Mini Review

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Lysosomal Storage Disorders in India: A Mini Review

Neerja Gupta, Bhawana Aggarwal, Madhulika Kabra

Division of Genetics, Department of Pediatrics, All India Institute of Medical Sciences, New Delhi, India

Lysosomal storage disorders are a group of rare inherited metabolic disorders with protean manifestations and variable severity ranging from attenuated forms to severe ones. It is necessary to diagnose and manage these disorders timely before irreversible damage occurs. Prior to the era of enzyme replacement therapy and newer therapeutics, only treatment option available was palliative care. Over the past two decades, extensive research in the lysosomal storage disorders has led to substantial expansion of our understanding about them. This mini review focusses on the spectrum, challenges faced in the diagnosis and therapy and remedial actions taken so far in lysosomal storage disorders in resource constrained country like India.

Keywords: Lysosomal storage disorders, Enzyme replacement therapy, India

Introduction

Lysosomal storage disorders (LSDs) are a group of genetically heterogenous inherited disorders. Lysosomal enzymes break down various macromolecules, thus facilitating their disposal. Inherited qualitative/quantitative deficiencies of these acid hydrolases or lysosomal transport proteins result in accumulation of partially degraded macromolecules in various organs, resulting in various manifestations of different LSDs. About 50 different LSDs have been described with a combined incidence of 1:1,500 to 1:7,000 births[1]. However, there is a scarcity of comprehensive studies on the prevalence of these disorders in India. Most of these are inherited as an autosomal recessive trait, except Fabry, Hunter and Danon diseases which carry X linked inheritance. This mini review aims to review the status of LSDs and its management in India and address the challenges associated with their diagnosis and management.

Materials and Methods

Literature search was performed for the scientific articles submitted to the database at the National Center for Biotechnology Information (NCBI; http://www.ncbi.nlm.nih.gov/pubmed) to retrieve all the published articles with atleast one contributing author affiliated to an Indian institution using combination of key words including Lysosomal storage disorders AND India AND Prenatal diagnosis; Lysosomal storage disorders AND India AND Diagnosis; Lysosomal storage disorders AND India AND Enzyme replacement therapy; Lysosomal storage disorders AND India AND Hematopoietic stem cell transplantation. Number of published articles related to diagnosis, prenatal diagnosis, enzyme replacement therapy and hematopoietic stem cell transplantation were 191, 15, 30 and 4 respectively (accessed on 15th May 2018). Only original articles written in English language were reviewed.

1. Common LSDs in India

The burden and the spectrum of various LSDs in India has been described by various studies[2-4]. Our hospital based data revealed that Gaucher disease is the most common LSD seen in the Indian population. This is followed by Metachromatic leucodystrophy (MLD), Mucopolysaccharidosis (MPS) type I and II, and MPS IV A unpublished data. This differs a little from the spectrum shown by Sheth et al.'s study[4], which revealed Gaucher disease, MLD,

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Correspondence to: Neerja Gupta
Division of Genetics, Department of Pediatrics, All India Institute of Medical Sciences, Ansari Nagar, New Delhi 1100608, India
Tel: +91-9999995630, Fax: +91-1126588663, E-mail: neerja17aiims@gmail.com

Tay Sach disease and GM1 Gangliosidosis being commoner than MPS. This finding may be because of founder effect of Tay Sachs disease in Gujrat.

2. Status of diagnostic testing and the prevalent mutations

Early diagnosis and treatment initiation in LSDs are paramount for better outcomes. However, earlier the diagnosis was mainly based on the clinical grounds, supportive evidence on the neuroimaging, and limited biochemical tests available and confirmed diagnosis of various LSDs was used to be delayed[3,5]. One of the contributing factors was the limited availability of quality assured labs for enzyme analysis restricted to few major cities and also, transportation of samples was a major hurdle. Secondly, the awareness amongst physicians was limited. However, over past five years and with ICMR multicentric taskforce project on lysosomal storage disorders, the diagnostic facilities for lysosomal storage disorders enzyme assay as well as molecular testing is now widely available across India. Simultaneously, the efforts have also been made to improve awareness amongst medical students, physicians, and stakeholders through CMEs and parent support groups. Availability of various biomarkers such as plasma chitotriosidase has also been helpful in diagnosis and monitoring response to enzyme replacement therapy[6].

Recently, the utility of dried blood spot (DBS) has been postulated to take care of the sample transportation problems from the remote areas[7]. DBS can be used both for biochemical and molecular testing. A study by Supriya et al. described age and gender specific reference ranges for few of the lysosomal enzymes in the DBS in Indian population, due to continuous efforts in the direction to improve diagnostics in LSDs[8]. This can be a major milestone to establish new born screening programs in India.

Few studies have attempted to elucidate the mutational spectrum of various LSDs among the Indian population[9-17]. These initial studies have been helpful in establishing common mutations, founder effects and genotype phenotype correlations. Table 1 shows few common mutations and hot spot exonic regions for different LSDs that may be tested first by direct sequencing.

3. Status of enzyme replacement therapy (ERT)

Treatment involves replacement of the deficient enzyme either via ERT or HSCT.

The history of ERT dates back to 1991 when alglucerase be-

Table 1. Prevalent mutations and hot spot regions in various LSDs across Indian population

Disorder	Common mutations	Subjects	Common exons	Region	Reference
Gaucher disease	L444P(c.1448T>C)	21/33 patients	Exons 8, 10	Pan India	Ankleshwaria et al.[9]
NPD A, B		60 families	-	Pan India	Ranganath et al.[10]
	p.(Arg542*)	21.67%			
	p.(Arg418*)	6.6%			
MLD	c.459+G>A in intron 2	2/20 patients	-	Predominantly North India	Shukla et al.[11]
GM1 Gangliosidosis	c.75+2dupT	5/16 patients	Exons 1, 14, 10	Western India	Bidchol et al.[12]
MPS I		30 patients	Exons 14, 8	Pan India	Uttarilli et al.[13]
	p.Arg619*	25%			
	p.Ala75Thr	20%			
MPS II		30 patients	Exons 9, 3	Pan India	Uttarilli et al.[13]
	p.Gly374sp	40%			
	p.Arg88His	20%			
MPS IVA		68 families	Exons 8, 1, 7	Pan India	Bidchol et al.[14]
	p.Ser287Leu	8.82%			
	p.Phe216Ser	7.35%			
	p.Asn32Thr	6.61%			
	p.Ala291Ser	5.88%			
MPS VI	p.W450C (c.1350 G>C)	4/14 families	Founder mutation	Pan India	Uttarilli et al.[15]
	p.L98R		p.L98R (c.293 T>G)		
Tay Sachs disease	c.1385 A>T (p.E462V)	6/15 families		Gujrat	Mistri et al. [16]
	-	9 families	Exons 5-12	Pan India	Sheth et al.[17]

came the first ERT to be marketed. The treatment of LSDs has evolved with discovery of ERTs for other diseases and at present ERT is commercially available for 10 LSDs[18]. Currently, ERT is approved by FDA for *Gauchers disease (Imiglucerase-Sanoffi-Genzyme, Velaglucerase-Shire USA, Taliglucerase-Pfizer), MPS I (Aldurazyme – Sanofi – Genzyme), MPS II (Elaparase – Shire USA), Pompe disease (Myozyme- Sanoffi Genzyme), Fabry disease (Fabrazyme– Sanoffi Genzyme), MPS IV (Vimzim – Biomarine) and MPS VI (Naglazyme (galsulfase)-Biomarine)*, MPS VII-vestronidase alfa (Mepsevi by Ultragenyx Pharmaceuticals), Lysosomal acid lipase deficiency -Sebelipase (Kanuma by Alexion), Neuronal ceroid lipofuscinosis type 2-Cerliponase (Brineura by Biomarine). Various recombinant ERT that are available in India are mentioned in italics. Studies examining efficacy of recombinant enzyme therapy is underway for alpha mannosidosis, Niemann Pick disease B and Farber disease.

In India, first LSD to be treated with ERT was Gaucher disease in the year 1999. The treatment of Gaucher disease with ERT is most gratifying in terms of results among all the LSDs as demonstrated by retrospective review by Nagral et al.[19]. At present, ERT is available at few centers in India restricted to major cities. In view of the exorbitant cost, for most patients enzyme replacement therapies are provided by drug companies like Sanofi Genzyme and Shire Human Genetic Technology as a compassionate access program barring a few for whom parents are getting reimbursement from the employers who are entitled to support free health care to their employees. As per the recently collated data, about 238 patients are receiving enzyme replacement therapy for Gaucher disease (N=105), MPS I (N=20), II (N=27), Pompe disease (N=23), Fabry disease (N=20) under different compassionate access program (N=195) and through government agencies (N=43)[20]. Prohibitive cost, lack of any health insurance cover, non-productivity of enzyme through any drug company in India are the limiting factors for the use of ERT.

4. Status of HSCT

Hematopoietic stem cell transplantation (HSCT) works by providing cells to replace the deficient enzyme in various LSDs. However, the treatment success depends on the nature of enzyme deficiency and the stage of the disease at which it is performed. LSDs where HSCT has been tried with some success include MPSI, MPS II, MPS VI, MLD, Krabbe disease, Gauchers disease[21]. There is paucity of data on HSCT in LSDs as reinforced by latest systematic review by Somaraju and Tadepalli.[22]

As per the available guidelines[23], transplantation should be performed in less than 24 months of age in MPSI patients, to have better neurological outcomes. There is paucity of any published data from India on HSCT. However, due to high recurrent cost involved in ERT and decrease in the overall mortality and morbidities with newer conditioning regimens, HSCT could be a viable option for some of the LSDs and warrants a systematic study for selected LSDs.

5. Status of prenatal diagnosis

Role of genetic counselling and prenatal diagnosis in LSDs is of paramount importance due to unavailability of treatment for many of these disorders and prohibitive cost for the treatable ones. The confirmation of diagnosis in the index case either by enzyme assay or mutation studies is a must before embarking upon prenatal diagnosis (PND), which can be done on uncultured chorionic villi (CV), cultured CV, or cultured amniotic fluid (AF). Maternal contamination, sample transport errors, and dilemma as a result of pseudodeficiency pose significant problems in the diagnosis. In India, prenatal diagnostic facilities for LSDs are available for more than two decades[24] and has now expanded to several centres[25-27]. Verma et al.[28] conducted PND on 331 subjects and found that about (124/331) 37% were biochemically affected. PND was conducted on the basis of previous affected index case, confirmed either by enzymatic assays/molecular studies. Prenatal molecular confirmation was done in 43 cases out of 124 biochemically proven and was found to be highly concordant (41/43). Gaucher disease, Neimann Pick disease, GMI gangliosidosis, MPS VII were the commoner LSDs for which prenatal diagnosis have been reported. This could possibly be due to relatively early onset and poor outcome leading to early death in the previous affected child. Over decades with improved expertise and infrastructure, many of the families with an affected child have benefitted with the PND services at major centres across India.

6. Parent support groups

About 10 years ago, Lysosomal Storage Disorders Support Society (LSDDS) was formed to bring parents of LSDs together at a single platform. It is a non-profit organization headed by a group of parents of LSD patients. It has approximately 600 families. This society has been instrumental in bringing the families together, establishing a dialogue between stakeholders, bureaucrats and physicians. It works by coordinating facilities for the diagnosis and treatment of those suffering from these rare diseases.

Organisation for Rare Diseases India (ORDI) is another organisation that caters to the unmet needs of patients suffering with rare diseases in India[29]. It has team members from diverse backgrounds and utilises experience of organisations in USA, European Union and other rare disease foundations in India.

7. Government initiatives

The Government of India has a crucial leadership role to play in advancing progress in this field to help millions of hopeful and needy patients. In this regard several initiatives have already taken place in past five years. In 2015, Department of Health Research (DHR) and Indian council of Medical Research (ICMR) initiated a multicenter collaborative project on research in Lysosomal Storage Disorders with the objective of clinical, biochemical and molecular characterization of LSDs and study genotype phenotype correlation. The ultimate aim is to establish a database of the mutations and sequence variations and to establish a smooth network of referral and counselling facilities for affected families across India. The project is near completion and final report is expected soon. In 2017, government released a rare disease policy for the treatment and prevention of rare disorders (https://mohfw.gov.in/sites/default/files/Rare%20Diseases%20Policy%20FINAL.pdf). This policy focusses on establishing rare disease registries, improve diagnostics and manufacturing of therapeutic drugs by Indian companies and reducing the cost of ERT by waiving off the import duties. A rare disease cell has also been created in the ministry of family and health welfare. More recently ICMR has also announced about launch of a hospital based rare disease registry which includes LSDs which is an important step to have some insights into the burden of these disorders though will not be able to generate data on the exact disease prevalence.

8. Challenges and ways ahead

Enhancing awareness among physicians, cardiologists, nephrologists, hematologists and other specialitists to suspect these disorders early to maximize the therapeutic benefit is the key step to tackle LSDs. Medical education during undergraduation can help to significantly reduce the misdiagnosis/delayed diagnosis of these disorders. Access to the biochemical diagnosis though has improved over a period of time due to wider availability of lab and use of DBS for the screening test for LSDs but still there is a need to have quality assurance in place. The diagnostic labs are not present throughout the country and are restricted to a limited quality assured labs at private and government set ups. At present, medical genetics services are being provided as a separate department or under paediatrics in various cities including New Delhi, Lucknow, Vellore, Chandigarh, Hyderabad, Bangalore, Pune, Ahmedabad, Kochi, Trivandrum, Chennai, Manipal, Mumbai. However, the scenario is changing with the improved facilities for the easy and safe transport of the samples for diagnostic purposes.

With now increasingly available biochemical diagnosis, wide access to next generation sequencing, and gradually improving awareness, it is likely that more cases will be diagnosed. With continuing efforts towards awareness and ensuring quality of lab results, it is essential to initiate efforts to make ERT widely accessible. Latter can be achieved with public private partnership under corporate social responsibility. Producing ERT by Indian pharmacological companies will ultimately reduce the cost as has happened with special diets for small molecule inborn errors of metabolism. Since the ERT has to be administered lifelong, it requires joint efforts from the treating physicians, parents, pharmaceutical companies and policy makers to make it happen. There is a need to incorporate genetic disorders in the health insurance policy. Efforts towards the development of the orphan drug act in India has to be initiated.

Conclusion

Lysosomal storage disorders constitute an important group of genetic disorders amenable to treatment through various traditional and newer therapies. The stage is now set in India to initiate and strengthen efforts towards ensuring the availability of standard approved therapies for the patients. It also demands cooperation from the families and physicians to provide good supportive and multidisciplinary care. Prevention by prenatal diagnosis of the high risk families remains the only option till the time the access to the palliative and curative treatment is universally available.

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