Journal of the ASEAN Federation of Endocrine Societies

CASE SERIES

Laron Syndrome: A Tale of Two Siblings

Niladri Das, Silima Subhasnigdha Tarenia, Souvik Saha, Prashant Manohar Gaikwad, Deep Kamlesh Hathi, Soumik Goswami, Arjun Baidya, Nilanjan Sengupta

Nilratan Sircar Medical College and Hospital, Kolkata, India

Abstract

Primary growth hormone (GH) resistance or growth hormone insensitivity syndrome, also called Laron syndrome, is a hereditary disease caused by mutations in the GH receptor or in the post-receptor signaling pathway. This disorder is characterized by postnatal growth failure resembling GH deficiency. Differentiating the two conditions is necessary. We present the cases of two siblings, a 16-year-old female and a 9-year-old male, born from a consanguineous union. Both had normal birth weights with subsequent severe short stature and delayed teeth eruption, with no features suggestive of any systemic illness. Serum insulin-like growth factor 1 (IGF1) and insulin-like growth factor binding protein 3 (IGFBP3) were both low. Suspecting GH deficiency, provocative testing with clonidine was done revealing peak growth hormone >40 ng/mL in both patients. In view of low IGF1 and IGFBP3 and high GH on stimulation, IGF1 generation test was done for both siblings, with values supporting the diagnosis of GH insensitivity or Laron syndrome.

Key words: growth hormone insensitivity, Laron syndrome, short stature

INTRODUCTION

Laron syndrome, also known as growth hormone insensitivity, is an autosomal recessive disorder. It is caused by mutations, most commonly deletions, in the GH receptor gene or in the post-receptor signaling pathway, inducing low levels of IGF1.[1,2] Zvi Laron, an Israeli physician, first described this syndrome in 1966.[3] An estimated 350 individuals are affected by this syndrome globally, with a prevalence of 1 to 9 per 1,000,000. There are two large cohorts of patients with this syndrome living in Israel and Ecuador.[4]

Laron syndrome presents short stature, delayed dentition, delayed puberty, obesity and hypoglycemia. Genetic analysis is not always possible, particularly in resource-limited settings. As the disease resembles GH deficiency, it is imperative to differentiate the two for appropriate management. We present two cases of GH insensitivity from eastern India. Informed consent was obtained from their legal guardian (father).

CASE 1

A 16-year-old female born from a consanguineous marriage in Bengal, India, presented with severe short stature with unremarkable antenatal and perinatal history. Her birth weight was 2.8 kg. Birth length could not be recalled. At two to three years of age, her parents noticed no gain in height as compared to peers. She had a history of delayed tooth eruption. There was no family history of short stature or any personal history of systemic illness.

Examination revealed a height of 120.5 cm (<3rd centile) with height standard deviation score (SDS) -5.84 and body weight of 27.10 kg (<3rd centile) with weight SDS -2.41, according to the World Health Organization (WHO) 2006 and Indian Academy of Pediatrics (IAP) 2015 combined chart for girls. Mid-parental height was 141 cm. Upper-to-lower body segment ratio (US:LS) was 0.9. The patient had a prominent forehead and depressed nasal bridge indicative of facial dysmorphism, small hands and feet, crowded teeth with caries, a high-pitched voice, and thin, but not easily plucked scalp hair (Figure 1). Sexual Maturity Rating (SMR) was B4P2A+. No Turner's stigmata were present. Bone age was determined to be 13 years.

Complete hemogram, kidney function and liver function tests were normal. Hormonal assays revealed normal thyroid stimulating hormone (TSH) [1.6 mIU/mL, reference value (RV) 0.5 to 5 mIU/mL], free thyroxine (FT4) (0.9 ng/dL, RV 0.8 to 1.8 ng/dL), follicle stimulating hormone (FSH) (9.0 mIU/mL, RV 2 to 12 mIU/mL, follicular phase), luteinizing hormone (LH) (6.3 mIU/mlL, RV 1.0 to 18.0 mIU/mL, follicular phase) and cortisol (14 μg/dL, RV 5 to 25 μg/dL). Low basal IGF1 (34 ng/mL, RV 98 to 180 ng/mL)

eISSN 2308-118x (Online)
Printed in the Philippines

Received: March 14, 2023. Accepted: May 16, 2023.
Published online first: September 18, 2023.
https://doi.org/10.15605/jafes.038.02.22

Corresponding author: Souvik Saha, MD
Research scholar, Nilratan Sircar Medical College and Hospital
138, Acharya Jagadish Chandra Bose Road, Sealdah, Raja Bazar, Kolkata, West Bengal 700014, India
Telefax No. of Institution: +91 33 2286 0033
E-mail: souvik.saha14@gmail.com
ORCiD: https://orcid.org/0000-0002-2640-7533

and IGFBP3 (504 ng/mL, RV 2,600 to 9,000 ng/mL) were also found.[5] Growth hormone stimulation test with clonidine revealed peak GH values more than 40 ng/mL (Table 1). Magnetic resonance imaging (MRI) of a the pituitary showed slight enlargement of the pituitary gland measuring 9 mm × 13.8 mm × 9.5 mm. (Figure 2). Ophthalmological evaluation revealed no blurring of vision, visual field defects or any other abnormalities.

In view of low IGF1 and IGFBP3 and high GH on stimulation, IGF1 generation test was done by injecting recombinant human growth hormone (hGH) at 33 μg/kg/day for 4 consecutive days. IGF1 level measured 12 hours after the last dose of hGH remained low (20 ng/mL), thus supporting the diagnosis of GH insensitivity or Laron syndrome. On Savage scoring, she fulfilled five out of seven parameters.[6] Genetic analysis was not performed due to financial limitations.

CASE 2

A 9-year-old male sibling of the female described in Case 1, born from the same parents, presented with severe short stature with unremarkable antenatal and perinatal history.

Figure 1. The patients **(A)** were a 16-year-old female (left, Case 1) and a 9-year old male (right, Case 2). Their heights were 120.5 cm (<3rd centile) **(B)** and 99.2 cm (<3rd centile) **(C)**, respectively, based on the WHO 2006 and IAP 2015 combined chart.

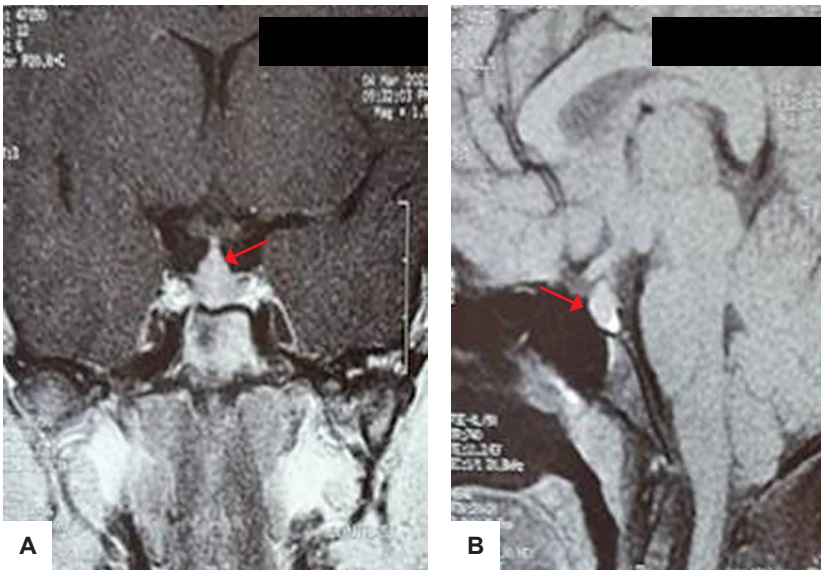

Figure 2. Magnetic resonance images of Case 1 showing an enlarged pituitary gland on coronal **(A)** and sagittal **(B)** views measuring 9 mm x 13.8 mm x 9.5 mm *(red arrow)*.

His birth weight was 3 kg. Birth length could not be recalled. At two to three years of his age, his parents noticed no height gain as compared to his peers. He also had a history of delayed tooth eruption.

Examination revealed a height of 99.2 cm (<3rd centile) with height SDS -5.04 and body weight of 14.20 kg (<3rd centile) with weight SDS -2.04, according to the WHO 2006 and IAP 2015 combined chart for boys. Mid-parental height was 154.5 cm. US: LS was 0.98. The patient had a prominent forehead and depressed nasal bridge suggestive of facial dysmorphism, small hands and feet, crowded teeth with caries, a high-pitched voice, and thin but not easily plucked scalp hair. SMR was prepubertal, with a stretched penile length of 3.4 cm indicative of micropenis. Bone age was determined to be at 3 years.

Complete hemogram, liver and kidney function tests were normal. Hormonal assays showed normal levels of TSH (2.9 mIU/mL, RV 0.5 to 5 mIU/mL), FT4 (1.2 ng/dL, RV 0.8 to 1.8 ng/dL), FSH (0.3 mIU/mL, RV 1 to 13 mIU/mL), LH (0.3 mIU/mL, RV <0.3 mIU/mL, prepubertal) and cortisol (12 μg/dL, 5 to 25 μg/dL). Basal IGF1 (15 ng/dL, RV 98 to 180 ng/mL) and IGFBP3 (398 ng/mL, RV 2,600 to 9,000 ng/mL) were both low.[5] Growth hormone stimulation test with clonidine revealed peak GH values of more than 40 ng/mL (Table 1). MRI of the pituitary gland was normal. An ophthalmological evaluation revealed no blurring of vision, visual field defects or any other abnormalities.

In view of low IGF1 and IGFBP3 and high GH on stimulation, the IGF1 generation test was done by injecting hGH at 33 μg/kg/day for 4 consecutive days. IGF1 level measured 12 hours after the last dose of hGH remained low (12 ng/mL), supporting the diagnosis of GH insensitivity or Laron syndrome. He fulfilled 5 out of 7 parameters on Savage scoring.[6] Genetic analysis was not performed due to financial limitations.

DISCUSSION

Laron syndrome or growth hormone insensitivity is a rare disorder. It is characterized by postnatal moderate to severe growth retardation in patients with normal birth weight and length. The height of patients varies between -4 to -10 SDS.[4] Final adult height in untreated patients ranges between 116 to 142 cm in males and 108 to 136 cm in females.[4] Features include prominent forehead; saddle nose; midfacial hypoplasia; thin, sparse and easily plucked hair; delayed dentition with overcrowding; high-pitched voice; micropenis; hypogonadism; hypoglycemia; obesity despite poor appetite; and a normal pituitary gland on imaging. Prior reports from India showed children with Laron syndrome may not be overweight.[7] None of our patients were obese or hypoglycemic. One of our patients is prepubertal with micropenis, while the other has delayed puberty. A comparative table between typical Laron syndrome and our cases is given in Table 2. The pituitary gland appears normal or hypoplastic on MRI in Laron syndrome, in contrast to the enlarged gland found in Case 1.[8] Although pituitary enlargement in Laron syndrome has not been reported in literature, this finding may be explained by pubertal enlargement or due to loss of feedback control of IGF1 to somatotrophs. The latter is similar to the feedback pathophysiology of adenoma in long-standing untreated primary hypothyroidism. This may be proven either by histopathology or by a decrease in size of the pituitary gland by IGF1 treatment. Due to GH resistance, patients with Laron syndrome have elevated GH but very low serum IGF1 that does not rise on exogenous administration of hGH.[9] These findings were also seen in our patients.

There are at least 10 different protocols of IGF1 generation tests for the diagnosis of GH insensitivity.[10] Some protocols use lower- (25 μg/kg/day) or high-dose (50 μg/kg/day) hGH over a period of four to seven days. The standard protocol uses recombinant GH at a dose of 33 μg/kg/day for seven days. Serum IGF1 is measured at baseline and 12 hours after the last dose of GH injection. Here, we used GH at a dose of 33 μg/kg/day for 4 consecutive days.

The only option for medical therapy in patients with Laron syndrome is recombinant human IGF1. The dose varies between 80 to 120 μg/kg twice daily administered subcutaneously.[11] Side effects include overgrowth of specific tissues, such as lymphatics, facial bones and kidneys; excessive increase of fat mass; hypoglycemia; hypokalemia;

Table 1. Results of growth hormone stimulation test with clonidine

Timing (min)	Growth hormone (ng/mL)	
	Case 1	Case 2
0	2.8	7.05
30	11.7	22.70
60	>40	>40
90	>40	>40
120	28.6	22.20

Table 2. Comparison of features of typical Laron syndrome and reported cases

Features	Typical Laron syndrome	Case 1	Case 2
Consanguinity	Usually present	Present	Present
Birth weight	Diminished or normal	Normal	Normal
Hypoglycemia	Usually present	Absent	Absent
Micropenis	Present	NA	Present
Height	Severely retarded	Severely retarded	Severely retarded
Bone age	Retarded	Retarded	Retarded
Dentition	Delayed	Delayed	Delayed
Midfacial hypoplasia	Present	Present	Present
Prominent forehead	Present	Present	Present
High-pitched voice	Present	Present	Present
IGF1, IGFBP3	Low	Low	Low
Stimulated GH levels	High	High	High
Pituitary imaging	Normal	Enlarged	Normal

water retention; and hypercalciuria. Non-availability of IGF-1 in India is a barrier to the treatment of children with Laron syndrome. However, even for untreated patients, normal life expectancy has been recorded up to 70 years in studies by Laron as well as by Rosenbloom in Ecuador.[4,12]

CONCLUSION

We have described two siblings with Laron syndrome who were referred for evaluation of short stature. To diagnose Laron syndrome, a high index of clinical suspicion is required in evaluating children with short stature with features of GH deficiency, high GH and low IGF1. Because recombinant IGF1 is not readily available, many patients are lost to follow up.

LEARNING POINTS

Laron syndrome is a rare but important cause of severe short stature, having clinical features similar to GH deficiency.

A high index of clinical suspicion is required for the diagnosis of Laron syndrome or growth hormone insensitivity in a child with severe short stature having high GH but low IGF1 and IGFBP3.

In Laron syndrome, the pituitary gland may be enlarged due to feedback stimulation secondary to GH resistance.

Ethical Considerations
Parental consent was obtained before submission of the manuscript.

Statement of Authorship
The authors certified fulfillment of ICMJE authorship criteria.

CRediT Author Statement
ND: Conceptualization, Methodology, Investigation, Resources, Data Curation, Writing – original draft preparation, Writing – review and editing, Visualization; **SST:** Conceptualization, Methodology, Resources, Writing – original draft preparation, Writing – review and editing, Visualization; **SS:** Methodology, Data Curation, Writing – original draft preparation, Writing – review and editing, Visualization; **PMG:** Conceptualization, Investigation, Writing – review and editing, Supervision, Project administration; **DKH:** Writing – review and editing; **SG:** Supervision, Project administration; **AB:** Resources, Supervision, Project administration; **NS:** Supervision, Project administration.

Author Disclosure
The authors declared no conflict of interest.

Funding Source
None.

References
1. Eshet R, Laron Z, Pertzelan A, Arnon R, Dintzman M. Defect of human growth hormone receptors in the liver of two patients with Laron-type dwarfism. Isr J Med Sci. 1984;20(1):8-11. PMID: 6321400.
2. Berg MA, Argente J, Chernausek S, et al. Diverse growth hormone receptor gene mutations in Laron syndrome. Am J Hum Genet. 1993;52(5):998-1005. PMID: 8488849. PMCID: PMC1682057.
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;2(2):152-5. PMID: 5916640.
4. Laron Z. Laron syndrome (primary growth hormone resistance or insensitivity): The personal experience 1958-2003. J Clin Endocrinol Metab. 2004;89(3):1031-44. PMID: 15001582. https://doi.org/10.1210/jc.2003-031033.
5. Dehiya RK, Bhartiya D, Kapadia C, Desai MP. Insulin like growth factor-I, insulin like growth factor binding protein-3 and acid-labile subunit levels in healthy children and adolescents residing in Mumbai suburbs. Indian Pediatr. 2000;37(9): 990-7. PMID: 10992336.
6. Savage MO, Blum WF, Ranke MB, et al. Clinical features and endocrine status in patients with growth hormone insensitivity (Laron syndrome). J Clin Endocrinol Metab. 1993;77(6):1465-71. PMID: 7505286. https://doi.org/10.1210/jcem.77.6.7505286.
7. Chakraborty PP, Basu AK, Mandal SK, Dipanjan B. Laron's syndrome in two siblings. Indian J Pediatr. 2007;74:870-1. PMID: 117901683. https://doi.org/10.1007/s12098-007-0159-y.
8. Kornreich L, Horev G, Schwarz M, Karmazyn B, Laron Z. Pituitary size in patients with Laron Syndrome (primary GH insensitivity). Eur J Endocrinol. 2003;148(3):339-41. PMID: 12611615. https://doi.org/10.1530/eje.0.1480339.
9. 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. 1968;2(7561):191-3. PMID: 4173406. https://doi.org/10.1016/s0140-6736(68)92623-8.
10. Blum WF, Cotterill AM, Postel-Vinay MC, Ranke MB, Savage MO, Wilton P. Improvement of diagnostic criteria in growth hormone insensitivity syndrome: Solutions and pitfalls. Acta Paediatr Suppl. 1994;399:117-24. PMID: 7949595. https://doi.org/10.1111/j.1651-2227.1994.tb13303.x.
11. Ranke MB, Wölfle J, Schnabel D, Bettendorf M. Treatment of dwarfism with recombinant human insulin-like growth factor-1. Dtsch Arztebl Int. 2009;106(43):703-9. PMID: 19946434. PMCID: PMC2780013. https://doi.org/10.3238/arztebl.2009.0703
12. Rosenbloom AL, Guevara-Aguirre J, Rosenfeld RG, Francke U. Growth hormone receptor deficiency in Ecuador. J Clin Endocrinol Metab. 1999;84:4436-43. PMID: 10599699. https://doi.org/10.1210/jcem.84.12.6283
13. Laron Z. Laron syndrome (primary growth hormone resistance or insensitivity): The personal experience 1958-2003. J Clin Endocrinol Metab. 2004; 89(3):1031-44. PMID: 15001582. https://doi.org/10.1210/jc.2003-031033.