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Long-term IGF-I treatment of children with Laron syndrome increases adiposity

Zvi Laron [a,*], Shira Ginsberg [a], Pnina Lilos [a], Mira Arbiv [b], Nahum Vaisman [b]

[a] *Endocrinology and Diabetes Research Unit, Schneider Children's Medical Center, 14 Kaplan Street, 49202 Petah Tikva, Israel*
[b] *Department of Clinical Nutrition, Sourasky Medical Center, Tel Aviv, and Sackler School of Medicine, Tel Aviv University, Israel*

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Abstract

Laron syndrome (LS) is an autosomal recessive disease caused by deletions or mutations in the GH receptor gene leading to an inability of insulin-like growth factor I (IGF-I) generation. Among the major resulting body changes are dwarfism and obesity. The only effective treatment is daily administration of biosynthetic IGF-I.

Body composition determination by DEXA (dual energy X-ray absorptiometry) of three girls with LS treated by IGF-I for 1, 3 and 11 1/2 years, respectively, revealed that concomitantly with the increase in growth there was a significant increase in body adipose tissue to double or triple the normal values. Due to the underdevelopment of the muscular and skeletal systems body mass index (BMI) did not accurately reflect the degree of obesity. In conclusion, IGF-I similar to insulin, exerts an adipogenic effect.

Keywords: Laron syndrome; Primary GH insensitivity; Body composition; Obesity; IGF-I treatment; IGF-I adipogenic effect

1. Introduction

Laron syndrome (LS = primary GH insensitivity or resistance), is an autosomal recessive disease caused by deletions or mutations in the GH receptor gene leading to an inability of insulin-like growth factor I (IGF-I) generation [1]. Among the resulting major body changes are dwarfism [2,3] and obesity [2,4]. The only effective treatment to promote linear growth in these patients is daily administration of biosynthetic IGF-I [5–7]. Reports on the effect of IGF-I on body adiposity are scant and contradictory depending on the duration of IGF-I treatment. During the first months of treatment a reduction in skinfold thickness was observed [8] with variable changes during the second year [5–7]. During IGF-I treatment of four or more years an increase in BMI and skinfolds was reported in almost all patients [9,10] [Laron unpublished].

Forthwith for the first time are data of body composition determinations by DEXA in children with LS on long-term IGF-I treatment.

2. Subjects

Three girls with classical LS diagnosed and treated by IGF-I in our clinic were studied. All were examined and measured by the same person (ZL). All three had normal thyroid, adrenal and kidney functions. Serum growth hormone levels were high and IGF-I levels were very low to undetectable.

3. Methods

Body composition was determined using DEXA (dual energy X-ray absorptiometry, Model DPX-IQ 8565-A, Lunar Radiation Corp., Madison, Wisc.,

* Corresponding author. Tel.: 972 3 9253610/1; fax: 972 3 9222996.
E-mail address: laronz@clalit.org.il (Z. Laron).

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USA). This method does not measure muscle mass. Body weight was measured by an electronic scale. Skinfolds were measured with a Harpender caliper. Nutritional intake was calculated from the detailed food intake listed by the parents and patients over a period of 7 days. The composition of the daily food intake was calculated using the norms published by the Israel Ministry of Health (Nutritional Tables, H. Meir, A. Reshef, Jerusalem 1996). Biosynthetic IGF-I (FK 780, Fujisawa, Osaka, Japan) was injected subcutaneously once daily during breakfast in doses ranging from 150–180 μg/kg body weight [5]. Serum IGF-I levels were determined at each follow-up visit. Control values were taken from published data for healthy children and adolescents [11–13]. The study was approved by the Hospital Ethical Committee.

4. Results

Table 1 shows the age, degree of height deficit, BMI, summed skinfold thickness at initiation of IGF-I treatment as well as the molecular defects of the GH receptor. Figs. 1a and 2a illustrate the appearance of Patients 2 and 3 in the early stages of treatment. Table 2 presents the changes in height, weight, BMI, summed skinfold thickness and percent body fat compared to normal control values. It is evident that concomitantly with an increase in height there was a marked increase in body adiposity to values double or triple the normal mean. For the three patients the percent of fat distribution between trunk, upper and lower extremities showed variations with a tendency to be higher in the limbs than the trunk.

It is of note that the BMI values do not reflect the degree of adiposity due to the underdevelopment of the skeletal and muscle tissues in this syndrome (1). Thus, in patients 1 and 2 the BMI appears normal. The mean kcal/kg daily intake ranged between 60 and 74 kcal which falls within the recommended daily allowances for the respective age groups [14]. Patients 1 and 2 are prepubertal. Patient 3 is in her early puberty (B2, G2, AH±, PH+).

Figs. 1b and 2b illustrate the body appearance of patients 2 and 3 on long-term IGF-I therapy. The serum total cholesterol levels in the three girls were in the normal range (140, 185, 180 mg/dl) as were the insulin levels

Table 1
Pertinent data of three girls with Laron syndrome at initiation of IGF-I treatment

Pt. no.	Age (years)	Height (cm) (SDS)[a]	Weight (kg)	BMI		Skinfolds[b] (mm)	Molecular defect of the GH-R
				(kg/m^2)	Centile[c]		
1	$7^{6/12}$	99.7 (−4)	19.6	19.3	(90)	56	3,5,6 exon del
2	9	83 (−7.9)	12	17.4	(50)	48	R43X (exon 4)
3	$3^{7/12}$	77.5 (−4.6)	9.8	16.54	(75)	33	785−1; G to T (intron 7)

GH-R, growth hormone receptor.
[a] SDS, height standard deviation score.
[b] The sum of suprailiac, triceps and subscapular skinfolds.
[c] Centiles for healthy girls from Ferrandez et al. [13] according to age.

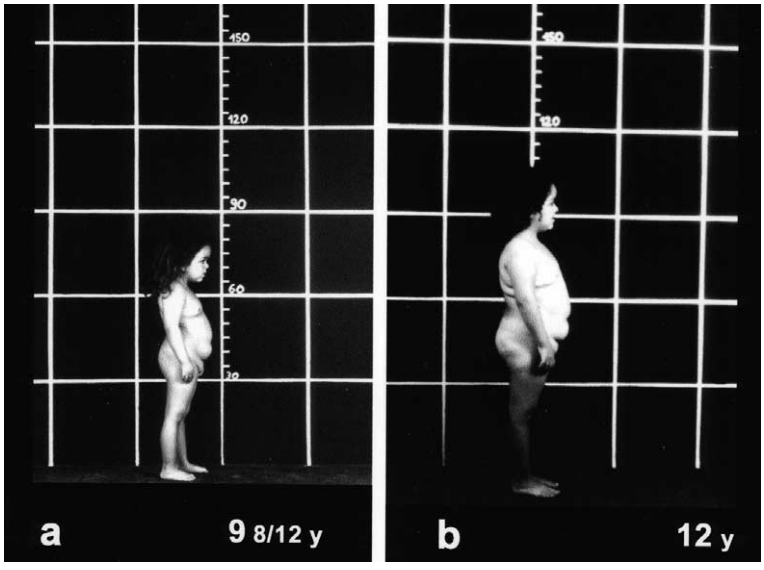

Fig. 1. (a) Lateral view of patient no. 2, aged $9^{8/12}$ years, months after initiation of IGF-I treatment and (b) after 3 years IGF-I administration. Note increase in degree of obesity.