Long-term auxological and pubertal outcome of patients with hereditary insulin-like growth factor-I deficiency (Laron and growth hormone-gene deletion syndrome) treated with recombinant human insulin-like growth factor-I

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ABSTRACT. Background: GH-IGF-I axis is mainly involved in the complex process of somatic growth but emerging evidence suggests that it also influences hypothalamic-pituitary-gonadal (HPG) function. Subjects: We report some data regarding long-term auxological and pubertal outcome of five female patients with hereditary forms of GH-IGF-I deficiency (Laron and GH-gene deletion syndrome) and a mean age of 23.4±5.3 yr (range 19-32). Methods: All the patients received recombinant human IGF-I (rhIGF-I, Pharmacia and Upjohn, Stockholm, Sweden, and rhIGF-I, Genentech, San Francisco, CA, USA) from a mean age of 8.6 yr (range 3.2-14.2) up to the final height. Results: Final height was very disappointing (≤ –5.0 SD scores) and lower than target height in all the patients. Pubertal onset was delayed in most of them but menarche occurred spontaneously in all the patients. Median age at menarche was 15.1 yr. Menstrual cycles were regular for several years. Median duration of gynecological follow-up was 8.3 yr with the longest span of 17.2 yr. Conclusion: We can assert that GH-IGF-I axis has an essential role in promoting linear growth in humans and its physiological action cannot be replaced by pharmacological treatment in most patients with hereditary forms of IGF-I insufficiency as demonstrated by their subnormal final height. Our clinical observations can also support an essential role of IGF-I in genitalia growth but not in the function of HPG axis as demonstrated by the maintenance of regular menstrual cycles in the presence of subnormal levels of IGF-I after treatment discontinuation. (J. Endocrinol. Invest. 34: 292-295, 2011) ©2011, Editrice Kurtis

INTRODUCTION

GH-IGF-I axis is involved in the complex process of somatic growth and development but emerging evidence suggests that it also influences hypothalamic-pituitary-gonadal (HPG) function (1). The secretion of GH stimulates the synthesis of IGF-I in the liver and other organs, such as lung, kidney, thymus, spleen, heart, muscle and gonads, and this mediator acts by binding to its receptors, localized in numerous tissues, including ovary and brain (2, 3). Both in vitro and in vivo observations indicate that IGF-I has a modulatory effect on the reproductive axis and links somatic development to the reproductive system. IGF-I acts at different levels of the HPG axis; it exerts paracrine effects at the ovary and stimulates GnRH at the hypothalamic-pituitary level (4). Most of this evidence, about the relationship between IGF-I and HPG axis, comes from animal studies because of ethical and practical limitations in studying humans. Only few reports have been published that demonstrate a modulatory but not essential role of IGF-I on female sexual maturation (5). Therefore, we believe that reporting some data regarding pubertal development of patients with hereditary forms of GH-IGF-I deficiency (Laron and GH-gene deletion syndrome) may be of special interest. We also describe the growth response to recombinant human IGF-I (rhIGF-I) treatment and auxological evolution up to the final height.

SUBJECTS

Patients’ characteristics

We collected molecular, auxological and pubertal data of five girls with hereditary deficiency of GH-I, secondary to insensitivity to GH action (Laron syndrome) in four of them and GH-gene deletion in the remaining one (Tables 1 and 2). We describe the growth response to rhIGF-I therapy up to the final height and the overall pubertal development (Tables 1 and 2). The distinctive feature of these patients was severe height deficiency, starting in the first years of life. Most of them were referred to an Endocrinological Unit with suspected GH deficiency at a chronological age <2 yr (Table 1) and in all of them the diagnosis was ascertained before they were 4 yr old by molecular analysis of either GH gene or GH receptor gene (Table 1). Height deficiency at diagnosis varied moderately but was >4 SD scores (SDS) below the mean in all of them, with a median value of – 5.2 SDS (Table 1). GH secretion was blunted in the girl with GH-gene deletion and not evocable after pharmacological stimulation tests (clonidine,
rhIGF-I therapy in hereditary IGF-I deficiency

levo-dopa), while in the four patients with Laron syndrome, both basal GH and its peak after stimulation test were very high (>70 μg/l). Basal IGF-I concentration was very low or undetectable in all the patients, both at diagnosis and in adulthood (Table 2).

Only one girl (#5) was treated with GH, but her outcome was very disappointing in terms of statural gain because 2 yr after the start of GH treatment, she produced anti-GH antibodies that blocked GH therapeutic effects (6). For this reason GH treatment was stopped and replaced with rhIGF-I but her final height was subnormal (128.6 cm=–5.5 SDS) (Fig. 1) and lower than her target height (153.6 cm=–1.9 SDS) (Table 1).

All the remaining patients received rhIGF-I from a mean age of 8.6 yr (range 3.2-14.2) up to the final height (Table 1). rhIGF-I was administered sc in two daily doses of 40 μg/kg for the first 6 months, then at a dose of 80 μg/kg till pubertal onset and at a dose of 120 μg/kg during pubertal phase and up to the final height achievement.

**Auxological and clinical results after rhIGF-I treatment**

In spite of a long-term treatment with IGF-I, final height was subnormal and significantly lower than target height in all the treated patients (p<0.001) (Table 1).

Pubertal onset was delayed in most of them but menarche occurred spontaneously in all the patients. Median age at menarche was 15.1 yr in our patients, older than their mothers' menarcheal age (11.6 yr). Menstrual cycles were regular for the subsequent years (Table 2). Median duration of gynecological follow-up was 8.3±5.8 yr, with the longest span of 17.2 yr. One of the five patients (#1) received a short-term treatment (12 months) with LHRH analog in order to prolong the period of pre-pubertal growth and maximize the effect of rhIGF-I on final height (7).

In all the patients, gonadotropins and estrogen levels were normal for pubertal stage; sonography showed subnormal size of pelvic organs (uterus and ovaries) in comparison with reference range (8) (Table 2).

All the patients maintained subnormal IGF-I levels in adulthood (Table 2). None of our patients experienced important side effects on treatment.

**METHODS**

Supine lengths and standing heights were measured with a supine measuring table and a wall-mounted stadiometer (Harpenden and Holtain Ltd, Crymmych, UK). The target height was calculated as [(father's height + mother's height ± 13) / 2]. SDS for height and target height were calculated according to the data of Tanner and Whitehouse and the Italian standards (9, 10). Puberty onset was defined as the chronological age at which breast development appeared, corresponding to Tanner breast stage 2 (9).

Serum GH and IGF-I concentrations were measured by radioimmunoassay using commercially available kits (Biodata, Milan, Italy). The molecular analysis of GH receptor gene and GH gene was performed by PCR amplification and direct sequencing of the entire coding region (6, 7, 11).

rhIGF-I was supplied by Pharmacia and Upjohn, Stockholm, Sweden, and by Genentech, San Francisco, CA, USA.

For those patients who discontinued the medical check-up, the notes about gynecological life were obtained by a telephone interview.

The treatment protocol for rhIGF-I was approved by the Ethics Committee of each University and written informed consent was obtained from the patients' parents.