GROWTH HORMONE DEFICIENCY AND OTHER INDICATIONS FOR GROWTH HORMONE THERAPY – ADULT

1. Medical Condition

Growth Hormone Deficiency and other indications for growth hormone therapy (adult).

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. Adults who have GHD include individuals who have been diagnosed with GHD as a child and those who have acquired GHD as an adult due to hypothalamic-pituitary disease. For the individual who has been diagnosed with GHD as a child, 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. Adults who develop GHD de novo include individuals with hypothalamic-pituitary disease, e.g. pituitary tumors, subarachnoid hemorrhage, surgery or irradiation in these cranial areas or traumatic brain injury. Such individuals may have pituitary hormone deficiencies. In general, the diagnosis of GHD should be determined by an endocrinologist with expertise in pituitary disorders.

B. Diagnostic criteria

The diagnosis of GHD requires an appropriate/plausible clinical setting and is confirmed through biochemical testing. Evaluation for GHD should be performed in patients with evidence of hypothalamic-pituitary disease (e.g. pituitary tumors), after cranial irradiation, after significant traumatic brain injury (TBI) and in some individuals who have been treated for GHD as a child.

The diagnosis of GHD rests on:

- Evidence for hypothalamic-pituitary disease;
- Subnormal serum IGF-1 levels;
- Abnormal GH stimulation test.

1) Re-evaluation for the adolescent/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 certain 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 (for threshold levels of these tests refer to Ho et al. Consensus Guidelines or Cook et al. AACE Medical Guidelines, both are listed below):
      1. Insulin Tolerance Test;
      2. GHRH+Arginine Test - with BMI adjustments for obesity;
      3. Glucagon Stimulation Test.

When evaluating individuals with traumatic brain injury, **the timing of the evaluation is critical.** The evaluation should be undertaken no sooner than 12 months after injury.

In addition to the investigations above, the diagnostic workup of the adult with new onset GHD requires the following additional assessment:

MRI of brain with specific attention to hypothalamus and pituitary.

C. <u>Relevant medical information</u>

   a. GH and IGF-1 results must be expressed in mass units;
   b. Low IGF-1 concentration below normal range is insufficient evidence for GHD. GH stimulation testing must be performed unless there is conclusive other evidence of hypothalamic-pituitary dysfunction (such as an organic lesion and hypopituitarism with more than 3 additional pituitary hormones being deficient or the presence of the genetic disorders listed above);

c. Therapeutic use exemption (TUE) for the treatment of GHD should be granted for only those who have conclusive evidence of GHD;
d. Subjects should be investigated for other pituitary hormone deficits and these should be adequately replaced before biochemical evaluation for GHD is performed.

3. Medical Best Practice Treatment

A. Name of prohibited substance

Recombinant growth hormone, e.g. Genotropin, Humatrope, Norditropin, Nutropin, Omnitrope, Saizen, Valtropin, TevTropin

B. Route

Subcutaneous injections

C. Dosage and Frequency

a. Women – 0.3 mg/day (may need higher dosage if taking oral estrogens);
b. Men – 0.2 mg/day.

Adjust dose dependent upon clinical assessment, adverse effects and IGF-1 levels maintained at 0 – +1 SD unless previous history of malignancy.

D. Recommended duration of treatment

a. Adult onset GHD requires lifelong treatment (continuing treatment for the aging population is the decision of the treating endocrinologist);
b. 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:

a. Decreased quality of life;
b. Decreased bone mineral density;
c. Increased fat mass;
d. Increase in cardiovascular risk factors.

6. Treatment Monitoring

Treatment should be periodically monitored using the following:

a. BMI;
b. IGF-1 levels;
c. Blood glucose and Hemoglobin A1c (oral glucose tolerance test may be indicated based on results of Hgb A1c or strong family history of Diabetes Mellitus);
d. Cardiovascular risk markers should be assessed and managed appropriately;
e. Bone density may be affected negatively in those with GHD and should be monitored;
f. As part of therapy, quality of life (QoL) may be monitored by use of GHD specific questionnaires, e.g. QoL-AGHDA.

7. TUE Validity and Recommended Review Process

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

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

8. Any Appropriate Cautionary Matters

Due to the significant risk for abuse of growth hormone for performance enhancement, these requirements must be strictly followed. The diagnosis should be confirmed by an endocrinologist with expertise in hypothalamic-pituitary disorders.

Given the potential controversy associated with the approval of a TUE for Growth Hormone, the opinion of an independent endocrinologist with expertise in hypothalamic-pituitary disorders is strongly suggested.

Also, the TUE reviewers working on behalf of the national anti-doping agencies (NADOs) and international federations (IFs) should be endocrinologists with expertise in hypothalamic-pituitary disorders.

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 administered to the athlete must be strictly controlled and limited by prescription.

References

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