Growth hormone deficiency – Child and adolescent

Prohibited substances: Human Growth Hormone

1. Introduction

Growth Hormone Deficiency (GHD) in children and adolescents may be isolated or part of a syndrome of multiple anterior pituitary hormone deficiencies. It may be congenital or acquired. Treatment with recombinant human growth hormone (hGH) is appropriate as long as the epiphyses of the long bones are open.

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 standard deviation (SD) score below the population mean, or pathologically diminished height velocity, may be present in those with 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, Prader-Willi syndrome, and growth hormone (GH) insensitivity syndrome can also impair growth and must be considered when evaluating a child/adolescent for GHD. Pituitary tumors, cranial surgery or irradiation, head trauma or central nervous system (CNS) infections may also result in GHD. Idiopathic short stature (ISS) is defined as height below -2 SD score (or below the 2.3 height centile) without any concomitant condition or disease that could cause decreased growth. ISS is an approved indication for treatment with hGH in many countries. Please refer to the document TUE Physician Guidelines for Short Stature which includes non-growth hormone deficient conditions.

Since not all children with GHD will require continued treatment into adulthood, the transition period is critical. 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, re-establishment of a GHD diagnosis may be required and thereafter 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 in children with evidence of hypothalamic-pituitary disease, after cranial irradiation, in individuals who have other pituitary hormone deficiencies, or in 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 causing GHD/MPHD, PROP-1, POU1F1 (Pit-1), LHX-3, LHX-4 and other recently individuated genes by the NGS panel. Moreover, some well-defined genetic conditions, such as Prader Willi syndromes, will present GHD/MPHD.
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. GH 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
        vi. Other new proposed GHD stimulation test such as macimorelin or other oral GH secretagogues

Please note: If the diagnosis of GHD was made without pre-pubertal sex hormone priming, then consideration should be given to repeat GH stimulation tests during pubertal maturation to validate persistence of GHD.

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 not be permanent. 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. A GH stimulation test is not required when 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. When needed, 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 -2 SD for age/puberty stage is insufficient evidence for GHD in a child and adolescent. GH 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

25-50 mcg/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.

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. Ten 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 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

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.