

# Growth Hormone Deficiency and other Indications for Growth Hormone Therapy – Child and Adolescent

## Prohibited Substances: Human Growth Hormone

### 1. Medical Condition

Growth Hormone Deficiency (GHD) and other indications for human growth hormone (hGH) therapy in children and adolescents.

### 2. Diagnosis

#### a. Medical History

GHD is a result of dysfunction of the hypothalamic-pituitary axis either at the hypothalamic or pituitary levels. The prevalence of GHD is estimated between 1:4000 and 1:10,000. GHD may be present in combination with other pituitary deficiencies, e.g., multiple pituitary hormone deficiency (MPHD) or as an isolated deficiency. Short stature, i.e., height more than 2 SD below the population mean, may represent GHD. Low birth weight, hypothyroidism, constitutional delay in growth puberty, celiac disease, inflammatory bowel disease, juvenile arthritis, or other chronic systemic diseases as well as dysmorphic phenotypes such as Turner's syndrome and genetic diagnoses such as Noonan's syndrome and growth hormone (GH) insensitivity syndrome must be considered when evaluating a child/adolescent for GHD. Pituitary tumors, cranial surgery or irradiation, head trauma or CNS infections may also result in GHD.

Idiopathic short stature (ISS) is defined as height below -2 SD score (SDS) without any concomitant condition or disease that could cause decreased growth. ISS is an acceptable indication for treatment with hGH in many countries.

Since not all children with GHD will require continued treatment into adulthood, the transition period is very important. The transition period can be defined as beginning in late puberty (the time when near adult height has been attained) and ending with full adult maturation (6-7 years after achievement of adult height). During this period, ongoing hGH therapy may be necessary to attain somatic maturation, normal intermediary metabolism and appropriate quality of life. However, periodic re-evaluation is necessary.

## b. Diagnostic Criteria

Auxology (comparison of the child's growth pattern to established gender and ethnicity norms) is the clinical basis for suspecting GHD in children. Any child with severe short stature ( $< -3SD$ ), severe growth deceleration (height velocity  $< -2SD$ ), less severe short stature ( $< -2SD$ ) and growth deceleration ( $< -1SD$ ), history of brain tumor, CNS infection, cranial irradiation, other organic pituitary abnormality or radiologic evidence of pituitary abnormality is a candidate for GHD evaluation.

The diagnosis of GHD is established by evaluation of the GH-IGF-1-IGFBP axis and confirmed through biochemical testing. Evaluation for GHD should be performed with evidence of hypothalamic-pituitary disease, after cranial irradiation, for individuals who have other pituitary hormone deficiencies, or for individuals who have been treated for GHD as a child.

Evaluation of child with suspected GHD should include:

1. History and physical exam specifically investigating presence of chronic diseases or dysmorphic genetic disorders;
2. Measurement of height with comparison to gender and ethnic norms;
3. Calculation of height velocity;
4. Evaluation for genetic disorders e.g., PROP-1, POU1F1 (Pit-1), LHX-3, LHX-4 when indicated.
5. Radiological evaluation:
  - a. Bone age estimation from x-ray of left wrist and hand;
  - b. MRI of hypothalamic-pituitary region.
6. Measurement of growth factor concentrations:
  - a. Insulin-like growth factor-1 (IGF-1)
  - b. Insulin-like growth factor binding protein (IGFBP-3)
  - c. Growth hormone stimulation tests; there should be a cutoff of 7 ng/ml on at least two of the following tests
    - i. Insulin Tolerance Test
    - ii. Arginine
    - iii. GHRH + Arginine
    - iv. Glucagon
    - v. Clonidine

## c. Transition period (as defined above in Section 2 A.)

1. Re-evaluation for the adolescent/young adult who is transitioning, having been treated for childhood GHD, is mandatory because some forms of childhood GHD may recover. For emerging adults who were diagnosed with GHD as children/adolescents an IGF-1 level should be measured after 2-4 weeks off hGH therapy. However, in some conditions a GH stimulation test is not required because GHD is almost certain on clinical or genetic grounds.

This applies to patients with:

- a. More than three additional pituitary hormone deficits and a low IGF-I level (strong evidence for hypopituitarism);
  - b. Transcription factor mutation known to result in pituitary mal-development and hypopituitarism (e.g., *POU1F1* (Pit-1), *PROP-1*, *LHX-3*, *LHX-4*);
  - c. Mutations in genes known to result in isolated GHD (e.g. *GH-1* or *GHRH-R*).
2. This re-evaluation should be performed when linear growth has ceased and includes:
- a. Height, weight, BMI, anthropometric measurements
  - b. Serum IGF-1 levels
  - c. GH Stimulation tests
    - i. Insulin Tolerance Test (< 5 ng/mL)
    - ii. Glucagon Stimulation Test (<5 ng/mL)
    - iii. Macimorelin Test (<2.8 ng/mL)
  - d. Other relevant medical information
    1. GH and IGF-1 results must be expressed in mass units.
    2. IGF-1 concentration below normal range is insufficient evidence for GHD in a child and adolescent. Stimulation testing must be performed if there is no other evidence of hypothalamic-pituitary dysfunction.
    3. Subjects should be investigated for other anterior pituitary deficits, and these should be addressed and monitored.
    4. Cardiovascular risk markers should be assessed and managed appropriately.
    5. Bone density may be subnormal in those with GHD and should be monitored.

### 3. Treatment

a. Name of prohibited substance

Human growth hormone (hGh)

b. Route of administration

Subcutaneous injections

c. Starting Dose

0.025-0.050 mg/kg/day

#### d. Adjusting treatment doses

Adjust dose, depending upon growth response (change in height SDs or change in height velocity), adverse effects and IGF-1 levels maintained at 0 to +1 SD unless previous history of malignancy in which case suggested IGF-1 levels < 0 SD.

#### e. Duration

The GH status of individuals with childhood onset GHD requires re-evaluation within the transition period.

### 4. Non-prohibited alternative treatments

No alternative for hGH substitution.

### 5. Consequences to health if treatment is withheld

The following consequences to health for individuals with untreated GHD include:

1. Persistent growth failure
2. Decreased quality of life
3. Decreased bone mineral density
4. Increased fat mass
5. Increased cardiovascular risk with negative effects on cardiovascular risk factors:
  - a. inflammation
  - b. dyslipidemia
  - c. insulin resistance

### 6. Treatment Monitoring

Treatment should be monitored using the following:

1. Linear growth, when applicable
2. IGF-1 levels
3. Bone age

## 7. TUE duration

1. Eight years if genetic, congenital, or hypothalamic-pituitary structural abnormality, or irradiation.
2. Four years if due to brain trauma or idiopathic.

The results of regular monitoring should be submitted annually for review.

## 8. Appropriate precautionary matters

Due to the significant risk for abuse of hGH for performance enhancement, these diagnostic and monitoring requirements must be strictly followed. The diagnosis should be confirmed by a pediatric endocrinologist. Also, the reviews of these TUEs should be performed by a pediatric endocrinologist.

Most patients with GHD self-administer GH. Although self-administration may seemingly present difficulty with monitoring, a logbook of hGH prescriptions and administration should be maintained by the athlete. The administration logbook may be subject to review at any time including for the annual review.

Quantities of hGH delivered to the athlete must be strictly controlled and limited by prescription

## References

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