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CASE REPORT

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Laron Syndrome (LS) – A Rare Case Report

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Abstract

Laron syndrome or growth hormone insensitivity (GHI) is a rare genetic disease inherited in an autosomal recessive manner. A 6 $\frac{1}{2}$ year-old-female child was bought to Paediatric OPD for short stature which was noticed by parents since 3 years of age. Child is first born to second degree consanguineous married couple with no significant birth history, and family history of short stature. Child presented with weight of 10 kg (<3rd centile), height of 90 cm (<3rd centile). Growth Hormone (GH) stimulation test done with tablet Clonidine revealed high GH levels suggestive of partial/total resistance. IGF-1 generation test was done which also showed low IGF-1 levels supporting the diagnosis of GH insensitivity or Laron Syndrome. A high index of clinical suspicion is required for the diagnosis of LS or GH insensitivity in a child with severe short stature having high serum GH levels but low levels of IGF-1 and IGF- BP3.

Keywords: Laron Syndrome; Growth Hormone; Insulin like growth factor1(IGF1)

1 Introduction

Laron syndrome (LS) or growth hormone insensitivity (GHI) is a rare genetic disease inherited in an autosomal recessive manner. It is associated with mutations in the growth hormone receptor (GHR) leading to growth hormone (GH)/insulin like growth factor type 1(IGF1) signaling pathway defect. It was first described by Zvi Laron in 1966.[1] An estimated 350 individuals are affected by this syndrome globally, with a prevalence of 1 to 9 per 1,000,000. LS presents with short stature, delayed dentition, delayed puberty, obesity and hypoglycemia.[2] It is diagnosed through clinical, laboratory and genetic work up.

2 Case History

A 6 $\frac{1}{2}$ year-old-female child was bought to Paediatric OPD for short stature which was noticed by parents since 3 years of age. Parents noticed that she was the shortest in class and did not outgrow her clothes. Child had history of developmental delay till 3 years of age with delay in motor and language milestones. Child is first born to second degree consanguineous married couple with no significant birth history, and family history of short stature. Child presented with weight of 10 kg (<3rd centile), height of 90 cm (<3rd centile) with height Standard Deviation Score of - 4.3 and upper to lower segment ratio of 0.9:1 (Figure 1). Expected mid-parental height was between 50th -75th centile and child's height was below mid parental height target range. The child had prominent forehead and eyes, depressed nasal bridge, and a high-pitched voice. Level 1 investigations (complete blood count, kinetics of iron, urinalysis, serum cortisol, renal and hepatic function tests, HbA1c and serum calcium) were normal. Bone age estimation by Greulich-Pyle method was 4 years (Figure 2). Level 2 investigations (Thyroid profile and Karyotyping (46XX) were also normal. Level 3 investigations (MRI-brain with pituitary focus) were also normal. Growth Hormone (GH) stimulation test done with tablet Clonidine revealed high GH levels suggestive of partial/total resistance with a peak level of 21.3ng/ml with fasting GH being 8.22ng/ml; low Insulin like growth factor 1 (IGF-1) levels (17ng/ml) and low Insulin like growth factor binding protein (IGFBP3) levels. IGF-1 generation test was done which also showed low IGF-1 levels supporting the diagnosis of GHI or LS. Genetic testing was not done due to financial constraints. Due to suspected partial growth hormone (GH) resistance, the child was initiated on high-dose GH therapy (50mcg/kg/day) via subcutaneous injection. Regular follow-up appointments have been scheduled to monitor progress. The parents have been informed and counselled on the potential need for recombinant IGF-1 therapy if the child does not respond adequately to high-dose GH. Encouragingly, the follow-up assessments have shown a positive outcome, with a significant gain in height (4cm in 3 months) with a height velocity of 16cms/year following initiation of growth hormone with no adverse effects.

Fig 1. Child with severe short stature

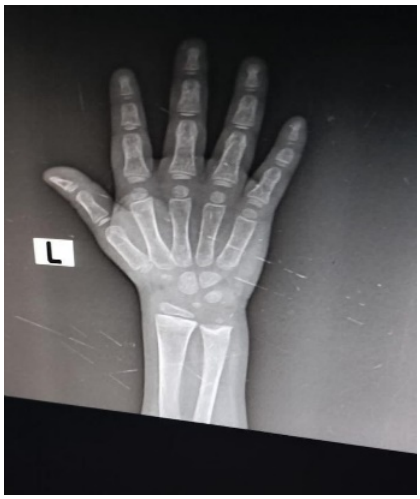

Fig 2. Left hand x-ray wrist

3 Discussion

LS or GHI is a rare genetic disorder characterized by inability to respond to endogenous or exogenous GH. It is associated with mutations in the GHR, leading to GH/ IGF-1 signalling pathway defect. Patients with LS have characteristic biochemical features, such as high (or normal) serum level of GH and low IGF-1 concentration.[2] The diagnostic approach for GHR encompasses the measurement of IGF-1 levels and GH stimulation tests, excluding basal GH levels due to its pulsatile secretion pattern. The interpretation of these tests is as follows: a peak GH level <7 ng/mL confirms complete Growth Hormone Deficiency (GHD), while levels between 7-10 ng/mL suggest partial GHD. Additionally, stimulated GH levels >15 ng/mL accompanied by IGF-1 levels below -2 standard deviations (SDS) indicate GHR.[3] Based on Savage scoring, clinical and laboratory criteria can be considered for diagnosis of LS or GHI.[4] In this child, savage scoring was 5 which fits into diagnosis of LS. The treatment of LS is recombinant IGF-1. Recombinant IGF-1 is not readily available in India, but it can be obtained through importation. However, due to financial constraints, it was not a viable option for the parents, who were informed of its potential benefits. As a result, the child was administered a high dose of GH on a trial basis, with the suspicion of partial GHR. The response to GH therapy will be monitored through regular assessments of serial IGF-1 levels, performed at intervals of every 6 months. The dosage of GH may be

titrated as needed, based on the comprehensive results and clinical evaluations, to achieve optimal therapeutic efficacy and ensure personalized treatment outcomes.[5]

Similar case series was reported by H. Boro et al.[1] in children aged 7 years and 12.5 years. Niladri Das, et al.[2] described LS in two siblings aged 16 years and 9 years. Villela et al.[6] also reported siblings with LS. Rajalakshmi, et al.[7] described 5 children with LS (two girls and three boys) with the mean age group of 5.9 $\pm$ 1.7 years. Phanse-Gupte, et al.[8] in their case series described 9 Indian children with LS. The challenges that are faced in treating such cases are the financial constraints for diagnosis with genetic tests and procurement of recombinant IGF-1 at an affordable cost. This article highlights the need for bodies like the Indian Society for Paediatric and Adolescent Endocrinology to take up the cause of affected families and take necessary steps to ensure that the drug is available for Indian children at an affordable cost.

4 Conclusion

A high index of clinical suspicion is required for the diagnosis of LS or GHI in a child with severe short stature having high serum GH levels but low levels of IGF-1 and IGF-BP3.

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