Spectrum of Lysosomal storage disorders in India and Pakistan

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Abbreviations : GAG - Glycosaminoglycans, LSD – Lysosomal Storage Disease, MLD - Metachromatic leuko-dystrophy, MPS–Mucopolysaccharidoses.

Introduction : Lysosomal enzymes break down macromolecules, either those from the cell itself or those acquired outside the cell. Inherited defects or deficiencies of lysosomal enzymes (or other lysosomal components) can result in accumulation of undegraded metabolites, leading to lysosomal storage diseases.

Lysosomal storage disorders include approximately 50 different diseases with a combined incidence of 1:1500 to 1:7000 births. The majority of these genetic anomalies are inherited in an autosomal recessive manner, with the exceptions of Fabry, Hunter and Danon diseases which are X linked[3].

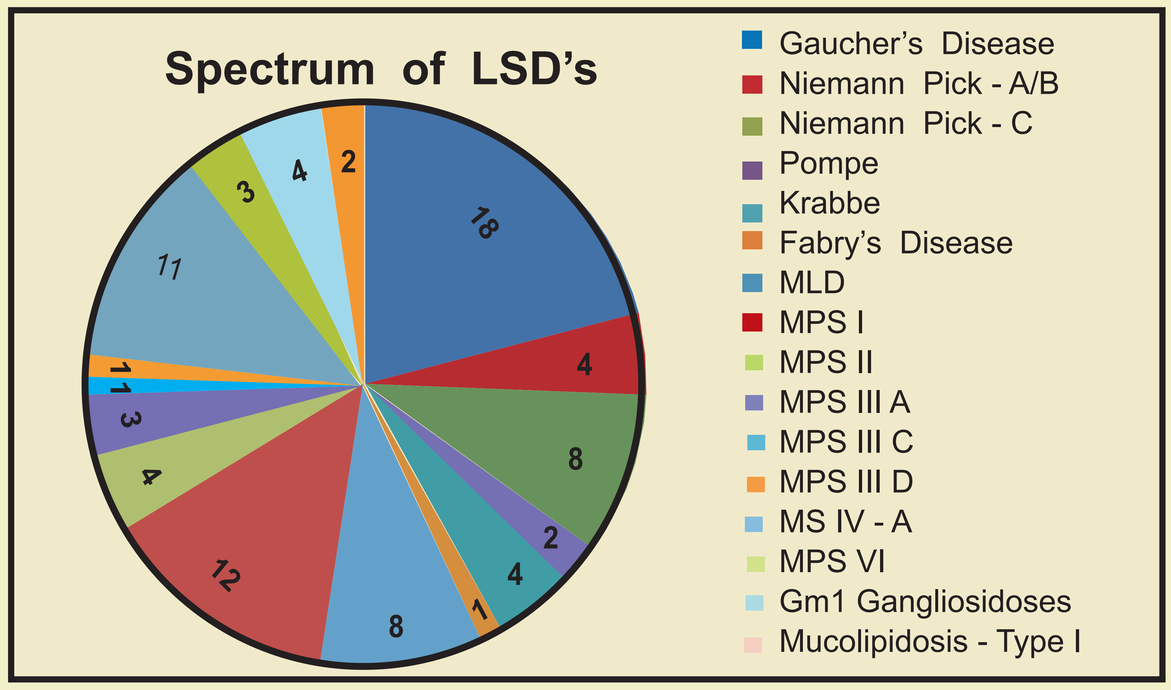
Objective : To find out the spectrum of Lysosomal storage disorders in patients from India and Pakistan.

Method : This study was carried out over a period of 4 years from 2011 to 2014. The patients were referred from all over India and Pakistan. Most common phenotypes for referral included coarse facies, short stature, dysostosis - multiplex, corneal clouding, hepatosplenomegaly, delayed development, cherry red spots etc.

Analysis was performed in serum, leukocytes and urine. Biochemical investigations included urine GAG analysis, urine MPS Electrophoresis, leukocyte enzyme studies, urine oligosaccharides, Chitotriosidase and CCL18. Molecular analysis was performed at Centogene AG, Germany.

Results : A total of 86 cases were confirmed by DNA studies out of 150 biochemically suspected cases. Gaucher's disease (20.9%) had the highest incidence, followed by MPS I (14%) and MPS IV-A (12.8%).So far in our cohort, we have no cases of Wolman's disease, β Mannosidosis, Fucosidosis, Schindler disease, Aspartyl-glycosaminuria, MPS IVB and Farber disease. Many patients were referred to us with Bone marrow biopsy as in India there is undue reliance on this technique to diagnose LSDs like Gaucher's Disease and NPD[1]. Bone marrow Biopsy is invasive, painful and there may be excessive bleeding[1]. We neither perform BMBx, nor promote it for the diagnosis purpose of LSD. The most common mutation in case of Gaucher's disease was **Ex 10 – c. 1448T>C(homo)/p.L483P** and in MPS I was **Exon 10: c.1469T>C (homo)/ p.L490P**

Disorders	Biochemically diagnosed	Confirmed by DNA
Gaucher's Disease	32	18
Niemann Pick - C-A/B	5	4
Niemann Pick – C	29	8
Pompe	4	2
Krabbe	6	4
Fabry's Disease	1	1
MLD	20	8
MPS I	13	12
MPS II	4	4
MPS IIIA	4	3
MPS IIIC	1	1
MPS IIID	1	1
MS IV - A	18	11
MPS IV - B	9	0
MPS VI	3	3
MPS VII	3	0
GMI Gangliosidoses	4	4
Mucolipidosis - Type I	2	2
Total	150	86



Discussion : India has witnessed an increase in burden of genetic diseases, including LSDs[1]. Awareness amongst patients and many pediatricians is very poor and therefore the diagnosis is delayed or missed in many cases. In India, since there are no formal studies or newborn screening related to IEM and specifically related to LSDs, the true incidence is unknown.

Agarwal S. et. al had molecular analysis for 21 patients out of 119 biochemically confirmed cases of LSD's. Out of the 21 cases diagnosed by molecular analysis, 16 were Gaucher disease and one each of Niemann–Pick, Pompe, MPS VI, MLD and Farber disease[1]. Jayesh Sheth et. al in a cohort of 387 affected children, had molecular analysis for 28 cases, all of which were for Tay - Sach's disease. By Biochemical diagnosis, they found that Gaucher's disease (16%) Tay - Sach's disease (10 %) and Sandhoff disease (7.8 %) and mucopoly saccharidosis were the commonest LSD's in India and the prevalence of MPS IV A was higher than MPS IV B[2]. These findings are in accordance with our findings.

It is important to identify LSDs, as now for many disorders a therapy is available. Treatment options currently available in India are, ERT(Enzyme replacement therapy), Bone marrow transplant and Hematopoietic stem cells transplant and substrate reduction therapy e.g. Genistein. ERT is now available at 4 centers across India for Gaucher's Disease and for Infantile Pompe Disease.Genistein, a natural isoflavin occurring in soy, is a small molecule and is reported to inhibit GAG synthesis through inhibition of tyrosine kinase activity of the epidermal growth factor receptor, which controls GAG synthesis[4]. It has been found to be effective in vitro on mouse models of MPS II and MPS IIIB[4]. Genistein is also available in India and we have used it for 4 MPS III patients (personal experience).

Conclusion : Gaucher's disease, MPS I and MPS IV A were found to be the commonest disorders in the patients from India and Pakistan. The most common mutation in case of Gaucher's disease was **Ex 10 – c.1448T>C(homo)/p.L483** and in MPS I was **Exon 10: c.1469T>C (homo)/p.L490P.**

Conflict of Interest : None

References :

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