Growth hormone therapy in the Prader-Willi syndrome

W F Paterson, M D C Donaldson

Who should receive it and when?

In November 2000 the Department of Health in England granted a licence to Pharmacia Limited for the use of their recombinant growth hormone, Genotropin (somatropin rbe), in the Prader-Willi syndrome. The indications for use were given as “improvement of body composition and growth”. In this leading article we shall attempt to examine the role of growth hormone in the Prader-Willi syndrome by considering linear growth and body composition in untreated and treated individuals, the pathophysiology of the abnormal linear growth, and the scope for future research.

While the growth and body composition aspects of the Prader-Willi syndrome are important, they must be seen in the context of a disabling disorder with major implications for the individual and family. Therefore a brief account of the condition is in order.

GENERAL ASPECTS OF THE PRADER-WILLI SYNDROME

The Prader-Willi syndrome results from loss of an imprinted gene or genes on the long arm of chromosome 15 within the q11–13 region, usually as a result of a deletion on the paternal chromosome or a long arm of chromosome 15 within the paternal q11–13 region, usually as a result of a deletion on the paternal chromosome or a long arm of chromosome 15 within the paternal q11–13 region. The Prader-Willi syndrome results from the loss of an imprinted gene or genes on the paternal chromosome or a long arm of chromosome 15 within the paternal q11–13 region, usually as a result of a deletion on the paternal chromosome or a long arm of chromosome 15 within the paternal q11–13 region.

ABNORMAL LINEAR GROWTH IN UNTREATED PRADER-WILLI SYNDROME

While length at birth is normal or slightly below normal in Prader-Willi syndrome, linear growth in infancy is slow, in association with poor feeding. Thus the child is noticeably short from around the first year of life and remains short throughout childhood (mean height standard deviation score (Ht SDS) around −2) despite a relatively normal growth rate. Note that there is no enhancement of growth velocity in response to high energy intake in obese Prader-Willi subjects, in contrast to children with simple obesity. During adolescence the growth rate declines as a result of absence of the pubertal growth spurt. In Prader-Willi subjects the adult height centile will be lower than the childhood height centile, with mean final heights in the UK of 147 cm (−2.8 SD) for girls and 155 cm (−3.2 SD) for boys.

BODY COMPOSITION

In simple obesity, fat mass (FM) is increased while fat free mass (FFM) is normal or increased. In Prader-Willi syndrome, body composition is unusual with reduced FFM and increased FM, even in lean subjects. In addition, bone mineral content is lower than in simple obese subjects. Even in infancy, when body mass is low, fat content is relatively increased. Energy expenditure is reduced, partly attributable to the reduction in FFM. Energy requirement per unit of body weight is lower in Prader-Willi subjects than normal controls, and this must be taken into account when calculating the optimal daily food intake.
interpreted as low, but with considerable individual variation, in four.1-3 However, these data are difficult to interpret because of differences in assays and references ranges between the different centres. Definitive assessment of IGF-1 status in Prader-Willi syndrome will require measurement of sufficient samples in a single laboratory with robust aged related reference ranges.

It is known that in children with simple obesity, spontaneous and stimulated growth hormone levels are impaired, although IGF-1 levels are normal.13 Is it possible, therefore, that the apparent growth hormone deficiency seen in most Prader-Willi syndrome patients is secondary to the obesity? Two studies shown in table 1 have examined GH levels in obese and non-obese patients, with conflicting results. Corrias and colleagues reported that, in response to three provocative stimuli, GH levels were lower in 43 Prader-Willi subjects (36 obese; seven normal weight) compared with 25 normal children, but similar to those in 24 children with simple obesity. In contrast, Grunig and colleagues found blunted responses to two provocative stimuli in 16 Prader-Willi subjects, in comparison with both simple obese and normal short subjects.

Pituitary morphology in Prader-Willi subjects has been examined by magnetic resonance imaging (MRI) as an indirect measure of GH function, since somatotrophs account for 30% of the anterior pituitary mass. Miller and colleagues found no significant difference in the height of the anterior pituitary in 15 Prader-Willi subjects, in comparison with normal controls or children with isolated growth hormone deficiency. However, in four patients the posterior pituitary bright spot was either absent or small, reflecting a physiological disturbance in the hypothalamus. Twelve of the 16 Prader-Willi subjects described by Grunig and colleagues had MRI performed. In contrast to Miller’s group, all had abnormalities of the anterior pituitary gland and/or stalk, including nine with small anterior lobes and two with empty sellas.

To summarise, the combination of short stature, impaired growth response to obesity, and reportedly low IGF-1 levels provide evidence that the low GH levels frequently observed reflect impaired hypothalampituitary secretion of GH rather than artefact related to obesity. However, the normal GH and/or IGF-1 levels and the morphologically normal anterior pituitary gland seen in some patients in some studies indicate that classical GH deficiency is not a constant feature.

**LINEAR GROWTH IN RESPONSE TO GROWTH HORMONE TREATMENT**

For a comprehensive summary of the response to GH therapy in Prader-Willi syndrome, the reader is referred to the excellent monograph of Urs Eiholzer.15 All studies to date have shown a significant first year response. Of particular note is the 1999 study of Lindgren and Ritzen,16 showing the results of five years GH therapy (0.1 or 0.2 IU/kg/day) in 18 patients aged 3–12 years. Ht SDS increased during the first year of treatment and the attained centile position was maintained thereafter. After five years therapy, mean Ht SDS remained above average for chronological age. In 2000, Eiholzer and l’Allemand17 reported a mean increase in Ht SDS of 1.8 SD in 18 prepubertal subjects aged 0.3–9.5 years treated with growth hormone in a dose of 18 IU/m/week (age <2 years) or 24 IU/m/week (age ≥2 years) for 1.5–5.5 (median 4.0) years. However, a waning effect occurred after three years treatment. In 2000, Tauber and colleagues18 reviewed retrospectively 14 patients treated with 0.3–0.6 IU/kg/week GH for a mean of 3.6 years (range 1–9.3 years) and compared them with 14 untreated patients. In the treated group growth velocity showed the maximum increase during the first year of therapy, but remained greater than the pretreatment velocity throughout the course of treatment.

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>No. patients</th>
<th>Age range (y)</th>
<th>Stim. agent</th>
<th>GH (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angulo et al</td>
<td>1991</td>
<td>15</td>
<td>1–15.5</td>
<td>I</td>
<td>9.4±0.2 [8.0] (2.5–20.4)</td>
</tr>
<tr>
<td>Grosso et al</td>
<td>1998</td>
<td>5</td>
<td>7.9–11</td>
<td>I</td>
<td>8.4±3.9 [8.0] (3.9–13.5)</td>
</tr>
<tr>
<td>Carroll et al</td>
<td>1999</td>
<td>54</td>
<td>4–16</td>
<td>C</td>
<td>2.0±1.9</td>
</tr>
<tr>
<td>Conias et al</td>
<td>2000</td>
<td>43</td>
<td>3–22</td>
<td>C</td>
<td>4.1±1.0 [n=33]</td>
</tr>
<tr>
<td>Grugni et al</td>
<td>2001</td>
<td>16</td>
<td>12.8–38.4</td>
<td>GHbH+P</td>
<td>14.4±3.1 [n=43]</td>
</tr>
<tr>
<td>Donaldson and Paterson</td>
<td>2002</td>
<td>12</td>
<td>3–16.3</td>
<td>I</td>
<td>7.2±4.2 [7.2] (1.8–14.0)</td>
</tr>
</tbody>
</table>

1 I, insulin; C, clonidine; D, l-dopa; O, ornithine; GHRH, growth hormone releasing hormone; A, arginine; P, pyridostigmine.

Results are given as mean ± SD [median] (range). *Mean ± SE in this study.

In summary, short term growth hormone treatment, data on final height are scarce. In the long term studies described, Lindgren and Ritzen16 reported four children at final height, all within ±2 SD of target height (range −1.1 to +0.9 SDS). Only nine of the 28 patients described by Tauber and colleagues18 had reached final height: six untreated (mean adult Ht SDS = −2.5) and three treated (mean adult Ht SDS = −3.5).

In summary, short term growth hormone administration improves height velocity and height SDS in growing subjects with Prader-Willi syndrome, but there is a waning effect after 1–3 years. There is no evidence as yet that growth hormone therapy improves final height in Prader-Willi syndrome, and in particular that growth hormone can compensate for the poor pubertal growth phase.

**THE EFFECT OF GROWTH HORMONE ADMINISTRATION ON BODY COMPOSITION**

Given the uncertainty as to the long term efficacy of growth hormone as a growth promoting agent in Prader-Willi syndrome, the potential metabolic benefits of treatment may provide better justification for its use in this condition.
Data on the effect of growth hormone on body composition are encouraging, with most studies showing improvement, at least in the short term. Thus, Lindgren and Rittenboer showed a dramatic decrease in body mass index standard deviation score (BMI SDS) during the first year of growth hormone therapy. BMI then increased during a six month period of non-treatment and stabilised following reintroduction of growth hormone therapy. However, two patients in their series developed non-insulin dependent diabetes mellitus in association with rapid weight gain while on therapy, withdrawal of growth hormone resulting in normalisation of glucose homoeostasis.

Elhoffer and l’Allemand similarly reported normalisation of weight for height in their growth hormone treated group during the first 2–3 years of therapy, body composition then remaining the same. Tauber and colleagues reported normalisation of weight for height is seldom the principal concern. We therefore do not recommend growth hormone therapy to improve height alone as standard practice. However, we believe that growth hormone therapy has a role where the child has showed short stature, is showing a reduced height velocity in the context of normal weight, and is from a well-nourished family in whom good compliance can be realistically expected. In the absence of clear evidence as to optimal dosage, we recommend a starting dose of 15 IU (5mg)/m²/week as for classical GH deficiency, adjusting this in relation to growth response and IGF-1 levels. The current data on improved body composition are not in our view sufficiently compelling to advocate routine institution of growth hormone therapy at present, and dietary control remains the cornerstone of good management.

The improved muscle strength and agility described by Myers and colleagues in growth hormone treated patients is of considerable potential interest in the treatment of preschool children with Prader-Willi syndrome. An improvement in body composition and muscle mass in this age group could have a significant impact on their mobility, with earlier achievement of gross motor milestones and in quality of life. A randomised trial of growth hormone in Prader-Willi children aged 1–3 years is indicated, the hypothesis being that treated children would show an improvement in body composition, mobility, and quality of life, with no adverse effects in terms of cardiovascular health and glucose homoeostasis. Such a trial would only be viable if conducted on an international basis. Similarly the effectiveness of GH in improving final height outcome depends on treating a sufficient number of patients in a consistent fashion for many years. Given the small number of suitable patients in any given centre, this goal can only be achieved with disciplined collaborative study using an agreed dosage schedule.

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REFERENCES