

GROWTH HORMONE DEFICIENCY AND OTHER INDICATIONS FOR GROWTH HORMONE THERAPY – CHILD AND ADOLESCENT

1. Medical Condition

Growth Hormone Deficiency and other indications for growth hormone therapy in children and adolescents.

2. Diagnosis

A. Medical History

Growth hormone deficiency (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 GH insensitivity syndrome must be considered when evaluating a child/adolescent for GHD. Pituitary tumors, cranial surgery or radiation, 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 Growth Hormone in some but not all 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 growth hormone therapy may be necessary to attain somatic maturation, normal intermediary metabolism and appropriate quality of life. However, re-evaluation is necessary.

TUE Physician Guidelines
Growth hormone deficiency and other indications for
growth hormone therapy – child and adolescent

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. GHRH + Arginine
 - iii. Glucagon
 - iv. Clonidine

TUE Physician Guidelines
Growth hormone deficiency and other indications for
growth hormone therapy – child and adolescent

C. Transition period (as defined in Section II 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 rhGH 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 maldevelopment and hypopituitarism (e.g. *POUIF1* (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. 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. Therapeutic use exemption (TUE) for the treatment of GHD should be granted for only those who have confirmed Growth Hormone Deficiency (GHD).
4. Subjects should be investigated for other anterior pituitary deficits and these should be replaced and monitored.
5. Cardiovascular risk markers should be assessed and managed appropriately.
6. Bone density may be subnormal in those with GHD and should be monitored.

3. Medical Best Practice Treatment

1. Name of prohibited substance
 - recombinant human growth hormone
2. Route
 - Subcutaneous injections
3. Starting Dose
 - 0.025-0.050 mg/kg/day
4. 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.
5. Duration
 - The GH status of individuals with childhood onset GHD requires re-evaluation within the transition period.

4. Other non-prohibited alternative treatments

No alternative for human growth hormone 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

TUE Physician Guidelines
Growth hormone deficiency and other indications for
growth hormone therapy – child and adolescent

7. TUE validity and recommended review process

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. Any appropriate precautionary matters

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

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

Quantities of growth hormone delivered to the athlete must be strictly controlled and limited by prescription.

TUE Physician Guidelines
Growth hormone deficiency and other indications for
growth hormone therapy – child and adolescent

References

1. Grimberg A et al. Guidelines for Growth Hormone and Insulin-Like Growth Factor-1 Treatment in Children and Adolescents: Growth Hormone Deficiency, Idiopathic Short Stature, and Primary Insulin-Like Growth Factor-1 Deficiency: a statement of the Pediatric Endocrine Society. *Hormone Research in Paediatrics*, 86: 361-397. 2016.
2. Cook, DM and Rose, SR. A Review of Guidelines for Use of Growth Hormone in Pediatric and Transition Patients, *Pituitary*, 15: 301-310. 2012
3. Collett-Solberg PF, Jorge AAL, Boguszewski MCS, et al Growth hormone therapy in children; research and practice-a review *Growth Hormone and IGF Research* 2019; 44:20-32.
4. Richmond, EJ and Rogol AD, Testing for Growth Hormone Deficiency in Children. *Growth Horm IGH Res.* 50: 57-60. 2019.
5. Yuen KCJ et al. AACE 2019 Guidelines: American Association of Clinical Endocrinologists and American College of Endocrinology Guidelines for Management of Growth Hormone Deficiency in Adults and Patients Transitioning from Pediatric to Adult Care. *Endocrine Practice*. Vol 25(11):1191-1232.
6. Garcia, JM et al. Macimorelin as a Diagnostic Test for Adult GH Deficiency. *J Clin Endocrinol Metab*, August 2018, 103 (8): 3083-3093.