Severe Juvenile Hypothyroidism: Treatment with GH and GnRH Agonist in Addition to Thyroxine

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PROLONGED juvenile hypothyroidism results in a permanent loss in height that is related to the duration of thyroxine deficiency before adequate thyroxine replacement treatment [1]. We report a 13-yr-old girl and an 11-yr-old girl with this condition, of 7 years' and of 3 years' duration, respectively, treated with GH and GnRH agonist.

Methods

Serum LH, FSH, GH, and thyroid stimulating hormone (TSH) were measured by two site immunoradiometric assay (Daiichi Radioisotope Co, Tokyo). Bone age was assessed by the Greulich and Pyle atlas.

Case Report

Case 1 (Fig. 1)

The girl studied showed average gain in height until the age of 6 yr but subsequently had a sudden reduction in height velocity and her condition has been in part reported [2]. At 13 yrs of age her height for chronological age (SD score) was -6.6 SD and her bone age was 5.8 yr. She had overt hypothyroidism, and no sign of pubertal development. Serum thyroxine was undetectable

and the TSH concentration was 510 mIU/l. The patient was diagnosed as having juvenile hypothyroidism of 7 years' duration. She was treated with thyroxine. Two months after the start of the thyroxine replacement, LH and FSH levels in response to LHRH infusion test were pubertal levels (Table 1). We administered intranasal GnRH agonist (buserelin 1800 μ g/day four times a day) between 14.7 and 16.2 yr. At the age of 15.3 yr her bone age was 12.5 yr. During this regimen GH secretion was impaired: peak values of GH in response to insulin and arginine were both less than 7 μ g/l (see Table 1). The patient was treated with daily GH injections (0.5 IU/kg/week) in addition to thyroxine and GnRH agonist from age 15.3 until 17 yr. Menarche was noted three months after stopping GnRH agonist (16.5 yr). At 20 yr of age her height was 157 cm (-0.18 SD score).

Case 2 (Fig. 2)

The girl studied showed an average gain in height until the age of 8 yr, but subsequently had a sudden reduction in height velocity. At 11.3 yr of age her height for chronological age (SD score) was -3.7 SD and her bone age 7.0 yr. She had overt hypothyroidism, and no sign of pubertal development. Serum thyroxine was undetectable and the TSH concentration was 1400 mIU/l. The TSH receptor antibody level was 18.6%. An atrophic thyroid gland was confirmed by ultrasonography. The patient was diagnosed as having juvenile hypothyroidism of 3 years' duration. She was treated with thyroxine and the dose was thereafter adjusted to maintain normal

Fig. 1. Growth velocity and longitudinal growth curve for Case 1.

thyroxine and TSH concentrations. The peak GH after GRF infusion were $19.0 \mu\text{g/l}$ (before thyroxine treatment) and $41.2 \mu\text{g/l}$ (three months after thyroxine). She gained 4.3 cm in height during the first 4 months of thyroxine replacement. At 11.6 yr, LH and FSH levels were pubertal levels in response to $75 \mu\text{g}$ GnRH infusion (see Table 2) and bone age was 7.5 yr. We had treated the patient with GnRH agonist (leuporelin $1440 \mu\text{g/day}$ once

a month) since the age of 11.8 yr. At the age of 12.3 yr her bone age was 10 yr. During this regimen GH secretion was impaired: peak values of GH in response to GRF and arginine were $7.8 \mu\text{g/l}$ and $4.7 \mu\text{g/l}$, respectively. The patient was treated with daily GH injections (0.5 IU/kg/week) in addition to thyroxine and GnRH agonist from the age of 12.7 yr. At 14 yr of age her height and bone age were 141 cm (-2.8 SD score) and 11.5 yr,

Table 1. Serial data in case 1.

13 yr 6 m (at first diag.)	LH-RH test
Height age 7 yr	LH 0.4 → 1.4 IU/l
Bone age 6 yr	FSH 7.0 → 10.7 IU/l
T4 < 0.1 µg/dl	
2 m after T4	LH-RH test
Bone age 8 yr	LH 6.1 → 15.9 IU/l
T4 5.3 µg/dl	FSH 14.1 → 18.4 IU/l
On GnRH agonist	GH secretion
C.A. 15 yr	Insulin 5.2 ng/ml
Bone age 12.5yr	Arginine 6.5 ng/ml
	mean overnight 2 ng/ml

Table 2. Serial data in case 2.

11 yr 3 m (at first diag.)	LH-RH test
Height age 7 yr	LH 0.6 IU/l
Bone age 7 yr	FSH 15 IU/l
T4 < 0.1 µg/dl	
3 m after T4	LH-RH test
Bone age 7 yr 6 m	LH 0.3 → 21.7 IU/l
T4 12.1 µg/dl	FSH 2.7 → 19.1 IU/l
On GnRH agonist	GH secretion
C.A. 12 yr 4 m	GRF 7.8 ng/ml
Bone age 11 yr	Arginine 4.7 ng/ml

Fig. 2. Growth velocity and longitudinal growth curve for Case 2.

respectively. She was currently growing 6.6 cm annually.

Discussion

After the start of thyroxine treatment most patients' catch-up growth occurs during the first three years and is accompanied by a marked advance in bone age [1]. Our patients also showed an early disproportionate effect of thyroid hormone on bone age maturation. The higher average age of children with juvenile hypothyroidism makes their catch-up difficult to achieve because of the shorter residual period [1]. In this regard, it is important to note that, in both patients, gonadotrophin secretion reached pubertal levels

shortly after thyroxine replacement, with normal TSH and thyroxine levels, and puberty commenced during catch up growth. The mechanism is unknown, but Anasti *et al.* showed that the precocious puberty in severe juvenile hypothyroidism is consistent with stimulation of the FSH receptor by the very high TSH levels [3].

In juvenile hypothyroidism, low GH production has not been considered to be a major factor in incomplete catch-up growth [1]. We found impaired GH secretion in these patients during gonadal suppression treatment and have demonstrated height gain with GH treatment. GH plus GnRH agonist treatment appeared to contribute to the attainment of normal height gain in patients with threatened pubertal progression during catch up growth [2].

References

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