

# Treatment of Children With Down Syndrome and Growth Retardation With Recombinant Human Growth Hormone

Short stature is known to be one of the features of Down syndrome (DS). The authors treated 13 children with DS who were short for age (standard deviation score [SDS] -1.19 to -3.5), microcephalic (-1.58 to 6.60 SDS), and had no heart disease. Before treatment, peak serum growth hormone (GH) concentrations were less than 10 µg/L after levodopa and clonidine stimulation tests in 5 patients, after clonidine in 3 patients, and after levodopa in 3 patients. Three patients had nocturnal integrated GH concentrations of 0.5, 1.5, and 0.65 µg/L, respectively. The endocrine findings before treatment were normal with respect to luteinizing hormone, follicle-stimulating hormone, estrogen, testosterone, prolactin, thyroid-stimulating hormone (TSH), thyroxine, and triiodothyronine.

The patients were given recombinant human GH (rhGH), 0.1 mg/kg subcutaneously, 3 days a week for 1 year. The mean growth rate before treatment was  $5.4 \pm 1.6$  cm/yr and increased to  $12.2 \pm 3.2$  cm/yr ( $P < 0.001$ ) after 12 months of rhGH treatment. The mean head circumference SDS before treatment was  $-3.1 \pm 1.3$  and increased to  $-2.3 \pm 1.2$  ( $P < 0.001$ ) at 12 months.

Two patients in whom elevated serum TSH concentrations developed while on rhGH treatment for 6 months were started on levothyroxine treatment. Bone age increment during the year of treatment corresponded to the increment in chronologic age. Plasma hemoglobin A<sub>1c</sub> concentration remained normal. The mean plasma concentrations of insulin-like growth factor 1 at baseline and at 12 months were  $0.54 \pm 0.19$  U/mL and  $1.25 \pm 0.97$  U/mL, respectively ( $P < 0.02$ ). The authors concluded that rhGH therapy can result in a significant increase in annual growth rate and head circumference in children with DS, without significant side effects.

Torrado C, Bastian W, Wisniewski, et al. *J Pediatr* 1991;119:478-483.

**Editor's comment:** *This provocative paper offers rhGH as a treatment for short stature and microcephaly in children with DS. The most impressive part of the study is the remarkable response of DS patients to GH treatment. They exhibited catch-up growth with a mean of  $12.2 \pm 3.2$  cm/yr, which is impressive even for patients with hypopituitarism. However, we have to point out several pitfalls of this study, including the lack of data to ascertain the possible causes of GH alterations in DS.*

*First of all, the height and weight of the patients were compared with growth charts for normal children rather than the standards for children with DS. The growth pattern of these*

*patients should be compared with children who have the same chromosomal defect.<sup>1</sup> No details were given about the age, sex, and pubertal stage of the patients.*

*Second, the authors come to the conclusion that neurosecretory problems were the cause of growth retardation. However, only 3 patients had integrated GH studies showing decreased GH levels. The criteria for neurosecretory dysfunction of GH in otherwise normal children are being debated.<sup>2</sup> In patients with problems such as DS, there would be much more debate to establish the criteria for this diagnosis. These patients did not meet the classic criteria of neurosecretory GH dysfunction. The growth velocity before treatment was above normal (5.4 cm/yr) instead of the usual decreased growth rate (below 4 cm/yr). Only 2 of the 13 patients had normal secretion of GH with pharmacologic provocative tests, which differs from the classic criteria and implies a normal response to pharmacologic stimulus and decreased physiologic levels. However, further explanations need to be sought for the excellent response to GH therapy. If this response was not associated with puberty or other factors in medical care that improve growth, it might suggest that DS patients present with a form of GH resistance as seen in other conditions, ie, uremia.*

*There might be another explanation for the GH unresponsiveness to pharmacologic stimulus. The body weights of these patients were not reported. Nonetheless, the SDS for weight ( $-1.0 \pm 0.7$ ) was higher than the SDS for height ( $-2.2 \pm 0.8$ ). It is a well-known fact that obesity is associated with decreased GH responsiveness.*

*This paper, despite its deficits, does imply that further double-blind, placebo-controlled studies should be undertaken to clarify the pathogenesis of growth retardation and to confirm the response to rhGH treatment in DS. Moreover, changes in head circumference and its correlation with intelligence must be studied in more detail. Caution should be exercised in initiating GH treatment in DS patients, unless it is undertaken as part of a carefully controlled and well-designed scientific study.*

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## References

1. Cronk C, et al. Growth charts for children with Down syndrome: 1 month to 18 years of age. *Pediatrics* 1988;81:102.
2. Bercu BB. Disorders of growth hormone neurosecretion. In: Lifshitz F, ed. *Pediatric Endocrinology* New York, NY: Marcel Dekker;1991:43-60.