Traditionally, short stature is defined as a height that lies more than two standard deviations (SD) below the mean for age compared with gender-specific standards based on an appropriate healthy population. In multi-ethnic societies, it is important to compare children with controls from an appropriately matched normal population. Additionally, the genetic background of an individual's family is crucial. The majority of children with short stature do not have an underlying hormonal or genetic disease. Using the classical threshold of a height standard deviation score (SDS) equal to or below -2.0 identifies 14% of children as being of short stature with an organic cause, while reducing the threshold to -3.0 increases the yield to 58%. The genetic background is also crucial in determining the need for possible evaluation, and any child with a height more than 1.4 SD below the mid-parental height warrants assessment. Once familial short stature and organic causes of growth failure have been excluded, there remains a small number of children with unexplained short stature. Of these, a few will be found to have a hormonal cause for their growth failure.

**Growth Hormone Deficiency**

Growth hormone deficiency (GHD) is reported to occur in approximately one in 3,000–4,000 individuals, but this may be an overestimate given the reversibility of GH deficiency in 25–75% of patients with GHD (see below).

**Physiology**

GH is secreted by somatotropes in the anterior pituitary gland in a pulsatile manner characterised by peaks and troughs. Secretion is age- and gender-dependent. The human GH gene (GH-N or GH1) forms part of a cluster of five homologous genes (human GH (hGH)-N, human chorionic somatomammotropin-like (hCS)-L, hCS-A, hGH-V and hCS-B) located on the long arm of chromosome 17. Its expression is regulated by not only a proximal promoter, but also a locus control region (LCR) 15–32 kilobases (kb) upstream of the hGH-1 gene. The LCR confers pituitary-specific, high-level expression of hGH. The full-length transcript from the hGH-N gene encodes a 191-amino-acid 22 kilo Dalton (kDa) protein that accounts for 85–90% of circulating GH. Alternative splicing of the messenger RNA (mRNA) transcript generates a 20kDa form of GH that accounts for the remaining 10–15%.

Once GH has been secreted by the somatotropes, it binds to two binding proteins, high-affinity GH-binding protein (GHBP) and low-affinity GHBP, in the circulation. Little is known about low-affinity GHBP, while high-affinity GHBP is a 61kDa glycosylated protein that represents a soluble form of the extracellular domain of the GH receptor that can bind to both 20kDa and 22kDa hGH and thereby prolong the half-life of GH. GH then interacts with its receptor (GHR), which is present in a number of tissues. The hormone sequentially demerses its receptor, activating the receptor-associated tyrosine kinase janus kinase 2 (JAK2) that, in turn, is auto-phosphorylated and also phosphorylates the GHR. This then leads to signal transduction using the mitogen-activated protein kinase (MAPK), signal transducers and activators of transcription (STAT) and phosphomonoisotide-3 (PI3) kinase pathways. The end-result is activation of a number of genes that mediate the effects of GH, such as c-jun, c-fos and c-myc, implicated in cell growth, proliferation and differentiation, and insulin-like growth factor 1 (IGF-1), which mediates the growth-promoting effects of GH.

IGF-1 and -2 are single-chain polypeptide hormones that are widely expressed and, together with a family of specific binding proteins, are believed to mediate most of the actions of GH. Extensive and authoritative reviews cover this aspect of the GH axis.

**Aetiology**

In the past, the majority of GHD cases were thought to be idiopathic. However, the last ten years have led to major advances in the understanding of pituitary and somatotrope development and, hence, the aetiology of some of these cases of idiopathic GHD (IGHD) and multiple pituitary hormone deficiency (MPHD). The pituitary gland consists of anterior,
Recently, type 2 GHD, an autosomal dominant receptor (GHRHR) are associated with IGHD. The gene encoding the GH-releasing hormone (GH1) and POU domain, class 1, transcription factor 1 (POU1F1) or Pit1 are associated with GH, PRL, ACTH deficiency. Additionally, a number of gonadotropin deficiency, with later evolution of CPHD in the form of GH, PRL, TSH and ACTH deficiency. Mutations within PRO1 (PROP1) are associated with CPHD and a short neck domain genes LIM homeobox 3 (LHX3) and LHX4 are associated with variable hypopituitarism and high-mobility group (HMG)-box gene 3 (SOX3). Mutations of the SRY-related high-mobility group (HMG)-box gene 3 (SOX3) are associated with variable hypopituitarism and learning difficulties. Mutations within the LIM domain genes LIM homeobox 3 (LHX3) and LHX4 are associated with CPHD and a short neck with a steep cervical spine in the case of LHX3 and an abnormal cerebellum in the case of LHX4. Mutations within the homeobox gene HESX1 are associated with IGHD, CPHD, and septo–optic dysplasia (SOD), a condition characterised by forebrain, pituitary and eye abnormalities, such as optic nerve hypoplasia. Craniospinal irradiation used in the treatment of posterior fossa tumours and total body irradiation lead to abnormal hypothalamo–pituitary function. Craniospinal irradiation used in the treatment of posterior fossa tumours and total body irradiation (TBI) used in conditioning regimens for bone marrow transplant are also associated with epiphysial damage with subsequent disproportionate short stature.

The origins of the anterior and posterior lobes of the pituitary gland are embryologically distinct. Rathke’s pouch, the primordial anterior pituitary, arises from the oral ectoderm, whereas the posterior pituitary derives from neural ectoderm. A number of signalling molecules and transcription factors have been identified that are implicated in normal pituitary development. Recently, genetic abnormalities in some of these transcription factors have been identified in children who were previously thought to have IGHD or combined pituitary hormone deficiency (CPHD). In some cases, extra-pituitary manifestations may be associated. For example, mutations in the paired-like homeobox gene HESX1 are associated with IGHD, CPHD, and septo–optic dysplasia (SOD), a condition characterised by forebrain, pituitary and eye abnormalities, such as optic nerve hypoplasia. Mutations and duplications of the SRY-related high-mobility group (HMG)-box gene 3 (SOX3) are associated with variable hypopituitarism and learning difficulties. Mutations within the LIM domain genes LIM homeobox 3 (LHX3) and LHX4 are associated with CPHD and a short neck with a steep cervical spine in the case of LHX3 and an abnormal cerebellum in the case of LHX4. Mutations within the homeobox gene HESX1 are associated with IGHD, CPHD, and septo–optic dysplasia (SOD), a condition characterised by forebrain, pituitary and eye abnormalities, such as optic nerve hypoplasia. Craniospinal irradiation used in the treatment of posterior fossa tumours and total body irradiation (TBI) used in conditioning regimens for bone marrow transplant are also associated with epiphysial damage with subsequent disproportionate short stature.

Clinical Features

Severe GHD as part of a CPHD phenotype often presents in the first few days of life with jaundice, hypoglycaemia and micrognathia, often with undescended testes and hypothyroidism. Phenotypic features of GHD include characteristically immature faces with a prominent forehead and depressed midline development. Bone maturation and dentition are delayed. Body composition is characterised by low muscle bulk and increased subcutaneous fat. The hair may be thin and sparse, nail growth slow and the voice high-pitched. Associated abnormalities include midline defects of the face, a single central incisor or optic nerve hypoplasia. Metabolic effects include increased low-density lipoprotein (LDL) cholesterol at diagnosis. The principle mode of presentation of IGHD is with short stature and low growth velocity for age. That GH plays a role in foetal growth is evidenced by a modest reduction in birth weight and length in GHD individuals compared with controls. Subsequently, there is a rapid reduction in height SDS during the first two years. Children with untreated severe GHD achieve only 70% of their full growth potential, leading to a deficit of 38cm on average in males and 33cm in females. Children with less severe GHD present with short stature and a reduced growth velocity later in life.
**Diagnosis**

The diagnosis of GHD is based upon an inadequate GH response to provocation. The use of provocation tests and their interpretation is subject to considerable controversy, not least because of safety issues. The picture is complicated by the availability of up to 34 GH provocation tests, and a large number of monoclonal assays for the measurement of GH. The National Institute for Clinical Excellence (NICE) in the UK has recommended that at least two tests of GH provocation should be performed in order to establish a diagnosis of GHD/GH insufficiency (GHI). In those patients with defined central nervous system (CNS) pathology, a history of irradiation, MPHP or a genetic defect, one test will suffice. Even with these stringent criteria, a large majority of patients can actually reverse in terms of the biochemical GHD when re-tested after one to six months.

Low plasma concentrations of IGF-1 and IGF-binding protein 3 (IGFBP-3), both of which are regulated by GH, may aid in making the diagnosis, although in isolation the specificity and sensitivity of the test are poor. The secretion of other pituitary hormones, such as TSH, PRL, the gonadotropins and cortisol, will also need to be assessed. Recently, the use of neuroimaging has been proposed as a valuable adjunct to the diagnosis of IGHD and CPHD. Midline abnormalities, such as absence of the septum pellucidum, may be observed in children with SOD. Reduction in the size of the anterior pituitary, an attenuated or absent hypothalamo-pituitary stalk and a posterior pituitary that has remained ectopically positioned at or just below the tuber cinereum (40–60% of GHD patients) are all associated with pituitary dysfunction. In some children with IGHD due to mutations within GH1 or in association with other pituitary hormone deficiencies due to mutations within POU1F1 or PROP1, the size of the anterior pituitary may, in fact, be normal or even enlarged. Neoplasia, Rathke’s pouch cysts and a thickened pituitary stalk indicative of either a germinoma or histiocytosis may also be identified on magnetic resonance imaging (MRI) scanning. In some patients, the identification of a genetic mutation within the GH1 or GHRHR genes, or one of the transcription factors associated with CPHD, can definitively establish the diagnosis. However, to date, no genetic basis has been established for the majority of patients with IGHD.

Given the lack of reproducibility that is inherent in provocative tests of GH secretion, it is not surprising that there is considerable inter- and intra-individual variability in GH responses and that the results can be difficult to interpret. The reversibility of the GH response to provocation suggests that many of the children diagnosed as having IGHD in the absence of any congenital or acquired structural anomaly of the hypothalamo–pituitary–somatotroph axis may have been incorrectly diagnosed. A number of these children will have been diagnosed in the peri-pubertal period when GH secretion is generally blunted. Priming with sex steroid, measurement of IGF-1 and IGFBP-3 concentrations and MRI of the brain and pituitary may actually reduce the false positive rate associated with provocative GH testing.

**Treatment**

Recombinant hGH is used for the treatment of GHD. In children treated early, catch-up growth is excellent, with a normal final height. On average, a final height gain of 30cm can be expected, but this figure is affected by variables such as birth weight, age at start of treatment, degree of GHD, duration of treatment and frequency of GH injections, height at start of treatment and height at start of puberty. Final height gain can be particularly variable in children who have had treatment for malignancies. The GHD is often complicated by skeletal damage following TBI or craniospinal irradiation, early puberty, hypothyroidism, gonadotropin deficiency, malnutrition and concomitant chemotherapy. In this group of patients, gonadotropin-releasing hormone analogue (GnRHa) therapy to arrest early puberty has been used in conjunction with GH treatment, with encouraging results. GnRHa reduces the concentration of sex steroid, thus delaying epiphyseal fusion. However, GH and GnRHa combination therapy in children with GHD is not widely used at present. It may be beneficial under certain circumstances, for example where the diagnosis of GHD has been delayed, but the effects of GnRHa in the long term are unknown, and, additionally, the cost of this combination therapy would need to be weighed against its benefits.

GH treatment in childhood can also normalise body composition, with a reduction in body fat, although effects on lean body mass are less evident. It is also associated with reversible insulin insensitivity and an increase in the ratio of high-density lipoprotein (HDL) to total cholesterol. Glomerular filtration rate (GFR) is increased and density lipoprotein (HDL) to total cholesterol.

Previously, GH treatment was discontinued when linear growth was complete. However, data now suggest that GH has other effects in adulthood. Discontinuing GH treatment in young adults with GHD results in reduced lean body mass with reduced muscle strength, increased...
Prescribing Information

Nutropin® Aq

10mg / 2ml solution for injection in a cartridge.

Presentation:
Cartridge containing 10mg (30 IU) of somatropin, recombinant DNA origin, Escherichia coli.

Indications:
Growth failure in children due to inadequate growth hormone secretion; growth failure associated with Turner syndrome or with chronic renal insufficiency; growth hormone deficiency in adults.

Dosage & administration:
Via daily subcutaneous injection:
Growth failure:
In children due to inadequate growth hormone secretion (0.025-0.035 mg/kg body weight); associated with Turner syndrome or with chronic renal insufficiency (up to 0.05 mg/kg body weight).
Growth hormone deficiency in adults:
Initially, 0.15-0.3 mg per day, doses may then be titrated upwards depending on serum IGF-1 values. Final dose typically 0.5 mg/day. Lower doses may be necessary in older or overweight patients. Conversion: 1 mg = 3.6 IU.

Contraindications:
Hypersensitivity to somatropin, growth promotion in patients with closed epiphyses, active neoplasms, cranial nerve dysfunction due to compression by an anterior pituitary adenoma, or multiple endocrine neoplasia type 1.

Precautions & Warnings:
Previous malignant disease, history of intracranial lesion, Prader Willi syndrome especially in patients with severe obesity or respiratory malfunctions. Monitoring of patients for glucose intolerance and intracranial hypertension is recommended. Patients with diabetes or glucose intolerance are at increased risk of developing diabetes. Patients should have their glucocorticoid therapy carefully adjusted.

Interactions:
Monitor if administering in combination with drugs known to be metabolised by CYP450 liver enzymes.

Pregnancy & Lactation:
There is no clinical experience of use during pregnancy and treatment should be discontinued if pregnancy occurs. It is not known whether somatropin is excreted in human milk.

Side-effects:
Most frequently: injection site pain; uncommonly: headache and bone disorder; rarely: diabetes mellitus, oedema, hyperglycaemia, intracranial hypertension, CNS neoplasm, urticaria, naevi, gynaecomastia.

Storage:
2°C-8°C. Do not freeze.

Legal Category:
POM, CD Anab (Sch 4, Part II).

Basic NHS Cost:
£215.57 (10mg / 2ml cartridge).

Pack size:
1 cartridge pack.

Marketing Authorisation Number:
EU/1/00/164/003.

Marketing Authorisation Holder:
Ipsen Ltd, 190 Bath Road, Slough, Berkshire, SL1 3XE, UK. Tel. 01753 627777.

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Date of preparation:
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Nutropin®Aq Pen

for use with

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[somatropin, recombinant DNA origin, Escherichia coli]

A GROWING SOLUTION

Because growing up is complicated enough

Prescribing Information

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Growth failure in children due to inadequate growth hormone secretion; growth failure associated with Turner syndrome; growth failure associated with chronic renal insufficiency; growth hormone deficiency in adults.

**Dosage & Administration**

- **Growth Failure**:
  - In children due to inadequate growth hormone secretion (0.025-0.035 mg/kg body weight);
  - Associated with Turner syndrome or with chronic renal insufficiency (up to 0.05 mg/kg body weight).

- **Growth Hormone Deficiency in Adults**:
  - Initially, 0.15-0.3 mg per day, doses may then be titrated upwards depending on serum IGF-1 values. Final dose rarely exceeds 1.0 mg/day.

**Contraindications**

- Hypersensitivity to somatropin,
- Growth promotion in patients with closed epiphyses,
- Active neoplasm,
- Acute critical illness due to complications following open-heart or abdominal surgery,
- Multiple accidental traumas or to treat patients having acute respiratory failure.

**Precautions & Warnings**

- History of intracranial lesion, Prader Willi syndrome, especially in patients with severe obesity or respiratory malfunctions.
- Monitoring of patients for glucose intolerance and intracranial hypertension is recommended. Patients with diabetes or glucose intolerance should be monitored closely.
- Patients should have routine thyroid function tests. Treatment should be terminated after renal transplantation.
- Patients with ACTH deficiency should have their glucocorticoid therapy carefully adjusted.

**Interactions**

- Monitor if administering in combination with drugs known to be metabolised by CYP450 liver enzymes.

**Pregnancy & Lactation**

- There is no clinical experience of use during pregnancy, and treatment should be discontinued if pregnancy occurs. It is not known whether somatropin is excreted in human milk.

**Side-effects**

- Most frequently: injection site pain;
- Uncommonly: headache and bone disorder;
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fat mass and reduced bone mass. Additionally, there is reduced physical and cardiac performance, insulin resistance, reduced fibrinolysis and an abnormal lipid profile. Reduced levels of vitality, energy and physical mobility, decreased libido and feelings of social isolation are also part of the adult GHD syndrome. Cardiovascular mortality is increased in patients with hypopituitarism, particularly in women.

Many of these changes are reversed by GH treatment, although the efficacy of GH in terms of reductions in cardiovascular disease, bone fracture and mortality and improvement in quality of life remains unknown. Short-term (four months) improvements in lean body mass, exercise capacity and muscle strength have been documented with reduction in total body fat. Improvement in cardiac function has also been documented in one study, with a return to pre-treatment values six months after cessation of GH treatment. In some studies, quality of life measures, such as energy levels, mood, emotional lability and physical mobility, improved with GH treatment. Recent guidelines published by NICE have recommended that GH treatment should only be considered in adults who have fulfilled criteria on a quality of life questionnaire. The dose recommended by the Growth Hormone Research Society is 0.15–0.3 mg/day. It has been suggested that, at the end of natural growth, GH secretion should be re-assessed in all patients after a wash-out period of at least one to three months. In 25–75% of patients, the GH response to provocation is in the normal range; in the remainder, GH therapy should be continued in those with severe GHD (a peak GH of <3 µg/litre). Patients with moderate GHD (a peak GH of 3–7 µg/litre) should be followed up by an adult endocrinologist. In these individuals, adverse changes in body composition, quality of life and bone mineral density may be an indication to recommence GH treatment, although it is less likely that these individuals will develop adult GHD syndrome. In patients with MPH, GHD due to a congenital lesion and GHD secondary to radiotherapy, surgery or a mass lesion, the GHD is highly unlikely to reverse.

GH therapy is considered to be a relatively safe form of treatment. Recently, long-term follow-up of these patients has revealed a higher than expected incidence and mortality of colonic cancer and Hodgkin's disease. However, these data need to be put in context. The affected patients had been treated with high GH doses given two to three times per week. Hence, it could be speculated that the IGF-1 concentrations generated by the GH may be excessive. IGF-1 concentrations at the upper end of the normal range (top quartile for colon and prostate and top tertile for breast) have been associated with colon, breast and prostatic cancer. Given that lower doses of GH are given on a daily basis, it would be incorrect to extrapolate the data from the earlier studies to the present treatment regimens. In the past, concerns have been raised about a possible increased risk of relapse in children who had previously received treatment for malignancies such as brain tumours and leukaemia. However, available data neither support an increased risk of tumour recurrence in children subsequently treated with GH, nor provide any evidence to suggest an increased risk of neoplasia in children without additional risk factors. It would nevertheless be sensible to use GH with caution, and treatment is contraindicated in syndromes with an increased risk of chromosomal breakages and malignancy, such as Down's syndrome, Bloom syndrome, Fanconi anaemia and neurofibromatosis-1 (Lawson Wilkins Pediatric Endocrine Society (LWPES) consensus and Growth Hormone Research Society (GHRS) consensus).

Adverse effects include an increase in the number and size of pigmented naevi, and benign intracranial hypertension, particularly in girls with Turner syndrome and children with cranio-pharyngioma. Discontinuation of GH treatment resolves the problem, and a gradual reintroduction of GH is not associated with recurrence. Slipped capital femoral epiphysis has been reported as a side effect of GH treatment, but the incidence of the complication is only increased in children with organic GHD, and not in children with IGHD. GH treatment is associated with insulin insensitivity. The incidence of type 1 diabetes mellitus is not higher in patients with IGHD than in the general population, but the incidence of type 2 diabetes mellitus is greater in those patients treated with GH.

**Conclusions**

Over the last 20 years, major advances have been made in the understanding of GHD; particularly, molecular advances have enhanced the understanding of the aetiology. Recombinant hGH is now available to treat both children and adults with GHD. The importance of the metabolic role of hGH is becoming clearer. However, patients need careful follow-up with respect to safety and efficacy. The coming 20 years or so will answer many of the unanswered questions with respect to the aetiology, diagnosis and treatment of this rare but important condition.

_A version of this article, with references, can be found in the Reference Section on the website supporting this business briefing (www.touchbriefings.com)._