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Abstract Title:- Adult-onset lysosomal storage disorders in India: Experience from a tertiary genetic centre and review of literature

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Aims:-Adult-onset lysosomal storage disorders (AO-LSDs) have milder phenotype and variable age at presentation compared to the classical LSDs. Several studies have described the phenotype, genotype and treatment outcomes for AO-LSDs like Gaucher disease, Fabry disease, Pompe disease and others. However, there is no systematic epidemiological data available for AO-LSDs. We describe the first systematic study on the prevalence of AO-LSDs from a tertiary genetic centre in India. Furthermore, we outline the key clinical signs for AO-LSDs obtained from literature review that can aid in early detection of these cases

Methods:- Of 2102 biochemically diagnosed LSD cases at our centre between 2008-2023, 31 patients were identified with AO-LSDs. In patients suspected with mucopolysaccharidosis, a preliminary test from urine sample was performed for the detection of glycosaminoglycans (GAG). For all 31 patients, based on the clinical suspicion, enzyme study from leukocyte or plasma was carried using enzyme specific fluorogenic substrates. 20 patients were subjected to a molecular genetic study to identify the causative variant by sequencing the respective gene.

Results:- Of the 30 adult patients, we observed a maximum percentage of 42% (n=13) cases with Gaucher disease in our cohort, followed by 13% (n= 4) cases with Fabry disease. We found 10% of cases with MPS IVA and MPS I, and 7% cases with Pompe and metachromatic leukodystrophy. Single cases of adult mucolipidosis III, type 1 sialidosis and Niemann-pick disease B were identified. We observed two variants p.Leu483Pro and p.Ala487Thr in the GBA1 gene in 23% cases with adult Gaucher disease instead of the common p.Asn370Ser variant commonly reported in the Ashkenazi Jewish adults with type I Gaucher disease. No common variants were observed in case of other LSDs. Remarkably, we observed 50% of Fabry patients, 4% of Gaucher patients and 2.6% of Pompe patients biochemically diagnosed at our centre to be adults. The prevalence of AO-Pompe patients in our cohort was low as compared to 80% reported in the Caucasian population. Also, AO-LSDs namely, MPS III, GM1/GM2 gangliosidosis, Krabbe disease were not identified in our cohort.

Conclusions:- Overall, data from our cohort highlights Gaucher and Fabry disease to be among the common AO-LSDs in India, which is in concordance with reports by other groups. However, common variants previously reported in adult Gaucher and Fabry patients were not identified in our cohort, suggesting global genetic heterogeneity. Lastly, awareness among adult neurologists and psychiatrists is necessary for detection of other rare AO-LSDs.

Keywords:- adult-onset, lysosomal storage disorders, phenotype, genotype, neurologists