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Letter to the Editor

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Ways to Improve the Diagnosis of Growth Hormone Deficiency

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Dear Editor,

With interest, we read the Commentary by David B. Allen on the diagnosis of growth hormone deficiency (GHD) [1] in response to the paper by Bright et al. [2]. The latter paper rightly emphasizes that in children with short stature, most positive results of growth hormone stimulation testing (GST) will be false positives due to the low prevalence of GHD in short children and the high false-positive rate of GST. This often results in prescribing recombinant human GH (rhGH) to children misdiagnosed as GHD. With this letter, we wish to support the proposition by Allen that various steps can be taken to improve the value of GST in making a clinical diagnosis. However, we offer several comments to the four steps mentioned by Allen [1] and discuss a potential fifth step.

We fully agree with the first step proposed by Allen [1], i.e., a meticulous selection of candidates for GST. In a recent paper by our group, we proposed to estimate the individual pre-test clinical likelihood of GHD in any patient referred for growth failure and interpret the result of serum IGF-I concentration (as part of the laboratory screening of any child referred for growth failure) against the background of the pre-test likelihood [3]. We defined a number of positive and negative clinical clues for GHD that could help such estimation and proposed that if the pre-test clinical likelihood of GHD would be considered (very) low, GST would only be indicated if serum IGF-I and/or IGFBP-3 would be <−2 SDS for age and sex, taking pubertal stage into consideration [3].

We also endorse the second step proposed by Allen [1] to minimize false-positive diagnosis of GHD by resisting adherence to traditional pass/fail diagnostic GH cut-offs and instead interpret results to formulate a diagnosis along a continuum [1]. We acknowledge that this continuum could be arbitrarily divided into three categories ("actual GHD –> provisional GHD –> not GHD") [1], but we believe that such categorization would still be of little practical use for clinicians. Already for more than 30 years, the Dutch Growth Hormone Advisory Group (DGHAG) and Dutch Growth Research Foundation (DGRF), which jointly determine the criteria for acceptance of rhGH treatment for GHD and other indications in the country, have used a categorization based on the estimated likelihood that a low GH secretion is the rate limiting factor for the slow growth of the child. This is based on GST and serum IGF-I results against the background of pre-test clinical likelihood of GHD (Table 1) [4]. The DGRF evaluates centrally all Dutch rhGH requests for children. If

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Table 1. Categories of likelihood of GHD based on results of serum IGF-I and GST (against the background of pretest clinical likelihood) and consequences for rhGH treatment*

Category	GH peak, µg/L, AND IGF-I SDS	Likelihood of GHD	rhGH indicated?
1	<1.7 AND <−2	Certain	Yes
2	<3.3 AND <0	Almost certain	Yes
3	<3.3 AND >0 3.3–6.7 AND <0	Probably partial	Yes
4	3.3–6.7 AND >0 6.7–10 AND <−2	Possibly partial	Yes
5	6.7–10 AND (between −2 and 0)	Low likelihood	No
6	>6.7 AND >0	Unlikely	No
7	>10 AND <−2	No GHD, consider other causes of IGF-I deficiency	If positive response to IGF-I generation test

* Since 2021, in overweight or obese children the cut-off for the GH peak can be adjusted (see text).

patient data submitted to the DGRF are consistent with one of the categories that are considered appropriate for rhGH treatment, rhGH will be reimbursed and can be prescribed by a paediatric endocrinologist. Furthermore, in case of uncertainty about the diagnosis of GHD, anonymized patient data are discussed by a panel of three paediatric endocrinologists to assess whether GHD is plausible and rhGH should be prescribed. The effect of rhGH treatment in these patients is then evaluated after 1 year of treatment. All data of rhGH-treated children are collected in a national registry, which fortunately has maintained its funding over the years, thanks to the tireless exertions of the director of the DGRF, Prof. Anita Hokken-Koelega. We believe that national registries like ours play a fundamental role in collecting data on efficacy and safety of rhGH, as recently acknowledged [5].

Allen [1] rightly points at the difficulties to differentiate between GHD and constitutional delay of growth and puberty (CDGP). However, we wish to note that by definition the diagnosis of CDGP cannot be made if the patient's age is below the upper limit of the age range of pubertal onset in the population (in most countries 13 and 14 years in girls and boys, respectively). We therefore prefer to label short prepubertal children and teenagers who are younger than these age limits as idiopathic short stature (ISS) (if a pathological cause has been excluded during the diagnostic process [6]), even if the delayed bone age and a positive family history suggest that they may end up being diagnosed as CDGP. This is also in line with the International Classification of Pediatric Endocrine Diagnoses [7]. Such patients often show reduced responses during GST if they are not primed with sex steroids, and this is the reason that sex steroid priming before GST has been mandatory in the Netherlands since the late 1980s [4], in line with the recent US guideline [8]. Unfortunately, there is still little consensus among paediatric endocrinologists in the world about the need for priming, as well as about the choice of the pharmacological substance and optimal age range of sex steroid priming. In the Netherlands, priming with oestradiol p.o. is done in girls ≥8 years if Tanner stage is *B* ≤3 and with testosterone ester i.m. in boys ≥9 years if testicular volume ≤8–10 mL. However, we acknowledge that these age limits are arbitrary and not evidence-based.

There is some evidence that short boys with documented pubertal delay (so older than 14 years) require a longer duration of priming with sex steroids, to reduce false-positive test results [9]. In such boys, the DGHAG advises 3 months of pubertal induction therapy with i.m. testosterone esters. If this results in an increase of growth velocity and an IGF-I increase of >1 SDS (while testicular volume is still <10 mL), this is considered suggestive of CDGP. If the response is considered inadequate, primed GST is recommended.

Another factor that makes the interpretation of GST problematic is that the GH peak in GST is inversely correlated with body mass index. Until recently, there was no established method to adjust for this [3], but a recent paper has now presented data that can be used to adjust (i.e., decrease) the threshold for a "normal" GH peak in overweight or obese children [10].

The third opportunity to limit the overdiagnosis of GHD proposed by Allen is to introduce a 3–6 month period of observation or consider treatment with low-dose oxandrolone. Although Allen refers to a publication of our group on "novel approaches to short stature therapy"

[11], we wish to note that in that paper we advised against the use of oxandrolone in children with ISS, mainly because of the modest effect on height velocity and absence of effect on adult height. The other reference on the use of oxandrolone [12] mentioned by Allen [1] is associated with several inconsistencies as previously specified [13]. We therefore do not support Allen's suggestion to consider oxandrolone treatment to "provide a useful growth-sustaining 'bridge' to the onset of puberty" [1]. This applies particularly to girls, where adverse events are not negligible, even at a low dosage [14]. Furthermore, it has become exceedingly difficult to prescribe oxandrolone in most European countries, including ours.

The fourth opportunity to limit the persistence of a false-positive diagnosis of GHD proposed by Allen [1] is to subsequently question and re-examine the diagnosis. The major tool to do this is GH retesting, which can either be done a few months after the initial preliminary diagnosis [15], after 1 year [16], or at mid-puberty [17, 18]. Five years ago, we revised the Dutch national guideline on rhGH treatment inferring that children with idiopathic isolated GHD who have been treated with rhGH for at least 3 years are retested at mid-puberty. We initiated a nationwide prospective multicentre study on the effect on adult height when rhGH treatment is discontinued (based on patient's preference) at mid-puberty in adolescents who show a normal result at retesting. Such study is necessary since confirmation is needed of the claims in previous reports that discontinuing rhGH at that stage would not negatively affect adult height outcome [17, 18]. If such confirmation can be obtained, this procedure may avoid several years of unnecessary treatment in a significant number of patients. Analysis of the data of our study will start this year.

We wish to add a fifth opportunity to limit the number of false-positive diagnoses, which we recently discussed in a review on the differential diagnosis of IGF-I deficiency [19]. This relates to the observation that there is a refractory period after a spontaneous GH peak [20], illustrated by a higher proportion of patients with stimulated peak values ≤7 and ≤5 μg/L who had a spontaneous peak within 2 h before the start of GST compared with patients with no such preceding spontaneous peaks [21]. In this Swedish study, GST was often preceded by a 12-h GH profile, so that also the spontaneous nightly GH secretion could be assessed. This observation would suggest that if a 12-h GH profile is not feasible for practical or financial reasons, a 2-h period in which serum GH is measured every 20–30 min before the start of GST may detect children in whom a low stimulated GH peak is probably due to a recent spontaneous peak. In such children, the low test result would warrant additional GST in order to make a definite diagnosis of GHD. However, we acknowledge that this approach has negative practical consequences because of prolonging the test duration.

We believe that a potential future study suggested by Bright et al. [2], i.e., to identify "predictive enrichment markers" to increase the number of true-positive and true-negative diagnoses of GHD by analysing the response to rhGH treatment in a physiological dosage in children with various percentiles of growth response, is challenging. It is not only difficult to assess what constitutes "physiologic replacement," and what constitutes "amelioration of clinical sequelae", but one should also realize that the growth response to rhGH of children with partial GHD is similar to that of children with ISS [22]. In Europe, ISS is not an approved indication for rhGH treatment.

In conclusion, we agree that there are many opportunities to limit the number of false-positive diagnoses. Applying these opportunities would not only limit the number of rhGH prescriptions based on an incorrect diagnosis of GHD but also lead to early discontinuation of rhGH treatment in children in whom the diagnostic label of GHD is removed at retesting before reaching near-adult height.

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Conflict of Interest Statement

J.M.W. is a consultant to Merck, LUMOS, AGIOS, and Aeterna Zentaris, has received speaker's fees from Pfizer, Sandoz, Lilly, Merck, JCR, Ipsen, and Novo Nordisk, and is member of the editorial board of Hormone Research in Paediatrics. The other authors have no conflicts of interest to declare.

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Author Contributions

J.M.W. initiated the initial version of the manuscript and coordinated subsequent revisions. All authors contributed to the writing process and approved the final version.

References

1 Allen DB. Diagnosis of growth hormone deficiency remains a judgment call – and that is good. Horm Res Paediatr. 2021;94:406–409.
2 Bright GM, Morris PA, Rosenfeld RG. When is a positive test for pediatric growth hormone deficiency a true positive test? Horm Res Paediatr. 2021.
3 Wit JM, Bidlingmaier M, de Bruin C, Oostdijk W. A Proposal for the Interpretation of Serum IGF-I concentration as part of laboratory screening in children with growth failure. J Clin Res Pediatr Endocrinol. 2020;12(2):130–9.
4 de Muinck Keizer Schrama SM, Rikken B. Growth hormone deficiency: diagnosis and treatment Groeihormoondeficientie: diagnostiek en behandeling. Tijdschr Kindergeneeskd. 1992;60(5):147–54.
5 Giacomozzi C. Genetic screening for growth hormone therapy in children small for gestational age: so much to consider, still much to discover. Front Endocrinol. 2021;12:671361.
6 Wit JM, Kamp GA, Oostdijk W. on behalf of the Dutch working group on T, diagnosis of growth disorders in C: towards a rational and efficient diagnostic approach in children referred for growth failure to the general paediatrician. Horm Res Paediatr. 2019;91(4):223–40.
7 Quigley CA, Ranke MB. international classification of pediatric endocrine diagnoses. Rotterdam: Growth Analyser; 2016.
8 Grimberg A, DiVall SA, Polychronakos C, Allen DB, Cohen LE, Quintos JB, et al. Guideline for growth hormone and insulin-like growth factor-I treatment in children and adolescents: growth hormone deficiency, idiopathic short stature, and primary insulin-like growth factor-I deficiency. Horm Res Paediatr. 2016;86(6):361–97.
9 Couto-Silva AC, Trivin C, Adan L, Lawson-Body E, Souberbielle JC, Brauner R. Management of boys with short stature and delayed puberty. J Pediatr Endocrinol Metab. 2005;18(8):807–13.
10 Abawi O, Augustijn D, Hoeks SE, de Rijke YB, van den Akker ELT. Impact of body mass index on growth hormone stimulation tests in children and adolescents: a systematic review and meta-analysis. Crit Rev Clin Lab Sci. 2021;58(8):576–95.
11 Wit JM, Oostdijk W. Novel approaches to short stature therapy. Best Pract Res Clin Endocrinol Metab. 2015;29(3):353–66.
12 Salehpour S, Alipour P, Razzaghy-Azar M, Ardeshirpour L, Shamshiri A, Monfared MF, et al. A double-blind, placebo-controlled comparison of letrozole to oxandrolone effects upon growth and puberty of children with constitutional delay of puberty and idiopathic short stature. Horm Res Paediatr. 2010;74(6):428–35.
13 Wit JM, Hero M, Nunez SB. Aromatase inhibitors in pediatrics. Nat Rev Endocrinol. 2012;8(3):135–47.
14 Sas TC, Gault EJ, Zeger BM, Menke LA, Freriks K, Perry RJ, et al. Safety and efficacy of oxandrolone in growth hormone-treated girls with turner syndrome: evidence from recent studies and recommendations for use. Horm Res Paediatr. 2014:289–97.
15 Loche S, Bizzarri C, Maghnie M, Faedda A, Tzialla C, Autelli M, et al. Results of early reevaluation of growth hormone secretion in short children with apparent growth hormone deficiency. J Pediatr. 2002;140(4):445–9.
16 Vuralli D, Gonc EN, Ozon ZA, Alikasifoglu A, Kandemir N. Clinical and laboratory parameters predicting a requirement for the reevaluation of growth hormone status during growth hormone treatment: Retesting early in the course of GH treatment. Growth Horm IGF Res. 2017;34:31–7.
17 Zucchini S, Pirazzoli P, Baronio F, Gennari M, Bal MO, Balsamo A, et al. Effect on adult height of pubertal growth hormone retesting and withdrawal of therapy in patients with previously diagnosed growth hormone deficiency. J Clin Endocrinol Metab. 2006;91(11):4271–6.
18 Cavarzere P, Gaudino R, Sandri M, Ramaroli DA, Pietrobelli A, Zaffanello M, et al. Growth hormone retesting during puberty: a cohort study. Eur J Endocrinol. 2020;182(6):559–67.
19 Wit JM, Joustra SD, Losekoot M, van Duyvenvoorde HA, de Bruin C. Differential diagnosis of the short IGF-I-deficient child with apparently normal growth hormone secretion. Horm Res Paediatr. 2021;94(3–4):81–104.
20 Eliakim A, Brasel JA, Cooper DM. GH response to exercise: assessment of the pituitary refractory period, and relationship with circulating components of the GH-IGF-I axis in adolescent females. J Pediatr Endocrinol Metab. 1999;12(1):47–55.
21 Lennartsson O, Nilsson O, Lodefalk M. Discordance between stimulated and spontaneous growth hormone levels in short children is dependent on cut-off level and partly explained by refractoriness. Front Endocrinol. 2020;11:584906.
22 Ariza-Jimenez AB, Leiva Gea I, Martinez-Aedo Ollero MJ, Lopez-Siguero JP. Isolated growth hormone deficiency and idiopathic short stature: comparative efficiency after growth hormone treatment up to adult height. J Clin Med. 2021;10(21):4988.