Case Report

Laron syndrome: a case report

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ABSTRACT

Laron syndrome (LS) is a rare, genetic disorder inherited in an autosomal recessive manner. The disease is caused by mutations of the growth hormone (GH) gene, leading to GH/insulin-like growth factor type 1 (IGF1) signalling pathway defect. A 13-month-old, male child, born of second-degree consanguineous marriage presented with short stature (57 cm, below-3 SD) with normal head size, mild motor developmental delay, micropenis and bone age of 9 months. Basal GH was 28.7 ng/ml (normal 1-13.6 ng/ml). IGF-1 was less than 20 ng/ml (normal up to 170 ng/ml). GH stimulation test done using clonidine revealed increased levels. Post stimulation levels at 30 min, 60 min, 90 min (ng/ml) were 29.3, 37.9, 29.3 respectively, which was suggestive of resistance to GH that is laron dwarfism. Treatment is focused on improving growth and generally includes injections of insulin-like growth factor 1 (IGF-1). This case is being reported for its rarity and early detection.

Keywords: Short stature, Growth hormone, IGF1

INTRODUCTION

Growth hormone (GH) insensitivity can cause laron syndrome (LS), a rare genetic disorder caused by a growth hormone receptor (GHR) variant. The main mode of inheritance is autosomal recessive and the clinical manifestation is in the form of postnatal growth failure. Other features include obesity, small genitalia, and severe hypoglycemia.

Patients present with a typical head configuration, a small face and a protruding forehead, resulting in a saddle nose. Their voices are high-pitched and they are sparse haired. The majority of patients with STAT5B mutations also present severe immune dysregulation and elevated prolactin levels.

The characteristic feature is very low serum levels of insulin like growth factor-1 (IGF-1) inspite of increased GH levels. These children clinically resemble those with isolated GH deficiency. The prevalence of LS is 1-9/10 lakh. We present a rare case of short stature- LS or GH resistance.

CASE REPORT

A 13-month-old male child, born of second-degree consanguinuity, presented with short stature (57 cm, below-3 SD), mild motor developmental delay with gross motor age of 9 months. There was no history of hypoglycemia or any chronic systemic illness. Perinatal period was uneventful with birth weight of 2.5 kg but the birth length was not available. Anthropometry was interpreted using WHO growth charts. Weight-age was 2 months and length corresponded to 3 months. Weight-for-length was between-2 SD to 3 SD. Head circumference was 41.5 cm (below- 3 SD but normal for length with Dine's correction). Upper segment: lower segment ratio was...
1.2:1. The mid-parental height was 160 cm. Examination revealed an active child with dysmorphism in the form of frontal prominence, saddle nose, flat nasal bridge and midfacial hypoplasia (Figure 1). The anterior fontanelle measured 1x1 cm, posterior fontanelle was closed and sparse hair was noted. Primary dentition was delayed with a high-pitched voice. Micropenis was present with stretched penile length being 2 cm. Systemic examination was normal.

![Figure 1: A 13-month-old boy with short stature.](image)

The hematological, renal, liver and thyroid function tests, fasting blood sugar and serum electrolytes, Arterial blood gas analysis, IgA-TTG levels were normal. Bone age was estimated to be 9 months. Thyroid function tests and serum Cortisol were within normal limits. Basal GH level was 28.7 ng/ml (normal 1-13.6 ng/ml). GH stimulation test done using clonidine revealed increased levels. Post stimulation levels at 30 min, 60 min and 90 min (ng/ml) were 29.3, 37.9 and 29.3 respectively. IGF-1 level was less than 20 ng/ml (normal up to 170 ng/ml). Thus, a diagnosis of GH resistance was made. Insulin-like growth factor binding protein-3 (IGF-BP3) and genetic studies could not be done.

**DISCUSSION**

Children with LS are clinically indistinguishable from isolated GH deficiency. GHR is encoded by a single gene on the short arm of chromosome 5 (5p13-p12). A variety of homozygous point mutations in the GHR gene can cause LS. Mutations in the extracellular domain of the GHR interfere with binding of the GH thus resulting in GH insensitivity. In LS, IGF-1 and IGF-BP3 levels are markedly decreased despite normal or elevated serum GH levels and there is lack of response to both endogenous and exogenous GH. Molecular studies can confirm primary GH resistance due to GHRD, STAT5b mutations or IGF-1 gene mutation. Specific molecular defect in GHR gene will confirm the diagnosis but could not be done in our case due to financial constraints.

Clinical presentation is usually with extreme short stature, the length being more than 4 SD below the mean by the age of 1 year. Antenatal and birth history is uncomplicated with the birth weight and length within the normal range. Following infancy, the deficit in length/height often ranges between 4 and 10 height SDS below the median. Skeletal maturation is delayed starting from in utero period and continuing throughout life. Prominent forehead, sunset appearance of eyes, saddle nose and a high-pitched voice, short limbs with small hands and feet (acromicria) with upper segment: lower segment ratio being more than 1, which are the typical features of LS were seen in our case. The delay in motor development in infancy was also seen in our patient. In LS, there is delayed puberty (by 3-7 years) without the pubertal growth spurt; but, full sexual development with normal fertility is seen in both genders. Complications of GH insensitivity including seizures due to hypoglycemia and fractures secondary to osteopenia were not present in our case.

The available specific treatment is replacement therapy with (recombinant human IGF-1) rhIGF-1, given subcutaneously (75 mg/kg/day). Adverse effects include retention of water, dys-electrolytemia and calciuria. Owing to its high cost and difficult availability, not everyone can afford the therapy as in case of our child. The replacement must be started early and although IGF-1 replacement can improve growth velocity, full skeletal maturity is not achieved in complete absence of GHR. A multi-disciplinary management is necessary. A high protein and low-fat diet may augment response to IGF-1 and reduce the development of obesity. The prognosis regarding final height in males is 116-142 cm and for females is 108-136 cm. Despite the appearance of premature signs of aging such as thin and wrinkled skin, patients have a long life. These patients are protected from malignancy but, due to reduced IGF-1 levels, there is increase in cardiovascular aging.

**CONCLUSION**

A high index of suspicion is required for the diagnosis of GH insensitivity. Currently, the only treatment is daily administration of insulin-like growth-factor-1 from early childhood.

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**REFERENCES**
