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Consensus and controversies about diagnosing GH deficiency: a Delphi survey by the GH research society

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Abstract

Purpose Biochemical tests are required for diagnosing GH-deficiency in children and adults, but controversies remain regarding diagnostic criteria and type of biochemical tests. The aim of the study is to map the clinical practices of GHD diagnosis in children and adults.

Methods The Growth Hormone Research Society members initiated a Delphi survey of the diagnosis of GHD in children and adults. Pediatric (n = 18) and adult (n = 25) endocrinologists from 14 countries participated and rated their extent of agreement with 61 statements using a Likert-type-scale (1–7). Consensus was predefined as ≥ 80% of panelists rating their agreement unidirectionally as either ≥ 5 (agreement) or ≤ 3 (disagreement).

Results The pediatric panel reached consensus on 17 of 29 (59%) statements on diagnosis in children, whereas the adult panel reached consensus on 28 of 32 (88%) statements on adult patients. There was general agreement to test for GHD in an appropriate clinical context and also on the timing of testing for GHD in both children and adults. A subnormal IGF-I level was considered diagnostic in both children and adults with panhypopituitarism. In children, there was consensus to recommend the arginine stimulation test and the glucagon test. The insulin tolerance test (ITT) was considered gold standard in adults and there was also consensus to recommend the macimorelin test. A stimulated GH cut-off < 5µg/l was consistent with severe GHD in children, whereas test-specific cut-offs were recommended in adults.

Conclusion Consensus on the GHD diagnosis was lower in pediatric practice**,** mainly with respect to choice and interpretation of GH stimulation tests.

Keywords Growth hormone deficiency · Pediatric endocrinology · Adult endocrinology · Diagnosis · GH stimulation tests · Consensus guideline

Introduction

Growth hormone deficiency (GHD) in children and adults are recognized clinical disorders for which growth hormone (GH) replacement therapy is approved [1–3]. Although the phenotypic differences of childhood vs adult GHD are quite distinct, both disorders require GH replacement. Accordingly, establishing a rigorous diagnosis of GHD is vital prior to initiating long-term replacement requiring significant patient and physician commitment and surveillance [1, 4, 5]. Nevertheless, controversial issues remain regarding the diagnostic criteria. Biochemical tests are used for screening and are required as part of the diagnosis in both children and adults, but there are differences between the two patient groups regarding which tests should be used, how they are interpreted and the usefulness of serum Insulin-like Growth Factor-I (IGF-I) levels [4].

Short stature and growth deceleration commonly occur in children, frequently prompting referral to a pediatric endocrinologist for evaluation of GHD, but other causes must

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be excluded [1]. While hypothalamic-pituitary disease and genetic causes exist, GHD is an uncommon cause of short stature in children and the diagnosis is based on clinical aspects, biochemical and radiological exams, and endocrine dynamic tests [6].

In adults, according to current guidelines, GHD should be considered only in an appropriate clinical context of either overt hypothalamic-pituitary disease, such as hypopituitarism caused by a juxtasellar mass lesion or its treatment, certain neurologic disorders such as traumatic brain injury or childhood-onset GHD reconfirmed in adulthood [2, 3, 7].

The Growth Hormone Research Society (GRS) undertook a structured survey based on the Delphi method[8] with the aim of mapping the current clinical practices of GHD diagnosis in children and adults, with a particular emphasis on identifying areas of consensus, as well as lack of consensus. This involved an interactive and iterative process, during which anonymized ratings of statements were fed back to the same expert panel in a series of rounds to identify areas of agreement or disagreement.

Methods

A scientific committee (SC) composed of five GRS members developed the study objectives and invited 60 pediatric and adult endocrinologists to participate in the survey of which 43 endocrinologists (panelists) from fourteen countries accepted the invitation.

The Delphi survey consisted of two rounds. First, panelists were provided with an electronic link to the online survey, which was answered anonymously with the option to skip any questions. The survey contained 61 statements developed by the SC, which focused on (1) Whom to test, (2) When to test, (3) How to test, and (4) How to interpret test results. For each statement, the panelists were asked to rate their agreement or disagreement on a Likert-type scale as follows: (1) strong disagreement, (2) disagreement, (3) some disagreement, (4) neutral, (5) some agreement, (6) agreement, and (7) strong agreement. Consensus was predefined as $\geq$ 80% of panelists rating their agreement unidirectionally as either $\geq$ 5 (indicating agreement) or $\leq$ 3 (indicating disagreement) on the Likert-type scale.

Prior to the second round, aggregated and anonymized data from the first round were made available to the panelists, and they were invited to rate each statement again. In this second round, the average scores from the first round plus the panelists' own first-round rating of each statement were displayed on the screen. The statements were unaltered from the first to the second round.

All panelists were asked to rate all 61 statements. Thus, pediatric and adult endocrinologists answered statements regarding both pediatric and adult practice.

Results

Forty-three endocrinologists participated in the survey (16 females, 27 males, with an average clinical experience of 26 years [range 6 to $\geq$ 31 years]), of whom eighteen worked with children and transition patients, and twenty-five worked with transition and adult patients. Unless otherwise specified, the results presented from the survey regarding diagnosis in children originate from the pediatric panelists and outcomes regarding diagnosing of adults are derived from adult endocrinology panelists.

After the second round, the pediatric panel reached consensus on 17 of 29 (59%) statements pertaining to the diagnosis of GHD in children, whereas the adult panel reached consensus on 28 of 32 (88%) statements regarding the diagnosis in adult patients.

Who to test for GHD

Children

The pediatric panel reached consensus on 64% of the statements regarding the indications for GHD testing in children. There was consensus to test children exhibiting signs of growth deceleration, children with a history of being small for gestational age without catch-up growth by age 2 years, children with short stature and an intracranial pathology or brain irradiation, short children with obesity and neonates with persistent hypoglycemia and prolonged jaundice. There was also consensus to recommend a pituitary MRI in children diagnosed with GHD. Panelists also agreed that any concomitant anterior pituitary hormone deficiency should be adequately replaced prior to testing for GHD. Consensus was not reached, however, regarding testing children with either height $\geq$ -2SD below the mean or an IGF-I standard deviation score (SDS) of < -1 or testing children with a contraindication to GH therapy.

Adults

Panelists reached consensus on 77% of the statements regarding who to test. There was agreement to test adult patients with pituitary or hypothalamic mass lesions if there was an intention to treat with GH replacement. In addition, panelists agreed upon testing adults with a history of deficiency of anterior or posterior pituitary hormones. There was also consensus to test adults with suspected GHD, not to exclude those in remission from a previous history of acromegaly, and to retest adults with childhood-onset, isolated GHD after planned cessation of GH replacement therapy. In addition, there was consensus not to test patients with

a contraindication for GH therapy or patients not desiring GH replacement therapy. Among adult endocrinologists, there was also agreement to replace any concomitant anterior pituitary hormone deficiency prior to testing for GHD. Disagreement, however, prevailed pertaining to conditions in adults where testing for GHD is not recommended, i.e. patients without an antecedent history of pituitary disease or traumatic brain injury, patients without a genetic syndrome that causes hypopituitarism or childhood-onset GHD, patients with checkpoint-inhibitor induced hypophysitis and patients with an IGF-I SDS of > 0.

When to test for GHD

Children and adults

Statements concerning the timing of testing for GHD reached 100% consensus in both children and adults. There was consensus to retest patients with childhood-onset GHD when adult height is achieved if GH therapy is discontinued for at least 1–2 months prior to testing. Panelists also agreed that in patients with acromegaly, testing should not be performed until at least 3–6 months after pituitary surgery, and that testing should not be considered during pregnancy or in critically ill patients.

How to test for GHD

Children

Panelists achieved consensus on 54% of the statements concerning diagnostic tests in pediatric patients. Plasma IGF-I level was considered a valuable screening test. Regarding GH stimulation tests, the arginine stimulation test and the glucagon stimulation test were recommended, whereas controversy prevailed about the usefulness of stimulation testing with clonidine, insulin, or macimorelin. There was also consensus that a physical exercise test was not useful in children. Consensus was not reached on sex steroid priming prior to GH testing in peripubertal children with short stature.

Adults

In adults, consensus was reached for 90% of the statements. The insulin tolerance test (ITT) was recognized as the gold standard but not considered safe in patients with a history of cardiac disease, stroke, or seizures. There was consensus to use a GH stimulation test for the initial diagnosis of adult GHD. The exception to this was patients with panhypopituitarism and low serum IGF-I levels who can be diagnosed with GHD without the need for a stimulation test. There was also consensus that the growth hormone-releasing hormone (GHRH) + arginine stimulation test and the macimorelin test were well validated diagnostic tests in adults, but not clonidine, L-dopa, arginine, or exercise tests. There was 73% agreement regarding the usefulness of the glucagon test among adult endocrinologists.

How to interpret test results

Children

Consensus regarding interpretation of test results was obtained in approximately half of the statements. There was consensus that two GH stimulation tests with a peak GH value < 5 µg/l confirmed the diagnosis for GHD, whereas disagreement prevailed concerning peak levels above 5 µg/l.

Adults

In adults, consensus was reached on 100% of the statements. This included the requirement for test-specific GH cutoffs. Also, it was agreed that a low IGF-I level cannot stand alone to diagnose GHD unless the patient has multiple pituitary deficiencies, while, on the other hand, some patients with GHD may have IGF-I levels within the normal range.

Comparison of the scores between pediatric and adult endocrinologists

All panel members were encouraged to score all 61 statements to compare the views of pediatric and adult endocrinologists. While the pediatric and adult endocrinologists agreed on the majority (72%) of statements, several discordant ratings were revealed (Table 1). Consensus to test short children with obesity for GHD was only reached among pediatricians. Conversely, only adult endocrinologists opted to refrain from testing patients in whom GH therapy was contraindicated and patients who were unwilling to take GH replacement. Pediatricians agreed that two GH stimulation tests with peak value < 5 µg/l are diagnostic for severe GHD in children and considered the arginine and the glucagon tests as excellent tests, neither of which reached consensus among adult endocrinologists. In contrast, adult endocrinologists considered a single GH stimulation test sufficient for diagnosing GHD in adults and considered the macimorelin test useful, neither of which reached consensus among pediatric endocrinologists.

Discussion

Biosynthetic human GH has been available as a therapeutic compound since 1985, thereby enabling GH replacement therapy in children and adults with GHD [9]. The

Table 1 Specialty-specific consensus on topics pertaining to the diagnosis of GH deficiency in children and adults during the second Delphi round

Statements on diagnosing GH deficiency	Total	Adult endocrinologists	Pediatric endocrinologists
Whom to test—children			
1. Children with growth deceleration with a deflection in height of at least 0.3 SDS/year, after exclusion of any other cause of poor growth	97% disagreement	95% agreement	**100% agreement**
2. Children with a height ≥ -2SD (below the mean)	75% agreement	86% agreement	**63% agreement**
3. Children with an IGF-I SDS score of < -1 should be tested for GHD	49% agreement	38% agreement	**63% agreement**
4. Neonates with persistent hypoglycemia and prolonged jaundice should be tested for GHD	92% agreement	86% agreement	**100% agreement**
5. Short children with a history of being SGA and fail to demonstrate catch-up growth by 2 years of age should be evaluated for GHD	84% agreement	80% agreement	**88% disagreement**
6. Short children with obesity should be tested for GHD	52% agreement	43% disagreement	**87% agreement**
7. Short children with two or more pituitary hormone deficiencies do not need GH stimulation testing as the likelihood of GHD is very high	72% agreement	75% agreement	**69% agreement**
8. Short children with a CNS insult such as a brain or pituitary tumor, or brain irradiation, should be tested for GHD	98% agreement	95% agreement	**100% agreement**
9. Children with uncontrolled or untreated hypothyroidism, adrenal insufficiency or hypogonadism should not be tested for GHD until replacement is adequate	97% agreement	95% agreement	**100% agreement**
10. Short children who have a contra-indication to GH therapy, for example, an active malignancy, should not be tested for GHD	75% agreement	95% agreement	**47% agreement**
11. Children with a diagnosis of GHD should always be evaluated with an MRI	100% agreement	100% agreement	**100% agreement**
Whom to test—adults			
12. Patients without an antecedent history of pituitary or brain disease/injury, a genetic syndrome that causes hypopituitarism or childhood-onset GHD should not be tested for GHD	64% agreement	**73% agreement**	50% agreement
13. Patients who have a contra-indication for GH therapy, for example, an active malignancy, should not be tested for GHD	67% agreement	**86% agreement**	57% disagreement
14. Patients who state that they would not take GH replacement therapy should not be tested for GHD	61% agreement	**86% agreement**	79% disagreement
15. Adults with childhood-onset isolated GHD who stopped GH therapy at epiphyseal closure should be retested for GHD	94% agreement	**100% agreement**	86% agreement
16. Patients with pituitary or hypothalamic tumors or masses should be tested for GHD	97% agreement	**95% agreement**	100% agreement
17. Patients with one or more of the following should be tested for GHD: central diabetes insipidus (AVP deficiency) secondary hypothyroidism, secondary hypoadrenalism and/or secondary hypogonadism	100% agreement	**100% agreement**	100% agreement
18. Patients with lymphocytic or idiopathic hypophysitis should be tested for GHD	94% agreement	**91% agreement**	100% agreement
19. Patients with checkpoint-inhibitor induced hypophysitis should not be tested for GHD	56% agreement	**68% agreement**	36% agreement
20. Patients with uncontrolled diabetes, poorly controlled hypothyroidism, adrenal insufficiency or hypogonadism should not be tested for GHD until replacement therapy is adequate	100% agreement	**100% agreement**	100% agreement
21. Patients with an IGF-I SDS score of > 0 should not be tested for GHD	61% agreement	**55% agreement**	71% agreement
22. GH testing including IGF-I measurement should not be part of a screening exam for middle-aged or older patients as part of an "anti-aging" regimen	100% agreement	**100% agreement**	100% agreement
23. Patients with panhypopituitarism and a low IGF-I level (< -2 SD) do not need testing for GHD as the likelihood of GHD is very high	97% agreement	**100% agreement**	93% agreement
24. Patients with suspected GHD and a history of treated acromegaly should be tested for GHD	92% agreement	**86% agreement**	100% agreement
When to test—children			

Table 1 (continued)

Statements on diagnosing GH deficiency	Total	Adult endocrinologists	Pediatric endocrinologists
25. Children who have been treated for isolated GHD should stop treatment and be retested after final adult height is achieved	100% agreement	100% agreement	**100% agreement**
When to test—adults			
26. Patients should not be tested for GHD if they are critically ill or pregnant	97% agreement	**100% agreement**	93% agreement
27. Patients with childhood-onset GHD should be retested after adult height is achieved and epiphyses are closed	100% agreement	**100% agreement**	100% agreement
28. In patients undergoing pituitary surgery, GH testing must await adequate replacement of any additional pituitary hormone insufficiencies	100% agreement	**100% agreement**	100% agreement
29. In patients with acromegaly, testing for GH deficiency should not be performed until at least 3–6 months after pituitary surgery to confirm remission from GH excess	97% agreement	**96% agreement**	100% agreement
30. In patients who are currently taking GH, testing for GHD should not occur until the patient has stopped the GH therapy for at least 1–2 months	100% agreement	**100% agreement**	100% agreement
How to test—children			
31. Serum IGF-I levels is a useful screening test in children with short stature	89% agreement	85% agreement	**94% agreement**
32. GHD can be confirmed only with GH provocative testing	75% agreement	80% agreement	**69% agreement**
33. Two GH provocative tests should be performed in all children to diagnose GHD	72% agreement	75% agreement	**69% agreement**
34. In patients with multiple pituitary hormone deficiencies, GH provocative testing is not required since the likelihood of GHD is very high	89% agreement	95% agreement	**81% agreement**
35. Children with short stature and IGF-I SDS ≤—2 do not require GH stimulation testing prior to beginning GH therapy	84% disagreement	80% disagreement	**88% disagreement**
36. The knowledge of the GH assays/standards used to measure GH is required for the interpretation of the measurement of GH	97% agreement	100% agreement	**94% agreement**
37. All children with short stature during the peripubertal period should receive sex steroid priming prior to provocative GH testing	65% agreement	60% agreement	**69% agreement**
38. The clonidine stimulation test is an excellent test to diagnose GHD in children	40% agreement	37% disagreement	**63% agreement**
39. The insulin tolerance test is an excellent test to diagnose GHD in children	63% agreement	74% agreement	**50% agreement**
40. The arginine stimulation test is an excellent test to diagnose GHD in children	80% agreement	79% agreement	**88% agreement**
41. The glucagon stimulation test is an excellent test to diagnose GHD in children	69% agreement	58% agreement	**81% agreement**
42. The macimorelin stimulation test is an excellent test to diagnose GHD in children	26% agreement	32% agreement	**19% agreement**
43. Exercise is not an adequate stimulation test to diagnose GHD in children	95% agreement	95% agreement	**94% agreement**
How to test—adults			
44. GH stimulation testing is necessary to make the de novo diagnosis of GHD in adults except for those patients with panhypopituitarism and a low serum IGF-I	100% agreement	**100% agreement**	100% agreement
45. Insulin tolerance testing is the gold standard to test for GHD, but there are many contraindications	100% agreement	**100% agreement**	100% agreement
46. Glucagon stimulation test is an excellent test for GHD in adults	76% agreement	**73% agreement**	79% agreement
47. Macimorelin stimulation test is an excellent test for GHD in adults	75% agreement	**86% agreement**	57% agreement
48. GHRH + arginine is an excellent stimulation test for GHD in adults, but GHRH is not available world-wide	94% agreement	**100% agreement**	86% agreement
49. GHRH (as a single agent) and macimorelin testing may fail to diagnose GHD that is caused by hypothalamic defects	86% agreement	**90% agreement**	79% agreement

Table 1 (continued)

Statements on diagnosing GH deficiency	Total	Adult endocrinologists	Pediatric endocrinologists
50. Clonidine, L-dopa and arginine are not adequate for testing for GHD in adults	82% agreement	**95% agreement**	64% agreement
51. Exercise is not adequate for testing for GHD in adults	89% agreement	**95% agreement**	79% agreement
52. A single GH stimulation test is sufficient to diagnose GHD	71% agreement	**86% agreement**	50% agreement
53. Insulin tolerance testing is contraindicated in patients with cardiac disease or a history of stroke or seizures	100% agreement	**100% agreement**	100% agreement
How to interpret test results—children			
54. Children with two GH provocative tests with a peak value < 3 µg/l are considered to have complete GHD	89% agreement	84% agreement	**94% agreement**
55. Children with two GH provocative tests with peak value < 5 µg/l are considered to have complete GHD	74% agreement	63% agreement	**88% agreement**
56. Children with two GH provocative tests with peak value between 5 and 7 µg/l are considered to have partial GHD	71% agreement	68% agreement	**75% agreement**
57. Results of GH provocative testing should be adjusted for BMI	83% agreement	100% agreement	**63% agreement**
How to interpret test results—adults			
58. For each stimulation test, there is a different cut-off value to determine GHD	92% agreement	**100% agreement**	80% agreement
59. In the glucagon stimulation test, there are lower cut-offs to diagnose GHD for patients who have BMI > 30	79% agreement	**87% agreement**	67% agreement
60. Some patients with GHD may have a serum IGF-I level in the normal range, although the IGF-I level is usually < 0 SDS for age	97% agreement	**100% agreement**	93% agreement
61. In the absence of hypopituitarism, a low IGF-I level is not diagnostic of GHD	100% agreement	**100% agreement**	100% agreement

Results in bold types derive from adult endocrinologists rating statements pertaining adult patients and pediatric endocrinologists rating pediatric statements, respectively

availability of this expensive treatment modality prompted the development of clinical guidelines concerning indications, contraindications and diagnostic criteria for its use [1, 3] and also raised concern about improper use and overtreatment in both children [5] and adults [10]. In this survey, we focused on the diagnostic aspects of GHD in both children and adults and convened a panel of experts among experienced pediatric and adult endocrinologists. We used the Delphi method as an iterative process to seek consensus and highlight lack of consensus [8, 11]. Overall, the pediatric panelists achieved consensus on 59% of their statements, whereas the adult panelists achieved consensus on 88% of their statements, mainly with respect to choice and interpretation of GH stimulation tests.

In children, consensus regarding indications for testing for GHD was reached in the presence of growth deceleration, a history of being small for gestational age without catch-up growth by age 2 years, growth retardation in the presence of a CNS insult or brain irradiation, and neonates with persistent hypoglycemia and prolonged jaundice, respectively, which is in line with current guidelines [12, 13]. There was also agreement to adequately replace other anterior pituitary hormone deficiencies in children prior to testing for GHD. In addition, there was also a consensus that children diagnosed with GHD should have a pituitary MRI performed.

Adult and pediatric panelists agreed that patients with childhood-onset isolated idiopathic GHD who discontinued GH therapy at epiphyseal closure should be retested for GHD in line with current recommendations [2, 13], since a majority of these patients exhibit a normal GH response when retested [14, 15]. There was consensus to test adults who present with pituitary or hypothalamic tumors or evidence of anterior or posterior pituitary insufficiencies in accordance with current guidelines [3, 13, 16]. Also, there was consensus that patients with panhypopituitarism and a low serum IGF-I level do not need testing since the likelihood of GHD is very high [17]. There was agreement not to test adult patients before other pituitary insufficiencies have been fully replaced. Finally, there was consensus not to test adult patients with either a contra-indication, e.g. active malignancy, or those who prefer not take GH replacement.

As regards how to test, it was agreed that serum IGF-I measurement is a useful screening test in children with short stature. The obvious advantages of IGF-I as a screening tool are that it involves a single blood draw and shows minimal diurnal variation [18, 19]. In addition, the sensitivity of serum IGF-I for diagnosing childhood GHD ranges between 70 and 100% with an overall specificity of 70% [20–23]. It must be noted that in children following cranial irradiation or in case of an activated gonadal axis, a normal IGF-1 does

not exclude GH deficiency. This implies that, in case of a strong clinical suspicion for GHD, GH stimulation testing is recommended even in case of a normal IGF-1 concentration [24]. It was agreed that, in children with low IGF-1 concentrations, GH stimulation testing was necessary to confirm a childhood GHD diagnosis except in children with short stature, growth deceleration and an IGF-I SDS <—2 or in the presence of multiple pituitary deficiencies. Of note, IGF-I concentrations are not only GH-dependent, but nutritionally dependent, and should be interpreted with caution in children with relative underweight or malnutrition, i.e., those with low BMI or failure to thrive.

In children, GH stimulation testing with arginine and glucagon was recommended, whereas disagreement existed regarding the usefulness of other stimulation tests including macimorelin. Macimorelin use for diagnosing GHD is so far approved in adult patients [4], whereas the experience in children is limited [25], but a global multi-center macimorelin trial for the diagnosis of GHD in children is underway (NCT04786873). There was consensus on using a peak value of < 5ug/l to define complete GHD although different cut-offs are reported in the literature [26–28]. Additionally, in the appropriate clinical context, partial GHD may be considered at higher thresholds. Though consensus was not reached regarding peak GH values between 5 and 7 µg/l, 75% of the pediatric panel agreed to define partial GHD in children with a peak GH response between 5 and 7 µg/L.

The use of sex steroid priming prior to GH stimulation testing in peripubertal children was supported by 69% of the panelists. Serum GH levels rise during puberty in an estradiol-dependent manner, which results in higher peak GH levels during GH stimulation testing in pubertal children and in children who have received short-term treatment with estrogen or testosterone [29, 30]. The most recent guidelines from the Pediatric Endocrine Society recommend sex hormone priming in prepubertal boys older than 11 years and prepubertal girls older than 10 years [13]. Sex-steroid priming increases the stimulated GH release thereby resulting in fewer patients meeting the threshold required for a diagnosis of GHD [31]. However, determining whether a child is GH deficient or sufficient is distinct from identifying which very short children may benefit from GH therapy, particularly given that GH therapy is approved in many countries for multiple growth-retarding conditions other than GH deficiency. These indications were not explored in the current survey.

It was unexpected that consensus not to test adult patients *without* a history of either pituitary disease or a genetic syndrome or childhood-onset GHD was not reached, since current guidelines emphasize that an 'appropriate clinical context' is a prerequisite for GHD testing [3]. By contrast, consensus was reached to test patients *with* a history of either a pituitary mass lesion, known anterior or posterior pituitary insufficiency or childhood-onset GHD. There was consensus to perform a stimulation test in adults except for patients with panhypopituitarism and a low IGF-I, and the ITT was considered gold standard. The adult panel also valued the GHRH + arginine stimulation test and the macimorelin test. Of note, macimorelin is the first oral GH secretagogue to be approved as a diagnostic test for adult GHD [4]. A single stimulation test in adult patients was considered sufficient, which is in accordance with current guidelines provided that the clinical context is relevant [3, 16]. It should be noted that in the United States and other countries as well, neither macimorelin nor GHRH are currently commercially available and the ITT is rarely performed, therefore glucagon has become the most commonly used test.

The survey also revealed differences between pediatric and adult endocrinologists regarding the diagnostic approach to GHD. Consensus to test short children with obesity for GHD was reached only among pediatric endocrinologists. In both children and adults, obesity is a major negative determinant of GH secretion [32–34], and BMI correlates inversely with stimulated peak GH levels in children and adults [35, 36]. Thus, although particular care must be taken when interpreting GH stimulation test results in obese individuals, pediatric panelists agreed that a diagnosis of GHD in short obese children deserves consideration. That may be due to the phenotype of pediatric GHD including both decreased growth/short stature and increased adiposity, whereas simple obesity tends to accelerate growth in children. Conversely, only adult endocrinologists selected not to test patients when GH therapy was contraindicated such as in the context of active malignancy or if patients were unwilling to undergo GH replacement. These discrepancies may reflect the distinct malignancies observed in pediatric versus adult populations, as well as the more immediate clinical consequences of GHD in children, particularly its direct impact on linear growth and developmental outcomes. Discrepancies were also observed in the choice and interpretation (cut offs) of GH stimulation tests, which probably reflects inherent differences between the two patient populations. It is therefore not surprising that adult endocrinologists ranked questions pertaining to childhood patients differently than pediatric endocrinologists and vice versa.

The Delphi method is a valuable tool for evaluation of consensus among experts but has certain limitations. These include the composition and expertise of panel members, which is essential to the study outcome. In addition, the threshold of 80% for consensus is arbitrary but has been employed in prior consensus-building surveys [37].

In conclusion, the Delphi format provides a helpful tool to quantify consensus as well as illuminate areas lacking consensus. This report reflects an international perspective, with transparent differences in many countries for available GHD testing and its interpretation. Furthermore, our expert panel

composition allowed responses to be stratified according to clinical specialty, emphasizing the importance of exchanging knowledge between pediatric and adult endocrinologists. Our survey also highlights the need for additional research on the topics wherein consensus was not achieved.

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Data availability The dataset generated and analysed during the current study is available from the corresponding author on request.

Declarations

Competing interests MCAS has received lecture fees from Pfizer. MB has served as speaker and/or consultant for Sandoz-Hexal, NovoNordisk, Pfizer, Roche, IDS, ConsilientHealth and Pharmanovia. GJ has served as a consultant for Novo Nordisk, Shire, and Astra Zeneca and has received lecture fees from Novo Nordisk, Shire/Takeda, Pfizer and Pharmanova. AG received lecture fees from Pfizer, Ascendis Pharma and Novo Nordisk. BB has served as an occasional consultant for Ascendis, Novo Nordisk and as PI of a research grant to Massachusetts General Hospital from Ascendis. CCS received speaker fees from Novo Nordisk. AH has served as a consultant for Ascendis. PB is a consultant for, and has received honoraria from Novo Nordisk, Ascendis Pharma, BioMarin Pharmaceutical, Cavalry Biosciences, Ipsen Biopharmaceuticals, and Upsher-Smith Laboratories. PC has received unrestricted research and educational grants from Ipsen, Novo-Nordisk, and Pfizer on behalf of the Service of Endocrinology and Reproductive Diseases, Hôpitaux Universitaires Paris-Saclay and Association Recherche Endocrinologie Bicêtre, has served as principal investigator for clinical trials funded by Prolor Biotech and Æterna Zentaris, has been on advisory boards for Æterna Zentaris and Pharmanovia and gave lectures for Ipsen, Pfizer and Consilient Health. All the fees and honoraria are paid to his Institution or Research Association. EC has received grants and lecture and consulting fees from Novo Nordisk and Pfizer. SC has served as a consultant for Crinetics, Novo-Nordisk and Sandoz, and has received lecture fees from Sanofi. PEC has served as a consultant to Lumos Pharma US and has received grants from Novo Nordisk and lecture fees from Merck. MF has received research support to the Oregon Health Sciences University from Ascendis and consulting fees from Novo Nordisk for occasional scientific consulting. GA is editor-in-chief of Pituitary, CH has received lecture fees from Sandoz, Pfizer and Novo Nordisk. AJ received speaker fees from Novo Nordisk, IPSEN and Sandoz, and received unrestricted grant support from Novo Nordisk and Lundbeck. KKM has received study medication and investigator-initiated research grants from Amgen and has equity in Bristol-Myers Squibb (BMS), GE Healthcare Technologies, Boston Scientific, and Becton Dickinson. SM has served as a consultant for Novo Nordisk. SJCMMN has occasionally served as speaker or consultant for Novo- Nordisk, Pfizer and Pharmanovia. NK has served as a speaker, investigator and Scientific Advisory Board for Pfizer. LS has served as speaker and/or consultant for Sandoz-Hexal, Novo Nordisk, Merck, and Pfizer. KS has received lecture fees from Pfizer and Novo Nordisk and has served as a consultant for Pharmanovia and Novo Nordisk. PFCS has received travel grants and speaker fees from Pfizer, Merck-Serono, Novo Nordisk, Sandoz and Biomarin. CJS has occasionally served as speaker or consultant for Sandoz-Hexal, Novo Nordisk, Ascendis, Pfizer, Consilient Health and Pharmanovia. HVS has received an investigator-initiated research grant from Pfizer and Rhythm and has served as a consultant for Rhythm. KCJY has received research grants to Barrow Neurological Institute from Ascendis, received lecture fees from Novo Nordisk and Ascendis and served as an occasional advisory board member for Novo Nordisk and Ascendis. JOLJ has received grants and consulting fees from Novo Nordisk and Pfizer and has been on an advisory board for Pharmanovia. In addition, JOLJ is an associate Editor for The Journal of Clinical Endocrinology & Metabolism and played no role in the Journal's evaluation of the manuscript. The other authors have nothing to declare.

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