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LARON DWARFISM-A RARE CAUSE OF SEVERE SHORT STATURE

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ABSTRACT Patients with Growth Hormone Insensitivity have characteristic phenotypic features and severe short stature. The underlying basis is mutations in the growth hormone receptor gene. We present a 12-year-old girl evaluated for short stature (-4.8 SDS) without Turner stigmata . She has sparse hair, depressed nasal bridge, mid-facial hypoplasia, high pitched voice. Biochemical analyses revealed normal GH levels with low serum insulin-like growth factor-1(IGF-1). IGF1 generation test revealed growth hormone insensitivity. The massive expense incurred in the diagnosis and treatment with suboptimal therapeutic response necessitates a judicious approach in this regard in a resource limited setup.

KEYWORDS : Laron Syndrome, Dwarfism, Micropenis, Growth Hormone Insensitivity, IGF1, IGFBP3, Recombinant Human Growth Hormone, Pituitary Hypoplasia

Introduction:

The term Laron Syndrome was first coined in 1958 when Dr. Zvi Laron was consulted with for two children with severe short stature (1). However, no immunoassay for growth hormone (GH) was available at that time. In the following years, Laron convened 22 children with the same features, all of whom were from the Middle East (1). They had severe short stature (with height SDS of –4 to –8) (1), obesity with dyslipidaemia, micropenis, short limb length compared to trunk length and neonatal hypoglycaemia. Interestingly, glucose intolerance was seen later in them with some going on to develop Type 2 Diabetes and cardiovascular disease (1). They also had small face with a protruding forehead, sparse hair, saddle nose, high pitched voice and a subnormal head circumference (1). They were diagnosed to have dwarfism with hypoglycaemia due to endogenous hyperinsulinism at that time (1). Later on with advancement of bioassays, when GH immunoassays became available, it was found that these children had markedly elevated serum GH levels (1). It was also seen that GH itself was genetically and structurally normal in these cases (1). Also, exogenous GH administration did not show any response {i.e. rise in serum insulin-like growth factor-1 (IGF-1) (1), which is secreted by the liver following GH stimulus}. It was not until 1984 that 'GH resistance' per se was proven, when Laron, using I125rGH, found that it did not attach to liver membranes in contrast to healthy controls (1) and was further confirmed after GH receptor (GHR) cloning in two of the patients revealed a partial gene deletion (2). Through PCR technique, numerous mutations in the GHR gene have been identified (1). The phenotype however varies with the degree of GH resistance which depends on the type of associated mutation. As the classic clinical manifestations of Laron Syndrome are not present in all patients, diagnosis becomes difficult in several cases with patients being wrongly labelled as idiopathic short stature. Treatment with rhIGF-1 of Laron Syndrome children in doses ranging from 150 to 220 µg/kg once daily have resulted in rapid height, brain, head circumference and organ growth (1, 3, 4) with minimal metabolic benefit. However, rhIGF-1 is unavailable in most parts of the world. Till date, the major cohorts of Laron Syndrome patients have been identified in Israel with approximately 70 patients, Ecuador with over 100 patients, Chile, Brazil, and one US patient of Mexican origin, estimating a total of roughly 250 patients world-wide. (1, 6)

Our patient:

A 12-year-old girl was referred to our Endocrinology OPD for evaluation of short stature. Parents noticed poor gain of height for the last 5 years and she was evaluated by several physicians with the cause remaining unidentified. There was no history suggestive of chronic illness, poor scholastic performance, headache, visual disturbance, head trauma, snake bite, radiation exposure, malabsorption, psychosocial deprivation, polyuria, or polydipsia. She was born out of non-consanguineous union and birth weight was 2.8 kg with normal perinatal and developmental history. She was on a healthy diet and regularly played outdoor games during leisure. There was no history of any significant past illness and vaccination was up to date. She had not achieved thelarche or menarche.

On examination, her height was 118 cm {<3rd percentile for age, –4.8 SDS (standard deviation scores), height age 5.5 years, upper segment: lower segment=0.9}, and weight was 30 kg (5th to 10th percentile for age) (Fig. 1, 2) and she had symmetric and well-developed limbs. She has no Turner stigmata though she had sparse hair, depressed nasal bridge, mid-facial hypoplasia, high pitched voice (suggesting 'classical' phenotype (Fig.3). (7) Puffy face and high arched palate (Fig.4) was also present. No dental or ear abnormality was detected. Her Tanner score was B1P1A0. Bone age was 9 yrs. Other systemic examinations were normal.

Laboratory tests revealed normal complete haemogram, renal function test, liver function test, urine analysis, stool analysis. Anti tissue transglutaminase antibody was negative, urine and blood pH were normal; serum calcium, phosphorus, and 25(OH) vitamin D were normal. Thyroid function test was normal and serum prolactin was 10 ng/ml (3-20 ng/ml). Serum FSH and LH were 6.04 mIU/ml (1.79-8.78 mIU/ml) and 0.74 mIU/ml (2.12-10.89 mIU/ml) respectively. 30 cell karyotype was 46XX. Serum IGF-1 was 31 ng/ml (143-693 ng/ml), IGFBP-3 was 2.1 mcg/ml (2.7-8.9 mcg/ml, <-2SD) with a normal GH curve (basal value: 3.2 ng/mL with a maximal clonidine stimulation peak at 60 min of 22.4 ng/mL) (Fig. 5). MRI of hypothalamic-pituitary region showed hypoplastic anterior pituitary with preserved posterior pituitary bright spot (Fig. 6). The IGF1 generation test showed absence of significant increment (>15 ng/ml) in IGF1 (and IGFBP3) after 4 days of rhGH (33 mcg/kg/day)

administration (Table 1). The clinical and biochemical features of our patient suggested GH insensitivity.

There exists a scoring system to identify patients with GHI. The parameters of this scoring system are basal GH, IGF-1, IGF-1 Generation, Height SDS and Growth hormone binding protein(GH-BP) (Table 2).(8) The maximum possible score is 7 points and patients with a score of 5 or more are considered to have significant growth hormone insensitivity. Our patient had a score of 6 which suggests significant GH insensitivity.

Discussion:

Herein, we present a patient diagnosed with GH insensitivity (GHI). Clinical features like severe short stature, sparse hair, depressed nasal bridge, mid-facial hypoplasia, and endocrine analysis (low IGF-1 and normal GH response after clonidine stimulation) suggested GH insensitivity i.e. Laron Syndrome. However, our patient had hypoplastic anterior pituitary on MRI which has not been previously reported in GHI and appears to be a novel finding.

There is however controversies in the criteria used to make a diagnosis of GHI. The IGF-1 generation test has been criticised to have not been adequately characterised and has inadequate normative data. (9) In addition, the availability and costs of the tests for diagnosis of GHI in India is a hurdle.

Patients with GHI are not responsive to GH therapy, but usually responsive to treatment with IGF-1. However, the response of patient of GHI to IGF-1 therapy is variable and substantially less than that of a GH deficient patient treated with GH. Recombinant human IGF-1 (rhIGF-1) (Mecasermin, Increlex) has been used in children with GHI. In one study the height velocity increased from 2.8 cm/year at baseline to a mean of 8 cms/year during the first year of treatment and the height velocity remained above baseline for up to eight years following initiation of rhIGF-1 therapy. [10, 11]

In view of the costs of diagnosis and treatment and non-availability of rhIGF-1, in patients who cannot afford treatment, it is probably not cost effective to investigate for primary GHI. However, as clinicians, we need to have a pragmatic view and bank on phenotypic features in making a possible diagnosis of GHI in such patients. Providing a diagnosis of GHI also helps to prognosticate and counsel those with the disease.

Fig 1

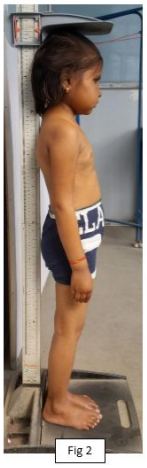
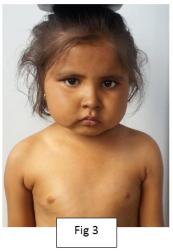


Fig 2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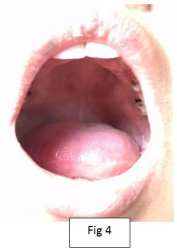
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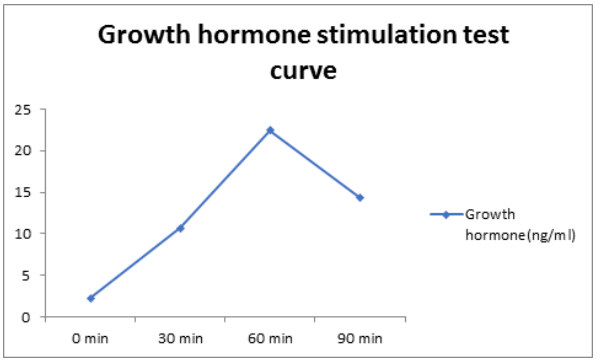

Fig 5

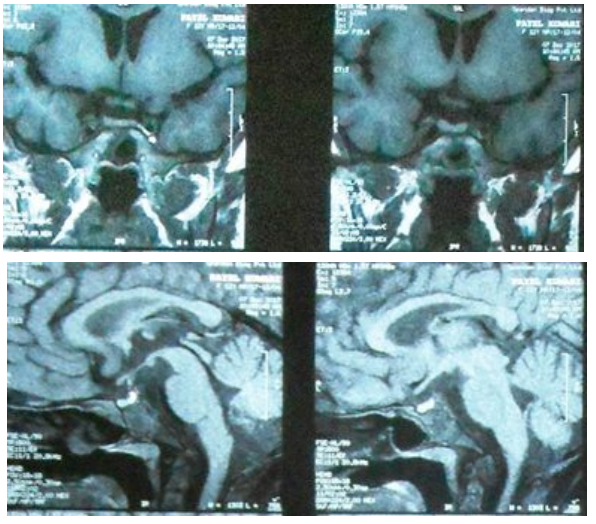
Fig 6

Table 1: IGF 1 generation test

Day of test	Procedure	Blood sample
1	1mg rhGH sc	IGF1=31 ng/ml(basal i.e. before 1st dose)
2	1mg rhGH sc	-
3	1mg rhGH sc	-
4	1mg rhGH sc	-
5	-	IGF1=39 ng/ml(after 4th dose)

Table 2:

Test	Parameter	Criterion	Score
Auxology	Height	<-3 SD score	1
Basal GH	GH	>2.5 ng/ml	1
Basal IGF-1	IGF-1	≤50 mcg/L	1
	IGFBP-3	<-2 SD	1
IGF-1	IGF-1 increase	<15 mcg/L	1
generation	IGFBP-3 increase	<0.4 mg/L	1
GH binding	% GH bound	<10%	1

GH: Growth hormone

Scoring system for the diagnosis of growth hormone insensitivity

REFERENCES

1. Laron Z & Kauli R 2016 Fifty seven years of follow-up of the Israeli cohort of Laron Syndrome patients-From discovery to treatment. Growth Hormone and IGF Research : Official Journal of the Growth Hormone Research Society and the International IGF Research Society 28 53–56. (doi:10.1016/j.ghir.2015.08.004)
2 Godowski PJ, Leung DW, Meacham LR, Galgani JP, Hellmiss R, Keret R, Rotwein PS, Parks JS, Laron Z, & Wood WI 1989 Characterization of the human growth hormone receptor gene and demonstration of a partial gene deletion in two patients with Laron-type dwarfism. PNAS 86 8083–8087. (doi:10.1073/ pnas.86.20.8083)
3 Fintini D, Brufani C, & Cappa M 2009 Profile of mecasermin for the long-term treatment of growth failure in children and adolescents with severe primary IGF-1 deficiency. Therapeutics and Clinical Risk Management 5 553–559.

(doi:10.2147/TCRM.S6178)
4 Kemp SF 2009 Insulin-like growth factor-I deficiency in children with growth hormone insensitivity: current and future treatment options. BioDrugs : Clinical Immunotherapeutics, Biopharmaceuticals and Gene Therapy 23 155–163. (doi:10.2165/00063030-200923030- 00002)
5 Aguirre GA, De Ita JR, de la Garza RG & Castilla-Cortazar I 2016 Insulin-like growth factor-1 deficiency and metabolic syndrome. Journal of Translational Medicine 14 3. (doi:10.1186/s12967-015- 0762-z)
6 Rosenbloom AL 2016 A half-century of studies of growth hormone insensitivity/Laron syndrome: a historical perspective. Growth Hormone and IGF Research : Official Journal of the Growth Hormone Research Society and the International IGF Research Society 28 46–50. (doi:10.1016/j.ghir.2015.08.001)
7. C.P. Burren K.A. Woods S.J. Rose M. Tauber D.A. Price U. Heinrich G. Gilli M. Razzaghy-Azar A. Al-Ashwal P.A. Crock P. Rochiccioli N. Yordam M.B. Ranke P.G. Chatelain M.A. Preece R.G. Rosenfeld M.O. Savage.Clinical and Endocrine Characteristics in Atypical and Classical Growth Hormone Insensitivity Syndrome. Horm Res 2001;55:125–130 [PMID: 11549873]
8. Woods KA, Dastot F, Preece MA, Clark AJ, Postel-Vinay MC, Chatelain PG, et al. Phenotype: Genotype relationships in growth hormone insensitivity syndrome. J Clin Endocrinol Metab. 1997;82:3529–35. [PubMed: 9360502]
9. Buckway CK, Guevara-Aguirre J, Pratt KL, Burren CP, Rosenfeld RG. The IGF-I generation test revisited: A marker of GH sensitivity. J Clin Endocrinol Metab. 2001;86:5176–83. [PubMed: 11701674]
10. Chernausek SD, Backeljauw PF, Frane J, Kuntze J, Underwood LE. Long-term treatment with recombinant insulin-like growth factor (IGF)-I in children with severe IGF-I deficiency due to growth hormone insensitivity. J Clin Endocrinol Metab. 2007;92:902–10. [PubMed: 17192294]
11. Collett-Solberg PF, Misra M. The role of recombinant human insulin-like growth factor-I in treating children with short stature. J Clin Endocrinol Metab. 2008;93:10–8. [PubMed: 18165284]