Criteria for diagnosis of growth hormone deficiency: *Does it exist?*

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ABSTRACT

Objective: Exploration of the criteria for diagnosing hormone deficiency used by physicians practicing in Saudi Arabia.

Methods: A questionnaire addressing the issue of criteria for diagnosing growth hormone deficiency was distributed to 104 physicians practicing in Saudi Arabia who were attending a course in endocrinology. Analysis of the data received from 48 physicians was carried out.

Results: Only one criteria from 10 clinical and biochemical criteria was chosen by 2 (4%), 2 by 9 (19%), 3 by 8 (17%), 4 by 15 (31%), 5 by 9 (19%), 6 by 2 (4%) and 7 by 3 (6%) physicians. The majority, 31 (65%) chose subnormal growth velocity as an important criteria. Twenty-four (50%) chose the subnormal physiological growth hormone values taken during sleep or after vigorous exercise, 26 (54%) chose the 2 provocative pharmacological tests, and 18 (37.5%) and 9 (19%) chose one and 3 pharmacological tests. Subnormal random single growth hormone measurement was chosen by 8 (17%) physicians. Low somatomedin C (IgF1) and subnormal IgF1 binding proteins were the choice of 18 (37.5%) and 4 (8%). Favorable biochemical response to growth hormone was the choice of 16 (33%). When the choices were combined only 3 (6%) physicians took the most likely correct combination choice ie subnormal growth velocity, delayed bone age coupled with subnormal growth hormone values taken during sleep or exercise, and 2 provocative pharmacological tests.

Conclusion: Definite diagnostic criteria for growth hormone deficiency is lacking in this country. A nationwide criteria, and subsequent central control of growth hormone is required.

Keywords: Criteria, growth hormone deficiency, diagnosis.

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Growth hormone deficiency (GHD) is an important, but relatively rare cause of short stature. Growth depends not only on the presence of normal circulating growth hormone but also on many other factors proximal and distal to the growth hormone producing pituitary cells. It has, therefore, become difficult to define growth hormone deficiency and ultimately many centers in different countries set a definite criteria.[1] We present the response of 48 physicians reflecting their view of defining growth hormone deficiency.

Methods. A one week didactic course in Endocrinology was organized by the College of Medicine, King Saud University, Riyadh. One hundred and four physicians attended this course. These physicians are practicing in different capacities in different centers in Saudi Arabia. A questionnaire was distributed and re-collected before giving a lecture on growth disorders. The questionnaire consisted of brief demographic data of the participants, and their choice of the minimal criteria used for growth hormone deficiency listed as follows: subnormal growth velocity, delayed bone age, subnormal random growth hormone value, subnormal growth hormone value taken during sleep

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or after vigorous exercise, subnormal growth hormone values in response to one provocative pharmacological test, subnormal growth hormone values in response to 2 provocative pharmacological tests, subnormal growth hormone values in response to 3 provocative pharmacological tests, low somatomedin C (IgF1) values, favorable biological response to 6 months growth hormone therapy, and subnormal growth hormone and IgF1 binding proteins (GHBP and IgFBPs). The response of participants was analyzed looking at minimum criteria chosen. Meaningful combinations of different criteria were combined and the responses analyzed.

Results. Forty eight (46%) physicians responded to the questionnaire. Thirty four (70%) were males, 24 (50%) were pediatricians, and 17 (35%) were internists. Ten (21%) stated that they were the only physicians in their area dealing with growth disorders. Thirteen (27%) were consultants, 8 (17%) were residents, and 25 (52%) were senior registrars, specialists or fellows. Thirty four (71%) stated that endocrinology was their area of practice or interest. The experience of these physicians was less than 2 years in 5 (10%), 2-5 years in 16 (33%), 5-10 years in 9 (19%), and more than 10 years in 8 (17%). Thirty (62.5%) were holding a speciality degree (board or equivalent), and 12 (25%) were diploma holders (a certificate given after one year of didactic teaching in the speciality). The response to the minimal criteria used for growth hormone deficiency was one criteria in 2, 2 criteria in 9, 3 criteria in 8, 4 criteria in 15, 5 criteria in 9, 6 criteria in 2, and 7 criteria in 3 out of the 10 options given. Table 1 illustrates the criteria chosen by the physicians and Table 2 illustrates a combination of responses thought by the author to be meaningful.

Discussion. The era of introducing biosynthetic growth hormone is also witnessing lack of definite criteria for the diagnosis of GHD. The aim of the diagnostic test is to identify the group of children who will eventually be labeled growth hormone deficient and receive growth hormone therapy on a longterm basis. Growth hormone is excreted in pulses. These pulses are important for its biological action. Furthermore growth hormone represents 'one' out of many factors important for normal growth velocity and achievement of normal adult stature. Many centers and countries have established certain diagnostic criteria for GHD. These centers continue to modify these criteria.[2] Subnormal growth velocity was chosen only by 31 (65%) of the responders. This is worrisome as this is the most important signal of GHD in children who have no other organic illness. This is much less than the figure (95%) found by Wyatt et al in a study on 251 pediatric endocrinologists in the United States of America.[3] This difference is most probably due to the fact that all participants in this study are not pediatric endocrinologists. It, however, raises a concern knowing that 34 (71%) stated that endocrinology is their area of practice or interest in

Table 1 - Criteria for diagnosis of growth hormone deficiency.

Criteria	Number	Percentage (%)
1. Subnormal growth velocity	31	65.0
2. Delayed bone age	22	46.0
3. Subnormal random growth hormone value	8	17.0
4. Subnormal growth hormone value taken during sleep or after vigorous exercise	24	50.0
5. Subnormal growth hormone values in response to one provactive pharmacological test	18	37.5
6. Subnormal growth hormone values in response to 2 provactive pharmacological tests	26	54.0
7. Subnormal growth hormone values in response to 3 provocative pharmacological tests	9	19.0
8. Low somatomedin C (IgF1) values	18	37.5
9. Favorable biological response to 6 months growth hormone therapy	16	33.0
10. Subnormal IgF1 binding proteins	4	8.0

Table 2 - Meaningful or interesting combination of choices

Choices as numbered in Table 1	Number	Percentage (%)
1 and 2	1	2.0
4 and 6	1	2.0
1 and 5	1	2.0
4 and 5	2	4.0
5 repeated	1	2.0
1, 2, 4 and 5	1	2.0
1, 2 and 5	2	4.0
1, 2, 4 and 6	3	6.0
1, 5 and 9	1	2.0
4, 8 and 9	1	2.0
1, 2, 6 and 9	2	4.0
1, 2, 4 and 6	3	6.0
1, 6, 8 and 9	1	2.0

addition to that, 20% were the only physicians in their area looking after children with growth disorders. Delayed bone age is usually an adjuvant finding in short children with GHD. It is normally used to support the other diagnostic criteria provided that an accurate bone age reading is done by an expert using Greulich and Pyle Atlas.[4] Forty six percent of responders in this study used it as a criteria. Growth hormone measurements are important, however, one has to be acquainted with the physiology of the growth hormone. As stated above, growth hormone is produced in pulses which are more frequent in certain physiological conditions e.g., sleep or following vigorous exercise,[5] and therefore have been recommended as a useful state to measure growth hormone reserve.[6,7] Random growth hormone measurement has a very low yield and has proven useless. Unfortunately, this was chosen by 17% of the responders, which may reflect deficient basic knowledge of growth hormone physiology. Due to the low number of growth hormone pulses during awakeness most authorities recommend more than one provocative pharmacological test. Agents which have been used for this purpose include clonidine, L-dopa, propanolol, insulin (to induce hypoglycemia), arginine, glucagon, and many others.[8-11] The choice among these agents was not explored in the study. New methods of diagnosing GHD are continuing to emerge. Examples include growth hormone releasing factor (GRF) stimulation test,[12] and measurement of urinary growth hormone.[13,14] These were not explored in the questionnaire as they are not locally feasible. Another relatively new test which was added in the questionnaire was the IgF1BPIII. This was chosen by 4 (8%) participants. This has been the subject of many studies in literature as one single test for growth hormone deficiency.[15] It is, however, confronted with criticism.[16,17] IgF1 itself, on the other hand, was selected by 18 (35.5%). Diagnosis by DNA analysis has been possible for the familial isolated GHD type 1-A, where the gene for growth hormone is absent. This rare form of GHD is characterized by very low growth hormone levels whatever method is used. Recombinant DNA probes may be developed to identify other forms of GHD which may replace all the growth hormone provocative stimulations listed above.[18,19] New pharmacological agents have been, and will, continue to be introduced. Examples include pyridostigmine combined with growth hormone-releasing hormone suggested by Ghigo et al.[20] A further prognostic approach for diagnosing GHD is growth hormone trial.[21] Sixteen (33%) physicians in this series chose this option. We believe in the era of a changing criteria for GHD, one should demonstrate subnormal growth velocity supplemented with 3 sets of growth hormone testing, one physiological (during sleep or post-exercise) and 2 pharmacological tests. This option which we believe is a reasonable approach at the present time was the choice of only 3 (6%) of responders (Table 2). It is always necessary to maintain restricted growth hormone usage to growth hormone deficient children with an agreed upon criteria. This can be prescribed and controlled by a limited number of well-trained physicians in the field in the form of a national body.

In conclusion, the heterogenous responses given in this series clearly indicates the lack of a clear national criteria for diagnosing GHD, which may lead to over diagnosing this condition and possible overuse of growth hormone therapy. In the view of the author, the criteria for diagnosing GHD should include: (1) short stature (2) suboptimal growth velocity (3) absence of obvious disease (4) delayed bone age (5) subnormal growth hormone values taken either: (a) during sleep (3 samples) or (b) after vigorous exercise (6) Subnormal growth hormone values in 2 provocative growth hormone testings using: (a) Glucagon (b) Clonidine (c) L-dopa - propranolol (d) Arginine (e) Insulin induced hypoglycemia.

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