Growth hormone treatment in non-growth hormone-deficient short children

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ABSTRACT. The unlimited availability of GH obtained by recombinant DNA technology has allowed optimization of treatment in GH-deficient (GHD) children. At the same time it has prompted a number of studies in conditions not characterized by GHD such as Turner syndrome, intrauterine growth retardation, chronic renal failure and other chromosomal and genetic abnormalities associated with short stature. Several controlled and uncontrolled studies have now reported the adult height of patients with short stature and normal GH secretion. Critical reviewing of the data shows that some short non-GHD children may benefit from a prolonged treatment with GH. However, further studies are needed in order to be able to identify the subjects for whom treatment is really beneficial.

INTRODUCTION

Until 1985 GH was extracted from human pituitaries, and because of the limited amounts its therapeutic use was confined to children with severe GH deficiency (GHD). Recombinant DNA technology has made it possible to obtain unlimited amounts of the hormone, thus allowing optimization of treatment in GHD patients as well as new therapeutic applications in conditions not characterized by GHD such as Turner syndrome, intrauterine growth retardation, chronic renal failure and other chromosomal and genetic abnormalities associated with short stature. In this paper we will review the use of GH in short children with normal GH secretion.

Definition of normal GH secretion

The definition of normal GH secretion is still a matter for debate. The GH response to stimulation has been used for decades in the diagnosis of GHD, although there is no general agreement on the cut-off limits for a normal response, i.e. a GH peak of 7 or 10 μg/l. Furthermore, a “normal” response to one stimulation test is taken to indicate that the child has no GHD, irrespective of the number of tests with “low” responses. One of the major problems of the provocative tests lies in their poor reproducibility and in the great number of falsely abnormal responses frequently observed in normal children (2-4). In a recent paper it has been shown that out of 33 children with a GH response to two pharmacological stimuli <10 μg/l, 29 showed a normal response when re-tested after 1-6 months (Fig. 1) (5). Furthermore, recent studies have shown that the GH response to stimulation normalizes at the attainment of adult height in the majority of childhood-onset GHD patients without magnetic resonance imaging (MRI) abnormalities of the hypothalamic-pituitary area (5, 6). These findings support the opinion that GH stimulation tests have very little accuracy in the diagnosis of GHD. Furthermore, patients with the clinical picture of GHD may have a normal GH response to stimulation tests but abnormal spontaneous GH secretion, and thus evaluation of 24 or 12 h spontaneous GH secretion has been advocated as a useful diagnostic test (7, 8). However, others have shown that spontaneous GH secretion offers no advantage over the stimulation tests in the diagnosis of GHD (9, 10). As in stimulation tests, spontaneous GH secretion is poorly reproducible (4, 11, 12). Determination of IGF-I alone also is not sufficiently accurate, since IGF-I concentrations can be normal in patients with recent-onset GHD (13). Furthermore,
target height. Familial short stature is characterized by a predicted height that is close to target height. Children with short stature and delayed skeletal maturation may have constitutional delay of growth and puberty (CDGP). However, in many cases a child with short stature does not fall exactly in one diagnostic group or the other, since delayed bone age can be found in children with familial short stature.

Some early papers showed that a short-term treatment with pituitary GH caused an acceleration of height velocity in non-GHD short children (18, 19). With the availability of unlimited amounts of GH from recombinant DNA technology, there has been an explosion of clinical studies in various conditions associated with short stature. It is doubtless that a short-term course of GH (6-12 months) increases height velocity in the great majority of children (20). The growth response during the first year of treatment is positively correlated to the dose of GH and to the frequency of weekly administration, and negatively correlated to pretreatment growth velocity (21, 22). Long-term data, however, show a wide inter-individual variability of responses (22, 23). Hopwood et al. (22) reported an increased growth velocity during the first 3 yr in 47 patients treated with a dose of 0.3 mg/kg/week, which resulted in a significant increase of mean standardized height. Moore et al. (23) have shown that the improvement of height velocity was maintained in only half of the 34 patients of their study treated with a dose of 0.3 mg/kg/week, and in none of them adult height was higher than target height. We reported final height in 15 non-GHD short children treated with GH for 4-10 yr (24). Eight children received a GH dose of 0.5 U/kg/week and the remaining 7 patients received a dose of 1 U/kg/week. Final height in both groups was not significantly different from predicted adult height or target height (Fig. 2). Final height was not correlated with any clinical or hormonal parameter or with the GH dose, whereas it was positively correlated with height at the onset of puberty. These findings have been lately confirmed by Kaplowitz (25) and Wit et al. (26). In the study by Wit et al. (25) the initial GH dose (2 U/m²/day) was doubled after the first year in the non-responder patients (increase in height velocity <2 cm), or thereafter when height velocity dropped below the 50th percentile for bone age. Final height in the 12 treated patients was similar to that observed in an untreated control group. The response to treatment resulted negatively correlated to pretreatment spontaneous GH secretion and to the peak GH response to pharmacological stimulation (26). Hindmarsh e Brook (27) reported final height in 16 patients treated for 4-9 yr at a dose of 12.2-21.0 U/m²/week for the first