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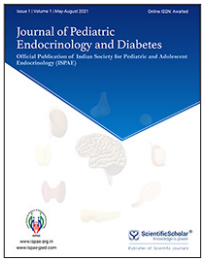

Original Article

Laron syndrome in South Indian children – A descriptive study

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ABSTRACT

Objectives: The objectives of this study were to describe the clinical and biochemical features of five children with Laron syndrome (LS) from South India.

Material and Methods: This is a prospective descriptive case series of five children with clinical and biochemical features of LS managed over 5 years.

Results: Five children (two girls and three boys) with LS with the mean age group of 5.9 ± 1.7 years and the mean age at diagnosis of 2.7 ± 0.8 years are described. All children were born out of consanguinity and all had typical phenotypic facies of LS. The mean Z-scores of height, weight, and body mass index on follow-up for the cohort were −7.0 ± 1.6, −5.9 ± 2.8, and −0.1 ± 0.7, respectively, and they were within ± 2 SD of the mean for children in LS chart. The median basal growth hormone level for age was 13 ng/mL and the median growth hormone levels at 30 min, 60 min, 90 min, and 120 min post-stimulation test were 35 ng/mL, 35 ng/mL, 44 ng/mL, and 50 ng/mL, respectively. All of them had insulin-like growth factor-1 (IGF-1) levels less than the 3rd percentile and no increment during the IGF-1 generation test. The prevalence of micropenis was 100% and one child had symptomatic hypoglycemic episodes. Genetic analysis was performed in two boys and both harbored variants in the growth hormone receptor gene.

Conclusion: LS should be suspected in children with clinical features of growth hormone deficiency along with elevated growth hormone levels and low IGF-1 levels with no increment of IGF-1 in the IGF-1 generation test.

Keywords: Laron syndrome, Growth hormone, Insulin-like growth factor-1, Short stature, Genetics

INTRODUCTION

Laron syndrome (LS), or primary growth hormone (GH) insensitivity, is an autosomal recessive disease caused by molecular defects in the growth hormone receptor gene resulting in GH resistance. LS is characterized by a typical phenotype that includes dwarfism, hypoglycemia, obesity, and hypogenitalism. This condition is caused by mutations or deletions of the GH receptor gene, causing elevated serum GH levels and undetectable serum insulin-like growth factor-1 (IGF-1) and insulin-like growth factor-binding protein-3 (IGFBP3) levels.[1] It was first described by Laron *et al.* in 1966 in three consanguineous Jewish siblings presenting with hypoglycemia and severe short stature.[2] Many more cases have been reported from the Mediterranean region, Ecuador, and recently from India and Sri Lanka, with a preponderance in consanguineous families.[3-5]

Recombinant human IGF-1 (Mecasermin, Increlex®; Ipsen Pharma, Boulogne-Billancourt, France) therapy stimulates linear growth in children with LS and improves adult height.[6] However, the high cost of this medication makes it inaccessible to many children in developing countries.

About 500 cases have been reported previously[1] and this case series is aimed at adding more to the existing literature, especially from the South Indian population.

MATERIAL AND METHODS

This is a descriptive case series of five children with clinical and biochemical features of LS under follow-up in the pediatric endocrinology clinic of a tertiary care center in South India managed between the year 2016 and year 2021. The study was conducted after ethics committee approval and informed consent from the parents. Clinical details including birth history, family history, consanguinity of parents, neonatal complications including hypoglycemia, and age of presentation were elicited.

A thorough clinical examination for the findings of clinical features of growth hormone resistance, facial dysmorphism, Tanner's stage at diagnosis and follow-up, and stretched penile length to identify micropenis (defined as stretched penile length <2 standard deviation [SD])[7] was done. Height, weight, and body mass index (BMI) at presentation and follow-up and midparental height were noted and plotted in standard Indian charts[8] and LS charts[9] and also presented in Z-scores.[8,10] Clinical exome sequencing to identify mutations in growth hormone receptor gene was performed based on logistic considerations and the details are presented.

GH stimulation test was performed using glucagon as a stimulant after ensuring normal basal cortisol and thyroid levels (chemiluminescence). Serum GH was first measured in the fasting state in the morning, following which glucagon was given in a dose of 30 μg/kg subcutaneously. Samples for stimulated GH levels were then collected 30 min, 60 min, 90 min, and 120 min after glucagon.[11] IGF-1 level below the 3rd percentile for age and sex was considered low.[12] IGF-1 generation test was performed as follows: rhGH in a dose of 33 μg/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 <15 μg/L was considered a failed test suggestive of GH resistance.[13] Diagnosis of LS was made based on clinical criteria and biochemical values of high serum values of growth hormone and low IGF-1 serum levels after the IGF-1 generation test.[4,14]

Systemic and secondary causes of growth retardation were ruled out with the help of complete blood counts, renal function tests, IgA tissue transglutaminase (celiac disease), liver function tests, lipid profile and ultrasound abdomen. Magnetic resonance imaging (MRI) brain was done to look for pituitary and other structural anomalies.

Statistical analysis

The results were entered into Microsoft Excel and were presented in percentages and mean with SD.

RESULTS

A total of five cases (two female and three male children) have been included in this study. The clinical and biochemical profiles are described in Table 1. The mean age group of the study subjects was 5.9 ± 1.7 years and the mean age at diagnosis was 2.7 ± 0.8 years. All of them were born out of consanguineous marriages and were index cases in their family. One child had an elder sibling die at 5 years due to an unrelated childhood illness. Two of the five children were small for gestational age at birth with a mean birth weight of 2.7 ± 0.4 kg. One child had a history of neonatal hypoglycemia and one child had neonatal jaundice.

All children had typical phenotypic facies, with frontal bossing, flat nasal bridge, midfacial hypoplasia, prominent eyes, small hands, and feet and two of them had delayed dentition. The presenting complaint for the pediatric endocrinology outpatient clinic was poor growth and reduced appetite in all five children. The mean height Z-score, weight Z-score, and BMI Z-score at diagnosis were −6.9 ± 2.0, −5.0 ± 1.7, and −0.7 ± 1.3, respectively. The mean Z-scores of height, weight, and BMI on follow-up for the cohort were −7.0 ± 1.6, −5.9 ± 2.8, and −0.1 ± 0.7, respectively. The mean midparental height Z-score was −1.2 ± 0.7. On plotting in the IAP growth charts, all of them were <3rd centile for age and sex and significantly discrepant from the target height percentiles. On plotting growth on the growth chart for children with LS, they were within the ± 2SD of the mean for children with LS. None of them belonged to the overweight or obese category; however, their BMI was on an increasing trend with age. All of them were prepubertal and micropenis with normal testicular volume was noted in all three boys.

The median basal growth hormone level for age was 13 ng/mL and the median growth hormone levels at 30 min, 60 min, 90 min, and 120 min post-stimulation test were 35 ng/mL, 35 ng/mL, 44 ng/mL, and 50 ng/mL. All of them had IGF-1 levels less than the 3rd percentile and no increment post-IGF-1 generation test [Table 1].

Thyroid function tests and cortisol levels were within normal reference values. MRI was done in three of the five children and hypoplastic anterior pituitary was detected in two of them. Molecular genetic testing was performed in two children and both had a homozygous variant in the growth hormone receptor gene. One male child (C5) harbored variants of

Table 1: Clinical, anthropometric, biochemical, and radiological profile of study subjects.

	C1	C2	C3	C4	C5
Chronological age (years)	5	6	8	3.5	7
Age at presentation (years)	1.4	3.7	3	3	2.8
Sex	Male	Female	Female	Male	Male
Birth weight (kg)	3	3.2	2.75	2.25	2.3
Height follow-up (cm)	82	70	74	70.5	93
Height Z-score	−5.7	−9.0	−7.9	−7.5	−5.0
Weight follow-up (kg)	11	7	7.2	7.2	14.5
Weight Z-score	−3.7	−8.9	−8.6	−5.4	−2.7
MPH Z-score	−0.4		−2.0	−1.7	−0.7
BMI (kg/m^2)	16.3	14.2	13.1	14.4	16.7
BMI Z-score	0.6	−0.3	−1.2	−0.2	0.5
SPL (cm)	2.5	-	-	3	3
Peak stimulated GH (ng/mL)	50	63	120	35	50
IGF-1 baseline (ng/mL)	<25	<25	<25	<15	<25
Post-IGF-1 generation test (ng/mL)	<25	<25	<25	<25	<15
MRI brain	Hypoplastic anterior pituitary, nodular heterotopia right lateral ventricle	Hypoplastic anterior pituitary	Normal	-	-
Genetic test	-	-	-	Pathogenic heterozygous 3' splice site variation in intron 1 and missense variation exon 6 of GHR	VUS homozygous deletion exon 3 and 5' splice site variation in intron 2 of GHR

MPH: Midparental height, BMI: Body mass index, SPL: Stretched penile length, GH: Growth hormone, GHR: Growth hormone receptor, IGF-1: Insulin-like growth factor-1, MRI: Magnetic resonance imaging, VUS: Variant of unknown significance

unknown significance (VUS), a contiguous homozygous deletion of exonic region 3 of the GHR c(157+1_158−1)_(157+1_158−1)del and a homozygous 5' splice site variation in intron 2 c.91+5G>A of the *GHR* gene. The other male child (C4) had pathogenic compound heterozygous 3' splice site variation in intron 1 of the GHR c.11-1G>A and heterozygous missense variation in the exon 6 of the *GHR* c.620A>G with both parents being asymptomatic carriers, mother having pathogenic heterozygous intronic splice variant, and father having VUS in exon 6 of the *GHR* gene in heterozygosity. The child C4 also had a hemizygous missense VUS in exon 9 of G6PD gene c.949G>A, for which he was evaluated and found to have normal G6PD levels. Hemograms, renal function tests, celiac screening, liver function tests, and lipid profile were normal for age for all of them and none of them had any other features of systemic or chronic disease.

The oldest child of the cohort had symptomatic hypoglycemic episodes frequently, while the rest of them were symptom free. None of the children had intellectual disability. All the families were counseled about treatment with recombinant IGF-1.

DISCUSSION

There are about 500 case reports of LS globally; however, many are suspected to be undiagnosed yet.[15] Although a few reports are from India, there is a clear lack of literature on LS from South India. Table 2 depicts the comparison of our data from other series described from various parts of India. The mean age at diagnosis of our cohort was 2.7 ± 0.8 years, which is earlier than the previous reports from India.[3]

LS is an autosomal recessive disorder with most cases having full penetrance and is common in consanguineous families. Up to 70 mutations have been described in the *GHR* gene, and different phenotypes of the same mutation and within the same family have been described.[14] All of the described cohorts here are born of consanguinity and mutations have been clearly identified in those children where genetic testing has been done. This highlights the need for proper genetic counseling and genetic testing in children and carriers suspected of *GHR* gene mutations.

Children with LS may have normal birth weight and length but present with moderate-to-severe postnatal growth failure.[16] Dwarfism being evident at birth has been reported; however, the birth length could not be traced in our series and two children were born SGA by weight at birth.[17] The mean height Z-score in our population was −7.0 ± 1.6, while the mean Z-score in another Indian cohort from West India was −5.2 ± 1.6. This is in comparison to the −6.1 SDS in the European and −6.1 SDS in the Israeli cohort.[1,3,18]

Table 2: Comparison with other Indian studies.

Data	Phanse-Gupta *et al.*[3]	Chakraborty *et al.*[5]	Guleria *et al.*[4]	Our study
Study sample	9	2 siblings	2 siblings	5
Setting	West India	East India	North India	South India
Age (SD) years	5.5 (2.9)	3, 6	5, 7	2.7 (0.8)
M: F	7:2	0:2	2:0	3:2
Consanguinity	33%	Yes	No	100%
Height Z-score (SD)	−5.2 (1.6)			−7.0 (1.6)
Weight Z-score (SD)	−5.1 (1.9)			−5.9 (2.8)
Hypoglycemia	Absent	Absent	Absent	One
Micropenis	42.8%		100%	100%
Birth weight	2.5 (0.2)			2.7 (0.4)
Basal GH (SD) (ng/mL)	13.7 (12.75)	8.97		13 (8)
Stimulated GH (SD) (ng/mL)	46.2 (25.6)	17.3	98	50 (35)
IGF-1	<5th percentile	<5th percentile	<5th percentile	<5th percentile
IGF-1 post-generation	Poor response			Poor response

SD: Standard deviation, GH: Growth hormone, IGF-1: Insulin-like growth factor-1

Neonatal complications such as hypoglycemia and neonatal jaundice are expected in LS[1] and reported in our study. Severe postnatal failure to thrive and insufficient appetite[3] are the major reasons for presentation to our clinic. The mean midparental height Z-score was consistent with the other Indian cohort.[3] All children had typical facies due to underdevelopment of facial bones including a protruding forehead, saddle nose, midfacial hypoplasia, small hands and feet, thin and sparse hair, and delayed dentition.[1,3,15] Micropenis was noted in 100% of our boys compared to 58% by Savage *et al*., and 42.8% by Phanse-Gupte *et al*.[3,18] The intellectual capacity of children with LS ranges from normal to intellectual disability. Although psychometric tests have not been carried out on our children, they have been doing well academically.[1] Two of our children had small anterior pituitary in contrast to Phanse-Gupte *et al*.[3] where they reported normal pituitary. These may be non-specific findings, yet require follow-up for other pituitary hormonal functions in the future. Marked retardation of bone age, thin bones with reduced bone mineral density, underdeveloped facial and skull bones, and paranasal sinuses and spinal stenosis of the cervical and lumbar spine are also frequently reported.[1,3,16,18]

Diagnosis is by the elevated circulating GH with an end-organ resistance and serum IGF-1 concentrations are often undetectable and do not improve on the administration of exogenous hGH. A GH cut-off of > 40 ng/mL post provocation may be considered as high.[19] This is observed in our study too. Savage *et al*. have developed a scoring system that includes height SD less than 3SD, basal GH > 2.5 ng/mL, basal IGF-1 < 50 µg/L, IGFBP3 < 2SD, IGF-1 increase in post-IGF generation test < 15 µg/L, IGFBP3 increase in post-IGF generation test < 400 ng/mL, and GH binding < 10%. If five of the seven are positive, diagnosis is made.[18] We have not measured IGFBP-3 in our children due to logistic reasons. Hence, we are unable to apply this scoring system to our children.

Children with LS may have their complete sexual development, yet may not have a pubertal growth spurt. They grow slowly and have a delayed and slow puberty that is more accentuated in boys.[9,20] The presented group of children is still pre-pubertal mandating proper counseling and follow-up with Tanner's staging at every visit.

Treatment with recombinant human IGF-1 (rhIGF-1) is established to promote linear growth in children with LS. Growth charts for monitoring children with LS have been developed from data from repeated measurements of 24 children from Israel.[9] There are no Indian charts for LS available. This highlights the need for the establishment of registries to collate longitudinal growth data of children with LS and the generation of growth curves for Indian children with LS. IGF therapy has a known safety profile except for spontaneous hypoglycemia, adenoid, or tonsillar hypertrophy with a potential risk for malignancy.[21] A study on 21 children treated with recombinant IGF-1 in Europe observed a height improvement from a baseline height Z-score of −5.6 to −4.6, −4.2, and −3.8 at the end of 1 year, 2 years, and 3 years, respectively.[21] A study on 20 children showed an increment in height SDS from −4.3 ± 0.8 to −3.2 ± 1.0 at 3 years of recombinant IGF therapy.[22] An increase in height SDS of 1.4 ± 0.9 was observed during the study. An Indian center has reported two cases treated with recombinant IGF-1 showing an increase in height from 100 cm to 114.5 cm over 3 years and from 99.5 cm to 110.3 cm over 2.5 years of irregular treatment.[23] Final adult height on long-term follow-up has been observed to be 116–142 cm in males and 108–136 cm in females.[24] A mean final height of 119.5 ± 8.5 cm and 124 ± 8.5 cm was observed in girls and boys on follow-up of 24 children with LS.[9]

A novel experimental therapy using a hepatocyte specific adeno-associated virus that can express the *GHR* gene in Laron dwarf mice that are GHR deficient has been recently described.[25] An increase in the auxology and internal organs were observed in the mice by the research group.

This article highlights the need for bodies like the Indian Society for Pediatric and Adolescent Endocrinology to take up the cause of affected families and take necessary steps to ensure that the drug is freely available for Indian children at an affordable cost.

CONCLUSION

The clinical, biochemical and radiological profile of South Indian children with LS is described in this paper.

Declaration of patient consent

Institutional Review Board (IRB) permission was obtained for the study.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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