Growth curves for Laron syndrome

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Abstract

Growth curves for children with Laron syndrome were constructed on the basis of repeated measurements made throughout infancy, childhood, and puberty in 24 (10 boys, 14 girls) of the 41 patients with this syndrome investigated in our clinic. Growth retardation was already noted at birth, the birth length ranging from 42 to 46 cm in the 12/20 available measurements. The postnatal growth curves deviated sharply from the normal from infancy on. Both sexes showed no clear pubertal spurt. Girls completed their growth between the age of 16-19 years to a final mean (SD) height of 119 (8.5) cm whereas the boys continued growing beyond the age of 20 years, achieving a final height of 124 (8.5) cm. At all ages the upper to lower body segment ratio was more than 2 SD above the normal mean. These growth curves constitute a model not only for primary, hereditary insulin-like growth factor-I (IGF-I) deficiency (Laron syndrome) but also for untreated secondary IGF-I deficiencies such as growth hormone gene deletion and idiopathic congenital isolated growth hormone deficiency. They should also be useful in the follow up of children with Laron syndrome treated with biosynthetic recombinant IGF-I.

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Laron syndrome is a recessively inherited disease^{1,2} that is clinically indistinguishable from growth hormone deficiency.³ It is characterised by high concentrations of circulating growth

hormone and very low concentrations of insulin-like growth factor-I (IGF-I).⁴ The pathogenesis of this syndrome has been found to reside in the growth hormone receptors⁵ and is due to molecular defects mostly in the extracellular domain of the receptor gene.⁶⁻⁸ This defect leads to an inability of the liver to synthesise the growth hormone dependent IGF-I⁴ resulting in a marked impairment of body and organ growth. The extreme short stature of these patients is very severe and starts in utero, and their final heights are very low. Their upper to lower body proportions are more than 2 SD above the normal mean² denoting a lag in growth of the lower limbs compared with the body.

We followed up a group of patients with Laron syndrome from infancy to final height and we present their growth curves, growth velocity curves, and the final heights of both sexes. These curves constitute a model for untreated hereditary/congenital deficiency of growth hormone releasing hormone, growth hormone, or IGF-I.

Patients and methods

Out of 41 patients with Laron syndrome who were diagnosed and examined at our clinic (30 of Jewish and 11 of Arab origin),⁹ 24 were followed up closely from infancy into adulthood, almost all being measured once or twice a year. At each visit they underwent a complete physical examination, including anthropometric measurements (length and height), performed by the same two nurses using Harpenden stadiometers. For sit-

Figure 1 Growth curve for height in girls with Laron syndrome from birth to 20 years.

Figure 2 Growth curve for height in boys with Laron syndrome from birth to 20 years.

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Figure 3 Growth velocity curve in girls with Laron syndrome from birth to 20 years.

ting height an anthropometer was used, the length of the lower segment being calculated by subtracting sitting height from total height. They were compared with charts designed for healthy Israeli children.¹⁰ The 24 patients (10 boys, 14 girls) were found to have sufficient measurements to allow their inclusion in the calculations of growth charts.

At first the growth increments over periods of 1–3 years were calculated for each sex separately. These increments enabled us to plot the growth velocity curve.

The height curves were constructed using the Tanner-Gupta method¹¹ as follows: the mean height was calculated for boys at age 10 and for girls at age 8 years. From these points the mean calculated yearly growth increments were added or subtracted going backwards to birth (age 0) or forward up to age 20. Both the growth velocity

Figure 4 Growth velocity curve in boys with Laron syndrome from birth to 20 years.

Figure 5 Upper to lower body segment ratios in 11 girls with Laron syndrome plotted on Arad/Laron charts.¹⁰

and height curves were smoothed using the 'Lowess' method.¹² The final height was established when the subjects grew less than 1 cm during one year.

Results

Twenty newborn infants had birth length measured⁹ and in 12 it ranged from 42 to 46 cm and was 2 SD or more below the normal length for sex and ethnic origin.¹³ In eight the birth length was within normal limits. Figures 1 and 2 represent the smoothed height growth curves as mean (2 SD) for girls and boys with Laron syndrome. From the two charts it is seen that the spread of the mean (2 SD) is wider in boys than in girls. The girls reached their final height between ages 16–19 years whereas the boys continued to grow beyond age 20. The mean (SD) final height of the girls was 119.5 (8.5) cm and that of the boys (reached around age 24 years and not shown on the graphs) was 124.1 (8.5) cm. Figures 3 and 4 illustrate the growth velocity curves of the girls and boys with Laron syndrome. It is evident that both sexes lack the typical pubertal growth spurt. The mean age at onset of puberty in girls was 10.7 (0.7) years and in boys 15.6 (2.6) years. Figures 5 and 6 show the upper to lower body segment ratio.

Figure 6 Upper to lower body segment ratios in 10 boys with Laron syndrome plotted on Arad/Laron charts.¹⁰

Discussion

The use of a reference growth chart is routine nowadays in any paediatric clinic. Height and growth are plotted on one of the several growth charts developed for normal children based on the Tanner-Whitehouse charts.¹⁴ For children with certain diseases characterised by marked growth retardation and a typical growth pattern, special growth charts have been established,¹⁵ thus there is a growth curve for achondroplasia,¹⁶ for girls with Turner's syndrome,¹⁷ and for Noonan's syndrome.¹⁸

Children with Laron syndrome^{1,2} grow at a subnormal rate because of their inability to generate endogenous IGF-I,⁴ which is caused by a molecular defect in the growth hormone receptors,⁵⁻⁸ and this results in a growth hormone resistant state. These patients present a uniform type of growth retardation. The opportunity we had to follow up a large group of patients throughout infancy and childhood into adulthood enabled us to construct growth curves for the patients with Laron syndrome and to learn about the role of growth hormone and IGF-I on body growth.

The fact that some of these patients are shorter than normal at birth suggests that, contrary to previous beliefs, IGF-I also influences intra-uterine growth to some degree. Postnatally the growth velocity slows, and after age 3 years maintains a velocity of 4–5 cm/year in girls and 3–4 cm in boys. This difference in velocity makes the mean height of the girls greater than that of the boys between ages 5–15 years but always much below the normal curves. Despite the fact that patients with Laron syndrome have full sexual development¹⁹ they do not have a pubertal growth spurt. They grow slowly and have a delayed and slow puberty that is more accentuated in the boys.²⁰ These facts explain why boys continue to grow even after age 20, an age at which the girls have already reached final height.

Our findings prove that postnatal growth proceeds even in the absence of circulating IGF-I, but the prenatal and perinatal deficit can never be made up. In the absence of IGF-I puberty is delayed and prolonged and this prevents the pubertal growth spurt. The significantly higher than normal upper to lower body segment ratio denotes that the deficient height is proportionately more in leg growth than it is in sitting height.

We have previously described that skull size as measured by head circumference is smaller than the normal in patients with Laron syndrome.^{2,21} Acromicria – small chin, hands, and feet – is also typical of this syndrome.^{1,2,19} The above findings document the important role that IGF-I, the effector hormone of pituitary growth hormone, has on total body and segmental growth.

The linear growth and growth velocity curves presented for boys and girls with Laron syndrome constitute a model not only for primary IGF-I deficiency and growth hormone resistance syndromes, but also for perinatal growth hormone/IGF-I deficiency and untreated growth hormone gene deletion.^{22,23} These charts should also be of use when following the recently introduced treatment regimen of those with Laron syndrome²⁴ and growth hormone gene

deletion type IA patients²⁵ with biosynthetic IGF-I.

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