



Pediatric Growth Hormone Deficiency: When Are Treatments Medically Necessary?

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Speaker Introductions

Moderator

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Presenter

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Webinar Overview

- Describe the role of growth hormone (GH)
- Categorize the common causes of pediatric GH deficiency
- Summarize the typical clinical features of GH deficiency
- Identify the tests and diagnostic criteria commonly accepted by healthcare plans to identify pediatric GH deficiency
- Review treatment options for pediatric GH deficiency
- Define the criteria for monitoring growth response and for continuing therapy in children
- Discuss how independent review organizations provide unbiased evaluation of medical necessity

Short Stature: A Common Concern

- Incidence of short stature associated with severe childhood growth hormone (GH) deficiency
 - Estimated to range between 1 per 4,000 to 1 per 10,000 live children
- Number of children receiving GH therapy
 - About 20,000 per year
 - 4,000 new children diagnosed annually as candidates
 - Boys are about two times more likely than girls to receive treatment for GH deficiency

Pediatric GH: An Overview

- GH is one of several hormones produced by the pituitary gland
 - Promotes linear growth
 - Has important physiologic and metabolic effects in adults long after final height has been reached
- GH deficiency
 - Pituitary gland produces inadequate amounts of GH or none at all
 - Presents with or without other pituitary hormone deficiencies

Classification of Causes of GH Deficiency

- Congenital (present at birth)
 - Genetic abnormalities of pituitary gland or genes for GH production or GH-releasing hormone (GHRH) synthesis
 - Congenital central malformations
 - Syndromes associated with midline defects and cleft palate
- Acquired (becomes evident during childhood)
 - Damage to the pituitary resulting from foot or breech delivery, brain tumor, cranial irradiation, head trauma, or infection
- Idiopathic
 - No cause can be found

Evaluation of Short Stature:

Typical Clinical Features of GH Deficiency

- Severe proportional short stature
- Height velocity abnormal for age
- Delayed bone age
- Delayed puberty
- Crowding of midface structures in congenital form
- Increased skinfold thickness
- Genital abnormalities in boys
- High-pitched voice

Clinical and Laboratory Findings to Consider When Evaluating Short Stature

- Prenatal history
- Birth and health history
- Parental health history
- Physical examination
- Growth history
- Puberty evaluation
- MRI
- Laboratory evaluation
- Genetic evaluation
- Bone age
- GH stimulation test

Evaluation for GH Deficiency

- First, exclude other causes of growth failure
 - Hypothyroidism
 - Chromosomal disorders (Prader-Willi syndrome, Turner syndrome)
 - Chronic systemic disease (renal failure, malabsorption)
 - Skeletal disorders
- Idiopathic GH deficiency
 - Diagnosis of idiopathic is based on marked short stature (ISS), >2.25 SD is made when there is no evidence of other pathology or syndromes, and it is based on marked short stature, >2.25 standard deviations (SD) below the mean

Identifying the Underlying Cause of GH Deficiency

- Common screening tests
 - Complete blood cell (CBC) with differential, sedimentation rate, hepatic and renal function tests, chromosomes in females (to exclude Turner syndrome), and thyroid function tests
- Most health plans require a definitive measure of GH using GH stimulation (provocative)
 - Measure ability of the pituitary gland to release GH
 - Should be performed after other causes of growth failure have been ruled out
- Random blood sampling to monitor GH levels is not reliable since GH is normally secreted in bursts (low levels during the day, spontaneous spikes during deep sleep)

Provocative Tests

- Measure GH levels in the blood following administration of medication that triggers the release of GH (measured every half hour for 3 hours)
- Common pharmacologic agents used to stimulate release of GH
 - Arginine, clonidine, glucagon, L-dopa, insulin, GHRH
- Diagnosis of GH deficiency can be made based on provocative tests in combination with current height and predicted adult height assessments

Interpreting the Results of Provocative Tests

- Peak concentration of <7 ng/mL in response to a provocative test is considered to be diagnostic with a higher-sensitivity for severe GH deficiency
- Many physicians consider values <10 ng/mL abnormal
 - This value is commonly referenced as a cutoff indicating GH deficiency
- Evaluation of GH deficiency should be based upon the results of two provocative tests
 - Some children may not always respond to a single stimulant
 - False-positive responses can occur in patients with normal pituitary function, as well as false-negative responses in pituitary deficient patients

Imaging Studies

- Bone-age x-ray of left hand
 - Determines maturity of child's bones, which may be different from child's chronological age
 - May be useful in determining child's growth potential
- MRI of the head for patients diagnosed with GH deficiency
 - Visualizes the pituitary gland to identify any anatomical abnormalities and to exclude a brain tumor
 - Profound GH deficiency is uncommon in patients with normal MRI findings, except in those with genetic causes

Treating GH Deficiency

- GH is available as a subcutaneous injection
- FDA-approved pediatric indications for recombinant human GH
 - Children with growth failure due to GH deficiency
 - Children with short stature associated with Noonan syndrome, Turner syndrome, and Prader-Willi syndrome
 - Children with short stature born small for gestational age who have not reached normal growth range by age 2 to 4 years
 - Short stature with homeobox-containing gene deficiency
 - Children with chronic renal insufficiency; children with ISS who are >2.25 SD below the mean in height and who are unlikely to catch up in height

Factors to Consider Before Initiating Therapy

- Accurate diagnosis
- Careful monitoring of growth velocity
- Estimation of final height by a pediatric endocrinologist
- Use of GH therapy for ISS indication remains controversial
 - Variability in reported height improvement
 - Poorly defined measures of therapeutic success
 - Debate regarding whether the goal of treatment should be a normal or maximum height

Monitoring Growth Response

- Children treated with GH should be monitored for height, weight, pubertal development, and side effects at 3- to 6-month intervals
- Adequate response to childhood GH therapy is shown by an increase in linear growth velocity within the first 6 months
- More definitive evidence of GH efficacy is the change in height SD score over the first year of therapy, which is typically when maximal growth response occurs

How Long Should Treatment Last?

- Treatment with GH should continue for several years until the child reaches final height, epiphyseal closure occurs, or the child no longer responds to treatment
- GH deficiency may or may not persist into adulthood
 - If GH deficiency persists into adulthood, continuation of GH therapy is recommended in order to optimize the metabolic effects of GH

Obtaining Approval: Medical Necessity for Treatment of Pediatric GH Deficiency

- Health plans require thorough documentation of:
 - Patient's growth chart and medical history, including laboratory test results such as scores from provocative tests
 - Information on the height of the patient's parents if this is a factor in the physician's decision to prescribe GH therapy
- Requests for coverage of GH therapy are often incomplete and missing critical data

The Role of Independent Medical Review in Determining Medical Necessity

- Allows access to a range of board-certified physician specialists who keep up-to-date with the latest medical research literature and with the latest standard of care
- Provides specialty match to allow healthcare plans to ensure that the requested treatment falls under the medical necessity requirements before approving a course of treatment
 - Especially important in the interpretation of clinical and laboratory findings and the determination of whether treatment endpoints are being achieved and whether the therapy is appropriate for the patient
- Avoids conflicts of interest (e.g., those relating to economics, lack of specialists to review cases)

Conclusions

- Early evaluation, diagnosis, and onset of therapy are critical in order to optimize intervention with GH therapy
 - Optimal treatment with GH allows prepubertal patients to catch-up and reach normal height before the onset of puberty
 - If not properly treated, GH deficiency can lead to decreased bone mass, delayed puberty, and psychological distress
- External independent medical review:
 - Facilitates effective treatment of pediatric GH deficiency
 - Allows ready access to board-certified specialists, which healthcare plans may lack internally
 - Makes timely unbiased determinations of whether the requested treatment falls under medical necessity guidelines

Questions and Answers

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Q and A Session Answers

- **Question:** Can you elaborate a little on the psychological distress that is considered an effect of GH deficiency? Also, the effect GH has on a Childs weight and cholesterol? Are these higher than a child without GH deficiency.
 - **Answer:** There is significant variability in the medical literature regarding GH deficiency and psychological stress. The studies are difficult to conduct and a large amount of the outcome may rest on the specific dynamics of the patient's family.

Q and A Session Answers

- **Question:** Are you familiar with the Magic foundation at Rush - Pres St. Lukes here in Chicago? This is an educational and support system; where by parents can actually speak to other parents who's children suffer from GH deficiency. How important do you feel it is for these parents to join these type of support groups.
 - **Answer:** Yes. It's a wonderful foundation. I think there is potentially tremendous benefit for parents who join these support groups as growth hormone therapy is intensive, of long duration, and (in some circles) carries some degree of stigma or controversy.

Q and A Session Answers

- **Question:** Regarding discontinuation criteria: if any one of those are met, is therapy considered to be stopped; or must all 3 be met (final, ht., epiphyseal closure and response)?
 - **Answer:** The decision to discontinue should be based on the specific elements of the clinical case. In general, we await epiphyseal closure regardless of height. In some patients in whom growth hormone deficiency might only be partial or have been transient (e.g. patients with an abnormally high IGF-1 level on therapy, patients whose height standard deviations far exceed their midparental height), a trial off of therapy prior to epiphyseal closure might be a good option.

Q and A Session Answers

- **Question:** Some endocrinologists state that a stimulation is required for ISS because they don't feel the patient is deficient. Would you recommend or require a stimulation test for those patients?
 - **Answer:** The value of stimulation tests is controversial because the results are not always perfectly indicative of the actual clinical situation. In my estimation, if the level of suspicion is high for growth hormone deficiency or ISS, it's useful as one element of the broader evaluation. Results that are abnormally high or low can be more helpful than results that are close to the cutoff and therefore a bit equivocal.

Q and A Session Answers

- **Question:** What is the usual length of time for this treatment?
 - **Answer:** It depends on when the therapy was started. Usually, it's from initiation to whenever the epiphyses fuse (there are exceptions, see #3).

Q and A Session Answers

- **Question:** What is your opinion on the use of leuprelide in children entering puberty with GH deficiency with advanced bone age?
 - **Answer:** Leuprolide (Lupron) is an important adjunct if there is true precocious puberty in a patient with true growth hormone deficiency as puberty will progress unless actively suppressed. In patients who are already in puberty and who started puberty at a normal age, it may have a negligible effect on final height because growth velocity often decreases a bit when Lupron is added.

Q and A Session Answers

- **Question:** What, if any, is the role of IGF-1 in diagnosing pediatric GHD.
 - **Answer:** IGF-1 is a protein whose level is dependent upon growth hormone activity. If there are normal levels of growth hormone but a mutation in the hormone itself or in its cell receptor, then IGF-1 is usually lower than normal. I find it to be a good screening tool because its levels do not fluctuate whereas growth hormone levels are variable throughout the day and night.

Q and A Session Answers

- **Question:** When evaluating when to stop GH tx, is there 1 parameter which is more important: epiphy closure vs. mid parental height, or reaching normal height range for boy/girl?
 - **Answer:** I believe that epiphyseal closure is the most important and trumps height because the benefits of growth hormone therapy go beyond height. Once the epiphyses have fused, you have a chance to evaluate to see if the patient might need growth hormone as an adult.

Q and A Session Answers

- **Question:** I've heard from MD's asking for approval that growth hormone can NOT be stopped once started. For example: transfer from another plan and criteria is not met with new plan. Is this correct?
 - **Answer:** If the diagnosis was accurate and appropriate, then growth hormone should not be stopped. We do have patients who may have months-long interruptions in growth hormone therapy and those interruptions are not urgently hazardous to the patient's health.

Q and A Session Answers

- **Question:** Is it true GH can reduce Heart disease in adults?
 - **Answer:** Yes, by way of improved lipid levels and decreased fat mass.

Q and A Session Answers

- **Question:** Why is GH so expensive and what can be done to encourage the decrease in cost?
 - **Answer:** I wish I knew!! Seriously, I've never gotten a good answer to this very salient question.

Q and A Session Answers

- **Question:** We have a case of a 14 yr old below 1st percentile at 6 yrs 8 mos., ht now -3.18 SDs below mean, GV 1.82cm/year. Low IGF-1 on 2 occasions. GH stim test 13.2 ng/ml. We consider this ISS. We do not consider ISS a disease or illness. Is this child determined to be GH deficient solely on other values? Parents are both <5ft 9in.
 - **Answer:** No, the patient doesn't fit 'classic growth hormone deficiency criteria' but the facts regarding the case indicate a clear abnormality in growth. This patient may be able to produce growth hormone if stimulated but not enough growth hormone over the course of the day to grow normally. It's not a good idea to look at the growth hormone stimulation results in isolation for that reason.

Q and A Session Answers

- **Question:** Why xray of left hand - is it the non-dominant hand?
 - **Answer:** Initially, the odds that it was the non-dominant hand was the reason for choosing the left. Dominance is not thought to have an effect on bone maturation, so we generally use the left hand because all of images for comparison in our reference atlases use the left hand and it's easier to compare.

Q and A Session Answers

- **Question:** Does the growth hormone treatment affect a child's ability to play sports? Are they better equipped to be good at sports or is their ability just based on family history and DNA?
 - **Answer:** Growth hormone therapy would have a beneficial impact on athletic performance if the patient was growth hormone deficient prior to therapy. If there is no existing growth hormone deficiency, any improvement in performance using conservative dosing (as we do for children with deficiency), would likely have a negligible impact. If growth hormone is abused by administering huge amounts, then one might build big muscles but would have a whole host of unwanted side effects.

Thank You



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