

Laron Syndrome: Siblings with Extreme Short Stature and Very High Growth Hormone

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Abstract Primary growth hormone resistance or growth hormone insensitivity syndrome (GHIS), also known as Laron syndrome, is a hereditary disease caused by deletions or different types of mutations in the growth hormone receptor gene or by post-receptor defects. This disorder is characterized by a clinical appearance attributable to severe growth hormone deficiency with high levels of circulating growth hormone in contrast to low serum insulin-like growth factor-1 (IGF-1) and low serum insulin-like growth factor binding protein (IGFBP-3) values. It is an autosomal recessive disorder and to date, more than 70 unique growth hormone receptor (GHR) mutations have been identified in more than 250 GHIS patients. We report the case of an 8-year-old boy and his 12-year-old sister born to first cousin parent that presented with severe short stature who had the classic feature of GH deficiency. Investigations revealed high plasma GH levels in both the cases. Subsequently, IGF-1 and IGFBP-3 assay were done and the levels were found to be very low. These reports along with elevated GH level in the context of typical picture of GH deficiency confirmed the diagnosis of GHIS. Genetic testing could not be done because of unavailability in our context. Regrettably specific therapy in the form of recombinant IGF-1 could not be offered as it is not commercially available in our country.

Keywords: Laron syndrome, growth hormone insensitivity, short stature, IGF-1, IGFBP-3

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1. Introduction

Growth hormone insensitivity syndrome (GHIS) or Laron syndrome is a rare autosomal recessive condition, characterized clinically by hypoglycemia in infancy and severe childhood growth failure, biochemically by high levels of growth hormone (GH), and low insulin like growth factor-1 (IGF-1), insulin like growth factor binding protein-3 (IGFBP-3) and acid-labile subunit (ALS) [1]. It was first reported by Laron and colleagues in 1966 in 3 Israeli Jewish siblings with hypoglycemia and clinical phenotype of GHD. Such cases have been reported from the Mediterranean, mideastern region and Indian subcontinent [2,3].

2. Case Presentation

We report the case of a 12-year-old sister and her 8-year-old brother born to a consanguineous family who presented with severe short stature. Their intrauterine periods were uneventful and they were delivered full term via vaginal delivery without any complication. Birth weight was approximately 3 kg though it lacks documentation. The girl was apparently alright till 2 years

of age with normal developmental milestone, failed to develop properly thereafter. Her height is almost constant for last 9 years as compared to her peers (Figure 1). The parents noticed their son also facing the same problem since he was 2 years of age (Figure 2). Their secondary sexual characteristics are also underdeveloped and there is no change of clothing and shoe size for last 8 years in case of the girl and last 5 years in case of the boy. They have 2 siblings, a 19-year-old elder brother of average height and a deceased sister who was apparently normal. A paternal aunt and an uncle who died at an age of 4 years and 2 years respectively were reported to have short stature (Figure 3). The siblings had typical dysmorphic facies: frontal bossing, shallow orbit with blue sclera, saddle nose, mid-face hypoplasia, thin and silky hair and pale texture of skin. In addition the boy had dental caries and bilateral undescended testes with microphallus (Figure 4 & Figure 5). Their intelligence seemed to be normal and they were very cheerful. The height of the boy was 78 cm, weight-17.5 kg, body mass index (BMI)- 27.68 kg/m² with an increased upper to lower segment ratio of 1.16, which were 85 cm, 20 kg, 28.76 kg/m² and 1.02 respectively in case of the girl. When plotted on age and sex appropriate growth chart the height and weight of both the siblings were well below 5th percentile; calculated mid-parental height for the boy was 163 cm whereas for the girl was 150 cm (Figure 6 & Figure 7). Sexual maturation rating of the girl by

Tanner staging revealed her to be at stage 1 (pre-pubertal). Routine hematologic and biochemical profiles were unremarkable thereby excluding any systemic illness. Bone age was markedly delayed in both the cases, around 2 years and 6-7 years for the boy and the girl respectively. Karyotyping was found to be normal, 46XY in case of the boy and 46XX for the girl. Oral glucose tolerance test (OGTT) was performed and interestingly 3 out of 4 values were found to be in the hypoglycemic range (fasting plasma glucose, FPG-2.4 mmol/L and 3.8 mmol/L, 2-hour-postglucose were-3.4 mmol/L and 4 mmol/L for the brother and sister respectively). Hormonal assay for anterior pituitary function revealed both of them to be euthyroid with normal basal serum cortisol and prolactin level. The girl had a pubertal response on GnRH stimulation test (Table 1). Surprisingly random plasma growth hormone (GH) level was found to be remarkably high rather than low (20.57 ng/ml and 31.89 ng/ml for the boy and the girl respectively). The GH levels were rechecked at another reliable, specialized lab and similar reports were obtained (38.1 ng/ml for the boy and 7.94 ng/ml for the girl). Typical clinical feature of GH deficiency in the backdrop of elevated plasma GH level pointed towards the diagnosis of GH insensitivity syndrome, popularly known as Laron syndrome. To confirm the diagnosis serum IGF-1 and IGFBP-3 levels were assayed at a pediatric reference lab and both the results were found to be low as was expected- IGF-1 level <25 ng/ml (bio-reference interval-64-345 ng/ml) in both the subjects and IGFBP-3 <0.500 μ g/ml and 0.51 μ g/ml (bio-reference interval-1.6-6.5 μ g/ml) in case of the boy and the girl respectively. Finally, MRI of the pituitary was done; it showed partial empty sella in both the cases which was probably an incidental finding (Figure 8 & Figure 9). As genetic testing is not locally available so it could not be performed. Unfortunately, recombinant IGF-1 which is the recommended treatment in such cases could not be offered as it is not commercially available in our country. We have planned to contact international organizations or foundations working for such children so that they might be benefitted.

Table 1. Hormonal profile of the patients

Hormonal profile	Boy	Girl	Reference level
T4	8.75	11.89	4.5-12 μ g/dl
TSH	2.37	2.28	0.47-5.01 μ IU/ml
Basal cortisol	21.0	26.10	3.7-19.4 μ g/dl
Prolactin	6.94	7.39	2.5-17 ng/ml
LH (basal)	-	1.70	0.31-5.29 IU/L
FSH (basal)	-	11.5	0.4-6.5 IU/L
LH (post-GnRH)	-	10.95	-
FSH (post-GnRH)	-	16.82	-
GH	20.57 38.10 (Repeat assay)	31.89 7.94 (Repeat assay)	0.03-14.90ng/ml
IGF-1	<25	<25	64-345 μ g/ml
IGFBP-3	<0.500	0.51	1.6-6.5 μ g/ml



Figure 1. the girl (on left) with age matched peer



Figure 2. The boy (on left) with age matched peer

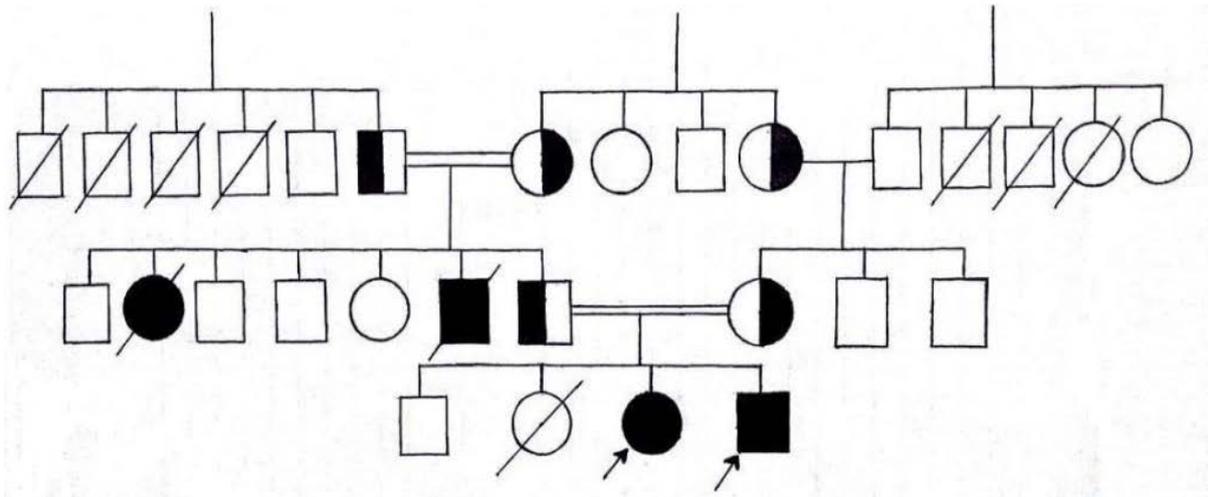


Figure 3. Pedigree chart for the studied subjects



Figure 4. Typical facies of the boy showing blue sclera, depressed nasal bridge



Figure 5. Typical facies of the girl

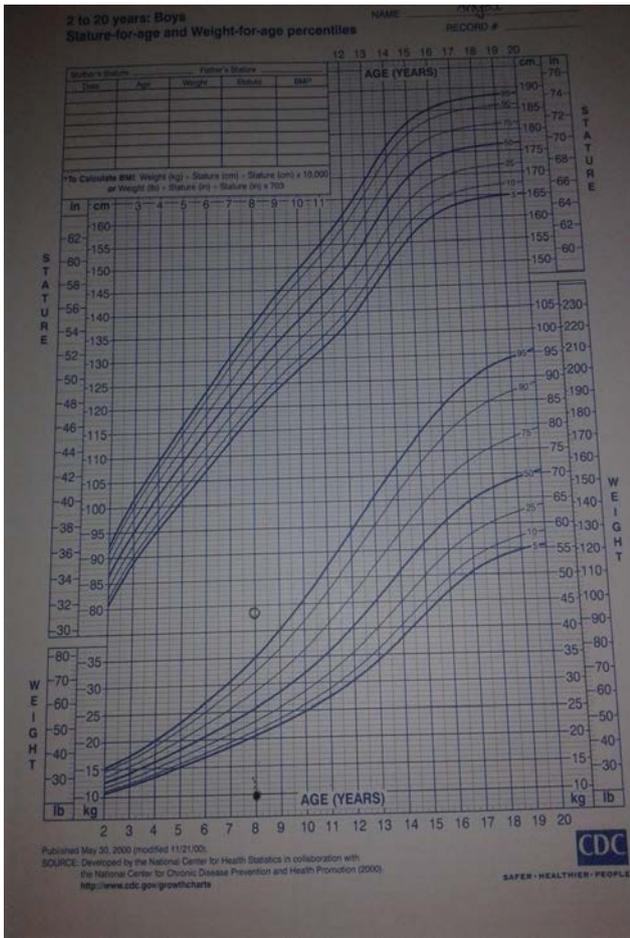


Figure 6. Growth chart of the boy

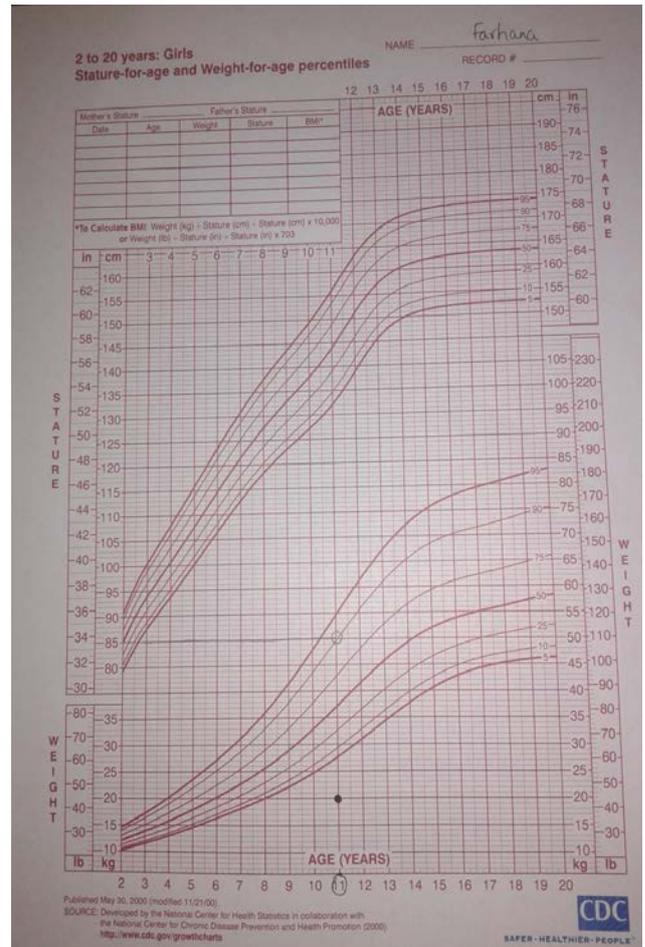


Figure 7. Growth chart of the girl



Figure 8. Sellar MRI of the boy showing partial empty sella

3. Discussion

Primary growth hormone resistance or growth hormone insensitivity syndrome, also known as Laron syndrome, is a hereditary disease caused by deletions or different types

of mutations in the growth hormone receptor gene or by post-receptor defects. This disorder is characterized by a clinical appearance of severe growth hormone deficiency with high levels of circulating growth hormone in contrast to low serum insulin-like growth factor 1 values [4].



Figure 9. Sellar MRI of the girl showing partial empty sella

In 1966, the description of the first cases, three Yemenite Jewish siblings, led to the discovery of the polymorphic defects of the GH receptor (GHR) which result in the inability to generate IGF-1 [5]. Nowadays, this disorder has been reported in more than 250 cases worldwide, being found mainly in consanguineous families from Mediterranean, Middle Eastern, or South Asian regions or in their descendants, including a large cohort identified in southern Ecuador who are considered to be descendants of *conversos* (Spanish Jews who became Catholic during the Inquisition) [6]. To date, more than 70 unique GHR mutations have been identified in more than 250 GHIS patients. These include missense or non-sense mutations, splice site mutations, and insertions or deletions [7,8] and the vast majority of the point mutations have compromised the extracellular domain. These mutations are almost all recessively inherited in either homozygous or compound heterozygous form.

Clinically, patients with GHIS present in a manner virtually indistinguishable from those with severe GH deficiency. Birth weight and length are likely to be within the reference ranges, but post-natal linear growth is strikingly abnormal with a rapid decline in growth velocity soon after birth. The natural history, without proper treatment, results in an extremely short adult stature ranging between 4 and 10 SDs below the median for normal height [9]. Relative obesity is present at birth and increases with age, with a relative excess of adipose tissue in the context of thin bones and diminished muscular mass. The upper-to-lower segment ratio is increased with regard to sex and chronologic age, denoting short limbs for trunk size. Congenital malformations, craniofacial abnormalities, and other physical features may be noted at birth. Facial bone growth is particularly retarded, and fontanels closure is delayed, leading to a disproportionate cephalofacial relationship because of the decreased vertical dimension of the face, with frontal bossing, a saddle nose, shallow orbits, and the setting sun sign of the eyes. Blue sclera may be noted, particularly in patients of Mediterranean or Middle Eastern origin. Hair growth is quite sparse in

infancy and through early childhood. It is silky and forms temporal and frontal recessions. Tooth development is delayed, and the teeth may often be defective. The larynx is narrow, resulting in a very high-pitched voice. The genitalia and gonads are small from birth. Pubertal development is delayed, and the pubertal growth spurt is absent, but adult sexual maturation is eventually achieved. Walking and other gross motor developmental milestones are delayed because of the underdeveloped musculature. The hands and feet are small (acromicria). The skin is thin and has a fine texture with wrinkles as in premature aging. Psychological evaluations suggest a great variability in intellectual development, ranging from normal intelligence to severe mental retardation [7]. Our sibs in the story had all the cardinal feature described above. In addition the boy had dental caries and cryptorchidism which have been described in related literature. Interestingly their intelligence graded from average to above average and the girl topped in her class. They were very sociable and looked like happy puppets. This proves that intelligence is widely variable in GHIS cases ranging from severe mental retardation as in IGF-1 mutation to normal as in our cases.

The cardinal biochemical features of GHIS are low levels of all GH-dependent proteins, including very low or even undetectable serum IGF-1 levels, IGFBP-3, and ALS in association with normal or increased GH levels. The regulation of GH secretion and feedback mechanisms are normal. The most important functional test for the diagnosis is the IGF-1 generation test because serum IGF-1 levels are low and do not increase with the administration of exogenous rGH for days or weeks, demonstrating the state of GH resistance in these patients [7]. Metabolic abnormalities include fasting hypoglycemia and hypercholesterolemia. The underlying metabolic defect lies in the lack of responsiveness of the target organs to endogenous GH. In 1984, it was proven by liver biopsy that GH does not bind to its receptors and therefore is unable to generate IGF-1 [10].

The only effective treatment is the daily administration of rIGF-1 starting from early childhood and probably throughout life. The rIGF-1 treatment accelerates linear

growth velocity, and appropriate dose titrating results in tripling of the baseline growth rate during the first year of treatment [11]. Even if these patients may never experience sufficient catch-up growth to bring their height within the normal range, they do achieve an adult height significantly greater than expected in the absence of therapy [11]. The main reasons could be, on one hand, the inability to replicate physiological IGF-1 distribution and action and, on the other hand, the inability to restore GH defects, because animal studies indicate that GH has growth-promoting effects apart from the IGFs [12].

The present knowledge of the effects of GH and IGF-1 deficiency on aging and lifespan suggests that untreated patients with congenital isolated IGF-1 deficiency seem to reach old age despite marked obesity, development of hyperlipidemia, and a tendency to develop diabetes and its complications, probably because the risk for cancer, a frequent cause of death in the general population, seems to be reduced in these patients [13].

Though we were able to reach the diagnosis yet we could not offer any remedy as recombinant IGF-1 is not locally available. It is to be regretted, to say the least that in our advanced society, a treatable disease remains untreated with the exception of a small number of children on time-limited clinical trials.

4. Conclusions

GHIS is a rare genetic disorder characterized by extreme short stature and hypoglycemia that may or may not be symptomatic. The catch in the diagnosis is the typical clinical picture of GH deficiency on one hand and elevated GH level on the other hand. To make a confident diagnosis demonstration of low level of IGF-1 at baseline or after IGF-1 generation test and low IGFBP-3 level is required. Genetic testing is done to identify the mutation. IGF-I is the treatment of choice and if initiated at birth or in infancy can maximize growth and prevent deleterious effects of the disorder.

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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