

Early Investigations: Characterizations of the Circulating Growth Hormone

2

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Core Messages

- The introduction of radioimmunoassays in the 1960ies led to the recognition that the patients who clinically resembled GH deficiency but had high serum hGH levels, had a new disease entity.
- This chapter describes the psychological pattern of circadian hGH secretion in Laron syndrome patients, and the response to stimulatory and suppressing agents. Immunological tests and radioreceptor assays showed that the hGH molecule is normal. Liver biopsies from 2 LS patients proved that the hGH receptor is defect.

2.1 Regulation of Growth Hormone Secretion

2.1.1 Introduction

Identification of patients who resembled GH deficiency, both clinically (dwarfism, obesity) and biochemically (tendency for hypoglycemia) (Fig. 2.1), and high FFA (Fig. 2.2), but who had abnormally high overnight fasting serum concentrations of circulating hGH (Laron and Mannheimer 1966; Laron et al. 1968; Laron 1984) (Fig. 2.3), led us to conclude that we had discovered a new disease entity (Laron et al. 1966). To explain the high serum human growth hormone (hGH), we considered

two possibilities: (a) an abnormal hGH molecule or (b) a defect in the hGH receptors (Laron et al. 1966), leading to end organ resistance (Laron et al. 1971, 1980).

As the serum hGH levels in the same patient varied on different days, as seen in Fig. 2.3, possibly due to not complete fasting, previous exercise, stress, or physiological fluctuations, we investigated the diurnal secretion and regulation of GH secretion in these patients.

2.1.2 *In Vivo* 24 h Diurnal Pattern of hGH Secretion

Using a nonthrombogenic continuous blood withdrawal pump (Cormed, USA), the hGH secretory pattern was studied every 30 min in 3 patients with Laron syndrome and 2 age-matched controls (Keret et al. 1988). The radioimmunoassay (RIA) used was that of Laron and Mannheimer (1966). Figure 2.4 illustrates the 24-h hGH secretory profile in two young females and Fig. 2.5 that in an adult male with Laron syndrome. It is seen that in Laron syndrome patients similar to healthy individuals, hGH is secreted in pulses and that the number of daily peaks in the young adult patients is similar to healthy controls; however, both the daily peaks, and especially those during sleep, are significantly higher than those in the control subjects resembling those registered in acromegalic patients. The quantity of hGH secretion during a pulse as expressed by area under the curves and their average integrated concentrations are shown in Table 2.1.

It is further seen that both in the 27-year-old Laron syndrome patient as well as in its control subject the hGH values are lower than in the late pubertal or young adult patients, a decline known to occur with age in healthy individuals of both sexes (Zadik et al. 1985;

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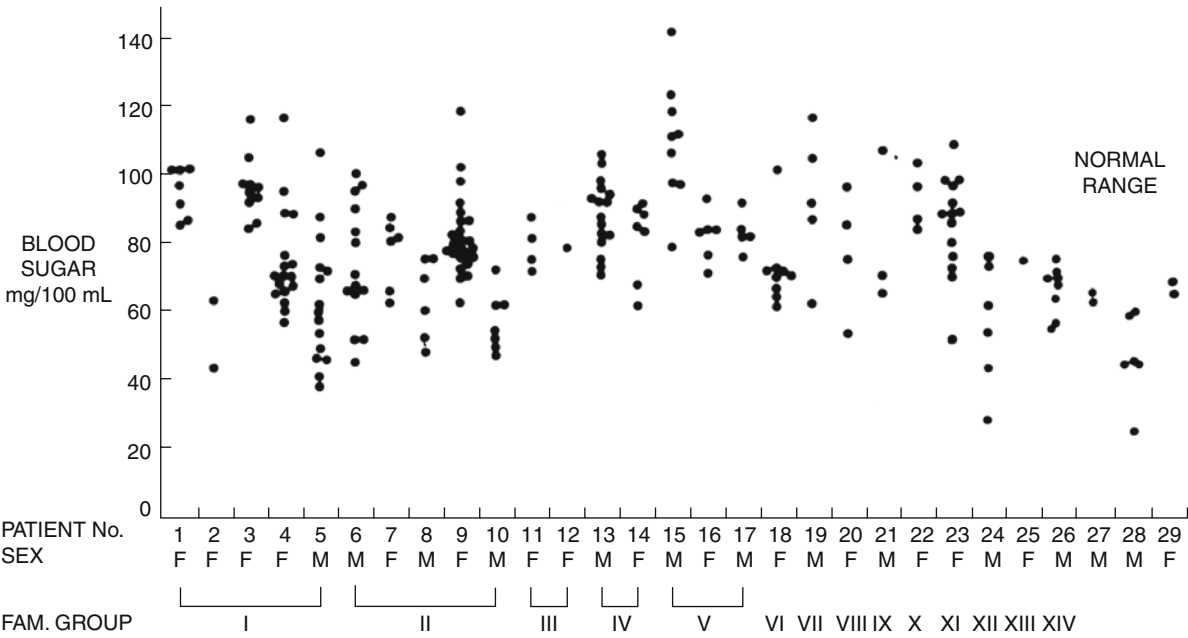


Fig. 2.1 Fasting blood glucose as total reducing substances in the first 29 patients. Reproduced with permission from Laron (1984)

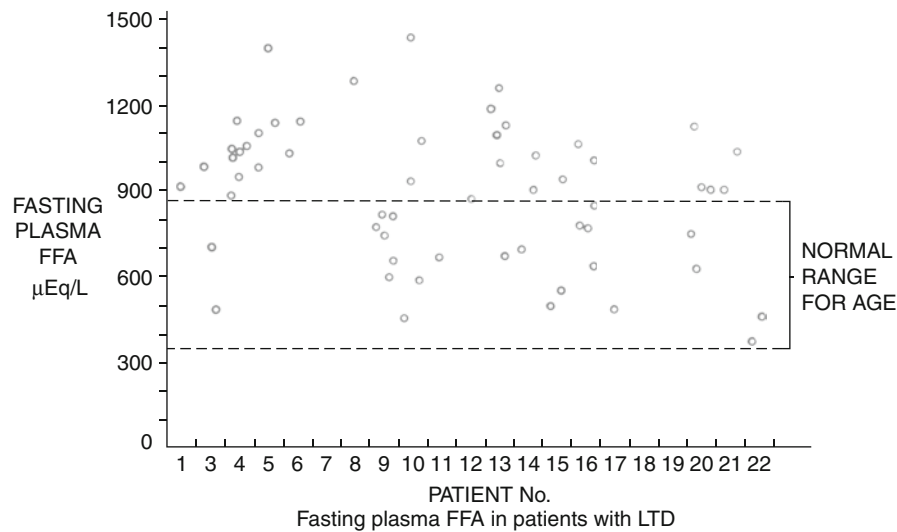
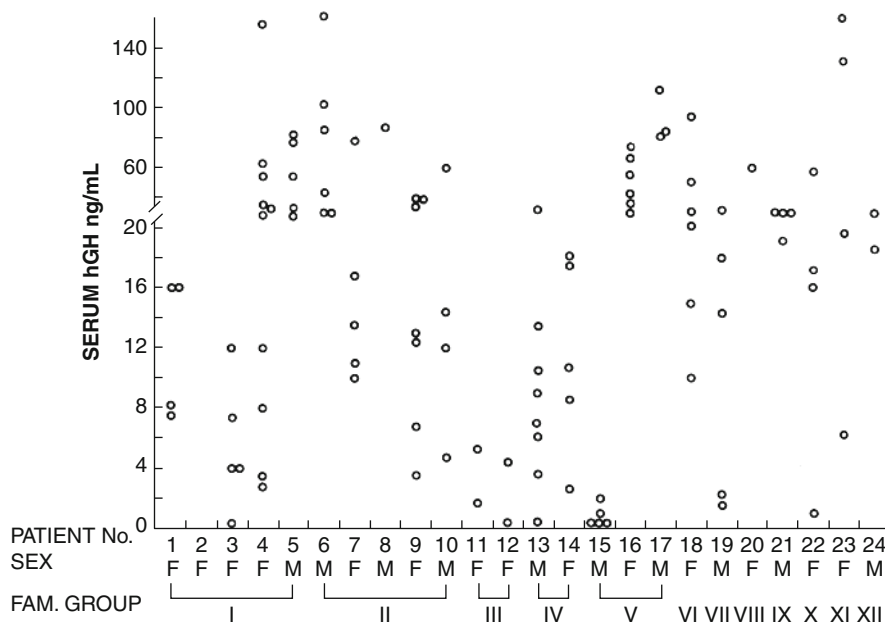


Fig. 2.2 Fasting plasma free fatty acids (FFA) in 22 patients with Laron syndrome. Reproduced with permission from Laron (1984)

Hartman 2000). Nevertheless, the secretion in the Laron syndrome patient is higher than that in the control subject (see also Chap. 26).
Calculating the production rate of hGH in Laron syndrome, we found it to be 2,480 ng/min, similar to that of patients with active acromegaly (MacGillivray

et al. 1970); on the other hand, the metabolic clearance rate was half that of control subjects (Keret et al. 1988). This can be explained by the reduced GFR in IGF-I deficiency (see Chap. 34) and the lack of functioning GH receptors in the kidney. It is of note that the values fall within the lower limit of the normal range (Owens

Fig. 2.3 Repeated serum growth hormone (hGH) levels in 24 patients with Laron syndrome. Reproduced with permission from Laron (1984)



et al. 1973). There is no doubt that both the increased production rate and reduced clearance rate contribute to the elevated serum hGH concentrations in Laron syndrome patients, which is primarily caused by the negative feedback induced by the IGF-I deficiency (Berelowitz et al. 1981).

2.1.3 Growth Hormone Stimulation Tests: The Insulin Tolerance Test (ITT)

In response to a bolus insulin (0.1 U/kg i.v.) to 17 children with Laron syndrome, there was a further rise in the elevated basal hGH levels up to 140–232 ng/mL. In 4 patients with high basal levels, there was a paradoxical response. Two patients had seizures so that future test doses were reduced to 0.05 U/kg i.v. (Laron et al. 1968). All children presented with hypoglycemia nonresponsiveness. Nowadays, we do not perform ITTs on Laron syndrome patients.

2.1.4 Arginine Test

Intravenous infusion of arginine (0.5 g/kg body weight infused over 30 min in a 10% solution) to 20

children with Laron syndrome showed a further increase of serum hGH in all Laron syndrome children (Fig. 2.6). No adverse effects were observed in this test.

2.1.5 Growth Hormone Suppression Tests

2.1.5.1 Somatostatin Administration

We studied the effect of intravenous injection of dihydrosomatostatin (SMS) (150 $\mu\text{g}/\text{m}^2$ over 5 min followed by 300 $\mu\text{g}/\text{m}^2$ over 40 min) on the hGH serum levels in 4 Laron syndrome patients (aged 7–18 years), one tested twice (Laron et al. 1977). The effect was compared to that obtained in one active acromegalic patient. The mean ($\pm\text{SD}$) results of the five tests on serum hGH, insulin, and glucagons in the Laron syndrome patients compared to an acromegalic patient are illustrated in Fig. 2.7.

It is seen that somatostatin acutely suppresses hGH, insulin, and glucagon. Due to discontinuation of the SMS infusion, the hGH levels made a significant rebound rise in both conditions, but more so in the Laron syndrome patients. The rebound of insulin after SMS was less in the Laron syndrome patients than in

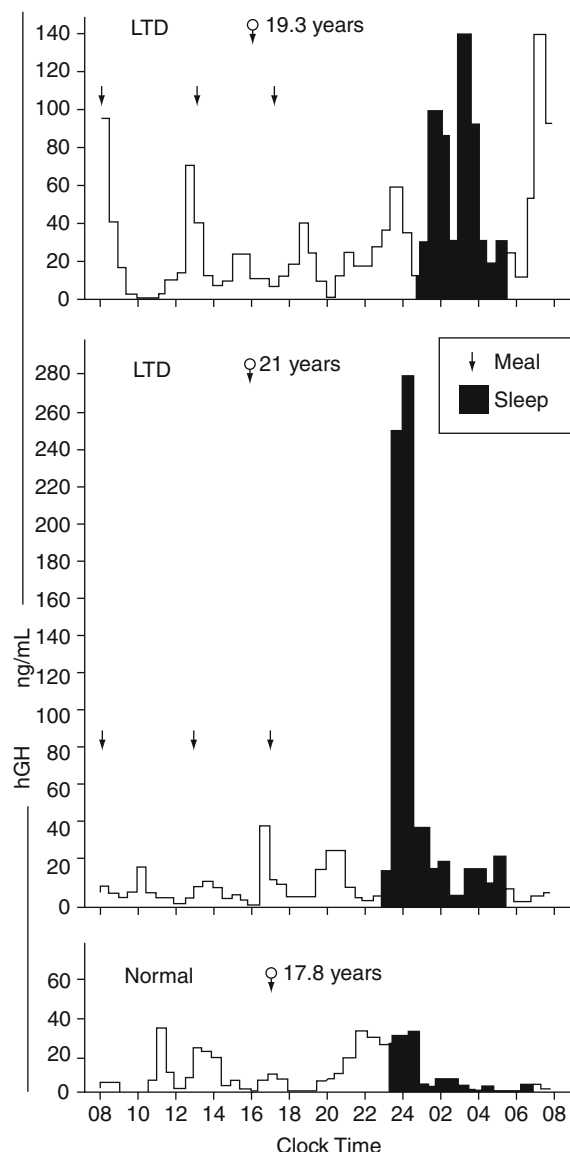


Fig. 2.4 24-h serum hGH profile in two young female adults with Laron syndrome compared to a healthy female control. Note the difference in hGH peak levels. Reproduced with permission from Keret et al. (1988)

the acromegalic patients. Somatostatin reduced also the serum TSH levels (not shown).

2.1.6 Oral Glucose Tolerance Test

Oral glucose administration (100 g/1.73 m² body surface) over 10–15 min in the fasting state to 10 Laron syndrome patients induced a reduction in serum hGH in variable degrees (Fig. 2.8).

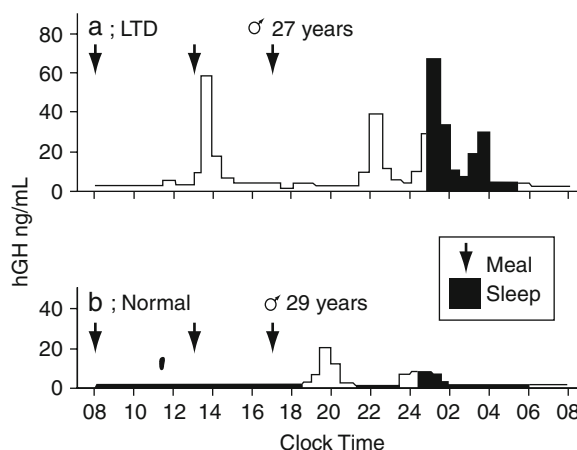


Fig. 2.5 24-h serum hGH profile in an adult male with Laron syndrome compared to a healthy control. Reproduced with permission from Keret et al. (1988)

2.1.7 Growth Hormone Response to Oral Corticosteroids

Administration of 6 alpha-methylprednisolone in divided doses of 10–15 mg daily for 3 days to 5 Laron syndrome children (4 females, 1 male) resulted in suppression of hGH in 2 patients and a paradoxical response in another 3 (Laron et al. 1968).

2.1.8 Conclusions

Both the secretory pattern and the regulatory behavior of hGH (stimulation and suppression) in patients with Laron syndrome were normal, but exaggerated. The next step we undertook was to find out whether the hGH of Laron syndrome patients is of normal structure. We decided to start with the immunological behavior of hGH in these patients.

2.2 Immunological Studies of the Serum GH from Patients with Laron Syndrome

2.2.1 Dilution Curves Using Radioimmunoassay

The shape of dilution curves obtained with serum hGH of patients with Laron syndrome (serum hGH

Table 2.1 Secretory dynamics of 24-h hGH secretion in three Laron Syndrome patients compared with normal subjects as controls

Subjects	Diagnosis	Sex	Age (year:months)	Serum hGH			
				Baseline range (ng/mL)	Maximal amplitude (ng/mL)	AUC	AIC (ng/mL)
Laron syndrome		F	19 ³	10	164	560	33.9
Laron syndrome		F	21	10	280	780	23.4
Control		F	17 ⁸	1–3	135	268	11.3
Laron syndrome		M	27	1–3	67	231	9.9
Control		M	29	1–3	19	51	2.2

Modified from Keret et al (1988)
AUC area under the curve; AIC average integrated concentration

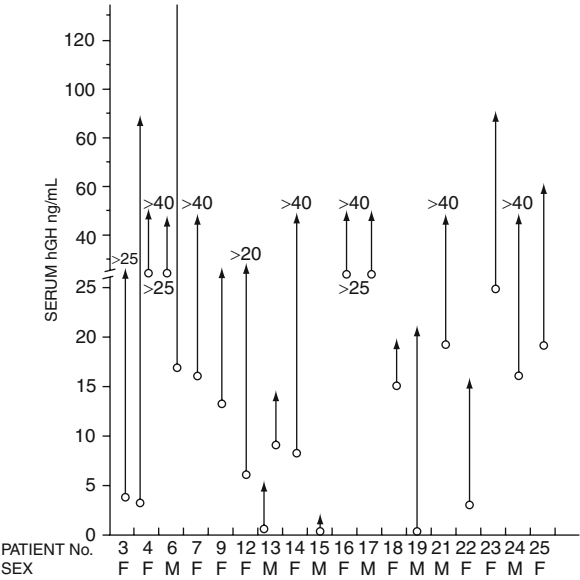


Fig. 2.6 Serum hGH response to arginine infusion in children with Laron syndrome. Reproduced with permission from Laron (1984)

concentrations of 10–68 ng/mL) was compared to that of serum hGH obtained from healthy children (stimulated serum hGH concentrations of 16–70 ng/mL), acromegalic patients (serum hGH 120–170 ng/mL), and healthy newborns (serum hGH concentrations of 16–70 ng/mL). The sera were tested with three different antisera (Eshet et al. 1973). The anti-hGH sera were one prepared by immunization of guinea pigs in our laboratory denoted AS-1 and another received from Yalow (NIH anti-hGH-2-5-19) denoted AS-2 and the serum of a patient who developed high titer of

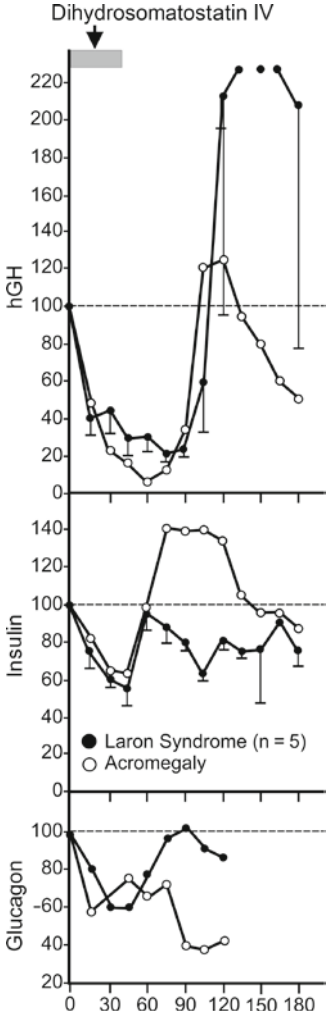


Fig. 2.7 Serum hGH, insulin, and glucagon response to intravenous somatostatin administration. Reproduced with permission from Laron (1984)

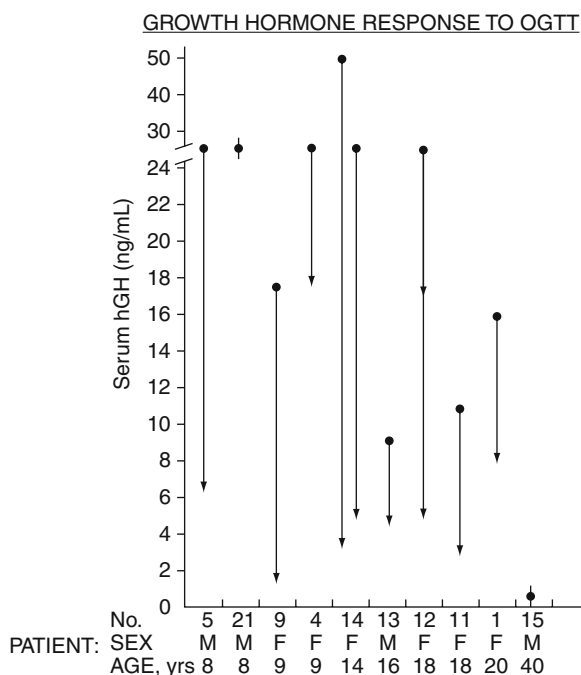


Fig. 2.8 Serum hGH response to an oral glucose load in 10 patients with Laron syndrome. Reproduced with permission from Laron (1984)

antibodies while on hGH therapy (kindly provided by Prader and Illig, Zurich) (AS-3). As all sera rendered similar results, we illustrate only the dilution curve with AS-1 (Fig. 2.9). Additional experiments used dilution curves of serum hGH of Laron syndrome patients in a hybrid system of RIA using ^{125}hGH and antiserum against HCS (human chorionic somatotropin) compared to anti-hGH serum. All the experiments revealed no differences in the immunological behavior of the hGH from patients with Laron syndrome compared to that in the control sera (Eshet et al. 1974).

2.2.2 Conclusions

The above findings were interpreted as suggestive that patients with Laron syndrome secrete hGH with a normal molecular structure. The next step to verify this assumption could be undertaken only when specific radioreceptor assays (RRA) for hGH became available.

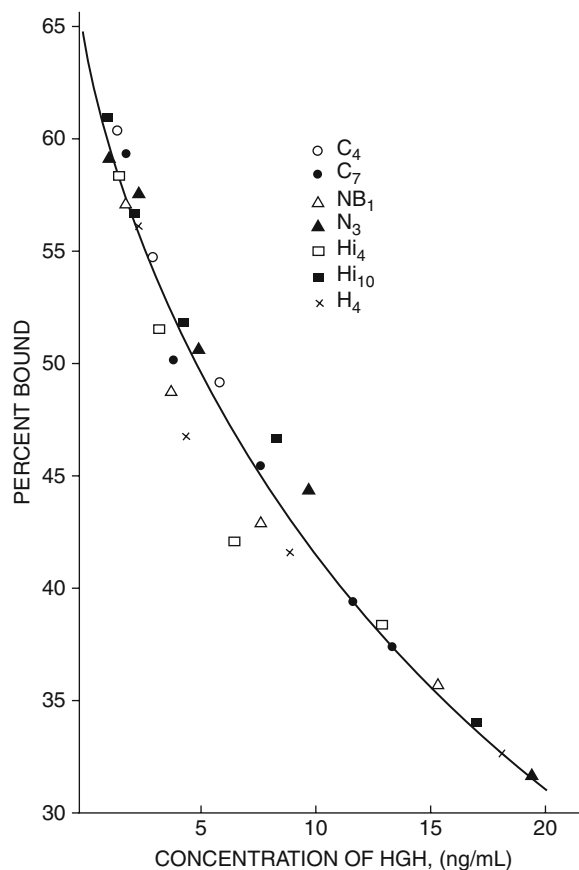


Fig. 2.9 Superimposition of dilution curves of serum hGH from Laron syndrome patients (*Hi*), compared with healthy children (*C*), newborns (*NB*), and acromegaly patients (*A*) on the standard curve using anti-hGH serum diluted $1:2 \times 10^{-6}$. The hGH of the various samples tested was brought to the same concentration (Eshet et al. 1973). Reproduced with permission from Laron (1984)

2.3 Comparison Between Radioimmunoassays and Radioreceptor Assays to Measure Circulating High in Patients with Laron Syndrome

Using a RRA for hGH (Tsushima and Friesen 1973) with a 100,000-g pellet of human liver tissue (obtained from a male donor of a kidney transplantation), serum hGH concentrations of 6 Laron syndrome patients, of healthy children, and of acromegalic patients were compared both by RIA and RRA (Eshet et al. 1985).

2.3.1 Methods

The RRA assay employed was as follows:

2.3.1.1 Specific Binding of ^{125}I -hGH to Human Livers in the Microsomal Fraction

Specific binding of hGH was demonstrated in six human liver samples tested in 31 different binding assays. The specific binding of these six liver specimens ranged from 3.9 to 12% with a mean value of 7.2% per 6 mg/mL of microsomal fraction protein. The binding experiments were performed using the liver of a 13-year-old donor.

2.3.1.2 Radioreceptor Assay

Precision. The specific binding of various amounts of ^{125}I -hGH to different concentrations of human liver microsomal receptors was tested. The most precise standard curve was obtained with 585 μg of microsomal fraction protein and 12.5×10^3 cpm of ^{125}I -hGH (0.7 ng).

Sensitivity. In seven separate RRA with human liver receptors using 585 μg /tube of microsomal protein and 0.7 ng of ^{125}I -hGH, the total binding in the absence of unlabelled hormone was $17.79 \pm 1.04\%$. Nonspecific binding, defined as the ^{125}I -hGH radioactivity bound in the presence of 5 μg /mL of unlabelled hormone, was $9.92 \pm 0.57\%$. Specific binding, therefore, was $7.86 \pm 0.82\%$.

Specificity. The ^{125}I -hGH bound by human liver receptors was displaced only by hGH. Other species of GH, e.g., bovine and ovine GH as well as hPRL, ovine and bovine PRL, hPL, did not inhibit the binding of ^{125}I -hGH to the human liver receptors even at a concentration of 10 μg /mL.

The results of the investigations are shown in Table 2.2. The hRRA/RIA ratio was better in the Laron syndrome patients than in the controls in whom the RIA values exceeded those found by the RRA. The dilution curves of the serum hGH from the Laron syndrome patients were parallel to the standard curve, denoting identical structure of the hGH at its binding sites.

2.3.1.3 Discussion

Previous reports of quantitative comparison of the hGH values obtained with the RIA and RRA in acromegalic and normal subjects using rabbit liver receptors showed a systematic overestimation by RIA (Herington et al. 1974; Sneyd et al. 1975). In our study with hRRA, we made the same observation (Table 2.2). Testing of the serum of Laron syndrome patients, however, showed a higher value of hGH in the RRA in four of the six patients. It is of note that Jacobs et al. (1976), who prior to this study had used a rabbit liver assay to test the serum of another seven of our Laron syndrome patients, found also an overestimation of the hGH values by RRA in two of these patients. These findings may be due to the fact that Jacobs et al. (1976) used a pregnant rabbit liver RRA which also binds lactogenic

Table 2.2 Comparison of hGH concentrations in serum as measured by RIA and human liver hRRA in patients with Laron syndrome, acromegaly, and a healthy control

Subjects	Sample number	RIA (ng/mL)	hRRA (ng/mL)	hRRA/RIA ratio, %	Slope of regression curve	F statistics
Laron syndrome patients	1	105.0	18.0	20	-2.645	0.47
	2	12.0	20.0	170	-4.631	
	3	90.0	140.0	150	-1.255	
	4	80.0	130.0	150	-1.453	
	5	17.5	40.0	200	-1.226	
	6	20.0	23.0	100	-3.517	
Acromegaly	12	352.0	50.0	14.6		
		168.0	45.0	25		
Normal control ^a	1	58.0 ^a	22.4	50		
Standard curve					-1.765	

The hGH values of each sample are expressed as the mean of three dilutions Modified from Eshet et al (1985)

^aThe values given for the normal subject is the peak value in a clonidine stimulation test

hormones in contradistinction to the human liver RRA we used and which was found specific for hGH (Eshet et al. 1985). The physiological meaning of discrepant findings is not clear and needs further investigation.

2.3.1.4 Conclusions

The immunological studies of hGH from Laron syndrome patients were interpreted as showing that the structure of the circulating pituitary GH of these patients is normal and that the RRA using human liver proved that their GH is biologically active.

2.4 Evidence that the Etiology of Laron Syndrome is a GH-Receptor Defect

2.4.1 Introduction

Having shown that the pituitary GH secreted by Laron syndrome patients has a normal immunological behavior and binds to human GH receptors, we disproved one of the early expressed possibilities that Laron syndrome patients secrete an abnormal GH. Thus, the second possibility of a GH resistant (insensitive) state had to exist (Laron et al. 1980). To prove this assumption, we convinced the mother of one 4-year-old Laron syndrome patient and a young adult Laron syndrome patient to agree to undergo an open liver biopsy to enable the preparation of GH receptors from Laron syndrome livers (Eshet et al. 1984).

Control liver tissue was obtained from kidney donors immediately after pronouncement of clinical death by traumatic causes (there were six donors, aged 13–47 years with a mean age of 24 years). The investigation was approved by the Ethical Hospital Committee.

2.4.2 Radioreceptor Assays Using Liver of Laron Syndrome Patients

2.4.2.1 Methods

The preparation of microsomes bearing hGH receptors was done as described by Tsushima and Friesen (1973). The liver tissue was homogenized in a 0.25 mM

sucrose solution and then centrifuged at 10,000 g for 10 min; the supernatant was then centrifuged at 100,000 g for 90 min yielding the microsomal pellet.

One gram of liver yielded 18 mg/mL of microsomal fraction protein. For the assay, 1.2 mg/100 μ L of this liver microsomal pellet fraction was incubated in duplicate with 0.7 ng/100 μ L of labeled hGH or insulin (specific activity 80 μ Ci/ μ g and 90 μ Ci/ μ g, respectively) in a 25 mM tris-HCl + 10 mM MgCl₂ buffer, pH 7.4 and 0.1% bovine serum albumin in a final volume of 0.5 mL. This mixture was incubated at 4°C with constant shaking for 48 h. Incubation was terminated by adding 2 mL ice-cold 0.1% bovine serum albumin tris/magnesium buffer. The fractions containing receptor-bound and free radioactivity were separated by centrifugation at 2,000 g for 30 min at 4°C. Radioactivity was measured in a 5260 Autogamma Scintillation Spectrometer (Packard, USA). Parallel incubations were made in the presence of excess (5 μ g/mL) unlabeled hormone. Specific binding is the difference between radioactivity bound in the absence (total binding) and in the presence (nonspecific binding) of excess unlabeled hormone, (in this case hGH) and is expressed as a percentage of the total radioactivity in the incubation mixture. The receptor binding studies made with the liver tissue from the 2 Laron syndrome patients were carried out concomitantly with those of the control liver tissue of a 13-year-old boy. The microsome preparations from the liver tissue of the six healthy control subjects were studied repeatedly.

2.4.2.2 Results

The liver microsomes from the Laron syndrome patients showed almost no specific binding of ¹²⁵I-hGH, (Table 2.3 and Fig. 2.10) whereas those from the healthy liver tissue showed specific binding ranging from 7.9 to 24% (average $14.5 \pm 3.2\%$) (Tables 2.3 and 2.4). Liver tissue from the 13-year-old control boy assayed concomitantly with that of the 2 Laron syndrome patients showed a specific binding of 28% for hGH. The microsomes of the Laron syndrome also showed binding of ¹²⁵I-insulin, which was comparable to those observed in healthy individuals. The serum levels of hGH prior to biopsy were 45 ng/mL in Patient 1 and 20 ng/mL in Patient 2; serum insulin was undetectable in Patient 1 and 48 mU/mL in Patient 2.

Table 2.3 Specific binding of ¹²⁵I-hGH and ¹²⁵I-insulin to liver microsomes from two patients with Laron syndrome and from one healthy control subject

Liver microsomes	Sex	Age (year)	Binding of ¹²⁵ I-hGH (%)			Binding of ¹²⁵ I-insulin (%)		
			Total	Nonspecific ^a	Specific	Total	Nonspecific ^b	Specific
Laron syndrome								
Patient 1	M	4	7.0	6.5	0.5	47.3	13.9	33.4
Patient 2	M	26	7.0	6.9	0.1	11.2	4.1	7.1
Healthy control subject	M	13	35.1	6.8	28.3	17.3	9.6	7.7

Liver tissue was tested per 12 mg/mL of microsomal fraction protein

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hGH human growth hormone; *M* male

^aWith 5 µg/mL hGH

^bWith 10 µg/mL insulin

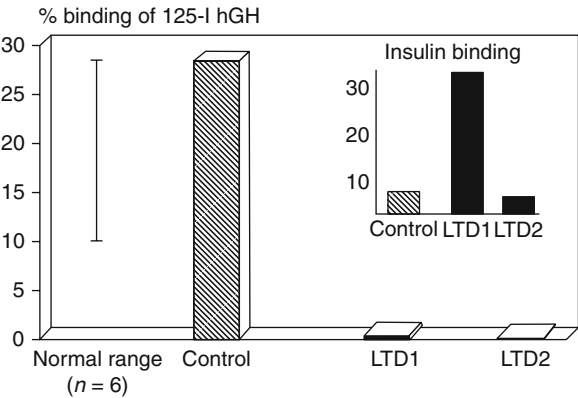


Fig. 2.10 Lack of ¹²⁵hGH binding to liver microsomes prepared from 2 Laron syndrome patients compared to liver microsomes from healthy controls. In contradistinction ¹²⁵I-labeled insulin bound to the liver microsomes from Laron syndrome patients

2.4.2.3 Discussion

Having shown that the liver of Laron syndrome patients is insensitive to hGH, the stimulus to generate IGF-I and the fact that the liver is the major source of IGF-I explain the lack of IGF-I secretion in this syndrome (Daughaday et al. 1969; Laron et al. 1971). This concept concurs with the findings of Golde et al. (1980) that erythroid colonies grown in vitro from 2 Laron syndrome patients were unresponsive to exogenous hGH in contrast to colonies from control subjects and patients with primary hGH deficiency. Further evidence found by us was that the addition of normal serum to cultures of fibroblasts from Laron syndrome patients enhanced the incorporation of ³H-thymidine (Nevo et al. 1977; Laron et al. 1980) (Table 2.5), whereas the addition of serum from Laron

Table 2.4 Specific binding of ¹²⁵I-hGH to liver microsomes taken from six normal-kidney donors

Sex	Age (year)	Number of assays performed	Specific binding (%)
Male	13	10	24.1 ± 4.3 ^a
Male	16	7	13.4 ± 3.0 ^a
Male	19	2	15.6 & 10.8
Female	20	5	16.2 ± 4.5 ^a
Male	30	2	7.3 & 8.6
Male	47	5	12.2 ± 3.2 ^a

Liver tissue was expressed per 12 mg/mL of microsomal fraction protein

hGH human growth hormone

Reproduced with permission from Eshet et al (1984)

^aValues are means ± SD

Table 2.5 Effect of sera (10%) from patients with Laron syndrome or, isolated GH deficiency (IGHD) and normal serum on the growth, in culture, of fibroblasts derived from 2 patients with Laron syndrome aged 10 and 12 years

Diagnosis (source of serum)	Number of sera	Protein per plate (µg ± SD)	³ H-thymidine (cpm/plate ± SD)
Laron syndrome	2	117 ± 13	927 ± 74
IGHD	7	105 ± 17	652 ± 168
Normal	Two pools	169 ± 6	1,251 ± 36
Without serum		8 ± 4	38 ± 21

All the trials were performed in triplicate.

Cells were allowed to grow for 72 h before harvest.

Statistical evaluation

Protein per plate: LS vs. control, *p* < 0.05; IGHD vs. control, *p* < 0.05 ³H-thymidine incorporation: LS vs. control, *p* < 0.002; IGHD vs. control, *p* < 0.002

Table 2.6 Effect of IGF-I deficient sera on the growth of normal human fibroblasts in culture^a

Source of serum	Number of sera ^b	Protein per plate ($\mu\text{g} \pm \text{SD}$)	³ H-thymidine (cpm/plate $\pm \text{SD}$)
Normal	One pool	200 \pm 17	360 \pm 23
Laron-type dwarfism	2	72 \pm 16	200 \pm 7
Isolated GH deficiency	5	118 \pm 44	252 \pm 82
Without serum		64 \pm 3	45 \pm 4

Statistical evaluation

Protein per plate: Laron syndrome vs. control, $p < 0.01$; IGHD vs. control, $p < 0.01$; ³H-thymidine incorporation: Laron syndrome vs. control, $p < 0.005$; IGHD vs. control, $p < 0.05$

Modified from Nevo et al. (1977)

^aThe fibroblasts were cultured from a superficial skin biopsy from a 15-year-old boy. All the trials were performed in triplicate. Cells were allowed to grow for 48 h before harvest. Sera were used in 10% concentration

^bEach patient's serum was investigated separately except those of the normal controls, which were pooled

syndrome and patients with IGHD caused a reduction in incorporation of ³H-thymidine into normal fibroblasts as well as a decrease in protein content (Table 2.6). Serum from Laron syndrome patients also did not stimulate the uptake of ³⁵S and ³H-D-glucosamine in calf-rib cartilage slices (Kleine et al. 1980). These findings indicate that the fibroblasts and the cartilage did not respond to IGF-I-deficient serum from patients with Laron syndrome in contradistinction to serum from control subjects containing active GH and IGF-I.

It can be assumed that the defect in hGH receptors in the Laron syndrome is not limited to the liver tissue and includes all tissues.

2.4.2.4 Conclusions

Our findings described were the first evidence that patients with Laron syndrome have a defect in the hGH receptors in their livers, which causes the resistance (insensitivity) to this hormone.

It thus took us 20 years from the description of this syndrome to obtain evidence of the etiopathology of the Laron syndrome, indicating that its defect is in the hGH receptors and explaining the lack of generation of IGF-I in the liver and may be other tissues.

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