NEW INDICATIONS FOR GROWTH HORMONE

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Many members of the public have heard about growth hormone (GH), and paediatric endocrinologists regularly find themselves explaining the limitations of GH therapy to families who have come looking for something to increase their child's height. GH was originally extracted from human pituitaries to treat children with GH deficiency. The introduction of recombinant GH in 1985 increased the supply of GH and trials were initiated in short stature conditions not associated with GH deficiency. The results of these trials have extended the range of conditions treated with growth hormone (table 1).

USE OF GH THERAPY IN SHORT STATURE

Turner syndrome

Turner syndrome is associated with short stature which is not explained by GH deficiency. Trials of GH treatment have demonstrated improved final height, but there is variation in the increment in final height reported, from no gain at all to 16 cm.[2] One of the difficulties in interpreting the data available is that there are few studies with an untreated control group. Most rely on comparison with height predictions or historical control groups. A mean untreated adult height of 143 cm was reported 1985,[3] but as in the general population, there has probably been a secular trend in the height of Turner women.[2] There have been two randomised controlled studies of GH treatment in Turner syndrome, reporting mean final heights of 142.9 cm and 147.3 cm, and 141.4 cm and 146.2 cm in untreated and treated groups, respectively.[4 5] A girl treated with GH using current standard treatment can expect an increase of approximately 6 cm in adult height.[6 7] Earlier start of GH treatment and higher GH dose may increase this, although this is also likely to increase the cost per centimetre gained—currently about £17 000 per cm.[8] Adult women with Turner syndrome have an increased prevalence of diabetes.[9] A fall in insulin sensitivity has been documented during GH treatment, with a return to normal after treatment is stopped.[10]

Prader Willi syndrome

Adult height in Prader Willi syndrome (PWS) is approximately 150 cm for females and 160 cm for males.[11] Individuals with PWS have increased fat mass and reduced GH secretion, but reduced GH secretion is not the complete explanation for the short stature.[12] Severe obesity is inevitable without careful management of the diet, but this can have an adverse impact on growth.[13] Trials of growth hormone in PWS have demonstrated increased height velocity ,[14] and limited data on final height suggests this is increased compared with untreated individuals.[15]

In children with PWS, GH treatment has been found to decrease body mass index (BMI) and increase lean body mass.[13 16] There is an increase in respiratory function and exercise capacity which is possibly related to increased muscle mass.[17 18] The most significant changes are at the start of treatment, and are sustained while treatment continues.[13] It is not known if the benefit continues after stopping GH. Adults with PWS have an increased mortality rate, mainly related to complications of obesity.[19] Twenty five per cent of adults with PWS have type 2 diabetes.[20] It is possible that the effect of GH treatment on BMI and body composition could improve this poor long term outlook, and might justify GH prescription even if height gains are not worthwhile. Studies monitoring glucose tolerance during GH treatment have not found any adverse effect.[14 21] Unexpected deaths have been reported in extremely obese individuals with PWS, shortly after starting on GH.[22 23] It is not clear if there is a link with GH treatment, but caution is advised in commencing GH in very overweight children.

Short stature in children who were small for gestational age

Around 70–80% of small for gestational age (SGA) infants catch up in growth during their first few years of life.[24] There have been a number of studies of GH treatment for children who fail to achieve catch up growth.[25] Two controlled studies have reported final height data in children who were SGA with normal GH secretion. The first started GH at an average age of 7.8 years, and final height was 1.5–2.0 standard deviations (SD) greater than the control group.[26] The second study started GH prepubertally, treating for an average of 3.1 years. Adult height in the treated group

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Table 1 The use of growth hormone (GH) therapy in short stature

- Treatment recommended by NICE guidelines 2002 in the UK[1]
  - GH deficiency, isolated or as part of multiple pituitary hormone deficiency
  - Turner syndrome
  - Prader Willi syndrome
  - Short stature associated with chronic renal failure
- Licensed indications in Europe
  - GH deficiency, isolated or as part of multiple pituitary hormone deficiency
  - Turner syndrome
  - Prader Willi syndrome
  - Short stature associated with chronic renal failure
  - Short stature associated with low birth weight
- Licensed in the USA, but not in Europe
  - Idiopathic short stature
- Short stature conditions where there have been trials of treatment with GH but outcome is not clear (not licensed indications)
  - Noonan syndrome
  - Skeletal dysplasia
  - Rheumatoid arthritis
  - Down syndrome
  - Short stature associated with prolonged steroid use
  - Aarskog's syndrome

NICE, National Institute for Clinical Excellence.

was 162 cm in males and 151 cm in females, compared to 159 cm and 147 cm in controls.[27] In an analysis combining several studies with different treatment regimens, de Zegher found an increase in height of 2.0–2.7 SD compared with baseline after six years of GH treatment.[28] Final height data are not available for this group.

Children who were SGA have increased fasting insulin values for their age, with reduced insulin sensitivity, and as adults have an increased risk of diabetes and cardiovascular disease.[29–31] There is a concern that the metabolic changes induced by GH treatment could add to long term cardiovascular risk factors for SGA individuals. Although a fall in insulin sensitivity has been demonstrated in SGA children on starting GH,[32] insulin sensitivity appears to return to pre-treatment values after stopping treatment.[33]

Idiopathic short stature and other short stature conditions

GH treatment of idiopathic short stature (short stature with normal GH secretion and no other underlying pathology) results in increased final height.[7] A placebo controlled study of 33 individuals to adult height (22 treated with GH) demonstrated an increase in adult height after a mean of 4.4 years treatment of 0.51 SD (equivalent to 3.7 cm). When parental heights were allowed for, the calculated gain from GH treatment was smaller. There were no adverse events but fasting glucose was higher in the treated group 12 hours after GH injection.[34] In the USA a licence has been granted for GH treatment of idiopathic short stature (children less than −2.25 SD below the mean, who are not likely to catch up). This indication is not licensed in Europe, and many paediatric endocrinologists feel that the potential gains in this group do not justify treatment.[35] Small scale trials of GH have been reported in a wide range of conditions of short stature (table 1). Most confirm an increase in growth velocity with treatment but final height data are lacking.

Table 2 Adverse events reported during GH treatment

Benign intracranial hypertension
Slipped upper femoral epiphyses
Worsening of scoliosis
Gynaecomastia
Oedema (almost exclusively in adults)

Possibly related to GH treatment
Malignancy
Reduced insulin sensitivity
Unexpected deaths in obese patients with Prader Willi syndrome

RISK BENEFIT OF GH TREATMENT

Assessment of the benefit of GH treatment

In discussion of treatment with families, it is important to give a realistic picture of potential gains in height. The variation in outcome should be explained, and it should be made clear that treatment will not necessarily give an adult height within the normal range. Families need to balance possible height gains against the burden of treatment (daily injections for up to 10 years). There are areas of uncertainty about potential for adverse effects in the future and this should be discussed.

Reported adverse events during GH treatment are rare (table 2). A long term follow up study of individuals in the UK who were treated with pituitary GH has reported an excess of malignancy over that expected in the population.[36] No other follow up data have suggested increased risk of malignancy.[37] The standard dose of GH used to treat Turner syndrome and SGA children is larger than that used in GH deficient individuals, and some study protocols have given even larger doses—the study on Turner syndrome which has demonstrated the greatest final height increment gave three times the dose used for GH deficiency.[38] One study has reported increased prevalence of type 2 diabetes during GH treatment, possibly caused by an acceleration of the disorder in predisposed individuals.[39] The use of GH (which reduces insulin sensitivity) in groups who have an increased diabetes risk raises issues which will only be answered with longer term follow up.

One of the problems in assessing the benefit in GH treatment is defining the disadvantage associated with short stature, and the benefit of an increase in height with treatment. Although there is a general impression of psychological disadvantage for short children or adults, there is conflicting evidence to support this.[40 41] The Wessex growth study, which followed a group of short normal children from school age to adult life, failed to confirm a psychological disadvantage associated with short stature during childhood or adult life.[42]

Practical issues in GH treatment

GH is given as a daily subcutaneous injection. Most families have no problems learning to give the injections. As with all very long term medications, adherence is an issue and missed doses are the most common reason for poor growth while on GH therapy. Children with GH deficiency have the greatest height benefit from GH treatment (9–10 cm) and there is little doubt that this group should have treatment.[7] For those with other indications for GH treatment, there are situations where starting treatment may not be appropriate—girls with Turner syndrome who have a height prediction in the normal range, or children with PWS who have such severe behaviour problems as to make GH treatment impractical.

GH treatment can benefit children with a number of short stature conditions not associated with GH deficiency. In PWS, changes in body composition may justify treatment, rather than height. For many indications there is still uncertainty about the optimum treatment regimen with GH, and about how much improvement in height can be expected. It is not clear how concerned we should be about long term metabolic effects of GH treatment. Discussion of the uncertainties rarely deters families from going ahead with treatment but can be helpful in giving them realistic expectations of likely outcome.

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