The clinical effects of gonadotropin-releasing hormone agonists for the treatment of children patients with central precocious puberty

Y. XUE, P. WANG, S.-Q. WANG, Y.-Q. GAO

Department of Endocrinology, Xuzhou Children’s Hospital, Xuzhou, Jiangsu, P.R. China

Abstract.

OBJECTIVE: We explored the clinical effect of gonadotropin-releasing hormone agonists for the treatment of children patients with central precocious puberty.

PATIENTS AND METHODS: From March 2012 to October 2015, 100 cases of children patients with central precocious puberty were enrolled in this study. Intramuscular injection of acetate acid triptorelin (50 to 100 pLg/kg) was made once every 4 weeks, and the treatment lasted for 4 months. Patients’ bone age/height differentials (ΔBA/ΔCA), bone age (BA), growth velocity (GV) and predicted adult height (PAH) were determined before and after treatment (after 6, 12, 24, 36 months). Differences before and after treatment were analyzed.

RESULTS: Sexual development symptoms in children patients were significantly improved 4 months after treatment (p<0.05). All patients completed the treatment, without any adverse drug reaction or severe complication. After one course of treatment (4 months), patients’ uterus and ovarian volumes shrank, FSH level peaked, and LH level was reduced, compared to those before treatment.

CONCLUSIONS: Acetate acid triptorelin is safe and reliable for treating central precocious puberty. We achieved the excellent clinical curative effect and were able to delay the growth rate in children patients. The predicted height and final height were improved.

Key Words

Gonadotropin-releasing hormone agonists (GnRH-a), Central precocious puberty, Clinical curative effect.

Introduction

With social progress and the continuous improvement of people’s living and nutritional standards, children’s growth and development levels have been accelerated. The number of children with central precocious puberty is in the rise. This condition seriously affects children’s normal life and their adulthood’s final height. Gonadotropin-releasing hormone agonists (GnRH-a) are the preferred drugs for treating central precocious puberty. We, in this study, explored the clinical effect of GnRH-acetate acid triptorelin for the treatment of children patients with central precocious puberty and achieved satisfactory results.

Patients and Methods

General Information

From March 2012 to October 2015, 100 cases of children patients with central precocious puberty were enrolled in this study. The age range was from 7.5 to 9.5 years (average=8.0±0.5 years). The study was approved by the Ethics Committee of Xuzhou Children’s Hospital. Signed written informed consents were obtained from the patients or guardians.

Inclusion criteria: (i) breast growth before the age of 8 or menarche before the age of 10; (ii) LHRH provocation tests: LHRH peak greater than 12 u/L, and LH peak/FSH peak greater than 0.6; (iii) ovarian increase (ovarian volume>1 ml); (iv) multiple follicles with average diameter greater than 4 mm; (v) bone age (BA) was older than the actual age (CA); (vi) RI or CT examinations excluded any brain, adrenal gland, and ovary organ lesions.

Exclusion criteria: (i) patients with precocious puberty caused by drugs; (ii) patients with combined chronic diseases, diseases related to the immune system and severe heart or cerebrovascular diseases were all excluded.

Tanner method was employed to determine patients’ sexual development stages. According to Tanner method, from the total 90 cases with early breast growth, 22 cases were in B2 phase, and 68 cases were in B3 phase. From the 100 cas-

Corresponding Author: Ying Xue, MD; e-mail: xueying96@yeah.net
es with pubic hair growth, 70 were in PH1 phase, 24 were in PH2, and 6 cases were in PH3 phase. We also had 26 cases of menarche and 28 cases of armpit hair growth. Pelvic B ultrasound examination showed that uterine volume was greater than 3 cm³, and ovarian volume was over 1 cm², with small follicles. The growth rate was speeded up and the height of patients was (1.1±0.3) times higher than normal children in the same age and gender. Luteinizing Hormone-Releasing Hormone (LHRH) provocation tests showed that luteinizing hormone (LH) peak >10.31 u/L, and LH peak/follicle stimulating hormone (FSH)>1.02 u/L.

**Treatment**

Patients received 50 to 100 t/g/kg GnRH-a-Triptorelin (Diphereline, Ipsen Pharma Biotech, France, import registration certificate H20140298). The intramuscular injection was conducted once every four weeks for 4 months. CHN method was used to evaluate BA; height was measured on a regular basis. WizardV2.1 software, from Shanghai Ruijin Hospital, was used to predict the ultimate height in adult age.

**Observation Indexes**

Bone age differential/height differential (ΔBA/ΔCA), BA, growth velocity (GV) and predicted adult height (PAH) were determined before and after treatment (6, 12, 24, 36 months after treatment). Patients’ sexual development symptoms, the changes in the uterus, the ovarian volume were monitored and recorded before and after treatment. During the treatment, we monitored blood pressure, heart rate, and other vital signs. We also regularly examined our patients to detect any possible adverse drug reactions or local reactions, headaches, fatigue, flushed face, and other serious complications.

**Statistical Analysis**

SPSS19.0 software was used for statistical analysis, and measurement data were presented by mean ± standard deviation (x±s). A t-test was used for comparisons and count data was verified by χ². p<0.05 indicated that the difference was statistically significant.

**Results**

ΔBA/ΔCA, BA and PAH values 6, 12, 24, 36 months after treatment were significantly different compared with those before treatment. Differences were statistically significant (p < 0.05). After treatment ΔBA/ΔCA and GV were significantly lower than those before treatment, while BA and PAH were significantly higher than those before treatment (Table I). Sexual development symptoms in patients were significantly improved 4 months after treatment (p < 0.05). The difference was statistically significant (Table II).

All patients completed the treatment, without any adverse drug reactions or severe complication. After one course of treatment (4 months), patients’ uterus and ovarian volumes shrank. Compared to those before treatment, FSH and LH level were reduced. Differences were statistically significant (p < 0.05) (Table III).

**Discussion**

Central precocious puberty, also known as gonadotropin-releasing hormone (GnRH) dependent precocious puberty, can lead to prematurity of secondary development. Patients with central precocious puberty usually experience early breast, pubic hair and armpit hair growth. Also, menarche and growth retardation caused by the

<table>
<thead>
<tr>
<th>Table I. Changes in monitoring indicators.</th>
<th>BA (year)</th>
<th>ΔBA/ΔCA</th>
<th>GV (cm/a)</th>
<th>PAH (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Before treatment</strong></td>
<td>10.30 ± 0.89</td>
<td>10.56 ± 0.98</td>
<td>9.01 ± 1.38</td>
<td>149.41 ± 4.18</td>
</tr>
<tr>
<td><strong>After treatment</strong></td>
<td>6 months</td>
<td>11.05 ± 0.76</td>
<td>0.86 ± 0.41</td>
<td>7.78 ± 1.31</td>
</tr>
<tr>
<td></td>
<td>12 months</td>
<td>11.24 ± 0.98</td>
<td>0.71 ± 0.31</td>
<td>6.56 ± 1.29</td>
</tr>
<tr>
<td></td>
<td>24 months</td>
<td>11.45 ± 1.02</td>
<td>0.52 ± 0.30</td>
<td>5.21 ± 1.17</td>
</tr>
<tr>
<td></td>
<td>36 months</td>
<td>11.99 ± 1.76</td>
<td>0.28 ± 0.22</td>
<td>4.50 ± 1.01</td>
</tr>
<tr>
<td><strong>F-value</strong></td>
<td>7.386</td>
<td>4.201</td>
<td>3.502</td>
<td></td>
</tr>
<tr>
<td><strong>p-value</strong></td>
<td>0.0285</td>
<td>0.4011</td>
<td>0.450</td>
<td></td>
</tr>
</tbody>
</table>

BA: bone age; CA: actual age; GV: growth velocity; PAH: predicted adult height.
early closing of bone line in the age of 8 can be observed, which can eventually affect children’s adulthood height\textsuperscript{10,11}. The incidence rate in females is higher than males with a ratio of 6:1\textsuperscript{12-14}. Patients often experience an early onset of central precocious puberty, or in other words, early development of physical, sexual and social psychological maturity. But the growth process is similar to normal puberty, which is also regulated by both the growth hormone axis and gonadal axis\textsuperscript{15,16}.

Due to an early gonad development, the growth rate in children with idiopathic central precocious puberty usually reaches the peak ahead of time. The growth time is shortened, which causes an elder bone age, and early closing of the epiphyseal line, leading to a final height beyond the reach of genetically targeted height. And at the same time, it can also lead to some psychological and social complications. GnRHa is universally recognized as the standard treatment for central precocious puberty\textsuperscript{17-19}.

GnRHa exerts a highly inhibitory effect on hypothalamic pituitary gonadal axis (HPGA) to restrain the secretion of gonadotropin (LH, FSH), and stop gonad development, so the level of sex hormone declines. Prior studies\textsuperscript{20} reported that the application of GnRH had relatively ideal clinical effects on motivating the growth potential in children patients and boosting their adulthood height, and at the same time had less influence on children’s physical condition. Results obtained from this study showed that after 6, 12, 24, 36 months of treatment with Triptorelin Acetate, ΔBA/ΔCA and GV were lower than those before treatment, while BA and PAH were significantly higher than those before treatment. As the treatment time increased, sexual development signs in patients improved gradually. After the treatment, sexual development symptoms in patients greatly improved, and the volume of the uterus, the ovary, and LH and FSH levels were much lower than levels recorded before the treatment. Our results showed that the use of GnRH-a-Triptorelin acetate for the treatment of central precocious puberty was safe and reliable\textsuperscript{21,22}.

### Conclusions

The application of Triptorelin Acetate for the treatment of central precocious puberty proved to be curative, and could effectively delay the growth rate in children patients, improve the predicted height, and improve the ultimate adult height.

### Table II. Improvements of the sexual development symptoms.

<table>
<thead>
<tr>
<th></th>
<th>Breast development</th>
<th>Pubes hair growth</th>
<th>Armpit hair growth</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B2</td>
<td>B3</td>
<td>PH3</td>
</tr>
<tr>
<td>n</td>
<td>n</td>
<td>n</td>
<td>n</td>
</tr>
<tr>
<td>Before treatment</td>
<td>22</td>
<td>68</td>
<td>6</td>
</tr>
<tr>
<td>After treatment</td>
<td>16</td>
<td>56</td>
<td>28</td>
</tr>
<tr>
<td>p-value</td>
<td>0.044</td>
<td>0.040</td>
<td>0.401</td>
</tr>
</tbody>
</table>

Perc. = Percentage

### Table III. Uterus, ovarian volume and hormone levels before and after treatment.

<table>
<thead>
<tr>
<th></th>
<th>Before treatment</th>
<th>After treatment</th>
<th>t-value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uterus volume (ml)</td>
<td>4.57 ± 1.60</td>
<td>2.89 ± 1.11</td>
<td>6.385</td>
<td>0.317</td>
</tr>
<tr>
<td>Ovarian volume (ml)</td>
<td>2.27 ± 1.23</td>
<td>1.67 ± 1.21</td>
<td>4.206</td>
<td>0.457</td>
</tr>
<tr>
<td>LH (U/L)</td>
<td>19.67 ± 8.82</td>
<td>14.67 ± 2.89</td>
<td>5.239</td>
<td>0.352</td>
</tr>
<tr>
<td>FSH (U/L)</td>
<td>5.28 ± 2.78</td>
<td>3.21 ± 1.62</td>
<td>5.287</td>
<td>0.349</td>
</tr>
</tbody>
</table>
Effects of gonadotropin-releasing hormone agonists for the treatment of children

Conflict of Interests
The Authors declare that they have no conflict of interests.

References