**Growth Hormone Deficiency (1 of 5)**

1. Patient presents w/ signs & symptoms suggestive of growth hormone deficiency (GHD)

2. **DIAGNOSIS**
   - Is GHD confirmed?

   - No → **ALTERNATIVE DIAGNOSIS**
   - Yes → **Patient/parental education**

   **Treatment**
   - Growth hormone (GH) replacement therapy
   - Surgery may be required for intracranial tumor

   **Follow-up & monitoring**

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**CLINICAL PRESENTATION**

- GHD is a congenital or an acquired GH axis disruption in the higher brain, hypothalamus or pituitary which results in short stature
- May occur at any age

**Signs & Symptoms**

- Variable & depends on the age of onset
- Noticeable slow growth/short stature (standard height deviation score usually below -2) w/ normal body proportions
- Growth failure after a period of normal growth (child w/ GHD may grow normally until about 2-3 yr old; then, signs of growth delay begin to show
- Hypoglycemia, prolonged jaundice or microphallus (for males) in neonates
- Immature face w/ prominent forehead & depressed midfacial development
- Delayed dentition
- Delayed puberty
- Increased subcutaneous fat esp in the trunk
- Excessive thirst & urination, increased urine volume
- Symptoms of a mass lesion in the hypothalamic-pituitary region (eg headaches, visual disturbances)

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Specific prescribing information may be found in the latest MIMS.
Growth Hormone Deficiency (2 of 5)

**Etiologies**

- **Congenital Conditions**
  - Defective pituitary development that leads to pituitary aplasia
  - Empty sella
  - Encephalocele
  - Midline defects
  - Septo-optic dysplasia
  - Panhypopituitarism
  - Genetic abnormalities

- **Acquired Conditions**
  - Tumors of the hypothalamic-pituitary region
  - Cranial irradiation
  - Infiltrative diseases
  - Trauma
  - Hypoxic insult
  - CNS infections

- **Idiopathic**

**History**

- Family history of GHD
- Perinatal history (e.g., difficult labor, traumatic delivery)
- History of cranial irradiation
- History of head trauma
- Growth chart & history of slow or no growth
- Symptoms of GHD in neonates & children

**Physical Exam**

- Height & wt evaluation
  - Plot wt & height measurements on growth charts which will graphically depict changes in growth & growth velocity
- Short stature may suggest GH deficiency & immediate investigation should be conducted if any of the following criteria based on the American Association of Clinical Endocrinologists (AACE) are present:
  - Severe short stature (defined as height <2.5 SD below population mean)
  - Height <2 SD below population mean or 1-yr height velocity >1 SD below mean for chronological age or (in child age >2 yr), a 1-yr decrease of >0.5 SD in height
  - In the absence of short stature, a 1-yr height velocity >2 SD below the mean or a 2-yr height velocity >1.5 SD below the mean (esp GH manifesting during infancy or in organic acquired GHD)
  - Height >1.5 SD below midparental height (average of father’s & mother’s)
  - Signs indicative of an intracranial lesion
  - Signs of multiple pituitary hormone deficiencies (MPHD)
  - Neonatal signs & symptoms of GHD

- Other manifestations of GHD in children
  - Increased subcutaneous fat, esp around the trunk
  - Immature facie, wrinkle forehead & depressed midfacial development
  - Delayed dentition
  - Delayed average age of pubertal onset
  - In males, the phallus may be small

**Lab Tests**

- **Serum GH Level**
  - In newborns, serum GH level <20 ng/mL is highly suggestive of GHD
  - GH level measured in neonates w/ hypoglycemia but no metabolic disorder
  - After the newborn period, random serum GH levels are not reliable indicators of GHD due to the pulsatile nature of GH secretion

- **GH Stimulation (Provocative) Tests**
  - At least 2 provocative tests are ideal to ascertain the GHD diagnosis because of the high frequency of false-negative results for each single test
  - Provocative tests in children w/ peak GH concentration <10 mcg/L supports GHD diagnosis:
    - Insulin tolerance test (ITT)
    - GH level <5.1 mcg/L indicative of GHD
    - GH level <4.1 mcg/L indicates GHD in a GH-RH-arginine test
    - Clonidine
    - Levodopa
    - Glucagon w/ or w/o beta-blockers
Lab Tests (Cont’d)

Insulin-like Growth Factor 1 (IGF-1) or Somatomedin Test & IGF-binding Protein 3 (IGFBP-3) Test
- Produced when the liver & other tissues are stimulated by GH
- Values >2 SD below the mean for IGF-1 or IGFBP-3 strongly suggest an abnormality in the GH axis, if other causes of low IGF have been excluded
- However, normal values for IGF-1 & IGFBP-3 can be found in children w/ GHD

Other Tests
- Lipid profile
  - Patients w/ GHD may have increased total cholesterol, low-density lipoprotein-cholesterol (LDL-C), apolipoprotein B & triglyceride (TG) levels & decreased high-density lipoprotein-cholesterol (HDL-C)
- Thyroxine & thyroid-stimulating hormone (TSH)
  - To rule out hypothyroidism
- Evaluate for possible causes of GHD: Congenital, genetic or acquired causes
- Karyotype
  - Used to evaluate the presence of genetic syndromes
- Increased type-1 plasminogen activator inhibitor (PAI-1) activity
- Increased fibrinogen levels

Imaging Studies
X-ray
- Assesses the bone age in children
- Reveals delayed bone age in children w/ GHD
- Bone age is estimated from a radiograph of the:
  - Left wrist & hand for children 1 yr of age or older
  - Knee for infants <1 yr old
- X-ray of the head may show skull problems
Bone Density Scan
- Reduced bone mineral density indicates an increased risk of osteoporotic fractures
Magnetic Resonance Imaging (MRI) or Computed Tomography (CT) of the CNS
- Performed to define the anatomy of the hypothalamic-pituitary region & to identify intracranial tumors, optic nerve hypoplasia, septo-optic dysplasia or other structural or developmental anomalies

PATIENT/PARENTAL EDUCATION
- Educate parents & their affected children about GHD
- Psychological counselling may help children w/ low self-esteem that may be related to GHD
- Patients & their parents must learn the technique of subcutaneous GH injection

TREATMENT

GH Replacement Therapy
- GH replacement therapy is best accomplished under the direct supervision of a clinical endocrinologist
- Goals of pharmacotherapy
  - To restore normal GH levels & to reduce morbidity
  - To enable short children to achieve normal height w/ early improvement of the psychosocial problems related to short stature

Somatropin or GH
- Synthetic polypeptide human GH of recombinant DNA (rDNA) origin
- Indicated for children w/ GHD, Turner syndrome & Prader-Willi syndrome
- GH trial therapy also recommended for children w/ otherwise unexplained short stature who pass GH stimulation tests, but who meet most of the following criteria:
  - Height >2.25 SD below the mean for age or >2 SD below the midparental height percentile
  - Growth velocity <25th percentile for bone age
  - Bone age >2 SD below the mean for age
  - Low serum IGF-1 & IGFBP-3
  - Other clinical features suggestive of GHD

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**Growth Hormone Deficiency (4 of 5)**

**B. TREATMENT (CONT’D)**

**Somatropin or GH (Cont’d)**
- **Effects:**
  - Induce normal stature growth
  - Correction of hypoglycemia
- **Target for treatment:**
  - Satisfactory response is defined as an increase of height velocity of at least 2-3 cm/yr above pretreatment velocity
  - Achieve acceptable adult height
- **Replacement is continued until attainment of bone age of 14 yr (girls) & 16 yr (boys)**

**Surgery**
- Surgery may be indicated for congenital anomalies & pituitary tumors

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**C. FOLLOW-UP & MONITORING**

**Prescribed End Points**
- IGF-I in normal range for age & sex
  - Increase dose if IGF-I is low & decrease dose if IGF-I is above normal range
- Improvement in blood lipid profile, body composition (change in lipolysis & increase in bone density) & waist-hip ratio
- Increased muscle strength & exercise performance
- Reduction in CV risk factors

**Patient Monitoring**
- Close follow-up care w/ an endocrinologist is recommended to monitor the child’s growth & to adjust the dose of GH therapy
- Initial follow-up should be every mth; thereafter, visits may be less frequent but should be at least 2x/yr
- Children should be evaluated every 3-6 mth, w/ increases in height & height velocity as the most important indicators of GH therapy response
- Monitor thyroid function every 6 mth
- Monitor patients for hyperglycemia because GH may reduce insulin sensitivity; patients w/ diabetes mellitus (DM) may need to adjust their insulin during treatment
- Funduscopic examination is recommended at the start of therapy & periodically during the course of treatment
- No consensus exists concerning when to cease growth hormone treatment
  - GH should be continued until growth ceases (ie final height or epiphyseal closure has been documented), at which point the GH axis should be retested w/ stimulation tests
  - GH treatment is meant to be a replacement therapy & can only be expected to make short children grow at a normal growth rate
  - Most children treated w/ GH replacement reach a normal adult height
    - Child’s growth usually increases most during the 1st yr, w/ an average increase of 8-10 cm/yr
    - Growth rate slows down over the next several yr

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## Dosage Guidelines

### GROWTH HORMONE

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Remarks</th>
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<tbody>
<tr>
<td>Somatropin (rDNA origin)</td>
<td>0.5-0.7 IU/kg/wk SC or 12-20 IU/m²/wk SC divided into daily doses or divided into 6-7 doses or 2.1-3 IU/m² BSA/day SC or 0.025-0.035 mg/kg/day SC or 25-35 mcg/kg/day SC or 0.7-1 mg/m² BSA/day SC</td>
<td>Administration • Administer in the evening to mimic nocturnal GH secretion, preferably in abdominal area • Rotate inj sites</td>
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<td>Adverse Reactions • Usually dose-dependent &amp; resolve w/ dose reduction or after 1-2 mth of treatment • Antibodies to growth hormone • Intracranial hypertension &amp; slipped capital femoral epiphysis (more common in children) • Hyperinsulinemia causing hypoglycemia • Inj site reactions (eg swelling, pain, erythema, itching, bruising &amp; lipoatrophy)</td>
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<td>Special Precautions • Contraindicated in active malignancy, carpal tunnel syndrome, benign intracranial hypertension, proliferative or pre-proliferative diabetic retinopathy, patients w/ closed epiphyses, intracranial lesion, pseudotumor cerebri &amp; hypersensitivity to active ingredients • Monitor patients w/ GHD secondary to an intracranial lesion should be examined frequently for progression or recurrence of the underlying disease process • Observe for evidence of glucose intolerance • Patients w/ coexisting ACTH deficiency should have their glucocorticoid replacement dose carefully adjusted</td>
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<td>0.045-0.05 mg/kg/day SC or 1.4 mg/m² BSA/day SC</td>
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<td>1 mg/m² BSA/day SC</td>
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<td>Chronic renal insufficiency: 50 mcg/kg/day SC or 0.045-0.05 mg/kg/day SC or 1.4 mg/m² BSA/day SC</td>
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<td>Turners syndrome: 1 IU/kg/wk divided into 6-7 doses or 30 IU/m² BSA/wk divided into 6-7 doses or 0.045-0.05 mg/kg/day SC or 1.4 mg/m² BSA/day SC</td>
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<td></td>
<td>Prader-Willi syndrome: 0.035 mg/kg/day SC or 25 mg/m² BSA/day SC</td>
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<td></td>
<td>Max dose for Prader-Willi syndrome: 2.7 mg/day</td>
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All dosage recommendations are for children w/ normal renal & hepatic function unless otherwise stated.

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Please see the end of this section for reference list.
Growth Hormone Deficiency


