

Therapeutic effect of aromatase inhibitor combined with recombinant human growth hormone on short stature boys with larger bone age

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Abstract: To analysis of the efficacy of aromatase inhibitor combined with recombinant human growth hormone and provide a clinical basis for the treatment of boys with larger bone age. All the boys were diagnosed as short stature and bone age ≥ 13 years in the Department of Endocrinology and Metabolism, Qingdao Women and Children Hospital from October 2017 to October 2019. Both were treated with aromatase inhibitor and recombinant human growth hormone. Observed the changes in height, weight, growth velocity, bone age, predicted adult height, testosterone, insulin-like growth factor-1 and side effects after baseline, 6 months and 12 months of treatment. After treatment with aromatase inhibitor and recombinant human growth hormone, the testosterone and insulin-like growth factor-1 levels in the children increased significantly, the bone age progressed slowly, and growth velocity and predicted adult height are improved, which was statistically significant ($P < 0.01$). During the treatment, the children were monitored for normal masculinization, and had no significant effect on BMI ($P > 0.05$), and the safety and tolerability were good. Aromatase inhibitor combined with recombinant human growth hormone to treat short stature boys with larger bone age can delay bone age progression, improve predicted adult height, and have good safety and tolerability in the short term.

Keywords: Letrozole; Recombinant human growth hormone; Larger bone age; Short stature; Boys

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1. Introduction

Short stature refers to the person whose height is lower than the 3rd percentile or reduced by 2 standard deviations of the same race, same sex and the same age healthy population, under the similar living environment[1]. The application of recombinant human growth hormone can effectively improve the growth rate of short stature children, and the effect of predicted adult height has been recognized. However, for short stature children with larger bone age, the growth potential is insufficient, and the treatment space is limited, resulting in the height of adults is not ideal. Recent studies have shown that aromatase inhibition (AI) combined with recombinant human growth hormone can effectively delay the progress of bone age and improve the predicted adult height ability.

However, at present, there are few related research samples at home and abroad, and the follow-up time is short, so there are some disputes about its efficacy and side effects. At present, the definition of macroskeletal age at home and abroad is not clear, combined with the literature report [2], this study analyzes the effect of AI combined with rhGH in the treatment of children with larger bone age and short stature, based on larger bone age is that bone age ≥ 13 years old.

2. Objects and methods

2.1. Objects

Twenty boys with short stature and BA ≥ 13 years old was diagnosed in Endocrinology Department of Qingdao Women and Children's Hospital from October 2017 to October 2019. It includes 2 cases of growth hormone deficiency and 18 cases of idiopathic short stature. Among them, there were 10 cases whose bone age lagged behind the actual age, 6 cases whose bone age was equivalent to the actual age, and 4 cases whose bone age exceeded the actual age. Exclusion criteria: organic lesions caused by intracranial and adrenal tumors or other causes; severe acute and chronic hepatorenal diseases; patients with abnormal glucose tolerance or diabetes mellitus; HBsAg or HBeAg positive in hepatitis B; asymmetrical short stature; 6) there are clear chromosome and gene abnormalities.

2.2. Therapeutic method

Recombinant human growth hormone and letrozole were used simultaneously to treat the children who met the research standard, rhGH (Sai Zeng, Chinese Medicine Quasi Character S20050025) 0.15IU/kg.d, hypodermic injection before sleep, letrozole (Jiangsu Heng Rui Chinese Medicine Quasi Character H19991001) 2.5mg/d, oral administration.

Height, weight, sexual development stage, sex hormone, blood glucose, thyroid function, liver and kidney function, insulin-like growth factor-1 (IGF-1) were monitored every three months during the treatment. Bone age was monitored every 6 months. The changes of height, growth velocity (GV), bone age (BA), predicted adult height (PAH), body mass index (BMI), testosterone (T), IGF-1 and their side effects were observed 6 and 12 months after treatment.

2.3. Evaluation method

BA was assessed using the China 05 method and was evaluated by the same professional.

PAH = current height / current bone age height as a percentage of adult height (the prediction of adult height is based on the relationship between bone age and the percentage of adult height in the Chinese 05 method [3]).

BMI = weight (kg) / height (m) ², height and weight of the same child were measured at the same time.

2.4. Statistical method

SPSS23.0 software was used for statistical

analysis, and the measurement data conforming of normal distribution was expressed by mean ± standard deviation. Self paired t-test was used for comparison before and after treatment, the difference was statistically significant (P < 0.05).

3. Results

3.1. Changes of BA / CA, GV and PAH before and after treatment

After treatment with AI and rhGH, the ratio of bone age to actual age decreased, but the growth rate was significantly higher than that before treatment, and PAH was significantly improved compared with that before treatment (P < 0.01), (Table 1).

3.2. Changes of T, BMI and IGF-1 levels before and after treatment

The level of serum testosterone and insulin-like growth factor-1 after AI combined with rhGH treatment was significantly higher than that before treatment, the difference was statistically significant (P < 0.01). BMI had no significant change compared with that before treatment (P > 0.05) (Table 2).

Table 1. Comparison of BA / CA, GV and PAH before and after treatment with letrozole and recombinant human growth hormone

project	People (number)	BA (year)	BA/CA	GV (cm/year)	PAH (cm)
before treatment	20	13.30±0.44	1.01±0.09	5.66±0.90	161.61±4.23
after 6 months of treatment	19	13.70±0.45*	0.99±0.10*	9.15±3.12*	163.38±4.65*
after 12 months of treatment	16	13.88±0.48*	0.99±0.09*	8.70±1.80*	165.09±3.51*

Note: * P < 0.01 than before treatment

Table 2. Comparison of T, BMI and IGF-1 levels before and after treatment with letrozole and recombinant human growth hormone

project	People (numble)	T (nmol/L)	BMI (kg/m ²)	IGF-1 (ug/L)
before treatment	20	8.35±6.21	21.21±3.51	164.93±56.39
after 6 months of treatment	19	31.83±11.16*	21.40±3.30	306.56±53.34*
after 12 months of treatment	16	32.57±9.80*	21.45±3.80	331.22±65.47*

Note: * P < 0.01 than before treatment.

3.3. Side effects

During the treatment, AI combined with rhGH in 20 larger bone age and short stature boys. The adverse reactions of AI combined with rhGH in the

treatment of 20 larger bone age and short stature boys included 5 cases of hyperandrogenemia (facial acne, emotional irritability, increased body hair, muscular strength of limbs), among them, 1 case had

lower extremity pain and 1 case had hypothyroidism. There were 3 cases of facial acne, emotional agitation, body hair and muscle strength. After full communication with parents, letrozole was stopped and the symptoms were relieved one month later. 2 cases of parents complained of the increase of facial acne. After treatment, the symptoms were relieved and AI combined with rhGH was continued. One case of AI combined with rhGH had pain in both legs after 4 months of treatment. His serum 25 hydroxyvitamin D level was low after repeated measurement, and no obvious osteoporosis was found in X-ray examination of both legs. Calcium supplement and vitamin D treatment was less effective after 1 month, but the symptoms improved in 2 weeks after letrozole was stopped. One case had hypothyroidism, and the thyroid function recovered quickly after taking levothyroxine sodium tablets (Euthyrox) by oral administration.

4. Discussion

There are two common conditions for children with larger bone age and short stature: the time of treatment is late, and the bone age at the time of treatment is ≥ 13 years old, including the situation that the bone age is equal to or behind the actual age; the bone age exceeds the actual age, which is often related to the rapid progress of adolescence. Research shows that [4,5], the effect of sex hormones on growth promotion is bidirectional. On the one hand, male and female hormones cooperate with growth hormone, thyroid hormone, cortisol and other hormones to promote the proliferation of epiphyseal chondrocytes. Estrogen will also accelerate the depletion of the proliferation ability of chondrocytes, aging the bone age and closing the epiphyses. At present, the principle of treatment for children with larger bone age and short stature is to delay the progress of bone age and increase the growth speed to the maximum extent. The common treatment methods are rhGH alone, AI alone, rhGH combined with GnRHa, rhGH combined with AI[6]. But each method has its own applicable population, advantages and disadvantages. We need to pay attention to the optimization of the treatment plan.

Letrozole is the third generation aromatase inhibitor. Its mechanism[7] is to inhibit or inactivate aromatase, inhibit the transformation of androgen to estrogen, and thus reduce the level of estrogen in vivo. Letrozole has been mainly used in the treatment of breast cancer, endometriosis and other estrogen related tumors for more than 20 years. In recent years, it has been found that estrogen plays a key role in the growth regulation of bone growth plate. Without the role of estrogen, the epiphysis will continue to open [8,9]. Based on this feature, AI has gradually been used to treat adolescent idiopathic

short stature, growth hormone deficiency, familial male precocious puberty, adolescent male breast development and other diseases after 2000 [10-12]. GnRHa can delay the development of bone age when it is used to treat the children with larger bone age and short stature. However, it can also inhibit sexual development, which may have psychological effects on the children with normal adolescence. Some studies have shown that [6,13] letrozole is used to treat larger bone age and short stature boys. On the one hand, it can delay epiphysis closure by preventing androgen from transforming to estrogen. Moreover, it can form high testosterone level which directly affects growth plate. It has the effect of promoting linear growth. It will not inhibit normal masculinity. It not cause psychological negative effects of children. Monika Bullinger et al. [14] investigated the quality of life of male adolescents with idiopathic short stature. The results showed that both growth hormone and aromatase inhibitor had a positive impact on the quality of life.

In 2005, Hero et al. [15] carried out a randomized, double-blind, placebo-controlled study on boys aged 9.0-14.5, BA < 14 years old, who were diagnosed as idiopathic short stature. After two years of follow-up treatment, letrozole treatment group predicted an average adult height of 172.8cm, 5.9cm higher than before treatment, and placebo group 166.9cm, significantly lower than letrozole treatment group. There was no difference in the proportion of puberty between the two groups different. Mauras et al. [16] conducted a multicenter, randomized, controlled clinical study on 52 adolescent boys with GHD in 2008. After 36 months of follow-up treatment, the progress of BA in AI group was significantly behind that in placebo group. PAH in AI group increased by (6.7 ± 1.4) cm, while that in placebo group increased by only 1.0 cm. Children in AI group had normal sexual development level, no significant difference from placebo group. Zhang Xianlai [17] in 2017, 56 children with larger bone age and short stature were randomly divided into single group and combined group. After 3 years of follow-up treatment, suggesting that recombinant human growth hormone combined with letrozole was more effective in the treatment of larger bone age short stature children. In this study, the therapeutic effect of AI combined with rhGH in the treatment of larger bone age short stature boys is to delay the progress of bone age and improve the prediction of adult height.

Some studies have shown that [18-20], AI has good safety, does not increase fat generation, low urinary calcium loss. AI does not affect the bone density and bone growth of children. AI also does not increase the incidence of vertebral body deformation. The study has no significant impact on low-density lipoprotein, triacylglycerol and insulin resistance index, and not affect the reproductive ability of boys.

It can cause the rise of androgen, with acne, erectile and other adverse effects. The reaction can be recovered after drug withdrawal. In the follow-up observation of this study, it was found that the testosterone level after treatment was significantly higher than that before treatment. BMI of children before treatment had no significant change compared with that after treatment. Among the 20 cases of bone age short stature boys, 5 cases had the symptoms of facial acne, emotional agitation, body hair increase and limb muscle strength caused by hyperandrogen. 1 case had pain in both lower limbs after 4 months of treatment, the serum 25 hydroxyvitamin D level was low after repeated tests, no obvious osteoporosis was found in the X-ray examination of both lower limbs. The effect of calcium and vitamin D supplementation was poor after treatment. The symptoms were improved after stopped letrozole treatment. 1 case had hypothyroidism, and the thyroid function recovered quickly after taking levothyroxine sodium tablet. The treatment of AI combined with rhGH in 20 bone age short stature boys had a normal course of masculinity in one year. The tolerance of adverse reactions caused by the increase of androgen was good. The cause of pain in both lower limbs in one case was unknown, which also suggested that the safety of letrozole should be further studied.

5. Conclusion

The safety and tolerance of 20 children with larger bone age and short stature in the treatment process of AI combined with rhGH are good, which can delay the progress of bone age, improve the prediction of adult height, and provide clinical basis for AI combined with rhGH in the treatment of children with larger bone age and short stature. However, the sample size of this study is small and no control group has been set up. The effect and adverse reactions of this study still need a larger sample size randomized control study and long-term follow-up observation.

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