**Section 1: GROWTH AND DEVELOPMENT**

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**Chapter 2:**

**Short stature, growth hormone deficiency and primary IGF-1 deficiency**

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**Abstract**Regular monitoring of a child’s growth, using height and weight measurements, is an essential part of the nursing role, as outlined in a previous chapter.   
Sequential measurements provide information regarding a child’s general health and are invaluable in assessing whether there is a concern regarding their growth pattern. Body proportions, general health and parental heights will give an indication as to whether the child fits their family pattern, or has a growth problem. Review of sequential measurements can help establish whether they have familial or idiopathic short stature, or if they may have a growth and / or other hormone deficiencies.

Growth hormone deficiency (GHD) affects approximately 1:4000 children. (1)  
It can be classified into congenital or genetically associated conditions, or maybe acquired due to insult or injury. It may be an isolated deficiency, or part of a more complex condition of multiple pituitary hormone deficiencies. Isolated Growth hormone deficiency (GHD) is primarily a clinical diagnosis, based upon auxological features, and confirmed by biochemical testing. Once a cause for short stature or GHD is established, treatment can be initiated, which requires daily injections of growth hormone. Growth Hormone Insensitivity Syndrome (GHIS) is rare, and requires twice daily injections of Insulin Like Growth Factor 1 (IGF-1)

A long term commitment to treatment is required by both the patient and their family for best results. A good understanding of the condition and ongoing education is essential to ensure the maximum benefits of treatment are attained.

Growth is a slow process, and often it is easy for families to become complacent or discouraged with treatment regimes. By examining patient behavior and any concerns they may have regarding their stature, we are in a position to encourage compliance with treatment by recognizing that short term pain (of injections) leads to long term gain, once final height is reached.  
This chapter explores the pathophysiology, clinical characteristics, investigations, and management of children with growth hormone deficiency and growth hormone insensitivity, the treatment required and nursing considerations needed to manage these children through the ages. The role of the multi-disciplinary team will be discussed with emphasis on the role of the Paediatric Endocrine Nurse Specialist in supporting these children and families through many years of treatment.

**Key words**

Short stature

Growth Hormone Deficiency

Multiple pituitary hormone deficiencies

Hypoglycaemia

Growth hormone insensitivity syndrome

Insulin like Growth Factor 1

**Key points**

1. Ongoing monitoring of a child’s growth is essential if determination of a growth problem is to be identified.
2. Growth Hormone Deficiency (GHD) is a rare condition : Growth hormone insensitivity syndrome (GHIS) is even more rare.
3. Treatment involves daily growth hormone injections, twice daily for GHIS.
4. The psychosocial aspects of extreme short stature need to be considered
5. Children should always be treated according to their age, not height.

**Abbreviations**

BG – Blood glucose

BSPED – British Society for Paediatric Endocrinology and Diabetes

CDGP – Constitutional Delay of Growth and Puberty

CPG – Capillary blood glucose

ENT – Ear, Nose and Throat

EU – European Union

GH – Growth hormone

GHD – Growth hormone deficiency

GHIS – Growth hormone insensitivity syndrome

GHR – Growth hormone receptor

GHRH – Growth hormone releasing hormone

IGF-1 – Insulin like growth factor 1

IGHD – Isolated growth hormone deficiency

MDT – Multidisciplinary team

MPHD – Multiple pituitary hormone deficiencies

PENS – Paediatric Endocrine Nurse Specialist

rhGH – Recombinant Growth Hormone

rhIGF-1 – Recombinant Insulin Like Growth Factor -1

SPIGFD – Severe Primary IGF-1 Deficiency

SS – Short stature

STAT5b – Signal Transducer Activator of Transcription

UK – United Kingdom

USA – United States of America

**3.1 Short stature**

**Short stature or slow growth**

At any age there can be a number of reasons for short stature (SS) or slow growth, and sometimes a cause is never found

**Why might a child be short?**

The causes of short stature can be many and varied. They can range from *normal variants* to *pathological conditions*  
*Familial short stature* is one of the commonest reasons in otherwise healthy children, meaning that if the child’s parents are short, then it is more likely for the child to be short also. However, this may not indicate that the family’s short stature is considered to be ‘normal’: there may be an identified growth disorder that runs in the family (2) Ethnic and racial growth patterns also need to be considered.

Delayed growth can present at any age and is often seen in teenagers with a delayed puberty and/or growth spurt. *Constitutional delay of growth and puberty* (CDGP) is more commonly seen in boys in comparison to girls and may require endocrine intervention. Criteria for this would include short stature, delayed secondary sexual characteristics, and psychological distress. Psychological distress should not be discounted, and can cover a multitude of representations, such as depression, school refusal due to bullying, poor self-image, and the difficulty in being admitted to age appropriate past times (ie, the cinema or fairground rides) (2)

*Intrauterine growth retardation* or babies born small for gestational age can cause abnormal programming of growth from birth, resulting in babies weighing at least 2 standard deviations (SD) below the mean for the infant’s gestational age.(3)

*Genetic conditions* can also cause abnormal growth patterns and a karyotype should be done in all children suspected of any genetic condition or if there is no known cause for the abnormal growth pattern. Such conditions can include Turner Syndrome (SEE CHAPTER ON TURNER SYNDROME), Prader Willi syndrome (SEE CHAPTER ON PRADER WILLI SYNDROME), Down syndrome, or Noonan syndrome (4), or if a child appears to have a Skeletal Dysplasia.

In children with Noonan syndrome, the diagnosis is not usually confirmed with a genetic diagnosis, but on clinical grounds, although there are some defined gene mutations. The condition is characterised by distinctive facial features, such as hypertelorism (where the distance between the inner eye corners is greater than normal), ptosis, and low set prominent ears. The child will often have a cardiac defect, usually pulmonary stenosis, and also have skeletal problems, including short stature, scoliosis, pectus excavatum and cubitus valgus.   
Other endocrine factors to consider would be gonadal problems: most boys have cryptorchidism, and also delayed puberty. There may also be a degree of mild learning difficulty. (3,5)  
  
*Nutritional problems*, chronic illness or unexplained (idiopathic) reasons despite investigation, are also reasons for concern in families. It is well documented in the literature that chronic illness has an impact on linear growth (2), due to the disease process, or its treatment (eg systemic corticosteroids) – this is commonly seen in children with asthma, inflammatory bowel disease, renal failure, and children with a decrease in calorie intake, such as cystic fibrosis, coeliac and Crohn’s disease.

***Psychosocial short stature***

Although seen less often, another cause for isolated GHD may be due to social deprivation. (5, 6) Growth failure observed without organic aetiology, but associated with behavioural disturbance and psychosocial stress, has been termed psychosocial short stature.

Children exposed to social deprivation, abuse or neglect, may exhibit signs of social withdrawal, bizarre eating habits, hyperphagia compulsive eating disorders, vomiting, and polydipsia. It has long been recognised that children who are exposed to psychological or physical abuse may present with signs similar to those of a child with isolated GHD. This condition encompasses failure to thrive, stunting secondary to chronic malnutrition, and idiopathic hypopituitarism.   
Some children show spontaneous catch-up growth when removed from the source of stress without further treatment, but for some, GHD persists and there are some indications that a possible genetic predisposition may exist. These tend to resolve when the situation is addressed.

***Idiopathic short stature***

This is defined as short stature due to an unknown diagnosis or physiological variants. Height is below -2SDS but the children have a normal birth weight and are GH sufficient. They usually have no finding of any disease when examined by a paediatric endocrinologist, and no identified cause for their short stature. Familial short stature and CDGP are commonly included under the umbrella of idiopathic short stature (7).

Hormonal deficiencies, particularly those with thyroid and growth hormone deficiency can present during infancy or at any age, and can have an impact on linear growth. Ongoing monitoring of a child’s growth using height and weight measurements is essential if determination of a growth problem is to be identified. Regular sequential measurements provide information regarding a child’s general health and are essential in assessing a child’s growth pattern. (SEE CHAPTER ON GROWTH) (See Table 3.1 (8))

**INSERT Table 3.1: Causes of Short Stature (8)**

**Why should short stature be investigated?**

Although short stature is the most common reason why a child is referred to a paediatric endocrine clinic, it is essential that it should be investigated, as there is a multitude of aetologies that can be the cause (9) As well as the obvious psychological impact short stature has on the child or young person, it is important to determine the reason, if any, as the pathological cause could be masking other underlying disease. Therefore, once idiopathic, clinical or other endocrine causes for short stature have been eliminated, then the diagnosis of growth hormone deficiency needs to be considered.

**3.2 What is growth hormone deficiency? (GHD)**

See Table 2 for causes for GHD (1, 2).

**INSERT Table 3.2**

GH deficiency occurs when the pituitary gland fails to produce sufficient levels of hormones, the chemical signals that regulate important biological functions, including growth. It may be an isolated deficiency or part of a condition known as multiple pituitary hormone deficiencies (MPHD). It is rare to have a complete lack of growth hormone but insufficient amounts will lead to poor growth.

The diagnosis of isolated growth hormone deficiency can often be missed in early childhood as the child may be healthy, apart from being smaller than other children their age. It may not be until a child starts school (or prior to starting at senior school) that the diagnosis is made as the size difference is noticeable compared to peers.

**3.3 Pathophysiology of GHD**   
The pituitary gland includes the anterior and intermediate lobes (adenohypophysis) and a posterior lobe (neurohypophysis) and produces a number of hormones, including GH. The release of GH-releasing hormone (GHRH) from the hypothalamus stimulates the release of GH, and somatostatin inhibits the release of GH.   
Growth hormone (GH) is secreted from the pituitary gland in a pulsatile fashion, with an increase in the frequency and amplitude of pulses at night. (see Figure 1) (10)

**INSERT Figure 3.1: GH Pulsatile Secretion (10)**

Its secretion is controlled by the hypothalamus through an interaction between releasing hormones (GHRH and ghrelin) and the inhibitory hormone somatostatin. It binds to receptors and activates the production of insulin-like growth factor 1 (IGF1). This in turn mediates the various growth-promoting actions of GH.

Concentrations of IGF1 correlate well with those of GH, but, low IGF1 levels may also be observed in many conditions (hypothyroidism, malnutrition, poorly controlled diabetes) and chronic disease.   
The vascular network of the hypothalamus and pituitary and the structure of the pituitary stalk make them susceptible to the effects of trauma or any other insult to the hypothalamic-pituitary region. Tumours in the hypothalamic-pituitary area may cause endocrine disturbance, either directly or secondary to treatment (surgery, radiotherapy), and early signs of endocrine dysfunction or GHD can be seen if there is growth failure.   
Therefore, GHD can be classified into *congenital or genetically associated* familial conditions, or may be *acquired* due to an insult or injury.   
It may be an *isolated deficiency*, or part of a more complex condition of *multiple pituitary hormone deficiencies.*   
The single most important clinical indicator of GHD is growth failure. Multiple pituitary deficiencies (MPHD or pan-hypopituitarism), tend to be identified earlier in life, especially if hypoglycaemia is present, but in some cases of congenital isolated GHD, the growth failure may not be established until later in childhood.

Most commonly, patients with IGHD present in late infancy or early childhood, typically with a low growth velocity and short stature. Most cases are idiopathic in origin. (See case study 1 in Box 1)

[PLEASE START BOX HERE]

**Case Study 1**

A young male presents at the age of 4.3yrs with a history of slow growth since the age of 2 years. Born at 42 weeks gestation at a birth weight of 3700g, he had the cord around his neck, but no other neonatal issues. It was noted that he had had an undescended testis, and an inguinal hernia, but the rest of his development was normal.

At presentation parents height were obtained with Mum being 168.4cm (72 centile) and Dad measuring 181cm (78th centile). This gave him a mid-parental height (MPH) of 181.2cms

(approximately 73rd centile).

On Examination it was noted that he was a small, healthy, non-dysmorphic, proportionate male with a height of 97.0cm (4th percentile) and a weight 14.6kg (10th percentile). He had 2 ml testes, now descended, and normal genitalia. Neurological and thyroid examination were normal, and no other body system abnormalities were detected on examination.

Baseline investigations included; FBC, ESR, biochemistry – all normal, a Coeliac screen which was negative, TSH 2.3mIU/l (0.4-5), FT4: 14.6pmol/l (10-20), IGF-1: 1.5nmol/l (6-25), Prolactin normal. Parents were provided with information regarding GH stimulation tests and had the opportunity to ask questions before proceeding with the Glucagon / Arginine stimulation test. GH peaks to both stimulation tests showed a blunted response of 3.9 & 4.1mIU/l (N>20). An appropriate cortisol peak of 621nmol/l (>500) was obtained. Bone age was delayed, being 3.5yrs at a chronological age of 4.5yrs.

A diagnosis of Isolated GH deficiency was declared and treatment with GH commenced at a dose of 4.5-6 mg/m2/week. This dose was reviewed 6 monthly (as per Australian gudelines) and adjusted according to increasing body surface area (BSA).

Long term progress has shown that no other pituitary deficiencies have evolved. At age 12.9 years he had 4 ml testes and by 14.1yrs has 8 ml testes, PH3, G3 and will continue on GH therapy until he reaches a bone age of 15.5yrs or his growth has slowed to be < 2cms/yr.

This will indicate that he has completed approximately 97% of his childhood growth.

Key Points to consider when assessing a child with short stature include considering a child’s height and EMH in the family context. Any child tracking below, or with EMH below target height range, warrants investigation. Evaluating growth velocity is a valuable indicator and doesn’t even require plotting on a growth velocity chart, as a falling height percentile or SD is the same.

[PLEASE INSERT GROWTH CHART FROM CASE STUDY 1 BOX 3.1]

[PLEASE END BOX HERE]

Untreated, children with GHD will be short and have delayed puberty, decreased pubertal growth spurt, and a final height standard deviation score (SDS) of -4 to -6, much lower than the general population (11, 12)

**Signs and symptoms**

Hypopituitarism or multiple pituitary insufficiencies, can cause a range of symptoms. Abnormalities in the development of the hypothalamus / pituitary access mean that presentation in the neonatal or early infancy period is common.

* hypoglycaemia,
* prolonged jaundice,
* micro phallus (in boys)
* impaired vision
* facial or midline defects such as cleft lip or palate or single central incisor
* Defects in genes associated with the development and function of the pituitary gland can also lead to a diagnosis of isolated GHD.(13)

These signs are more common in children with multiple pituitary hormone deficiencies diagnosed in the neonatal period, but may be present as isolated GHD with other deficiencies evolving over time. Recent data suggest that childhood IGHD may have a wider impact on the health and neurodevelopment of children, but it is yet unknown to what extent treatment with recombinant human GH can reverse this effect (14)

Acquired GHD can be due to a variety of causes including tumours in the hypothalamic pituitary region. These may be benign or malignant, cystic or solid, and may present as a craniopharyngioma, germinoma or teratoma. GHD may arise due to the tumour, as a result of surgery, or, more commonly, after radiotherapy. If cranial irradiation of the pituitary gland has been indicated for a condition such as leukaemia, medullablastoma, glioma/astrocytoma or rhabdomyosarcoma, this can also result in impaired function of growth hormone and other hormones further along in life. (SEE CHAPTER ON LATE EFFECTS)

*Whatever the cause of GHD, abnormalities in the growth pattern should be investigated*

**3.4 Clinical Characteristics**

Children with GHD are small compared to other children of their age but they will have normal proportions. In the first year of life, growth is more dependent on nutrition than on growth hormone secretion, and may be normal, even if growth hormone deficiency is present from birth.

They often have a characteristic facial appearance including, mid-facial hypoplasia, classic “cherubic” appearance, with chubby cheeks and increased truncal adiposity with dimpling of fat. Delayed dentition, single central incisor, and frontal bossing may also be present. Both puberty and bone age may be delayed.

It is worth noting that the condition is highly variable in its clinical presentation so evaluation in reference to other family members, including siblings should also be included.

In acquired GHD is, there can be a variety of presentations. Growth failure or a decline in height velocity, is sometimes only noticed when shoe or clothing size does not increase over a period of time. Increasing lethargy, vomiting, visual impairment or photophobia may all be reasons for initial presentation. Continuing visual impairment (of varying severity) can often be seen in patients after the removal of a suprasellar tumour (e.g. craniopharyngioma or optic glioma).   
Any child with a history of cranial irradiation, with decelerating growth, even if the height is within the normal range, should be evaluated. (15)(SEE CHAPTER ON LATE EFFECTS)

**Clinical investigations**Any child with severe short stature (3 standard deviation scores [SDS] below mean for population) should be referred to an endocrinologist for evaluation to establish a cause.  
The diagnosis of GHD is a stepped process. It is based on a combination of auxological data, the clinical phenotype, dynamic GH testing (SEE CHAPTER ON DYNAMIC FUNCTION TESTING), insulin-like growth factor 1 (IGF1) and IGF binding protein 3 (IGFBP3) levels, bone age X-Ray and other radiological findings including an MRI of the hypothalamic-pituitary area.

**Bone Age assessment**

The bone age is assessed by taking an X-ray of the non-dominant hand and wrist. Comparison is made to a photographic standardised set of x-rays for a child of the same age using the Greulich & Pyle, or Tanner-Whitehouse methods.   
This provides for an estimation of the skeletal maturation of the bones. (16-18)

A bone age assessment ( See Figure 2) can help determine the amount of growth left and give an estimation of what final height will be achieved.

**Figure 3.2: Bone age assessment**

In girls the epiphyses usually close around the age of 13.5yrs whereas in boys their epiphyses close around the age of 15.5yrs. The further behind the bone age is delayed behind the chronological age, the longer the growing period. As long as the growth plates remain open there is potential for continued growth. Once the bones reach the ages noted above, most of a child’s growth is complete.

A thorough medical history should be taken and physical examination done, to assess if there is any other cause for growth failure. See Table 3.3 for the diagnostic approach to short stature (19)

**INSERT Table 3.3: Diagnostic Approach to Short Stature**

Family history should be taken to determine if there is any heritable condition or any other systemic concern. Parental heights should be plotted on the growth chart to determine the mid parental height (MPH) (or target height) and establish if the child’s growth is out of keeping with other family member’s stature.   
Pituitary hormone deficiencies can evolve with time, so regular monitoring of both clinical as well as biochemical investigations, is considered good practice.   
Height more than 2 SDS below mean and a growth velocity over 1 year of more than 1 SDS below the mean, require investigation. A decrease in the height SDS of more than 0.5 over 1 year in children aged over 2 years, height SDS more than 1.5 SDS below target height SDS, or if the height velocity is more than 2 SDS below the mean over 1 year, or more than 1.5 SDS over 2 years, in the absence of short stature should all be evaluated. (20, 21)

**3.5 Investigations and Diagnosis**  
Baseline investigations will help determine the likelihood of GHD which can effectively be excluded in children with a normal bone age and height velocity.

Baseline investigations should include: (21)

A full blood count,

Blood chemistry, including thyroid stimulating hormone & free thyroxine level,

Coeliac screen and IgA (Immunoglobulin A) levels

25-OH Vitamin D level

Karyotype in ALL girls and boys with dysmorphism

IGF-1

More detailed laboratory evaluation for causes of growth failure, maybe carried out by a specialist once the initial evaluation is complete. IGF binding protein, hormones to evaluate puberty including luteinising hormone, follicle stimulating hormone, oestradial, testosterone and prolactin levels if concerned about pubertal delay should all be measured. Molecular testing or comparative genomic microarray for various genetic conditions may be considered.   
GH stimulation testing should be considered if the clinical criteria is insufficient to make the diagnosis of GHD. (22) Those with a known pituitary abnormality or deficiency of at least one other pituitary hormone, and with obvious growth failure, may not need testing. If there is enough information to determine the cause of growth failure, provocative testing for GHD may not be required.(23)

The most common test to assess GHD is a dynamic GH stimulation test. (SEE CHAPTER ON DYNAMIC FUNCTION TESTING) As GH is produced in a pulsatile fashion it is able to be stimulated to assess pituitary function. A variety of tests are available using pharmacological stimuli and two stimuli are best used to capture the peak levels of GH produced. Provocative agents such as insulin, glucagon, arginine, and clonidine can all be used to assess GH levels. Various cut-off levels have been used, but GHD is generally defined as a value of <10 micrograms/L (or 3ng/mL) on 2 occasions. (24)  
  
Testing should be done after an overnight fast, and in older children (girls> 10yrs and boys > 11yrs) is often done after priming with sex steroids for a few days prior to testing. This is done to lessen the chance of a false diagnosis, but there is still some discussion as to whether this is necessary and so is not mandatory. (22)(25)

Testing should be in a recognised testing facility by trained nurses due to the risk of hypoglycaemia associated with many of the stimulation tests.  
Finally an MRI of the brain/pituitary gland will establish if there are any midline defects, structural abnormalities, or evidence of a tumour or cystic mass.

**3.6 Treatment**

Children with GHD are unlikely to reach their adult potential without treatment. Recombinant growth hormone is the only treatment that can improve final height but can only influence the active growth phase whilst the bone epiphyses remain open.

In many countries GH treatment is commonly approved for those not only with GHD but other conditions of short stature as well, such as:

TS – Turner Syndrome

SGA – Small for Gestational Age

PWS – Prader Willi Syndrome

CRI – Chronic Renal Insufficiency

SHOX – Short stature homeobox –containing gene deficiency disorder

AGHD – Adult growth hormone deficiency

ISS – Idiopathic Short Stature (2)

Recombinant human growth hormone (rhGH) has also been used in variety of other conditions including Turner's syndrome, intrauterine growth restriction (IUGR), chronic renal failure (CRF), Prader-Willi syndrome, idiopathic short stature, and SHOX deficiency. (26) More recently GH has become available in some countries for use in adults with established GHD.

Treatment involves daily subcutaneous injections of recombinant human growth hormone (rhGH), also known as somatropin. Prior to 1985 hGH (human growth hormone) was only used in those with severe GHD, but was withdrawn when concerns regarding its association with Creutzfeldt-Jakob disease (CJD) arose. (27, 28)

Treatment today uses a variety of recombinant growth hormone products. Some products are a liquid formulation, whilst others require powder and diluent to be mixed to maintain product stability. Doses are based on either patient’s weight or body surface area depending on which country they reside in, and the clinical indication they are being prescribed for. There are a number of different devices designed for giving injections, with some that can actually hide the needle tip, but as the needles used are small, they are in most cases well tolerated. Each company has a device designed specifically for their product, so they are not interchangeable.  
Subcutaneous injections are given daily usually in the evening prior to bed as GH is released in pulses during the night (See Figure 3.1) and at a similar time each day where possible. Arms legs abdomen and buttocks are used as injection sites, and the 4-6mm needles used can usually be accommodated in most of these spots.

Current practice is to use each area for approximately one week, rotating on a regular cycle.   
Families, parents and older children, are instructed on injection technique at the time GH injections are commenced, but regular review of technique should be encouraged to uncover any problems parents may be having that may impact on compliance.

Adolescents giving their own injections should *always* be supervised by a parent.   
Assessment of the families understanding of *why* the treatment is being given should be part of the ongoing review at appointments.   
It is sometimes worthwhile reminding families that if injections are regularly missed the benefits of treatment may be compromised.

Side effects with rhGH are uncommon but should be clearly explained at the time of commencement of injections. Usually rhGH is safe and well tolerated. (29-31) Minor adverse effects such as bruising at injection sites usually diminish once treatment is established and parents become more confident at injecting their child.

Occasionally in the early stages of treatment some children may retain excess fluid and salt, causing headaches with some blurring of vision (benign intracranial hypertension). It is not commonly seen and usually disappears when the GH is ceased for a few days, and reintroduced at a lower dose, gradually increasing over time. If it does occur, referral to an opthalmologist should be made for on-going assessment in the first few months of treatment.

Slipped capital femoral epiphysis. (SCFE) has also been reported to be slightly more common in children receiving GH treatment. (32) This may cause pain in the hip and knee joints and appears to mostly occur in those with other risk factors such as obesity, trauma, other endocrine conditions, or those who have had previous radiation therapy, or very rapid growth.   
Scoliosis has also been observed in some children treated, (33) but is more the result of an increase in height velocity unmasking the tendency to a curved spine, than the GH itself.

Depending on family history, there may be an increased risk of developing type 2 diabetes mellitus, but as the doses of GH prescribed are mostly physiological the risk is relatively low.

Markedly elevated IGF1 concentrations have been associated with colon, breast, and prostatic cancer: However, there is no evidence to suggest an increased risk of malignancies using the current dosage recommendations for rhGH. In general, GH should not be given with an active malignant condition. The absence of tumour growth or recurrence should be documented for 12 months before commencing treatment. The long-term safety of GH treatment is, however, uncertain.

The most common questions asked by patients and parents alike when starting treatment is, how much will I grow, and how long will I need to take GH for?

Rapid short-term growth is usually followed by normalisation of long-term growth.   
Treatment should be continued until final height or epiphyseal closure is achieved. (34) For girls this is when the bone age is around 13.5yrs and for boys around 15.5years.  
A good predictor of response to treatment is the height gain attained in the first year of treatment. Other factors that can impact on the response to treatment include age and height at the start of treatment, duration of treatment, and, in patients with isolated GHD, the pre-pubertal growth available when receiving treatment.

Long term monitoring of treatment is essential and should include:

* Regular measurements, plotted on an age- and sex-appropriate growth chart.

On average, puberty contributes 20 cm to 25 cm of height in females and 25 cm to 30 cm in males, and this is dependent on adequate GH and insulin-like growth factor 1 (IGF1) concentrations.

* Frequency of monitoring patients with an acquired cause of GHD (e.g., tumours, radiation, etc) will depend on the individual condition.
* All patients on GH should continue receiving treatment until final height or epiphyseal closure is achieved
* Prior to transition to an adult endocrinologist, reassessment of IGF1 levels and possibly of GH levels should be undertaken.
* If after ceasing treatment the IGF1 level remains in the normal range GH stimulation testing should be undertakan to establish if the young persons GH levels have normalised, or remain low.

This will assist in determining whether after completion of growth and puberty patients with idiopathic isolated GHD are at risk of ongoing GHD and will ascertain the need for adult GH replacement. (SEE CHAPTER ON TRANSITION)  
In many patients (25% to 75%), when testing is repeated, the GH response is in the normal range. (21) The reason for this reversal of GHD is unclear. Pituitary hormone deficiencies can evolve with time, so regular monitoring, both clinically and with regular biochemical investigations, is recommended.

**Compliance and growth hormone device choice**

Growth hormone treatment involves a daily injection. For some families the thought of injecting their child on a daily basis is confronting, and the emotional factors and anxiety around administration can overwhelm them (or their child). There are a number of devices for giving GH available but nearly all require a needle to be inserted into the subcutaneous fat. Many devices can hide the site of the actual needle if required, and for most children the procedure becomes easier over time. In some countries allowing families some choice in the decision making around which device to use, compliance can be shown to be improved. Compliance often waivers especially in the adolescent years, as growth is slow, an immediate response cannot be seen, and the idea of having to remember to give an injection each night does not always sit easily in an adolescents life! Feedback regarding the devices assists in compliance as the family or young person feels they have contributed to their treatment in some way. This along with ongoing positive support from nursing staff assists in improving the patient experience. (35)

**3.7 Nursing considerations (36)**

When evaluating a child with short stature it is important to think about the following questions. Although the causes and clinical presentation of short stature vary by age group, the same questions are relevant for children of any age:

- How short is the child?  
- Is the child's height velocity (HV) impaired?  
- Are they in keeping with their family pattern?  
- What is the child's likely adult height?

By using these questions as a baseline for assessment, the health care professional can determine if there is a growth problem and evaluate how concerned are they about their height.

When assessing a child’s growth there are 4 main aims:

* To determine if the growth pattern is normal or as expected for the child’s family background
* To attempt to predict future growth and final adult height
* To determine if there are any modifiable medical or other issues that will improve growth
* To consider if there are any specific treatments that are possible and appropriate to improve growth

The most important assessment of growth is reliable, reproducible and regular measurements, done at 3-6 monthly intervals, and plotted on an appropriate growth chart.   
Children under the age of 2 years should have their length measured, and between the ages of 2-3 years all children should be assessed in a lying and standing position, as this is the age that they are usually least cooperative.   
This will provide the most accurate assessment, as long as that the same piece of equipment is used, it is calibrated regularly, the same the observer takes the measurement, and the growth is plotted on the same growth percentile chart, and once plotted the growth velocity can be calculated.   
Growth velocity is one of the most useful parameters when assessing growth as it determines the change in height over time. It should be calculated over *at least* a 6 month period as any less can lead to inaccuracy or misleading results. It is calculated as the difference in height on 2 different occasions annualised over 1 year, and is age and pubertal status dependent.   
Height that plots along a given percentile on the growth chart reflects normal growth velocity. Crossing percentiles or a decreasing velocity reflects poor growth velocity.

Plotting the growth is helpful in establishing if a child is just short (compared to his peers) but growing at a consistent rate, or if are they growing at a slower rate than their peers over time. Any child with a growth velocity under the 3rd centile at any time should have further evaluation no matter where they sit on the growth chart.

One of the most important things to remember however is that all children should be treated according to their **AGE** and **NOT** their **SIZE**. It is very common when assessing a child who may look younger and be much smaller than their peers, to speak down to them, or treat them inappropriately for their age, and there is nothing worse for a child. Often on further questioning, or once a relationship begins to develop, you may be able to determine if they are being bullied at school or in the playground, and if this is of concern to them. The issues that children with endocrine conditions may encounter, particularly if they do not fit into the social and emotional norms of their peers, can add to the distress of “being different” and isolate them even further. Children who are shorter than most of their peers, may find themselves being excluded from sporting teams or even just play dates as younger children. Some may find that they don’t have the energy to keep up with their friends particularly if they are severely growth hormone deficient, making interaction even more difficult. Online or cyber bullying and social media has created a whole new set of issues for those with body image and self-esteem concerns. (37) A full social history should always be undertaken in all patients, particularly those who present with poor weight gain and failure to thrive.

If growth hormone production is being assessed using a stimulation test, it is important that both the family and the child have an understanding of what the testing involves and what to expect both during and after the evaluation.  
Information sheets regarding the tests should be provided, (see Box 3.2) and the opportunity to ask questions prior to testing, must be considered.

**[START BOX HERE]**

**Box 3.2: GH Stimulation test information sheet**

**GLUCAGON / ARGININE STIMULATION TEST**

**INFORMATION SHEET**

**What is this test?**

This test is carried out to assess hormones that the pituitary gland produces. **Glucagon** causes a number of temporary hormonal signals resulting in the release of growth hormone from the pituitary gland and stimulation of cortisol production. These levels are then measured in a series of blood tests. **Arginine** is an amino acid which also stimulates Growth Hormone secretion in the hypothalamus and pituitary gland. Some older children may need to take low doses of priming hormones before the test if they have delayed puberty so that the testing is accurate; your doctor will have advised if this is needed.

**When is this test?**

Your Child is booked to attend for a Glucagon/Arginine Stimulation test on

**How should I prepare my child?**

* Your child will need to be admitted to the hospital for the day, (approximately 5hrs).
* **Your child should have nothing to eat or drink, except water, from 12midnight the night before the test.** Babies less than 12 months or children under 10kg need to fast for 4 hours, so should have an early morning feed.
* **Please call to confirm with the Endocrine testing nurse, the day before the test**
* If your child is unwell please contact us as the test may need to be rescheduled.
* Bring a favorite toy, activity, DVD or book on the day to keep your child occupied.
* You will be admitted by the clerk and directed to the Endocrine Testing area.

**What happens next?**

* The nurse will record your child’s height, weight, temperature, pulse and blood pressure, and oxygen saturations.
* Before we insert a cannula (a small needle with a plastic tube attached) into the vein, and so that we cause as little discomfort as possible, anesthetic cream or an ice stick can be used to anesthetize the area. We will need to take multiple blood samples during the test, and the cannula allows all the samples to be taken from the same site.
* At the beginning of the test a blood sample is taken and then an injection of Glucagon is given into the thigh muscle.
* Another blood sample is collected **one hour later, and further samples are then taken at ½ hourly intervals for another 2 hours.**
* The Arginine solution is then given via an intravenous drip into the cannula over 30 minutes.
* **4 more blood samples are then taken every 15 minutes once the infusion is completed.**
* Some children may feel nauseated or complain of abdominal pain during the test, but this is usually temporary. Occasionally a child may vomit. We can give medication to ease this.
* Your child’s blood glucose level is checked during the test, because low values sometimes occur and may need to be treated.

**And finally…. after the test?**

At the end of the test your child may eat, the cannula is removed and you will be discharged home.

Results are usually available after 2 weeks, so **before leaving make sure that you have details of the follow up appointment.** If you have any questions following the test contact your child’s doctor or endocrine clinic

**[END BOX HERE]**

The goal of growth hormone (GH) treatment should be to restore hormone levels as close to healthy levels as possible, and allow the child to reach their target adult height potential.

During the initial assessment and monitoring phase, it is important to establish a good relationship with the child and family. This allows time for consideration of the likelihood of managing daily GH injections when started on treatment, ongoing compliance with treatment, and also gives the opportunity to evaluate if height is of concern to them as an individual, or if it is more of a parental concern.   
Results of any tests done should be clearly explained in language that the family will understand, to ensure they have a good comprehension of why GH is required.

Once treatment is approved, the family and child should be educated in the day to day management of injections, the storage of medication and general information about expectations of treatment, and the importance of compliance.

**Emotional & social elements**

It is important to provide emotional support for the child with GH deficiency and to emphasize the child’s many good and valuable characteristics, so that the child’s stature does not limit his opportunities. Society (unfortunately) still places an emphasis on height, and children who are short for their age can initially have problems because friends and teachers treat them as though they are *younger* rather than just *smaller*. Parental expectations are often decreased as they feel their child is unable to do the same tasks as other children their age, and in turn children may then not act their age because it is not expected of them. Schools are sometimes unaware of the problems that children who are very small for their age have to deal with such as practical difficulties of being unable to reach a peg or desk or sit on the toilet. Teasing and or being called names such as “shorty” or “shrimp” or being carried around the playground because they are “cute and doll like” is not helpful in allowing the child to develop to their full potential. Sometimes a frank and open discussion with teachers and classmates may help alleviate some of the problems. Positive role modelling by parents is essential and as with all parenting issues, there must be consistency. Parents must agree on a unified approach to handling any problems. Discussing and role playing hypothetical situations and encouraging practice of these role plays can help children anticipate situations that may develop.   
Comments when out shopping or on the sporting field cannot be monitored, but the child can work to control their responses. A “toolkit” of responses is one of the best support mechanisms that can be given to parents and children, and the nurse can suggest that families work with their child to practice responses. The best responses are ones that are polite yet assertive, never rude, easy to remember (even in situations of high anxiety), and comfortable for a child to use. Work with the child and family to come up with a short list of responses that he or she can use in social situations when comments are made about stature.

When commencing GH treatment it is important that the child and family have realistic expectations. It is important to emphasize that growth takes time and that they are not going to grow overnight. Ongoing reassurance may be needed when the child is not growing as expected. Once there has been an initial response to treatment the possible benefit may include a general increased self-esteem and overall happiness that is gained with the increase in height.

**3.8 What is Primary IGF-1 deficiency/Growth Hormone Insensitivity Syndrome**

Growth Hormone Insensitivity Syndrome (GHIS) is a rare condition (<1:100,000) whereby the action of Growth Hormone (GH) is either absent or reduced resulting in extreme short stature.(38)

**3.9 Pathophysiology**

Childhood growth is regulated via the GH/Insulin like Growth Factor-I (IGF-I) axis. Primary Insulin-like Growth Factor 1 (IGF-1) deficiency is characterized by an inadequate production of IGF-1, despite sufficient secretion of growth hormone (39). Pituitary derived GH stimulates both the liver production of IGF-I and augments the actions of locally produced IGF-I, which result in longitudinal growth. Binding of the GH to its receptor results in activation of downstream signalling molecules which ultimately lead to IGF-I production. Thus abnormalities along this signalling cascade can cause GH Insensitivity. These may include defects in the GH receptor which inhibit GH binding, post-receptor signalling defects such as Signal Transducer Activator of Transcription (STAT)-5b or primary defects of IGF-I synthesis. (See FIGURE 3.3)

[INSERT]

Figure 3.3: GH-IGF-1 Axis

Marie – Not been published, slides courtesy of Drs who have drawn it (have put their names)

**3.10 – Clinical characteristics**

The clinical phenotype of primary GH insensitivity in its classic form is identical to severe GH deficiency and was first described by Laron and colleagues in 1966 (40). The clinical characteristics include severe post-natal growth failure, mid-facial hypoplasia, adiposity and hypoglycaemia. It is therefore important to exclude growth hormone deficiency as a cause for these features. Other features associated with the condition may include reduced muscle strength, dental abnormalities including delayed eruption of teeth and reduced number of teeth, distinctive facial features (protruding forehead, a sunken bridge of the nose, and blue [sclerae](http://ghr.nlm.nih.gov/glossary=sclera)) and thin, fragile hair, however it should be noted that the phenotype can vary even within the same family. Figures 3.4 and 3.5 demonstrate a child with Laron Syndrome

**INSERT FIGURES 3.4 AND 3.5 (PERMISSION GAINED)**

Abnormalities further downstream the GH/IGF-1 axis such as with (STAT)-5b signalling are associated with immune deficiency whereas IGF-I mutations have severe intrauterine growth retardation and intellectual delay. The biochemistry shows elevated serum concentrations of GH with low IGF-I levels due to an abnormal GH receptor.

Recombinant IGF-I (rhIGF-I) is licensed for use in the United Kingdom (UK), the European Union (EU) and the United States (US) and Canada for children with Severe Primary IGF-I Deficiency (SPIGFD). This is defined in children as a height less than -3 SDS, low IGF-I levels (<2.5th percentile for age and gender) and normal GH levels. Secondary forms of IGF-I deficiency such as malnutrition, hypothyroidism and use of pharmacological doses of glucocorticoids need to be excluded (23, 39). It should be borne in mind that although the term GHIS and SPIGFD may be used interchangeably they are distinct entities as the classical Laron’s phenotype is not required for the licensed indications.

**3.11 Diagnosis**

The UK has guidelines formulated by an IGF-1 user’s group and endorsed by the British Society for Paediatric Endocrinology and Diabetes (39). These state that diagnosis of primary IGF-1 deficiency does not necessarily require either a GH stimulation test or IGF-1 generation test when the presentation is classical. It is recommended that these children have genetic analysis of the Growth Hormone Receptor (GHR) for understanding the condition and to confirm the clinical diagnosis. Those children who do not have the classical features but have abnormal auxology and features of growth failure may need detailed evaluation which should include assessment of the GH-IGF-1 axis. This evaluation should include a GH stimulation test.

The guidelines also state that whilst an IGF-1 generation test may also be included in the evaluation, the clinical value of the test in reaching a diagnosis of SPIGFD is unclear. The protocol for the IGF-1 Generation test is illustrated in Box 3.3 below (24) (SEE CHAPTER ON DYNAMIC INVESTIGATIONS)

**INSERT Box 3.3 Protocol for the IGF-1 Generation test**

It is worth noting that some children with classical SPIGFD may present late as the extreme short stature may have previously been diagnosed as failure to thrive or familial short stature.

**3.12 Treatment**

Once a diagnosis has been determined the treatment options can then be discussed with the family. The current recommended treatment for SPIGFD in the EU, the UK and the US and Canada is twice daily injections with recombinant IGF-1 (rhIGF-1) therapy (23, 39), and the treatment objective is the long term improvement of adult height.

**Initiating therapy**

Both the UK and US and Canada guidelines advocate these patients be managed by a paediatric endocrinologist with experience of managing children with complex growth disorders. Table 3.4 details baseline procedures and checks both standard and optional that should be considered prior to commencing treatment as advised by the IGF-1 users group in the UK.

**INSERT TABLE 3.4 Baseline Assessment (41)**

The UK guidelines recommend a short admission may be needed, particularly in younger children due to the potential risk of hypoglycaemia following the injection. This may not always be possible but the Paediatric Endocrine Nurse Specialist (PENS) plays a vital role in supporting the family at this time to ensure safe initiation of therapy whether in the hospital setting or at home.

The starting dose of rhIGF-1 as recommended by the manufacturer should be 40ug/kg (micrograms per kilogram) twice daily. The dose should then be increased at regular intervals with the aim of reaching a maintenance dose of 120ug/kg twice daily approximately three months after starting treatment. (42)

As with GH injections the family are advised to rotate the injection sites with each injection to prevent lipohypotrophy.

One of the most common side effects of the medication is hypoglycaemia. It is therefore advised that the injection should be given after a meal or snack and if the child has not eaten then the dose should be omitted. An important part of the PENS role is to ensure the family are educated to recognise the signs, symptoms and treatment of hypoglycaemia.

It is also recommended that with initiation of treatment the Capillary Blood Glucose (CBG) should be measured both prior to the injection and post injection. Subsequently the family is advised to check pre and post dose CBG following any dose increase for at least two days and inform the PENS of any problems. Hypoglycaemia is defined in the UK guidelines as a CBG of less than 3.5mmol/L. (24)

All patients in the UK are asked to give consent for a web-based surveillance registry.

**Maintenance of therapy**

Once the young person has been established on treatment it is important they are monitored at regular intervals. Clinic visits are recommended 3-4 monthly and every patient should have an annual review. Table 3.5 details procedures and checks both standard and optional that should be considered during treatment as advised by the IGF-1 users group in the UK.

**INSERT TABLE 3.5 Maintenance Assessment (41)**

Each clinic visit should consist of auxology, discussion regarding injections and examination of injection sites. Targeted adverse events should also be discussed at each visit and any positive clinical history may require more detailed assessment e.g history of sleep disordered breathing may require oximetry/sleep studies and referral to ear, nose and throat (ENT) services. See Table 3.6 (41) for some of the more common adverse events as per the UK guidelines.

**INSERT TABLE 3.6 TARGETED ADVERSE EVENTS**

As previously discussed hypoglycaemia is the most common side effect of treatment. It is therefore important to continue to discuss this at clinic visits and check the families understanding of signs, symptoms and treatment of hypoglycaemia.

Treatment should be reconsidered if the patient has an increase in height velocity of less than 30% of baseline or a change in height SDS score of < 0.3 over a twelve month period, although there should be documented good compliance over this time period.

UK guidelines state treatment with a Gonadotropin-releasing hormone (GnRH) agonist may be indicated in pubertal children who are extremely short and have not received IGF-1 for a sufficiently long period. (39)

**3.13 – The multidisciplinary team (MDT)**

Although these children are primarily managed by a Paediatric Endocrinologist and PENS both their extreme short stature and treatment requiring twice daily injections is challenging for these families. Therefore, the involvement of other services and local teams is vital to their overall well being.

*Psychology*

As these children have extreme short stature they may benefit from input from psychology services. Although the aim of treatment is to improve their adult height they may still remain below the normal centiles once the treatment has completed and some of these young people will remain significantly smaller than their peers. Psychology may therefore be a useful service to help the young people discuss their feelings and adapt to the adult world.

*School*

Due to their extreme short stature, these children face a number of difficulties at school. It is important for the PENS to offer information, advice and support both to the family and school to enable the child to fully participate in school activities. As discussed earlier, issues may arise with bullying (37) Information should also include being aware of the signs and symptoms of hypoglycaemia and how to respond if the child were to become hypoglycaemic. The school nursing service should be approached to assist with supporting the child. This may also require liaison with occupational therapists to discuss any adaptations/equipment which may be needed.

*Community / Home Support Nurses*

Support nurses where available are a useful addition to the package of care for these families. In the UK they are able to offer home visits and phone calls over the duration of the treatment. This not only supports the family thereby helping them adhere better to long term treatment but also offers an adjunct to the service the PENS is able to provide.

*PENS*

The role of the PENS is extremely important with these children and families. They play a key role in supporting the families through diagnosis and lengthy treatment.

They can act as liaison between the different members of the MDT and are usually the main point of contact for the families.

**3.14 Nursing considerations**

The PENS is likely to have been involved with the family during the monitoring and investigations of their short stature.

As with GH therapy, the rhIGF-1 injections are likely to continue for many years until final height is reached. This requires support for the families undertaking this treatment to maximise adherence in order to gain the greatest benefit.

The role of the PENS is multi-faceted and includes acting as an educator, support service, advocate and liaison for the family throughout the period of both diagnosis and treatment.

It is important from the outset that the PENS is able to assess the family’s understanding of the condition and ability to undertake the treatment in order to individualise the care package to their needs.

Good written information is extremely important but as the family are also learning how to give injections, check CBG and monitor their child this needs to be discussed, demonstrated and taught effectively.

If the child is to be admitted to start treatment, the PENS role is to ensure this is a smooth process thereby reducing the stress on the family. This offers an opportunity for the PENS to meet with the family and teach them all the practicalities around administration, storage, side effects, omitting doses and checking CBG. All the equipment the family will need to give the injections and check CBG can be available on the ward on the day of admission. The PENS can also support the family through the first few injections until they become more accustomed to the procedure. Unlike GH, there is currently no pen device for the RhIGF-1 injections, therefore the family need to be taught how to draw up and administer the injections using needles and syringes. This can be a daunting prospect for some families. It is therefore extremely important to give the family clear instructions and the time needed for them to become confident with the technique.

This face to face interaction and support can be invaluable to the family whilst they are learning and can help to build a trusting relationship between the family and PENS. It is also important to give supporting literature for when they are discharged home including all necessary contact details.

If the treatment is to be started at home by a homecare nursing service it is important that there has been liaison between the homecare nurse and the PENS beforehand.

Over the course of treatment, the PENS continues to play an important role. They will see the family regularly at clinic visits and give ongoing support. Any concerns or problems they may be having can be discussed. Injection sites can be checked and ensuring continuing education and understanding regarding treatment and side effects should be a routine part of the appointment.

**3.15 Patient support groups and useful websites**

Patient support groups have been shown to be a highly valuable resource for patients and their families, (43) not just as a clinical and supportive tool, but by also enabling empowerment and enriching the relationship between the child and family and their caregivers (44). The advent of social media, with websites and online support groups can add to this, although children and families are advised on which are the more useful. Box 3.4 details the American support group MAGIC: **M**ajor **A**spects of **G**rowth **i**n **C**hildren. Further useful websites are listed below.

**INSERT Box 3.4 Patient support groups**

**Useful websites:**

<https://apeg.org.au/patient-resources/hormones-me-booklet-series/>  
<https://www.bsped.org.uk/clinical-resources/patient-information/patient-resources/>  
httphttp://magicfoundation.org

httphttp://pituitary.asn.au

[www.childgrowthfoundation.org.uk](http://www.childgrowthfoundation.org.uk)

http://hgfound.org/

http://www.saynobullying.org/

[www.noonansyndrome.org.uk](http://www.noonansyndrome.org.uk)  
<https://noonansyndrome.com.au>

[https://www.teamnoonan.org/#](https://www.teamnoonan.org/)!

http://[www.geneticalliance.org.au/...detail.php?Russell-Silver-Syndrome](http://www.geneticalliance.org.au/...detail.php?Russell-Silver-Syndrome)

https://magicfoundation.org/Growth-Disorders/**Russell**-**Silver**-**Syndrome**

<https://dwarfismawarenessaustralia.com>

[www.lpaonline.org](http://www.lpaonline.org)

[www.skeletaldysplasiagroup.org.uk](http://www.skeletaldysplasiagroup.org.uk)

[www.bsped.org.uk](http://www.bsped.org.uk)

**3.16 Chapter Summary**

Short stature is a common presenting problem to a general practitioner, and is one of the most common reasons a child is seen in a paediatric endocrine clinic (36). Any child presenting with a height outside of their expected potential for no known reason should be evaluated, and all girls being investigated should have a karyotype performed to assess for Turner syndrome.

Regular monitoring of growth using the same piece of equipment, the same technique, and where possible, the same observer, is essential to establish a child’s growth pattern. If the growth pattern alters, or growth velocity remains low, further investigation should be undertaken by a paediatrician or endocrinologist to establish whether there is cause for concern or not. Early detection allows for maximal response if treatment is undertaken.

Treatment should always be discussed in consultation with the family as it has been shown that compliance is improved if families have some input into the decision making. Commitment from the child / young person and family is imperative with regards to treatment compliance: treatment with GH is a once daily injection until final height is achieved, and a diagnosis of SPIGFD and treatment requires twice daily injections, both requiring long term commitment.

Paediatric endocrine nurses occupy a unique position in the evaluation of short stature and the ongoing management of those receiving GH treatment or IGF-1 therapy. Regular review of the child’s progress and ongoing support with treatment with the PENS are key to the child achieving the best possible outcomes. An important part of the PENS role is to understand both the clinical aspects of diagnosis and treatment and the effect this can have on the child and family and support them throughout this in order to achieve the best outcome.

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