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# Diagnosis of Growth Hormone Deficiency in Childhood

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## Abstract

**Purpose of Review—**The diagnosis of growth hormone deficiency (GHD) in childhood is challenging, in large part due to the lack of a true gold standard and the relatively poor performance of available diagnostic testing. This review discusses recent literature on this topic.

**Recent Findings—**Auxology and clinical judgment remain the foundation for the diagnosis of GHD. Provocative GH testing is poorly reproducible, dependent on factors such as body composition and pubertal status, and further limited by significant variability among commercially available GH assays. Measurement of IGF-I and IGFBP-3 is not diagnostically useful in isolation but is helpful in combination with other diagnostic measures. Neuroimaging is also useful to inform diagnosis, as pituitary abnormalities suggest a higher likelihood of GHD persisting into adulthood. Although genetic testing is not routinely performed in the diagnosis of GHD at the present time, multiple recent reports raise the possibility that it may play a more important role in diagnosing GHD in the future.

**Summary—**Beyond physicians' integrated assessment of auxology, clinical presentation, and bone age, current tools to diagnose GHD are sub-optimal. Recent literature emphasizes the need to reappraise our current practice and to consider new tools for diagnosis.

### Keywords

Growth hormone; growth hormone deficiency; IGF-I; IGFBP-3

## Introduction

Short stature, occurring by definition in 2.5% of children, is a common reason for pediatric endocrine evaluation. For cases in which other diagnoses – including genetic short stature, constitutional delay of growth and puberty, hypothyroidism, Turner syndrome, and chronic disease such as celiac disease – are excluded, the question of growth hormone deficiency (GHD) inevitably arises. The prevalence of GHD is estimated at approximately 1:4,000 to 1:10,000 (1–4). The diagnosis of GHD in conjunction with other pituitary deficiencies (i.e., multiple pituitary hormone deficiency, MPHD) and/or organic pathologies such as central nervous system (CNS) tumor is generally straightforward. The present review will focus on diagnosis of isolated GHD (iGHD), which can be significantly more challenging.

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Tools for the diagnosis of GHD include auxology, radiographic assessment of bone age, measurement of insulin-like growth factor 1 (IGF-I) and IGF binding protein 3 (IGFBP-3), provocative growth hormone (GH) testing, cranial magnetic resonance imaging (MRI), and, in certain cases, genetic testing. Growth velocity and the degree of short stature are primary considerations in the decision to pursue evaluation for GHD, as emphasized by the criteria for diagnostic assessment recommended by the Consensus Guidelines for the Diagnosis and Treatment of GHD in Childhood and Adolescence from the 2000 meeting of the GH Research Society (Table 1) (5). Given the difficulties with GH provocative tests and IGF-I and IGFBP-3 measurements discussed below, the clinicians' integrated assessment of history and physical examination, stature, growth velocity, and bone age is the most reliable element in the diagnosis of GHD. This review discusses recent literature regarding subsequent steps in diagnosis, including provocative GH testing, measurement of IGF-I and IGFBP-3, cranial MRI, and genetic testing.

## Provocative Growth Hormone Testing

Rightly or not, provocative GH testing continues to play a primary role in the diagnosis of GHD. The various stimuli and methods employed in GH testing have been reviewed in detail elsewhere (6, 7). Provocative tests are invasive, are typically 2–4 hours in length, and have potential risks and side effects. The most common provocative agents include insulin, glucagon, clonidine, arginine, and L-dopa. Growth hormone releasing hormone (GHRH) is not commonly used in early childhood due to the concern that children with hypothalamic disorders may falsely "pass" GHRH testing. The use of GHRP-2 as a novel provocative agent with minimal side effects has recently been explored (8), but extensive additional testing would be needed before clinical use.

Provocative GH testing remains the subject of much controversy, and there are significant issues concerning the validity and reproducibility of GH testing. Perhaps most obviously, the cut-off used to define GH deficiency is arbitrary. A peak stimulated GH of less than 10mcg/L is the usual cut-off for GH deficiency in children in the United States, whereas some countries employ cut-offs as low as 6mcg/L and, historically, cut-offs as low as 3mcg/L were used before the introduction of recombinant human GH. Although it is well-established that peak GH may vary according to the stimulus given (9, 10) and the assay employed for measurement (11**), a uniform cut-off value is generally used regardless of stimulus or assay. Moreover, although multiple groups have demonstrated that normal pre-pubertal children may falsely "fail" GH testing (12, 13), there is no consensus as yet regarding sex steroid priming for GH testing. Further, GH stimulation tests are non-physiologic, and results may depend on the pattern of GH secretion occurring immediately prior to the administration of stimulus (14). Peak GH responses are also highly dependent on both short-term nutritional status (15) and on BMI (16, 17*), with higher peak GH levels after short-term fasting and in those with lower BMI.

Multiple studies have also demonstrated that provocative GH tests are poorly reproducible. Lee et al. recently reported correlations between peak GH to various stimuli (clonidine, insulin, dopamine) in children with idiopathic short stature (ISS) who underwent identical stimulation testing on two occasions separated by a month (17*). They report that peak GH on the first and second occasions were not significantly correlated with each other for any of the stimuli (17*). Loche et al. report similarly poor reproducibility, as 28 of 33 (85%) children who had initially failed two provocative GH tests passed a third test performed 1–6 months later (18). Given this lack of reproducibility over a short-term period, it is not surprising that, upon re-testing in early adulthood, approximately half of individuals who were treated for iGHD during childhood no longer demonstrate GHD (19).

Variability of GH assays, recently reviewed by Bidlingmaier and Freda (20*), adds to the difficulty of interpreting GH stimulation testing. GH circulates in several isoforms, primarily a 22 kD molecule and a less prevalent 20 kD molecule, as well as hetero- and homodimers and multimers, and assay results vary considerably depending on reactivity with various isoforms (20*). An important recent contribution to the literature with respect to GH assays comes from Muller et al., who tested sera from 312 children to determine growth hormone values using 7 different commercial assays and 1 “in-house” assay (11**). Single samples varied by as much as 11.4mcg/L in different assays, and the means for assays also differed significantly, with the highest mean (5.44mcg/L, Immulite), exceeding the lowest mean (2.67mcg/L, BC-IRMA) by more than two-fold (11**). The between-assay coefficient of variation was 24.3±7.4%, and the diagnosis of GHD was dependent on the assay used in 27% of patients (11**).

Given the myriad concerns with provocative GH testing, some have suggested that provocative testing should not play a role in diagnosis (21), or that it should not be obligatory for cases in which the diagnosis is clear based on growth measures (22). At minimum, discussion and attempt at consensus are needed regarding optimal provocative stimuli, appropriate cut-off levels specific to GH assay and other factors such as BMI and pubertal status, utility of sex steroid priming, and standardization of testing protocols to minimize risk and discomfort while maximizing diagnostic sensitivity and specificity. In addition, use of other diagnostic tests, including IGF-I, IGFBP-3, cranial MRI and genetic testing, should be explored further for their potential to supplement or supplant provocative GH testing.

## Measurement of IGF-I and IGFBP-3

Both IGF-I and IGFBP-3 are reflective of circulating GH, and, in contrast to GH, both vary relatively little through the course of the day and thus can be measured easily as a screening test for GHD. IGFBP-3 may be acutely influenced by meal intake (23*), however, and IGF-I is influenced by chronic nutritional status, with lower values in states of poor nutrition. Age- and/or pubertal-stage-specific norms are needed to interpret both IGF-I and IGFBP-3, and norms for IGF-I are also gender-specific.

In young children, for whom IGF-I values are normally low, utility of IGF-I measurement is further limited by the sensitivity of the assay. In addition, numerous IGF-I assay issues, recently reviewed in detail by Frystyk et al. (23*), affect the accuracy of measurement. The majority of IGF-I circulates in a ternary complex with IGFBP-3 and acid labile subunit (ALS) or in binary complexes with IGFBP-3 or other IGF binding proteins (IGFBPs). IGFBPs interfere with both competitive and noncompetitive assays and are conventionally removed and/or inactivated prior to assay, such that the assay measures total rather than free IGF-I. Removal is often incomplete, however, and residual IGFBPs may considerably affect the IGF-I result, particularly in patients for whom IGFBPs are disproportionately elevated compared to IGF-I such as those with renal failure or type 1 diabetes (23*). Another issue is short-term within-subject variability of measurement, which, though considerably lower than inter-subject variability, may be as high as 20% (23*, 24). Of note, short-term within-subject variability of IGFBP-3 appears to be smaller than that of IGF-I, approximately 11% (24). Finally, although there is a standard preparation for calibration of IGF-I assays, considerable variation exists among different commercial assays (23*).

In spite of these issues, literature suggests that IGF-I and IGFBP-3 are useful in the diagnosis of GHD. An obvious difficulty in determining the diagnostic performance of any test for GHD is the lack of a gold standard to determine true GHD; thus, reports regarding the sensitivity and specificity of IGF-I and IGFBP-3 are not consistent. In general, however,

both IGF-I and IGFBP-3 are reported to have good specificity but relatively poor sensitivity for GHD (25, 26). Although these measures are not useful in isolation (27), they can be helpful when combined with other diagnostic measures with higher sensitivity. For instance, Cianfarani et al. combined IGF-I measurement with assessment of growth velocity (GV), which is sensitive but not highly specific for GHD, to achieve excellent specificity and sensitivity in those cases in which IGF-I and GV are concordant (i.e., both low or both normal) (26). Another advantage of IGF-I and IGFBP-3 is that they show superior reproducibility in comparison to stimulated GH levels (17*).

Another possible measure for diagnosis of GHD was proposed recently by Varewijck et al., who report on the utility of a kinase receptor activation assay to determine IGF-I bioactivity (28*). This assay does not require that IGFBPs be removed or inhibited prior to analysis. In 94 adult patients with GHD, either naïve to GH treatment or withdrawn from treatment for at least 4 weeks, the authors report that only 63.8% of patients had total IGF-I values below the 5$^{th}$ percentile, whereas 81.9% had IGF-I bioactivity below the 5$^{th}$ percentile, suggesting better diagnostic performance (28*). Although the study population was entirely adult, and the authors report a lower sensitivity of IGF-I bioactivity for those less than 40 years of age (28*), this and other assays to quantify bioactive IGF-I may hold promise as a future diagnostic strategy for GHD in childhood.

## Neuroimaging

In children with relatively high suspicion for GHD based on presentation, auxology, and laboratory findings, cranial MRI can contribute significantly to diagnosis. Coutant et al. demonstrated that, among patients diagnosed with GHD in childhood, those with MRI abnormalities had more severe short stature at diagnosis, younger age of diagnosis, and significantly greater catch-up growth in response to GH treatment compared to those with GHD but normal pituitary MRIs (29). Upon re-evaluation of growth hormone secretory status in adulthood, none of the individuals with abnormal MRI had peak GH response > 10mcg/L, whereas 63% of those with normal MRI had normalized GH secretion (29). Maghnie et al. have reported similar findings with respect to MRI abnormalities predicting persistence of GHD into adulthood (30). In their series of 35 young adults with GHD diagnosed in childhood, none of the patients with MRI abnormalities normalized GH secretion in adulthood, whereas all of 18 patients with iGHD and normal pituitary or small pituitary volume noted on MRI had normal GH secretion on retesting (30). Pituitary abnormalities on MRI of patients with iGHD have also been shown to predict development of additional hormonal deficiencies (30, 31). Jagtap et al. have recently added to this literature, showing that, in 103 children with congenital GHD, MRI was abnormal in 48.6% of patients with iGHD compared to 93.5% of patients with MPHD (32*). In this cohort, children with severe GHD (peak GH <3mcg/L) were far more likely to have MRI abnormalities than those with peak GH >3mcg/L(32*). Further, 2 children with iGHD and abnormal MRI developed other pituitary hormone deficits whereas no children with normal MRI had evolution of their presentation (32*). Taken together, these studies illustrate that children with GHD and abnormal MRI are more likely to have persistent GHD into adulthood and require close follow-up for the development of other pituitary deficiencies, whereas those with iGHD and normal MRI may demonstrate normal growth hormone secretion in young adulthood. It is unclear whether normalization of GH secretion in a large percentage of iGHD patients indicates that these individuals were misdiagnosed as having GHD in childhood, or rather if they may have had a partial or transient form of GHD. Further investigation using normal MRI results to guide re-testing in childhood would be helpful to answer this question.

It is important to note that some iGHD patients with MRI abnormalities have normal GH secretion when tested in adulthood (33), such that abnormal pituitary findings do not necessarily preclude the need for reassessment in the transition to adulthood. The 2011 Endocrine Society Clinical Practice Guideline for Evaluation and Treatment of Adult GHD recommends that individuals with iGHD undergo retesting with provocative stimuli, even in the presence of abnormal MRI, whereas, in individuals with MPHD and abnormal MRI, a low IGF-I at least one month after withdrawal from exogenous GH is sufficient to confirm the diagnosis of GHD (34**).

## Genetic Testing

Although genetic testing is not performed routinely in the diagnosis of GHD, numerous mutations leading to iGHD have been identified, and genetic screening may play a larger role in diagnostic algorithms in the coming years. Autosomal recessive, autosomal dominant, and X-linked recessive forms of iGHD have been described (Types I, II, and III, respectively), and multiple different mutations in the growth hormone 1 (GH1) and GHRH receptor (GHRHR) genes have been identified (35*, 36). Additionally, mutations in PROP1, POU1F1, HESX1, and other pituitary transcription factors may underlie MPHD, of which GHD may be the first manifestation (37). Wit et al. have recently provided an excellent review of genetic testing in short stature in which they recommend testing for GH1 and GHRHR mutations in children with severe iGHD and a family history of GHD (35*). In a cohort of 224 children and adults with iGHD, Alatzoglou et al. recently found mutations in GH1 or GHRHR in 11.1% of total cases (7.4% with GH1 mutations and 3.7% with GHRHR mutations) and in 38.6% of familial cases (38). The presence of mutations was not associated with specific MRI findings but was associated with a more significant degree of short stature compared to individuals without identified mutations. Cohorts with iGHD have also been screened for mutations in the GHRH gene itself, but no GHRH mutations have been identified as yet as contributors to iGHD (39).

In addition to mutations in GH1 and GHRHR, Gorbenko Del Blanco et al. recently identified a heterozygous deletion in the high mobility group A2 (HMGA2) gene, which encodes a transcription factor, in one of 105 patients with iGHD (40*). The patient with HMGA2 mutation had severe short stature, low IGF-I, abnormal response to provocative GH testing, and abnormal MRI, and responded well to growth hormone therapy (40*). Although functional studies were not definitive regarding the pathogenic mechanism of the mutation, the importance of the HMGA2 gene in growth has also recently been described through study of patients with 12q14 microdeletion syndrome, which is characterized by developmental delay, severe short stature, and abnormal facies (41). Lynch et al. recently demonstrated that children with 12q14 microdeletion in which the deletion includes the HMGA2 gene have extreme short stature, whereas children whose deletion ends prior to HMGA2, leaving HMGA2 intact, have only a mild degree of short stature (41). Further investigation is needed to determine the prevalence of HMGA2 mutations in children with iGHD and to elucidate mechanisms by which the HMGA2 gene product contributes to iGHD.

Of note, mutations in the active isoform of the growth hormone secretagogue receptor gene (GHSR1A) causing loss of constitutive activity of the receptor have also been identified in children with short stature (42). Inoue et al. recently assessed 127 children diagnosed with ISS or iGHD compared to 188 controls and found mutations in GHSR1A in 4.7% of patients compared to 0.5% of controls (43*). GH dynamics in children with GHSR1A mutation have not yet been described, and it is unclear if these individuals would respond to exogenous GH. With further investigation, however, mutational analysis of GHSR1A may be a useful tool in the future for children with familial short stature.

Testing for a polymorphism in the IGFBP-3 gene may also aid in diagnosis of GHD and prediction of response to therapy. An A to C change 202 basepairs upstream of the transcription start site (−202A/C) is a common polymorphism, with the A allele having higher promoter activity such that mean IGFBP-3 levels are highest in individuals with the AA genotype (44). In a cohort of 71 children treated for GHD, Costalonga et al. demonstrated that children homozygous for the A allele had higher IGFBP-3 levels and better response to growth hormone as measured by increased growth velocity compared to children with AC or CC genotype (45). Additionally, Domene et al. have recently shown that the diagnostic sensitivity and specificity of IGFBP-3 levels are significantly improved when genotype-specific normal ranges are used (46).

Screening for GH1 and GHRHR mutations is currently best reserved for children with family history of short stature or iGHD, and the relevance of other mutations described above to clinical practice is not yet clear. However, advances in our understanding of genetic contributions to iGHD and the use of genotyping to refine reference ranges and predict response to therapy open the possibility for a more rational approach to the diagnosis and management of iGHD.

## Conclusion

The diagnosis of GHD remains difficult, and recent literature largely serves to reiterate the unsatisfactory nature of our current diagnostic process. Literature continues to highlight the flaws in provocative GH testing, and such testing must be carefully interpreted in light of assay issues, lack of reproducibility, and variability according to type of stimulus, body composition, and pubertal status. Clinical assessment and auxology should be the basis for evaluation and diagnosis of GHD (22). Gascoin-Lachambre et al. have recently demonstrated that use of the auxological criteria proposed by the Growth Hormone Research Society (Table 1) (5) would reduce delay of diagnosis in children with pituitary stalk interruption syndrome (47), and use of these criteria may also prevent unnecessary testing and subsequent misdiagnosis in children without firm auxologic evidence of GHD. To supplement auxology and clinical assessment, IGF-I, IGFBP-3, provocative testing, and cranial MRI, remain the primary tools available in diagnosing GHD, whereas the continued evolution of genetic testing will hopefully provide more rational tools for the future.

### Key Points

- Clinical presentation and auxology are the most important factors in the diagnosis of GHD.
- The results of provocative GH testing are dependent on the assay used, the pubertal and nutritional status of the child, and the GH secretion pattern prior to testing. These tests are poorly reproducible.
- Although there is considerable overlap between IGF-I and IGFBP-3 values in children with GHD compared to normal children, these measures have reasonable specificity and are useful in conjunction with other diagnostic criteria.
- Abnormal findings on pituitary MRI indicate a relatively high likelihood that GHD will persist into adulthood and may suggest that subsequent pituitary deficiencies may develop.

- Children with iGHD and family history of GHD should have screening for GH1 and GHRHR mutations. Other genetic testing is not yet widely applicable in the diagnosis of GHD but may contribute to the diagnosis in the future.

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**Table 1**

Consensus Statement Criteria to Initiate Evaluation for GHD

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|---|
| 1. “Severe” short stature (height < −3 SD below mean) |
| 2. Height < −1.5 SD below mid-parental height |
| 3. Height < −2 SD below mean AND either height velocity < −1 SD below mean over past year or decrease in height SD of more than 0.5 SD over past year |
| 4. In the absence of short stature, height velocity < −2 SD below mean over 1 year OR < −1.5 SD below mean over 2 years |
| 5. Signs of an intracranial lesion |
| 6. Signs of multiple pituitary hormone deficiency |
| 7. Neonatal signs and symptoms of GHD, including hypoglycemia, prolonged jaundice, microphallus, or craniofacial midline abnormalities |

SD: Standard Deviation

From the Consensus Guidelines for the Diagnosis and Treatment of Growth Hormone Deficiency in Childhood and Adolescense: Summary Statement of the GH Research Society (5)