

Insulin-like Growth Factors I and II: Evaluation of Growth Retardation

Rosenfeld et al measured plasma insulin-like growth factor (IGF-I and IGF-II) levels in 197 normal-sized children, in 44 normal short-statured children (NL-SS) with normal growth hormone (GH) release in response to pharmacologic stimuli, and in 68 GH-deficient children. Because of the variation in IGF-I levels related to age and sex, the results were stratified by sex into six age groups. Normal percentile curves were constructed for each group. The results for all groups are shown in Table I.

Evaluation of the mean IGF levels according to patient status and age groups provided the following analysis. Mean IGF-I levels in GH-deficient children were significantly below the mean levels seen in children of normal stature in each of the six age groups. IGF-II levels were significantly below the mean levels in only 50% of the group with GH deficiency (GHD). There were significant differences between the mean levels of IGF-I and IGF-II in normal and NL-SS children who were younger than 8 years of age, but these differences were not consistent by gender.

Analysis of both assays according to patient status is shown in Table II. When IGF-I and IGF-II levels were used in combination, the distinction between normal and GH-deficient children was more pronounced than when either assay was used alone. Only one (0.5%) normal child and five (11%) short normal children had low plasma levels of both IGF-I and IGF-II. On the other hand, only three (4%) GH-deficient children had normal plasma levels of both somatomedins.

Table I. Percentile Curves

	IGF-I		IGF-II	
	5-95th*	< 5th*	5-95th*	< 5th*
Normal (197)	98%	2%	95%	5%
GHD (68)	18%	82%	58%	52%
NL-SS (44)	68%	32%	65%	35%

*Percentiles

Table II. Analysis of IGF-I and IGF-II assays

	NL/NL*	NL/L†	L/L‡
Normal (197)	93%	6%	1%
GHD (68)	4%	59%	37%
NL-SS (44)	46%	43%	11%

* Both IGF-I and IGF-II levels are between the 5th and 95th percentiles.

† Either the IGF-I or the IGF-II level is between the 5th and 95th percentiles.

‡ Both IGF-I and IGF-II levels are below the 5th percentile.

Editor's comment—The data from this large series of children may serve as a first order attempt at differentiating short normal (but GH-sufficient) children from those with GHD. If only it were so simple! First, IGF-II determinations are not routinely available. Although the children in each of the two short-stature groups were separated by responses to pharmacologic provocative tests for GH secretion, the categorization of children into GH-sufficient and GH-deficient groups is accurate only at the extremes. There are a number of children with a GH-deficient phenotype who respond to pharmacologic stimuli by releasing GH, but who do not grow well. Are they physiologically deficient in GH?

How one answers depends upon the "definitions" used. In fact, it is not so important to label or categorize each patient by GH response to stimuli, but to determine prospectively which children are likely to respond to exogenous hormonal therapy—be it recombinant human growth hormone (hGH) or (in the future) recom-

binant IGF-I. Thus, many short children may have a neurosecretory alteration that does not permit enough GH to be secreted at the proper intervals to maintain liver and tissue growth factor levels, thereby preventing the child from reaching his or her genetically determined growth potential.

The unavoidable implication of GH secretory pattern studies, especially when combined with the observations in this report, is that the diagnosis of GHD based on the results of provocative tests is both arbitrary and nonphysiologic. Suboptimal GH secretion or activity may be reflected in decreased GH pulsatility, reduced integrated GH concentrations, or suboptimal IGF-I and/or IGF-II levels. With the imminent availability of essentially unlimited quantities of hGH (and IGF-I), the ability to determine which short children are most likely to have accelerated growth (catch-up growth) in response to therapy with these growth factors becomes of paramount importance.

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