

Growth hormone in children with idiopathic short stature

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Findings by SBU Alert

Technology and target group: When it became possible to synthetically produce growth hormone in the mid 1980s, a debate arose concerning whether short children without growth hormone deficiency, ie, idiopathic short stature (ISS), would benefit from treatment. Growth hormone treatment for ISS is based on two assumptions, ie, that treatment will increase final height and that short stature leads to psychological suffering. Treatment is administered by daily injections and may often continue for about 10 years. Currently, ISS is not an approved indication for growth hormone treatment. The number of children seeking treatment for ISS in Sweden is estimated at 500 to 1 000 per year.

Patient benefit: In six controlled and two non-controlled studies, children with ISS received growth hormone treatment and were followed until they reached final height. The average effect of treatment on final height varies substantially among the studies, ranging from 2 cm to 9 cm. The distribution within the group was wide. Compiling the results of the studies suggests an average growth gain of 3 cm to 7 cm. It has not been established that growth hormone treatment reduces behavioral disorders and problems at school during childhood, or that treatment leads to a higher quality of life in adulthood. The rate of side effects from growth hormone treatment in children is low. Known, but uncommon, side effects include edema and diabetes.

Ethical aspects: Two important factors have ethical implications. First, one may question whether it is ethically defensible to subject healthy children to daily treatment for an extended period, with uncertain individual benefits. Second, the issue arises as to whether short stature in otherwise healthy individuals should be classified as a disease, or whether treatment that promotes growth in this group should be classified as "cosmetic". Hence, whether growth hormone treatment of children with ISS should be considered to be a task for health care should therefore be the subject of further discussions on prioritizations of medical needs versus resource allocation.

Economic aspects: The cost-effectiveness of growth hormone treatment in ISS has been estimated in a meta-analysis and in an economic evaluation from the NHS R&D HTA Programme. The incremental cost of growth hormone treatment for one child was estimated at 650 000 to 900 000 SEK. The incremental cost per centimetre gained in final height was between 175 000 and 350 000 SEK.

Scientific evidence: There is moderate* scientific documentation concerning the patient benefits derived from treatment of idiopathic short stature. There is poor* scientific documentation on the cost-effectiveness of the method.

*This assessment by SBU Alert uses a 4-point scale to grade the quality and evidence of the scientific documentation. The grades indicate: (1) good, (2) moderate, (3) poor, or (4) no scientific evidence on the subject. For further information please see "Grading of evidence".

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Technology

Since the mid 1980s it has been possible to produce growth hormone synthetically. Prior to that time, the hormone was extracted from pituitary glands in deceased individuals. Supply was very limited, and the only patients eligible for treatment were those with confirmed, severe growth hormone deficiency. Synthetic production assured greater supply of growth hormone, and trials were initiated in several countries to treat children who did not have confirmed hormone deficiency, so called "idiopathic short stature" (ISS).

The use of growth hormone to treat ISS is based on two assumptions; that treatment will increase final height and that short stature leads to psychological problems. However, it is uncertain whether short stature causes a psychological burden or has an impact on possible behavioral disorders [20,29].

Two studies suggest that children with ISS have more behavioral problems and greater difficulty in school than other children [22,23]. In children with ISS, 25 percent report that they were often teased in school about their short stature [18].

Target group

In this case the target group for growth hormone treatment consists of children in whom no cause for short stature can be found. The literature uses various terms to describe this group, eg, "normal variant short stature", "constitutional short stature", "idiopathic short stature", and "familial short stature".

In recent years, "idiopathic short stature" (ISS) has become the accepted term. ISS is defined as a height of at least two standard deviations "SD" below the average height for a given age and gender. In Sweden, the average height for individuals aged 18 years is 180 cm in men and 168 cm in women [2]. The average height minus 2 SD would mean 167 cm in men and 158 cm in women. In ISS, a child's final height is estimated to be even shorter. Furthermore, the following criteria must be met:

- Normal size at birth following correction for gestational age and normal or slow growth.
- Normal body proportions and no signs of chronic organic disease.
- No mental illness or severe emotional disorders.
- Normal dietary intake and no sign of endocrine dysfunction.

A medical explanation cannot be found in most children seeking care for short stature [13]. A diagnosis of ISS is generally established through the exclusion of other diagnosis [17]. The number of children seeking care for ISS in Sweden is estimated at 500 to 1 000 per year.

Relation to other technology

Theoretically, it should be possible to increase the final height in short stature children by extending their growth period. With puberty, the growth zones in the body ossify, rendering further height increase impossible. Puberty-inhibiting treatment is used in children with abnormally early puberty and can, in principle, also be used in ISS. In such cases, children would be treated with injections of synthetic gonadotropin-releasing hormone agonist (GnRHa) [4], which provides an effective and very specific inhibition of puberty. However, there is no evidence that treatment would provide the desired effect on final height in the ISS group.

In other treatment studies, children with ISS were given growth hormone releasing hormone (GHRH), which is a hormone that is normally emitted from the hypothalamus to the pituitary where it releases growth hormone [10,15]. The intent of treatment is to increase the release of the patient's own growth hormone, resulting in increased height. Clinical trials of this treatment have not demonstrated any benefits compared to growth hormone treatment, and GHRH is presently not available for human use.

With the type of short stature in boys, which is combined with late maturity, the administration of an anabolic steroid (oxandrolone) in low doses has been shown to increase the growth rate [1,14]. Final height in boys treated with oxandrolone is, however, not significantly different from height in untreated boys [9,14].

Estrogens are the most important factor found to induce ossification in growth zones in both girls and boys. It was recently shown [26] that administration of an aromatase inhibitor to block estrogen production in boys can increase the growth rate without accelerating skeletal maturity. The potential side effects of this method are unknown.

Patient benefits

In assessing growth hormone treatment in short stature children, the effects on final height represent the most important endpoint. Many studies have been performed in which children diagnosed with ISS were given growth hormone treatment. Only six controlled and two non-controlled trials have followed the children until final height. The average effect of treatment on final height varies considerably among these studies, from 2 cm to 9 cm. Reasons for this variation among studies are probably related to differences in inclusion criteria, duration of treatment, GH doses, and statistical management of dropout. The design of treatment has also varied. Some claim that a substantial increase in final height can only be achieved with daily, subcutaneous injections starting from 6 to 7 years of age and continuing for approximately 10 years. A compilation of the results from all studies presented reveals a weighted mean value for height gain of 6 cm in boys and 7 cm in girls. When consideration was given to the statistical heterogeneity of the studies, a somewhat smaller effect of height increase of 3 cm to 4 cm was shown [24,35]. A meta-analysis of 10 studies with and 28 studies without parallel controls suggested a gain of 4–6 cm after about 5 years of treatment [33].

Although final height was not influenced at all in one subgroup, the effects are substantial for a small group of patients [6,12]. An explanation for this may be that the latter group may have had undetected or minor cases of actual growth hormone deficiency. These patients can be expected to respond better to treatment. However, it is not possible to prospectively identify the patients who will receive the greatest benefit from treatment.

In studies that assessed the effects of treatment on quality of life, young short stature individuals were divided into the following three groups:

- Those with ISS who received growth hormone treatment.
- Those with ISS who sought care for short stature but were not treated.
- Short stature individuals in the population who did not seek care for their condition.

Differences in quality of life were found among the three groups. Untreated individuals with ISS who had sought care for this condition during childhood often reported daily problems due to their short stature, in contrast to short stature individuals who had not sought care [18]. The probability of having an adult partner was significantly lower among individuals in whom the ISS diagnosis was confirmed, compared to equally short stature individuals who had not sought care for this condition [7]. Of those who had been treated with growth hormone, fewer had a partner compared to the group who had been diagnosed with ISS but had not received growth hormone therapy. The difference was statistically significant. Perceived health among individuals with ISS did not differ from that of the normal population [18].

In one study where behavioral disorders were identified in children with ISS, the situation improved when they were treated with growth hormone [23].

After reaching adulthood, most of the individuals with ISS (both treated and untreated) expressed a desire to be taller. However, only a minority in each group was willing to make some type of sacrifice to achieve this, which was interpreted by the authors to mean that this desire was not particularly strong. Growth hormone treatment does not seem to enhance the quality of life, even if patients were satisfied with the treatment and attributed much of their final height to treatment. (Although subjects perceived a gain of 12 cm from treatment, in reality this gain was probably around 3 cm.) [18].

Complications and side effects

Known, but uncommon, side effects of growth hormone treatment in children include edema, hyperglycemia, diabetes, epiphysiolysis, lipodystrophy at the injection site, and benign intracranial hypertension [5,8]. Some concern has been expressed that growth hormone increases the risk for cancer in children [5] and in adults who have been treated with growth hormone during childhood [34].

In comparison with patients who were treated by growth hormone for other reasons, the ISS patients experienced fewer side effects, 1.6 percent side effects per year compared to 2.3 percent for other conditions [8]. Patients with various chronic diseases are included, eg, brain and pituitary tumors or concurrent deficiency of other pituitary hormones.

An important question is whether or not growth hormone treatment can influence the debut and duration of puberty. The findings from studies do not provide a uniform answer to this question, but the debut of puberty does not seem to be influenced. Nevertheless, growth hormone treatment tends to shorten the duration of puberty, mainly in boys, resulting in more rapid skeletal maturity [4,11,16,19,21,27,28].

Cost and cost-effectiveness

The cost of treating children until final height is achieved varies depending on the child's weight, the dose administered, and the duration of treatment. Frequently, treatment lasts for 10 years. The cost for growth hormone is approximately 470 SEK per day and patient [3]. Additional healthcare costs include checkups, treatment of possible side effects, and injection material. In a meta-analysis [33] and a systematic review and economic evaluation [32] the cost-effectiveness of growth hormone treatment in ISS has been estimated. The incremental cost of growth hormone treatment for one child was estimated to be between 650 000 and 900 000 SEK. The corresponding cost per centimetre gained in final height was between 150 000 and 350 000 SEK [32].

Ethical aspects

Growth hormone treatment has ethical implications. It is often the child's family that takes the initiative to seek care for short stature. Since treatment is often initiated during preschool ages, the children have little opportunity to participate in this complex decision. Treatment may have both social and psychological consequences. The potential suffering of the child as a direct result of daily injections for several years must also be taken into account. Another consideration is that the outcome of treatment is uncertain. A child who is treated with daily injections may gain the impression that it is exceptionally important to reach normal height. Furthermore, the child risks disappointment if the effects of treatment are not as good as anticipated [25].

One thing that differentiates people with ISS from other equally short stature individuals in the population is that they are categorized as "patients". Their short stature thereby becomes medicalized. This raises the question of whether short stature in otherwise healthy individuals should be classified as a disease, or whether height-promoting treatment is only "cosmetic", and should therefore receive a lower priority. Growth hormone treatment was discussed in the Prioritization Committee and was viewed as an example of treatment that should receive low priority [31].

If being of short stature causes suffering, it is partly due to negative attitudes and prejudice in society. The question then becomes whether the focus should be placed on increasing the height of short stature individuals or on increasing tolerance in society for deviations in stature.

Diffusion in Sweden

The sales of growth hormone in Sweden, for children and adolescents below 19 years of age, totaled about 289 million SEK in 2002. Since, in Sweden, idiopathic short stature is not an approved indication for growth hormone treatment but is being used within the framework of clinical trials, it stands only for a minor part of the sales.

Approved indications are diagnosed growth hormone deficiency, Turner's syndrome, Prader-Willi syndrome, and kidney failure in children awaiting transplantation. The cutoff points concerning what should be considered as normal or pathological levels of growth hormone in children are under discussion.

Current evaluation research

In Sweden treatment of children with ISS takes place within the framework of clinical trials. The children who participate are registered in the respective study.

Children who receive growth hormone treatment are included in a national registry. In 1999, just over 2 000 children were receiving such treatment [30], whereof 7 percent were diagnosed with ISS [3].

Experts

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Table 1. Controlled studies of ISS children treated with growth hormone. Author, year of publication, number of subjects, regimen, treatment time, and results.

Year	Study	No. patients	Control group	Treatment regimen	Treatment time	Results	Increase in final height
1992	Zadik et al.	28 (boys only) RCT	The patients were randomized to a treatment or control group	0.75 U/kg/week, 3 doses per week for 2 years, thereafter 0.75 U/kg/week divided into daily injections	At the start of the study, the patients were between 10 and 16 years of age, and treatment was continued until final height was reached	Patients treated by growth hormone reached expected height. Final height of the control group was significantly lower –but small difference in cm. Final height in treated group -1.5 ± 0.6 SD and in untreated group -2.7 ± 0.7 SD.	1.2 SD; since the study included only boys it can be estimated at approximately 6.1 cm.
1995	Wit et al.	21	Retrospective data from 27 untreated patients with the same inclusion criteria as in the study and 7 children with growth hormone deficiency who were treated with growth hormone.	2 U/m per day, 7 injections per week. After year 1 the non-responders (growth increase less than 2 cm/year) received a double dose.	The patients were more than 6 years of age when the study started.	Treated patients increased in final height appr. 2.4 cm on average compared with controls. There was no significant difference in final height between treated patients who received 2 U/m per day and those who received a double dose.	2.4 cm
1996	Hindmarsch et al.	23	7 patients who declined treatment.	12.2-21.0 U/m per week (0.02-0.04 mg/kg/day) divided into 6 injections per week for 2 years, thereafter 20 U/m per week.	Time treatment started was not reported.	Treatment increased final height by appr. 2.8 cm in boys and 2.5 cm in girls compared with controls. Final height in the treated group was -1.33 SD compared with -1.88 in the control group.	0.55 SD 2.8 cm in boys 2.5 cm in girls
1998	Buchlis et al.	94	Not reported if the patients were randomized to control group or treatment group, or if they were grouped in some other way	0.3 U/kg/week divided into daily injections	Time treatment started was not reported.	Treatment increased final height by 3.0 cm in boys and 6.8 cm in girls compared with controls. Variations in treatment effects. Final height for treated group -1.5 ± 0.8 SD and for untreated group -2.1 ± 1.0 SD	0.6 SD 3.0 cm in boys 6.8 cm in girls
1999	Hintz et al.	121	Three separate control groups, in total 291 children, both short stature and normal height.	The treated patients were randomized to either 0.75 U/kg/week divided into 3 injections/week or 0.75 U/kg/week divided into daily injections.	Time treatment started was not reported, but the patients treated for up to 10 years.	Treatment increased final height on average by 9.2 cm in boys and 5.7 cm in girls compared with controls. Some of the treated patients showed no apparent benefits from treatment. Base-line characteristics were the same in the groups.	9.2 cm in boys 5.7 cm in girls
2002	Wit et al.	53	34 nontreated individuals from the same centers, matched for age and pubertal stage. Height at start was -3.0 SDS, cf. -3.6 SDS for the treated group	Two doses: 2 or 4 IU/m ² /day (corr. To about 23 and 46 ug/kg). After 1 yr “poor responders” (increase of height velocity <2 cm/year). were given 4 IU/m ² /day	Patients and controls were 10 years of age when the study started. Treatment was continued until final height was reached.	Two studies were summarized. Final height are reported for 53 patients (in part the same patients as in Wit et al 1995)	7 cm with the higher dose (4 IU/m ² /day = 46 ug/kg/day), 3 cm with the lower dose (2 IU/m ² /day = 23 ug/kg/day).
	Weighted mean value for height increase	108 boys 35 girls	Information from Zadik et al, Hindmarsch et al, Buchlis et al, Hintz et al.				6.6 cm in boys 5.3 cm in girls

Table 2. Non-controlled studies of ISS children treated with growth hormone. Author, year of publication, number of subjects, regimen, treatment time, and results.

Year	Study	No. patients	Treatment regimen	Treatment time	Results
1994	Lande et al.	15	- group 1 (7 patients) 0.5 U/kg/week - group 2 (8 patients) 1.0 U/kg/week Weekly dose divided into 4-7 injections per week	Treatment start from 7.4 to 13.2 years of age. Treatment continued 4 to 10 years.	Final height did not differ from expected height regardless of the growth hormone dose given to the patient. All patients in the study reached their target height but did not exceed it. Average final height: - group 1: 159±7.1 cm - group 2: 162.1±6.7 cm
1997	Schmitt et al.	17	- group 1 (6 patients) 3 U/m/day - group 2 (6 patients) 4.5 U/m/day - group 3 (5 patients) 3 U/m/day for 1 year, thereafter 4.5 U/m/day	Time treatment started was not reported. Treatment continued for 5 years.	Final height achieved by 9 patients, remaining patients were still growing when the article was written. Average final height was, with wide individual variation, 2.4 cm above expected final height before treatment had started. Final heights were -1.81±0.34 SD; - appr. 167±2.3 cm in boys - appr. 154±2.0 in girls