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Diagnostic Value of Insulin-like Growth Factor-I in Short Stature

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For the present, to determine growth hormone(GH) deficiency in patients with short stature, many provocative tests using various pharmacological agents such as glucagon, insulin, clonidine, arginine, growth hormone releasing factor, etc. should be done. These are not only complicated but are also misleading in some patients. In search of a simple and accurate method of detecting GH deficiency that may replace the more complicated provocative tests, we measured basal plasma insulin-like growth factor-I (IGF-I) to see the correlation with the peak GH values in the GH stimulation test. But, in each group of patients with different types of short stature, IGF-I values were poorly correlated. In addition, IGF-I values of the patients with short stature compared to the age- and sex-matched normal ranges showed a significant overlap, and the difference between the proportion of patients with subnormal values in GH deficient patients and non-GH deficient patients was not prominent. Nevertheless, in response to human growth hormone (hGH) administration, both the yearly growth rate and IGF-I levels increased conspicuously. Therefore, even though it may not be feasible to use IGF-I as a single diagnostic measure of patients with short stature, the change in IGF-I values in the follow up of hGH therapy may well represent the response to hGH.

Key Words: Insulin-like growth factor-I, Growth hormone deficiency

For patients with short stature, the levels of maximum growth hormone (GH) reserve should be determined to diagnose growth hormone deficiency (GHD) and to make therapeutic plans. Up to now the most widely recognized method of detecting GHD is the GH stimulation test—either physiological (sleep and exercise) (Underwood *et al.* 1971; Cacciari *et al.* 1978; Saggese *et al.* 1987) or pharmacological (peak GH secretion induced by administering insulin, L-dopa, arginine, or clonidine) (Frasier *et al.* 1974; Bercu *et al.* 1987). But the ability to respond to artificial pharmacological stimuli may not necessarily reflect the actual secretory pattern of GH and may frequently fail to recognize the true GHD patients (Bercu *et al.* 1986). For this reason, the determination of 24 hour integrated concentrations of GH (ICGH) was needed for evaluation of physiological fluctuation of GH levels. However, both the GH stimulation test and the determination of ICGH are time-consuming, expensive, cumbersome to the patients and require hospitalization (Kowarski *et al.* 1978; Spiliotis *et al.* 1984). There were many studies in search of a simple and accurate screening test which would allow the diagnosis of GHD, and thus be of great help to the clinicians dealing with patients with short stature (Albini *et al.* 1988; Dean *et al.* 1982; Hayek *et al.* 1981; Rosenfeld *et al.* 1981; Rudman *et al.* 1981 & 1985).

Insulin-like growth factor I (IGF-I), also called somatomedin C (Klapper *et al.* 1983; Phillips *et al.* 1980), is a peptide hormone which has a structural resemblance to human proinsulin, and is synthesized mainly in the liver in response to GH but is also known to inhibit GH secretion by negative feedback (Melmed and Yamashita 1986). Unlike GH, which is secreted in a pulsatile fashion and varies significantly during the day (Bercu and Diamond 1987), IGF-I, mostly bound to plasma protein forming an IGF-I-protein complex, is slowly cleared from plasma and thus its plasma concentration is quite constant (Cacciari and Cicognani 1987; Kao *et al.* 1986; Hintz 1984). A single sampling of blood for IGF-I is sufficient for the measurement of its concentration (Kao *et al.* 1986). For this reason, plasma IGF-I has been a subject of study in many reports related to the diagnosis of GHD and the response to GH therapy. And if the IGF-I level

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correlates well with peak GH response to GH stimulation test, IGF-I may be used as a simple screening test for GHD. This study was designed to evaluate the feasibility of using IGF-I measurement as a screening test for GHD.

MATERIALS AND METHODS

Ninety seven children with short stature (43 girls and 54 boys), aged 5 to 16 years, were studied. All were euthyroid and in good health at the time of GH stimulation tests. Thirteen children with normal stature (5 girls and 8 boys), aged 6 to 14 years, were also included in the study as a control group. Short stature was defined as a height below the 3rd percentile in the age-matched population scales and below the 25th percentile in yearly growth velocity.

Intravenous routes were established for sequential sampling purposes the day before the GH stimulation test. Sixty minutes after the patients fell asleep, 5ml of blood was withdrawn for sleep-induced GH levels. The next day, just before initiation of the GH stimulation test (6:00 AM), another 5ml of blood was withdrawn for determination of the basal plasma IGF-I levels. The basal plasma IGF-I level was measured by RIA kit (INCSTAR corp, Stillwater, Minnesota, USA).

For the GH stimulation test, regular insulin 0.1U/kg in normal saline was injected intravenously, and L-dopa 500mg/1.73m^2 was administered orally. The blood samples for GH were obtained serially at the beginning and at 30, 60, and 120 minutes. GH level was determined by RIA method. To consider the results as satisfactory in the insulin provocative test, blood sugar levels after regular insulin injection had to be less than 50% of the basal level or below 45mg/dl (Kim 1988). Only the results satisfying this criterion were included in the presenting data.

The patients with short stature and a peak GH level below 7ng/ml were classified as complete GHD; between 7 and 10ng/ml, partial GHD; and above 10ng/ml, normal variant short stature (Kim 1988; Schaff-Blass *et al.* 1984). In each group, the peak GH levels during pharmacological stimulation tests and GH levels at postsleep 60 minutes were compared to the basal plasma IGF-I levels and their relationship was derived using multiple regression analysis. The IGF-I values of patient with short stature in different groups were compared to those of the control group using independent t-test and Mann-Whitney U test.

In addition, the basal plasma IGF-I levels were compared to the reference ranges of the age- and sex-matched norms. And the percentages of the cases with subnormal IGF-I levels were compared in GHD and non-GHD patients. Furthermore, in ten patients with short stature who were treated with hGH 0.1U/kg injected subcutaneously three times a week, the plasma IGF-I level was measured at 2 to 7 months (mean 5.6±2.1 months) after hGH administration. Both the pre- and post-treatment yearly growth rates and plasma IGF-I levels were compared in order to evaluate the effect of hGH therapy on the plasma IGF-I levels.

RESULTS

Patient population who underwent the GH stimulation test

Among the patients with short stature, 29 were normal variant short stature (NVSS), 35 partial GHD and 33 complete GHD. The mean age for each patient group was 11.5±2.5 yr, 11.4±2.6 yr and 11.1±2.1 yr respectively (Table 1). There was no age predilection in each group.

Relationship between IGF-I levels and peak GH levels in the GH stimulation tests

In each group, including the control group, the relationship between IGF-I and the peak GH levels in the GH stimulation tests was determined. A trend was observed that the higher the representative peak GH levels in each of the GH stimulation tests, the higher the IGF-I levels. However, IGF-I values were poorly correlated with the values of any one of the peak GH levels (sleep-induded GH level, insulin-induced GH level, and L-dopa-induced GH level) in each group (Table 2) including the complete GHD group (Fig. 1).

Table 1. Patients with short stature in growth hormone stimulation test

Group	Age (years)	Number of patients		
		Male	Female	Total
Control	11.2±2.3	8	5	13
NVSS[a]	11.5±2.5	14	15	29
GHD[b]				
Partial	11.4±2.6	19	16	35
Complete	11.1±2.1	21	12	33

[a] Normal variant short stature
[b] Growth hormone deficiency
Age is presented as mean±S.D.

Table 2. Relationship between basal plasma IGF-I levels and peak GH levels in growth hormone stimulation tests

Group	Peak GH levels (ng/ml) induced by			IGF-I (U/ml)
	Sleep[a]	Insulin	L-dopa	
Control	9.91±6.51	10.34±6.88	15.52±6.57	0.71±0.37
NVSS	11.19±6.92	7.48±5.41	12.73±6.07	0.79±0.39
GHD				
Partial	4.90±3.00	5.87±2.06	8.57±0.78	0.57±0.42
Complete	1.86±1.83	2.78±2.40	1.93±2.31	0.42±0.28

[a] Sleep: GH level at 60 minutes after falling asleep
Numbers represent mean ± S.D.
In each group the correlation between IGF-I and peak GH levels was not significant ($p>0.05$).

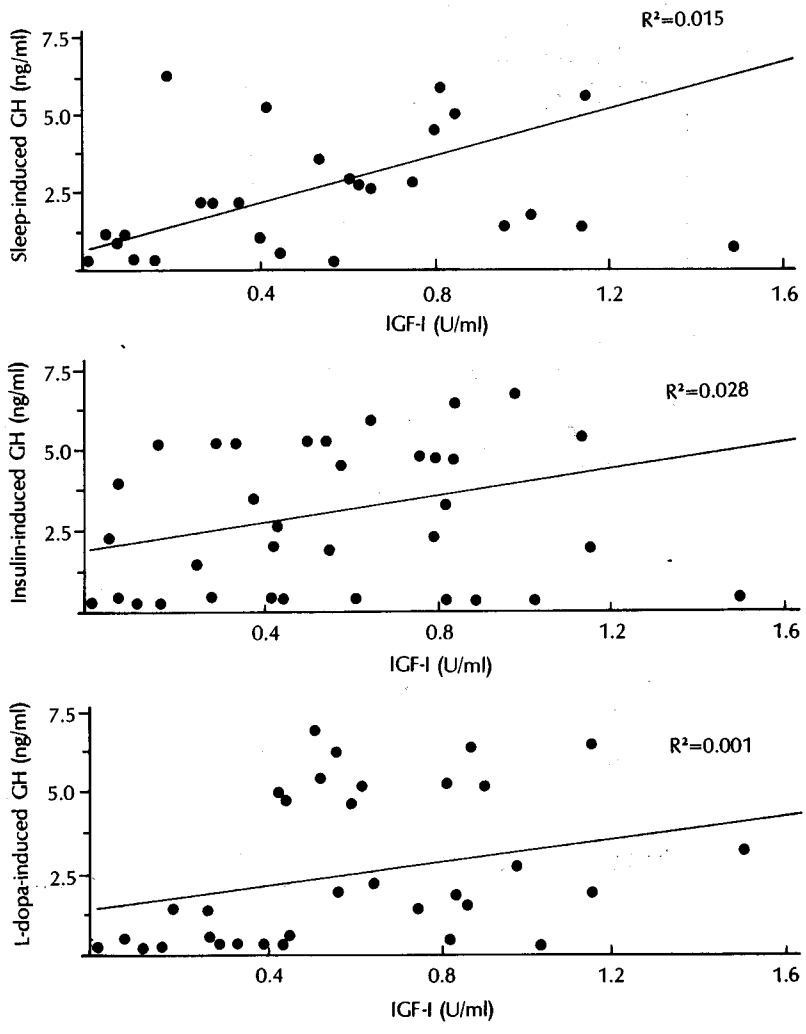

Fig. 1. *Relationship between basal plasma IGF-I level and peak GH levels in complete GHD patients.*

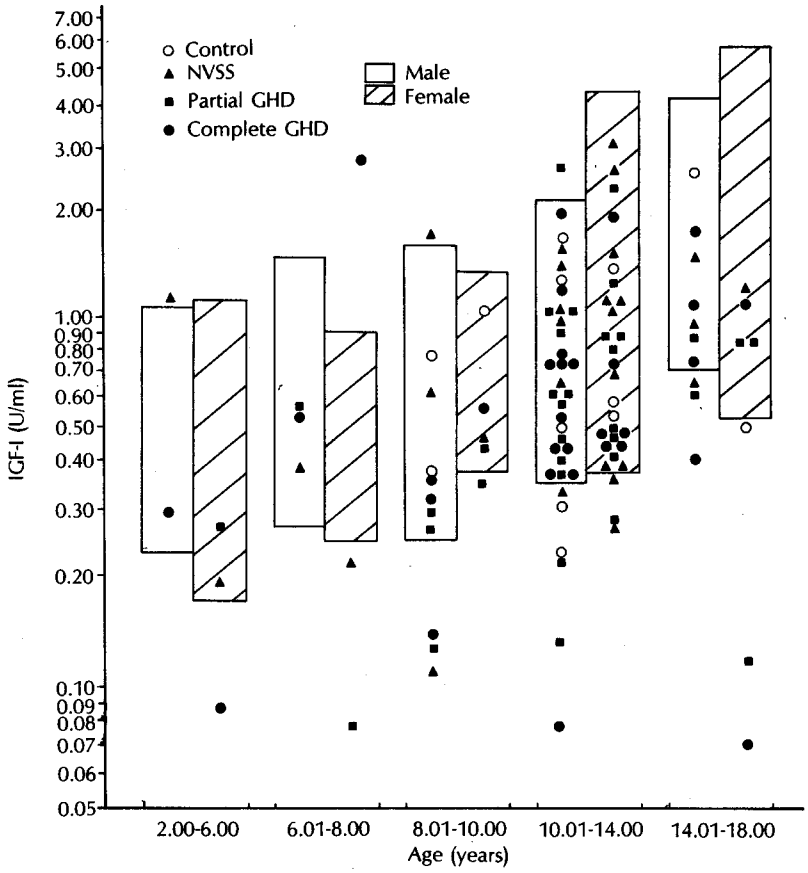

Fig. 2. *Age- and sex-matched IGF-I levels of the study subjects (control, normal variant short stature, partial GHD, and complete GHD) compared to normal ranges (supplied by INCSTAR Laboratory).*

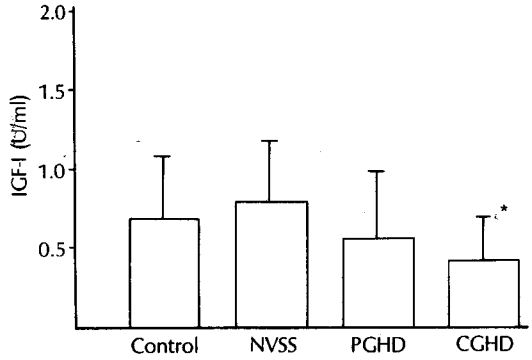

Fig. 3. *Comparison of mean basal plasma IGF-I levels.*
Values are mean ± S.D.
NVSS; Normal variant short stature
PGHD; Partial growth hormone deficiency
CGHD; Complete growth hormone deficiency
**; p<0.05, compared with values in the control group*

IGF-I levels of patients with short stature according to age and sex

The plasma IGF-I level is known to vary depending upon many different factors such as age, sex, nutrition, liver function, puberty, etc. In this study, the plasma IGF-I levels of the patients with short stature were plotted against age and sex compared to the normal reference ranges. Although some patients exhibited plasma IGF-I values lower than the normal ranges, most overlapped with the normal ranges. The plasma IGF-I levels were subnormal in 31.0% of the GHD patients in contrast to 23.1% of the non-GHD children (Fig. 2).

Table 3. Changes in IGF-I and yearly growth rate with human growth hormone therapy[a]

	Yearly growth (cm/year)	IGF-I (U/ml)
Pre-treatment	4.13±2.24	0.83±0.17
Post-treatment	6.96±3.61*	1.15±0.39*

[a] Human growth hormone 0.1U/kg SQ t.i.w. for 2 to 7 months (mean 5.6 months)

* $p<0.05$, as compared to pre-treatment values.

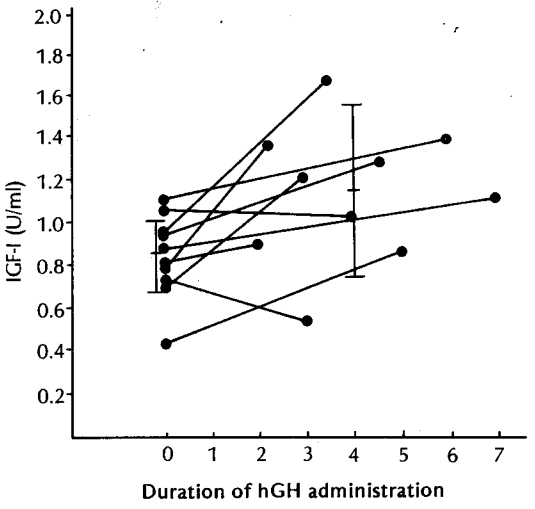

Fig. 4. *Alteration of IGF-I levels in response to hGH therapy*

Comparison of IGF-I levels of each type of short stature with control group

The mean IGF-I values of various short stature groups were compared with that of the control group. Between the normal variant short stature and the control (0.79±0.39 vs 0.71±0.37U/ml), as well as between the partial GHD and the control (0.57±0.42 vs 0.71±0.37U/ml), the difference in mean IGF-I values was not statistically significant. However, the mean IGF-I value of the complete GHD group (0.42±0.28U/ml) was significantly lower than that of the control group (Fig. 3).

Effect of hGH therapy on IGF-I

In order to study the effect of GH therapy on IGF-I, IGF-I was determined before and after the hGH therapy in 10 patients with short stature. There were 6 complete GHD patients, 3 partial GHD patients and one with normal variant short stature. In each patient the yearly growth rate was calculated before and after hGH therapy. The effect of hGH therapy was ascertained by the increase in the yearly growth rate from 4.13±2.24cm to 6.96±3.61cm ($p<0.05$). Similarly, the mean IGF-I value was significantly increased following GH therapy (0.83±0.17 vs 1.15±0.39U/ml, $p<0.05$) (Table 3, Fig. 4).

DISCUSSION

For the reason that the concentration of plasma IGF-I is rather constant in contrast to that of GH, and the effect of GH, besides its innate property of directly acting on body tissues for growth stimulation, is mediated by IGF-I produced in response to GH (Copeland *et al.* 1980; Cuttler 1987) for stimulation of tissue differentiation and multiplication (Hock *et al.* 1988), the concept of using IGF-I as a screening test for GH deficiency was evolved.

The most accurate method for GH evaluation is measurement of serum GH levels continuously over 24 hours in 20 minute intervals (Kowarski *et al.* 1971), which necessarily requires enormous time, painstaking effort, and a large amount of blood sampling which make it impractical for use in children. Thus the provocative test or so-called GH stimulation test has been used widely as the accepted method of determining GHD in patients with short stature. However, it is still a complicated method requiring hospitalization and presents the risks of hypoglycemia and discomfort to the patients.

As it is known that IGF-I is a GH-dependent peptide hormone whose plasma concentration is fairly constant (half-life approximately 16 hours) (Zapf *et al.* 1984; Cacciari and Cicognani 1987) even though temporal variation has been suggested in recent reports (Minuto *et al.* 1981), the use of single sampling of blood for the measurement of IGF-I was suggested in order to replace the more complicated method of determining GHD. Moore *et al.* (1982) measured random plasma somatomedin C (SmC) in 143 children with growth below the 5th percentile. Somatomedin C increased with increasing bone age in non-GHD patients while there was no change in GHD patients. And even though many of the non-GHD patients had SmC levels below 0.5U/ml, all GHD patients had their values below 0.5U/ml.

Bercu *et al.* (1986) found that IGF-I correlated with mean 24-h concentration of endogenous GH secretion and that provocative testing frequently does not

correlate with endogenous GH secretion. In another report by Kao (1986), it was suggested that a single-specimen assay for SmC provided a satisfactory index to the overall recent rate of secretion of GH by the pituitary gland. However, it was simultaneously stressed that the diagnosis of GHD and institution of GH replacement treatment should not be based solely on a low SmC level, because it is difficult to distinguish pituitary dwarfism from constitutional delay of growth (Lee and Rosenfeld 1987). In addition, Rayner (1988) reported that neither peak GH nor integrated GH in provocative tests were correlated with basal IGF-I. In this study, basal IGF-I values were not correlated with any of the individual peak GH levels induced by sleep, insulin, or L-dopa nor the peak GH levels regardless of the method of induction in provocative test. Therefore, it might be said that IGF-I does not reflect potential GH reserve secreted in a pulsatile manner. Nonetheless, the correlation between IGF-I and 24-h GH concentration (Zadik *et al.* 1985) must be examined for the possibility that IGF-I could successfully reflect the cumulative GH secretion.

In regard to the age-dependent variation of IGF-i values, many have confirmed and established the normal ranges for different age groups and sexes, even though there are some numerical variabilities depending upon the laboratories. During the first year of life, IGF-I concentration is low but the actual mechanism by which growth deceleration occurs seems to be due to the diminished sensitivity of the tissues to IGF-I rather than the concentration itself (Kaplowitz *et al.* 1982; Underwood and D'Ercole 1984). In childhood, it is still low but slowly increases during the adrenarchal period. A dramatic rise of IGF-I occurs during puberty (Underwood *et al.* 1980; Bala *et al.* 1981; Hall and Sara 1984; Furlanetto *et al.* 1977; Luna *et al.* 1983; Mansfield *et al.* 1988). However, the IGF-I surge does not clearly explain the mechanism of growth spurt (Pescovitz *et al.* 1985; Rappaport *et al.* 1987) and perhaps is mediated by sex steroids which stimulate GH secretion (Rosenfield *et al.* 1983). Clemmons *et al.* (1984) also performed a study on the mean SmC concentration of 800 children to show the rise from the value at birth (0.45U/ml) to a peak at age 11-13 years (2.12U/ml) in boys, while in girls the values were generally 10-20% higher. Thereafter, SmC concentration tends to fall with increasing age to a value of 0.67U/ml at the 7th decade. Furthermore, Rayner (1988) provided clinical data eliciting the usefulness of basal IGF-I in identifying GHD in patients with bone age less than 8 years compared to normal values. On the other hand, Dean *et al.* (1982) reported that the basal IGF-I was not a very sensitive test because a significant proportion of the GHD patients had basal IGF-I values in the normal range. In addition, IGF-I levels were not predictive of peak GH response nor could they be used to differentiate constitutional delay of growth and maturation from genetic short stature (Moore *et al.* 1982).

In our study, notwithstanding the control group, even the GHD patients followed the pattern already described, showing the peak value in the age group of 11-13. The percentage of the GHD patients having IGF-I values in the subnormal age- and sex- matched ranges (31%) was higher compared to that of the non-GHD patients (23%). However, the majority of the GHD patients had values that overlap with normal ranges as previously reported by others (Spiliotis *et al.* 1984; Zadik *et al.* 1985; Bercu *et al.* 1986; Plotnick *et al.* 1979; Lee and Rosenfeld 1987). It is needless to say that, based on this data, one cannot surely establish the diagnosis of GHD by low IGF-I values alone. Nevertheless, in cases of NVSS, in whom GH response to provocative tests was normal, IGF-I values may play a role in determining the use of exogenous GH in these patients (Bright *et al.* 983; Albertsson-Wikland and Hall 1987; Cacciari *et al.* 985).

As Lanes (1987) already reported, there was no difference between the mean IGF-I levels of the NVSS and normal control group. On the other hand, our results were compatible with the report by Furlanetto (1977) that a statistically significant difference exists between that of the complete GHD group and the normal control group. It is not definite what clinical significance can be endowed to this fact. But one may hypothesize that plasma IGF-I perhaps represents the endogenous GH secretion when the mean serum concentration of GH falls below a certain threshold level.

There are contradictory views concerning the value of plasma IGF-I in predicting the response to human GH administration. Gertner (1984), in his work of measuring IGF-I in short-term hGH administration, concluded that the growth response was not predicted by an acute rise in IGF-I and the measurement of IGF-I cannot be used to predict which children will respond to hGH injection. Similar views were held by other workers such as Rosenfeld (1981), Dean (1982) and Van Vliet (1983). Contrasting results that support the view that SmC and growth increment response to short-term exogenous GH therapy may precisely identify children who will benefit from long-term GH treatment were obtained by several workers (Hayek and Peake 1981; Rudman *et al.* 1981; Knudtzon and Aarskog 1987). In addition, in patients with short stature and normal GH response to provocative tests but with low spontaneous GH secretion who have

received injections of hGH, the growth increase was strongly correlated with the percent increase in serum IGF-I (Albertsson-Wikland and Hall 1987; Ranke 1987; Wilson and Rosenfeld 1987). In an attempt to explain the effect of hGH on growth, Copeland (1980) presented the evidence that the SmC rise in response to hGH was achieved by stimulation of *de novo* synthesis. Our results showing the increased IGF-I values in response to hGH administration in conjunction with the increase in yearly growth rate support the latter viewpoint.

It can be concluded that the plasma IGF-I level was poorly correlated with the peak GH levels in the GH stimulation tests in patients with short stature. Nevertheless, IGF-I may be used as an index of the response to hGH treatment during the follow-up period, and possibly to predict the long-term effect. However, which children will benefit from hGH treatment cannot be predicted accurately by the plasma IGF-I values.

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