Guidelines

Diagnosis, Genetics, and Therapy of Short Stature in Children: A Growth Hormone Research Society International Perspective

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Abstract

The Growth Hormone Research Society (GRS) convened a Workshop in March 2019 to evaluate the diagnosis and therapy of short stature in children. Forty-six international experts participated at the invitation of GRS including clinicians, basic scientists, and representatives from regulatory agencies and the pharmaceutical industry. Following plenary presentations addressing the current diagnosis and therapy of short stature in children, breakout groups discussed questions produced in advance by the planning committee and reconvened to share the group reports. A writing team assembled one document that was subsequently discussed and revised by participants. Participants from regulatory agencies and pharmaceutical companies were not part of the writing process. Short stature is the most common reason for referral to the pediatric endocrinologist. History, physical examination, and auxology remain the most important methods for understanding the reasons for the short stature. While some long-standing topics of controversy continue to generate debate, including in whom, and how, to perform and interpret growth hormone stimulation tests, new research areas are changing the clinical landscape, such as the genetics of short stature, selection of patients for genetic testing, and interpretation of genetic tests in the clinical setting. What dose of growth hormone to start, how to adjust the dose, and how to identify and manage a suboptimal response are still topics to debate. Additional areas that are expected to transform the growth field include the development of long-acting growth hormone preparations and other new therapeutics and diagnostics that may increase adult height or aid in the diagnosis of growth hormone deficiency.

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Introduction and Background

The Growth Hormone Research Society (GRS) convened a 3-day workshop to provide an expert perspective on the diagnosis and therapy of short stature in children [1]. Short stature and growth deceleration are common pediatric concerns [2]. Although established diagnostic and management paradigms exist, recent advances in molecular technologies have greatly broadened our understanding of the genetic causes of short stature, and this is altering our approach to children with these common problems. In particular, while evaluation of the growth hormone (GH)-insulin-like growth factor-I (IGF-I) axis is often part of the initial clinical assessment in growth disorders, the evolving understanding of growth plate physiology has led to an increasing focus on abnormalities in this tissue resulting in the potential for the development of innovative therapies [3]. In addition, discovery of novel mutations in genes encoding proteins responsible for pituitary development has increased our understanding of the genetic basis of hypopituitarism. The increased capability and availability of genetic and epigenetic testing in clinical practice has the potential to enhance the diagnostic process and inform appropriate treatment. Furthermore, novel treatment approaches, including use of long-acting GH formulations as well as new GH secretagogues that may serve both as diagnostic tools and as therapeutic agents, have prompted expert consideration.

Methods

The structure of this Workshop was adapted from prior workshops organized by the GRS [4]. The Program Organizing Committee invited 46 GH experts from 14 countries across 5 continents. These included pediatric and adult endocrinologists, basic scientists, representatives from the European Medicines Agency and the United States Food and Drug Administration, and representatives from the pharmaceutical industry. A review of the status of GH therapy and evaluation of short stature in children was published prior to the meeting [2].

Following presentations that summarized the relevant literature, 3 breakout groups addressed each topic in greater detail by discussing a list of questions formulated by the Program Organizing Committee and subsequently agreed upon by all participants. All attendees reconvened after each breakout session to share reports from the groups. At the end of days 1 and 2, a writing team compiled the breakout group reports into a document that was discussed and reviewed in its entirety and revised by participants on the final day. In a few cases where there was not a clear consensus, the majority opinion was determined by a vote of the participants. This draft document was edited further for formatting and references, and subsequently circulated to the academic attendees for final review after the meeting. Participants from pharmaceutical companies and regulatory agencies who were present at the Workshop joined in the breakout session debates but were not part of the writing team, did not

vote, and were not present during text revision on the final day. They were shown the manuscript prior to submission but only to identify any factual errors, and they noted none.

Studies used in this analysis were conducted within ethical standards. This publication about a meeting held with scientific and regulatory experts to review published data is exempt from ethics committee approval.

Evaluation of Children with Short Stature and/or Growth Deceleration

Referral criteria have been developed for health care providers aimed at early detection of growth disorders based on a combination of low height standard deviation score (SDS), discrepancy from target height, and growth deceleration [5–7]. Although WHO growth charts can be utilized for children up to 2 years of age, local growth charts, when available, are more appropriate for older children [8].

The evaluation of short stature has been described previously [1, 2, 9, 10]. The medical history should include information about consanguinity, use of assisted reproductive technologies, gestation, birth weight, length, head circumference, and family history including pubertal timing and anthropometry of relatives. In addition, it is important to elicit symptoms concerning hypothyroidism, precocious or delayed puberty, systemic causes of poor growth, and neurological symptoms. A full physical examination should be performed with special attention to dysmorphic features and body proportions.

In most instances, it is important to ensure repeated and accurate auxologic measurements. Children with any of the following characteristics should be considered for evaluation of pathology: short stature with a height SDS below –2, height that clearly deviates from the familial background [5, 11, 12], or a significant decrease in height SDS (i.e., a deflection of at least 0.3 SDS/year that is not explained by the normal channeling in infancy to adjust linear growth to target height trajectory [13], by the prepubertal growth dip or by pubertal delay) [5, 6]. However, a diagnosis of GH deficiency (GHD) does not require a height cutoff, particularly in the context of very young children with hypoglycemia and/or midline defects/pathologies, or recently developed GHD.

Children with short stature may be evaluated inadequately in several situations. These include familial short stature (FSS), short stature in girls, and growth in childhood cancer survivors. FSS is generally considered a normal variant of growth due to a combination of polygenic and environmental effects. More recently, additional understanding of the genetic underpinnings of growth has raised the possibility that a short child who has a short parent may have an underlying genetic cause requiring evaluation. Short stature in girls has historically been underinvestigated, and it is now recommended that girls and boys be similarly evaluated [14]. Childhood cancer survivors represent a group in whom growth disorders are common. However, diagnosis may be delayed, particularly when height velocity is falsely reassuring because of early onset of puberty [15]. Pubertal status must also be considered in children who may have constitutional delay of growth, as they have a decline in height percentiles when other children are having a growth spurt. Additionally, due to the delay in puberty, height velocity can decrease to what could, in other circumstances, be considered abnormal. Interpretation of a child's height and height velocity based upon his/her pubertal status reduces misclassification of children with delayed puberty as having GHD [16].

All patients should have their head circumference measured, as this can point to specific genetic abnormalities. Patients (and their short parents) should be assessed for disproportion by measuring sitting height and arm span [17, 18]. The use of sitting height/height ratio is believed to be more reliable and reproducible, and is preferred over upper/lower segment ratio when available. Patients should be assessed for dysmorphisms that may provide clues to the underlying diagnosis, such as a *SHOX* deficiency (mesomelia and Madelung deformity) or constitutive activation of *FGFR3* (macrocephaly and lumbar hyperlordosis).

Laboratory tests should be guided by clinical features rather than routinely applied to all patients with short stature. Most textbooks and the previous GRS consensus on the topic of short stature [9] recommend routine laboratory screening for occult disease in asymptomatic short children, although one study has suggested that such screening has a low yield in short children with a height velocity >5 cm/year, with the possible exception of celiac disease [19]. One aspect to take into consideration is that this study was conducted in a tertiary care center, and, consequently, many non-endocrine conditions may have already been investigated and ruled out by the primary care physician – hence the low yield in the pediatric endocrine clinic. Clinical discretion should be applied to the scope of testing for non-endocrine disease.

Bone age assessment can be useful in evaluating short stature, although its interpretation can be difficult. For

instance, while the bone age is typically delayed in patients with GHD, making investigation for GHD unnecessary in a child with long-term short stature without a delayed bone age, this may not be the case in recently acquired GHD. Bone age is also less helpful in children with obesity, in whom the bone age is typically advanced, and in very young children (<2 years old), in whom bone age assessment is less reliable. A hand and wrist radiograph performed to assess bone age may also be helpful in identifying subtle signs of skeletal dysplasia (e.g., mutations in genes encoding short stature homeobox [SHOX], fibroblast growth factor receptor-3 [FGFR3], natriuretic peptide 2 receptor [NPR2], and Indian hedgehog [IHH]) [20–22]. Advanced bone age in a family with dominantly inherited short stature may suggest a mutation in the gene encoding aggrecan [ACAN] [23]. Bone age may be advanced despite GHD in severe obesity, such as in patients with craniopharyngioma and hypothalamic hyperphagia [24]. New automated methods for bone age assessment are now available for clinical use in some countries [25], offering the opportunity for greater consistency in interpretation, but their use might increase the risk of missing radiological signs of skeletal dysplasia. Additionally, older bone age standards may not be applicable to all children. For example, the Greulich and Pyle standards (published in 1950) were derived from white children living in the United States and predominantly of North European ancestry [9, 26]. Further work is needed on bone age assessment and prediction models for various ethnicities.

A skeletal survey is not appropriate as first-line evaluation, but it may be indicated in some individuals with a phenotype suggestive of skeletal dysplasia, including those with disproportionate short stature. One challenge is access to radiologists with expertise in the interpretation of skeletal surveys. The development of automated methods to recognize patterns of skeletal abnormalities consistent with various skeletal dysplasias would be beneficial.

Testing for GHD

The diagnosis of GHD remains a clinical one, where one synthesizes auxologic, anatomic, and laboratory data to arrive at a diagnosis. It should not be made solely on laboratory testing.

IGF-I/IGFBP-3

IGF-I measurement should be undertaken using an assay with reliable reference data, with ranges based on age, gender, and pubertal status. Many factors contribute to the variability in assay results, including methodological factors and patient conditions such as malnutrition or undernutrition, chronic illness, and liver disease [27].

IGF-I values are an important component of the evaluation of a child with growth failure with low values being suggestive of a diagnosis of GHD. However, for children under the age of 3 years, the normal range of IGF-I values may include the lower limit of detection of the assay, and there is an overlap in values when comparing children with and without GHD. Thus, a low IGF-I in young children is difficult to interpret. An IGF-I level >0 SDS at any age makes GHD unlikely [28, 29]. IGF binding protein 3 (IGFBP-3) is considered a more reliable biomarker than IGF-I in children <3 years of age [9, 30] but is less sensitive than IGF-I after 3 years. A low IGFBP-3 in combination with a low IGF-I, while raising the likelihood of GHD, may also be found in other conditions, such as long-standing malnutrition and GH insensitivity, including genetic defects in GHR, STAT5B, and IGFALS [30, 31]. A low IGF-I associated with normal or elevated IGFBP-3 may be a sign of an IGF1 genetic defect [32].

Children with GHD may have delayed physical maturation, and, therefore, assessment of IGF-I must be interpreted in relation to pubertal status. IGF-I levels assessed in the context of pubertal status have the best positive predictive power for a diagnosis of GHD in peripubertal children [33]. Elevated IGF-I levels may be seen in patients with mutations in the IGF-I receptor (IGF1R) [34], IGF-I (IGF1) [35], or pappalysin 2 (PAPPA2) genes [36].

Pituitary MRI in the Evaluation of GHD

An MRI of the hypothalamus and pituitary gland should be performed in all patients diagnosed with GHD to detect anatomical defects of the hypothalamic-pituitary region, brain tumors, or other CNS disorders. This is important for predicting the likelihood of other pituitary deficiencies, the utility of genetic testing, and the likelihood of persistent GHD [37]. Further and repeated hormonal testing may be needed to assess other pituitary hormone deficiencies.

Cranial MRIs with a focus on the pituitary and hypothalamus are especially useful during the initial evaluation in newborns with midline defects, microphallus, and hypoglycemia. Beyond the newborn period, an MRI of the hypothalamus and pituitary should be ordered after confirming the diagnosis of GHD unless there is a high index of suspicion for a hypothalamic or pituitary lesion, such as complaints suggestive of neurologic abnormality associated with a low IGF-I level. MRI is *not* a test for establishing the diagnosis of GHD. If GHD has been excluded with biochemical tests, an MRI is typically not in-

dicated. If there are focal neurological symptoms or signs suggestive of a mass lesion in the hypothalamic-pituitary region, the MRI should be considered earlier. If large sellar masses or certain pituitary defects (such as a hypoplastic pituitary gland, hypoplastic or absent stalk, or ectopic posterior pituitary) are present, formal GH provocation testing may be unnecessary when there are other clinical features indicating GHD. Depending on the imaging results, genetic testing for pituitary developmental defects may also be advisable. Pituitary size should be interpreted in the context of pubertal status, as the pituitary gland markedly increases in size during puberty [37, 38]. The finding of a small pituitary gland by itself is not sufficient to make the diagnosis of GHD, but it may indicate the need for a more extensive evaluation of pituitary function. Findings on MRI that are most supportive of a diagnosis of GHD include absence of the anterior pituitary gland (empty sella), an ectopic posterior pituitary gland, and hypoplasia of the pituitary stalk and/or pituitary gland [39].

Appropriate Clinical Settings for GH Stimulation/Provocative Tests

In neonates with a high pretest probability of GHD, a random GH level <7 ng/ml in the first week of life supports this diagnosis [40]. A GH stimulation test is considered unnecessary in such neonates and also in infants with a combination of a history of hypoglycemia, hyperbilirubinemia, poor growth, midline defects [41], microphallus, low IGF-I and IGFBP-3, multiple pituitary hormone deficiencies, such as TSH and ACTH deficiency, and/or an abnormal cranial MRI (see above).

A GH stimulation test is not necessary when an alternative diagnosis for short stature is evident such as Turner syndrome, Noonan syndrome, Prader-Willi syndrome (PWS), aggrecan deficiency, SHOX deficiency, chronic renal insufficiency, Silver-Russell syndrome (SRS), or in children born small for gestational age (SGA) with unexplained persistent short stature. However, GH stimulation tests may be performed in these conditions when there is a suspicion of GHD in addition to the underlying condition based on disease-specific growth charts or very low IGF-I levels.

Performance and Interpretation of GH Stimulation Tests

GH stimulation tests should be performed in the fasting state after adequate replacement of other hormone deficiencies (hypothyroidism and hypogonadism). Multiple GH secretagogues [9] have been used in GH stimu-

lation tests, but there are no data to demonstrate that one is better than another. GHRH is not appropriate for use as a stimulant in children as theoretically it will not diagnose GHD of hypothalamic or pituitary stalk origin. Stimulation tests in current use include the insulin tolerance test, and tests using glucagon, arginine, clonidine, L-dopa, and GH-releasing peptide-2 (GHRP2) [42]. Failure to respond to 2 provocative stimuli is needed to diagnose GHD, which limits false-positive results while not eliminating these completely. However, if there is a high index of suspicion, a single test may suffice. A sufficient GH response in one test rules out GHD in most cases. However, GHD may evolve over time, and therefore retesting may be considered at a later point of time in patients with conditions such as a history of cranial irradiation, optic nerve hypoplasia, traumatic brain injury, or certain genetic conditions. It is a matter of debate whether falsely normal results of GH stimulation tests may be seen in children with hypothalamic damage including cranial irradiation [43, 44]. Peak GH levels following provocative testing correlate inversely with BMI, and thus may be low in children with obesity. The insulin tolerance test should be used with caution due to the risks associated with severe hypoglycemia.

Whether there is a spectrum of the degree of GHD remains controversial. Severe GHD is often defined as a peak GH level <3 ng/mL on provocative testing in combination with a high prior likelihood of severe GHD based on clinical, laboratory, and imaging information. In some analyses, a peak GH level <3 ng/mL was associated with higher height velocity in response to doses of recombinant human GH (rhGH) of <0.3 mg/kg/week, while children whose peak GH level was >3 ng/ml showed a height velocity that did not correlate with the peak GH following provocative testing [45]. However, other studies using higher rhGH doses have demonstrated a clear gradient of growth response, with an inverse correlation between peak GH (≤9 ng/ml) and the height velocity in response to treatment [46].

There are no new data regarding the normal range for stimulated GH levels. However, it is important to note that GH assays, with the advent of monoclonal antibody testing and newer standards, produce GH measurements that are approximately 40% lower than those obtained using older immunoassay-based testing [47]. Therefore, the cutoffs for GH deficiency should be correspondingly reduced to minimize false-positive results (misclassifying as deficient a child with normal GH secretion). This change has already occurred in many countries, including Australia, New Zealand, Canada, most European coun-

tries, and Japan. No exact threshold was agreed upon for a confirmatory diagnosis of GHD based on the present data, but the majority of delegates suggested that the threshold be revised to 7 ng/mL, depending on the assay. Adjustment of this threshold should be determined by the pediatric endocrinology society specific to the country or region, and children previously diagnosed with GHD under different thresholds should not be required to be retested or denied continuation of therapy until attainment of appropriate adult height.

Furthermore, there are rare patients who appear to have true GHD even though their stimulated GH peak exceeds traditional cutoffs. The combination of other clinical data (e.g., significant short stature, poor height velocity, delayed bone age, very low IGF-I, and abnormal head MRI) can indicate GHD irrespective of the GH level, and these patients may require GH therapy for adequate growth [48]. Such patients may warrant initiation of rhGH therapy with annual reassessment based upon growth response. While obesity may blunt the peak GH response after stimulation, there are currently insufficient data to modify pediatric cutoffs based on body weight or BMI [49].

Sex Steroid Hormone Priming as Part of Diagnostic Testing

Estrogen increases pituitary GH release. In children with an intact pituitary gland, existing data suggest that sex steroid priming increases GH secretion when development is earlier than Tanner stage III. Sex steroid priming may thus improve the specificity of the GH stimulation test [50, 51]. However, such priming has not been standardized, the ideal age to recommend priming has not been defined, and data are lacking regarding the need to adjust the cutoff for a diagnosis of GHD in patients who undergo sex steroid priming. Thus, its efficacy in improving the diagnostic performance of GH provocation testing in general is unclear, with the exception of those with suspected constitutional delay in growth and puberty (CDGP). Use of this strategy has varied widely among centers and regions.

Supporters of sex steroid priming believe that this would reduce the number of children incorrectly diagnosed with GHD (false positives). Others agree that there is excessive diagnosis of GHD in children but do not believe that there are strong data that adding priming will necessarily improve the accuracy of this diagnosis. Currently, no clear consensus exists for the use of GH priming outside of adolescence when there is delayed puberty.

Distinguishing CDGP from GHD

It can be challenging to differentiate CDGP from GHD as in both conditions there is a height SDS deflection and relatively low height velocity compared with cross-sectional population references. The majority of patients diagnosed with GHD in the peripubertal period are ultimately found to have CDGP rather than isolated GHD. When evaluating an adolescent, one should take into account the relative decline in height velocity and GH secretion [52] that occurs with pubertal delay. Currently, this is inferred by extrapolating from prepubertal growth on established growth charts. We recommend the use of appropriate height velocity references [53] and the development of appropriate growth charts for adolescents with pubertal delay, as this would aid in confirming normal growth patterns [16, 54].

Before treating a prepubertal adolescent with short stature or growth deceleration, an evaluation of the GH axis should be considered. While there are controversies about using sex steroid priming as a general rule before GH provocation testing, there is overall consensus that this is one setting in which this is an appropriate approach. A normal GH stimulation test excludes GHD in this group.

Children at an age when CDGP is typically diagnosed have a low risk of GHD unless it is an acquired form of GHD. However, when auxological phenotype and family history are not definitive, it is recommended to screen for GHD with IGF-I levels using appropriate references for pubertal stages [32]. If the diagnosis has been made in this setting and the pituitary MRI is normal, the diagnosis of GHD should be reconsidered, particularly following completion of statural growth [9].

Application of Genetic Testing for the Evaluation of a Child with Short Stature

Genomic technology continues to advance and is being applied in multiple clinical settings [55]. A growing number of genetic causes of short stature affecting the growth plate and the pituitary-IGF axis are now recognized [3, 56–58]. Making the diagnosis of a genetic condition may help predict the response to GH therapy. A glossary of related terms is shown in Table 1; Table 2 depicts the importance of identifying a genetic cause for short stature.

There was consensus that genetic and/or epigenetic testing is not required for all children with short stature, but that it should be utilized in the diagnostic assessment of specific groups of children whose phenotype suggests a high likelihood of a genetic cause. These include severe

Table 1. Glossary

Whole genome sequencing (WGS)
Technique in which essentially the entire genome (~3 billion base pairs) is sequenced. This includes noncoding regions such as introns that regulate gene expression.

Whole exome sequencing (WES)
Technique in which the exons (protein-coding portion of the genes) of all ~20,000 protein-coding genes are sequenced. This represents approximately 2% of the whole genome but is thought to include the majority of disease-causing mutations.

Single nucleotides polymorphism (SNP) array
A microarray chip which genotypes common SNPs across the entire genome. There are typically hundreds of thousands of SNP probes on each microarray chip. This array allows one to identify genomic deletions or duplications which can lead to growth disorders (often syndromic), as well as most forms of uniparental disomy (UPD).

Comparative genomic hybridization (CGH) array
Provides similar results as the SNP array except that UPDs are not detected.

DNA Methylation
An epigenetic modification of DNA in which methyl groups are added to specific nucleotides of the DNA. Methylation is found throughout the genome and typically suppresses gene transcription. Defects in methylation can cause growth disorders and are implicated in the regulation of imprinted genes (genes in which only one copy is expressed, depending on which parent it is inherited from).

Table 2. Importance of identification of a genetic cause for short stature

- Guide growth hormone treatment of some patients
- Provide prognostic information
- Facilitate surveillance for other associated conditions that may require treatment
- In rare cases, a genetic diagnosis may identify a disorder in which growth therapy is contraindicated (e.g., the Bloom syndrome)
- A genetic diagnosis can provide peace of mind for the patient and caregivers by ending the diagnostic odyssey
- Prompt genetic counseling for future offspring and family members
- Prompt identification of additional family members
- Inform pharmacogenomics in the future (this has not yet been demonstrated)

familial forms of isolated GHD or specific syndromic forms of multiple pituitary hormone deficiencies, severe short stature (<–3 SDS for the population or >3 SD lower than mid-parental target height), body disproportion and/or skeletal dysplasia, and SGA who did not present adequate catch-up growth [18, 59, 60]. Patients with syndromic short stature represent a complex group that may warrant referral for multidisciplinary assessment at a specialized growth center with expertise in genetic diagnosis and with genetic counselors available.

A genetic cause is more likely to be identified where there is familial segregation with an autosomal dominant or recessive pattern or with a history of consanguinity. Specific phenotypes can also point to specific genetic causes (e.g., advanced bone age and family history of early arthritis suggest an *ACAN* mutation).

Genetic test selection can be directed by a thorough phenotype assessment [2, 58]. The development of clinical scoring systems [61], including laboratory data, to guide clinicians to appropriate testing panels would be helpful.

In girls with short stature, a karyotype should be performed [62] due to the possibility of Turner syndrome. If karyotype is 46,XX and there is a strong clinical suspicion of Turner syndrome, a microarray or fluorescence in situ hybridization can be considered, preferably in a different cell type than blood cells (e.g., buccal smear or cells in urine). In girls without such suspicion, a SNP array has a better diagnostic yield because it can detect copy number variants (microdeletions and microduplications), as well as most forms of uniparental disomy, while its sensitivity for detecting Turner syndrome is equivalent to that of conventional karyotyping [63].

Subsequent genetic tests should be guided by phenotypic data, but increasingly the candidate gene approach is being replaced by a hypothesis-free approach using an SNP array, followed by a growth-specific whole exome sequencing-based gene panel. Whole exome sequencing should be focused on children with the most severe short stature (<–3 SDS from population or from mid-parental target height) and those with syndromic features. If genetic tests reveal no abnormality, a methylation analysis may be ordered (especially for SGA children) to identify methylation disorders including SRS and Temple syndrome [61]. In short children born SGA and short children born following assisted reproductive technologies, methylation studies may be indicated in the initial diagnostic evaluation depending upon the phenotype. Importantly, findings on methylation analysis may not be identified by other nonspecific molecular technologies such as SNP array, or whole genome or exome sequencing.

The identification of pathogenic genetic variants can be difficult [64]. Some variations (such as frameshift mutations) are obviously pathogenic, but others require ad-

ditional data for interpretation, including functional studies. When the genetic variant is rare or novel, incorporating phenotype/genotype correlation and familial segregation is critical in the interpretation of pathogenicity. Interpretation of rare or new variants should follow the current recommendations and may require collaborative input from growth experts and/or geneticists [64].

There are limitations in reporting novel or rare variants of uncertain significance. Clinicians must understand the limitations of the clinical laboratory report [65]. To this end, information about new genetic technologies and the interpretation of results from these genetic tests should be included in the training of pediatric endocrinologists.

Guidelines for Treating Children with rhGH

The goal of treatment of children with GHD is to replace the deficient GH for growth, metabolism, and well-being. The starting dose of rhGH and dose adjustments are mainly based on weight or body surface area and growth response [66].

rhGH Starting Doses
The dose of rhGH should be individualized according to GH responsiveness aiming for the lowest effective dose, i.e., the lowest dose at which there is an appropriate response in height velocity. This needs to be in harmony with local guidelines using doses that are within the indications of the various products and not limited by individual product labeling. Depending on the country, current regulatory recommendations vary for rhGH dosing. For example, for GHD, the starting dose is 25 μg/kg/day (0.18 mg/kg/week) in most countries in Europe, Canada, and Japan, very similar in Australia (4.5 mg/m^2/week), and up to 43 μg/kg/day in the USA (0.3 mg/kg/week). The initial dose of rhGH therapy for GHD should be guided by the severity of GHD. Patients with more severe GHD, as evidenced by lower peak GH levels, lower IGF-I levels, and clinical features (such as the severity of the growth deficit, bone age delay, presence of additional pituitary deficiencies, anatomical abnormalities on brain MRI, or genetic defects associated with GHD), should be initially treated with lower doses of rhGH. In such cases, a dose of 17–35 μg/kg/day (0.16–0.24 mg/kg/week), roughly equivalent to 0.7–1.0 mg/m^2 body surface area/day (5–7 mg/m^2/week) [67, 68], may suffice for catch-up growth and attainment of a normal adult height.

For other approved, non-GHD indications, the doses prescribed may need to be higher. We recommend starting rhGH at the approved dose ranges, possibly using prediction models [69] to aid in dose optimization. In certain conditions, such as with older SGA patients and in the late diagnosis of Turner syndrome, it is recommended that rhGH be started at a dose that is at the higher end of the approved range. In infants and adolescents, patients with obesity and those with PWS, rhGH dosing may be based on body surface area rather than weight [70].

rhGH Dose Adjustments
The main goal of rhGH treatment is to increase height velocity and adult height. Consequently, the principal parameter to adjust rhGH should be the growth response. The appropriateness of the rhGH dose should be assessed based on height velocity and change in height SDS every 6–12 months. The use of IGF-I serum levels may provide additional information about treatment efficacy, adherence, and, theoretically, safety. Prediction models can also be used to guide rhGH dosing [69, 71–73]. These models should be further validated in prospective studies. Prediction algorithms suggest that in most disorders the first-year response to a rhGH dose is one of the most important predictive variables for adult height, and the lowest dose necessary to optimize height velocity should be used in all indications for rhGH treatment.

Measurement of IGF-I levels should be considered annually but may be done more frequently (e.g., after a dose adjustment) or to monitor compliance. It may also provide earlier information regarding response to rhGH than change in height velocity. Some trials that used IGF-I-based rhGH dosing suggest that this strategy may optimize therapy in GHD and idiopathic short stature (ISS) [46, 74] while allowing for use of smaller doses [75]. When using IGF-I levels to adjust dose, the "ideal" level of IGF-I should, in general, be close to 0 SDS in GHD, but individual adjustments are typically necessary based on auxological measurements. For example, children with severe GHD may respond very well to rhGH doses that result in IGF-I levels below 0 SDS. A 20% rhGH dose adjustment usually leads to a 1 SDS change in IGF-I concentration in GHD patients [76]. Once catch-up growth is achieved in patients with GHD, consideration can be given to reducing the rhGH dose with close monitoring for continued normal height velocity [77].

In non-GHD conditions, such as ISS, IGF-I levels of approximately +1 SDS or higher are usual, but the target should be adjusted on an individual basis based on auxological measurements. When consecutive IGF-I levels are above +2 SDS, consideration should be given to reducing the rhGH dose to achieve long-term IGF-I levels in the

normal range, unless IGF-I insensitivity is likely. In certain conditions characterized by partial IGF-I insensitivity (such as SRS/SGA [61], PWS [78], and IGF-IR defects [34]), IGF-I levels above +2 SDS may be needed for effective growth. This is also true in some children with Turner syndrome [79]. In children, no upper limit of IGF-I has been demonstrated to be associated with rhGH-treatment-related safety issues [80], although long-term data are lacking. It may be important to counsel patients and caregivers about this dosing strategy, particularly when high IGF-I levels are targeted.

Low levels of IGF-I may indicate poor adherence, inadequate storage, or the presence of another condition affecting GH response. High IGF-I levels may reflect some degree of IGF-I insensitivity, especially if associated with poor growth response.

There is no compelling evidence to support the use of IGFBP-3, free IGF-I, acid-labile subunit levels, or the IGF-I/IGFBP-3 ratio in monitoring rhGH therapy. In patients with GHD and syndromes that increase cancer risk, including cancer survivors, an IGF-I target that is not above the mean may be preferred [81]. However, this remains theoretical, as there is no evidence that such a goal reduces the risk of cancer recurrence or second malignancy.

Definition and Management of Suboptimal Response to rhGH

An inadequate response after initiation of rhGH therapy in patients with GHD is often defined by one or more of the following criteria: Δheight velocity <2 cm/year, height velocity SDS <0, or Δheight SDS <0.3/year during the first 6–12 months of therapy [82], but there is considerable variation in response according to age and pubertal maturation. Clinicians should use age, sex, and etiology-specific (including for GHD) response charts to assess individual growth responses after starting rhGH therapy [83, 84]. This is particularly important for genetic syndromes. During adolescence, adequacy of growth response should also be judged according to pubertal status. In addition, prediction models can aid in assessing inadequate low initial responses, and the rhGH dose being used should be taken into consideration [69]. Cancer survivors who have received radiation to the spine or growth plates (e.g., total body irradiation) have a relatively low growth response [15] and may present disproportionate growth mainly due to spinal irradiation. For genetic syndromes, standard growth charts should not be used for reference, and disease-specific growth charts should be utilized when available.

When a suboptimal growth response for pubertal status is noted, a review of adherence and injection techniques is indicated. IGF-I levels can be used as a measure of adherence and help identify GH or IGF-I resistance conditions [4]. Re-evaluation of other etiologies of growth faltering should be performed even after a diagnosis of GHD or other conditions, as the onset of scoliosis and chronic illnesses (in particular, celiac disease and inflammatory bowel disease), hypothyroidism, inadequate nutrition, medications that impair growth, and challenges in the psychosocial environment may inhibit the response to GH. Additional diagnoses such as skeletal dysplasia and other genetic conditions should be considered. In rare cases of whole *GH1* deletions, the presence of neutralizing anti-GH antibodies should be assessed. If none of these conditions is present, and IGF-I levels are below the target range, the rhGH dose can be increased to determine whether height velocity and the IGF-I level increases. rhGH should be discontinued if suboptimal response persists.

Alternative Treatments for Children with Suboptimal Response to rhGH

Alternative therapies may be considered for particular situations identified in patients with inadequate growth response. These may include nutritional and other interventions. Although uncommon, lack of responsiveness to rhGH may be due to genetic forms of GH insensitivity; these patients may respond to rhIGF-I. Alternative therapy in the form of aromatase inhibitors in pubertal boys directed at delaying epiphyseal fusion could be considered, but this remains controversial [85] and off-label. The use of GnRH analogues to delay epiphyseal closure as a single agent to augment adult height is not indicated [86], but adding a GnRH analogue to rhGH therapy may be considered for children with GHD or SGA and/or SRS patients if height SDS is low at pubertal onset [87, 88]. This should be discussed in a personalized approach to treatment in centers of reference or in a pharmaceutical trial as this is off-label.

Safety of rhGH in Children

Side effects caused by rhGH therapy are uncommon, and there is a paucity of data linking the rhGH dose to treatment-related adverse events in children. In addition, there is no upper limit of IGF-I that has been associated with treatment-related safety issues, although long-term data are currently lacking [89]. There are some genetic conditions, such as Turner syndrome, that are associated with an increased risk for adverse events, as detailed in the GRS Growth Hormone Safety Workshop Position Paper [89].

Recent Developments

New Diagnostic Tests

Macimorelin, a ghrelin agonist that provokes GH release from the pituitary [90], was recently approved as a diagnostic test for GHD in adults in the USA and Europe. Advantages of this stimulant include oral administration, the requirement for fewer blood samples over a shorter period of time, the presence of fewer side effects than most other provocative agents, high sensitivity and specificity, and greater reproducibility than other stimuli [89]. There are no published data using this agent in children.

It is important to recognize that there are several differences between children and adults in testing for GHD. Most adults have acquired structural pituitary abnormalities and very low GH responses to stimulation testing, while some children are speculated to have congenital hypothalamic dysfunction, and the response of such patients to a ghrelin agonist is unknown. Additionally, children have a broader range of peak GH responses to provocative testing. The use of GH secretagogues as diagnostic tests in children may, therefore, fail to identify children with hypothalamic dysfunction.

GHRP2 is an intravenous GH secretagogue used in Japan with the advantage of stimulating ACTH release and the potential ability to assess the hypothalamic-pituitary-adrenal and GH axes simultaneously [42, 91, 92].

New Growth-Promoting Agents
Long-Acting GH

Several pharmaceutical companies have developed GH compounds with a longer duration of action than daily rhGH, and compounds are available for commercial use in China and Korea. These drugs can be administered weekly or even less frequently, which may improve adherence. They are currently being studied in pediatric and adult populations. As every long-acting GH molecule will be a new biologic entity, establishing the ideal timing of IGF-I measurement and the recommended ranges of IGF-I levels will be important for each agent. Understanding when to measure IGF-I will be key to individualizing drug doses for patients. Pharmacodynamic models of expected IGF-I levels across the duration of action will be helpful in guiding dose adjustment for each product. Long-term postmarketing longitudinal studies for safety surveillance that extend beyond the treatment period have been recommended for all approved compounds [81].

Oral Ghrelin Analogues under Consideration

Oral ghrelin analogues (such as LUM-201/MK677) are unlikely to be useful in children with severe pituitary forms of GHD but may have potential in children with hypothalamic GHD or milder degrees of pituitary dysfunction. They may also be effective in non-GHD children with low BMI, such as SGA, ISS, SRS, and Noonan syndrome given their orexigenic effects.

C-Natriuretic Peptide Analogues

C-natriuretic peptide (CNP) is expressed in the growth plate and is an important regulator of chondrocyte proliferation and differentiation, acting through the CNP receptor NPR2. CNP analogues (such as BMN111 and TransCon CNP) bind to NPR2, interfere with the downstream FGFR3 signaling cascade, and are under investigation in achondroplasia [93]. *FGFR3* is mutated and constitutively active in achondroplasia, hypochondroplasia, and associated disorders. CNP analogues may be theoretically useful in hypochondroplasia, CNP deficiency, heterozygous *NPR2* mutations, other skeletal dysplasias, and ISS.

Future Directions

Further research is clearly required in a number of areas related to the diagnosis and treatment of children and adolescents with short stature, with the following topics considered high priority by the expert group.

1. International standardization/harmonization of GH and IGF-I assays, as assay variability can impact these measurements.
2. Guidance regarding the ideal GH stimulation test, including evaluation of newer agents such as macimorelin.
3. Standardization of GH stimulation testing procedures.
4. Establishment of diagnostic cutoffs for GHD at different pubertal stages.
5. Investigation of the impact of obesity on the diagnosis of GHD in children.
6. Assessment of accurate and appropriate tests to diagnose persistent GHD during the transition years between childhood and adulthood.
7. Exploration of the metabolomic signature in children with GHD before and after rhGH therapy as this may reveal new biomarkers for diagnosis and efficacy of treatment.
8. To continue to unravel the many genetic and epigenetic factors that contribute to stature and response to growth promoting therapies.

9. Establishment of international registries providing phenotype and genotype data on rarer genetic causes of short stature; this could assist in establishing new diagnostic and treatment strategies and facilitate a personalized approach to the evaluation and treatment of children with growth disorders.

Statement of Ethics

This publication about a meeting held with scientific and regulatory experts to review published data is exempt from ethics committee approval.

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