

CASE REPORT

Laron Syndrome A Case Report

Javaid Ahmad Bhat, M.D.¹, Moomin Hussain Bhat M.D.², Hilal Bhat, M.D.³, Mona Sood M.D.⁴, Shariq Rashid Masoodi D.M.⁵

^{1,2,3,4}Senior Resident Department of Endocrinology, ⁵Prof. Department of Endocrinology SKIMS SOURA

ABSTRACT

Background : Laron & colleagues (1966) reported a rare genetic disorder in Israeli Jewish siblings which was characterized by insensitivity to growth hormone due to abnormality in growth hormone receptor or post receptor signaling pathway.

Case Report: We hereby report a case of a 5 year old female child who presented to us with features similar to Laron syndrome. The diagnosis was made & confirmed by various Lab. investigations like low IGF-I levels and managed accordingly. JMS 2017; 20 (2):104-106

Key words: Laron syndrome, IGF-I, GHR, IGHD

INTRODUCTION

Laron syndrome is a rare genetic disorder characterized by an insensitivity to growth hormone (GH), caused by abnormality in the growth hormone receptor (GHR) or post receptor signalling pathway¹. It is characterized by postnatal growth failure and very low serum levels of insulin like growth factor 1 (IGF-I) despite increased secretion of growth hormone (GH). It has an autosomal recessive inheritance and is clinically indistinguishable from isolated GH deficiency (IGHD).

It was first reported by Laron and colleagues in 1966 in 3 Israeli Jewish siblings with hypoglycaemia and clinical phenotype of GHD². Since then it has been reported from different countries of the world including Indian subcontinent³⁻⁶. We report a five year old girl who presented with short stature and was diagnosed to have Laron syndrome.

CASE REPORT

5 year old female child, product of non-consanguineous marriage, third in birth order born full term normal delivery

Correspondence

Dr. Javaid Ahmad Bhat M.D.

Senior Resident, Deptt of Endocrinology SKIMS Soura.

E-mail: Javaidasool711@gmail.com

with unremarkable perinatal events and normal developmental milestones presented with complaints of failure to grow. There was no history of hypoglycaemia, umbilical hernia, prolonged jaundice, excessive sleepiness or recurrent respiratory tract infections or any other chronic systemic illness.



Fig 1. Typical facial appearance of a 5 year old boy with Laron syndrome. (Note the sparse hair, protruding forehead, saddle nose, and small chin.)

Examination revealed alert playful child with sparse hair, normal hair texture and skin. She had craniofacial disproportion with midfacial hypoplasia and subtle dysmorphism with frontal prominence, saddle nose, flat nasal bridge, high arched palate and a bluish sclera. (Fig. 1)

She weighed 7.5kg (SDS = -5.21) and her length was 71.3cm (SDS = -8.14), both of which were well below the third centile. Her occipito-frontal circumference (OFC) was 46.5cm which was just below 3rd percentile. Her upper segment: lower segment ratio was 1.37 and body mass index was 14.26kg/m². Her bone age was 3 years at the chronological age of 5 years. There were no signs of rickets (wrist widening, genu valgum, rachitic beads, Harrison's sulcus) or Turner phenotype and her physical examination was unremarkable.

Her basic haematological, renal and liver function tests were normal as were her ammonium chloride test, celiac profile, and serum calcium level. Skeletal survey excluded a skeletal dysplasia. Her hormonal parameters are also given in Table 1. Based on the clinical profile and biochemical evidence of high levels of GH in the presence of low levels of IGF 1, diagnosis of growth hormone resistance was made but insulin-like growth factor binding protein-3 (IGF-BP3) or genetic studies could not be done.

Table 1: Hormone Profile of the Patient

T3	0.8 ng/ml (0.9 to 2.5)
T4	7.2 µg/dl (5.5 to 13.5)
TSH	3.44 µIU/ml (0.5 to 6.5)
Cortisol	18.4mcg/dl (12 – 25)
GH (Basal)	>40ng/ml, >40ng/ml, >40ng/ml
IGF	12.7ng/ml (58 – 180 ng/ml).

DISCUSSION

Laron syndrome is a familial disorder, with an autosomal recessive form of inheritance¹. The underlying metabolic defect is a lack of responsiveness to GH. Patients with Laron syndrome typically have low serum levels of IGF-I, despite normal or elevated levels of serum GH. Exogenous GH does not accelerate their growth or stimulate serum levels of IGF-I or insulin like growth factor binding protein-3 (IGFBP-3).⁷ Cellular unresponsiveness to GH was demonstrated in vitro by the failure of GH to stimulate erythroid progenitor cells from the peripheral blood of patients. First described in 1966 by Laron and colleagues who described 3 siblings with hypoglycemia and other clinical or lab signs of Growth hormone deficiency but with abnormally high levels of growth hormone. Since then it has been reported from different countries of the world. Number of cases have been documented and reported from valley of Kashmir^{5,6,8,9}. In 1995 two sisters were reported to have familial growth

hormone insensitivity syndrome⁵. In a retrospective analysis of 193 subjects 4.1% of subjects were reported to have Laron syndrome⁸. An overall prevalence of 1-9/1000000 has been described. (10) Ethnic background is known for approximately 90% of the patients reported to have Laron syndrome.

Laron syndrome is an inherited disorder consisting of a genetic defect in the GHR transmitted in an autosomal recessive fashion. Consanguinity has been a major contributor to its development in described populations. The diversity of mutations in the GHR gene that cause Laron syndrome is quite striking. Over 70 different GHR mutations (deletions, splice, nonsense, missense or frameshift mutations) have been reported, localized within exons and introns. Changes in the extracellular domain of the receptor are much more frequent than those in transmembrane or cytoplasmic domains¹¹. Most defects are in the extracellular hormone-binding domain, resulting in absence of circulating serum GH binding protein (GHBP)¹². Reports have also been made of mutations affecting the transmembrane and cytoplasmic domains of the GHR.

These children have features of GH deficiency so many of them are short at birth. However, apparent short stature is usually noted in infancy and childhood with limb growth being more severely affected. Majority of the patients are born with normal birth weight and birth length. There is gross motor delay (because of hypomuscularity) and decreased intelligence as described in Israeli cohort while normal intelligence in others. Craniofacial characteristics include sparse hair, frontal bossing, hypoplastic nasal bridge, shallow orbits, craniofacial disproportion because of decreased vertical dimension of face, blue sclera, delayed dental development and high-pitched voice. Other features include hip dysplasia - avascular necrosis of the femoral head, limited elbow extensibility, underdeveloped musculature, osteopenia and thin prematurely aged skin. There is markedly decreased ratio of lean body mass to fat mass seen in these patients. Male children have micropenis in childhood with normal genital growth during adolescence. Puberty is delayed, more in boys as compared to girls, with absence of pubertal growth spurt in both sexes. Both genders reach full sexual development and in early adulthood, there are no difficulties in reproduction¹². Like GH-deficient children, these children are also predisposed to suffer from hypoglycemia in the newborn period as well as in childhood and adulthood¹³.

Due to a state of GH resistance, children with the Laron syndrome have high levels of circulating GH with very low, often undetectable concentrations of serum IGF-1 concentrations that do not rise on administration of exogenous human growth hormone (hGH).

Treatment currently available for patients with classic growth hormone (GH) insufficiency (GHI), as in Laron syndrome (LS), is recombinant human insulin like growth factor-1 (rhIGF-I) in a dose of 75 mg/kg/day. IGF-I improves growth rate (8cm in the first year and 45 cm in the following years) and normalizes the biochemical abnormalities. The best response is seen in very young patients and treatment should therefore be started as early as possible¹⁴. Intermittent therapy is shown to be equally cost effective as daily treatment. There is an inverse relationship between age at start of rhIGF-I treatment and total height gain in patients treated for more than 4 years¹⁴. For those with secondary forms of GHI, the underlying cause (eg, malnutrition, liver disease) should be identified and treated appropriately. Infants with Laron syndrome may require more frequent feedings to avoid hypoglycemia. Periodic blood sugar monitoring is necessary for some patients with Laron syndrome and for all patients with Laron syndrome who are receiving rhIGF-I therapy.

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.

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.

REFERENCES

- Guleria S, Sharma J, Kaushik SL. Laron syndrome. *J Postgrad Med*. 2014 Sep; 60(3):322-3.
- Laron Z, Pertzelan A, Mannheimer S. Genetic pituitary dwarfism with high serum concentration of growth hormone--a new inborn error of metabolism? *Isr J Med Sci*. 1966 Apr;2(2):152-5.
- Laron Z. Growth hormone insensitivity (Laron syndrome). *Rev Endocr Metab Disord*. 2002 Dec;3(4):347-55.
- Chakraborty PP, Basu AK, Mandal SK, Bandyopadhyay D. Laron's syndrome in two siblings. *Indian J Pediatr*. 2007 Sep;74(9):870-1.
- Zargar AH, Laway BA, Masoodi SR, Salahuddin M, Siddiqui MA. Familial growth hormone insensitivity syndrome. *Indian J Pediatr*. 1995 Apr;62(2):244-7.
- Zargar AH. Growth hormone resistance. *Indian Pediatr*. 1990 Nov;27(11):1213-4.
- Merimee TJ, Hall J, Rabinowitz D, McKusick VA, Rimoin DL. An unusual variety of endocrine dwarfism: subresponsiveness to growth hormone in a sexually mature dwarf. *Lancet Lond Engl*. 1968 Jul 27;2(7561):191-3.
- Zargar AH, Laway BA, Masoodi SR, Wani AI, Salahuddin M. An aetiological profile of short stature in the Indian subcontinent. *J Paediatr Child Health*. 1998 Dec;34(6):571-6.
- Zargar AH, Masoodi SR, Laway BA, Salahuddin M. Sporadic growth hormone insensitivity syndrome. *Indian Pediatr*. 1995 Mar;32(3):369-70.
- Phanse-Gupte SR, Khadilkar VV, Khadilkar AV. Clinical features and endocrine profile of Laron syndrome in Indian children. *Indian J Endocrinol Metab*. 2014 Nov;18(6):863-7.
- Janecka A, Kołodziej-Rzepa M, Biesaga B. Clinical and Molecular Features of Laron Syndrome, A Genetic Disorder Protecting from Cancer. *In Vivo*. 2016 Jul 1;30(4):375-81.
- Laron Z. Laron syndrome (primary growth hormone resistance or insensitivity): the personal experience 1958-2003. *J Clin Endocrinol Metab*. 2004 Mar;89(3):1031-44.
- Laron Z, Lilos P, Klinger B. Growth curves for Laron syndrome. *Arch Dis Child*. 1993 Jun;68(6):768-70.
- Ranke MB, Savage MO, Chatelain PG, Preece MA, Rosenfeld RG, Wilton P. Long-term treatment of growth hormone insensitivity syndrome with IGF-I. Results of the European Multicentre Study. The Working Group on Growth Hormone Insensitivity Syndromes. *Horm Res*. 1999;51(3):128-34.