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The Role of Auxologic and Growth Factor Measurements in the Diagnosis of Growth Hormone Deficiency

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ABSTRACT. The use of auxologic measurements in the diagnosis of short stature in children has a long history in pediatric endocrinology, and they have even been used as the primary criteria in selecting children for growth hormone (GH) therapy. Certainly, an abnormality in the control of growth is more likely in short children than in children of normal stature. However, most studies have shown little or no value of auxologic criteria in differentiating short children who have classic growth hormone deficiency (GHD) from short children who do not. In National Cooperative Growth Study Substudy VI, in more than 6000 children being assessed for short stature, the overall mean height SD score was -2.5 ± 1.1 and the body mass index standard deviation score was -0.5 ± 1.4 . However, there were no significant differences in these measures between the patients who were found subsequently to have GHD and those who were not. There also was no consistent difference in the growth rates between the patients with classic GHD and those short children without a diagnosis of GHD. This probably reflects the fact that we are dealing with a selected population of children who were referred for short stature and are further selecting those who are the shortest for additional investigation.

Growth factor measurements have been somewhat more useful in selecting patients with GHD and have been pro-

posed as primary diagnostic criteria. However, in National Cooperative Growth Study Substudy VI, only small differences in the levels of insulin-like growth factor I and insulin-like growth factor binding protein 3 were seen between the patients who were selected for GH treatment and those who were not. Many studies indicate that the primary value of growth factor measurements is to exclude patients who are unlikely to have GHD or to identify those patients in whom an expedited work-up should be performed. The diagnosis of GHD remains difficult and must be based on all of the data possible and the best judgment of an experienced clinician. Even under ideal circumstances, errors of both overdiagnosis and underdiagnosis of GHD still are likely. *Pediatrics* 1998;102:524–526; *auxology, growth hormone, growth hormone deficiency, insulin-like growth factor.*

ABBREVIATIONS. GHD, growth hormone deficiency; GH, growth hormone; NCGS, National Cooperative Growth Study; SDS, standard deviation score(s); IGF, insulin-like growth factor; IGFBP, insulin-like growth factor binding protein.

In many cases, the diagnosis of growth hormone deficiency (GHD) is not straightforward, and the validity of the criteria currently used in the diagnosis of GHD has been criticized.¹ One illustration of the uncertainties in the diagnosis of GHD in childhood is the secular trend in the peak level of growth hormone (GH) in response to provocative stimuli that is considered diagnostic of GHD (Table 1). In the past 3 decades, the diagnostic cutoff concentration of GH has at least doubled, perhaps because of the increased availability of biosynthetic GH. Because of the difficulties in diagnosing GHD, some endocrinol-

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TABLE 1. Secular Trend in the Diagnosis of GHD

Year	Peak Stimulated GH Level ($\mu\text{g/L}$)
1965	5
1975	7
1985	10
1997	?

ogists have even questioned whether the diagnosis of GHD should be abandoned.¹ However, establishing the diagnosis of GHD is important for several reasons. First, persons with profound GHD frequently have deficiencies of other pituitary hormones that must be diagnosed and treated. An important example of this is the association of profound GHD, micropenis attributable to leutinizing hormone and follicle-stimulating hormone deficiency, and hypoglycemia in newborn boys. Also, GHD can be associated with tumors of the central nervous system, and prompt diagnosis and appropriate treatment is crucial. Finally, there is evidence that children with true GHD respond better to treatment than those without GHD.²

Understandably, many pediatric endocrinologists around the world have sought better ways to diagnose GHD, by using new tests and all available information on a patient with possible GHD. In this review, I discuss the use of auxologic and growth factor measurements in the diagnosis of GHD and summarize the positive and negative aspects of these diagnostic approaches.

AUXOLOGY IN THE DIAGNOSIS OF GHD

Auxology has a long history as an important part of the assessment of child health and the diagnosis of GHD. Height, weight, and growth velocity are very important components in the evaluation of the general health of growing children. It has never been proven conclusively, but the common belief is that short children are more likely to have abnormal GH secretion than are children of normal stature, and that the shorter the child and/or the lower the growth rate, the more likely it is that the diagnosis will be GHD. The growth patterns of children have been used to differentiate normal variance in growth and pathologic short stature.³

Because of its simplicity and freedom from the vagaries of the laboratory diagnosis of GHD, auxology has even been used as the primary criterion in selecting children for GH therapy. The most notable experience in using auxology as the primary criterion for GH treatment is in the OZGROW studies in Australia^{4,5} (Table 2). In 1988, the OZGROW study started selecting patients for GH treatment by using

TABLE 2. Auxology in the Diagnosis of GHD: The Australian Approach

	OZGROW I (1988–1994)	OZGROW II (1994–)
Height percentile	<3	<1
Growth-velocity percentile	<25	<25
New patients per year	100	<50
Cost per year (\$A, millions)	31	16

Data from Werther.⁴

TABLE 3. Auxology in the Diagnosis of GHD: NCGS Substudy II

	GHD	Idiopathic Short Stature
Height SDS	−2.8	−2.8
Body mass index (kg/m^2)	16.9	16.0
Growth velocity (cm/y)	4.2	4.2
Increase in height SDS after 1 year of GH treatment	1.3	1.2

the auxologic criteria of height below the 3rd percentile and growth velocity below the 25th percentile. By 1993, ~100 patients a year were being started on GH treatment in Australia, at a cost of A\$31 million a year. In 1994, the auxologic criteria were changed to require a height below the 1st percentile. The growth-velocity criterion remained at below the 25th percentile. This led to a dramatic fall in the number of new patients treated with GH to fewer than 50 a year, at a cost of A\$16 million a year.

However, most studies have shown little or no value of auxologic measurements in differentiating short children who have classic GHD and short children who do not. In National Cooperative Growth Study (NCGS) Substudy II (Table 3), in >700 GH-treated children, there were no differences in height standard deviation score (SDS), body mass index, growth velocity, or response to GH treatment in the first year between the patients with classically defined GHD and non-GH-deficient patients (idiopathic short stature).² In NCGS Substudy VI, in >6000 children who were assessed for short stature, the overall mean height SDS was -2.5 ± 1.1 and the body mass index SDS was -0.5 ± 1.4 . However, there were no significant differences in these measures between the patients who were subsequently found to have GHD and those who were not. There also was no consistent difference in the growth rates between the patients with classic GHD and the short children without GHD.⁶ This probably reflects the fact that pediatric endocrinologists are dealing with a selected population of children who have been referred for short stature and are further selecting those patients who are the shortest and slowest growing for additional investigation.

The advantages of using auxology in the diagnosis of GHD are that it is noninvasive and inexpensive and probably defines the population at risk. However, there are a number of pitfalls in the use of auxology in the diagnosis of short stature. It does not distinguish between patients with GHD and those with idiopathic short stature and, furthermore, aux-

TABLE 4. Growth Factors in the Diagnosis of GHD: Sensitivity and Specificity

	IGF-I		IGFBP-3	
	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
Rosenfeld et al ⁸	82	80	—	—
Juul and Skakkebaek ¹³	69	78	53	85
Tillmann et al ¹⁴	34	72	22	92

ology does not predict the response to GH treatment reliably.

GROWTH FACTOR MEASUREMENTS IN THE DIAGNOSIS OF GHD

Growth factor measurements have been somewhat more useful in identifying patients with GHD, and they have been proposed as a primary diagnostic criterion.⁷ Growth factor levels are used as an indirect assessment of GH secretion in the diagnosis in patients with GHD.^{8–12} The indirect means of assessing GH secretion and action include measuring the levels of insulin-like growth factor I (IGF-I), IGF-II, IGF binding protein 3 (IGFBP-3), IGFBP-2, IGF-related acid-labile subunit, and GH binding protein. All of these substances are under the control of GH. Almost all of the data on the use of growth factor measurements in the diagnosis of GHD relate to the use of IGF-I and IGFBP-3. The use of these indirect means of assessing GH secretion and action has potential advantages over the use of GH measurements. They are more reproducible than the direct assessments of GH, and the substances have much longer half-lives than GH. Thus, a single sample may reflect the integrated biologic actions of GH.

Many studies have shown significant differences in the mean growth factor levels between short children who have classic GHD and short children who do not have GHD. The sensitivity and specificity of IGF-I and IGFBP-3 in the diagnosis of GHD as determined in one classic report⁸ and two recent studies^{13,14} are summarized in Table 4. Acceptable levels of sensitivity are seen in the reports by Rosenfeld and associates⁸ and Juul and Skakkebaek.¹³ The relatively poor diagnostic sensitivity in the study by Tillmann and colleagues¹⁴ probably is explained by the high proportion of patients with central nervous system tumors as the cause of their GHD. It is known that patients with GHD attributable to a central nervous system tumor have higher growth factor levels than do patients with idiopathic GHD or panhypopituitarism, but the reasons for this are not clear. All of these studies show a high degree of specificity for both IGF-I and IGFBP-3 in the diagnosis of GHD. However, in NCGS substudy VI, only small differences in the levels of IGF-I and IGFBP-3 were seen between the patients who were selected for GH treatment and those who were not.² This apparent anomaly may be attributable to the fact that several criteria, not just growth factor measurements, were considered in selecting these children for GH treatment.

The advantages of using growth factor measurements in the diagnosis of GHD are that no pharmacologic stimulation or hospitalization is required and the tests are relatively inexpensive. Furthermore, because of the long half-life in the circulation, a sample can be taken at any time. A level of IGF-I or IGFBP-3 >-1 SDS essentially rules out classic GHD.^{8,15} Many studies indicate that the primary value of growth factor measurements is to exclude patients who are unlikely to have GHD and to identify those patients in whom an expedited work-up should be performed. The pitfalls in the use of growth factors in

the diagnosis of GHD are that there is not a complete discrimination between patients with classic GHD and short patients without GHD and that the levels of the growth factors do not predict the long-term response to GH therapy.

PERSPECTIVES

GHD is part of a spectrum of growth disorders, and there is a continuum in all of the parameters that have been used in the diagnosis of GHD. No one set of observations, or tests of GH secretion, is absolutely reliable. This means that the clinician must use a combination of extensive auxologic and biochemical assessments. The diagnosis of GHD remains difficult and must be based on all the data possible and the best judgment of an experienced clinician. Even under ideal circumstances, errors of both overdiagnosis and underdiagnosis of GHD are still likely.

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