Brief Communication

Clinical features and endocrine profile of Laron syndrome in Indian children

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ABSTRACT

Introduction: Patients with growth hormone (GH) insensitivity (also known as Laron syndome) have been reported from the Mediterranean region and Southern Eucador, with few case reports from India. We present here the clinical and endocrine profile of 9 children with Laron syndrome from India. **Material and Methods:** Nine children diagnosed with Laron syndrome based on clinical features of GH deficiency and biochemical profile suggestive of GH resistance were studied over a period of 5 years from January 2008 to January 2013. **Results and Discussion:** Age of presentation was between 2.5-11.5 years. All children were considerably short on contemporary Indian charts with mean (SD) height Z score -5.2 (1.6). However, they were within ± 2 SD on Laron charts. No child was overweight [mean (SD) BMI Z score 0.92 (1.1)]. All children had characteristic facies of GH deficiency with an added feature of prominent eyes. Three boys had micropenis and 1 had unilateral undescended testis. All children had low IGF-1 (<5 percentile) and IGFP-3 (<0.1 percentile) with high basal and stimulated GH [Basal GH mean (SD) = 13.78 (12.75) ng/ml, 1-h stimulated GH mean (SD) = 46.29 (25.68) ng/ml]. All children showed poor response to IGF generation test. **Conclusion:** Laron syndrome should be suspected in children with clinical features of GH deficiency, high GH levels and low IGF-1/IGFBP-3. These children are in a state of GH resistance and need IGF-1 therapy.

Key words: Failure of IGF generation test, high basal GH, Laron syndrome

Introduction

Laron syndrome is characterized by clinical features of growth hormone (GH) deficiency and biochemical findings suggestive of GH resistance.[1] An overall prevalence of 1-9/1000000 has been described.[2] The syndrome was first described by Zvi Laron in 1959 in 3 siblings with severe short stature, born to a consanguineous Jewish family. They resembled children with hypopituitarism but had very high levels of serum human GH (hGH).[1] Many more cases have been reported from the Mediterranean region, Eucador, and recently from India and Sri Lanka, with a preponderance in consanguineous families.[3,4] Our observations over a period of 5 years in a tertiary care pediatric endocrine clinic setting have shown that 1 in 100 children tested for GH deficiency is diagnosed with Laron syndrome (unpublished data). We have described the clinical and biochemical profile of Laron syndrome amongst Indian children in a scenario wherein treatment remains unavailable.

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Material and Methods

Nine children (7 boys, 2 girls; age range: 2.5-11.5 years) diagnosed with Laron syndrome based on clinical features and investigations were studied over a period of 5 years from January 2008 to January 2013. Clinical history including consanguinity, birth weight, history of neonatal hypoglycemia, onset of short stature, family history, and evidence of chronic illness or secondary causes were noted. A thorough examination was performed for clinical features of GH deficiency, pubertal status,

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and genital ambiguity including micropenis (defined as stretched penile length <2 SD of mean for age) and undescended testes.[5] Anthropometric measurements were recorded as per standard protocols,[6] and were plotted on contemporary Indian growth charts[7] as well as Laron syndrome charts.[8]

Hemogram, renal function, and anti-tissue transglutaminase IgA (if required) were performed to rule out chronic illness. Biochemical tests were performed in the morning in the fasting state. These included Insulin-like growth factor-1 (IGF-1, using enzyme-linked immunosorbent assay, ELISA), Insulin-like growth factor binding protein-3 (IGF BP-3, using ELISA), T3, T4, TSH (using chemiluminescence), and basal cortisol (using ELISA). GH stimulation test was also performed. Serum GH was first measured (using ELISA) in the fasting state in the morning, following which clonidine was given in a dose of 0.15 mg/m^2 orally. Samples for stimulated GH levels were then collected 1 hour and 2 hours after clonidine administration. Further, IGF generation test was performed as follows: rhGH in a dose of 33 mcg/kg was given subcutaneously at the same time of the day (preferably at bedtime) for 4 days and IGF-1 was measured on day 5. An increment in IGF-1 of less than 15 mcg/L was considered a failed test suggestive of GH resistance.[9] All patients underwent magnetic resonance imaging (MRI) of the brain to look for abnormalities of the pituitary gland as well as anatomical defects. Bone age was assessed from radiograph of the left hand and wrist (AP view) using Tanner-Whitehouse 3 method.

Diagnosis of Laron syndrome was based on clinical features along with investigations suggestive of high concentrations of GH and poor response to IGF generation test; we used the scoring system devised by Savage *et al.*[10]

Scoring involved assessment of the following 7 parameters: height SDS less than -3SD, basal GH > 2.5 ng/ml, basal IGF-1 < 50 mcg/L, IGFBP-3 < -2SD, IGF-1 increase post IGF generation test < 15 mcg/L, IGFBP-3 increase post IGF generation test < 0.4 mg/L and GH binding (i.e. %GH bound) <10%. The diagnosis of Laron syndrome was made if 5 of the 7 parameters were positive.[10]

Results

We present a series of 9 children diagnosed with Laron syndrome on the basis of the above scoring system.[10] Age and anthropometric and biochemical characteristics are illustrated in Table 1. Mean age (SD) at presentation was 5.5 years (2.9) (age range: 2.5-11.5 yrs). Three of 9 children were born of a third degree consanguineous marriage. Of the 3 children born of consanguineous parents, 2 were siblings born to short parents (MPH Z score = -2.8). The mean mid-parental height Z score was -1.3. Mean height Z score (SD) was -5.2 (1.6), mean weight Z score -5.1 (1.9) and mean BMI Z score (SD) was -0.9 (1.1). Plot on growth charts showed that all were below 3rd percentile and below mid-parental range. Plotting children's' height on Laron charts (Figure 1, permission for printing Laron chart sought from Prof. Zvi Laron by personal communication) showed that they were within ± 2 SD on the height chart (i.e, within the 3rd and 97th percentile of Laron charts). None was overweight with a BMI Z score of -0.92.[7] All children were born with average birth weight (2.5 ± 0.2 kg) with no history of neonatal hypoglycemia or jaundice. Short stature

Table 1: Anthropometry and investigation profile of patients

Case	C1	C2	C3	C4	C5	C6	C7	C8	C9
Chronological age (years)	2.6	5.8	9	3.1	3.6	11.6	4	5.1	5
Gender	M	M	M	M	M	M*	M*	F	F
Height (cm)	67	97.5	101	81	78	107	67	83	77
Height z score	−5.9	−3.0	−5.2	−2.9	−4.5	−5.7	−8.1	−5.1	−6.5
Weight (kg)	7.2	14	12.7	8.2	9.2	14.9	6.8	9	7
Weight z score	−5.2	−2.1	−5	−4.4	−3.8	−5.0	−8.6	−4.7	−7.3
Body mass index (kg/m^2)	16	14.7	12.5	12.5	15.1	13	15.1	13.1	11.8
Body mass index z score	0.7	−0.2	−2.0	−1.7	0.1	−2.0	0.1	−1.2	−1.93
Mid-parental height z score	−0.6	−0.8	−0.4	−1.19	−2.15	−2.15	−2.15	−1.25	−0.8
Bone Age (years)	<1	<2	5	<1	<2	7	2	<2	<2
Bone Age retardation (years)	1.6	3.8	4	2.1	1.6	4.6	2	3.1	3
Insulin like growth factor-1 (IGF -1) (ng/ml)	<25	29	<25	<25	<25	<25	25	<25	<25
Insulin like growth factor binding protein-3 (IGF BP3) (mg/L)	<0.4	UR	UR	UR	UR	UR	UR	UR	UR
Growth hormone (GH) stimulation test (ng/ml) using clonidine									
Basal GH (ng/ml)	18	29	4	6	5	9	40	6	7
1-h post stimulation GH level (ng/ml)	24	40	50.6	32	23	50	62	105	30
2-h post stimulation GH level (ng/ml)	22	15	20	10	45	11	15	60	22
IGF (Insulin like growth factor) generation test (ng/ml)									
Response	NI	NI	NI	NI	NI	NI	NI	NI	NI

*Siblings, C1-C9: case 1-case 9, M: Male, F: Female, UR: Un-recordable, NI: No improvement, IGF: Insulin-like growth factor, GH: Growth hormone, BP: Bwinding protein

had been noted since late infancy. Characteristic facies of GH deficiency with frontal bossing, depressed nasal bridge, mid-facial hypoplasia, high-pitched voice, and small hands and feet were a consistent finding.[1] In addition, prominence of eyes was a constant feature noted in all children. Three of 7 boys had micropenis and 1 had unilateral undescended testis; all were prepubertal (age < 11.5 years). Hemogram, liver function, and renal function tests were normal. IGF-1 was below the 5th percentile,[11] (<50 mcg/L as per criteria of Savage *et al*.[10]) and IGFBP-3 was below 0.1 percentile in all patients[12] (<-2SD, as per criteria of Savage *et al*.[10]). Mean (SD) basal GH was 13.7 ng/ml (12.75 ng/ml), 1-h post-stimulation GH was 46.3 ng/ml (25.7 ng/ml), while, 2-h post-stimulation GH was 25.6 ng/ml (17.7 ng/ml). Studies have quoted a cut-off of >40 ng/ml for GH level post provocation test as high.[13] IGF generation test showed poor response in all patients. Thyroid function and serum cortisol were within the reference range. Bone age was retarded in all with mean (SD) retardation of 2.8 years (1.1 years). MRI did not reveal any anatomical abnormality [Table 2 and Figure 2].

Discussion

Laron syndrome (also known as Laron dwarfism) is a condition wherein short stature (height SDS between -4 to -10SD) is associated with typical facies, obesity, acromicra, high basal GH, and low IGF-1. Patients with Laron syndrome are unresponsive to exogenous GH therapy.[1]

Table 2: Comparison studies of Laron syndrome

Study	Awan *et al*.[20]	Savage *et al*.[10]	Burren *et al*.[17]	Our study
N (number of cases)	*n*=21	*n*=27	*n*=50	*n*=9
Ethnic origin	Pakistan	Europe and Australia	Europe	Western India
Age (years)	5-17	2.8-22.6	Mean (SD) 8.6 (4.6)	2.5-11.5
Male: female	14:7	12:15	24:26	7:2
Consanguinity	66.6%	N.A.	N.A.	33%
Age z score	N.A.	Median -6.1 (-3.8 to -10.2)	Mean (SD) -6.7 (1.4)	Mean (SD) -5.2 (1.6)
Weight z score	N.A.	Median -3.2 SDS (-0.1 to -5.2)	N.A.	-5.1 (1.9)
Hypoglycemia	N.A.	33%	42%	Absent
Micropenis	N.A.	58%	79%	42.80%
Birth weight	N.A.	Median -0.72 SDS (1.75 to -3.29)	N.A.	2.5 (0.2)
Birth length	N.A.	Median -1.59 SDS (0.63- -3.63)	N.A.	N.A.
Bone age Retardation	N.A.	70%	N.A.	100%
Basal GH ng/ml	*n*=14 median 2.4 (1.0-12.0) *n*=7 median 25.4 (20.0-53)	Median 17 (0.5–7.9)	N.A.	Mean (SD) 13.7 (12.75)
Simulated GH ng/ml	*n*=14 median 22.9 (11.5-100) *n*=7 median 25.1 (14.5-37)	N.A.	N.A.	Mean (SD) 46.29 (25.68) 1 h 25.63 (17.67) 2 h
IGF-1	N.A.	<5th percentile		<5th percentile
IGFBP-3	N.A.	<5th percentile	Mean (SD) -8.6 (2.44)	<0.1 percentile
GHD features	N.A.	N.A.	Sparse hair, high pitched voice, blue sclera	Prominent eyes

GH: Growth hormone, IGF-1: Insulin like growth factor-1, IGFBP-3: Insulin like growth factor binding protein-3, GHD: Growth hormone deficiency, N.A.: Data not available, SD: Standard deviation

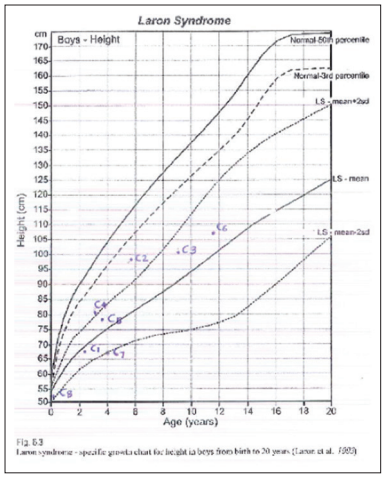

Figure 1: Plot of children on Laron chart

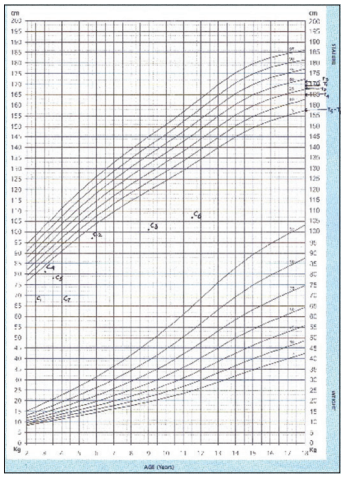

Figure 2: Plot of children on contemporary Indian charts

It is a fully penetrant autosomal recessive condition seen more commonly in consanguineous families. GH resistance occurs due to defects in the GH receptor or post-receptor pathways. Defects at various steps have been described. These include defects in the extracellular, transcellular, and intracellular domain of GH receptor. The most commonly described defect has been a mutation in the extracellular domain of the GH receptor, associated with low levels of GH-binding protein, which is the circulating form of this extracellular domain. Defects in the post-receptor pathway (JAK/sTAT), IGF-1 gene, and IGF receptor have also been described.[1]

These children have features of GH deficiency; 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. Children with Laron syndrome continue to grow at a lower speed throughout childhood resulting in very short adult stature. They are usually obese despite having a poor appetite.[1] We noted that the mean height Z score (SD) was -5.2 (1.6). Surprisingly, unlike previous reports they were not overweight and had low mean weight Z score [-5.1 (1.9)] and mean BMI Z score (SD) [-0.9 (1.1)]. In a study on 27 cases of Laron syndrome of European origin, Savage *et al*. have shown that the median height was -6.1 SDS and median weight was -3.2 SDS.[10] The median percentage weight for height was 111.3 (overweight). There are few reports from India showing that children with Laron syndrome may not be overweight.[3] Prof. Laron noted that in absence of treatment, these patients achieved final height in the range of 11-142 cm in males and 108-136 cm in females.[14] In a large Eucadorian study, the final height achieved was 95-124 cm for females and 106-141 cm for males.[15]

Facial features include a protruding forehead, saddle nose, and mid-facial hypoplasia. Hair are thin, sparse, and can be easily plucked, nails grow slowly, and teething is delayed and defective with overcrowding being a common feature due to a small mandible. Voice is high-pitched due to a narrow oropharynx. Boys often have hypogonadism and hypogenitalism in early childhood.[16] All our children had typical facies with remarkably prominent eyes and small hands and feet. Three boys had micropenis and 1 had unilateral undescended testis (in addition to micropenis) corroborating the finding of hypogenitalism in our children. In comparison to a prevalence of 42.8% in our boys, Savage *et al*. noted that micropenis was present in 58% of males (n = 12),[10] while Burren noted an incidence of 79% in 50 children in South Eucador with classical features of Laron syndrome.[17]

Like GH-deficient children, these children are also predisposed to suffer from hypoglycemia in the newborn period as well as in childhood and adulthood.[8] Savage *et al*. documented hypoglycemia in 33% of cases (n = 27),[10] while Burren noted hypoglycemia in 42% children.[17] None of our children reported hypoglycemia either in neonatal period or in childhood.

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 reproduction.[1] All our patients were under 11.5 years and prepubertal requiring follow up to comment upon their pubertal progression.

Effect of GH on the skeletal system is well documented. In absence of the action of GH, skeletal maturation is delayed, with closure of epiphyses of long bones occurring between 16-18 years in girls and 20-22 years in boys.[16] All our patients had bone age retardation, mean retardation being 2.9 years suggestive of significant delay in skeletal maturation. Savage *et al*. have also noted bone age delay in 19 of their 27 patients.[10]

Due to a state of GH resistance, children with the Laron syndrome have high levels of circulating GH with an end organ resistance. Serum IGF-1 concentrations are very low, often undetectable, and do not rise on administration of exogenous hGH; these findings were also seen in our patients.[18,19] Savage *et al*. have shown basal median serum GH 17 mcg/L (0.5-79), IGF values less than 5th percentile in all, percentage increment of IGF-1 during IGF generation test less than 0.1 percentile for age and a median IGFBP-3 value of 0.53 mg/L (0.1-1.17).[10] Awan *et al*. conducted a GH study in 273 short Pakistani children and found that 21 had high stimulated GH values (n = 14, 22.9, 11.5-100.0; n = 7, 25.1, 14.5-37), while only 7 had high basal GH values (median basal GH; n = 14, 2.4, 1.0-12.0; n = 7, 25.4, 20.0-53).[20] Secretion of thyroid hormones and adrenal hormones is normal, which was the case in our children as well.[21]

Interestingly, it has been observed that despite lifelong oversecretion of pituitary GH, MRI of the pituitary does not show an enlarged gland and the sella turcica is normal.[22] The fact that growth of all organs is IGF dependent could be the explanation. This possibly explains the normal-sized pituitary gland seen in our patients.

The only treatment for this syndrome is subcutaneous administration of IGF-1 in a dose of 75 mg/kg/day. Prolonged treatment improves linear growth, growth of hands, feet, chin, and nose as well as onset of puberty (1) Side effects include water and electrolyte retention and calciuria.[23,24]

As these patients have thin bones and weak muscles, they may need to be treated with IGF-1 for a long period before considering limb lengthening. Non-availability of IGF-1 in India is a major setback for children with Laron syndrome. However, untreated patients have normal longevity and have been recorded to live up to 70 years in studies by Laron as well as an Eucadorian study.[1] They may have signs of early aging such as skin wrinkling and joint pain as well as obesity and poor muscle strength in adulthood. Sleep apnea has also been noted related to obesity and a small oropharynx.[1]

Non-availability of treatment led to many children being lost to follow up, this was the major limitation of our study.

Conclusion

We described 9 cases with Laron syndrome referred to a tertiary level care pediatric endocrine unit for short stature with suspicion of GH deficiency. To diagnose Laron syndrome, a high index of suspicion is necessary while looking at an extremely short child with features of GH deficiency with high basal and stimulated hGH levels and low IGF level. Awareness of this disorder amongst pediatricians and endocrinologists will lead to accurate diagnosis of the condition. Availability of IGF-1 in India will change the outlook of children with this disorder.

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