International Journal of Contemporary Pediatrics
Kariyappa P et al. Int J Contemp Pediatr. 2022 Aug;9(8):757-761
http://www.ijpediatrics.com
pISSN 2349-3283 | eISSN 2349-3291

DOI: https://dx.doi.org/10.18203/2349-3291.ijcp20221860

Case Series

Clinical spectrum of lysosomal storage disorders in children

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Received: 28 May 2022
Revised: 22 June 2022
Accepted: 29 June 2022

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ABSTRACT

Lysosomal storage diseases (LSDs) are inherited metabolic diseases that are characterized by the accumulation of various toxic metabolites as a result of enzyme deficiencies. LSDs comprises of more than 50 diseases and are classified on a biochemical basis and the type of accumulated substrate. Most of the LSDs are inherited as autosomal recessive disorders with a few exceptions. Gaucher disease is the most common LSD. Clinical presentation of these children usually includes- anaemia, easy bruising, abnormally enlarged liver and/or spleen. We report a case series of 12 children with LSD. Among them 9 (75%) with GD, 3 (25%) with MPS. Based on the symptoms, in reducing order of frequency, children presented with generalised weakness, growth failure, abdominal distension, and developmental delay. 3 children with MPS had coarse facial features with reduced joint movements and hearing impairment. On examination, 5 children (41.6%) weighed less than third percentile, 9 (75%) had short stature, 10 (83%) had moderate to severe visceromegaly, CNS involvement in 2 children seen as hypotonia, occulomotor apraxia. Hematological parameters in all revealed- anaemia/leucopenia/thrombocytopenia- with two or more of the cell lines being affected. Bone marrow biopsy done in 9 (75%) children all of which were abnormal. Most of the children had enzyme activity levels between 0 to less than 15% of the normal reference range of the respective enzyme. ERT was initiated in 9 children (7 GD children and 2 MPS child) and followed up, showed a gradual amelioration in the symptoms by 1 year of regular ERT.

Keywords: Lysosomal storage disorder, Clinical features, Enzyme replacement therapy

INTRODUCTION

LSDs are a rare diverse group of hereditary metabolic disorders caused by defect in lysosomal function, due to mutation of genes that encode catabolism of enzymes involved in macro molecular degradation.[1] This results in accumulation of macromolecules such as proteins, polysaccharides or lipids in the cells leading to cellular dysfunction and progression of clinical disease.[2] They are most commonly due to deficiency of lysosomal enzymes, membrane transporters, or other proteins involved in lysosomal function. LSDs comprises of more than 50 diseases and are classified on a biochemical basis and the type of accumulated substrate, which include Gaucher disease, Mucopolysaccharidoses, Pompe's disease, Neimann pick disease etc. The most common LSD among these are lipid storage disorders followed by Mucopoly-saccharidosis (MPS). Gaucher disease is the most common treatable lipid storage disorder.[3] The predominant inheritance pattern is autosomal recessive.[1]

According to some authors, LSDs might be the most common group of IEM (Inborn Errors of Metabolism) affecting 1:5,000 newborns, with individual incidences

ranging from 1:60,000 to 1:100,0000.[4] Overall, their incidence has been estimated as 1 in 7000 to 1 in 8000 live births.[5] The prevalence of LSDs is about 7.5 and 23.5 per lakh live births in British Columbia and UAE respectively.[6] With 26 million births occurring in India annually, the extrapolated burden of LSD in India is nearly 3,700 to 17,000 affected babies born every year.[3] However the cases diagnosed in India at present represent the tip of an iceberg because of varied spectrum of the disease and diagnostic challenges. LSDs may present at any age with a clinical onset usually during childhood. Clinical manifestations may be multisystemic or organ specific. They include growth retardation, developmental delay, neuro-regression, corneal opacities, macular cherry red spot, angiokeratomas, and coarse facial features, hepatosplenomegaly, cardiomyopathy, dysostosis multiplex etc. A common feature among LSDs is the high clinical heterogeneity with different clinical phenotypes described according to age of onset, severity, central nervous system (CNS) involvement, and clinical progression.[8-10] Most LSDs are characterized by a progressive course, often resulting in severe disease manifestations and early death.

Therapeutic options available are ERT, substrate inhibitor and bone marrow transplant. Substrate inhibitors are oral formulations that reduce the synthesis of glucosylceramide by inhibiting glucosylceramide synthase. Bone marrow transplantation is also an available option, but is associated with significant morbidity and mortality from the procedure limiting its use as a treatment option. With the advent of ERT (enzyme replacement therapy) as therapeutic modality the survival of children with LSD have greatly improved. Early recognition and early initiation of treatment is crucial for improved quality of life and survival. The diseases for which ERT is currently the standard of care are Gaucher disease (imiglucerase, velaglucerase, taliglucerase), MPS I (laronidase), MPS II (idursulfase), pompe disease (alglucosidase alpha), fabry disease (agalsidase beta, agalsidase alfa) and MPS VI (galsulfase). These drugs are human recombinant products manufactured in in-vitro tissue culture systems. ERT alters the natural history of these diseases and reverses many of the symptoms. However, as the drugs do not penetrate the blood-brain barrier, there is no impact on CNS disease.[11] Diagnosis of LSD is a challenge for clinicians considering the clinical variability, the low frequency of these diseases, and lack of specificity of the signs and symptoms. Therefore, diagnostic approximation for LSDs requires the assessment of clinical and other laboratory tests, enzyme assays and genetic test results.

CASE SERIES

We present a case series of 12 children diagnosed to have LSD and followed up at our centre. Among them 7 (58%) were male and 5 (42%) were female children. The age of onset of symptoms ranged from 6 months to 2 years with mean age of 1.2±0.6 years and the age of diagnosis was much later, ranging from 11months to 9 years with a mean age of 2.9±1.1 years.All these children were symptomatic and diagnosed based on enzyme assay and by molecular genetic assay except one child (patient 2), who was detected on screening family members of the affected sibling. Consanguinity was noted in 5 (41.2%) families of the affected children. All children were born normally with no significant birth history and presented with either one or multiple symptoms as early as 6 months of age. Heterogenous clinical spectrum of each of the disease is noted as given in the figure (Figure 1).

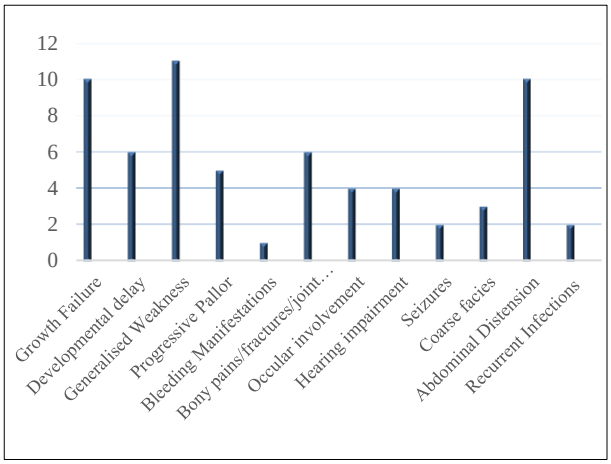

Figure 1: Common symptomatology of children with LSD.

The most common symptoms were generalised weakness and easy fatiguability (91%), growth failure (83%) and abdominal distension (83%). Progressive pallor is seen in 5 (41.6%) children. Children with MPS 3 (25%) had coarse facial features with reduced joint movements and hearing impairment. Children weighed less than third percentile according to IAP and WHO combined charts for appropriate age and gender. Nine children (75%) had short stature. Two children with MPS had umbilical hernia. 10 children (83%) had moderate to severe visceromegaly. The mean size of liver below the right costal margin was 7.4±4.4 cm ranging from 5 cm to 13.5 cm and average spleen palpable measuring 14.1±6 cm ranging from 5 cm to 22 cm. All children had anaemia with mean haemoglobin of 8.4±1.8 g/dl. Leucopenia and thrombocytopenia were noted in 3 (25%) and 10 (83%) children respectively with mean total count of 2166 cells/cumm and platelet count. Bone marrow biopsy was done in 9 children with Gauchers disease, which showed Gaucher cells. Most of the children had enzyme activity levels between 0 to less than 15% of the normal reference range of the respective enzyme at diagnosis. Based on the genetic mutation analysis, of the 9 (75%) children with Gauchers disease, majority 8 (88.8%) were diagnosed as type 3 Gauchers disease and one child (patient 6) was diagnosed as type 1. Among 3 children diagnosed as MPS, 2 (66.6%) were Hunter (type 2 MPS) and 1 (33.3%) Hurler (type 1 MPS) i.e. patient 11. Skeletal

survey was done in 2 children with MPS, both of which were abnormal showing osteopenia and characteristic beaking of vertebrae, widening of phalyngeal and carpal bones. Cardiac evaluation done in Gaucher disease children was normal while MPS children had abnormal findings like Thickened valve leaflets, mitral valve prolapse, dilated cardiomyopathy with reduced ejection fraction. MRI brain and spine was done in 8 children with Gauchers all of which were normal. Audiometry was abnormal in all MPS children suggesting hearing loss. In addition to the above-mentioned features, patient 1 had neurological involvement in the form of hypotonia, developmental delay, seizures and oculomotor apraxia. Patient 2 was asymptomatic and diagnosed during family screening. Patient 5 also had neurological involvement in the form of developmental delay with oculomotor apraxia.ERT was initiated in 9 children (7 Gauchers disease children and 2 MPS children) and were monitored every monthly for improvement in symptomatology, growth and haematological parameters. Follow up duration for one of the child with MPS type 2 (patient 12) was only 4 months as ERT was initiated late. There were no significant adverse effects with ERT. 8 of them showed a gradual amelioration in the symptoms by 1 year of regular ERT. One child with GD type 3 (patient 1) could not be followed up beyond 1 year of ERT as they were lost for follow up. Growth parameters significantly improved by 1 year of starting ERT and normalization by 2-3 years. Children whose weight and height were less than third centile increased to above third centile by 1.5 years to 2 years in most of the children. Improvement in weight and height of children with ERT has been depicted in (Figure 2-3).

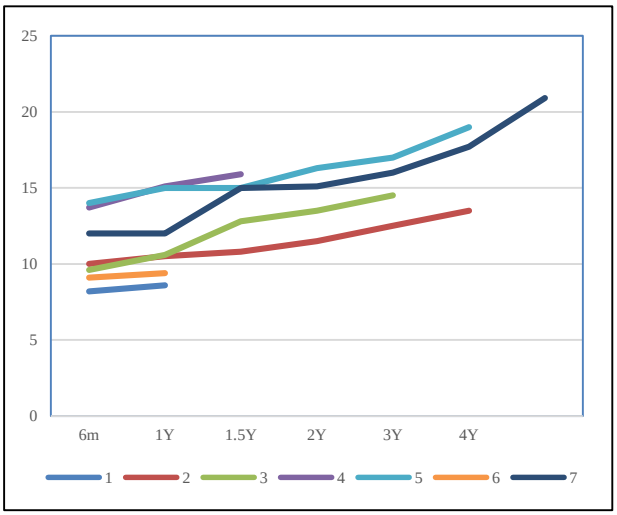

Figure 2: Improvement in weight in children with ERT.

Improvement in hematological parameters in children with GD were noted within 1 year of start of ERT (Figure 4-5). The mean Hb by one year of ERT was 11 g/dl and mean platelet count was 3 lakh/cumm. There was no much improvement in EF in 2 children (patients 11, 12) with MPS who were started with ERT. There was no change in Joint contractures, hearing impairment and ocular changes in children with MPS on ERT. One child succumbed within 1 year of ERT due to severe dengue (patient 7). Flowchart as depicted in (Figure 6) mentions the details of diagnosis, initiation or ERT and follow up of the cases.

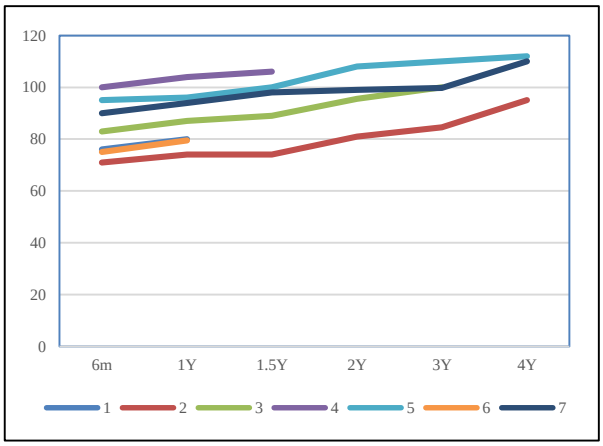

Figure 3: Improvement in height in children with ERT.

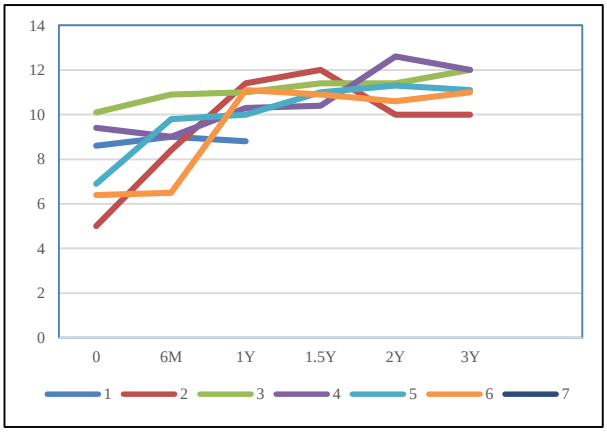

Figure 4: Improvement in Hb levels following start of ERT.

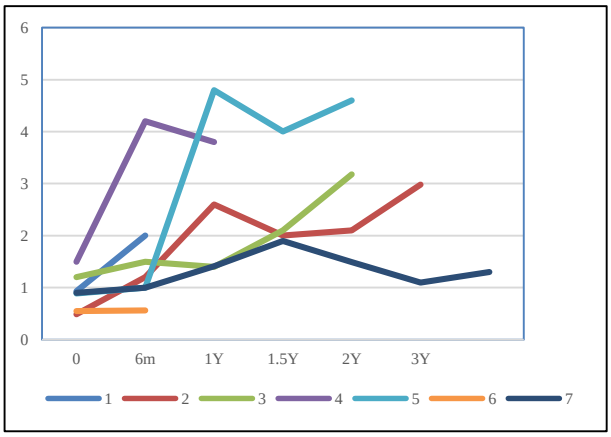

Figure 5: Improvement in platelet count following start of ERT.

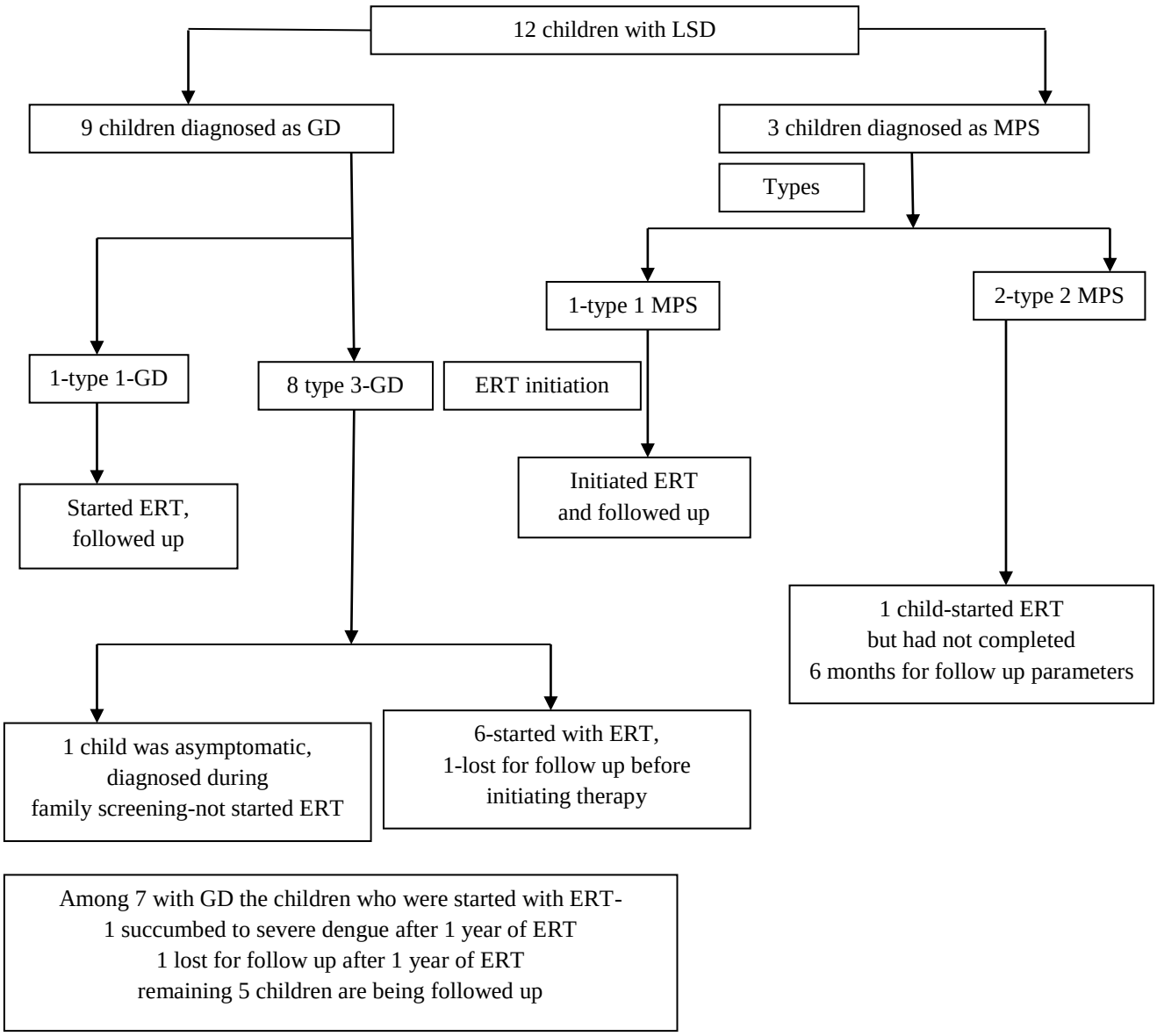

Figure 6: Details of diagnosis, initiation or ERT and follow up of the cases.

DISCUSSION

The age of presentation and clinical manifestations of LSDs depend on the substrates accumulated, the rate and the magnitude of their intracellular accumulation, the percentage of residual functional enzyme and presence of alternative functional pathways.[10,12] In this case series majority of children with LSD were Gauchers disease followed by MPS, which is similar to study by Singh et al.[13] Consanguinity was seen in 41.6% of families of LSD children similar to the study by Verma et al (32.4%).[7] Non-specific symptoms and lack of definite physical findings often lead to mis-diagnosis of LSD. Thus the age at diagnosis is much later as compared to age of presentation. In our study we found the age of onset of presentation ranged from 6 months to 2 years with mean age of 1.2±0.6 years. In contrast, study by Magar et al observed the age of presentation varied from 5months to 11 years.[14] This variation could be due to a larger sample size in their study. Commonest clinical features in our study were growth retardation, visceromegaly, developmental delay similar to studies by Magar et al and Verma et al.[7,14] The enzymatic activity level was less than 15%of the normal reference range. The diagnosis must be kept in mind in any patient with suggestive features. This is especially important as effective enzyme replacement therapy (ERT) is now available for many LSDs and early and timely institution of ERT can prevent/ameliorate the morbidity and mortality of the disease.

CONCLUSION

LSD is one among the common storage disorders, pan-ethnic in inheritance. Clinical manifestations are vivid making the diagnosis challenging. Screening of family members of the affected individual is equally important

for early diagnosis. As there is definitive management available in the form of ERT, early diagnosis and initiating therapy has a good clinical outcome.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Kariyappa P, Manjunath D, Sarode S, Rao US. Clinical spectrum of lysosomal storage disorders in children. Int J Contemp Pediatr 2022;9:757-61.