Growth hormone deficiency in the young

This article focuses on growth disorders in children and young people and the management of growth hormone deficiency using recombinant growth hormone

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GROWTH in childhood is an overall indicator of health and development. Growth failure may be caused by a number of underlying factors, such as hormone imbalances, genetic or congenital abnormalities, chronic medical conditions and malabsorptive states. Short stature in a schoolchild can have negative psychological and physical implications, such as bullying and poor performance in sports, impacting on the child’s overall quality of life.

Normal growth in childhood

Growth is affected by a complex combination of genetic predisposition and environmental factors. Normal growth exhibits many different patterns and shows variation between individuals and populations. The infancy-childhood-puberty (ICP) growth model describes the theoretical process of growth and may be used to predict final height. In this model, linear growth is broken down mathematically into three components. The infancy component may begin mid-gestation and is thought to be nutritionally driven. The childhood component is thought to correspond to the effect of growth hormone, and the puberty component to the stimulation of growth hormone by oestrogen and testosterone.

Growth should always be considered in a longitudinal context; therefore accurate, repeatable measurements recorded on standardised growth charts over time are essential to diagnose any abnormalities. The UK-WHO growth charts for zero to four years and the UK90 charts for over four years of age are currently used in the UK. Parental height should also be considered when assessing stature, with a target height expected to be a function of mother and father’s height, adjusted for the sex of the child.

Growth charts are used in everyday practice and can record weight, height (or length) and head circumference and are based on Gaussian normal distribution of the population at any given age; the 50th centile represents the most common measurement, the 98th centile the upper end of normal and the second centile the lower end of normal. Children are expected to grow along the centile on which they are born. Growing at a slower than expected rate (“falling-off their centile”) may indicate failure to thrive or growth failure.

Causes of growth failure

There are a number of different causes of growth failure in children, ranging from malnutrition to complex medical disorders. Some of the most common causes are listed in the table below.

<table>
<thead>
<tr>
<th>Causes of growth failure</th>
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<tbody>
<tr>
<td>- Malnutrition</td>
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<tr>
<td>- Congenital abnormalities</td>
</tr>
<tr>
<td>- Chronic medical conditions</td>
</tr>
<tr>
<td>- Hormone imbalances</td>
</tr>
<tr>
<td>- Genetic or congenital abnormalities</td>
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SDSs is that a statistical comparison between peer groups is simplified. A child near the 98th centile has a height SDS of about +2 and a child near the second centile has a height SDS of about –2.

KEY POINTS

- For maximum benefit, growth hormone treatment should be started at the youngest possible age.
- Growth hormone is best administered at night to mimic endogenous secretion and to aid adherence.
- The European Medicines Agency is reviewing the safety of somatropin (recent findings show an association with increased mortality due to bone tumours and cardiovascular disease) but current advice is that there is no immediate concern as long as indications and doses are followed.
The Growth Hormone

Diagnosis of GHD in childhood is a complex process requiring clinical and auxological (growth) assessment, combined with biochemical tests of the growth hormone/insulin-like growth factor system (sometimes called “axis”) and radiological evaluation of the pituitary by magnetic resonance imaging. The Growth Hormone Society’s consensus guidelines state that the evaluation of GHD in a short child should not be initiated until other causes of growth failure have been excluded. Criteria for immediate investigation include:2

- Severe short stature, defined as a height more than 3 SDSs below the mean
- Height more than 1.5 SDSs below the mid-parental height
- Height more than 2 SDSs below the mean and a height velocity over a year more than 1 SDS below the mean for age, or a decrease in height SDS of more than 0.5 over a year in children over two years of age
- In the absence of short stature, a height velocity more than 2 SDSs below the mean over a year or more than 1.5 SDSs sustained over two years
- Signs of an intracranial lesion
- Signs of multiple pituitary hormone deficiencies
- Neonatal symptoms and signs of GHD (eg, hypoglycaemia, prolonged jaundice, microgenitalia in boys)

GHD should be confirmed at least once by an appropriate provocation test. The choice of test used depends on local policy, but the most appropriate tests include the oral glucose tolerance test (OGTT) and the growth hormone stimulation test. Both simulate the growth hormone secretion by inducing hypoglycaemia and should only be undertaken in tertiary centres with appropriately trained staff. In a child with clinical criteria for GHD, a peak growth hormone concentration less than 10 μg/L after provocation has traditionally been used to support diagnosis.2

Somatropin

Pituitary extracted growth hormone (somatropin) was first used as a treatment for GHD in children in 1958. However, because supplies relied on the availability of cadaveric pituitaries, only the most severely affected children were treated. Then, in 1985, cadaveric growth hormone was withdrawn after a number of treated patients developed Creutzfeldt-Jakob disease. Recombinant human growth hormone (somatropin) has been available since 1985 and is marketed by several pharmaceutical companies. The amino acid sequence is identical to that of human growth hormone produced by the pituitary gland. Dosage varies depending on the indication (see Panel 2) and must be given by subcutaneous injection, usually once daily, at night. Injecting at night mimics the endogenous secretion of growth hormone, and often makes it easier for patients to remember to take it as part of their bedtime routine. Taking the somatropin out of the refrigerator 30 minutes before administration may make the injection more comfortable.

It is important that the dose of somatropin is adjusted at regular intervals as the child grows, usually at clinic appointments with an endocrinologist. In cases of non critical illness (eg, cough and cold, chickenpox), the recommendation is to continue growth hormone treatment because it may help to increase glucose levels during illness. Some patients with hypopituitarism may be unable to mount a stress response and might need cortisol support during illness (due to an associated cortisol deficiency). If a dose is missed, the next dose should be taken as usual, at the normal time — the dose should not be doubled. Long-term overdosing could result in symptoms of growth hormone excess, such as overgrowth of jaw, hands and feet. Overdose might also lead to increased blood glucose levels.

The aims of growth hormone treatment in growth failure are to provide adequate catch-up growth to the mid-parental height centile, a normal growth velocity, a normal pubertal growth spurt and a target height within the reference range for the population. Treatment should be initiated at the youngest possible age to get maximum benefit and, given that height at the onset of puberty is a marker of final height, early treatment allows for sufficient growth time before puberty. In some instances, the onset of puberty may be delayed pharmacologically with gonadotrophin-releasing hormone analogues, to allow this to happen.3

Side effects

Somatropin has been in use for over 25 years and is known to be safe and well tolerated — serious adverse effects are uncommon with...
Hypothyroidism has been reported in 5–10
dominate and may require transient dose
Symptoms are usually transient and dose-
Hypothyroidism has been reported in 5–10
Rarely, benign intracranial hypertension has
Symptoms are usually transient and dose-
Symptoms are usually transient and dose-

Safety
The European Medicines Agency is currently
The investigators reported a 30 per cent increased
Risk of death was reported to be increased
The risk of death was reported to be increased
The risk of death was reported to be increased
The risk of death was reported to be increased

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Somatropin treatment in children with GHD

Other parameters monitored are:
Thyroid function annually or when indicated
Bone age assessment annually or when indicated
Assessment of pituitary status (other hormone deficiencies may be unmasked by treatment)

Duration of therapy
There are different thoughts on how long
alternatively, therapy can be discontinued

Selection
The choice of which brand of somatropin
to supply is controversial. Ideally, choice should
be directed by licensed indications and patient preference of device. However, in the current
cost must be considered since there is no evidence of superiority of one product over
another in terms of clinical efficacy and side effect profile.6 Patient involvement in choice of
device, training and support (in the hospital and at home) and home delivery services are all
toward improved adherence.

There are a range of growth hormone products available and these are compared in

<table>
<thead>
<tr>
<th>Product</th>
<th>Licensed indication</th>
<th>Device</th>
<th>Storage</th>
<th>Cost per mg*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotropin</td>
<td>GHD, Turner’s syndrome, chronic renal insufficiency (CRI), small for gestational age (SGA), Prader-Willi syndrome</td>
<td>Miniquick pre-filled syringes, cartridges (pen), needle-free device</td>
<td>Miniquips: Store up to six months below 25°C. Un-reconstituted. Once reconstituted, 24 hours at 2–8°C. Cartridges: Refrigerate or store up to 28 days below 28°C. Store up to 28 days at 2–8°C once reconstituted.</td>
<td>£23.18</td>
</tr>
<tr>
<td>Humatrope</td>
<td>GHD, Turner’s syndrome, chronic renal insufficiency (CRI), small for gestational age (SGA), SHOX deficiency</td>
<td>Cartridges (pen)</td>
<td>Refrigerate. Store up to 28 days at 2–8°C once reconstituted.</td>
<td>£18.00</td>
</tr>
<tr>
<td>Norditropin</td>
<td>GHD, Turner’s syndrome, CRI, SGA</td>
<td>Cartridges (pen)</td>
<td>Refrigerate. Store up to 28 days at 2–8°C once reconstituted or up to 21 days below 25°C.</td>
<td>£21.27</td>
</tr>
<tr>
<td>NutropinAq</td>
<td>GHD, Turner’s syndrome, CRI, SGA</td>
<td>Cartridges (pen)</td>
<td>Refrigerate. Store up to 28 days at 2–8°C once reconstituted.</td>
<td>£20.30</td>
</tr>
<tr>
<td>Omnitrope</td>
<td>GHD, Turner’s syndrome, CRI, SGA</td>
<td>Cartridges (pen)</td>
<td>Refrigerate. Store up to 28 days at 2–8°C once reconstituted.</td>
<td>£18.26</td>
</tr>
<tr>
<td>Säizen</td>
<td>GHD, Turner’s syndrome, CRI, SGA, Prader-Willi syndrome</td>
<td>Click, easy cartridges, needle-free device</td>
<td>Store below 25°C un-reconstituted or 28 days refrigerated at 2–8°C after reconstitution.</td>
<td>£23.18</td>
</tr>
<tr>
<td>Zomacton</td>
<td>GHD, Turner’s syndrome</td>
<td>Cartridges, needle-free device</td>
<td>Refrigerate. Store up to 28 days at 2–8°C once reconstituted.</td>
<td>£19.92</td>
</tr>
</tbody>
</table>

*Excluding VAT. Based on BNF60. Costs may vary in local settings based on negotiated procurement discounts.
Excellence reviewed and updated its Prescribing guidelines for NHS trusts in the current financial climate. This is of interest to a number of NHS drug budget licensees while delivering equivalent licensing allows for cost savings within the biosimilar product. Potential differences from the branded version of the product, with a different side effect profile. However, this has yet to arise. The first growth hormone biosimilar, Omnitrope, was launched in 2006, referenced to Genotropin. The agents were compared in head-to-head trials demonstrating the biological equivalent of generic medicines. Biosimilar growth hormone Biosimilars are the biological equivalent of generic medicines. Unlike normal drugs, biologics exhibit high molecular complexity, and may be sensitive to manufacturing process changes. Although a biosimilar manufacturer does not have access to the original's molecular clone, original cell bank, fermentation or purification process it does have access to an original reference product. Potential differences from the original in terms of impurities and breakdown products has raised concern that biosimilars may perform differently from the original branded version of the product, with different side effect profiles. However, this has yet to arise. The first biosimilar growth hormone, Omnitrope, was launched in 2006, referenced to Genotropin. The agents were compared in head-to-head trials demonstrating Omnitrope was comparable in efficacy compared in head-to-head trials demonstrating the biological equivalent of generic medicines.

Home delivery services The long-term therapy required for patients with growth hormone disorders means that ongoing repeat supply from the centre supervising care can be difficult especially if the patient lives a significant distance away. These challenges have allowed secondary care pharmacists to look at different ways of supplying growth hormone to patients (ie, through home-care deliveries). Centres with a number of patients on growth hormone are necessarily looking to maximise efficiency of service by outsourcing the dispensing and delivery of growth hormone to home-care companies. There are a number of benefits to patients, pharmacists and the NHS to using a home delivery service:

- Exemption from VAT on dispensed items
- Regular deliveries in agreed installments direct to the patient's home
- Home training, stock rotation and adherence assessment to ensure successful treatment outcomes and reduce waste
- Reduction of pharmacy administration and dispensing time

Organisation, distribution and reimbursement of growth hormone therapy are, therefore, common roles for paediatric pharmacists in secondary care to undertake to ensure continuity of care.

Pharmacist's role Pharmacists can play an important role in supporting patients and their families and carers by ensuring that NICE-related prescribing guidelines are adhered to, shared care protocols are in place, regular audits against NICE criteria are undertaken and, more importantly, clear communication pathways are available for both staff and patients. Effective communication with the patient's primary care trust is invaluable in ensuring continued access to treatment. Pharmacists in primary care can also play a role supporting patients, for example, by ensuring they are rotating injection sites and by advising on disposal of needles. Repeat

Pituitary extracted growth hormone was first used as a treatment for GHD in children in 1958 (Kenneth Edward SPL).