**Combined GH and LHRH Analog Treatment in Short Children**

TOSHIKI TANAKA***, MARI SATOH**, AND ITSURO HIBI*

*Division of Endocrinology & Metabolism, National Children's Hospital, and
**Department of Endocrinology & Metabolism, National Children's Medical Research Center, Tokyo 154, Japan

Abstract. It has been reported that the final height in short children is strongly related to the height at the onset of pubertal development, and pubertal height gain in GH-treated children is not exceed the gain in normal children. Therefore, it is now the consensus that insufficient height at the onset of puberty leads to short final height. We have already demonstrated that the final height in GH-deficient children with spontaneous puberty with gonadal suppression therapy by medroxyprogesterone or cyproterone acetate was significantly taller than GHD with spontaneous puberty without gonadal suppression therapy. In this study, we treated short boys who started puberty at height shorter than 130 cm with combined GH and LHRH analog. Final height was predicted by the height SD score for bone age. Although pubertal growth spurt was not recognized in short children on combination treatment, bone age maturation over 11.5 years decelerated significantly to the rate of one year in three or four years. Even during this slow bone maturation period, growth velocity remained at 4 cm/year due to GH treatment. Therefore, height SDS for bone age was improved in combination with the elongation of treatment period by the slow bone maturation. Some investigators recommend not to delay induction if puberty much beyond the normal age to avoid psychological problems and ennuchoid proportion in these children. When we explained to our Japanese patients the chance of increasing the final height with gonadal suppression treatment and the risk of delaying the pubertal development, almost all children preferred taller final height to pubertal development and they did not experience much psychological trouble. The differences in social and cultural circumstances do, however, influence patients' preferences.

Key words: GHD, Non-endocrine short stature, Puberty, Gonadal suppression treatment, GH treatment

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**Final Height in Isolated GHD**

Though 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 mean final height standard deviation (SD) score in GH-treated patients without gonadotropin deficiency does not exceed $-2$ SD [1]. The main reason why GH-treated patients without gonadotropin deficiency have not achieved normal height is their relatively early pubertal onset when 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], non-GHD short children [4] and normal children [5]. Figure 1 shows the natural linear growth in twelve non-GHD short boys at 7 years, onset of pubertal growth spurt, and 18 years. Only two short boys' height SD score exceed $-2$ SD [6]. Age at the onset of pubertal growth spurt is not so early, but height is shorter than in normal children.

Since pubertal height gain is no greater in these short children than in normal children, they end
up shorter than normal as adults. Most of these children are classifiable as intrauterine growth retardation (IUGR) or familial short stature (FSS). Short height at the onset of puberty is therefore the main reason for short adult height in non-GHD short stature: once short children enter puberty, they will be short as adults.

Gonadal Suppression Treatment in Combination with GH Treatment

We have already reported that combined gonadal suppression therapy and GH treatment could increase final height in GHD patients [7]. As shown in Figs. 2 and 3, final height was significantly shorter in patients with spontaneous puberty without gonadal suppression treatment (GST) than in patients with combined gonadotropin deficiency, whose pubertal development was induced at an older age. The presence of normal gonadal function did therefore not help to achieve normal adult height with GH treatment. This advantage in GHD with spontaneous puberty could be overcome partially by combined GST. The mean duration of GST was 4.4 years. GST significantly increased the duration of puberty and total pubertal height gain. The gonadal suppressive agents used in previous studies were medroxyprogesterone or cyproterone acetate. 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 boys who enter puberty short with the combined LHRH analog and GH to increase their final height.

The LHRH analog used for the combination treatment was leuprolide acetate in microcapsule form (30-90 µg/kg, subcutaneous injection every four weeks) or tryptorelin in microcapsule form (60 µg/
kg, intramuscular injection every four weeks); the GH was Genotropin (0.5–1.0 U/kg/week, daily subcutaneous injection). Bone age was estimated by the Tanner-Whitehouse (TW) 2 RUS method standardized for Japanese children [8]. Predicted adult height was estimated by the Bayley-Pinneau method standardized for Japanese children [9] and by the projected height SD score for bone age.

Figure 4 shows data from a typical patient with familial short stature. His testicular enlargement began at 10.5 years, when his height was at 123 cm and bone age was 10.5 years; at the time when his adult height was predicted to be 156.3 cm by the projected height SDS for bone age method and 152.1 cm by the Bayley-Pinneau method. His treatment was started with 60 µg/kg of tryptorelin at 10.92 years and 0.5 U/kg/week of GH at 11 years. Growth velocity was 6.7 cm/year in the first year and 5.2 cm/year in the second year. GH was increased to 1.0 U/kg/week and the increased GH dose effectively maintained growth velocity: his growth velocity remained at 6.0 cm/year in the third year, 6.4 cm/year in the fourth year and 5.4 cm/year in the fifth year. He has been treated with the combination treatment for 5.83 years. His bone age has advanced only 2.9 years and his height more than 30 cm during this treatment period. Although his pubertal stage remained at 6 ml of testicular volume, the penis at Tanner stage 3, and pubic hair at Tanner stage 2, he has not complained about pubertal delay and is still eager to become taller. He discontinued LHRH analog at 16.75 years at 159.4 cm, when his predicted adult height was 171.6 cm by the projected height SDS for the bone age method and 172.6 cm by the Bayley-Pinneau method. His pubertal stage was Tanner 3 at the start of treatment and remained at almost the same level during the combination treatment. He gained almost 10 cm while taking GH after the cessation of LHRH analog and his puberty developed to Tanner stage 5 in two years. He is satisfied with his height.

Twenty-one boys who entered puberty shorter than 130 cm were enrolled in the combination treatment with informed consent. Their mean predicted adult height was estimated to be 171.6 cm by the projected height SDS for the bone age method and 172.6 cm by the Bayley-Pinneau method. Seven patients discontinued LHRH analog treatment when their mean age was 17.11 years and their mean height was 155.1 cm after a mean treatment period of 4.96 years, when their predicted adult height was 169.8 cm and 169.2 cm, respectively. The remaining fourteen are receiving the combi-
nation treatment after a mean period of 3.75 years. All except one patient are continuing GH treatment alone after cessation of LHRH analog and will continue it until they reach their final height.

Combined LHRH analog and GH treatment can increase the adult height of short children who entered puberty early for height, but although there were no serious adverse events of these patients during the treatment, there are some problems in this combination treatment. The main problem is perhaps the psychosocial problems caused by delayed puberty, since this combined treatment must continue for at least three years. Before the treatment, we explain to both patient and parents the chances of increasing final height with the combination treatment and the risks of delaying pubertal development. We treat only those patients who strongly wish for a taller adult height. There may be cultural differences among countries: in Japan most patients prefer taller final height to normal pubertal development. Another problem may be decreased bone mineral density caused by depressed sex steroids. This is now being studied.

A couple of points can be improved. The first is the timing of the start of the combination treatment. Since bone age is not decelerated before 11.5 years anyway, we can wait to start the treatment until the bone age exceeds 11.5 years. This delayed start may induce further pubertal development as well as a stronger pubertal growth spurt and may shorten the treatment period. The second is the timing of the cessation of LHRH analog treatment. We could stop the combination treatment earlier according to the predicted adult height, but we do not yet know the accuracy of the adult height prediction, since these methods were based on the data from normal children. Both methods appear to overestimate final height at the cessation of LHRH analog. Nor do we know exactly how much the patients will grow after the cessation of LHRH analog. A better treatment regimen will be established after all these patients who are now being treated reach their adult height.

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References


