

# The Incidence of Growth Hormone Deficiency: Does Anyone Know?

Much attention is being directed by clinical investigators, pharmaceutical firms, geneticists, and pediatric endocrinologists to the incidence of growth hormone (GH) deficiency. Investigators are interested in this because the incidence dictates the number and type of studies that can be performed. Pharmaceutical firms are interested because the incidence will determine the market for the sale of native or DNA-recombinant hormone. Geneticists are interested because of the multiple biochemical or anatomic lesions that might be associated with GH deficiency. Pediatric endocrinologists are interested because they are the physicians primarily responsible for the diagnosis and treatment of GH deficiency.

No one knows for certain what the actual incidence of GH deficiency is. The reason for this is related to our inability to define GH deficiency itself. According to a study by Vimpani et al (*Brit M J* 1977;2:247), GH deficiency is present if the GH concentration is  $<9$  ng/ml to two stimuli; the height is  $>2.5$  SD below the mean height for age; and the height velocity falls at or below the 25th percentile for chronological age. The prevalence of idiopathic GH deficiency in Scotland, according to Vimpani's study, is approximately 1:5,000 (4,000 to 6,500) births. Extrapolating from this ratio, there would be 14,500 such patients under 21 years of age in the United States.

This incidence, however, does not take into account those patients with organic hypopituitarism resulting from tumors of the hypothalamus or pituitary, or from other lesions, such as histiocytosis X, that produce GH deficiency. A review of several articles suggests that one case of organic hypopituitarism occurs for every four cases of obvious idiopathic GH deficiency. During the past ten years in our own clinic at the University of Virginia Medical Center, 84 patients with idiopathic GH deficiency and 36 patients with craniopharyngiomas or other causes of organic hypopituitarism have re-

ceived GH. If our figures are representative, approximately 20,000 cases of hypopituitarism exist nationwide in children less than 21 years of age.

However, there are other questions that should be considered before we accept this figure even as an approximation. What about patients with partial GH deficiency? What about patients who have what could be an immunologically active but biologically inactive hormone? What about other children who have the phenotype of GH deficiency and low somatomedin-C determinations, but who have significant levels of GH when tested? What about the patients who have severe constitutionally delayed growth and adolescent development?

There are many patients who might be considered GH deficient if one takes these patient groups into account. Patients with partial GH deficiency include those like the seven patients described by Spiliotis (see page 8 of this issue), who are believed to have GH neurosecretory dysfunction. The criteria consistent with the clinical picture of GH deficiency were present in these patients, although they had GH concentrations greater than 10 ng/ml when tested with pharmacological agents. Compared with normalized children, these patients had decreased integrated concentrations of GH over a 24-hour period and a decreased number of GH secretory episodes during the 24 hours. They responded to GH injections with growth rates comparable to those patients who were classified as GH deficient. Rudman et al (*N Eng J Med* 1981;305:123), Hayek et al (*J Peds* 1981;99:868), and others have described similar patients, although integrated concentrations of GH have not always been determined. The patients of Rudman et al and Hayek et al also have responded to GH with growth comparable to that observed in patients who are unequivocally GH deficient.

The problem of determining the incidence of GH deficiency may even be more complex than cited

above. Patients with constitutional delay of growth may have a relative GH deficiency (Bierich and Polthoff, *Monatsschr Kinderheilkd* 1979;127:561), as determined by low nocturnal GH levels, when compared with children without constitutional growth delay. If these patients have GH deficiency, it may be transient and is often reversed when adolescence begins. Of interest is the observation that 10% to 20% of patients believed to have GH deficiency prepubertally, and who have been treated with GH, do not have GH deficiency as adults. This percentage range was determined from our studies of more than 60 adults who were treated with GH as children because they were found to be GH deficient by pharmacological testing. Gourmelin et al have also drawn attention to transient partial GH deficiency in prepubertal children with growth delay (*Pediatr Res* 1979;13:221).

Thus, it bears repeating that no one really knows the actual incidence of GH deficiency. In the United States, the incidence is undoubtedly much greater than the 14,500 cases estimated from the data of Vimpani et al. Even discounting patients with constitutional growth delay, there are probably 20,000 or more American children with complete or relative GH deficiency. Unfortunately, the tedious nature and expense of determining integrated concentrations of GH over a 24-hour period will prevent the diagnosis of GH deficiency in many patients who have the phenotype of GH deficiency, but who respond normally to provocative stimuli with GH release.

At this time, it should be emphasized that methods other than those currently available, including therapeutic trials, must be designed to determine the incidence of GH deficiency as a cause of short stature. Therefore, it is essential that we devote special attention in the next few years to research concerning the incidence, diagnosis, and treatment of GH deficiency.

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