

Review article

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Growth hormone treatment in non-growth hormone-deficient children

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Until 1985 growth hormone (GH) was obtained from pituitary extracts, and was available in limited amounts only to treat severe growth hormone deficiency (GHD). With the availability of unlimited quantities of GH obtained from recombinant DNA technology, researchers started to explore new modalities to treat GHD children, as well as to treat a number of other non-GHD conditions. Although with some differences between different countries, GH treatment is indicated in children with Turner syndrome, chronic renal insufficiency, Prader-Willi syndrome, deletions/mutations of the *SHOX* gene, as well as in short children born small for gestational age and with idiopathic short stature. Available data from controlled trials indicate that GH treatment increases adult height in patients with Turner syndrome, in patients with chronic renal insufficiency, and in short children born small for gestational age. Patients with *SHOX* deficiency seem to respond to treatment similarly to Turner syndrome. GH treatment in children with idiopathic short stature produces a modest mean increase in adult height but the response in the individual patient is unpredictable. Uncontrolled studies indicate that GH treatment may be beneficial also in children with Noonan syndrome. In patients with Prader-Willi syndrome GH treatment normalizes growth and improves body composition and cognitive function. In any indication the response to GH seems correlated to the dose and the duration of treatment. GH treatment is generally safe with no major adverse effects being recorded in any condition.

Keywords: Child, Growth, Growth hormone, Insulin-like growth factor I

Introduction

Until 1985 growth hormone (GH) was extracted from human pituitaries, and because of the limited amounts its therapeutic use was confined to children with severe GH deficiency (GHD). With the unlimited amounts of the hormone obtained from recombinant DNA technology it has been possible to optimize treatment in GHD patients as well as to test its efficacy in a number of other conditions. Nowadays, GH treatment is approved to treat patients with Turner syndrome (TS), chronic renal insufficiency (CRI), Prader-Willi syndrome (PWS), Noonan syndrome (NS), *SHOX* (short stature homeobox containing gene) deficiency (*SHOX-D*), children born small for gestational age (SGA) and children with idiopathic short stature (ISS). In this paper we will review the use of GH for the treatment of all these conditions.

Turner syndrome

TS is the most common chromosome abnormality in females affecting approximately 1:2,000–2,500 live female births and is one of the most common cause of short stature in girls. It is caused by the absence or by structural abnormalities of one of the X chromosomes. Affected females typically present short stature, hypergonadotropic hypogonadism and mild

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skeletal dysplasia. Growth failure usually starts prenatally and a progressive decline of height standard deviation score (SDS) is commonly observed in the first years of life^{1,2}.

The cause of short stature in girls with TS is probably multifactorial. Recent findings indicate that haploinsufficiency of the *SHOX* gene located in the pseudoautosomal region of the sex chromosomes as one of the leading causes³. In this regard it has been shown that bone alteration of the hand and wrist are similar between girls with TS and patients with *SHOX* haploinsufficiency⁴. The final height in untreated girls with TS is approximately 20 cm below that of normal female subjects².

The use of GH to treat short stature in TS patients has been one of the first approved indications, and many studies have shown its efficacy in improving height velocity and final height⁵. The first randomized controlled trial up to final height showed that treatment resulted in an average height gain of 7.2 cm in the treated group⁶. In this study, 61 girls aged 8–12 years were treated for a mean of 5.7 years with 0.3 mg/kg per week. A more recent trial showed that in 27 girls of a mean age of 8.4 year GH treatment at a dose of 0.1 mg/kg three times per week for a mean of 7.4 year resulted in a mean adult height of about 5 cm in the GH treated girls⁷. Both studies were started in mid to late childhood, at a time when growth failure was already the evident complain. Other studies have demonstrated that GH treatment initiated before the age of 4 can correct growth failure and normalize height^{8,9}. However, data on long-term efficacy and safety in girls with TS in whom GH treatment is started at a very young age are still lacking. The recommended dose of GH in girls with TS (0.035–0.050 mg/kg daily) is higher than that used for GHD. Overall, the safety profile of GH treatment is good, since no major side effects related to treatment have been documented so far⁵. However, routine monitoring of insulin-like growth factor -I (IGF-I) concentrations and glucose metabolism is recommended².

Anabolic steroids have been extensively used to ameliorate growth in girls with TS². Two recent papers conducted in Europe^{10,11} have shown that addition of oxandrolone to GH treatment results in better height gain than GH alone. In the Dutch study¹⁰, the combination of GH (0.045 mg/kg daily) plus oxandrolone (0.03 mg/kg daily) resulted in mean increase in height of 2.3 cm over GH alone. A slight delay in breast development was reported in the group treated with oxandrolone. In the study from UK¹¹ the addition of oxandrolone (0.05 mg/kg daily) produced a mean increase in adult height of 4.5 as compared to the group treated with GH alone (0.05 mg/kg per week in daily injections). No adverse effects have been reported in this study.

Girls with TS almost always require estrogen treatment for ovarian failure. Up to recent years the common practice was to initiate estrogen treatment at about mid teens, to avoid the reduction in adult height due to estrogen-mediated epiphyseal fusion. There is still controversy on the effect of delaying pubertal maturation in girls with TS. Quigley et al.¹² showed that low dose estrogen administration since 8 years of age produces no better effects on adult height than GH alone. Other

studies have shown that GH and estrogen treatment initiated at a relatively normal pubertal age (around 12 years) leads to normalization of final height¹²⁻¹⁴. However, a randomised, double blind, placebo controlled trial conducted in the UK showed that estrogen treatment started at 14 years of age produced a mean height gain of 3.8 cm over that observed in girls treated since the age of 12¹¹. Recent findings indicate that ultra-low doses of estrogen initiated as early as 5 years of age produce beneficial effects on growth as well as other clinical parameters⁷. In this double-blind placebo-controlled trial, estrogen (or placebo) was administered at a daily dose of 25 ng/kg in girls aged 5 to 8 years and 50 ng/kg in those aged 8 to 12 years. Then all patients received pubertal estrogen-replacement therapy according to an escalating dose regimen. A third group received only placebo, and a fourth group was only treated with GH. Mean adult height in the girls treated with estrogen plus GH was 0.37 SDS greater than that after GH alone.

Chronic renal insufficiency

The majority of patients with CRI show short stature and decreased growth rate that is often not normalised by dialysis. A combination of several factors is generally responsible for the growth failure observed in children with CRI. Among these, malnutrition, malfunctioning of the GH/IGF-I axis, and corticosteroid therapy are the most important factors¹⁴. A number of studies have shown that GH treatment increases the growth rate and improves the standardized height in children with chronic renal failure¹⁵. Haffner et al.¹⁶ followed 38 initially prepubertal children with CRI (mean age, 10.4±2.2 years; mean height, 3.1±1.2 SD below normal) treated with GH (0.33 mg/kg weekly) for a mean of 5.3 years. Fifty matched children with CRI. The mean final height of the GH-treated children was 165 cm for boys and 156 cm for girls. The mean final adult height of the GH-treated children was 1.6±1.2 SD below normal, which was 1.4 SD above their standardized height at baseline ($P < 0.001$). In contrast, the final height of the untreated children (2.1±1.2 SD below normal) was 0.6 SD below their standardized height at baseline ($P < 0.001$). In a large study involving 240 patients with chronic kidney disease treated with GH at a mean dose of 0.30 mg/kg per week (KIGS [Pfizer International Growth Database]: 45% on conservative treatment, 28% on dialysis, and 27% right after renal transplantation) near final height was within normal in 40% of the subjects¹⁷. They showed that patients on dialysis or with severely delayed puberty had the less favourable response. The KIGS database was also used to develop a prediction model for the first year response¹⁸. In this model, age at start, weight SDS, underlying renal disorder, glomerular filtration rate at baseline and GH dosage explained 37% of the overall variability of the growth response. The recommended dose for treatment of growth failure in children with CRI is 0.05 mg/kg daily.

Prader-Willi syndrome

PWS is a rare genetic disorder characterized by multisystem abnormalities including hypotonia, feeding problems, small hands and feet, hyperphagia and excessive weight gain, hypogonadism, short stature, general developmental delay, and cognitive impairment. Central and obstructive sleep-disordered breathing is also frequent in children with PWS¹⁹. It has an incidence of approximately 1:25,000 live births. PWS results from lack of expression of paternally expressed genes located on chromosome 15 due to paternal deletion, maternal uniparental disomy, imprinting defects or chromosomal translocations^{19,20}.

Many of the characteristic features of PWS resemble those observed in patients with GH deficiency, including reduced growth and muscle strength, and altered body composition. About 80% of children with PWS have GH deficiency, and show subnormal GH responses to a variety of stimuli²¹⁻²⁴, as well as reduced spontaneous GH secretion²⁵. Serum IGF-I concentrations are reduced in most children²⁶. GH treatment in children with PWS has the scope of promoting growth during childhood and ameliorating body composition. Controlled studies have shown that GH treatment of PWS children improves growth, body composition, muscle strength^{27,28}, and has a positive effect on cognition²⁹. Consensus guidelines for GH therapy in patients with PWS have recently been published³⁰. Exclusion criteria for starting GH treatment include severe obesity, uncontrolled diabetes, untreated severe sleep apnea, active cancer, and active psychosis. Treatment can be started as early as 2 years, before the onset of obesity, although some data suggest starting treatment between 4 and 6 months of age^{31,32}. A number of sudden deaths have been reported in severely obese PWS patients treated with GH³⁰. In these patients treatment should be started only after polysomnographic studies³⁰. Treatment should be started with a daily dose of 0.5 mg/m² with subsequent adjustments toward the recommended dose of 1.0 mg/m² (0.035 mg/kg daily). IGF-I levels should be maintained in the physiological range. Particular care in monitoring safety and efficacy of treatment in children with PWS is mandatory³⁰.

Noonan syndrome

NS is an autosomal dominant disorder with an estimated incidence of 1/1,000–1/2,500 live births³³. The clinical characteristics include early feeding difficulties, typical facial features, heart defects (pulmonary valve stenosis or hypertrophic cardiomyopathy), chest and spinal deformities, and mild mental retardation. About 50%–70% of patients with NS have short stature. Mean adult stature ranges from 145–162.5 for men and 135–151 for women³⁴. NS is caused by mutations in genes that encode proteins of the RAS-MAPK signal transduction pathway³⁵. About 30%–60% of NS is caused by mutations of the *PTPN11* gene that encodes for the protein tyrosine phosphatase SHP2³⁵. Other mutations have been described in *KRAS*, *RAF1*,

SOS1, *NRAS*, and *SHOC2* genes. However, not all patients with NS have an identifiable mutation. Short stature is most prevalent in patients with mutations in the *PTPN11* gene. This is probably due to the fact that SHP2 is involved in GH receptor signalling. Some studies have reported reduced response to GH treatment as well as reduced IGF-I serum concentrations in *PTPN11*-positive patients^{36,37}, while others have shown improvement of growth after long-term treatment in children with NS with and without *PTPN11* mutations³⁸. The use of GH in patients with NS has been recently approved by the U.S. Food and Drug Administration (FDA). The reported studies³⁹ indicate that short-term GH therapy increases growth velocity. Dahlgren⁴⁰ reported a review of final height data in patients with NS, and the height gain was 0.6–2.0 SDS from pretreatment. Romano et al.⁴¹ published the results of a retrospective study of 65 patients with NS enrolled in the National Cooperative Growth Study in the US and treated with GH (mean dose, 0.047 mg/kg daily) for a mean of 5.6 years. Mean gain in near-final height above projected height was 10.9±4.9 and 9.2±4.0 cm for males and females, respectively. In the reported studies, the dose ranged between 0.035 and 0.066 mg/kg daily, and the outcome was correlated to the dose and duration of treatment. No treatment-related adverse events have been reported. However, controlled studies in NS are still lacking. GH use for NS is not licensed in Europe.

SHOX deficiency

The *SHOX* gene is located in the pseudoautosomal region of the sex chromosomes. Haploinsufficiency or complete loss of function of *SHOX* determine atypical proliferation and differentiation of chondrocytes causing delayed growth of the long bones with different modalities between the embryonal period and the following periods of intrauterine and postnatal life⁴². *SHOX-D* has been demonstrated in a number of conditions including Léri-Weill syndrome, Langer mesomelic dysplasia, TS, and in children with ISS^{3,43,44}. Interestingly, prepubertal girls with TS and children with isolated *SHOX-D* show similar bone geometry at the radius⁴. In a two-year randomized trial, GH treatment (0.05 mg/kg daily) improved growth in patients with *SHOX-D*⁴⁵. A more recent study up to final height showed that 57% of the patients with *SHOX-D* (n=28) and 32% of patients with TS treated with GH for a mean period of 6–7 years reached a final height greater than –2 SD⁴⁶. Pubertal maturation was not affected by treatment, and no GH-related adverse effects were reported.

Small for gestational age

Children born SGA, i.e., with a weight/length < 2 SD for their gestational period, are at risk of becoming short adults. Although most of them do catch-up growth in the first 2–3 years of life, about 10 % will have persistent short stature^{47,48}. A number of trials have been published on GH treatment in

SGA children which led the regulatory authorities in US in 2001 to approve the use of GH at a dose of 0.07 mg/kg daily in children born SGA which fail to catch-up at the age of two years. One year later treatment was approved also in Europe at a dose of 0.035 mg/kg daily after the age of four years. So far, more than thirty studies have been published⁴⁹ and 4 of them were controlled trials⁵⁰⁻⁵³. In their randomized trial, van Pareren et al.⁵⁰ treated two groups of 28 and 26 SGA children (men age, 8 years) at a dose of 0.033 mg/kg daily and 0.067 mg/kg daily, respectively for 7,9 and 7,5 years. Adult height was 1.2 and 1.4 SDS greater than in the control group, respectively. Carel et al.⁵¹ treated 102 patients aged 12.7 at a dose of 0.067 mg/kg daily for a mean of 2.7 years. Adult height was 1.1 SDS greater than in controls. The study by Dahlgren et al.⁵² reported the results of 77 patients aged 10.7 years treated at a dose of 0.033 mg/kg daily for 5.5–8.8 years. Mean final height was 0.6 SDS greater than in untreated subjects. However, they also showed that final height was significantly greater (by 0.4 SDS) in the patients in whom treatment was started more than 2 years before the onset of puberty. Van Dijk et al.⁵³ treated 37 patients aged 8.5 years at a dose of 0.033–0.066 mg/kg daily for 7.3 years. Again, final height in the treated patients was 1.2 SDS higher than in the controls. Maiorana and Cianfarani⁴⁹ in their meta-analysis concluded that among the 391 children involved in the 4 controlled studies the adult height of the treated children exceeded that of the controls by 0.9 SDS, with no significant differences between the two dose regimens. The response to treatment is influenced by the dose, age at start, stature at start, and mean parental height⁴⁹. Genetic background also may play a role⁵⁴. Treatment has positive effects on body composition, bone mineral density and muscle function^{55,56}. No adverse effects have been recorded so far⁵³.

Since treatment around the onset of puberty has been shown to produce limited effects⁵², Lem et al.⁵⁷ studied the effect of GH and gonadotropin releasing hormone analogue in a randomized trial. They concluded that when SGA children are short at the start of puberty, they could benefit from combined GH/GnRH treatment.

Idiopathic short stature

According to a recent consensus⁵⁸ ISS is defined as a condition in which the height of an individual is more than 2 SDS below the corresponding mean height for a given age, sex, and population group without evidence of systemic, endocrine, nutritional, or chromosomal abnormalities. Children with ISS have normal birth weight. ISS describes a heterogeneous group of children consisting of many presently unidentified causes of short stature, and includes short children with constitutional delay of growth and puberty and familial short stature.

A number of studies have shown that a short-term course of GH (6–12 months) increases height velocity in the great majority of children⁵⁹. The growth response during the first year of treatment is positively correlated to the dose of GH

and to the frequency of weekly administration, and negatively correlated to pretreatment growth velocity⁵⁹⁻⁶¹. To date, more than 20 studies report final or near-final height in children with ISS treated with GH⁶². Only three of them are randomized and controlled⁶³⁻⁶⁵. McCaughey et al.⁶³ have reported the results of a randomized study in ten girls aged 6.2±0.4 years with short stature treated for a mean period of 6.2 years at a dose of 0.06 mg/kg daily. Mean final height resulted 7 cm greater than that observed in the control group, and all treated girls reached their genetic target, whereas only 38% of the untreated girls reached the genetic target. Leshek et al.⁶⁴ reported that mean final height in 22 children with ISS (age, 12.5±1.6 years) treated at a dose of 0.22 mg/kg per week (divided in three injections per week) for 4.4±1.6 years was 0.5 SDS greater than the control group. In the study of Albertsson-Wikland et al.⁶⁵ mean final height of 49 children with ISS (age, 11.5±1.3 years) treated with GH at a dose of 0.033–0.067 mg/kg daily was 0.6 SDS greater than in the control group. A large individual variability of response was observed in all studies⁶²⁻⁶⁵. A number of factors have been indicated as predictive of the final outcome, including age at start of treatment (the younger the better), height at start of treatment (the taller the better), first year response, dose of GH, and mid parental height^{59,62-65}. The controlled studies up to final height in children with ISS were recently analysed in a meta-analysis⁶⁶, and the results have shown that the adult height of the treated subjects exceeded that of the controls, with a mean difference of 0.65 SDS (about 4 cm). Overall, GH treatment in ISS has a favourable safety profile, similar to GH deficient patients⁶⁷.

Conclusions

GH treatment is indicated in patients with GHD and in a number of non-GH-deficient conditions including children with TS, CRI, PWS, short children born SGA, and patients with SHOX-D. The FDA has approved GH therapy also for children with ISS and with NS. The available data indicate that GH treatment is beneficial in all these condition since it improves adult height and has also positive effects on body composition and bone metabolism. However, the response shows a large interindividual variability and is difficult to predict. Therefore, in the individual child all clinical, auxological, and psychosocial issues should be carefully considered to decide about treatment. The response to GH seems to be correlated primarily with age at start of treatment and to the dose. Almost three decades of experience with the use of recombinant GH have shown that treatment is generally safe with no major adverse effects being recorded in any indication.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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