# Assessment and investigation of children with short stature. Diagnosis and management of children with growth hormone deficiency.

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| Title:<br>A) Identification, assessment and investigation of children with short stature and/or abnormal growth.<br>B) Diagnosis and management of children with growth hormone deficiency. | | | |
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| **Target Audience:** | A) Clinicians in primary care or general paediatrics who may be involved in the initial assessment of children with short stature or slow growth, their preliminary investigation and potential onwards referral to paediatric endocrinology if deemed appropriate.<br><br>B) Tertiary level paediatric endocrinologists involved in making a diagnosis of growth hormone deficiency and deciding to commence treatment with exogenous growth hormone. | | |
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## Version Control

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# Contents

## 1.0 Purpose

To provide guidance for clinicians identifying and assessing children with short stature or slow growth.

## 2.0 Scope

Part A) will be used by clinicians in primary care or general paediatrics for the initial assessment of children with short stature or slow growth, their preliminary investigation and potential onwards referral.

Part B) is aimed at tertiary level paediatric endocrinologists who may make a diagnosis of growth hormone deficiency and decide to commence growth hormone therapy.

The aim of this guideline is to help differentiate those children who are short but growing normally from those who are more likely to have a pathological cause for their short stature. We also hope that this guideline will help to ensure a consistent approach to the assessment, investigation and management of these patients.

## 3.0 Definitions

There are several definitions of short stature and/or slow growth. Children meeting any of the following criteria should be considered for further assessment:

- Severe short stature, defined as a height below the 0.4$^{th}$ centile
- Height of 2 centiles or more below the mid-parental height (see appendix 1 for example of how to plot this on a growth chart)
- Height below the 2$^{nd}$ centile and a height velocity over 1 year less than the 25$^{th}$ centile
- Crossing more than 1 height centile in 1 year, in a child aged 2 years or over
- In the absence of short stature, a height velocity of less than the 3$^{rd}$ centile over one year or the 10$^{th}$ centile sustained over 2 years. Sustained growth at this rate will result in centile crossing with time.

Height velocity charts are available for reference in the paediatric endocrinology department.

## 4.0 Main content

This guideline has been adapted from the Growth Hormone Research Society, consensus statements[1.2.]

## Part A) Preliminary consultation and investigations for short stature, guidance for general practitioners and paediatricians.

All patients who present with concerns regarding short stature or slow growth should have a thorough general paediatric history taken and examination performed. Robust measurements of the patient and ideally both parents should be plotted. See appendix 1 for plotting of mid-parental centile.

Many children with abnormal growth will have other chronic conditions and therefore may be best managed by their own speciality team.

If the patient fits any of the criteria listed in section 3.0, then onwards referral to paediatric endocrinology should be made, or if already being seen in a paediatric clinic, the following baseline investigations should be performed prior to referral:

- **FBC, UEs, LFTs, TFTs, ferritin, coeliac screen**

The following investigations are very likely to be requested in the endocrine clinic. Therefore, it may save the patient time and distress to perform these together with those listed above if deemed appropriate:

- **IGF1**
- **Karyotype** (essential if female, should be considered for males, especially if any issue with genital development)
- If the child is of pubertal age or showing signs of puberty, then they should also have **LH, FSH, oestradiol in girls, testosterone in boys**.
- **Bone age X-ray** (request X-ray of left hand and wrist)

If the patient does not fit any of the criteria in section 3.0, then further assessment may still be warranted at the discretion of the responsible clinician.

Consideration should be made to skeletal disproportion, and if this is suspected clinically, then sitting and standing measurements should be taken and plotted on appropriate charts. Guidance for this can be obtained by contacting the paediatric endocrine nurse specialists.

# Part B) Diagnosis and management of children with growth hormone deficiency (GHD), guidance for paediatric endocrinologists.

For patients referred directly from general practice to the paediatric endocrinology clinic, see section A) above for suggested initial investigations.

In particular circumstances, there may be a clear indication to perform tests of pituitary function at the first consultation. For example:

- Signs indicative of an intracranial lesion
- Signs of multiple pituitary hormone dysfunction (MPHD)
- Past history of neonatal symptoms and signs of GHD, eg hypoglycaemia, micro phallus

## Endocrine Investigations

- **IGF1**

  This a useful marker of GH production and a random level can be easily obtained as part of the provisional work-up. Results are returned with age appropriate reference ranges. If below the mid-point of the reference range, in combination with the clinical criteria listed above, then the patient should proceed to further tests of GH production with a provocation test.

- **Insulin tolerance test (ITT)**
  This is the current GH provocation test performed in the Royal Hospital for Children and Young People in Edinburgh. It is undertaken in the Planned Investigation Unit by the endocrine specialist nurses with the help of the PIU junior doctor. It involves administration of insulin in order to induce hypoglycaemia. The "stress" of this should result in a surge of GH from the anterior pituitary and this is measured by serial blood sampling. The full protocol for this test can be found in the Laboratory Handbook, accessed via the intranet.

  **Interpretation of results**
  This is a contentious issue and there are no nationally or internationally agreed cut-offs to define GHD. Interpretation of results is also hugely assay specific. In Lothian, using our current Immulite assay, the following cut-offs are applied:

  - A GH peak of **7.7mcg/L or above** can be considered **normal** [3.]
  - A GH peak **below 5mcg/L** can be considered **abnormal**, this is diagnostic of GHD
  - A GH peak **below 3.3mcg/L** is diagnostic of **severe GHD**, patients may be candidates for ongoing treatment into adult life.

- A GH peak **between** 5 and 7.6mcg/L requires interpretation in context and one of the following 3 approaches can be taken:

  a) Reviewing the child's growth velocity in clinic over the period of 6 months to 1 year
  b) Performing a second GH provocation test
  c) Considering a trial of GH treatment for 1 year with rigorous re-assessment of their growth velocity and consideration given to stopping treatment if there is no improvement.

- **Other GH provocation tests**

  There are many alternative agents which can also provoke GH secretion. These include glucagon, arginine and clonidine. Full protocols for these tests can be found in the Scottish Paediatric Endocrine Group (SPEG) Dynamic Function Tests Handbook accessed via the SPEG website.

  Currently, ITTs are only performed in the paediatric hospitals in Edinburgh and Glasgow. Any patient who fails an alternative provocation tests should be referred to either Edinburgh or Glasgow for an ITT as this is considered the gold standard for diagnosis.

- **Repeated GH provocation tests**

  For isolated GHD, two independent provocation tests are recommended[4] and this may be particularly indicated in the case of borderline results. In those with a history of defined central nervous system pathology, history of irradiation, genetic defect known to cause GHD or multiple pituitary hormone deficiency, one provocation test will suffice.

- **Alternatives**

  Research has suggested that the "stress" of fasting and intravenous cannulation, may in itself be a stimulus for GH production as many patients undergoing an ITT will produce their GH peak after cannulation but before induced hypoglycaemia[5].
  Therefore, those working in district general locations could **consider** baseline and serial GH measurements after simple cannulation as a starting point in their investigations. This could also be a practical option in children undergoing fasting and cannulation for another reason alongside their ongoing investigations for short stature. If a sufficient GH peak is produced from this stimulus alone, then the patient can be deemed to be GH sufficient and does not need to proceed to a formal provocation test.

- **Pituitary MRI scan**

Pituitary MRI is required in all patients with confirmed GH deficiency, in addition to those with known or suspected intracranial tumours, optic nerve hypoplasia/septo-optic dysplasia or other neurodevelopmental anomalies.

## Gold standards for clinical practice: initiation of treatment with GH

- All IGF-1 assays are performed centrally in Scotland and results are returned with age dependant cut-off values. These normative data should be used when interpreting results.
- Priming all peri-pubertal children with sex steroids prior to their GH provocation test is recommended in order to optimise their GH response. Priming should be done for both girls and boys who have a bone age >10 years but no signs of puberty (no breast development in girls and testicular volume <8mls in boys). Ethinyloestadiol is a suitable sex steroid for both girls and boys and is given at a dose of 100mcg orally, once daily for the 3 days prior to their ITT.
- MRI should be performed on all children with confirmed GHD and should include specific views of the hypothalamic-pituitary axis.
- GH should be prescribed as per the BNFc guidance, using weight or body surface area to calculate this at each visit and doses increased appropriately.

  In other centres, IGF-1 levels are sometimes used to titrate doses. We do not favour this approach but measurement of IGF-1 may be useful when there is a question about compliance.
- At the initiation of GH therapy, there should be a discussion with the family/carers about expected outcomes and re-evaluation of the treatment decision based on response.
- There are a range of GH products available on the market and choice of specific product at initiation will be most likely made on the basis of cost effectiveness.

## Gold standards for clinical practice: monitoring of children with GHD

- The response to GH therapy should be assessed after 1 year of treatment. If there has been no or a poor improvement in growth, adherence should be closely scrutinised and the diagnosis of GHD should be reconsidered. Published response curves are available for reference[6].
- BSPED guidelines[7] state that it is the responsibility of the supervising endocrinologist to monitor the patient's growth, pubertal development and general condition at **4-6 monthly** intervals following initiation of therapy. Dose adjustments should also be made depending on the child's height and weight and clearly communicated to the prescribing GP.
  It is also the responsibility of the supervising consultant to decide upon the cessation of treatment at final height, reassess and transition to adult endocrine care where necessary.

- Adverse effects of GH treatment are infrequent, but attention should be paid to possible symptoms of these rare complications at each follow-up visit: benign intracranial hypertension, fluid retention, slipped capital femoral epiphysis (SUFE) and insulin resistance.

**Blood monitoring:**

- There is no source of national guidance regarding the frequency of blood test monitoring in children receiving GH. However, it is recognised that unmasking or evolution of other endocrine dysfunction may occur during treatment. Therefore, it is recommended that thyroid function tests are monitored regularly and consideration made to checking gonadotrophins at the appropriate time for puberty. Monitoring of IGF-1 may be helpful, particularly if poor adherence to treatment is suspected. Finally, HBA1c may be a useful measure of evolving insulin insensitivity.

- For these reasons, we recommend at least annual monitoring of:

  **TFTs, Glucose, HBA1c, IGF-1 and gonadotrophins and sex steroids** at the time of puberty.

## 5.0 Evidence base


1. http://www.ghresearchsociety.org/files/Eilat.pdf
2. Murray PG, Dattani MT, Clayon PE. Controversies in the diagnosis and management of growth hormone deficiency in childhood and adolescence. *Archives of Disease in Childhood.* 2016; **101**: 96-100.
3. Wagner IV, Paetzold C, Gausche R et al. Clinical evidence-based cutoff limits for GH stimulation tests in children with a backup of results with reference to mass spectrometry. European Journal of Endocrinology. 2014; **171**: 389-397.
4. https://www.nice.org.uk/guidance/TA188/chapter/1-Guidance
5. Hawkes CP, Mavinkurve M, Fallon M et al. Serial GH measurements after intravenous catheter placement alone can detect levels above stimulation test thresholds in children. *Journal of Clinical Endocrinology and Metabolism*. 2015; **100**(11): 4357-4363
6. Bang P, Bjerknes R, Dahlgren J et al. A comparison of different definitions of growth response in short prepubertal children treated with growth hormone. Hormone Research in Paediatrics. 2011; **75**(5): 335-345.
7. https://www.bsped.org.uk/clinical/docs/SharedcareGH_July2015.pdf


## 6.0 Monitoring and review

The authors plan to prospectively audit departmental adherence to this guideline following publication.

Review date TBC

# Appendix 1

**How to plot the mid parental centile on Trak electronic growth charts:**

- Select your patient's EPR on Trak.
- Click on the link on the left hand menu called "Observations/measurements".
- Toward the bottom of the page, there is a section called "Questionnaire profile: additional data for growth chart" and adjacent to this there is a link "+New". Click on this and then click on "additional data for growth chart"
- A screen will then appear with boxes for both mum and dad's heights in cm. Enter these. There is no need to correct as this calculation will be automatically performed.
- Enter your Trak password and click "update"
- Mum's height will now appear as a pink box at age 18 years and dad's as a blue box. The mid parental centile is the point midway between the 2 boxes.