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Puberty in Laron Type Dwarfism

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Abstract. The onset and progress of puberty was followed in 18 patients (7 males and 11 females) with Laron-type dwarfism (LTD). The boys had delayed puberty, testicular enlargement occurring between 12–14 years being the first sign. The first conscious ejaculation occurred between 17–21 years and full maturity was reached after the age of 22. In girls menarche occurred between 13–14 years and full maturity was reached between 16–19 years. Two patients—one male and one female—have children.

Key words: Puberty – Laron-type dwarfism – Growth hormone – Pituitary dwarfism.

Introduction

In 1966 we described a syndrome of familial dwarfism which was indistinguishable both clinically and in many of the laboratory findings from pituitary dwarfism [7] but in which there were abnormally high plasma concentrations of immunoreactive human growth hormone (IR-hGH). This syndrome was named in the literature Laron-type dwarfism (LTD).

Later studies comprising a greater number of patients [8, 10] revealed the absence of serum somatomedin activity. The exact etiology of this syndrome has not yet been elucidated but it has been suggested that the defect may lie either in the liver cells which produce somatomedin or in the pituitary cells [12].

In an earlier review of these patients [11] we reported our observation that patients with this syndrome undergo sexual maturation. This was also the case in the patient described by Merimee et al. [14]. This paper describes in detail the pubertal process in patients with LTD.

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Subjects and Methods

We were able to follow the process of puberty in 18 of the 30 patients with LTD under care and observation in our clinic. Table 1 shows the country of origin of the parents of each of the 18 patients, the listing being according to family order within each sex. There are 7 males and 11 females belonging to 13 families, all of Jewish Oriental origin.

During the long term follow-up all patients underwent a complete physical examination in addition to body measurements. The appearance of the secondary sexual signs and developmental changes in the sex organs were carefully registered. The testicular volume was measured using an orchidometer [16] employing the norms of Zilka and Laron [20]. Penile length was measured with a caliper by unforced stretching [3] using the norms of Schonfeld and Beebe [18]. Breast measurements were made with the aid of a caliper for measurement of the diameter or tape for measurement of the half circumference [2]. The stage of development of the nipples and areolae was registered as well. During puberty the patients were questioned about the appearance of menarche or first conscious ejaculation at each visit [13], enabling us to establish the exact age at which milestones were passed. Bone age was assessed by hand and wrist X-ray in accordance with the Atlas of Greulich and Pyle [5] at least once a year, and also close to menarche or the first conscious ejaculation.

Results

Sexual Signs-Boys. All seven boys have reached the age of at least 15 years. The sequence of appearance of pubertal signs is shown in Fig. 1. The first sign was testicular enlargement in 6 boys. The 7th patient (No. 2), now aged 20 years, has no pubertal signs; lack

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Table 1. Distribution of 18 patients with Laron-type dwarfism in whom puberty was observed

Family	Patient No.	Name	Sex	Country of origin	Age at referral (yrs : mos)	Age at least examination (yrs : mos)	Final height (cm)
A	1	Sh.S.	M	Yemen	3 : 4	24	119.0
A	2	S.S.	M	Yemen	Newborn	20	
B	3	G.J.	M	Yemen	0 : 5	20	
C	4	J.L.	M	Iraq	7 : 8	25	128.0
D	5	R.B.	M	Iraq	1 : 0	16	
E	6	N.A.	M	Iran	11 : 11	15	
F	7	S.E.	M	Iran	5 : 10	16	
A	8	R.S.	F	Yemen	1 : 7	21	128.5
B	9	R.J.	F	Yemen	3 : 7	23	112.5
C	10	M.L.	F	Iraq	5 : 6	22	110.5
D	11	S.B.	F	Iraq	2 : 8	18	117.0
G	12	E.C.	F	Afghanistan	9 : 8	28	119.5
G	13	R.C.	F	Afghanistan	8 : 5	27	108.5
H	14	S.C.	F	Iran	13 : 3	28	120.5
I	15	R.S.	F	Iraq	9 : 9	29	113.5
J	16	P.M.	F	Iran	2 : 0	18	136.0
K	17	F.J.	F	Iran	12 : 10	13	
L	18	Y.M.	F	Iraq	0 : 5	12	

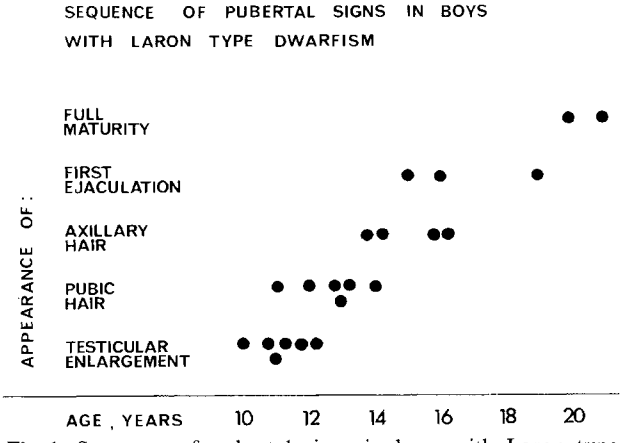

Fig. 1. Sequence of pubertal signs in boys with Laron type dwarfism

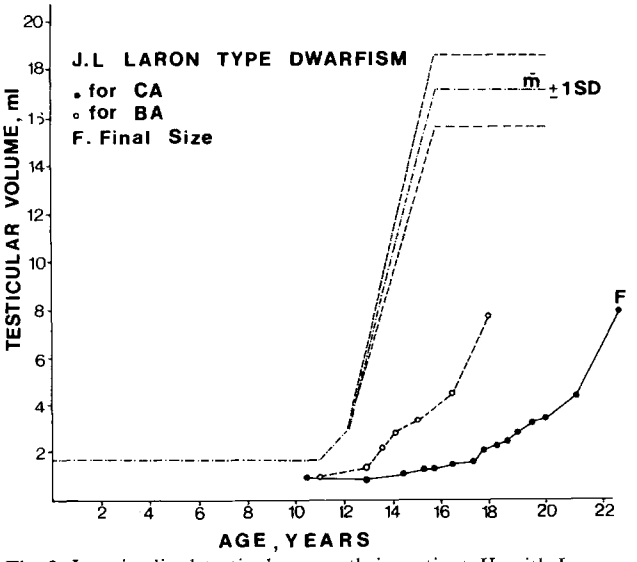

Fig. 2. Longitudinal testicular growth in patient JL with Laron type dwarfism. CA = Chronological age; BA = Bone age

of cooperation prevented us from investigating him. In the remaining boys the pubertal process was slightly delayed. Testicular enlargement started between 12–14 years. The appearance of pubic hair was between 13–16 years and of axillary hair after 16 years. The first conscious ejaculation was registered in 3 boys at 17, 18 and 21 years of age. Full maturity was reached after age 22 in 2 patients (Nos. 1 and 4). The slowness of the pubertal process is illustrated in the longitudinal growth of the testes and penis in these 2 patients (Figs. 2–5). The testes remained small, as was also found in another patient who is the father of two affected children [10]. The penis enlarged to within the low normal range, as illustrated in patient Sh.S. (No. 1) (Fig. 5). Plotting the size for bone age decreases the lag but does nor normalize it. The appearance of one of these patients at full maturity can be seen in Fig. 6.

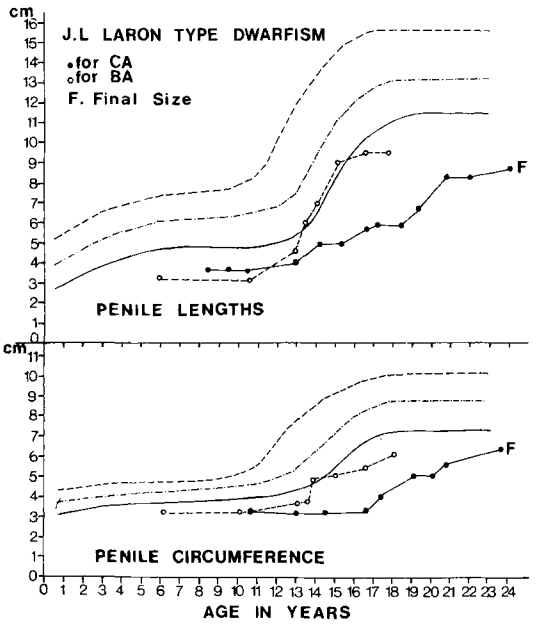

Fig. 3. Longitudinal penile growth in patient JL with Laron type dwarfism

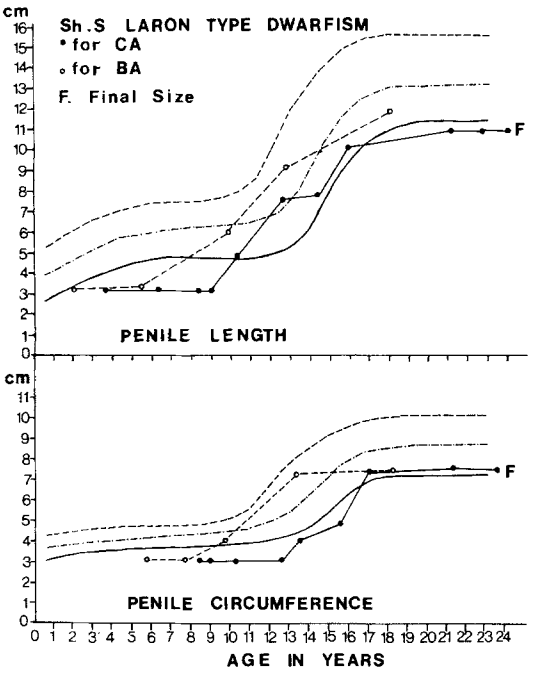

Fig. 5. Longitudinal penile growth in patient ShS with Laron type dwarfism

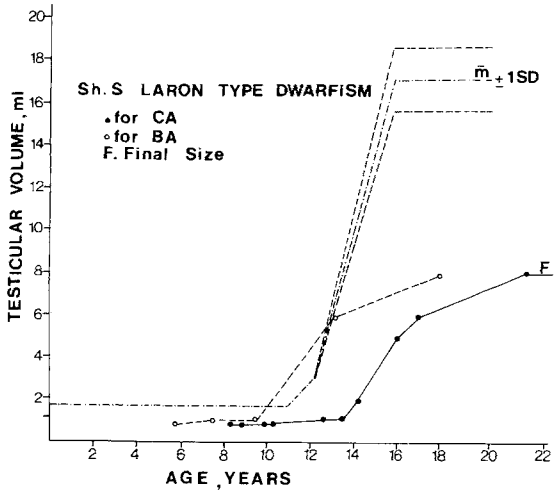

Fig. 4. Longitudinal testicular growth in patient ShS with Laron type dwarfism

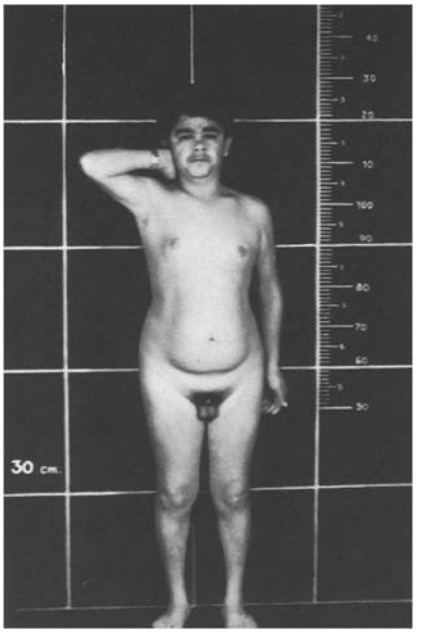

Fig. 6. The appearance of patient JL with Laron type dwarfism at age $19^{2}/_{12}$ years. Note full sexual development

Sexual Signs-Girl. The sequence of appearance of pubertal signs is shown in Fig. 7. Ten girls have passed the age of 13 years and show signs of active puberty. The first signs were breast budding and the appearance of pubic hair. Despite relatively slow initial development, 6 of the 9 girls entered menarche between 13–14 years of age. Full maturity was reached between the ages of 16–19 years, the breast size being normal or even large for the size of the patient (Fig. 8). Patient No. 14 was not followed regularly but we know that her age at menarche was $13^{6}/_{12}$ years. She is at present 28 years old, married and the mother of two children.

Pubertal Growth Spurt. For appraisal of the natural growth spurt in this syndrome we included only those patients who were measured in our clinic on a regular

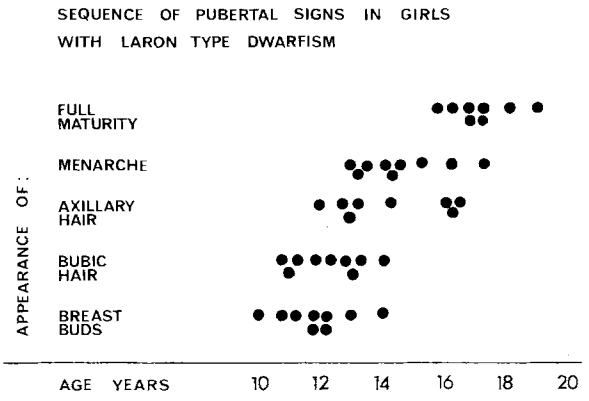

Fig. 7. Sequence of pubertal signs in girls with Laron type dwarfism

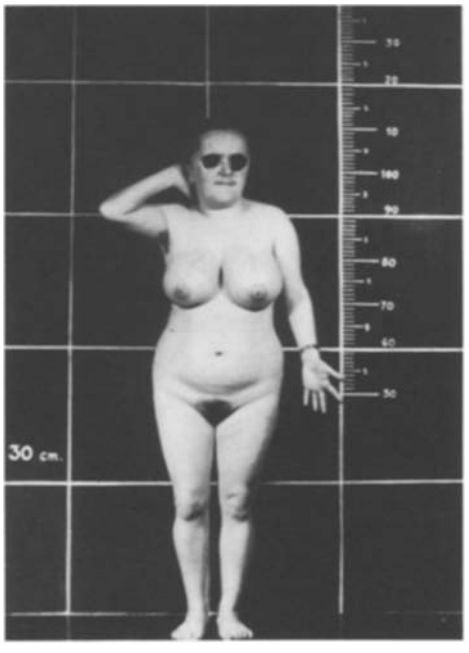

Fig. 8. The appearance of patient RC with Laron type dwarfism at $19^{10}/_{12}$ years. Note full sexual development, especially the large breasts relative to body size

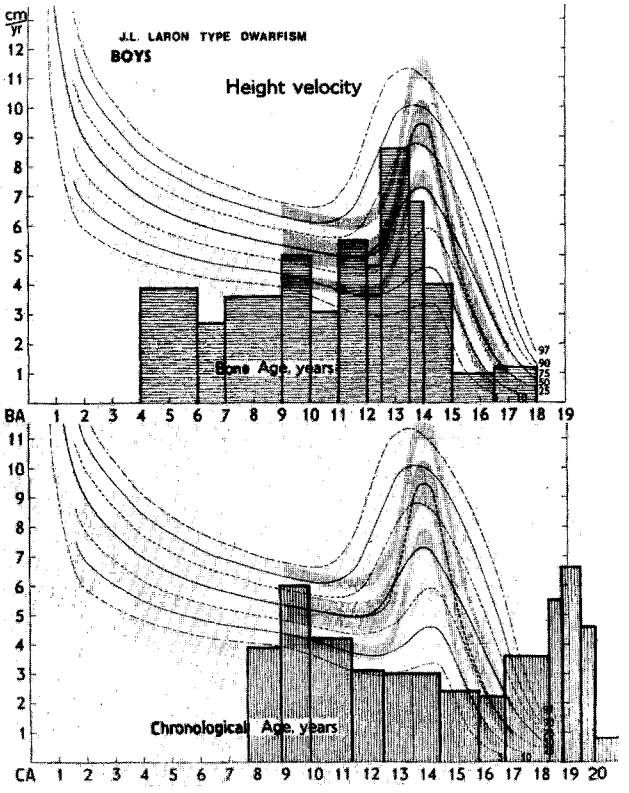

Fig. 9. Growth velocity chart of patient JL with Laron type dwarfism. The growth velocity is related to the chronological as well as to bone age

basis before and throughout puberty. We excluded patients who had received thyroid preparations or androgens for long periods, as well as the younger patients. Eight patients (3 males and 5 females) conformed with the above criteria. Of these, 5 patients (3 males and 2 females) showed a clear pubertal growth spurt (Table 2). In 3 females (Pts. Nos. 9–11) there was no spurt. It is seen that the maximal growth spurt ranged between 6–7 cm/year for both sexes which corresponds to the normal range of pubertal spurt. The age of the initiation of the spurt and the peak rate

Table 2. Pubertal growth spurt in five patients with Laron type dwarfism

Patient No.	Sex	Growth velocity		Age at			
		Before puberty	Maximal pubertal spurt	Start of spurt		Maximal spurt	
				CA	BA	CA	BA
		cm/y		yrs : mos			
1	M	3.1	7.0	14:7	12:0	16:3	13:0
3	M	2.6	6.0	13:8	9:0	17:0	14:6
4	M	2.2	6.6	16:9	12:9	18:9	13:0
8	F	3.6	7.0	11:6	9:6	13:0	11:0
16	F	2.8	6.0	11:0	10:6	12:0	12:0

ranged widely, but when related to the bone age, the range was quite narrow and corresponds to the normal limits (Fig. 9).

Discussion

The present survey on the development of puberty in boys and girls with Laron-type dwarfism revealed that there was a definite delay in the onset of puberty in the boys. This is particularly striking in view of the finding that normal Jewish Israeli boys of Oriental origin mature earlier than boys of European origin [6]. Furthermore, the process of puberty in boys with LTD is slower and they reach full puberty later than normal boys. Their testes remain small in adulthood although sexual function is normal [12]. In contradistinction, the girls showed no evidence of delayed puberty. The reason for this difference is not clear at present.

If we consider that Laron-type dwarfism is an extreme model of congenital and long-standing deficiency of hGH and somatomedin activity, the findings described should exemplify what happens in hereditary or congenital isolated growth hormone deficiency (IGHD). Despite difficulty in verifying this hypothesis because of lack of sufficient data on patients with IGHD who have not received any treatment and have been followed regularly from prepuberty into puberty, the observations available support the view that hGH deficiency delays the age at which spontaneous puberty starts [17, 19], and that initiation of hGH treatment accelerates the appearance of puberty [4]. The delay in puberty in IGHD occurs despite a normal secretion of gonadotrophins [15]. The lack of pubertal spurt observed in 3 of the girls with LTD has also been reported for isolated growth hormone deficiency [17]. However, in contradistinction to our observation in LTD, some females with IGHD also seem to have delayed puberty [17, 19]. This difference may be due to individual variation and the small number of patients in each group.

In conclusion, hGH or somatomedin not only influence the size of gonads and genitalia [9] but also the initiation and progression of puberty by a mechanism of interdependence with the sex hormones which appears to be more prominent in males [1] than in females. Further longitudinal observations in both sexes, accompanied by repeated endocrine evaluation, will help to clarify these issues.

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