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Review of Childhood-Onset Growth Hormone Deficiency: Diagnosis, Management, Monitoring, and Predictors for Persistence into Adulthood

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ABSTRACT

Background: Idiopathic growth hormone deficiency (IGHD) in childhood is a significant clinical condition, primarily characterized by growth failure and short stature (SS). It may also be associated with metabolic disturbances and cognitive dysfunction. Growth hormone replacement therapy (GHRT) plays a crucial role in management. Diagnosis typically involves a combination of clinical assessment, laboratory testing, and often brain imaging. Patient response to growth hormone stimulation test (GHST) varies, with lacking consensus on specific cut-off value.

Objective: This study aimed to review the best practices and current guidelines for the diagnosis of IGHD, with a focus on GHST cut-off values at different time periods including during transition period, and the role of IGF-1, IGFBP, and brain imaging in diagnosis and follow-up.

Methods: An electronic search was conducted using the Cochrane Library, Embase, Medline, and NHS websites esp., in the last 5 years for RCT, cohort, and case control studies and meticulous reviews to identify Pediatric Endocrine Society guidelines, consensus statements, and relevant English-language publications. Extracted data included patient demographics, epidemiology, clinical features, laboratory cut-off values, types of growth hormone replacement therapy (GHRT), indications for brain imaging, and predictors of persistent growth hormone deficiency into adulthood.

Results: long-term GHRT is required if persistent GHD evident by GHST with cut-off value appropriate for adolescent transition plus or minus ILGF-1 and MRI pituitary criteria. Adherence issues prompt trials of sustained-release preparations.

Conclusion: This review offers insights into GHD diagnosis, GHST cut-offs, clinical and laboratory monitoring, brain imaging, transition assessment with its predictors.

Keywords: short stature, transition, growth hormone deficiency.

INTRODUCTION

Growth hormone deficiency (GHD) is a clinical syndrome presented mainly with SS that is height-for-age curve deviated down across 2 major Height (Ht) percentile curves, multiple cognitive, and behavioral problems. The incidence of GHD is 1/30,000 in childhood while it is 1.2/100,000 in adulthood (1, 2, 3). Short stature may result from non-pathological causes, which are the most common and include familial SS, constitutional GF and idiopathic short stature (ISS). The later has normal results of GHST. Some ISS cases have pathologic cause that wasn't diagnosed during a standard evaluation. They are candidates for GHRT (3, 4, 5).

There is wide range of clinical presentation of GHD ranging from mild to severe GHD and severe growth hormone resistance (GHR). Diagnosis of GHD is challenging that needs combination of clinical, laboratory by GHST+/- ILGF-1 level and Magnetic resonance imaging (MRI) for brain and hypothalamo-pituitary area. Different cut-off value is considered for GHST as per age and the used stimulation method for growth hormone (GH) (3, 6, 7, 8). There is lack of consensus about tailored guidelines for diagnosis, therapeutic indications and monitoring of GHRT. In this review article, we provide a global overview of the diagnosis of GHD in children and predictors of adolescence transition. We are also discussing the indications of GHRT, and monitoring of the response.

Physiology of Growth hormone and Insulin like growth factor -1:

Normal random GH level is 5-40 ng/mL in newborns and 0-20 ng/mL in children. Its secretion peaks after an hour from deep sleep onset and decreases from maximum 150 mcg/kg during puberty to 25mcg/kg in elderly. This is could be attributed to decrease in body mass index (BMI). Secretion of GH is pulsatile and in between pulses can only be detected by ultrasensitive measures (1, 2, 5, 9).

Insulin-like growth factor-1:

It is a critical protein induced by GH. It acts as growth and differentiating factor that directly inhibits GH secretion, and GH receptor (Rc) function by a negative feedback regulation loop. It is produced by local synthesis in many tissues as the central nervous system (CNS) Erythroid cell precursors, peripheral tissues and liver. Growth hormone stimulates sulfate uptake by cartilage in vivo and GHRT stimulate it in vitro through IGF-1(1, 3, 6).

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***Insulin like growth factor binding proteins*:**

More than 99% of plasma Insulin-like growth factor-1 is bounded to high affinity Insulin like growth factor binding proteins (IGFBP) from 1-6, which share a similar high-affinity structure. They act as intermediate for GH function (mainly IGFBP-3) and control ILGF-1 reaction to ILGF-1 Rc. Blood levels of IGFBP-3 varies by age, sex, BMI and puberty. They transport IGF to the extravascular space, facilitating their localization and distribution in target tissues (1, 3, 6). Under the influence of GH, osteoblasts and chondrocytes increase IGF-1 production which regulates linear growth. IGF-1 induces differentiation of chondrocytes, skeletal myoblasts, vascular endothelium, cardiomyocytes and neural cells. This differentiation response is modulated by IGFBPs. Laron dwarfism (another name for GHR) is associated with normal or high serum GH, low serum IGHBP and low IGF-1 level (1, 5, 10).

Diagnosis of growth hormone deficiency

Recent studies clinically define GHD when Ht is less than -3 SDS from the mean Ht of the same age and sex or Ht ≤ -2 SDS plus growth velocity (GV) /year ≤ -1.0 SDS, during at least 6 months duration, or decrease in Ht of 0.5 SDS/year in children older than two years. Another definition is Ht ≤ -1.5 SDS compared to the genetic target plus GV/year ≤ -2 SDS or ≤ -1.5 SDS in 2 consecutive years (1, 11, 12). In the absence of SS and after exclusion of other pathological causes for growth deficiency, GHD can be identified clinically when only GV/year ≤ -2 SDS or ≤ -1.5 SDS after two consecutive years (1, 2, 12). Hypothalamic-pituitary lesions evident by neuro-radiological imaging can alone define GHD (1, 2, 8).

Growth hormone deficiency is diagnosed biochemically using various GHSTs. Commonly used agents include the insulin tolerance (ITT), levodopa, GHRH using growth hormone-releasing peptide 6 (GHRP-6), glucagon, and clonidine (1, 7, 11). However, stimulation test cut-off still a matter of debate. Some studies have set it at 7-10μg/L at 2GHST(1, 13, 14). The recent tests use more specific monoclonal antibody against GH in serum allowing modification of cut-off value from 10 to 7 μg/L (1, 12, 13). Another study suggested cut-off value for GHD as 8 μg/L except with GHRH+ arginine, cut off value is 20 μg/L (11). Disadvantages of GHST in young children old are low specificity, non-reproducibility and high false pathological responses (1, 11, 13). It is contraindicated to be used in < 2years old due to safety concern (2, 7, 12).

Another matter of debate is that GHST results are normal in children with genetically confirmed isolated GHD due to mutations in the GH-1 gene (1, 2, 7). Some recent studies define short children with abnormal GHST result, without definite radiological or genetic diagnosis of GHD, as short stature unresponsive to stimulation tests (SUS) (1, 2, 12). Most studies advocate combining ILGF-1 assessment, together with the results of GHST and clinical characters. ILGF-1 values ranging from 0 to -2 SDS from the mean for age and sex to diagnose GHD (1, 2, 11, 12, 15). For children below 3 years old, measurement of IGFBP-3 can add diagnostic value esp., in cases of resistance or insensitivity to either GH or ILGF-1 (1, 11, 15).

We advocate the following diagnostic guidelines for GHD:

1) We generally recommend a cut-off value for GHST <7 μg/L for GHD diagnosis in children, in association with the auxological clinical criteria esp. that correlate with their target Ht (+/- IGF-1 and IGFBP-3), pituitary and hypothalamic imaging and genetic testing (if indicated) (1, 2, 12).
2) Acquired GHD (due to intracranial tumors, radiotherapy or trauma) doesn't require GHST for diagnosis (2, 7,12).
3) Newborns with multiple pituitary hormone deficiencies (MPHD) or with any of the following: pituitary hypoplasia, ectopic posterior pituitary (EPP) or abnormal pituitary stalk are diagnosed as GHD by GH conc. ≤5ng/mL (2, 5, 7).
4) Indication of genetic testing including chromosomal abnormalities: suspected Turner, short men with genital abnormalities, congenital hypopituitarism, positive family history, early onset of GF, Ht more than 3SDS below the mean for age and sex, extremely low GH in GHST, very low IGF-1 & IGFBP-3 conc. MRI brain and GHST may be normal in most common mutations in GH1 and GHRHR genes (1, 11, 14).

Recombinant growth hormone therapy

It is the main stay and safe therapy for children and adult with GHD. It is indicated for GHD in: short children with open epiphyses, esp., at younger age, IGF-1 less than 1st percentile for age/sex with GH peak value in GHST less than 7-10 μg/L. For cases of ISS, SUS, SGA if didn't achieve catch-up growth, CKD, Noonan syndrome, Prader-Willi syndrome, Turner syndrome and for newborn with hypoglycemia due to GHD (mostly will be complete sever GHD type) in order to prevent further hypoglycemia, and mutations in the SHOX gene (2, 10, 12, 16, 17, 18).

Most children with GHD are treated with subcutaneous (SC) biosynthetic recombinant human growth hormone (rhGH). Several commercial brands are available in multi-dose pen devices, which facilitate ease of administration. Sustained release (SR) formulations of rhGH are administered SC once weekly or biweekly. Long-acting preparations are suitable more for children who are: poorly compliant as teenagers, very young,

frequent travelers or living in many homes, transitioning to self-injection, much scared from needle, neurological or behavioral disorders, receiving multi- injection as insulin, or receiving multiple medications to avoid drug-drug interaction (19, 20, 21). Lonapegsomatropin, somatrogon and somapacitan are SR preparations given once per week and are as safe as daily injection. They give the same or even higher linear response to ILGF-1 that can be measured to adjust their dose (1, 19, 20).

Dose of GH is between 16-24 mic/kg/week. Doses up to 30mic/kg/week are approved by FDA. Patients with severe GHD are started on lower dose of nearly 20mic/kg/week because they have excellent growth responses at this dose. Dose can be adjusted based on either body weight, surface area, growth response, occurrence of side effects or IGF-I conc. (18, 20, 22)

Insulin like growth factor-1 therapy:

The co-administration of IGFBP-3 with IGF-1, enhances bone mineral density (BMD) and promote linear growth more effectively than IGF-1 administration alone. Indications for Insulin like growth factor-1 therapy include: GH insensitivity (GH-Rc mutations), Ht <-3 SDS with normal to elevated conc. of GH, IGF-1 level <-3 SD with normal to elevated conc. of GH, Ht <2.5SD plus low serum IGF-1. It stimulates whole body protein synthesis, and inhibit proteolysis esp. by coadministration with GH (1, 6, 11).

Monitoring of the therapy:

The 75th percentile curve for HV is an appropriate target to define an adequate growth response to GH, in the initial "catch-up" growth period (1, 6, 12). Monitoring also by IGF-1 and IGFBP3 as they are more stable in serum. One measurement of any of them is better than one GH measurement without GHST. However, It is still not fully advised by PES due to absence of data about adult Ht outcomes (1, 6, 11,15).

We measure ILGF-1, 4weeks after beginning GHRT or any dose adjustment, aiming to keep the target ILGF-1 between +0 to +2 SDS. If the result is below the target, GH dose will be increased by 10-20%. If the IGF-I level is >+2 SD, to decrease the dose by 10-20 % for the safety issue as per PES recommendation (1, 6, 12, 19). After 4-6 months of GHRT, the growth response is more appropriate index of improvement than IGF-I levels. If IGF-I levels are in the target range, Ht will be checked /4-6months (or/ 2-3months in infants) then HV will be calculated, compared with curves of normal HV for age in children without GHD (6, 15, 23). Targeting serum IGF-I to +0 SDS is shown to be better dose-sparing than targeting weight-based dose adjustment and has yielded better Ht response (1, 3, 24). So, we recommend ILGF-1 level not to exceeds +2 SDS for safety and cost issues.

In patients with MPHD: it is essential to reassess free T4 (as central hypothyroidism may not be detected through TSH screening alone). Serum cortisol should be re-evaluated between 8:00 and 9:00 AM, a few months after initiating GHRT, and monitored periodically thereafter (1, 13, 23). Several factors may contribute to a reduced response to GHRT. These include incorrect diagnosis, development of hypothyroidism in MPHD, inadequate dosing, associated malnutritional states, development of neutralizing antibodies which are diagnosed by serum antibodies levels, and are treated by ILGF-1 preparation (1, 15, 23).

During puberty

Dose is temporarily increased (to 70-100mic/kg/week). This approach is still debatable due to its safety and efficacy (3, 9, 25). In many systematic reviews concluded that GHRT promote earlier age of puberty as in ISS but not in SGA, chronic renal failure or Turner patients which are sometimes resistant cases that requires higher GH doses in puberty to promote adequate adult Ht. GHRT is continued at least until linear growth decreases to < 2.0-2.5cm/year (HV <1cm/year) (3, 9, 26). Patients then should be retested for GHD during transition period to decide if GHRT to be continued into adulthood for metabolic indications (15, 23, 27). The cut-off value for GHST is lower in adulthood (< 3 μg/l) than in transitional state (4-6 μg/l) than in childhood (<7 μg /l) (9, 27, 28).

Effects of Growth Hormone Replacement Therapy (GHRT):

The GH / IGF-1 axis integrity is important in the signaling pathway in neurogenesis and brain development. Growth hormone replacement therapy has demonstrated positive effects on body composition, physical performance, and quality of life (QoL). In adults, it has also been shown to improve certain surrogate cardiovascular markers (1, 4, 15). Development of diffusion tensor imaging (DTI) and volumetric MRI has allowed examination of brain white matter (WM) structure, estimation of the volumes and possibly the function of different brain areas. In individuals with IGHD, neuroimaging has revealed WM abnormalities in the corpus callosum and corticospinal tracts, along with reduced volumes of the thalamus and globus pallidus. These structural changes have been associated with cognitive deficits, learning difficulties in the spelling, reading, arithmetic domains and impaired motor performance (8, 29, 30, 31).

Several recent studies have documented the effect of GHD and decreased IGF-1 level on different brain areas. These studies have shown that improvement on GHRT and ILGF-1 levels were strongly correlated with the left thalamus, left pallidum, and right putamen volumes (24, 29, 30, 31).

Correlation of the severity of GHD with MRI brain abnormalities:

Several studies have showed that IGHD patients with pituitary abnormalities can easily progress to MPHD at follow-up than IGHD patients without pituitary abnormalities. Children diagnosed as IGHD with pituitary abnormalities had better GHRT response than IGHD children who didn't have MRI abnormalities. Pathogenic MRIs were uncommon in patients diagnosed with GHD except with peak GH<3ng/mL (1, 8, 32, 33).

Mild brain abnormalities with GHD are less likely to be associated with MPHD. Severe Mid brain abnormalities with GHD (including optic nerve abnormalities, septo-optic dysplasia, and abnormal corpus callosum (CC) are more likely associated with MPHD (29, 32 33). The MPHD group of patients showed a higher percentage of sellar & parasellar abnormalities and PSIS than the IGHD patients (5, 8, 32).

We recommend the following indications for MRI brain in GHD patients:

1. Recommendation of the growth hormone research society (GRS) to do MRI on hypothalamic-pituitary region for any child with GHD at diagnosis and for newborns with midline defects and hypoglycemia (1, 11, 29, 33, 34).
2. Mostly no need for imaging for mild GHD, but rather it should be performed in severe GHD, MPHD, intractable headaches, or visual problems (1, 33, 34).
3. Diagnosis of GHD and MPHD (≥ 2 hormonal deficiencies), or neurological disorders, plus abnormal brain MRI can diagnose GHD without need for GHSTs (1, 32, 34).
4. Brain MRI is suggested as first-line in children <4years to allow earlier start of GHRT (1, 32, 34).
5. The primary aim is to identify brain tumors and secondary role is identifying abnormalities in the pituitary anatomy as pituitary size, location and stalk connection. These findings validate more the GHD diagnosis, helps in the prognosis and follow-up of patients (1, 32, 34).

Predictors of Transition in the Adolescence and Persistence of GHD:

Normalization of GH secretion occurs in a substantial proportion of patients with childhood-onset idiopathic growth hormone deficiency (IGHD) after reaching their final adult Ht. The predictive factors of persistence of IGHD diagnosed in childhood is not fully addressed (9, 13, 27). Persistence of GHD could be indicated by low IGF-I level at least 1month off GHRT, a peak value GH <6 μg/L after GHST (3, 9, 27, 28).

Several factors have been associated with persistence of GHD including: history of anatomical hypothalamic-pituitary disease or MPHD (100% positive predictive value (PPV) persistent GHD). Early response and Ht gain after 1st year of GHRT. Serum IGFBP-3 SDS < -2 and ILGF-1 < -5 SDS (estimated ≥ 6 weeks after completion of GHRT (PPV 100% for both). Female gender seems to be protective (1, 27, 28, 32, 35). However, most of these studies were retrospective. Differences in diagnostic criteria between these studies and variations in the kits used for measuring markers, affect results of these studies.

CONCLUSIONS

Diagnosis of CO-GHD should be done after both clinical and laboratory evaluation. Cuts-off for GHST differ by age, methodology of stimulation and type of kits used. There are evolving role ILGF-1and IGBP role both in diagnosis and follow-up response to treatment. Management of GHD includes GHRT sometimes with ILGF-1 esp., in GHR cases. Their dynamics and safety profile are still concerning. Evaluation by MRI brain on hypothalamo-pitutary and evaluation for MPHD should be performed at GHD diagnosis. Evolution of volumetric and functional evaluation of different brain areas help in better understanding and monitoring on GHRT. We recommend more future studies for better delineation of brain regions functions to determines GHD severity that may guide individualized GHRT administration. Long-term data are needed to fill current gaps and allow the creation of comprehensive evidence-based recommendations and consensus guidelines.

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