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Review Article

Lysosomal Storage Disorders: An Indian Perspective

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Abstract

Lysosomal storage diseases (LSDs); frequently present as paediatric neurodegenerative diseases are a group of more than seventy diseases which are characterized by deficiencies in normal lysosomal function and by intralysosomal accumulation of undegraded substrates, most of which are inherited as autosomal recessive traits. LSDs affect almost all organ systems, including the central nervous system and have high morbidity and mortality. Most of the genes encoding the deficient lysosomal enzymes in LSDs have been cloned, and animal models have been obtained for almost each disease. Now knowledge has improved about the disease pathogenesis and there is progress in the treatment approach by the development of multiple therapeutic approaches. Different modalities of treatment, including enzyme replacement therapy, stem cell transplantation, substrate reduction therapy, and others are available and have been shown to improve outcome. This review summarizes the clinical features, diagnosis, and management of LSDs with an emphasis on the burden in Indian population.

Keywords: Lysosomal Storage Diseases; Niemann-Pick Disease; Gaucher Disease; Newborn Screening; Tandem Mass Spectrometry

Abbreviations

IEM: Inborn Errors of Metabolism; LSDs: Lysosomal Storage Diseases; MPS: Mucopolysaccharidosis; MLD: Metachromatic Leukodystrophy; ML: Mucolipidosis; NPC: Niemann-Pick Disease-C; MS/MS: Tandem Mass Spectrometry; LC-MS/MS: Liquid Chromatography Tandem Mass Spectrometry; DBS: Dried Blood Sample; ERT: Enzyme Replacement Therapy; CNS: Central Nervous System; NIHF: Nonimmune Hydrops Fetalis.

Introduction

Lysosomal storage disorders (LSDs) comprise a heterogeneous group of IEM due to defects in either a lysosomal enzyme, transport, or membrane protein (Table 1) [1]. The resulting accumulation of intermediate metabolites leads to a variable clinical phenotype, depending on the nature and severity of the defect and organ systems involved. In the known LSDs, the most common are: Gaucher disease, Pompe disease, Fabry disease, Niemann-Pick disease, mucopolysaccharidosis I, and Krabbe disease. Most of the LSDs are

OMIM No.	Disease	Inheritance	Deficiency Enzyme
257200	Niemann-Pick A (infantile cerebral type)	AR	Sphingomyelinase
	Niemann-Pick B (juvenile noncerebral type)	AR	Sphingomyelinase
257220	Niemann-Pick C (subacute juvenile or chronic neuronopathic type)	AR	Deficient esterification of exogenous cholesterol
230800	Gaucher I (adult type)	AD	Glucocerebrosidase (ß-glucosidase)
230900	Gaucher IIA (infantile cerebral type)	AR	Glucocerebrosidase (ß-glucosidase)
245200	Krabbe, infantile type short survival	AR	Galactocerebrosidase
228000	Farber Lipogranulomatosis	AR	Ceramidase
301500	Fabry disease	XLR	α-Galactosidase A
230500	GM1 gangliosidosis type I (infantile)	AR	ß-Galactosidase
272800	GM2 gangliosidosis, type I, infantile Tay-Sachs	AR	Hexosaminidase A (α-unit mutation)
250100	Metachromatic leukodystrophy, infantile	AR	Arylsulfatase A (cerebroside sulfate sulfatase, or sulfatidase)
272200	Multiple sulfatase deficiency	AR	Deficiency of 7 sulfatases due to inability to convert a cysteine to 2-amino 3-oxopropionic acid
309900	Hunter syndrome (MPS II)	XLR	Iduronate 2-sulfatase

Table 1: Major lysosomal storage disorders.

OMIM indicates online Mendelian Inheritance in Man (see www.ncbi.nlm.nih.gov/sites/entrez?db=omim); X-LR, X-linked recessive; AR, autosomal recessive.

inherited as autosomal recessive traits, except for the X-linked Fabry, Hunter diseases and Danon disease. Although individually rare, the cumulative incidence of LSDs may be as high as 1:2,000 live births or higher in certain ethnic groups owing to founder effects [2]. However, collectively, LSDs are far more common, approximately 1 in 6000 to 8000 birth with the highest occurrence of Gaucher disease followed by GM2 gangliosidosis and mucopolysachharide disorder [3]. The clinical phenotype represents a continuous spectrum; more severe cases typically present during the neonatal period and infancy, with milder cases presenting during adulthood.

The LSDs are multisystem disorders, which result from a mutation in a gene encoding an intralysosomal enzyme, enzyme coactivators, membrane protein, or transporter proteins [4]. All LSDs share the common pathologic process of accumulated metabolic substrate within the lysosome. The progressive accumulation of these products leads to cellular dysfunction. The LSDs are primarily classified in line with the character of the stored material, but some are grouped by the protein deficiency. The major classes are mucopolysaccharidoses, Sphingolipidoses, Olygosaccharidoses (glycoproteinoses), Glycogenoses, Lipid storage diseases, Post-translational modification defects, Integral membrane protein disorders, Neuronal ceroid lipofuscinoses and lysosomerelated organelles (LRO) disorders [5]. Many LSDs have central nervous system (CNS) involvement, with or without somatic features [6]. Tissues that normally have a high flux of the accumulating substrate are most affected. Clinical characeriristics suggestive of LSD may include delay, progressive regression after a period of normal development, ataxia, seizures, weakness, and dementia [7]. An LSD diagnosis should also be considered in the presence of course facial features, bone abnormalities, unexplained bone pain or psychiatric problems. Enzyme-replacement therapy is available for Gaucher disease, Fabry disease, MPS I, MPS II, MPS VI, and Pompe disease. Chaperone therapy employing a tiny molecule to stabilize a misfolded enzyme, granting traditional targeting to the lysosome, is in clinical test for Fabry, Gaucher, and Pompe diseases [8].

Diagnosis and treatment

Lysosome is the site for macromolecule catabolism, recycling and signalling, and defects in any of these functions can cause the accumulation of undigested and/or partially digested macromolecules in lysosomes or defect in the transport of molecules, which can result in irreversible cellular damage, leading to pathogenesis of LSDs. Diagnosis is based on clinical symptoms, and confirmation of increased storage or genetic changes using several diagnostic tests, including enzymatic analysis and gene sequencing.

Different assays using either fluorometry, MS/MS, LC-MS/MS, digital microfluidics or immunoquantification have been used for high-throughput analysis of lysosomal enzymes in dried blood sample (DBS). The development of MS/MS methods for use with DBS has transformed high-throughput screening for IEM including LSDs [9,10]. There may also be evidence to suggest that MS/MS methods have potentially lower screen false-positive rates than equivalent digital microfluidic methods. MS/MS combines the advantages of improved selectivity and excellent sensitivity with multiplexing capacities. The first MS/MS methods for LSDs including enzyme-specific substrates and internal standards were developed by Gelb and coworkers, who reported a single multiplexing MS/MS assay for Pompe, Fabry, Gaucher, Niemann-Pick A/B, and Krabbe diseases [11,12] and later for MPS I and II [13,14].

Pathogenic mutations lead to a decreased amount of protein and subsequent reduced enzyme activity in lysosomal storage disorders. This observation was exploited in the development of immunoquantification assays [15]. Enhanced performance immune quantification assays using immunocapture microbead technology have been developed in multiplex format for up to eleven LSDs for use with DBS [16]. It is useful for NBS in the identification of patients with Pompe, Fabry, Gaucher diseases, and MPS II [17-20]. Variations of the immunoquantification assay incorporating additional biomarkers such as α- N -acetylglucosaminidase and chitotriosidase may increase the diagnostic efficacy of the method for Pompe and Gaucher diseases [21].

There is safe and efficacious treatment for only a few lysosomal disorders. Even for those disorders for which therapy is available, early detection, before the onset of irreversible changes, is critical. This applies to bone marrow transplantation in some of the enzyme deficiencies as well as cysteamine treatment for cystinosis. Hence, newborn screening would be a huge benefit for the treatment of lysosomal storage disorders [22]. The most studied techniques have involved directly measuring enzyme activity, and mass spectrometry appears to better differentiate affected from non-affected individuals when compared to fluorometric assays [23]. Newborn screening is mandatory in many regions of the world for LSDs; including Gaucher disease, Pompe disease, Mucopolysaccharidosis I, Krabbe disease, Fabry disease, and Niemann–Pick disease types A and B [7].

Indian studies

The developments in the field of diagnosis and treatment in LSDs are being reflected in the India for the last ten years. Even though individually rare, prevalence of LSDs is 1 in 7000 worldwide. For a larger population in India, the absolute number of cases must be larger. However, the cases diagnosed in India at present are very few. Presence of high level of consanguinity in India increases the burden in LSDs [24].

Sheth J., et al. studied 432 children with clinical symptoms suggestive of LSD and 309 (71.5%) were diagnosed with different lysosomal storage disorders as the underlying cause of neuroregression. In these LSDs, the major categories; 50.2% were glycolipid storage disorders 21.7% were mucopolysaccharidosis 17.5% were sulphatide degradation defects [25]. A study conducted by Pradhan., *et al.* diagnosed a total of 55 cases of LSDs during a 12-year period; of these, 31 were non-Gaucher and 24 cases were of Gaucher disease [26]. In the retrospective study by Kadali., *et al*. included 1558 patients with clinical symptoms suggestive of LSDs referred to Sandor Lifesciences Pvt Ltd during 2007 to 2012. In the patients

467 (30%) of the cases were positive for LSDs, with sphingolipidoses as the most common subgroup, followed by mucopolysaccharidoses, and Gaucher disease as the most frequently occurring individual lysosomal storage disorder [27]. Agarwal., *et al*. retrospectively studied 5,858 suspected patients; he diagnosed LSDs in 119 cases (2.03% of all referrals). Majority of patients were diagnosed with Gaucher disease (31.93%) followed by Mucopolysaccharidoses (20.16%). Mutation analysis was available in 21 patients (17.64% of the diagnosed cases) [28].

In another study by Sheth J., *et al*; selected 1,110 children, in which 387 (34.8%) were found to be affected with LSDs. In these glycolipid storage disorders were the major one (48%), mucopolysaccharide disorders (22%) and sulfatide degradation defect (MLD and Krabbe disease) in 14% of the patients. Glycogen storage disorder type II (Pompe disease), protein degradation defect (Batten disease), lysosomal trafficking protein defect (ML II/III and NPC), and lysosomal transporter defect (sialic acid storage disorder and galactosialidosis) were found to be less common. Consanguinity was present in 115 cases (29.6%). He also detected three common mutations c.1277_1278insTATC in 14.28% (4/28), c.964G>T (p.D322Y) in 10.7% (3/28) and c.1385A>T (p.E462V) mutations in 21.42% (6/28) for Tay-Sachs disease. Gaucher disease was one of the most common glycolipid storage disorders observed with a high frequency in this study 64.5% (40/62) [29].

Prenatal enzymatic diagnostic study of LSDs (Gaucher, Fabry, Pompe, Niemann Pick A/B, Tay Sach, Sandoff, GM1, mucoplysaccharidoses, Wolman, Krabbe, Metachromatic leukodystrophy and Batten diseases) using uncultured chorionic villi samples revealed highest frequencies for Gaucher disease. In 331 prenatal enzymatic diagnosis, 207 fetuses (67%) were normal and 124 (37%) fetuses were affected [30]. Sheth J conducted molecular genetic analysis of 37 biochemically confirmed subjects having Tay-Sachs disease and 32 subjects with Gaucher disease. Molecular genetic analysis was carried out for all exons and exon-intron boundaries of HEXA and GBA gene by bidirectional sequencing method. In HEXA gene, 21 mutations were identified in 34 unrelated families in Tay-Sachs disease, 15 of which were novel [3]. Lysosomal storage disorders (LSDs) are rare inherited inborn errors of metabolism which may present as nonimmune hydrops fetalis (NIHF) during pregnancy. A study of lysosomal enzyme was carried out in 33 NIHF cases; among these, seven cases (21.1%) of nonimmune hydrops fetalis were found to be associated with different LSDs [31]. Treatment in the form of Enzyme replacement therapy (ERT) is available for LSDs. ERT is available for Gaucher disease (Imiglucerase), MPS I, MPS II, Pompe disease,Fabry disease and MPS VI. Muranjan conducted ERT with Imiglucerase in Twelve individuals with Gaucher disease (10 with type I) [32].

In a detailed screening for common metabolic disorders including 150 children, 30 children were selected for the leukocyte enzyme study. Of these 21 were confirmed to have LSDs. The major one was GM2-gangliosidosis (47.61%, 10/21) followed by mucopolysaccharidosis (33.33%; 7/21) [33]. During the 3-year study period 93 patients were suspected to have LSDs on the basis of their clinical features; in these 68 patients were confirmed to have different types of LSDs, in the study by Verma., *et al.* [34]. Patients (1,033) clinically suspected to have LSDs were selected for enzymatic diagnosis in dried blood samples using modified fluorometric assays; 30% (307/1,033) were confirmed to have one of the LSDs tested [35]. In 2004; 41 LSD patients were reported by Nalini., *et al;* 51.2% patients were from consanguineous parents [36]. Mistri., *et al*. identified the mutation spectrum in 15 Tay Sachs disease patients with founder mutation p.E462V [37]. A study by Shukla., *et al*. revealed the pathogenic mutations in 13 metachromatic leukodystrophy (MLD) patients [38].

Conclusion

About 2000 cases of LSDs were reported from different unicentric/multicentric studies in India. The burden of these disorders is predicted to be high in India because of the large population, coupled with the practice of consanguineous marriages. Gaucher disease is the commonest lysosomal storage disease seen in India followed by mucopolysachariosis. Each lysosomal disorder is unique, with singular pathology and manifestations in different organ systems. Each disease is moreover a consequence of different pathological mechanisms causing disruption of membrane flow and molecular storage in the lysosomes. More work generally is needed across the country in the fields of medicine to understand lysosomal diseases and their critical consequences on the whole perception of life quality by those who suffer from them. Poor access to diagnostic facilities, and costly therapies are the major causes of increased burden of LSDs in India. Therefore, there is a major need for accurate and economical diagnostic facilities and consideration of therapies before irreversible complications occurs.

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