

## Case Report

# An unusual cause of short stature-Laron syndrome

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**Received:** 08 February 2016

**Accepted:** 15 March 2016

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### ABSTRACT

Laron syndrome is an autosomal recessive disorder characterized by an insensitivity to growth hormone (GH), caused by a variant of the growth hormone receptor. 15 month old, male child, born of third degree consanguineous marriage presented with short stature (57 cm, below the 3<sup>rd</sup> centile) with normal head size, mild developmental delay, undescended testis and micropenis. Normal thyroid profile, serum cortisol was normal and bone age of 1 year. MRI brain showed small sized pituitary. Random growth hormone was 21.4 ng/ml (normal more than 10 ng/ml), IGF-1 level less than 25 (normal: upto 70 micro/L), IGF-1 generation test with pre-test IGF-1 levels less than 25 and post-test less than 25 which was suggestive of resistance to growth hormone or growth hormone insensitivity that is Laron dwarfism. Parents were counselled about the possible outcome and prognosis. In conclusion for the diagnosis of growth hormone insensitivity a high index of suspicion and the important functional test is insulin-like growth factor 1 generation test. Currently only treatment is daily administration of insulin-like growth factor-1 from early childhood.

**Keywords:** Growth hormone, Growth hormone receptor, Growth hormone receptor insensitivity, Laron syndrome

### INTRODUCTION

Laron syndrome is a rare genetic disorder characterized by an insensitivity to growth hormone (GH), caused by a variant of the growth hormone receptor (GHR).<sup>1</sup> The production of growth hormone is normal but there is inability to produce insulin like growth factor-1 (IGF-1); leading to short stature.<sup>2,3</sup> The overall prevalence of Laron syndrome is 1-9/1000000.<sup>4</sup> We present a rare case of Laron syndrome or growth hormone insensitivity (GHIS) as a cause of short stature.

### CASE REPORT

A 15 month old, male child, born of third degree consanguineous marriage, presented with short stature (57 cm, below the 3<sup>rd</sup> centile or -3 SD), mild developmental delay with gross motor age of 8 months and fine motor age of 11 months (Figure 1). There was no history of hypoglycemia, excessive sleepiness or recurrent respiratory tract infections or any other chronic

systemic illness. Perinatal period was uneventful. Weightage was 6 months. Height (Length) age corresponded to 6 months. Weight for length was between median and - 1 SD. Head circumference was 45 cms (5<sup>th</sup> to 50<sup>th</sup> centile). Upper segment: Lower segment ratio was 1.6:1 (6 months). The mid parental height was 160 cms. The skull was dolichocephalic in shape with anterior fontanelle measured 3.5×4 cms, with open frontal and metopic sutures and sparse hairs. The patient had predominant frontal prominence, saddle shaped nose and low set ears. Delayed primary dentition was present in oral cavity with a high pitched voice. Genital examination showed micropenis with stretched penile length being 1.8 cms. Bilateral testes were palpable in inguinal canal. Short hand and limbs were noted in relation to head size. Systemic examination was normal. Liver and renal functions were normal. Fasting blood sugar, serum electrolytes and blood PH was normal. Bone age of 1 year. The Free T3 level was 2.6 (2.8-11.8 pmol/L), Free T4 was 1.8 (0.8-2.2ng/dl) and TSH: 5.0 (0.5-5.5 mIU/L). Serum cortisol was 14 (7-28 µg/dL).

MRI brain revealed small sized pituitary. Random growth hormone was 21.4 ng/ml (normal more than 10ng/ml). IGF-1 level less than 25 micro/L (normal upto 70 micro/L), IGF-1 binding protein levels were normal. IGF-1 generation test was performed with pre-test IGF-1 levels less than 25 micro/L and post-test less than 25 micro/L which was suggestive of resistance to growth hormone or “growth hormone insensitivity” that is Laron dwarfism. Further molecular studies as well as treatment with recombinant human insulin like growth factor - 1(rhIGF-I) were advised. Parents were counseled about the possible outcome and prognosis.



**Figure 1: A 15 month old male child with short stature.**

## DISCUSSION

Laron syndrome, an autosomal recessive disease, is primarily associated with mutations in the growth hormone receptor gene.<sup>1</sup> GH binds to GHR leading to production of IGF-1 which acts on end organs to produce biologic effects such as linear growth. GH can bind either defectively to the ectodomain of GHR or there is diminished effectiveness in dimerization of the receptor after the hormone occupies receptor leading to block in signalling cascade which finally results in decreased IGF-1 and ultimately holds up the mitogenic effects of GH.<sup>2-6</sup> Hence in Laron syndrome though the growth hormone levels are high IGF-1 levels are remarkably low.

Our child with normal birth length and weight, proportionate short stature, severe growth failure with chronological age less than bone age suggested an endocrine cause. The dysmorphic faces and normal levels of thyroid and serum cortisol levels led to possibility of growth hormone deficiency and ruled out panhypopituitarism. The high levels of resting GH with low levels IGF-1 levels suggestive of abnormal GH- IGF-1 axis. Hence standard IGF-1 generation test (IGFGT) which is most commonly used was done. Though the sensitivity and specificity of either standard, 4-day or 7-day low- or high-dose IGFGT in identifying severe GHIS is not high enough in children with dwarfism, it aids in diagnosis of severe GHIS.<sup>7</sup> The result of IGFGT was high levels of GH and low levels of IGF-1 despite stimulation thus indicating GHIS or Laron syndrome.<sup>7</sup>

Post receptor forms of Growth hormone insensitivity like mutation in gene for signal transducer and activator of transcription 5b (STAT5b) is unlikely because the child did not have chronic pulmonary infections. Whereas the child had normal prenatal growth but impaired postnatal growth with normal head circumference makes IGF-1 gene or IGF-1 receptor gene abnormalities improbable.<sup>6,8</sup>

Molecular studies will confirm primary GH resistance with growth failure due to GHRD, STAT5b mutations or IGF-I gene mutation.<sup>6-8</sup> Demonstration of specific molecular defect in GHR gene gives a final diagnosis which may not always be feasible and could not be done in our case due to financial constraints.<sup>9</sup>

Specific treatment available is rhIGF-1 is given subcutaneously at a dose of 75 mg/kg/day.<sup>4</sup> Not all patients can afford the therapy owing to its high cost as in case of our child.<sup>2,3</sup> IGF-1 replacement can improve growth velocity but in complete absence of GHR full skeletal maturity is not achieved.<sup>3,10</sup> The replacement therapy must be started at a young age.<sup>3</sup> Adverse effects can be retention of water and electrolyte also calciuria.<sup>4</sup>

A multi-disciplinary approach with dentist consultation for delayed teeth eruption, dietitian to advise a high-protein and low-fat diet that seems to augment response to IGF-I and thereby decrease the development of obesity with rhIGF-I treatment.

The prognosis with respect to final height in males is 116 to 142 cms and Females is 108 to 136 cms.<sup>5</sup> Despite the appearance of premature aging signs, like thin and wrinkled skin, patients with LS have a long life.<sup>4,11</sup> There is delay in attainment of puberty by 3-7 year and does not display the typical pubertal growth spurt. Sexual function and fertility among both sexes are normal.<sup>4,9,12</sup> These patients are protected from malignancy.<sup>11,13</sup> But there is increase in cardiovascular aging which is due to low levels of IGF-1.<sup>14</sup>

Complications of GHI include seizures due to low blood sugar and bone fractures because of osteopenia were not present in our case.<sup>5,12,14</sup>

## CONCLUSION

For the diagnosis of Laron syndrome or growth hormone insensitivity the clinical features with high index of suspicion teamed with important functional test, insulin-like growth factor 1 generation test are imperative. Currently only treatment is daily administration of recombinant insulin-like growth factor-1 from early childhood.<sup>3,5,12</sup>

*Funding: No funding sources*

*Conflict of interest: None declared*

*Ethical approval: Not Required*

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**Cite this article as:** Somale AK, Ahmed M. An unusual cause of short stature-Laron syndrome. *Int J Adv Med* 2016;3:435-7.