Growth Hormone Treatment of Short Children: Clinical Perspective

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**Final Height and Psychosocial Aspects in GH-treated GHD**

Although GH treatment has been employed in Japan for more than 20 years since 1975, the final height of GH treated patients is still unsatisfactory. The Foundation for Growth Science conducted a national survey of GH-treated GH deficient (GHD) patients. Figure 1 (a) (b) shows the distribution of final height in GH-treated GH deficient (GHD) patients in the report. Approximately 40% of these patients did not exceed \(-2\) SD (standard deviation) and the mean final height SD score for these patients without gonadotropin deficiency was below \(-2\) SD (1). Several reasons for unsatisfactory final height are proposed. The first reason is the late start of GH treatment: the mean age at start of the GH treatment was approximately 12 years. The second reason is the low GH dosage and low weekly injection frequency: the mean GH dosage was approximately 0.3 U/kg/week and most patients received two or three injections per week. The third and most important reason why GH-treated patients without gonadotropin deficiency did not achieve normal height is their relatively early pubertal onset while still short and rather smaller pubertal height gain than in normal children (2). Height at the onset of puberty is closely related to final height in children with GHD (3).

**Fig. 1** Distribution of final height in GH-treated GHD.
Of 709 GHD patients who reached adulthood, only 30 men and 32 women married: 6.0% and 17.2%, respectively (1). These percentages are lower than those in the general population of the same age group. Many patients expressed anxiety about sexual relationships, since 65% of them had GHD in association with multiple pituitary hormone deficiency. Although unemployment rate is low in these patients, they are not very well adapted to social life.

**GH Treatment for Non-GHD Short Stature**

Guyda (4) reported the final height of GH-treated non-GHD short stature (the International Task Force Report). The mean height SD score only improved from $-2.76$ SD to $-1.96$ SD in boys and from $-2.86$ SD to $-1.90$ SD in girls which did not reach the target height SDS despite GH treatment for over four years. Recent epidemiological Japanese data show that approximately 60% of short children ($<-2$ SD) at 6 years exceed $-2$SD of height SDS at 17 years (5). Mean height SDS in these children increased from $-2.41$ SD to $-1.72$ SD in boys and $-2.41$ SD to $-1.92$ SD in girls without any treatment (Fig. 2). Kawai et al. reported that the final height of GH-treated non-GHD short boys was $154.2 \pm 4.2$ cm, while that of untreated control short boys was $162.0 \pm 5.4$ cm (6). The effect of GH treatment in non-GHD short children should therefore be evaluated carefully by a well-organized control study. We also have to consider who should be treated and how.

It is well known that GH plays an important role in gonadal function by inducing local production of IGF-I in the ovary and testis. It has also been shown that there is a significant positive correlation between age at the start of GH treatment and age at the onset of puberty in GHD (Fig. 3) (3) as well as in non-GHD short children (7). Since short children generally enter puberty later, pubertal induction by GH does not induce precocious puberty but does induce puberty while still short. Since pubertal height gain is no greater in these GH-treated non-GHD boys...
short children than in normal children, they end up shorter than normal as adults.

**Perspectives of GH Treatment**

The main therapeutic goals of GH treatment are to make short children catch up to normal height early, which will solve the psychosocial problems related to short stature during childhood and to treat them to reach normal adult height and adapt them to social life in adulthood. To achieve these goals, the dosage of GH must be reevaluated. GH treatment is supposed to be replacement therapy. If GH treatment is replacement therapy, GH treatment should be only expected to make short children grow at normal growth rate, but since GH treatment induces catch-up growth for a few years at the beginning, this catch-up growth is misunderstood as the main effect of GH replacement therapy and normalization of the growth rate after a few years is called “the waning phenomenon” (Fig. 4). The normal growth rate observed after a few years is the expected effect of GH replacement treatment, but the catch-up growth is said to be caused by an unknown mechanism of GH treatment. GH treatment is overestimated because of the catch-up growth.

For early normalization of height and normal height at onset of puberty, high dose GH treatment is the treatment of choice (Fig. 5). High dose treatment can cause catch-up growth to continue to normal height, since gigantism can cause overgrowth due to increased secretion of GH. Stepwise increasing dose trials and high dose trials are now proceeding in Japan. High dose trial in non-GHD short children (8) and short children with IUGR (9) have been reported. When non-GHD short children enter puberty at normal height after catch-up growth due to high dose treatment, GH treatment can be stopped and normal final height can be expect-

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**Fig. 4** Catch-up growth in a GHD patient treated with replacement dose of GH.

**Fig. 5** Catch-up growth in a GHD patient treated with high dose of GH.
Short height at the onset of puberty is the main reason for short adult height in non-GHD short stature as well as GHD. When children enter puberty while they are still short, the treatment of choice is combined GH and LHRH analog treatment. We have already reported that combined gonadal suppression treatment (GST) and GH treatment could increase final height in GHD patients (10). As shown in Fig. 7, final height was significantly shorter in patients with spontaneous puberty without GST than in patients with GST. Their gonadal suppressive effect was insufficient, however, and side effects such as obesity and general malaise have been reported.

Since LHRH analog has a strong gonadal suppressive effect without serious side effects, we have treated children who enter puberty short with the combined LHRH analog and GH to increase their final height. The results are not conclusive yet, because only a few patients reached their final height, but they are promising (11). Combined LHRH analog and GH treatment can increase the adult height of short children who entered puberty early for height by decelerating bone age maturation, elongating treatment period and consequently increasing pubertal height gain. Although there were no serious adverse events affecting these patients during the treatment, psychosocial problem caused by delayed puberty must also be dealt with and bone mineral density must be followed carefully.

References

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