gonzalez and Baldo point out in their article.

In the last chapter, written by Ortolano, small molecules that reduce the level of storage material by inhibiting its synthesis, compounds that activate a misfolded enzyme, or substances that overcome a nonsense mutation are described and their advantages and disadvantages discussed.

As outlined in the articles of this special issue, the increasing understanding of the pathophysiology of LSD will facilitate the development of drugs that show a higher efficacy in comparison to those that are presently available. In spite of the progress that has been achieved in the area of gene therapy, this therapeutic approach is still a challenge, and many questions, particularly regarding safety, have not yet been answered. For example, the site of insertion of the transferred gene into the host genome must be carefully controlled, specifically, whether it may affect regulatory elements. This problem, however, will likely be solved using the CRISPR-Cas9 methodology.[1] Immune reactions toward the gene product and/or the vector should be kept in mind, and finally, vectors should be developed that are more tissue specific. These issues must be addressed before gene therapy can be declared a routine therapeutic procedure.

Some limitations of therapeutic interventions are possibly due to the timing of initiation therapy, and early treatment may be more efficient. Therefore, newborn screening programs for LSD have been developed in many countries. However, because a strict genotype–phenotype correlation does not exist for most of these conditions, screening programs will probably not be generally introduced until the phenotype of the newborn can be exactly predicted.

Each of the therapeutic options presented in this issue is directed to only 1 or a few aspects of the complex

pathophysiology of LSD. We hold out hope, however, that in the future better clinical outcomes can perhaps be achieved by the combination of several therapies rather than by 1 therapeutic regimen alone.

I believe that in the future, our patients with LSD will profit more and more from the results of the investigations and studies that are performed by researchers and scientists from all over the world. It is my hope that this supplement may give a general insight in many aspects of LSD, such as pathophysiology, genetics, and treatment, and that the reader profits from the excellent contributions of these expert opinion leaders.

Michael Beck
Guest Editor

Reference

1. Gori JL, Hsu PD, Maeder ML, et al. Delivery and specificity of CRISPR-Cas9 genome editing technologies for human gene therapy. *Hum Gene Ther*. 2015;26(7):443-451.