The Effects of Recombinant Human Growth Hormone on Height and Serum IGF-1 in Children with Idiopathic Short Stature

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Abstract
Objective: To investigate the effects of recombinant human growth hormone (rhGH) on height and serum IGF-1 in patients With Idiopathic Short Stature (ISS).

Methods: We selected 64 children diagnosed with ISS in our hospital from January 2013 to October 2015. According to whether patients' parents were willing to accept the rhGH treatment, they were distributed into treatment group and control group. The control group took normal nutrition therapy, meanwhile the children in treatment group were treated with rhGH (dosage 0.12~0.15IU/(kg d), subcutaneous injection 30 minutes before bedtime once a day) based on control group. The treatment duration was 12 months. The indicators observed included height, weight, bone age, height growth, variation in bone age, fasting blood-glucose, thyroid function, IGF-1 and IGFBP-3.

Results: After treatment period, height and height growth in the treatment group were notably higher than that in control group [(123.8±5.4) cm vs. (118.3±6.3) cm, (10.8±3.0) kg vs. (4.5±1.8) kg] (P<0.05). There were no significant differences in weight, bone age and variation in bone age between the two groups (P>0.05). The levels of IGF-1 and IGFBP-3 in treatment group were notably higher than that in control group [(310.52±63.44) ng/mL vs. (210.20±55.74) ng/mL, (6.75±1.26) μg/mL vs. (5.44±1.18) μg/mL] (P<0.05). During the treatment, no obvious side effects were observed except transient mildly elevated fasting blood-glucose in two cases and skin injection site infrared in one case.

Conclusion: Recombinant human growth hormone can improve IGF-1, IGFBP-3 levels in the children with idiopathic short stature, and then promote the children's growth with good clinical curative effect and high safety.

Keywords: recombinant human growth hormone, Idiopathic short stature, Height, Serum IGF-1.

Introduction

Idiopathic short stature (ISS) was considered as a type of short stature with normal growth hormone level and no potential pathological condition.

The heights of most children with ISS are just slightly below that of normal children at the same age. But some of them are as particularly short as those children with growth hormone deficiency[1-3]. If not treated, children with ISS will have shorter final height than their peers[4,5]. US Food and Drug Administration approved recombinant human growth hormone (rhGH) to treat the children with ISS in June 2003[6,7]. It is able to promote the growth of bones and muscles, regulate the endocrine system and promote protein synthesis[8,9]. Related studies show that the hormone can improve the children's growth rate and won't lead to bone maturation and early puberty[9-11]. This study analyzes the effect of rhGH on height and IGF-1 in children with ISS. The details are reported as follows.

Subjects and Methods

Subjects: 64 children (aged 6~11.2 years) diagnosed as ISS in child health clinic of our hospital from January 2013 to December 2015 were selected, including 29 boys and 35 girls. The inclusion criteria are [3]: 1. Born with singleton full-term pregnancy, height and weight were normal at birth. 2. Current height is more than 2standard deviations below the average height of children with the same age and gender, or the current height is below P3 of the height of children with the same age and gender. 3. Growth rate is less than 5cm per year. 4. Body is shapely. 5. Growth hormone peak is larger than 10ng/mL in growth hormone stimulation test. 6. Chromosome is normal. 7. No chronic systemic disease, pituitary disease, thyroid dysfunction, precocious puberty or other diseases. 8. No serious emotional or psychological disorders. Food intake is normal.

Methods: Children were distributed into treatment and control groups according to whether their parents are willing to accept rhGH therapy. The patients in control group received normal nutrition therapy and reasonable guidance on diet, exercise, sleep and other aspects. In addition to what given to control group, treatment group received rhGH through subcutaneous injection, 30 min before bedtime once a day. The dosage was 0.12~0.15IU/ (kg·d). The duration of treatment for all children was 12 months. Height, weight, thyroid function through venous

blood, fasting glucose, IGF-1, IGFBP-3, and other indicators were measured in regular follow-up every three months. Bone age was checked through left hand X-ray every 6 months. The variations in bone age and height growth in two groups were observed. The variation in bone age was equal to the bone age after treatment minus that before treatment.

The height growth was equal to the height after treatment minus that before treatment. Adverse drug reactions in treatment group, like thyroid function, fasting glucose, swelling and numbness at injection site were monitored.

Statistical Methods: SPSS 18.0 was used for statistical analysis. Measurement data, such as height, weight, variation in bone age, height growth and so on, were represented as $\bar{x}\pm s$. t-test was used for inter group comparison. Adverse reactions and other count data were represented as (n, %). $\chi 2$ test was used for inter group comparison. The difference is considered of statistical significance when $P < 0.05$.

Results

Comparisons of age, height, weight and bone age between two groups before treatment: The average age of 64 children was 8.3±2.1 years (aged 6.0 ~ 11.2 years). The treatment group includes 34 cases and control group includes 30 cases. The differences in age, height, weight and bone age between two groups are of no statistical significance. See table 1.

Table 1
Comparisons of age, height, weight and bone age between two groups before treatment ($\bar{x}\pm s$)

	Treatm	Control	P value
Age (years)	8.21±2.	8.40±1.	*P*>0.05
Gender	15/19	14/16	*P*>0.05
Height	113.2±5	113.9±6	*P*>0.05
Weight	21.5±3.	22.0±4.	*P*>0.05
Bone age	7.9±1.3	8.2±1.2	*P*>0.05

Comparisons of height, height growth and weight between two groups after treatment: No significant differences were observed in height and weight between the two groups before treatment. After treatment, the height and height growth in treatment group were notably higher than that in control group ($p < 0.05$). There were no significant differences in weight between the two groups ($P > 0.05$). See table 2.

Table 2
Comparisons of height, height growth and weight between two groups after treatment ($\bar{x}\pm s$)

	Treatment group （*n*=34） vs Control group （*n*=30）			
	3 months	**6 months**	**9 months**	**12 months**
Height(cm)	(116.3±5.1) vs (114.3±5.9)*	(119.2±4.8) vs (115.5±6.2)*	(121.9±5.3) vs (117.1±6.4)*	(123.8±5.4) vs (118.3±6.3)*
Height growth (cm)	(2.9±0.9) vs (1.5±0.8) *	(5.5±1.2) vs (2.1±1.0) *	(8.2±1.8) vs (3.3±1.2) *	(10.8±3.0) vs (4.5±1.8) *
Weight(kg)	(22.0±4.0) vs (22.2±4.5)	(22.7±3.8) vs (22.3±4.8)	(23.5±4.3) vs (22.9±4.7)	(24.1±4.0) vs (23.2±4.8)

Note: * indicates the difference is of statistical significance, P < 0.05.

Comparisons of bone age and variation in bone age between two groups: No significant differences in bone age and variation in bone age were observed between two groups after treatment ($P > 0.05$). See table 3.

Table 3
Comparisons of bone age and variation in bone age between two groups after treatment ($\bar{x}\pm s$)

	Treatment group （*n*=34） vs Control group （*n*=30）	
	6 months	**12 months**
Bone age (years)	(8.4±1.7) vs (8.8±1.5)	(9.0±1.9) vs (9.1±1.8)
Variation in bone age (years)	(0.6±0.2) vs (0.6±0.1)	(1.0±0.3) vs (0.9±0.2)

Comparisons of fasting blood-glucose, thyroid function, IGF-1 and IGFBP-3 levels before and after treatment: There were no significant differences in the levels of fasting glucose, free T3 (FT3), free T4 (FT4), thyroid stimulating hormone (TSH), IGF-1 and IGFBP-3 between the two groups before treatment ($P>0.05$). See table 4. After treatment, the levels of IGF-1 and IGFBP-3 in treatment group were significantly higher than that in control group ($P<0.05$). See table 5. At the same time, no significant differences were observed in the levels of fasting glucose, FT3, FT4 and TSH between two groups ($P>0.05$).

Safety Analyses: During the treatment, slight transient fasting glucose increase appeared in 2 children who received rhGH therapy, and the glucose level got back to normal without any special treatment. 1 case of redness at injection site appeared at the beginning of treatment, and there was no

further adverse reaction and thyroid function abnormality in the following treatment.

Table 4
Comparisons of fasting blood-glucose, FT3, FT4, TSH, IGF-1, IGFBP-3 levels before treatment($\bar{x}\pm s$)

	Treatment group（*n*=34）	Control group（*n*=30）	P value
Fasting glucose (mmol/L)	4.57±1.02	4.13±0.98	*P*>0.05
FT3 (pg/ml)	3.72±0.95	3.58±1.02	*P*>0.05
FT4 (ng/dl)	1.10±0.17	1.43±0.19	*P*>0.05
TSH (μIU/ml)	3.97±1.2	4.12±1.5	*P*>0.05
IGF-1 (ng/mL)	183.47 ±42.56	192.56 ±51.02	*P*>0.05
IGFBP-3 (μg/mL)	5.25±1.07	5.17±1.32	*P*>0.05

Table 5
Comparisons of IGF-1, IGFBP-3 levels after 12 months of treatment($\bar{x}\pm s$)

	Treatment group（*n*=34）	Control group（*n*=30）	P value
IGF-1(ng/mL)	310.52± 63.44	210.20± 55.74	*P*<0.05
IGFBP-3(μg/mL)	6.75±1.26	5.44±1.18	*P*<0.05

Discussion

The incidence report of ISS in countries around the world varies. A study in American 2001 shows that from 2476 cases of short stature children, the number of ISS cases is 475, accounting for 19%[12]. The retrospective analysis from Iran shows that the portion of ISS is 4.5% in short stature children 4-18 years old[13]. At present large amount and multi-center data still lacks in China. Children with short stature often have varying degrees of problems in social skill, self-esteem, cognition development, self-confidence and personality, which cause serious impact to their future development.[14-17] Therefore, early diagnosis and effective treatment methods are quite important.

Growth hormone is a secreted protein under the effect of pituitary cells. The secretion is pulsatile. It can promote bone growth, bone cell proliferation, protein synthesis and metabolism, and cell proliferation. The promotion effect is significant when it is used in the children who diagnosed with short stature[5]. rhGH has the similar effect to growth hormone and is able to promote the growth of children with short stature. It is approved to treat growth hormone deficiency[7-9]. Related researches show that the adult height of children with ISS can be improved when appropriate dosage of rhGH was given, and this is largely related to that the functions of IGF-1 and IGFBP-3.[9,18-20]

IGF-1 is a combination of 70 basic peptides of amino acid. It belongs to a single polypeptide chain type, and is mainly secreted by liver cells. It is capable of promoting proliferation and growth, and plays an important regulatory role in body growth. IGFBP-3 is a macromolecular glycoprotein and its content in serum is large. It has high affinity with IGF-1. IGFBP-3 can be combined with IGF-1 in serum to extend the half-life of IGF-1, affecting the binding and transport of IGF-1 and its receptors. The escape of IGF-1 from blood is regulated, the localization of IGF-1 is coordinated, and the concentration of IGF-1 is maintained. Thereby the effect of promoting body growth is achieved. Studies reported that serum IGF-1 and IGFBP-3 can be effective indicators to predict and determine the treatment efficacy of children with ISS[9,20]. Our study shows that compared with control group, the increment in the levels of serum IGF-1 and IGFBP-3 in ISS children with rhGH treatment are more significant. It indicates that the levels of serum IGF-1 and IGFBP-3 can be increased by rhGH, and then promote the children's growth.

In conclusion, rhGH can significantly increase the levels of IGF-1 and IGFBP-3 in children with ISS and then promote the children's growth. It has good clinical efficacy and high safety and is worth to be further popularized in clinical use.

References

1. Rapaport R., Idiopathic short stature, *N Engl J Med*, **355(11)**, 1178 **(2006)**

2. Cohen P. et al, Consensus statement on the diagnosis and treatment of children with idiopathic short stature: a summary of the Growth Hormone Research Society, the Lawson Wilkins Pediatric Endocrine Society, and the European Society for Paediatric Endocrinology Workshop, *J Clin Endocrinol Metab*, **93(11)**, 4210-7 **(2008)**

3. Liu G.L., Idiopathic short stature, *Chinese Journal of Practical Pediatrics*, **20(8)**, 454-456 **(2005)**

4. Jeong H.R. et al, Comparative Study of Growth Hormone Treatment in Children with Idiopathic Short Stature and Growth Hormone Deficiency, *Curr Drug Metab*, **16(10)**, 940-6 **(2015)**

5. Zayed S. and Madlon-Kay D.J., Growth Hormone for Treatment of Idiopathic Short Stature in Children, *Am Fam Physician*, **92(1)**, 64 **(2015)**

6. Wilson T.A. et al, Update of guidelines for the use of growth hormone in children: the Lawson Wilkins Pediatric Endocrinology Society Drug and Therapeutics Committee, *J Pediatr*, **143(4)**, 415-21 **(2003)**

7. Bryant J. et al, Recombinant growth hormone for idiopathic short stature in children and adolescents, *Cochrane Database Syst Rev*, DOI:10.1002/14651858.CD004440.pub2 **(2007)**

8. Dang G.J. and Pei D., The effect of recombinant human growth hormone therapy with idiopathic short stature in 49 children, *Chinese Journal of Child Health Care*, **22(5)**, 552-553 **(2014)**

9. Kim H.S. et al, Efficacy of short-term growth hormone treatment in prepubertal children with idiopathic short stature, *Yonsei Med J*, **55(1)**, 53-60 **(2014)**

10. Crowe B.J. et al, Effect of growth hormone dose on bone maturation and puberty in children with idiopathic short stature, *J Clin Endocrinol Metab*, **91(1)**, 169-75 **(2006)**

11. Jeong H.R. et al, The effect of growth hormone treatment on height in children with idiopathic short stature, *J Pediatr Endocrinol Metab*, **27(7-8)**, 629-33 **(2014)**

12. Wyatt D., Lessons from the national cooperative growth study, *Eur J Endocrinol*, **151(Suppl 1)**, S55-9 **(2004)**

13. Moayeri H. and Aghighi Y., A prospective study of etiology of short stature in 426 short children and adolescents, *Archives of Iranian Medicine*, **7(1)**, 23-27 **(2004)**

14. Noeker M., Management of idiopathic short stature: psychological endpoints, assessment strategies and cognitive-behavioral intervention, *Horm Res*, **71(Suppl 1)**, 75-81 **(2009)**

15. Visser-van Balen H. et al, Motives for choosing growth-enhancing hormone treatment in adolescents with idiopathic short stature: a questionnaire and structured interview study, *BMC Pediatr*, **5(1)**, 15 **(2005)**

16. Tanaka T. et al, Evaluation of Quality of Life in Children with GH Deficiency and Idiopathic Short Stature Using the Child Behavior Checklist, *Clin Pediatr Endocrinol*, **18(1)**, 15-22 **(2009)**

17. Tanaka T. et al, Effect of growth hormone treatment on quality of life in Japanese children with growth hormone deficiency: an analysis from a prospective observational study, *Clin Pediatr Endocrinol*, **23(3)**, 83-92 **(2014)**

18. Smyczynska J. et al, Significant increase of IGF-I concentration and of IGF-I/IGFBP-3 molar ratio in generation test predicts the good response to growth hormone (GH) therapy in children with short stature and normal results of GH stimulating tests, *Neuro Endocrinol Lett*, **34(3)**, 222-8 **(2013)**

19. Lundberg E. et al, Growth hormone (GH) dose-dependent IGF-I response relates to pubertal height gain, *BMC Endocr Disord*, **15**, 84 **(2015)**

20. Kristrom B. et al, IGF-1 and growth response to adult height in a randomized GH treatment trial in short non-GH-deficient children, *J Clin Endocrinol Metab*, **99(8)**, 2917-24 **(2014)**.