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Treatment with Growth Hormone in Short Children Born with Intrauterine Growth Retardation

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In the past 10 yr, the potential benefits of treatment with growth hormone (GH) in children born with intrauterine growth retardation (IUGR) have been well documented. In this study, 46 children with IUGR received 3 yr of GH treatment (0.2 IU/kg of body wt) followed by a further 3 yr of observation without treatment. Height velocity (HV) increased dramatically during the first year of treatment, and over the 3-yr treatment period there was a 2 standard deviation score (SDS) gain in height (from –3.3 ± 0.7 SDS to –1.3 ± 0.3 SDS). Bone age (BA) was increased by 4 yr during treatment. A dramatic decrease in HV was observed in the second phase of the study when patients were no longer receiving GH. Similarly, the gain in BA during the observation period was only half that observed during the treatment period. No clinically significant changes were observed in laboratory test results, and no clinical adverse events could be related to treatment. In conclusion, the data provide evidence of a beneficial effect of GH treatment in IUGR children. However, adequate treatment duration is critical, because growth velocity decreases dramatically on discontinuation of GH treatment.

Key Words: Growth hormone; intrauterine growth retardation; height velocity; bone age.

Introduction

Modern treatments have changed the mortality and morbidity of children born with intrauterine growth retardation (IUGR). Only 10% of children who received appropriate perinatal care fail to achieve sufficient catch-up growth during infancy and remain short throughout childhood; this proportion is much lower than previously reported but remains an important complication of being short at birth and a severe handicap for life. The potential of growth hormone (GH) to improve the conditions of children with IUGR has been explored, and the abundant data published in the past 10 yr are extremely positive in terms of growth and body composition of these children. The safety data meticulously collected by most investigators in these trials are also reassuring. In the near future, therefore, it is possible that GH treatment, which until now has been used in most countries only in clinical trials, will be available for the treatment of severe short stature owing to IUGR.

In this article, we present data on 3 yr of treatment with GH in a group of children with IUGR followed by 3 yr of observation without the administration of GH. The aim of the study was twofold: to assess whether or not the administration of GH improves linear growth, and to assess growth velocity during 3 yr off treatment.

Results

Growth Data

Table 1 summarizes all parameters concerning height, height age (HA), height velocity (HV), and bone age (BA). It can be seen that HV increased dramatically during the first year of treatment and it decreased thereafter but remained above the HV measured during the year preceding the treatment period. This sustained increase in HV resulted in an important height gain: during the 3-yr period the entire group gained 2 standard deviation score (SDS) (from –3.3 ± 0.7 SDS at inclusion to –1.3 ± 0.8 SDS at the end of the 3-yr treatment period).

GH treatment accelerates BA maturation. At the start of treatment BA was retarded by 1.5 yr, and during the 3 yr of treatment the total gain in BA was 4 yr (Table 1). However, the ΔHA:ΔBA ratio was higher than the theoretical value of 1.0 and reached 1.0 at the end of the 3 yr, which demonstrates a significant increase in predicted final height.

During yr 3–6, when the patients were off GH treatment, a dramatic decrease in HV was observed. When expressed in HVSDS, at the end of the 6-yr period (3 yr on GH and 3 yr off GH) the HVSDS was very similar to the value observed at inclusion. As a consequence, a significant reduction in height SDS (HSDS) was observed. After 3 yr off treatment, however, HSDS was –2.0 ± 0.9, which is above the value at inclusion. During the same period, the BA maturation slowed down: in 3 yr the BA progressed by 1.7 yr, a value almost half that observed during the treatment period. As a result, the ΔHA:ΔBA ratio at the end of 6 yr was above the theoretical value of 1.0.

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Table 1
Parameters and Growth During 6 yr
of Observation in 46 Patients with Short Stature IUGR[a]

Study months	HV (cm/yr)	HVSDS	HSDS	BA	ΔHA/ΔBA
GH treatment					
0	6.0 ± 1.7	−1.3 ± 1.1	−3.3 ± 0.7	3.5 ± 1.7	—
12	9.9 ± 1.7	3.8 ± 1.5	−2.2 ± 0.8	4.8 ± 1.8	1.2 ± 0.5
24	7.8 ± 1.1	2.2 ± 1.4	−1.6 ± 0.8	6.1 ± 2.0	1.2 ± 0.5
36	6.9 ± 1.0	1.4 ± 1.2	−1.3 ± 0.8	7.4 ± 2.1	1.0 ± 0.5
Without GH treatment					
48	3.9 ± 2.1	−2.2 ± 2.6	−1.6 ± 0.9	8.5 ± 2.1	0.7 ± 0.6
60	3.3 ± 2.1	−2.2 ± 2.6	−1.6 ± 0.8	9.3 ± 2.0	0.9 ± 0.6
72	4.3 ± 1.3	−1.4 ± 1.5	−2.0 ± 0.9	10.2 ± 1.9	1.1 ± 0.6

[a]Patients received 3 yr of GH treatment followed by a further 3 yr without treatment.

Laboratory Parameters and Adverse Events

During the GH treatment period, no clinically significant changes were observed in hematology, lipid profiles, or thyroid panel. One child developed hyperthyroidism of autoimmune origin after 27 mo of treatment.

Adverse events were carefully recorded at the regular visits to each center. No adverse events of clinical significance could be related to the treatment.

Eleven biochemical events were considered to be related to the treatment. Two patients had elevated fasting blood glucose levels at 18 and 24 mo (7.4 and 5.7 mmol/L, respectively; normal: <5.5 mmol/L). In one patient, HbA1C was elevated at 9 mo (5.9%; normal: <5.7%) and returned to the normal range although the patient was still on GH treatment. Three children developed signs of impaired glucose tolerance during oral glucose tolerance test (OGTT), with values above the threshold of 140 mg% at 120 min, at baseline, and after 18 and 36 mo of treatment (144, 157, and 146 mg%, respectively). The changes in glucose tolerance were inconsistent and variable. Following GH withdrawal, no signs of glucose intolerance were observed during the 3 yr of observation.

Five children were positive for anti-hGH antibodies for a least one serum sample during treatment. No anti–host cell protein antibodies were found, and the development of antibodies was not associated with any of the adverse events, nor did it have any adverse effect on growth. Because of the very low antibody titers, binding capacity of the antibodies could not be determined. Only one child still had low antibody titers after 36 mo of treatment.

Discussion

This study demonstrates that GH increases growth velocity and improves HSDS in short, prepubertal children born with IUGR. This treatment induces an acceleration of bone maturation, but, as BA was retarded at the beginning of GH therapy, the final height prognosis was improved.

The second conclusion that can be drawn from these results is that when these children are off GH therapy, there is a reduction in HV so that most of the height gain achieved during the 3 yr of GH administration is lost during the following period. This is an important observation that should be taken into account in the design of future therapeutic strategies with GH.

In the past 10 yr, much has been learned about the treatment of short children born with IUGR. There is now a consensus that GH will significantly increase growth velocity if the dosage given is 50–100% higher than replacement therapy *(5–7)*. The usual dosage given to GH-deficient children will not induce a significant and sustained increase in growth velocity. To improve their growth velocity and ameliorate their final height prognosis, these children should be treated with dosages close to 0.4 mg/(kg·wk). Whether this treatment over a long period should be continuous or not is still debated. A meta-analysis of four studies performed in Europe has shown that the 4-yr growth response was similar between continuous GH use (3 IU/[m^2·d] for 4 yr) and noncontinuous GH use (6 IU/[m^2·d] for 2 yr followed by 2 yr off GH treatment) *(8)*, suggesting that the cumulative GH dose received by the patient is more important than the daily dose administered. Further studies are needed to confirm these findings.

As reported in other trials, the present study has demonstrated the beneficial effect of GH treatment over a period of 3 yr. In a few controlled studies *(6)*, untreated children showed no significant catch-up, indicating that they will be short at adult age. Other studies *(5–7)* have also shown that bone maturation was accelerated by GH treatment but height prognosis was still improved after 3 yr of treatment.

The striking feature of the present study is that during the second part of the observation period (i.e., without GH treatment) a reduction in growth velocity was observed. This demonstrates that the gain in growth velocity and height is totally GH dependent. It is also probably insulin-like growth factor-1 (IGF-1) dependent, because many investigators have shown an increase IGF-1 plasma concentration in GH-treated IUGR children *(6,9)*. This provides evidence in favor of continuous GH treatment until puberty and probably also during puberty, although data on this last point are lacking.

The results of 5 yr of treatment of short children born with IUGR have recently been published *(9)*. After 5 yr of GH treatment, almost every child had reached a height well within the normal range for healthy children and in the range of their target height SDS. GH treatment was associated with an acceleration of bone maturation but at the end of the study predicted that adult height had increased significantly.

As reported previously *(5–9)*, we found that tolerance to GH was excellent. No adverse events of clinical significance were observed. The most important observation was that glucose tolerance remained normal at the end of the 3 yr off GH therapy.

The primary goal in treating children born with IUGR is the normalization of height. This is obtained by 3 or 5 yr of treatment with GH and does not cause any adverse effects.

Data on final height are not available for most studies conducted to date. However, when such data become available, they will not bring any important information for a final evaluation of the efficacy of GH because the period of treatment in trials decided 10 yr ago has been too limited. The data by Sas et al. *(9)*, however, and our own data herein are very much in favor of continuous treatment until puberty.

There are other beneficial effects to expect from the administration of GH in these children. Leger et al. *(10)* have shown that 3 yr of GH treatment in short children with IUGR has a profound effect on muscle mass and adipose tissue. This demonstrates that it is not only cartilage that is sensitive to GH but that other tissues might also benefit from this treatment.

GH is registered in France for short children born with IUGR. We hope that in the future this indication will also be accepted in other countries, although we still have more to learn and need to improve treatment modalities. Information on final height and long-term safety is still required; however, we believe that the data available are very much in favor of a beneficial effect of GH treatment in short children with IUGR.

Materials and Methods

Patients

Forty-six children with short stature and IUGR were followed over a 6-yr study period. The children formed part of a larger study of 69 children *(11)*, but data for the entire 6-yr period are only available for the subgroup of 46.

The children were intrauterine growth retarded at birth, defined as birth weight less than the tenth centile of the gestational age–related standards of Leroy and Lefort *(12)*. The mean (±SDS) birth weight of the children was 2030 ± 530 g for gestational age of 37.8 ± 2.9 wk. Children were included in the study if they were of short stature with a height of 3.0 SDS or more below the mean height for chronologic age *(13)*. At inclusion, the mean age was 5.0 ± 1.9 yr, and the height, expressed in HSDS, was −3.3 ± 0.7. Other inclusion criteria were as follows:

1. Chronologic age ranging between 2 and 8 yr.
2. BA <7 yr using the Greulich and Pyle method *(14)*.
3. HV, calculated over a pretreatment observation period of 12 mo, of less than +0.5 SDS of the mean HV for chronologic age.

All children enrolled in the study had a normal GH peak serum concentration of >10 ng/mL following a pharmacologic stimulation test. Free T4, hepatic transaminases, and glucose tolerance during OGTT were within normal ranges.

Children were excluded from the study if they had known dysmorphic features, body hemihypertrophy, severe psychomotor retardation, or chromosomal anomalies; or if they were receiving ongoing hormone treatment or had previously received hormone treatment; or if parents or siblings had type 1 or 2 diabetes mellitus.

Treatment

The patients were followed for 6 yr, and the investigation was conducted in two phases. During the first 3 yr the patients were treated with a daily dose of r-hGH (Saizen®) (0.2 IU/kg of body wt [0.067 mg/kg]) administered subcutaneously in the evening. The dose was adjusted each month according to weight gain. In the second 3-yr study period, patients were followed up without treatment.

Ten centers in France participated in the study, which was approved by the University Hospital Ethics Committee in Nancy and at Necker-Enfants Malades in Paris. Written informed consent was obtained from each parent/guardian prior to entering the trial.

During the prestudy period, each child was seen at regular intervals and pretreatment HVs were calculated. During the 6 yr of the study, children were seen at 3-mo intervals, and height, weight, and pubertal status were determined. The height reported at each visit was the mean of three successive measurements usually performed by the same physician using the same stadiometer. HV was calculated using growth data from a 12-mo (±6 wk) period.

X-ray radiographs of the left hand and wrist were taken at baseline and then every 12 mo thereafter. BA was assessed centrally by one trained radiologist (Dr. M. Sempe, Lyon, France) and was performed in a blind fashion.

Laboratory Tests

Laboratory tests comprising complete blood count and differential blood chemistries, lipids, thyroid panel, and glycosylated HbA1C were conducted at the start of treatment and then at 3-mo intervals during the first year, at 6-mo intervals during the second and third years, and annually thereafter until the end of the study.

Anti-hGH and anti–host cell protein antibodies were determined centrally using a published technique at the start of treatment and 3, 6, 12, and 36 mo thereafter *(15)*. OGTTs were performed in all children after 18 and 36 mo of treatment, and then annually thereafter for 3 yr. The World Health Organization criterion of glucose intolerance was used (glucose value > 140 mg% [7.8 mmol/L] at 120 min during the OGTT).

Statistical Analyses

Intragroup analyses were performed using paired *t*-tests. The level of significance was set at $p < 0.05$. All data are reported as means with SDS unless otherwise stated.

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