

White Paper: Pediatric Growth Hormone Deficiency: When are Treatments Medically Necessary?

For Health Plans, Medical Management Organizations and TPAs

Executive Summary

Growth in humans is a complex biologic process, and growth disorders, which are most apparent in childhood, are equally complex. The diagnosis and management of pediatric growth hormone (GH) deficiency poses a number of challenging issues for both pediatric endocrinologists and health plans.

In 2003, the number of patients eligible to receive GH therapy increased significantly when the U.S. Food and Drug Administration (FDA) expanded the indications for GH to include the treatment of pediatric patients with idiopathic short stature (ISS). Although GH therapy has been shown to be associated with short-term increases in growth in children, its use remains controversial among pediatric endocrinologists. Further complicating matters is the increased public awareness of the ISS indication, resulting in requests for GH therapy.

When evaluating a child with short stature, pediatric endocrinologists must integrate various clinical and laboratory data rather than relying on the results of a single test. Evaluation for GH deficiency in a child who is short should not be initiated until other causes of growth failure have been excluded. Comprehensive clinical assessment should be combined with a bone-age x-ray and provocative tests. Assessment of growth consists primarily of a careful evaluation of the child's growth rate and velocity and family history of growth and height patterns. The complexities of GH deficiency can pose challenges for healthcare plans that lack specialists on staff.

About 20,000 children per year receive growth hormone therapy, with about 4,000 new children diagnosed annually as candidates for this treatment. Boys are about two times more likely than girls to receive treatment for growth hormone deficiency.

The evaluation of medical need for treatment of pediatric GH deficiency can be facilitated using independent medical review by an independent review organization (IRO) that employs a vast network of physician reviewers and has easy access to pediatric endocrinologists and other specialists. These cases require an in-depth understanding of the clinical and laboratory findings of the condition and the available treatment options that only trained specialists can truly comprehend. In addition, this process is the key to identifying whether the treatment requested is actually medically necessary.

Introduction

Short stature is one of the most common concerns presenting to pediatric endocrinologists. The incidence of short stature associated with severe childhood growth hormone deficiency has been estimated in several studies to range between 1 per 4,000 to 1 per 10,000 live children. About 20,000 children per year receive GH therapy, with about 4,000 new children diagnosed annually as candidates for this treatment. Boys are about two times more likely than girls to receive treatment for GH deficiency.

Not all children who are short are GH deficient. Many children who are short have normal GH levels, grow at a normal rate, and will achieve an adult height similar to their biological parents. Other children have an illness or disease (e.g., diabetes, malabsorption, or hypothyroidism) that affects their size and growth rate, but they are not GH deficient.

Overview of Pediatric Growth Hormone

Growth hormone is one of several hormones produced by the pituitary gland. It promotes not only linear growth in children, but it also has important physiologic and metabolic effects in adults long after final height has been reached. When a child's pituitary gland is producing inadequate amounts of GH or none at all, the child is diagnosed as GH deficient. Sometimes it occurs by itself, but it can present with other pituitary hormone deficiencies.

There are many causes of GH deficiency, and these are typically classified as happening prior to birth (congenital) or after birth (acquired). When no cause can be found, which is often the case, the GH deficiency is classified as idiopathic. Children with congenital GH deficiency are born with the deficiency, which may not be obvious for several months. Causes of congenital GH deficiency include genetic abnormalities of the pituitary gland or the genes for GH production or GH-releasing hormone (GHRH) synthesis, congenital central malformations, and syndromes associated with midline defects and cleft palate.

Acquired GH deficiency becomes evident during childhood, resulting from damage to the pituitary caused by foot or breech delivery, brain tumor, cranial irradiation, head trauma, or infection.

Diagnosing Pediatric Growth Hormone Deficiency

Evaluation of Short Stature

The most apparent feature of GH deficiency is growth failure or growth retardation. Children with GH deficiency present with varying clinical characteristics, which depend on the underlying etiology and severity of the insufficiency. Please see Table 1 for a list of the typical clinical findings of a child with GH deficiency.

Table 1: 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

Evaluation for GH deficiency is generally performed when the child's growth has slowed and pubertal and skeletal growth appear delayed. If GH deficiency has been present for a long period of time, the child may be significantly shorter than other children the same age.

Since there is currently no diagnostic gold standard, the pediatric endocrinologist takes into account various clinical and laboratory findings (please see Table 2) rather than rely solely on the results of one particular test. A comprehensive assessment should include careful evaluation of the child's growth rate and velocity, family history of growth and height patterns, bone-age x-ray, and biochemical tests of growth hormone stimulation.

Table 2: 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

A number of conditions and disease states must be considered and ruled out in children presenting with short stature. Evaluation for GH deficiency in a short child should not be initiated until other causes of growth failure, such as hypothyroidism, chromosomal disorders (Prader-Willi syndrome, Turner syndrome), chronic systemic disease (renal failure, malabsorption), or skeletal disorders, have been excluded. The diagnosis of ISS is made when there is no evidence of pathology or syndromes, and it is based on marked short stature, greater than 3 standard deviations (SD) below the mean without evidence of other pathology. Some physicians consider less severe short stature of 2 to 3 SD below the mean as indicating a need for further evaluation.

Common Laboratory Tests

In addition to focusing on growth, laboratory tests should be performed to rule out other causes of disease, or the cause of GH deficiency should be verified (e.g., pituitary tumor). Common screening tests include 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, or provocative, tests. Stimulation testing for GH should be performed after other causes of growth failure have been ruled out. These tests measure the ability of the pituitary gland to release GH by measuring the level of GH 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 the release of GH include arginine, clonidine, glucagon, L-dopa, insulin, or GHRH. Although physicians commonly use the insulin stimulus tests, no test has both high sensitivity and specificity. False-positive responses occur in patients with normal pituitary function, as well as false-negative responses in pituitary deficient patients. Evaluation of GH deficiency should be based upon the results of two provocative tests because some children may not always respond to a single stimulant.

A diagnosis can be made based upon provocative tests in combination with current height and predicted adult height assessments. In general, a peak concentration of <5 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, and this value is commonly referenced as a cutoff indicating GH deficiency.

Random blood sampling to monitor GH levels is not reliable since GH is normally secreted in bursts, with very low levels seen during the day and six or seven spontaneous spikes most commonly occurring during deep sleep.

Imaging Studies

A bone-age x-ray of the child's left hand is done to determine the maturity of the child's bones, which may be different from the child's chronological age. In some short children, the maturity of the bones lags behind the child's actual age. Bone age may be useful in determining a short child's growth potential. For example, a 9-year-old boy who has a bone age of 7 years may have about 2 years more growth potential, or room to grow, than the average 9 year old.

Patients diagnosed with GH deficiency should undergo magnetic resonance imaging (MRI) of the head in order to visualize 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, with the exception of those with genetic causes.

Treatment and Follow-Up

Pediatric Indications for GH Therapy

Growth hormone is available as a subcutaneous injection. Please see Table 3 for the pediatric indications for recombinant human GH approved by the U.S. Food and Drug Administration (FDA).

Table 3: 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 (TS), and Prader-Willi syndrome (PWS)
- ▶ 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 idiopathic short stature (ISS) who are >2.25 SD below the mean in height and who are unlikely to catch up in height

Consideration for treatment should occur only after accurate diagnosis, careful monitoring of growth velocity, and estimation of final height by a pediatric endocrinologist. Use of GH therapy for the ISS indication remains controversial, partly due to the variability in reported height improvement, but also due to poorly defined measures of therapeutic success, and debate about whether the goal of treatment should be simply a normal height or a 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. Increases in height and height velocity are the most important indicators of response to GH. For comparative purposes, data should be expressed as the increase in height SD score for age and sex.

Adequate response to childhood GH therapy is shown by an increase in linear growth velocity within the first 6 months. It may be helpful to have an accurate pretreatment growth velocity with which to compare the response. 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.

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. Growth hormone deficiency may or may not persist into adulthood. Growth hormone has major metabolic functions that are important for body composition and health in adults, as well as children. If GH deficiency persists to adulthood, continuation of GH therapy is recommended in order to optimize the metabolic effects of GH.

Role of Independent Medical Review in Determining Medical Necessity for Treatment of Pediatric Growth Hormone Deficiency

Health plans require physician documentation that establishes the medical necessity for treatment of GH deficiency. In many cases, requests for coverage of GH therapy are incomplete and missing critical data. Necessary data include the 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 should also be provided to the payer if that is a factor in the physician's decision to prescribe GH therapy.

Most children who are short are healthy and normal. However, some children will have age-appropriate growth that diminishes over time, possibly indicating a pituitary problem affecting GH production or secretion.

Continual research findings that suggest the benefits of GH therapy often complicate the process of establishing evidence-based criteria for practice guidelines and reimbursement for GH therapy. Independent review organizations (IROs) that conduct independent medical reviews, which are normally used by healthcare payers, employ specialists who can look at whether or not therapy was medically necessary.

The board-certified physician specialists who work with IROs keep up-to-date with the latest medical research literature and with the latest standard of care. These specialists allow healthcare plans to make sure that the requested treatment falls under the medical necessity requirements before approving a course of treatment.

Physicians who review cases for IROs stay on top of treatments as they are studied more extensively and potentially accepted into clinical guidelines.

The specialty-match reviews that IROs provide is 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. An IRO can also avoid conflicts of interest, which can relate to economics, lack of specialists to review cases, or having the same doctor who denied a case review an appeal.

Conclusions

Most children who are short are healthy and normal. However, some children will have age-appropriate growth that diminishes over time, possibly indicating a pituitary problem affecting GH production or secretion. 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.

By providing unbiased evaluation of medical need for the treatment of pediatric GH deficiency, independent medical review facilitates effective treatment of the condition, which, if not properly treated, can lead to decreased bone mass, delayed puberty, and psychological distress. An IRO can also provide ready access to specialists, which healthcare plans may lack internally, allowing for timely determination of whether the requested treatment falls under medical necessity guidelines.

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