

Evidence for Partial Growth Hormone Insensitivity Among Patients With Idiopathic Short Stature

Reported in this study are 511 children with idiopathic short stature (ISS) (height standard deviation score [SDS] of ≤ 2 ; maximum stimulated growth hormone [GH] $> 10 \mu\text{g/L}$; and no other reason for short stature) who were treated with GH. Growth hormone-binding protein (GHBP) was measured before GH treatment. In 101 (20%) patients GHP SDS ≤ -2 , whereas in the remaining 410 (80%) patients GHP SDS > -2 . Patients with low GHBP levels had lower mean extracted insulin-like growth factor 1 (IGF-1) SDS (-3.3 ± 1.1 vs -2.5 ± 1.4 ; $P < 0.0001$) and higher mean 12-hour GH values (2.8 ± 1.1 vs $2.3 \pm 1.1 \mu\text{g/L}$; $P < 0.0001$) when compared with patients with normal GHBP levels. A direct correlation was found between GHBP SDS and extracted IGF-1 SDS, whereas an inverse correlation was present between GHBP SDS and mean 12-hour GH values. Growth velocity before and after 1 year of treatment with GH was not different between prepubertal patients with low and normal GHBP. No correlation was found between first-year growth rate with GH treatment and GHBP SDS. The authors conclude that ISS patients who have low levels of GHBP are partially insensitive to GH, as suggested by a lower IGF-1 and a higher 12-hour mean GH concentration. The authors also present a proposal for a redefinition of normal growth and growth disorders based on the evaluation of endogenous GH secretion and GH responsiveness assessed by the GHBP.

Editor's comment: This is an excellent study with a large number of short-statured patients studied in a sophisticated prospective manner. Unfortunately, the authors did not separate the results by growth velocity measured before and after treatment with GH. They reported a mean pretreatment growth velocity of $4.0 \pm 1.7 \text{ cm/y}$ in the low GHBP group and of $4.2 \pm 1.9 \text{ cm/y}$ in the normal GHBP group. The great variability implied by the mean ± 2 SD (ie, growth velocities before initiation of therapy ranging from 0.6 to 7.7 cm/y and from 0.4 to 8.0 cm/y, respectively) indicates that there were some patients who were growing very well and some others who were growing poorly. The responses to GH were also reported as a mean of the whole group, thus individual variations cannot be discerned. Patients growing at a decreased rate who significantly increased their growth after GH treatment would differ from those patients originally growing at normal rates who had a minimal increase of growth rate after GH treatment. These data are important to understand the significance of the findings reported.

The more we look for magic bullets to diagnose growth abnormalities, the more compelling becomes the old adage: careful measurements of growth velocity are necessary to ascertain the need for therapy and the response to it. The reader is referred to a recent article in the *New England Journal of Medicine* (1995;333:1093-1098); for a report of the mutations of the GH receptor in children with ISS.