Treatment with a gonadotropin-releasing-hormone analog and attainment of full height potential in a male monozygotic twin with gonadotropin-releasing hormone-dependent precocious puberty

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Abstract We report on a pair of male monozygotic twins, one unaffected and the other affected with gonadotropin-releasing hormone (GnRH)-dependent precocious puberty, and discuss the role of treatment with a GnRH analog in the attainment of full height potential in GnRH-dependent precocious puberty. At 1.6 years of age, the affected twin was studied for tall stature (+3.8 SD), and was diagnosed as having GnRH-dependent precocious puberty due to a hypothalamic hamartoma of the tuber cinereum. He was treated with oral cyproterone acetate (110–170 mg/m² daily) from 1.8 through 5.0 years of age, with oral cyproterone acetate and intranasal buserelin acetate (700–900 μg/m² daily) from 5.0 through 7.5 years, and with intranasal buserelin acetate alone (1100–1400 μg/m² daily) from 7.5 through 12.6 years. He attained a final height of 171.0 cm at 14.9 years of age (+0.10 SD) and his twin 170.0 cm at 15.3 years of age (−0.10 SD), with their target height being 174.5 ± 9.0 cm.

Conclusion This study indicates that GnRH analog treatment may preserve near full height potential in some patients with GnRH-dependent precocious puberty.

Key words Precocious puberty · Hypothalamic hamartoma · Monozygotic twins · GnRH analog · Final height

Introduction

Precocious puberty is often associated with accelerated skeletal maturation that leads to a short final height if untreated [4]. Treatment with a gonadotropin-releasing hormone (GnRH) analog has been shown to improve the height prognosis of patients with GnRH-dependent precocious puberty [1–6, 8–10]. It has been reported, however, that patients given GnRH analog treatment rarely attain their full height potential [1, 2, 4–6, 8, 9]. Further, most such reports have evaluated the final heights of treated female patients, since only a few male patients have been studied. There are only two reports describing the final heights of male patients treated with GnRH analog to date. Oerter et al. [5] and Paul et al. [9] reported that the mean final heights of their two cohorts of six treated male patients were −1.3 ± 1.3 SD and −1.7 ± 1.6 SD, respectively, below the target height.

To determine whether GnRH analog treatment can preserve the full height potential in GnRH-dependent precocious puberty, the most meaningful method would be to compare the final heights of treated patients to those of untreated patients in a randomized double-blind study. This approach is ethically unacceptable. We report on a pair of monozygotic twins, one unaffected and the other affected with GnRH-dependent precocious puberty, which provides a useful hitherto undescribed model for assessing the efficacy of such treatment.

Case reports

Male monozygotic twins were born at 37 weeks of gestation to non-consanguineous and healthy Japanese parents in an uneventful...
pregnancy and delivery. The father measures 175.4 cm, and the mother 156.6 cm. The target height of the twins is $174.5 \pm 9.0$ cm [7].

The affected twin (Twin A) measured 46.0 cm (±2.5 SD) and weighed 2340 g (±2.6 SD) at birth. Twin A was referred to Keio University Hospital because he was tall at 1.6 years of age: height 91.2 cm (+3.8 SD), weight 16.4 kg (+7.8 SD) (Fig. 1). Mental and motor development were appropriate for age. Bone age (BA) was 5.0 years, and the height for BA was −3.8 SD. Serum gonadotropin and testosterone levels were elevated within the pubertal range (Table 1). Other pituitary hormones including thyroid-stimulating hormone were within the normal range (data not shown).

Twin A was diagnosed as having GnRH-dependent precocious puberty. A hamartoma of the tuber cinereum was revealed by computed tomography of the brain at 1.7 years of age and magnetic resonance imaging at 3.7 years. The tumor was pedunculated and 1.5 cm in diameter. It has not changed in shape and size with time (Fig. 2).

Twin A was treated with oral cyproterone acetate (110–170 mg/m² daily), a progestational agent, from 1.8 through 5.0 years of age (BA from 5.0 through 11.0 years), with oral cyproterone acetate (140–170 mg/m² daily) and intranasal buserelin acetate (700–900 µg/m² daily), a GnRH analog, from 5.0 through 7.5 years (BA from 11.0 through 13.1 years), and with intranasal buserelin acetate alone (1100–1400 µg/m² daily) from 7.5 through 12.6 years (BA from 13.1 through 16.0 years). After buserelin acetate treatment began, serum gonadotropin and testosterone levels were suppressed within the prepubertal range (Table 1), and the BA/chronological age (CA) ratio was reduced (less than 1.0) (Table 2). During buserelin acetate treatment, levels of serum insulin-like growth factor 1 were within the normal range (361.0–613.0 ng/ml), the average increase in height was maintained at 5.4 cm/year, and the height age (HA)/BA ratio was maintained at more than 1.0 (Table 2).

Testicular volumes were 6 ml at 5.8 years of age, 12 ml at 8.2 years, and 15 ml at 11.2 years of age. Pubic hair appeared at 8.5 years of age, and axillary hair at 12.6 years. Nocturnal emission occurred at 13.0 years of age. Gonadotropin and testosterone levels resumed within the pubertal range four months after the end of the treatment.

**Table 1** Endocrinological data for the affected twin. Normal reference range of basal luteinizing hormone, follicle-stimulating hormone and testosterone levels are shown in parentheses. All values were determined by radioimmunoassay, but LH and FSH at 13.0 years were measured by immunoradiometric assay.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>CA at study (years)</th>
<th>LH (IU/l)</th>
<th>FSH (IU/l)</th>
<th>Testosterone (µg/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>1.7</td>
<td>13–142 (0.0–8.1)</td>
<td>6–13 (1.0–6.0)</td>
<td>3.2 (&lt;0.1)</td>
</tr>
<tr>
<td>Cyproterone acetate</td>
<td>4.8</td>
<td>18–32 (0.0–8.1)</td>
<td>6–8 (1.0–6.0)</td>
<td>0.9 (&lt;0.1)</td>
</tr>
<tr>
<td>Cyproterone acetate</td>
<td>5.9</td>
<td>&lt;2–2 (0.0–8.1)</td>
<td>5–11 (1.0–6.0)</td>
<td>0.2 (&lt;0.1)</td>
</tr>
<tr>
<td>Buserelin acetate</td>
<td>11.8</td>
<td>&lt;0.5 (0.0–8.1)</td>
<td>0.5 (1.6–6.5)</td>
<td>&lt;0.1 (0.2–1.5)</td>
</tr>
<tr>
<td>None</td>
<td>13.0</td>
<td>4.0 (0.2–12.4)</td>
<td>8.4 (2.6–10.1)</td>
<td>5.0 (2.2–6.2)</td>
</tr>
</tbody>
</table>

a Basal–peak after gonadotropin-releasing-hormone test (100 µg/m² i.v., blood sampling at 0, 30, 60, 90 and 120 min)