Effect of insulin-like growth factor-I treatment on serum androgens and testicular and penile size in males with Laron syndrome (primary growth hormone resistance)

Z Laron and B Klinger

Endocrine and Diabetes Research Unit, Schneider Children's Medical Center, and Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel

(Correspondence should be addressed to Z Laron, Endocrine and Diabetes Research Unit, Schneider Children's Medical Center, 14 Kaplan Street, Petah Tikva 49202, Israel)

Abstract

Serum gonadotrophins, androgens, insulin and insulin-like growth factor-I (IGF-I) were determined before and during long-term treatment with recombinant IGF-I of seven males with Laron syndrome, and the changes correlated with changes in testicular volume and penile size. The subjects were four boys below the age of 5, two boys aged 10 and 14 but prepubertal and one 28-year-old fully sexually developed adult. IGF-I was administered by a once daily subcutaneous injection of 150 µg/kg per day to the boys and 120 µg/kg per day to the adult patient.

In the very young boys no change in serum gonadotrophins, androgens, gonads or genitals was registered. In the two older boys and the adult patient, there was a progressive rise in luteinizing hormone, follicle-stimulating hormone and testosterone. Concomitantly, there was an increase in size of the testes and penile length. The two boys started puberty. As very high serum IGF-I levels were registered in the adult patient, the daily dose was progressively decreased to 70 µg/kg per day. Stopping the IGF-I administration in this patient, according to the protocol, led to a return to pretreatment serum levels and testicular and penile size.

This report shows for the first time a direct effect of IGF-I on sex hormones and sex organs in the male.

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Introduction

Primary insulin-like growth factor-I (IGF-I) deficiency (Laron syndrome or primary growth hormone (GH) resistance or insensitivity) (1, 2) is characterized by small testes and penis (3, 4). These findings indicated that *in utero* levels of IGF-I influence prenatal sexual development. The micropenis described in some newborns with GH deficiency (5) also seems to be due to early IGF-I deficiency. It was therefore of interest to find out whether postnatal exogenous IGF-I administration influences male sexual development.

We herewith describe for the first time the effect of long-term IGF-I treatment on serum androgens and testicular and penile size in seven males with Laron syndrome.

Subjects and methods

Seven male patients with Laron syndrome were included in this study. Their pertinent clinical data are shown in Table 1. Four boys were prepubertal, two started puberty during IGF-I treatment and one was a young adult. Patient 5 started puberty one year after the

initiation of IGF-I treatment with a bone age of 8 years. Patient 6 started delayed puberty at age 16 years 6 months at a bone age of 11 years 6 months, i.e. 2 years after initiation of IGF-I treatment.

IGF-I (FK780; lots 115707K, 115807K, 710725K) synthesized by recombinant DNA technology (Fujisawa Pharmaceutical Co. Ltd, Osaka, Japan) with an identical amino acid sequence to that of natural IGF-I (6) was freshly dissolved and injected once daily by the s.c. route 15 min before breakfast to avoid hypoglycaemia. The boys received 150 µg/kg per day. The adult patient was started on a dose of 120 µg/kg per day, but because of a progressive increase in basal serum IGF-I levels and those at 4 h after the injection, the dose was progressively reduced to 70 µg/kg per day. In the adult patient the treatment was stopped after 9 months according to the protocol. The children were treated from 1 to 5 years. Serum samples were withdrawn in the morning after an overnight fast for measurement of all hormones, i.e. 24 h after the last IGF-I injection. An additional sample was taken 4 h after the injection to ascertain the serum IGF-I levels reached.

Serum IGF-I was measured by RIA after acid-ethanol extraction, followed by cryoprecipitation (7). Plasma

Table 1 Pertinent clinical data of male patients with Laron syndrome at initiation of IGF-I treatment.

Patient	Chronological age (years)	Bone age (years)	Height (cm)	Height SDS
1	0.5	0.2	55.7	-5.34
2	3.0	2.0	76.8	-4.54
3	3.4	1.5	69.0	-7.12
4	5.0	1.8	70.5	-7.97
5	10.1	7.0	112.2	-3.95
6	14.6	9.0	110.3	-6.50
7	28.0	Adult	139.0	-5.40

SDS, standard deviation score.

insulin was measured by a double-antibody RIA with an insulin standard donated by Novo Research Institute (Novo-Nordisk, Gentofte, Denmark). $\Delta 4$ -Androstenedione was measured by RIA with a kit from Diagnostic Systems Laboratories (TX, USA) dehydroepiandrosterone sulphate (DHEA-S), oestradiol and testosterone were measured by RIA with kits from Diagnostic Products Corporation (Los Angeles, CA, USA). Luteinizing hormone (LH) and follicle-stimulating hormone (FSH) were measured by immunoassays (Dia Sorin Diagnostics s.r.l., Saluggia, Italy). Testicular size was measured by bimanual palpation using an orchidometer. The stretched penile size was measured with a caliper.

Results

The gonadotrophins, testosterone and adrenal androgen levels in the four young prepubertal boys were low and did not change during the IGF-I treatment (data not shown), nor did their small testicular volume (Fig. 1) or penile length. In the two boys aged 10 and 14 (patients 5 and 6), there was a progressive rise in gonadotrophins and testosterone but no change (patient 5) or a decrease (patient 6) in $\Delta 4$ -androstenedione (Table 2). Concomitantly, there was an increase in size of testes (Fig. 1) and penile length. A gonadotropin-releasing hormone test was performed in patient 5 once puberty had started (testes volume 4 ml), and the peak serum LH was found to be 9.2 IU/l.

The adult patient who started treatment at age 28 with full sexual development showed further increase in testicular size (Fig. 1) from 13 to 18 ml and his stretched

Figure 1 Testicular volume of seven male patients with Laron syndrome before (○) and during (●) IGF-I treatment.

penile length increased from 12 to 13.5 cm. Stopping the administration of IGF-I led to a decrease in testicular volume and penile length to the pretreatment size. The hormonal changes in this patient are shown in Fig. 2. It can be seen that the dose of IGF-I (120 μ g/kg per day) usually used in adult patients with Laron syndrome (8) led to an increase in serum LH and FSH, total testosterone and DHEA-S (with fluctuations) and a decrease in the mean levels of $\Delta 4$ -androstenedione.

Of note is the observation that, during the period of IGF-I administration when serum IGF-I levels progressively increased, there was a reduction in insulin levels (Table 3), with a definite rise after the interruption of therapy in the adult patient. Weight changes during these periods were slight; however, there was a reduction in subscapular skinfold thickness from 27 to 17 mm in the adult and slightly less in the children.

Discussion

There is indirect evidence for a relationship between GH or IGF-I and sex hormones in man, as shown by clinical

Table 2 Serum gonadotrophins and androgen levels before and during IGF-I treatment of three male patients with Laron syndrome.

Patient	LH (mIU/ml)		FSH (mIU/ml)		Testosterone (nmol/l)		$\Delta 4$ -Androstenedione (nmol/l)	
	Basal	IGF-I	Basal	IGF-I	Basal	IGF-I	Basal	IGF-I
5	<0.3	1.5	0.9	1.7	<0.7	5.8	2.7	2.3
6	<0.3	1	0.8	1.8	0.9	3.8	4.2	1.9
7	0.3	6	3.0	7.3	18.6	28.0	6.8	2.8

Figure 2 Serum IGF-I (basal (open bars) and 4 h after injection (cross-hatched bars)), insulin, androgens and gonadotrophin before, during and after IGF-I treatment of a 28-year-old patient with Laron syndrome.

observations and laboratory data. This relationship, seemingly an interdependence on reciprocal activity, exists already in utero; thus newborns with primary IGF-I deficiency (Laron syndrome) or GH gene deletion have a small penis and testes (3–5). In the prepubertal period, the response of endogenous GH to pharmacological stimuli often becomes evident only after priming with sex hormones (10–12). During puberty the secretion of both GH and IGF-I increases (13, 14). Kamp *et al.* (15) in a recent review of available data concluded that GH treatment of prepubertal short children results in a somewhat faster rate of progression in boys and an earlier onset of puberty in girls. Children with Laron syndrome have delayed puberty which is more pronounced in boys (16, 17).

The present report indicates that IGF-I has a stimulating effect on gonadotrophin secretion, which in turn increases testicular testosterone secretion, without obvious effects on adrenal androgens. This effect was not observed in the four very young prepubertal boys, including one infant, but became evident in the 10- and 14-year-old boys and the adult. In the latter, who had reached full sexual development, IGF-I treatment further increased serum gonadotrophin and testosterone, with a concomitant increase in size of testes and penis. Treatment with IGF-I clearly advanced the age of onset of puberty and rate of pubertal progress in the two older boys (patients 5 and 6) when compared with previously untreated children (4) and also advanced their bone age more rapidly.

Table 3 Serum IGF-I (basal and 4 h after the s.c. IGF-I injection, at the first injection and during IGF-I treatment) and basal serum insulin (before and during IGF-I treatment).

Patient	IGF (nmol/l)				Insulin (μ U/l)	
	Before injection (O)	First injection (4 h)	Long-term IGF-I		O	Long-term IGF-I (Basal)
			Basal	4 h		
5	2.7	34	10	56	7	9
6	4.7	24	11	54	11	3
7	5.5	37	38	119	19	9

O, Overnight fasting before first IGF-I injection; Basal, overnight fasting.

The changes in serum FSH and androgens occurred concomitantly with a dramatic rise in basal serum levels of IGF-I and those observed 4 h after IGF-I injection (as seen in Fig. 2), reaching supraphysiological levels. Reduction of the daily IGF-I dose from 120 μ g/kg to 95 and 70 μ g/kg resulted in a parallel reduction in total testosterone. With the interruption of treatment in the adult patient, there was a fall in serum total testosterone, DHEA-S, FSH and LH and a reduction in testicular and penile size to pretreatment measurements. These data prove that the rise in IGF-I is the inducing stimulus for the rise in sex hormone secretion. This was also demonstrated in a previous study (9) in which we reported that four of six female patients with Laron syndrome (two girls and two young adults) progressively developed clinical signs of hyperandrogenism (oligo/amenorrhoea and acne) during IGF-I treatment. Laboratory determinations showed significant elevations in the serum LH/FSH ratio, testosterone and Δ 4-androstenedione. The hyperandrogenism occurred concomitantly with a rise in serum IGF-I to supraphysiological levels 4 h after injection. Reduction of the IGF-I dose or interruption of the IGF-I treatment restored androgen levels to normal values, and the clinical signs of hyperandrogenism disappeared. It is of interest that, in the females, IGF-I treatment also caused a rise in serum Δ 4-androstenedione concentration, whereas in the males this level decreased (in two patients) or did not change (in one patient). It is possible that this was related to serum IGF-I levels, which were higher in the females. The effect of IGF-I on serum DHEA-S, the regulation of the secretion of which is not known, was variable.

The androgen stimulation registered during long-term IGF-I administration in both males and females (9) occurred in parallel with suppression of insulin secretion and cannot therefore be attributed to this hormone, as was suggested in the case of polycystic ovary syndrome (18, 19).

The present and our previous report on female patients with Laron syndrome demonstrate that pharmacological levels of IGF-I encountered during IGF-I treatment induce hyperandrogenism. These effects were

shown to be dose-dependent. As there was also a rise in both gonadotrophins, LH and FSH, it is probable that the primary effect of IGF-I is on the gonadostat. This may also explain the lack of effect on androgens, gonads and genitalia in very young prepubertal children. On the other hand a direct effect of IGF-I on the sex hormone-producing cells cannot be excluded, IGF-I receptors having been found in granulosa cells (20), and a rise in circulating IGF-I may be able to enhance the action of FSH on Sertoli and Leydig cells (21, 22).

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