Growth Hormone Insensitivity Syndrome (GHIS): Clinical Presentation and Effects of Treatment with Recombinant Human Insulin-like Growth Factor I (rhIGF-I) European Experience

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Abstract. Growth hormone insensitivity syndrome (GHIS) is a pathological state characterised by disturbance of the normal relationships between growth hormone (GH) secretion, insulin-like growth factor I (IGF-I) synthesis and GH action. Laron syndrome (LS) is the most severe form and is related to defects of the GH receptor gene. Twenty-seven cases of LS from 8 European countries and Australia were characterised clinically and endocrinologically. Clinical features (median) were; age 2.8-22.6 years, 12 males, 15 females, birth weight -0.72 SDS, birth length -1.59 SDS. Hypoglycaemia occurred in 33 % and micropenis in 58 % of males. Height was -6.0 SDS, weight -3.2 SDS, % weight for height 111.3. Bone age was delayed in 19 of the 27 patients. Endocrine values (median) were; GH 17 µg/L, IGF-I <5th centile, with % increment during IGF-I generation test < 20%. IGFBP-3 was < 5th centile, GH-BP was low or undetectable in 20 and normal in 7 subjects.

Treatment with recombinant IGF-I offered the only form of effective therapy. Treatment of 13 patients with IGF-I, 120 µg/kg bid induced a change in mean height velocity from 4.1 cm/year before treatment to 10.2 cm/year at 6 months and 8.8 cm/year at 12 months. Adverse effects were minimal. Facial appearance showed a change in maturity associated with capital hair growth. Further studies to define the optimum dose regimen of IGF-I are in progress.

Key words: growth hormone insensitivity, Laron syndrome, IGF-I therapy

Introduction

GH insensitivity states may be classified into primary or genetically-determined conditions and secondary or acquired disorders (1). GHIS, the most severe clinical form, was first described by Laron et al. (2) and is caused by one of a number of possible mutations of the GH receptor gene (3).

GHIS is characterised by a disturbance of the biological effect of GH and of the physiological relationships between GH secretion and IGF-I production. Characteristics are; high circulating GH levels, low IGF-I levels and in children, impaired linear growth (4). GHIS may be further defined by the IGF-I generation test, during which there is no increase of serum IGF-I after stimulation with exogenous hGH (5). This paper
describes the clinical features of a large heterogeneous series of predominantly European patients with GHIS (6). All these patients have been fully documented from the endocrine point of view and have been shown to have the characteristics of classical Laron Syndrome. The preliminary effects of treatment with recombinant IGF-I are also reported (7,8).

Subjects and Methods

Series of Patients with GHIS

A series of 27 patients with GHIS has been assembled by Pharmacia (Kabi Peptide Hormones), Stockholm, Sweden (6). These subjects have all been demonstrated to have the typical clinical and endocrine features of GHIS, fulfilling accepted criteria for this diagnosis (5). Unlike previous series of GHIS patients, either from Israel (9) or Ecuador (10), this series is geographically and genetically heterogeneous.

Clinical features

The 27 patients were resident in: Australia (n=1), Belgium (n=2), Denmark (n=1), France (n=7), Germany (n=1), Italy (n=3), Spain (n=3), Slovenia (n=1) and United Kingdom (n=8). Clinical details are shown in Table 1. Twelve patients were male and 15 female. Parental consanguinity was present in the cases of 3 subjects and the series contained 2 pairs of siblings. Birth weights for gestational age (n=26) were: median -0.72 SDS, range 1.75 to -3.29. Birth lengths for gestational age (n=13) were: median -1.59, range 0.63 to -3.63. Eight patients had experienced hypoglycaemia and 7 out of the 12 patients had micropenis.

Auxological features

The severity of growth failure varied considerably (Fig. 1). The median height SDS value was: -6.0, range -3.2 to -8.9. Median sitting height (n=20) was: -6.1 SDS, range -3.8 to -10.2. Median weight SDS was: -3.2, range -0.1 to -5.2.

Table 1 Clinical details of patients with GHIS

<table>
<thead>
<tr>
<th>n</th>
<th>Sex (M/F)</th>
<th>Age (yr)</th>
<th>Birth Wt (SDS [n=26])</th>
<th>Birth L (SDS [n=13])</th>
<th>Ht (SDS [n=20])</th>
<th>S.Ht (SDS [n=20])</th>
<th>Wt (SDS)</th>
<th>Wt for Ht (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>27</td>
<td>12/15</td>
<td>2.8 -</td>
<td>-0.72</td>
<td>-1.59</td>
<td>-6.0</td>
<td>-6.1</td>
<td>-3.2</td>
<td>111.3</td>
</tr>
<tr>
<td></td>
<td>22.6</td>
<td>(1.75 -</td>
<td>(0.63 -</td>
<td>(-3.2 -</td>
<td>(-3.8 -</td>
<td>(-0.1 -</td>
<td>(72 -</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>-3.29)</td>
<td>-3.63)</td>
<td>-8.9)</td>
<td>-10.2)</td>
<td>-5.2)</td>
<td>(271)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: Weight (Wt), Height (Ht), Length (L), Standard Deviation Score (SDS), Sitting Height (S.Ht)
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Percentage weight for height was: median 111.3, range 72 - 271% (Table 1).

Details of pubertal development were given in 26 patients. Nineteen were prepubertal and 7 pubertal. Puberty was absent in 2 boys aged 15 years and in 3 girls aged 13 years. Bone age assessment was performed in 25 patients at chronological ages ranging from 3.7 to 22.9 years. The bone age was delayed, i.e. difference between bone age and chronological age > -0.5 years, in 19 patients (median -2.03 years, range -6.52 to -0.72 years), advanced in 3 (+1.17, +1.95, +2.5 years respectively) and equivalent to chronological age in 3.

Discussion

Treatment with rhIGF-I

The severe short stature associated with GHIS (Fig. 1) presents the clinician with a considerable therapeutic challenge. As the patient is unresponsive to both the high levels of endogenous GH secretion and to therapy with exogenous hGH, the only possible way of stimulating linear growth is to use the peptide, normally generated beyond the site of the GH receptor defect; namely IGF-I. A preparation of recombinant IGF-I has now been developed and we report early results of its use in GHIS. Due to the deficiency of IGFBP-3 in GHIS, exogenous IGF-I is rapidly cleared from the circulation following injection. Pharmacokinetic studies have demonstrated increased clearance of IGF-I and markedly reduced half-life of 6 hours in GHIS patients, compared with 20 hours in normal subjects (11).

Published data on the effect of IGF-I in GHIS come from several sources, namely patients reported by Laron in Israel (12) and the first results of the treatment of our own series (7). Data from the Ecuadorian series are included in this supplement. Both the two published reports show a significant increase in height velocity over a 6-month period. Laron also reports an increase in head circumference (12).

Short-term treatment of Laron Syndrome with IGF-I has also been shown to have metabolic and anabolic effects (13, 14). The dose of IGF-I used in long-term therapy has varied from 40 μg/kg bid given by subcutaneous (sc) injection (15) to > 120 μg/kg once daily (12). The linear growth response to treatment has generally been greater when the higher dose has been used. With a dose of 40 μg/kg twice daily bid growth rates in two patients returned to pre-treatment values after 18 months of therapy (15).

Lipolytic and anabolic effects

Clear lipolytic and anabolic effects also occur during IGF-I therapy. Laron reported a reduction in skinfold thickness values in his patients (12) and similar findings accompanied by maintenance of mid-arm circumference mea-

Fig. 1 Individual heights of 27 patients with GHIS from the European series.
surements and weight gain, indicating a net anabolic effect, were demonstrated in the present multi-ethnic 'European' series.

**Change in facial appearance**

A striking change in facial appearance in children and adolescents with GHIS has been described during treatment with IGF-I. Although difficult to quantitate, the face becomes more mature, there is a loss of sc fat, and a definite increase in quantity and thickness of hair is seen. This is most striking in the eyebrows. It has been said that these patients are starting to look 'acromegalic', however time will tell if this is the case.

Auxological observations of facial height, indicate a dramatic increase in the growth of the mid-face, indicating an IGF-I effect on endochondral bone growth (17).

**Table 2** Clinical details of patients with GHIS at start of therapy with recombinant IGF-I

<table>
<thead>
<tr>
<th>Patients (n)</th>
<th>23</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>12m, 11f</td>
</tr>
<tr>
<td>Age (median, range)</td>
<td>11.1 (4.4 - 22.9)</td>
</tr>
<tr>
<td>Puberty</td>
<td>16 prepubertal, 7 pubertal</td>
</tr>
<tr>
<td>Height SDS  (mean ± SD)</td>
<td>-0.86 ± 1.48</td>
</tr>
<tr>
<td>Height velocity (mean ± SD) (cm/yr)</td>
<td>3.78 ± 1.86</td>
</tr>
</tbody>
</table>

**Results**

In the present 'European' series, 32 patients comprising 30 with GHIS and 2 with type IAGH gene deletion were started on IGF-I therapy. During the first six months of treatment, 7 were withdrawn due to a number of adverse effects which are described later. Clinical details of the remaining 23 patients are shown in Table 2.

**Linear growth**

The 23 patients are divided into 3 treatment groups according to the dose of IGF-I used. The relationship of dose of IGF-I to the linear growth response is shown in Table 3. In the first group, treated with 40 µg/kg bid (n=5), the response was good. Two of these patients were subsequently published (15). The second group (n=5) also started on 40 µg/kg bid but responded

**Table 3 Growth Response in relation to dose of IGF-I in patients with GHIS**

<table>
<thead>
<tr>
<th>Dose of IGF-I (µg/kg sc b.d.)</th>
<th>Patients</th>
<th>Pre-treatment (n)</th>
<th>6 month (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>height velocity (mean ± SEM) (cm/yr)</td>
<td>height velocity (mean ± SEM) (cm/yr)</td>
</tr>
<tr>
<td>40</td>
<td>5</td>
<td>3.28 ± 0.89</td>
<td>9.28 ± 1.71</td>
</tr>
<tr>
<td>40 changed to 120</td>
<td>5</td>
<td>3.32 ± 0.79</td>
<td>5.02 ± 1.44</td>
</tr>
<tr>
<td>120</td>
<td>13</td>
<td>4.15 ± 0.53</td>
<td>10.22 ± 0.35</td>
</tr>
</tbody>
</table>
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poorly and were changed to 120 µg/bid. The third group (n=13) were treated from the start with 120 µg/kg bid and showed an increase in mean height velocity from a pretreatment value of 4.2 cm/y to 10.1 cm/y at 6 months and 8.8 cm/y at 12 months of therapy (Fig. 2). Change in height velocity was inversely related to bone age at start of treatment (Fig. 3). We have also studied the suppression by IGF-I of GH secretion in Laron Syndrome (16) and have shown that pulsatile GH secretion was completely suppressed following a sc injection of IGF-I 120 µg/kg in two subjects with GHIS. However the biological effect was short-lived with a return of GH secretion within 4 and 7 hours respectively after IGF-I administration.

Adverse effects of recombinant IGF-I

Treatment of IGF-I in GHIS has hitherto been associated with few serious side effects. Hypoglycaemia occurred in some of the younger patients although this was generally preventable by ensuring calorie intake before the IGF-I injection. Hypokalaemia normally occurred transiently during the first 48 hours of therapy. Headaches, associated in two patients with mild and transient papilloedema, have also been documented. The headaches normally resolved after 4-6 weeks of treatment.

Conclusion

Recombinant IGF-I currently provides the only therapeutic option in patients with GHIS. A definite effect on linear growth has been demonstrated in these patients, however the optimal dose regimen has still to be defined. The presence of lipolytic and anabolic effects also

Fig. 2 Height velocity during treatment with recombinant IGF-I 120 µg/kg bid in 13 patients with GHIS.

Fig. 3 Relationship between 0 and 6 month difference in height velocity and bone age at start of treatment with recombinant IGF-I 120 µg/kg bid.
demonstrate that IGF-I is a potent new therapeutic agent. Longer term studies to determine whether the extreme short stature which exists in adult life in subjects with GHIS may ultimately be preventable with long-term replacement therapy with recombinant IGF-I are currently being performed. It is important to remember that at the time of writing this paper, the world experience of IGF-I therapy amounts to a little more than 2 years. Consequently a great deal still needs to be learned about this new form of therapy.

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**References**


