Translational Science of Rare Diseases 4 (2019) 133–157
DOI 10.3233/TRD-190047
IOS Press

Practical management of lysosomal storage disorders (LSDs)

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Abstract. Lysosomal Storage Disorders (LSDs) comprise a group of disorders causing defects at the organelle and sub-organelle level with a wide range of pathophysiologies and clinical consequences. Signs and symptoms of LSDs involve multiple organ systems. The main pathological mechanism of most LSDs was previously thought to be cytotoxic effects of a specific storage substance secondary to functional impairment or insufficient lysosomal enzymes. Other pathophysiologic mechanisms of LSDs have been discovered such as dysfunction of cell signaling, disturbance of cell homeostasis, inflammatory process and dysfunction of autophagy. The goal of treatment is to balance equilibrium of the enzyme and the accumulated substance. Replacing deficient enzyme through exogenous enzyme replacement therapy (ERT) or stem cell transplantation has been the main method of treatment for several years. The ability of ERT to alleviate neurologic symptoms is limited owing to the inability of the exogenous enzyme to cross the blood-brain barrier. The benefit of stem cell transplantation on neurologic symptoms has been demonstrated for Hurler syndrome, but it is not clear for most LSDs. Other strategies, such as gene therapy, have been under development to overcome this limitation and provide a better outcome. Early treatment or pre-symptomatic treatment could also slow disease progression and improve prognosis. The scope of this article is to review current and new therapeutic strategies as well as disease non-specific management.

Keywords: Lysosomal storage disorders, management

Introduction

Lysosomal storage disorders (LSDs) are a group of inherited inborn errors of metabolism (IEM), currently including over 70 disorders. More than two-thirds of LSDs are neuropathic LSDs in which the main clinical symptom is neurodegeneration [1–3].

LSDs are classified based on the type of primary substrates that accumulate in lysosomes and the mechanism of disease. There are many enzymatic steps involved in synthesis. The interruption in any synthetic step leads to lysosomal enzyme dysfunction or deficiency, which consequently interferes with the intralysosomal macromolecule degradation process. Most LSDs are caused by a deficiency of lysosomal acid hydrolases. Other mechanisms include defects of an enzyme modifier or activator, trafficking defects, or lysosomal membrane transporter defects [4–6].

Although the incidence of each disease is rare, the cumulative incidence is common: 1 in 5,000 live births. The most common LSDs are Fabry disease, Gaucher disease, metachromatic leukodystrophy and Pompe disease [4]. Certain ethnic groups have high carrier frequency for specific diseases. For example, Gaucher disease type I, Niemann–Pick type A, mucolipidosis type IV, and Tay–Sachs disease have a high prevalence in the Ashkenazi Jewish population whereas Salla disease and aspartylglucosaminuria have a high prevalence in the Finnish population [7].

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Most LSDs are inherited in an autosomal recessive pattern. Exceptions include Fabry disease, mucopolysaccharidosis II (MPS II or Hunter syndrome), and Danon disease (a defect in lysosomal membrane associated protein 2 or LAMP2), which are inherited in an X-linked pattern. Autosomal dominant inheritance has been reported in adult-onset neuronal ceroid lipofuscinosis (ANCL).

1. Physiology of lysosome, synthesis of lysosomal enzymes and lysosomal function

Lysosomes are cytoplasmic organelles surrounded by a single-layer lipoprotein membrane. They are components of all animal eukaryotic cells, except red blood cells [8]. Lysosomes contain a variety of acid hydrolases, which are not active in neutral pH environments and are required for degrading macromolecules such as polysaccharides, proteins, lipids, and nucleic acids. The products of degradation, such as sugars (e.g., glucose, galactose) and lipids (e.g., ceramide, sphingosine), are released to the cytoplasm and then recycled for biosynthetic purposes. The process of degradation and reusing breakdown products for biosynthesis is called metabolic salvage [1, 9]. Therefore, lysosomes are important for maintaining cell homeostasis involving metabolic salvage. Homeostasis helps cells adapt to a changing environment and maintain normal function [10]. Furthermore, lysosomes are involved in many cellular processes, such as cholesterol homeostasis, autophagy, phagocytosis, membrane repair, bone and tissue remodeling, immunity, neurotransmission, intracellular signaling, ion homeostasis, calcium signaling, and apoptosis. Lysosomes, thus, not only function as "end point degradative compartments," but also play important roles in complex cellular regulation and metabolic salvage [11, 12].

The production of the majority of lysosomal acid hydrolases starts in the ribosomes and endoplasmic reticulum (ER). In general, proteins are synthesized on ribosomes and translocated across the ER membrane as unfolded polypeptide chains during their synthesis on ribosomes. In the ER lumen, acid hydrolases are folded into three-dimensional conformations [13]. This process is facilitated and monitored by the ER molecular chaperones (protein quality control mechanisms or PQC). ER PQC protects nascent proteins from degradation by promoting normal folding and providing a time-sensitive response to facilitate refolding-cycles of misfolded protein. If the acid hydrolases protein folding is not corrected within a certain timeframe, the misfolded proteins accumulate in the ER and interfere with the folding of other proteins. These events result in ER stress which leads to abnormal ER homeostasis. ER stress later triggers the cellular response mechanism called unfolded protein response (UPR) to restore abnormal ER homeostasis. Multiple changes are stimulated by UPR, such as increasing expression of ER chaperones, reducing amount of protein delivered to the ER by inhibiting protein translation, and activating ER-associated degradation (ERAD) to degrade unfolded protein.

On the other hand, if the precursors of acid hydrolases are folded properly, they are transported from the ER to the Golgi apparatus where post-translational protein modification reactions occur. [14]. The precursors of acid hydrolases are modified and tagged with mannose-6-phosphate (M6P) in the Golgi apparatus as a part of posttranslational modification and targeting processes. The acid hydrolases containing M6P move to the trans-Golgi network, where *N*-acetylglucosamine residues of M6P are removed by an uncovering enzyme (*N*-acetylglucosamine-1-phospho-diester α-*N*-acetylglucosaminidase), exposing the M6P-enzyme complex to an M6P receptor. The interaction between the acid hydrolases and the M6P receptors facilitates enzyme trafficking to the late endosomes, also called prelysosomal compartments. Once the receptor–ligand complexes are transported to the late endosomes, M6P is released from late endosomes and transported back to the trans-Golgi network via transport vesicles for reuse. Late endosomes mature to be lysosomes (endosome-lysosome system or E/L system).

Interestingly, a small portion of the enzyme precursors does not bind to the M6P receptors and are secreted with other proteins from the trans-Golgi network. These enzyme precursors are recaptured

in clathrin-coated pits (CCP) by cation-independent M6P receptors. They are transported to early endosomes, and the late endosomes which later mature into the lysosomes [11, 15, and 16].

Lysosomes degrade molecules captured by endocytosis, phagocytosis and autophagy [9, 13]. After phagocytic and autophagic vacuoles combine with the E/L system, macromolecules in vacuoles are delivered and broken down by the lysosome [11]. Some lysosomal enzymes, especially lipid hydrolases, require special proteins, sphingolipid activator proteins (Saps), to present the lipid substrates to the lysosomal enzymes [4].

2. Pathophysiology of Lysosomal storage disorders

LSDs are not one enzyme one substrate relationship, but the result of the dysfunction of complex cellular signaling mechanisms [18, 19]. Both accumulated substances and insufficient products are involved in the pathophysiology of LSDs.

Impairment or deficiency of lysosomal enzyme leads to accumulation and storage of a substrate (primary storage material) within the lysosome. The primary storage material can cause a series of secondary impairment of other biochemical pathways, as well as dysfunction in a variety of cell types. The interruption of other biochemical pathways leads to build-up of secondary co-accumulated substances, which may disturb fusion and intracellular trafficking of vesicles, impair autophagy, cause oxidative stress, alter signaling pathways and calcium homeostasis, induce inflammatory processes, and ultimately lead to cell death [6, 18, 20].

Alteration of macrophage and microglial cell function impairs the innate immune system, which consequently increases levels of proinflammatory response, including chemokines and cytokines. In addition, dying or damaged cells can activate microglia to initiate an inflammatory response. Inflammation plays an important role in the pathophysiology of neurodegeneration associated with many neuropathic LSDs, including GM1 gangliosidosis, GM2 gangliosidosis, mucopolysaccharidosis IIIB (Sanfilippo type B), Niemann-Pick type C (NPC), and neuronal ceroid lipofuscinosis (NCL). Inflammation has been described as part of the pathophysiology of hepatosplenomegaly in Gaucher disease, as well [6, 20–23]. Interestingly, aggregation of protein and inflammatory response in the nervous system are characteristic of adult neurodegenerative disorders such as Alzheimer's and Parkinson's disease; therefore, neuropathic LSDs likely share similar pathophysiology with common adult-onset neurodegenerative conditions.

Enzyme blockage also decreases the products of degradation. These products are precursors of metabolic biosynthesis and are sources of energy for cells. Thus, insufficiency of metabolic products results in energy deprivation and affects other metabolic pathways.

3. Classifications

Lysosomal storage disorders can be classified according to the major accumulated substrate, underlying mechanism, or the type of defective enzyme. Subgroups are usually divided by age of onset. The commonly used classification is by the type of major accumulated substrate (Table 1) [5, 24–26]. Owing to the improved understanding of the pathophysiology, some experts classify LSDs based on the mechanisms of the diseases (Table 2) [4].

4. Clinical manifestations

Clinical manifestations of LSDs can involve multiple organs, including neurologic (both central and peripheral nervous systems), cardiovascular, ophthalmologic, gastrointestinal, musculoskeletal, and

Table 1
Lysosomal storage disorders classification

Type	Subtype
Glycogen	
Pompe disease	infantile and later onset (IOPD and LOPD)
Danon disease (defect of LAMP2)	
Lipid	
Niemann-Pick disease type C (NPC)	
Lysosomal acid lipase deficiency (LALD)/Wolman disease	
Monosaccharide/Amino Acid Monomer	
Free sialic acid storage disorders	infantile free sialic acid storage disease (ISSD)
	intermediate severity Salla disease
	Salla disease
Mucolipidoses (ML)	
Mucolipidosis type II (I cell disease)	
Mucolipidosis type III (pseudo Hurler polydystrophy)	
Mucolipidosis type IV	
Mucopolysaccharidoses (MPS)	
MPS type I (Hurler, Hurler-Schie and Schie)	type I H (Hurler or severe form); type I HS (Hurler–Scheie or intermediate form) and type I S (Scheie or attenuated form) OR severe and attenuated form
MPS type II (Hunter)	severe and attenuated form
MPS type III (Sanfilippo)	type A, B, C, and D
MPS type IV (Morquio)	type A and B
MPS type VI (Maroteaux–Lamy)	
MPS VII (Sly)	
MPS IX (Natowicz)	
Multiple Enzyme Defects	
Multiple sulfatase deficiency (MSD)	neonatal, infantile and juvenile
Galactosialidosis	early infantile, late infantile and juvenile/adult
Neuronal Ceroid Lipofuscinosis (NCLS)	
CLN1 (Haltia-Santavuori disease and INCL, palmitoyl protein thioesterase PPT1 deficiency)	infantile, late infantile, juvenile, and adult
CLN2 (Jansky-Bielschowsky disease, tripeptidyl peptidase TPP1 deficiency)	late infantile, and juvenile
CLN3 (Batten-Spielmeyer-Sjogren disease)	juvenile

CLN4 (Parry disease and Kufs type A and B)	adult
CLN5 (Finnish variant late infantile)	late infantile, juvenile, and adult
CLN6 (Lake-Cavanagh or Indian variant)	late infantile, and adult
CLN7 (Turkish variant)	late infantile, and juvenile
CLN8 (northern epilepsy, epilepsy mental retardation)	late infantile, and juvenile
CLN10 (Cathepsin D)	congenital, juvenile, and adult
CLN11 (Granulin)	adult
CLN12 (Kufor-Rakeb syndrome)	juvenile
CLN13 (Cathepsin F)	adult
CLN14 (Potassium channel tetramerization domain containing 7)	infantile, and late infantile
Oligosaccharidoses (Glycoproteinosis)	
Alpha-Mannosidosis	
Beta-Mannosidosis	
Fucosidosis	
Schindler disease	
Aspartylglucosaminuria (AGU)	
Sialidosis type I (Cherry-red spot myoclonus syndrome)	
Sialidosis type II (Mucolipidosis type I)	
Peptide	
Pycnodysostosis	
Cystinosis	
Sphingolipidoses	
GM1 gangliosidosis	infantile, late infantile, and adult
GM2 gangliosidosis	Tay–Sachs disease, Sandhoff disease and GM2 activator deficiency (AB variant)
Gaucher disease (GD)	type I, II, and III
	Saposin C deficiency
Niemann–Pick	types A and B
Farber disease	
Farber lipogranulomatosis	
Krabbe (globoid cell leukodystrophy)	early infantile, late infantile, and adult
	Saposin A deficiency
Metachromatic leukodystrophy (MLD)	late infantile, juvenile, and adult
	Saposin B deficiency
Multiple Sphingolipids	
Prosaposin deficiency (pSap)	

Table 2
Lysosomal storage diseases classification based on mechanism of diseases

Mechanism of Disease	Diseases
1. Enzyme deficiency disorders	
	Mucopolysaccharidoses (MPS)
	MPS type I,II,III,IV,VI,VII and IX
	Glycogen storage disease II (Pompe disease)
	Oligosaccharidoses
	A-mannosidosis
	B-mannosidosis
	Fucosidosis
	Aspartylglycosaminuria (AGL)
	Schindler disease
	Sialidosis
	Sialidosis type I and II
	Galactosialidosis
	Sphingolipidoses
	GM1 gangliosidosis
	GM2 gangliosidosis
	Krabbe disease
	Metachromatic leukodystrophy (MLD)
	Fabry disease
	Farber disease
	Niemann-pick type A/B
	Lipid storage disease
	Lysosomal acid lipase deficiency (LALD)
2. Post-translational modification disorders	
	Multiple sulfatase deficiency
	Mucolipidoses
	Mucolipidosis type I and II
3. Integral membrane protein disorders	
	Cystinosis
	Danon disease
	Action myoclonus-renal failure syndrome
	Free sialic acid storage
	Mucolipidosis type IV
	Niemann-pick type C
4. Neuronal ceroid lipofusinosis (NCL)	
	NCL
	NCL type 1–14
5. Disorders of lyosome-related organelles (LROs)	
	Hermansky-Pudlak syndrome (HPS)
	HPS type 1–9
	Griscelli syndrome
	Chediak-Higashi syndrome

respiratory systems. Some features are disorder-specific, while others are observed in several LSDs. For example, several oligosaccharidoses and the majority of mucopolysaccharidoses share similar presentations, as both can present with delayed development, coarse facial features, corneal clouding, hepatosplenomegaly, and dysostosis multiplex. The clinical severity is variable within the same enzyme defect. For all LSDs, the age of onset is broad, encompassing both prenatal, such as hydrops fetalis, and adult presentation [4, 24].

The common signs and symptoms are described as follows:

(4.1) **Neurologic manifestations**

(4.1.1) Intellectual disability, macro- or microcephaly, epilepsy, myoclonus, peripheral neuropathy, spasticity, hypotonia, dysphagia, stridor, cerebellar ataxia, other extrapyramidal signs, aggressive behavior, and psychiatric problems

(4.1.2) Characteristic abnormal eye movements are noted in some neuropathic LSDs.

- Abnormal saccades are seen in late-onset GM2 gangliosidosis and Gaucher disease type II.
- Horizontal supranuclear gaze palsies are seen in Gaucher disease types II and III.
- Vertical supranuclear gaze palsies are seen in Niemann-Pick C (NPC) disease.

(4.2) **Non-neurologic manifestations**

(4.2.1) Facial features

- Coarse facies
- Bushy eyebrows and puffiness of eyelids
- Flattening of nasal bridge
- Thick lips and macroglossia

(4.2.2) Bone and joints

- Dysostosis multiplex: short stature, thickened skull, enlarged J-shaped sella, short neck, odontoid hypoplasia, atlanto-axial instability, spinal beaking, platyspondyly, broad ribs, pointing of proximal part and broad distal part of metacarpal (bullet-shaped appearance) and underdeveloped lower ilia
- Limitation of joint mobility
- Carpal tunnel syndrome

(4.2.3) Ophthalmology

- Anterior segment: cataracts and cornea clouding
- Posterior segment: cherry-red spot, retinitis pigmentosa and optic atrophy

(4.2.4) Ears and hearing

- Hearing impairment
- Recurrent otitis media and chronic otitis media

(4.2.5) Cardiovascular

- Valvular abnormalities
- Cardiomyopathy
- Disturbance of conduction system
- Coronary artery disease

(4.2.6) Pulmonary

- Narrowing of upper and lower airway and sleep apnea
- Pulmonary infiltration
- Impaired pulmonary function

(4.2.7) Gastrointestinal
- Hepatosplenomegaly
- Cholestatic liver disease
- Cirrhosis
- Umbilical hernia

(4.2.8) Hematology
- Pancytopenia
- Anemia
- Thrombocytopenia

(4.2.9) Skin
- Hirsutism
- Angiokeratoma
- Multiple mongolian spots
- Hypopigmented to skin-colored papules/ nodules (pebbling of the skin)
- Xanthomata

5. Newborn Screening

Newborn screening (NBS) is a public health program to screen newborns during their first few days of life for certain conditions. The rationale is early detection and treatment of conditions that can cause serious health problems, long-term complications, or death if treatment is not started early enough. In general, the conditions tested in the NBS program were chosen based on evidence of early treatment benefiting the patient, availability of effective treatment, and ability to methodically screen.

In the United States, the Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC) provides advice and recommendations to the Secretary of the Department of Health and Human Services (HHS) on newborn screening activities. ACHDNC also provides recommendations for states to screen certain conditions as part of their state universal NBS programs [27]. The Recommended Uniform Screening Panel (RUSP) is a list of disorders that the HHS recommends for states to screen. The first LSD condition included in RUSP was Pompe disease in 2015; MPS I was added in the following year.

While RUSP-recommended disorders have clear diagnosis and treatment guidelines, other LSDs do not, and their inclusion on NBS has questionable efficacy. However, owing to therapeutic advances in several LSDs, some LSDs that were not included in RUSP have been included in newborn screening panels in several US states. For example, Missouri has screened for Pompe disease, MPS I, Gaucher disease, and Fabry disease since 2013 [29], and New York State has screened for Krabbe disease since 2006 [30].

As with many conditions included in NBS, the incidence of LSDs since NBS began has increased, and adult-onset cases have been identified through NBS. For example, in the United States, the combined incidence of all forms of Pompe disease was 1:40,000, with infantile onset being 1:100,000 and late onset being 1:57,000 (or 1:1.7 ratio) prior to NBS implementation [31]. After NBS for Pompe was implemented, the reported incidence increased; Illinois reported incidence of all forms as 1:15,133 [28], Missouri reported incidence of all forms as 1:9,625; infantile onset as 1:38,500 and late onset as 1:12,800, for a ratio of infantile onset vs. late onset cases of 1:3 [29].

6. Treatment

In general, the treatment and follow-up guidelines have been established based on the natural history of the disease, clinical observation of therapeutic consequences, and results from clinical trials (if

available). Several expert groups and organizations have also established guidelines for each disorder. Every guideline provides disease-specific recommendations, such as enzyme replacement therapy and organ-specific, multidisciplinary approaches [33]. There are 2 main types of treatment: specific and supportive.

6.1. Specific treatment

Early diagnosis and treatment are essential owing to the progressive nature of storage diseases. Early treatment improves the clinical outcomes since it can slow or prevent intra lysosomal accumulation. The clinical observation supporting the importance of early treatment is shown in sibling case studies, which demonstrate that younger siblings receiving enzyme replacement therapy (ERT) in the first 6 months of life have better outcomes than older siblings who do not [34].

Specific treatment is available for some LSDs. To date, 12 treatments for LSDs have been approved by the US Food and Drug Administration (FDA) and/or European Medicine Agency (EMA) (Table 3).

Although the cytotoxic effect of accumulated substrates is not the only pathophysiologic basis of LSDs, the main purpose of current treatments is to decrease storage materials with the expectation that lowering accumulation may reverse pathology. The goals of treatment are to 1) balance the equilibrium of storage material by decreasing the amount of substrate or 2) increase substrate degradation.

Principle of treatment

6.1.1 To reduce accumulated substrates and balance influx, the treatment can be achieved by:

(1) Increasing enzyme activity or improving residual enzyme activity

The main strategy is to provide enzyme from exogenous source or increase the activity of residual enzyme. This strategy can be accomplished by:

(1.1) Exogenous recombinant enzyme replacement therapy (ERT)
(1.2) Hematopoietic stem cell transplantation (HSCT) and bone marrow transplantation (BMT)
(1.3) Enzyme enhancement therapeutics (EETs): pharmacological chaperone (PC) and proteostasis regulator (PR)
(1.4) Nucleic acid-based therapy: gene therapy and genome editing

(1) Increasing enzyme activity and improving residual enzyme activity

(1.1) Enzyme Replacement Therapy (ERT)

Gaucher disease type I is a prototype for exogenous enzyme therapy. ERT for this condition, Alglucerase, was the first commercially available ERT. Alglucerase was extracted from human placental tissue, but production was discontinued owing to the risk of transmitting infection from the placenta, logistical challenges of harvesting, and manufacturing cost. A purified glucocerebrosidase produced by recombinant DNA technology in a Chinese hamster ovary (CHO) cell line (recombinant glucocerebrosidase or imiglucerase) replaced Alglucerase [36].

Since Alglucerase was approved in 1991, ERT has become standard of care for many forms of LSDs. Currently, FDA has approved ERT for Fabry disease, MPS type I, II, IVA, VI, and VII, lysosomal acid lipase (LAL) deficiency, Pompe disease, and late infantile neuronal ceroid lipofuscinosis (CLN2). Exogenous enzyme is administered through intravenous infusion, except for cerliponase alfa, an ERT for CLN2 that is administered through intraventricular infusion. The majority of recombinant enzymes are manufactured in CHO cell. Other sources of recombinant enzymes for LSD treatment are human cells, plant cells, and chicken eggs [36]. Some recombinant enzymes contain M6P, which facilitates the enzyme trafficking to the lysosomes.

Clinical trials are underway for an ERT for Niemann-Pick A and B, an ERT for alpha-mannosidosis, and new forms of ERT for Pompe disease (recombinant ERT coadministered with pharmacological chaperone) are underway.

The benefits, safety, and tolerability of ERT have been studied, and the treatment is well tolerated overall. ERT improves quality of life, hematological parameters, bone disease, and visceromegaly as well as reduces the risk of clinically significant long-term sequelae of Gaucher disease type 1 patients; however, response to treatment for each parameter is highly variable [29, 47]. In patients with MPS, ERTs have been shown to decrease liver and spleen volume as well as improve cardiac pathology, respiratory function, joint movement, mobility and quality of life. Biomarker excretion (glycosaminoglycans or GAGs) was also reduced [36].

Unfortunately, current treatment with ERT cannot completely resolve or prevent symptoms. There are multiple limitations that can be summarized as follows:

- Low penetration to poorly vascularized areas such as skeleton, cardiac valves, and corneas [36].
- Intravenous ERT is unable to cross the blood–brain barrier (BBB); therefore, it is not beneficial for neuropathic LSDs.
- Luminally-expressed cation-independent M6P receptor is a transporter at the neonatal BBB. This transporter allows exogenous enzymes which contain M6P to access the neonatal brain. However, this receptor-mediated transport is inactive in adult BBB [37–40].
- Irreversible pathology may not respond to ERT.
- Some clinical symptoms of LSDs are not caused by cytotoxic effects of the accumulated substrates but by other mechanisms such as autophagy and inflammation. Therefore, ERT may or may not affect symptoms resulting from these pathogenic factors.
- ERT is a feasible strategy only for enzymes that are soluble, not for those that are membrane-bound.
- Treatment is lifelong and requires administration weekly to monthly; some ERTs require more than 2 to 5 hours of infusion time.
- Infusion-associated reactions.
- Immunogenicity.
- Cost.

Limitations and strategies to overcome the limitations of ERTs

Short-term limitations of ERT

1. Infusion-Associated Reactions (IARs)

Infusion-associated reactions (IARs) are any adverse events (AEs), regardless of drug relationship and including anaphylaxis and severe allergic reactions that occur anytime from the start of an infusion through the end of the day after an infusion [41]. Reactions can be related to IgE-mediated or other mechanisms such as anaphylactoid reactions (for example, complement-mediated hypersensitivity). Common IARs include rash, urticaria, angioedema, bronchospasm, tachycardia, fever/chills, and pain in muscle, bone, and/or joints, and gastrointestinal symptoms. The most severe IAR is anaphylactic reaction. The majority of patients who experienced IARs can tolerate subsequent infusions, especially when interventions are provided.

IAR: Prevention and Practical management

IAR: Prevention

- Premedication with sedating or non-sedating H-1 blocker antihistamine. Additional medications, including H2-blockers, leukotriene receptor antagonists, steroids and antipyretic agents, could be considered for patients with IAR risk factors, such as history of IARs or atopic disorders [41].

- Patients with underlying sleep apnea should have airway patency evaluation prior to initiating ERT. Patients who use oxygen or continuous positive airway pressure (CPAP) during sleep should have oxygen and equipment available during infusion [16, 17].
- Postponing an infusion should be considered in patients with acute infection, fever, or respiratory illness at the time of ERT, as they may be at risk of severe hypersensitivity reactions [17].
- For patients who have a history of IARs, many approaches may prevent future IARs, including adding premedication, adding post-infusion antihistamine, and modifying the infusion protocol (such as decreasing the initial infusion rate to 25% to 50% of the recommended rate and slowing the ramping regimen during the first 1 to 2 hours of infusion).

IAR: Practical Management

Management of IARs should be based on the severity of the reactions.

- For mild to moderate reactions, treatment includes slowing or temporary interruption of the infusion (such as, reducing the infusion rate to 50% until the symptoms resolve, then ramping the infusion rate to the last tolerated rate). For mild reactions, treatment may also include administering additional antihistamines, antipyretics, and/or steroids.
- For severe and anaphylaxis reactions, treatment includes immediately discontinuing the infusion, evaluating the airway, breathing, and circulation, and providing other appropriate interventions or medicines (such as, epinephrine intramuscular injection, intravenous fluids for hypotension, and oxygen supplementation).

2. Immunogenicity

Humeral-mediated immune response is the most common mechanism of immunogenicity against ERT. IgE-mediated immune response causes IARs, and IgG-mediated immune response can impair the efficacy and bioavailability of exogenous enzymes. Most ERTs induce IgG anti-drug antibodies (ADAs). There are 2 types of ADA: neutralizing (antibodies bind to the uptake or catalytic/functional domains of enzyme) and non-neutralizing (antibodies bind to non-functional segments of enzyme). ADAs, especially neutralizing ADAs, can reduce efficacy of ERT by altering enzyme targeting, reducing half-life of the enzyme, and/or inhibiting a catalytic domain. The likelihood of developing ADAs is high in patients with absent or low levels of residual endogenous enzyme. The residual endogenous enzyme is measured by Western blot and defined as cross-reactive immunologic material (CRIM); presence of residual endogenous enzyme although low is classified as CRIM-positive and absence of endogenous enzyme is classified as CRIM-negative.

In general, the severity of pathological variants is related to levels of enzyme production. Patients with 2 null mutations usually cannot produce endogenous enzyme (CRIM-negative) and are at higher risk to develop a destructive immune response to ERT; their immune system recognizes exogenous enzymes as foreign and develops high and sustained ADA levels that lead to poor clinical response to ERT. On the other hand, the immune system of CRIM-positive patients is exposed to residual endogenous enzymes, though non-functional; therefore, such patients' immune systems generally tolerate ERT better.

Patients may have low or initially detectable ADA titers that decrease over time. The correlation between the levels of ADA and clinical response has been studied extensively in Pompe disease, especially infantile-onset Pompe disease (IOPD).

Immunogenicity: Prevention and Practical management

The current best strategy to alleviate the effect of immune intolerance is immune tolerance introduction (ITI), the goal of which is to prevent or suppress ADAs. Ideally ITI should be started before initiation of ERT since it is easier to eradicate naïve antigen-specific T and B cells than memory

cells [42]. Efficacy, safety, and tolerability of ITI have been reported by several institutes. Various regimens have been developed, such as a methotrexate-only regimen or a rituximab, methotrexate, and intravenous immunoglobulin (IVIG) regimen [43]. Prophylactic ITI is considered as a standard of care for CRIM-negative IOPD [43].

Long-term limitations of ERT

ERT has a limitation to reach targeted organs owing to BBB, poorly vascularized organs, and enzyme mistargeting. The low penetration of ERT through the BBB leads to low CNS penetration and limits the efficacy of all ERTs to neurologic symptoms.

Strategy to overcome CNS penetration limitations

- Direct administration of ERTs to the targeted organ is a strategy that has been used mainly in neuropathic LSD patients. For example, ERT for CLN 2 disease, cerliponase alfa (Brineura®), was approved by FDA in 2017. Cerliponase is a recombinant form of human tripeptidylpeptidase 1 (TPP1). The drug is administered into cerebral spinal fluid (CSF) via an intraventricular access device. Efficacy of cerliponase was studied in 22 patients aged 3 to 8 years old. The initial study showed preserved walking ability compared to untreated patients in a natural history study [44]. Intrathecal ERT for neuropathic LSDs such as MPS I, II, and IIIA is currently being studied (www.clinicaltrials.gov). Intrathecal enzyme infusion was shown to improve symptoms of meningitis in a patient with MPS VI [45]. The main limitations of direct ERT administration into the brain are the short half-life of enzymes, risk of infection and developing immune intolerance, as well as complications from procedures such as sedation.
- Enzyme modification that takes advantage of existing transport systems has been studied. As mentioned previously, carbohydrate chains of the exogenous enzymes can be modified to contain M6P in order to improve cellular uptake. Non-carbohydrate modification methods have also been studied. Fusion or conjugation of enzymes with specific peptides, recognized by specific receptors, can enhance enzyme uptake by targeted organs.
- Regimens of higher doses have shown some benefit in Gaucher and Pompe disease. ERT for Pompe disease, alglucosidase alfa, at a dose of 40 mg/kg every 1 to 2 weeks may benefit CRIM-positive Pompe patients (both IOPD and LOPD) compared to the current recommended dose of 20 mg/kg every 2 weeks [46]. Case et al. reported improvement of total gross motor function in 2 groups of patients: those with clinical decline and those with lack of improvement on standard dose. [46].

(1.2) Hematopoietic stem cell transplantation (HSCT) and bone marrow transplantation (BMT)

HSCT/BMT provides donor-derived cells, which can cross the blood–brain barrier and enter the brain. After migration into the brain, the donor-derived cells differentiate into microglia. In somatic organs, donor-derived cells can differentiate into other cells such as macrophages and Kupffer cells. After engraftment, donor-derived cells become a permanent source of the enzyme and may ultimately restore biochemical function through cross-correction. HSCT/BMT may modify the CNS inflammatory response, an important pathophysiology of neuropathic GM1 gangliosidosis, GM2 gangliosidosis, NCL, and NPC. The efficacy of HSCT in reducing inflammation has been demonstrated in mouse models [47–49]. HSCT/BMT has been used in conditions where ERT is not effective or available, especially for neuropathic LSDs. Cell sources for these transplants include bone marrow and unrelated donor-umbilical cord blood transplantation (UCBT) [50].

In general, neurologic outcomes are better for HSCT/BMTs performed in pre-symptomatic, early-stage or mild phenotype individuals than those performed in symptomatic individuals or severe

phenotype individuals. Early treatment can improve cognitive outcomes. HSCT when performed within 3 to 9 months of age can slow the rate of cognitive decline and preserve normal cognitive development [51]. Improvement of neurologic symptoms after HSCT has been demonstrated in patients with MPS IH (Hurler), early-stage infantile onset Krabbe disease, late-onset Krabbe disease, and early-stage juvenile/adult MLD. In MPS I, successful HSCT/BMT has been shown to preserve the remaining neurocognitive function. HSCT has also been shown to decrease liver and spleen size, improve pulmonary and cardiac function, and enhance the quality of life in patients with MPS I. If the transplant is performed during the first 2 years of life, improvements are significant. However, benefits to cornea, heart valves, and bone are limited. During the first year post-transplantation, continued deterioration in development may be observed owing to the slow process of donor-derived microglia replacement in the CNS. Unsatisfactory outcomes of symptomatic-stage transplantations may be related to the process of engraftment and cross-correction, which might not occur quickly enough to counteract the rapid progression of disease [40, 49, 52–55].

The advantages of HSCT/BMT in other LSDs have been reported with a small number of patients. These LSDs include alpha-mannosidosis [56, 57], fucosidosis [58], Farber disease [59], aspartylglucosaminuria [54, 60, 61], sialidosis (mucolipidosis type I), I-cell disease [62], and Wolman disease [63, 64].

Studies of the combinations of HSCT and ERT have been conducted. ERT initiated prior to transplantation (with or without ERT after transplantation) and continued until full engraftment has been shown to be well tolerated and beneficial. It has been demonstrated that this combination of treatments does not disturb engraftment or increase morbidity [55, 65, 66].

(1.3) Enzyme enhancement therapeutics (EETs): pharmacological chaperone (PC) and proteostasis regulator (PR)

Mutations resulting in lysosomal hydrolase enzyme misfolding without impairment of catalytic function are the main target of EETs approach.

EETs correct enzyme folding, therefore rescuing ER clearance and extending half-life of mutant enzyme.

(1.3.1) Pharmacological chaperones (PC)

A pharmacological chaperone is a small-molecule membrane-permeable ligand with good biodistribution to many organs, and includes molecules that can cross the BBB. Pharmacological chaperones are useful for treating LSDs caused by enzyme misfolding. Some types of mutations, including missense mutations, in-frame deletions, and splice-site mutations, cause enzyme misfolding but do not impair an active site of the enzyme. Chaperones promote enzyme activity by enhancing refolding and promoting enzyme delivery to the lysosomes. The restoration of 10% to 20% of enzyme activity is adequate to prevent clinical symptoms of the disease [14].

The only approved PC drug is migalastat for the treatment of Fabry disease. Approximately 265 mutations account for 35% to 50% of Fabry disease patients, which can be treated by migalastat.

This concept of PC was studied in both animal models and clinical trials. The examples are Gaucher disease, Fabry disease, Pompe disease, MPS IIIB, and GM1/GM2 gangliosidosis [35, 37, 39]. One example of a PC drug currently under development is ambroxol for Gaucher disease. In an animal study, ambroxol was able to cross BBB and increase glucocerebrosidase activity [67].

(1.3.2) Proteostasis regulators

Proteostasis, or protein homeostasis, is the process of controlling biological pathways and the balance of proteins. The proteostasis network maintains proteostasis by 3 major processes: 1) protein synthesis,

2) polypeptide folding and 3) protein degradation by the ubiquitin-proteasome system (UPS) and the autophagy-lysosome system. Molecular chaperones connect all these processes [68].

A proteostasis regulator (PR) is a membrane-permeant ligand that does not bind to the specific mutant enzyme. PR acts on degradation process by shifting the folding equilibrium away from protein degradation and transporting the protein to lysosome via the secretory pathway [14]. These agents change cellular elements that mediate ER-PQC, the unfolded protein response (UPR), intracellular protein trafficking, and the cytosolic heat shock response (HSR). Three examples of PRs are MG-132 (26 S proteasome inhibitor), celestrol (proteasome chymotrypsin-like activity inhibitor), and arimoclomol (heat shock protein amplifier) [14, www.clinicaltrials.gov]. The efficacy of MG-132 and celestrol was shown in an *in vitro* study of Gaucher disease and Tay-Sachs disease fibroblasts; however, the limitation is the toxicity of both compounds, which leads to apoptosis. An arimoclomol clinical trial is ongoing in NPC and Gaucher disease patients.

(1.4) Nucleic acid-based therapy

This therapy includes gene therapy and gene expression manipulation and both are still in clinical trial stages.

(1.4.1) Gene therapy

The goal of gene therapy is to provide a permanent and continuous source of enzyme at a therapeutic level. This treatment may also reach the end organs, including the bones and CNS, better than other methods. Gene therapy can be achieved by *ex vivo* and *in vivo* gene therapy.

- *ex vivo* therapy (indirect gene transfer): Human stem cells, such as CD34+ HSCs, are collected from patients and transfected with the gene using a viral vector *in vitro*. Gene-corrected cells are then transplanted to patients (autologous stem cell therapy) after bone-marrow ablation chemotherapy-based preparation regimens [69].
- *in vivo* gene therapy (direct gene transfer) uses the liver or brain as a depot organ for viral vectors.

Vectors

Lentiviral (LV) and retroviral (RV) vectors are commonly used for *ex vivo* gene therapy. LV-based HSC gene therapy can be used to produce a supranormal level of enzyme, and this approach has been studied at a preclinical trial stage in patients with MLD and MPS I [69].

Adeno-associated virus (AAV) vectors are commonly used for *in vivo* gene therapy owing to their 1) ability to infect different cell types and both non-dividing and dividing cells, 2) long transgene expression, especially when non-dividing cells are infected, and 3) low risk of insertional mutagenesis and genotoxicity. In addition, specific AAV serotypes such as AAV9, AAVrh10, and AAVrh8 can cross the BBB; therefore, these viral vectors are able to reach CNS target organ after intravascular infusion. Unfortunately, AAV vectors have a few major limitations 1) delayed expression that usually takes 1 to 2 weeks to reach peak levels since AAV is single-stranded DNA, which requires a second strand synthesis or annealing for gene expression [69, 70], 2) the vectors are non-replicating, therefore, the transgene expression declines over time and vector re-administration may be necessary, 3) immunogenicity of AAV vectors both developed before or after gene therapy can complicate the outcome of treatment. Pre-existing immunity to viral vectors may interfere with vector transduction, especially when the anti-vector antibody level is high. Pre-existing immunity seems to affect somatic organs more than CNS. Some patients developed neutralizing antibodies to vector after receiving gene therapy. Neutralizing antibodies may interfere with the efficacy to readminister AAV vectors especially in children who may lose their new transgene or in dividing cells such as the liver.

Route of vector administration

Different administration routes can be used to deliver viral vectors to target tissues such as blood, liver, brain, and cerebrospinal fluid (CSF). CNS delivery may be accomplished by intracerebral, intrathecal and intraventricular injection. CSF delivery may target non-CNS organs as a result of an outflow of viral vectors into the blood stream. Alternatively, as mentioned previously, owing to the ability of AAV9 serotype to cross the BBB, the CNS can be infected by AAV9 vector after intravascular infusion.

Gene therapy studies and clinical trials

Gene therapy studies have been conducted in animal models and clinical trials, including LOPD, Fabry disease, CLN 2, 3, and 6, MPS I, II, IIIA, IIIB, and VI, MLD, and Krabbe (www.clinicaltrials.gov). Benefits have been demonstrated in several studies; for example, one study showed a significantly slower rate of neurologic decline in 10 children with late infantile CLN2 after adeno-associated virus serotype 2 vectors was injected in several locations in the CNS [35].

(1.4.2) Gene expression manipulation

Gene expression manipulation can be done by stop codon readthrough therapy or genome editing.

Stop codon readthrough therapy for LSDs has not been studied in humans. The concept is to have in-frame premature termination codons overridden by using small molecules such as gentamycin. This concept has been studied in Duchene muscular dystrophy (DMD).

Genome editing technology has been studied in both preclinical and clinical studies. This technique can precisely deliver a corrected gene product to the targeted locus, unlike gene therapy in which gene insertion may occur randomly. Genome editing can be mediated by different nucleases including meganucleases (MNs), zinc finger nucleases (ZFN), transcription activator-like effector nucleases (TALENs), or CRISPR/Cas9 nucleases.

Examples of mechanism of nucleases editing

- ZFNs are created by fusion of zinc-finger DNA-binding domains of ZF protein and the cleavage domain of FokI endonuclease. At the desired DNA sequence in a genome, ZFN creates double-strand breaks (DBS) that are later repaired by non-homologous end joining or homologous recombination.
- CRISPR-Cas nucleases recognize and target sequences through RNA and DNA base paring [71].

The first genome editing trials are underway for MPS I and II. A corrected copy of a gene is targeted to the albumin locus in hepatocytes through *in vivo* ZFN-mediated genome editing. The corrected gene copy is transcribed by a strong albumin promoter gene leading to significant expression of the corrected gene product in liver cells [69, 70].

(2) Reducing accumulated substrates by inhibiting biosynthesis of substrates or facilitating substrate transport through subcellular compartments can be accomplished by:

(2.1) Substrate reduction therapy (SRT)
(2.2) Small molecules that facilitate substrate transport
(2.3) Nucleic-acid based SRT

(2.1) Substrate reduction therapy (SRT)

The objective of substrate reduction therapy (SRT) is to inhibit synthesis of accumulated substrates and accordingly reduce the amount of substrate of the deficient lysosomal enzyme. Clinical improvement after SRT treatment is slower compared to ERT owing to slow substrate turnover.

Two SRTs have been approved by FDA; miglustat and eliglustat for the treatment of Gaucher disease and miglustat for the treatment of NPC (Table 3). Medications are administered orally and are not immunogenic.

Table 3
Summary of Approved therapies

Disorders	Therapeutic mechanism	Drug name
Gaucher disease	Enzyme replacement therapy	Imiglucerase
		Velaglucerase alfa
		Taliglucerase alfa
	Substrate reduction therapy	Miglustat
		Eliglustat
Fabry disease	Enzyme replacement therapy	Agalsidase beta
		Agalsidase alfa
	Chaperone therapy	Migalastat
Pompe disease	Enzyme replacement therapy	Alglucosidase alfa
MPS I	Enzyme replacement therapy	Laronidase
MPS II	Enzyme replacement therapy	Idursulfase
MPS IVA	Enzyme replacement therapy	Elosulfase alfa
MPS VI	Enzyme replacement therapy	Galsulfase
MPS VII	Enzyme replacement therapy	Vestronidase alfa
Niemann-Pick disease type C	Substrate reduction therapy	Miglustat
Lysosomal acid lipase deficiency/Wolman	Enzyme replacement therapy	Sebelipase alfa
CLN 2 (tripeptidyl peptidase TPP1 deficiency)	Enzyme replacement therapy	Cerliponase alfa*
Cystinosis	Facilitating substrate transport	Cysteamine bitartrate**

*Intraventricular administration. ** oral and eye drop.

• Miglustat

The imino sugar *N*-butyl-deoxynojirimycin (NB-DNJ or miglustat) is a chaperone that blocks sphingolipid synthesis by inhibiting glucosylceramide synthase. NB-DNJ was first approved in patients with Gaucher disease type I. Glucosylceramide is a precursor of many sphingolipids and miglustat can cross the BBB; therefore, it was demonstrated that miglustat can slow progression of neurologic symptoms in patients with neuropathic LSDs. Miglustat has been studied in GM1 gangliosidosis, GM2 gangliosidoses (Tay–Sachs and Sandhoff diseases), and Niemann-Pick type C [37, 72].

Among juvenile/adult patients with Niemann–Pick type C, miglustat stabilized symptoms and either delayed neurologic regression or progression of neurologic symptoms in children. [73, 74]. Significant improvement in extrapyramidal symptoms and seizures was reported in a child with NPC after 40 days of treatment with NB-DNJ [75]. Currently, the drug has been approved for use in NPC in Europe.

• Eliglustat

Eliglustat is a glucosylceramide synthase inhibitor. This drug was approved in the United States in 2014 as a first-line therapy for adults with Gaucher disease type 1 who have CYP2D6 extensive, intermediate, or poor metabolizer phenotypes. The dosage is adjusted based on CYP2D6 metabolizer status. Patients who are CYP2D6 ultra-rapid metabolizers may not achieve adequate concentration of eliglustat. Eliglustat is metabolized mainly by CYP2D6 and to a lesser extent by CYP3A; therefore, coadministering eliglustat with medications that inhibit CYP2D6 or CYP3A may increase eliglustat concentrations [76]. Unlike miglustat, eliglustat cannot cross the BBB and, therefore, is strictly used to treat Gaucher type I.

SRT clinical trials

- Isoflavones, particularly genistein, inhibit synthesis of glycosaminoglycans (GAGs). Isoflavones can reduce GAGs in cultured human fibroblasts obtained from MPS IIIA and

MPS VII patients. A pilot study conducted in children with MPS IIIA or IIIB demonstrated a decline of GAGs concentration as well as improvement of hair morphology and cognitive function after treatment with isoflavones. More studies need to be conducted to determine the efficacy, dosage and safety of isoflavones to treat MPS IIIA [77, 78].
- Ibiglustat for Gaucher and Fabry diseases
- Lucerastat for Fabry disease
- Odiparcil for MPS VI

(2.2) Small molecules that facilitate substrate transport

- Cysteamine is a good example of a drug in this class. This drug is used to treat cystinosis. Cystinosis is caused by impairment of the lysosomal cystine transporter. Accumulation of cystine in the lysosome is the main pathophysiology of this condition. The major problem is renal Fanconi syndrome (proximal tubular defect) leading to polyuria, polydipsia, rickets, failure to thrive and end-stage renal failure. Other organs are affected as well, such as photophobia due to cornea crystals and retinal damage, and muscle weakness due to myopathy.

Cysteamine is approved for the treatment of cystinosis and is available orally for systemic symptoms and as an eye drop for ophthalmologic symptoms. Cysteamine binds with cystine to form cysteine and cysteine-cysteamine complexes. Cystine can leave the lysosome via the cystine transporter and cysteine-cysteamine complex can leave the lysosome via a cationic amino acid transporter. Reducing cystine in the lysosome can decrease the rate of renal function deterioration and improve/prevent extra renal manifestations [76].

- Another example is hydroxypropyl beta cyclodextrin (HPBCD) or Cyclodextrins. HPBCD are cyclic oligosaccharides which can form water-soluble complexes with insoluble hydrophobic compounds; this property is an important mechanism to deliver unesterified cholesterol trapped in late endosomes/lysosomes out of the cells. [76, 79]. Murine studies have shown that HPBCD can mobilize cholesterol from late endosomes/lysosomes and improve neurodegeneration, liver function, and longevity of mice affected with NPC. It has been used in patients with NPC1. Currently, cyclodextrin clinical trials are underway.

(2.3) Nucleic acid-based SRT

RNA-based therapy has been studied extensively in the past few years. One technique is to use antisense oligonucleotides (AONs) to block or modify RNA processing. Antisense oligonucleotides (AONs) can reduce the translation of abnormal protein by binding target mRNA. AONs also can rescue or increase normal splicing of mutated transcripts to have normal protein product, especially when the mutations affect pre-mRNA splicing process. This technique has been approved by FDA for the treatment of DMD and spinal muscular atrophy (SMA).

Both properties of AONs have been studied as potential treatment for LSDs. Two important studies conducted by different research groups discovered 2 splicing-silencer sequences within exon 2 and intron 1 of the *GAA* gene that could be used to treat LOPD caused by the common splice site mutation, c.-32-13T>G. *In vivo* studies demonstrated that when AONs were used to block splicing-silencer sequences, normal splicing was partially rescued and alpha-glucosidase (GAA) activity was above disease threshold. In addition, the use of AONs against the silencer within exon 2 could reduce the accumulation of glycogen in myotubes harvested from patients [80]. Inhibiting the production of accumulated substrates could provide clinical benefit similar to SRT.

(3) Other therapy

(3.1) Combination standard therapy

- HSCT and ERT for treatment of MPS1
- PC and ERT combination: PC may enhance the stability of recombinant enzyme by different mechanisms, such as immobilizing the active site of recombinant enzyme at neutral pH and increasing enzyme half-life [14].

(3.2) Anti-inflammatory therapy

Inflammation plays an important role in the pathophysiology of neuropathic LSDs and chronic osteoarthritis associated with skeletal dysplasia of patients with MPS. The use of anti-inflammatory and immunosuppressive agents to inhibit pro-inflammatory cytokines such as IL-1 and tumor necrosis factor (TNF) alpha has been studied in several LSDs, such as Gaucher disease, Fabry disease and MPS.

- Pentosan polysulfate (PPS) is approved by FDA for the treatment of interstitial cystitis. It also has a weak anti-coagulant property and has been used for thrombosis prophylaxis and phlebitis treatment in Europe. Subcutaneous injection of PPS reduced inflammation and improved pathology of bones and mobility of joints in animal studies. In addition to its anti-inflammatory mechanism, PPS was hypothesized to reduce GAG accumulation by inhibiting GAG synthesis or promoting GAG degradation. In addition, PPS may directly up-regulate type II collagen and aggrecan as well as down-regulate type I collagen, and as a result, promote chondrogenesis. Clinical trials of PPS for MPS I and II are underway [81].
- Anti-TNF alpha drugs have been studied in both animal and clinical trials. A mice study showed infliximab may improve joint and bone pathology in MPS VI mice [81]. Adalimumab, another anti-TNF alpha drug, is in the clinical trials for treatment of patients with MPS I and II [www.clinicaltrials.gov]

6.2. Supportive and symptomatic care

Although specific treatment is available for several LSDs, most therapies cannot eliminate all symptoms, and some symptoms can progress despite treatment. Furthermore, most LSDs do not have an FDA approved treatment. Evaluation and management of patients with LSD are best undertaken by multiple specialists and coordinated by a physician who specializes in the care of persons with complex medical problems. The team should include a geneticist, neurologist, neuromuscular specialist, neurodevelopment specialist, cardiologist, pulmonologist, orthopedist, neurosurgeon, ENT, ophthalmologist, nutritionist, psychologist, social worker, and a therapy team that may include physiatrists, speech therapists, respiratory therapists, physical therapists, and occupational therapists [82].

6.2.1 Management of common symptoms and problems

Neurologic symptoms

Non-surgical management

- Anti-epileptic drugs (AEDs) seems to be effective in most patients with seizures; however, careful attention and close monitoring of seizure frequency and/or severity needs to be followed because in rare occasions, AEDs may worsen epilepsy. Owing to bulbar involvement and respiratory compromise, monitoring side effects of anti-epileptic drugs, such as sedation and respiratory depression, is strongly recommended [83].
- Benzodiazepines have been used for spasticity and irritability found in neuropathic Gaucher disease. Benzodiazepines including midazolam and lorazepam are also the first line treatment for status epilepticus; second line therapies are phenytoin and fosphenytoin. Baclofen also has been used for spasticity.

- Other symptomatic treatments include melatonin for sleep problems and anti-parkinson and antipsychotic drugs such as risperidone, clonazepam, and sulpiride for Parkinson-like or psychiatric symptoms. Before initiating anti-parkinson and antipsychotic drugs, drug-drug interactions should be carefully reviewed, and each drug should be selected with proper precautions. In addition, the safest and most commonly used drugs in the lowest possible doses are recommended [84–86].

Surgical management

- Ventriculoperineal shunt (VPS) is indicated for communicating hydrocephalus with increased intracranial pressure and clinical signs of hydrocephalus. Endoscopic third ventriculostomy (ETV), with or without choroid plexus coagulation (CPC), has been suggested as an alternative method to treat hydrocephalus especially when obstructive component is present [87].

Musculoskeletal symptoms
Non-surgical management:

- Braces and splints can benefit patients with mild kyphoscoliosis and joint contraction [82].

Surgical management:

- Orthopedic procedures to correct deformity of extremities such as lower extremity malalignment and hip subluxation are often required for patients with dysostosis multiplex such as MPS IV.
- Spine surgery to treat complications, such as upper cervical spine instability, spinal cord compression, and severe progressive thoracolumbar kyphosis, is often required for patients with dysostosis multiplex and neuromuscular scoliosis.

Cardiac symptoms

- Cardiac valve involvement may require placement of a bioprosthetic or prosthetic valve.
- Standard guidelines for cardiomyopathy and heart failure treatment can be applied to LSD patients.

Ear, nose, and throat and respiratory symptoms
Non-surgical management

- Positive airway pressure and/or tracheostomy are treatment for diffuse narrowing of the airway.
- Ventilation tubes may improve conductive hearing impairment secondary to chronic middle ear effusion. Hearing aids are indicated for mixed hearing loss and sensorineural hearing loss.
- Influenza, pneumococcal as well as routine immunizations should be offered to all patients if there is no contraindication [82].

Surgical management

- Adenotonsillectomy is recommended when patients have upper-airway obstruction and obstructive sleep apnea related to enlarged adenoid-tonsils.

Ophthalmology
Non-surgical management

- Routine monitoring should be undertaken for common LSD problems, including visual acuity, cloudy cornea, retinopathy, optic atrophy, and glaucoma. Standard treatment can be applied to LSD patients.

Surgical management

- Keratoplasty may be required in some patients with severe cloudy cornea.

Preoperative evaluation

Risk of anesthesia is significant in patients with LSDs. Several underlying conditions could increase risk of sedation significantly, such as difficult intubation due to short neck, immobile jaw, narrowing and anatomical changes in the upper airways, anteriorly positioned larynx, unstable atlantoaxial joint, and risk of post-obstruction pulmonary edema post-extubation. Other underlying conditions such as cardiac problems, scoliosis, joint contractures and respiratory muscle weakness should be considered.

Preoperative evaluation by a multidisciplinary team experience in caring for LSD patients is necessary for most LSD patients [82].

Supportive Therapies [82]

Supportive therapies provided by trained providers include:

- Physiatrist to optimize mobility and autonomy
- Physical therapist to optimize mobility, muscle strength, and stretching exercises
- Speech therapist to optimize communication and oromotor function including feeding therapy since neuropathic LSD patients often develop difficulty swallowing and risk of aspiration. Instruction to prevent aspiration, management by feeding teams and speech pathologists, considering G-tube feeding, and nutritional support are important.
- Occupational therapist to optimize autonomy
- Educational professionals to optimize the learning environment for patients with complex medical problems
- Social workers to evaluate and provide resources for home care
- Psychological support to optimize coping skills and quality of life for patients and their families
- Genetic counseling to help families making medical decisions and prepare for any subsequent pregnancies; counseling also helps to identify other affected family members and facilitates early treatment of these patients
- Hospice for end-of-life care; physicians should consider starting the conversation about this service early to help in planning and family coping as well as decision making

7. Treatment monitoring

In addition to history, physical examination that includes thorough neurological examination, and developmental assessment, special investigations are also necessary. Since several organs are affected at different degrees of severity, the frequency and type of investigations generally can be individualized to match patient needs.

Most patients and conditions require special assessments, including hearing test, pulmonary function test, polysomnography, endurance tests (such as 6-minute walk test), electrocardiogram and echocardiogram, and disease burden measurement (such as, quality of life questionnaires).

In terms of laboratory tests, both routine and disease-specific tests are necessary. Routine laboratory tests are required to monitor progression of disease and determine if patients have responded to the specific treatments: for example, CBC to monitor thrombocytopenia for Gaucher diseases, and renal function and urine protein tests to monitor renal function for Fabry disease. Routine laboratory tests also can be used to monitor general health and nutrition status.

Special laboratory tests such as biomarkers and IgG ADA are usually necessary to monitor treatment. Commonly used biomarkers are urine/blood GAGs for MPS, urine HEX4 for Pompe disease, blood

chitotriosidase and glucosylsphingosine for Gaucher disease, and serum globotriaosylceramide (GL3) for Fabry disease. IgG ADA monitoring is recommended for patients with Pompe disease, Fabry disease, MPS I and II who receive ERT.

Imaging studies such as X-ray, ultrasound, MRI, bone density, and swallow study are required in some situations; it is not usually necessary to perform these studies routinely. The exceptions are bone density and MRI of the spine and extremities, which are used to monitor patients with neuromuscular/neurodegenerative problems and severe dysostosis multiplex, respectively.

Conclusion

Treatment strategy by replacing missing enzyme was first proposed by de Duve 5 decades ago, and it took 3 decades to translate this knowledge from research to clinical practice [88]. In 1991, the first enzyme replacement therapy for Gaucher disease was approved by FDA, and the number of available ERTs and other treatments has increased significantly in the past 28 years [88]. Currently, specific treatment is only available for some diseases. Those treatments can alleviate non- neurologic symptoms and improve quality of life. Unfortunately, none of the current therapies successfully cure neurological and bone manifestations or eliminate all the clinical manifestations of the LSDs. As a result of an increasing understanding of the molecular biology and mechanism of diseases, multiple approaches have been studied specifically for CNS manifestations. In addition to nucleic acid-based therapy such as gene therapy and genomic editing, small molecule treatment such as SRT, pharmacological chaperone, and proteostasis modifiers are also attractive treatment options.

With new therapeutic options available or under development and knowing that 60% to 70% of patients have neuropathic LSDs, it is important to consider an LSD diagnosis in a patient with unexplained neurologic symptoms, such as regression of milestones and behavioral problems. The molecular and genetic heterogeneity of these disorders further complicate the clinical diagnosis of these conditions; however, a structured workup based on clinical manifestations, family history, metabolites, enzyme activity, and biomarkers is the most likely way to yield the correct diagnosis.

Since presymptomatic and early treatment can slow the progression of some LSDs, several states in the United States and several countries have implemented some LSDs in their newborn screening programs. Genetic counseling is also an important tool to determine additional persons at risk, which can lead to appropriate family planning and identify presymptomatic affected family members.

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