Diagnosis and Growth Hormone (GH) Therapy in Children with GH Deficiency: Experience in King Chulalongkorn Memorial Hospital, Thailand

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Background: *Diagnosis of growth hormone deficiency (GHD) needs both clinical and biological aspects such as auxological data and GH provocative tests, and active metabolites of GH including IGF-I and IGFBP-3. In GHD children, rhGH has been used worldwide with minimal serious side effects. The aims of the present study were to describe the experience in King Chulalongkorn Memorial Hospital regarding diagnosis and treatment with rhGH in GHD children.*

Material and Method: *Clinical data of 173 short children was retrospectively reviewed. Two GH provocative tests used in the present study were insulin tolerance test (ITT) and clonidine test. To make the diagnosis of GHD, the children had to fail both GH provocative tests (peak GH < 10 ng/ml). Baseline clinical data, IGF-I, and IGFBP-3 were compared between the group with true positive test and the group with false positive test. Thirty-five children with GHD, who had been treated with rhGH, were evaluated in terms of growth response, changes of IGF-I SDS and the relationship between these parameters.*

Results: *From the present study, ITT could diagnose GHD with true positive 57% and false positive 43% and clonidine could diagnose with true positive 67% and false positive 33%. Clinical data including chronological age, bone age, HtSDS, WtSDS, IGF-I SDS, and IGFBP-3 SDS were not different between the true positive and false positive group. rhGH with a mean dose of 29.3 $\pm$ 4.6 μg/kg/day increased height velocity (HV) from 3.9 $\pm$ 2.5 to 9.3 $\pm$ 2.5, 8.1 $\pm$ 1.5, 7.2 $\pm$ 2.2, 6.8 $\pm$ 2.2, 7.6 $\pm$ 2.4, and 6.5 $\pm$ 1.8 cm/yr after 6 months, 1,2,3,4, and 5 years after treatment, respectively. This also improved HtSDS during treatment and brought the HtSDS into the target range after 3 years of treatment. At the end of the first year of treatment, the difference of IGF-I SDS ($\triangle$IGF-I SDS) $\geq$ 1 could predict a good response ($\triangle$HtSDS $\geq$ 0.5) with sensitivity of 88.9% and specificity of 60% respectively. At the end of the second year, $\triangle$IGF-I SDS $\geq$ I could predict a good response with sensitivity and specificity of 100% and 29%, respectively.*

Conclusion: *From the present study, the authors demonstrated the investigation and treatment practices of short children with GHD. The growth response is satisfactory even with a lower dose than suggested. In addition, measurement of IGF-I and IGFBP-3 cannot be used in diagnosing GHD but can predict the height outcome at least by the first 2 years of the treatment. However, long-term outcome need to be clarified.*

Keywords: *Growth hormone deficiency, Insulin-like growth factor, Growth hormone provocative test*

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Diagnosis of growth hormone deficiency (GHD) needs both clinical and biological aspects such as auxological data, GH provocative tests and active metabolites of GH including IGF-I and IGFBP-3. In short children due to GHD, recombinant human GH (rhGH) replacement therapy has been used worldwide with minimal serious side effects. However, less than 40% of GHD children in Thailand have been continuously treated with rhGH because they cannot afford the treatment[1]. King Chulalongkorn Memorial Hospital

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is one of the biggest university hospitals in Thailand where many short children have been referred to for further investigations by general pediatricians who work in the rural area and in private hospitals. The aims of the present study were first, to describe the results of investigation for diagnosis of GHD, second, to describe the growth responses to rhGH in these children in King Chulalongkorn Memorial Hospital and third, to evaluate the relationship between clinical and biochemical responses.

Material and Method

The authors retrospectively reviewed the clinical data of short children presented at the Endocrine unit, Department of Pediatrics, Chulalongkorn Memorial Hospital for evaluation of GH status. Other causes of short stature were excluded. They included skeletal dysplasia, syndromes with short stature, hypothyroidism, electrolyte disturbance, and short stature due to chronic illnesses.

Diagnosis of GHD

To make the diagnosis of GHD, short children had to fail two GH provocative tests (peak GH less than 10 ng/mL). In the present study, 173 short children had GH provocative tests performed. One hundred and fifty one short children had insulin tolerance test (ITT) performed as a first test. If they failed the first test, they would come to do the second test, which is a clonidine test. Twenty-two children came to have clonidine test performed as the first test. If they failed, they would come for the second test, the ITT.

GH therapy

Thirty-five children, who were diagnosed with GHD (male 22, female 13) and regularly treated with recombinant human GH in King Chulalongkorn Memorial Hospital, were evaluated for the growth and biochemical responses. Baseline clinical data is shown in Table 1.

The mean dose of recombinant human GH (rhGH) was 29.3 $\pm$ 4.6 µg/ kg/day. Height was converted to height standard deviation score (Ht SDS) by using height of normal Thai children as a reference. Serum IGF-I and IGFBP-3 were measured before and during treatment and the results were converted to IGF-I SDS and IGFBP-3 SDS by comparing with normal Thai children[2]. All data were summarized with mean and standard deviation (SD) for continuous variables and number (%) for categorical variables. Non-parametrics tests were used for comparison of before and after treatment. Significant was set at $p < 0.05$.

Table 1. Baseline clinical data of 35 GHD children

Clinical data	Mean	SD
Chronological age (yr)	8.8	2.8
Bone age (yr)	5.8	3.0
Ht SDS	-2.2	0.9
Wt SDS	-0.8	0.7
Pre-treat height velocity (cm/yr)	3.9	1.0
Peak GH (ng/mL)	5.6	2.7
IGF-I SDS	-0.6	0.8
IGFBP-3 SDS	-1.6	1.3

Results

Evaluation of GH provocative tests

One hundred and fifty one short children had ITT performed and 36 of them passed the test (peak GH > 10 ng/mL). Ninety of them had clonidine test performed as the second test (25 children were lost to follow up). Fifty-one of 90 still failed the clonidine test (peak GH < 10 ng/ml). Therefore, true positive of ITT was 57% and false positive of ITT was 43%. Twenty-two short children had the clonidine test performed; seven of them passed the test. Six of them had ITT performed as a second one (9 were lost to follow up). Four of six still failed the test. Therefore, true positive of the clonidine test was 67% and false positive of the clonidine was 33%. The clinical data of fifty-five children who had true positive for both tests were compared with those of forty-one children who were false positive for both tests. The authors found that Ht SDS, Wt SDS, IGF-I SDS, and IGFBP-3 SDS were not different between the two groups (Table 2).

GH therapy in GHD children

Thirty-five children with GHD were treated

Table 2. Clinical data of 55 short children with true positive for both tests and 41 short children with false positive for both tests

	True positive, mean (SD)	False positive, mean (SD)
CA (yr)	8.3 (3.4)	9.3 (3.1)
BA (yr)	6.1 (3.5)	6.5 (3.0)
Ht SDS	-1.5 (1.0)	-1.4 (0.7)
Wt SDS	-0.9 (1.2)	-0.9 (1.2)
IGF-I SDS	-0.6 (0.8)	-0.5 (0.7)
IGFBP-3 SDS	-1.8 (1.1)	-1.9 (0.9)

with recombinant human GH. Mean peak GH during GH provocative test was 5.6 ± 2.7 ng/ml. Twenty-three were defined as complete GHD and 22 were partial GHD. Thirty-three children were isolated GHD and three had multiple pituitary hormone deficiencies (1 with hypogonadotropic hypogonadism, 1 with secondary hypothyroidism and small pituitary gland demonstrated by MRI, 1 with panhyhypopituitarism due to postoperative tumor removal). Mean GH dose was 29.3 ± 4.6 μg/kg/day, 6-7 times per week. During treatment, nine of male children and six of female children had spontaneous puberty at the mean age of 12.8 ± 0.8 and 11.7 ± 1.6 years, and the mean bone age of 12.0 ± 0.8 and 10.5 ± 1.1 years, respectively.

Growth response

Height velocity (HV) increased from 3.9 ± 1.0 cm/yr before treatment to 9.3 ± 2.5,8.1 ± 1.5,7.2 ± 2.2, 6.8 ± 2.2, 7.6 ± 2.4, and 6.5 ± 1.8 cm/yr after 6 months 1, 2, 3, 4, and 5 years after treatment. (Fig. 1) In addition, Ht SDS was also improved during treatment as shown in Fig. 2. Ht SDS was not significantly different from mid-parental height SDS at 3, 4, and 5 years after treatment.

IGF-I and IGFBP-3

IGF-I and IGFBP-3 SDS before and during treatment is demonstrated in Fig. 3. The authors divided the children into two groups according to the difference between IGFI SDS at 1-year after treatment and that before treatment. In group 1, the difference was ≥ 1 and in group 2, the difference was < 1. The growth response was defined as good response if treatment could change Ht SDS ≥ 0.5 and poor response if that was < 0.5[3]. The authors studied only the children who were still in prepuberty. During the treatment, those children who started into the puberty were excluded from this analysis.

At the end of the first year of treatment, eight of nine children who had the difference of IGF-I SDS ≥ 1 were in the good response group. Six of 10 children who had the difference of IGF-I SDS < 1 were in the poor response group. This showed that the change of IGF-I SDS at 1 yr (≥ 1) could predict the response with a sensitivity of 88.9% and a specificity of 60% (Fig. 4). At the end of the second year of treatment, all nine children who had a change of IGF-I SDS ≥ 1 were in the good response group. Two of seven children who had a change of IGF-I SDS < 1 were in the poor response group. Therefore, change of IGF-I SDS at 2 year ≥ 1 could predict the response of treatment with the sensitivity of 100% and specificity of 29%.

Discussion

The diagnosis of GHD can be difficult, owing to the wide range of physiological GH secretion and responses to pharmacological stimuli. Previous studies showed a variety of clinical use in diagnosing GHD including clinical data, study of spontaneous GH secretion, GH provocative test, study of GH action and neuroimaging[4-6]. However, many pediatric endocrinologists still use GH provocative tests as the good standard in their clinical practice. From the present study, the authors found no clinical parameters that

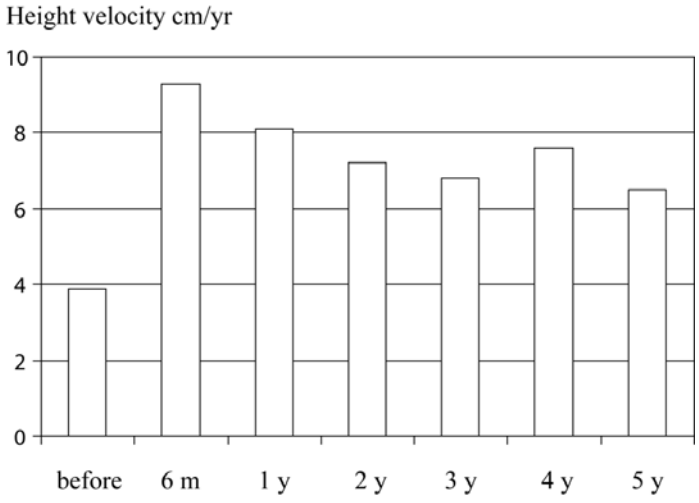

Fig. 1 Height velocity in GHD children treated with GH

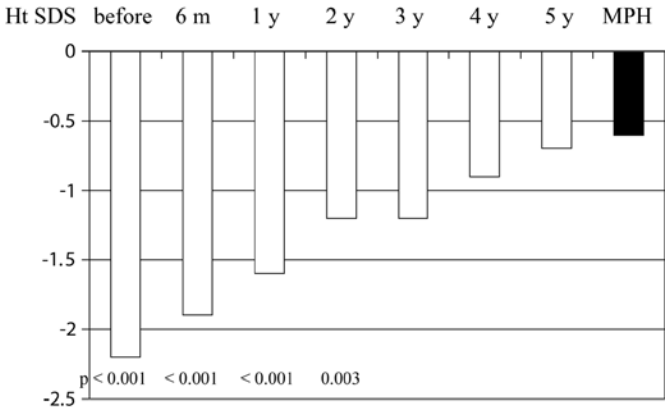

Fig. 2 Ht SDS before and during treatment with GH compared with mid-parental height (MPH)

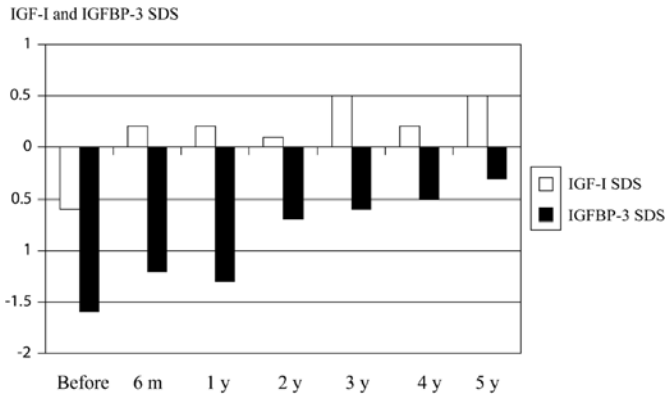

Fig. 3 Changes of IGF-I and IGFBP-3 SDS before and during treatment with GH

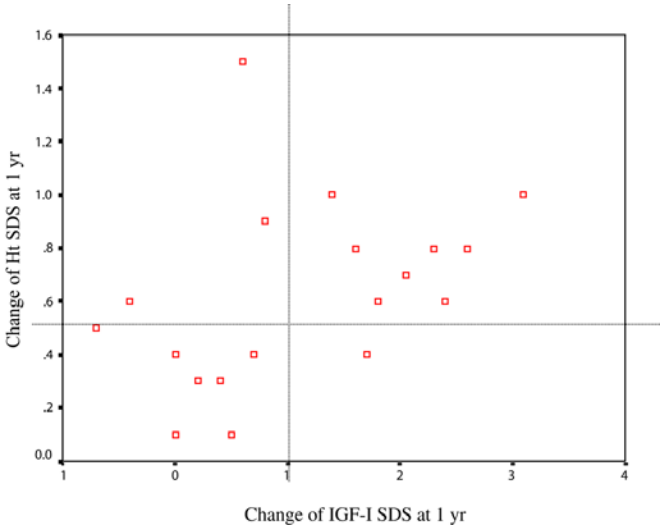

Fig. 4 Change of IGF-I SDS compared with changes of Ht SDS at I year of GH treatment

could be used as the diagnostic test. Even the active metabolites of GH, including IGF-I and IGFBP-3 could not be used. This is similar to other studies showing the overlapping of IGF-I and IGFBP-3 in GHD children with normal children[7].

GH therapy was proved effective to improve height in the studied Thai children with GHD and this brought HtSDS into the target range of parental height within 3 years of therapy. The mean dose of GH used in the present study was lower than suggested by other studies which recommended the dose around 30-50 μg/kg/day [8].

In clinical practice, the predictor of GH therapy in individual children is to monitor height velocity and adjust the dose of GH accordingly. Many studies demonstrated the predictors for final height outcome such as age at diagnosis and treatment, midparental height, GH doses, sex, and presence of abnormal MRI. However, no prediction models are accepted in routine practice[9]. In the present study, the authors demonstrate that the change of IGF-I is one of the factors that can be used to predict height outcome after 1 and 2 years of treatment. As suggested in the international workshop on the diagnosis and treatment of GHD, a predictor model for response to GH therapy should be developed, based on the prospective collection and uniform evaluation of a set of standardized parameters in a group of patients who meet consistently, well defined criteria for the diagnosis of GHD. In addition, monitoring of IGF-I and IGFBP-3 should be routinely applied in clinical practice to avoid serious side effects such as cancer[9].

In summary, from the present study, the authors demonstrate the experience of practice to investigate and treat short children with GHD. The growth response is satisfactory, even with a lower dose than suggested. Measurement of IGF-I and IGFBP-3 cannot be used in diagnosing but can predict the height outcome at least by the second year of the treatment. However, long-term outcome needs to be further investigated.

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การวินิจฉัยและรักษาด้วยฮอร์โมนเจริญเติบโตในเด็กโรคขาดฮอร์โมนเจริญเติบโต: ประสบการณ์ในโรงพยาบาลจุฬาลงกรณ์

สุทธิพงศ์ วัชรสินธุ, วิชิต สุพรศิลป์ชัย, สุภาพ อรุณภาคมงคล, สุมาลี ศรีวัฒนา

ภูมิหลัง: *การวินิจฉัยโรคเด็กขาดฮอร์โมนเจริญเติบโตจำเป็นต้องอาศัยอาการแสดงทางคลินิก การตรวจวัดสัดส่วนของร่างกาย การทดสอบด้วยการกระตุ้นฮอร์โมนเจริญเติบโต และการตรวจต่างๆทางห้องปฏิบัติการอื่น ๆ ได้แก่ IGF-I และ IGFBP-3 เป็นที่ยอมรับว่าการรักษาด้วยฮอร์โมนเจริญเติบโตในเด็กกลุ่มนี้มักได้ผลดีและมีผลข้างเคียงน้อย*

วัตถุประสงค์: *เพื่อรวบรวมดูผลของการวินิจฉัยเด็กโรคขาดฮอร์โมนเจริญเติบโตและรักษาด้วยฮอร์โมนเจริญเติบโตในโรงพยาบาลจุฬาลงกรณ์*

วัสดุและวิธีการ: *ได้ศึกษาข้อมูลในเด็กตัวเตี้ยที่มารับการทดสอบฮอร์โมนเจริญเติบโตที่หน่วยต่อมไร้ท่อจำนวน 173 คน โดยผ่านการทดสอบด้วยการทำ insulin tolerance test (ITT) และ clonidine test และเกณฑ์ในการวินิจฉัยโรคขาดฮอร์โมนเจริญเติบโต เมื่อพบว่าค่าสูงสุดของ GH (growth hormone) ต่ำกว่า 10 นาโนกรัม/มิลลิลิตร ข้อมูลพื้นฐานทางคลินิก และระดับ IGF-I และ IGFBP-3 ถูกนำมาเปรียบเทียบกันระหว่างกลุ่ม true positive และ กลุ่ม false positive เด็กโรคขาดฮอร์โมนเจริญเติบโตจำนวน 35 คนได้รับการรักษาด้วยฮอร์โมนเจริญเติบโตและมีการติดตามผลตอบสนองของการรักษาโดยดูจากข้อมูลการเจริญเติบโต ระดับการเปลี่ยนแปลง IGF-I SDS และหาค่าความสัมพันธ์ของการเปลี่ยนแปลงในด้านการเจริญเติบโตกับการเปลี่ยนแปลงของระดับ IGF-I*

ผลการศึกษา: *จากผลการศึกษาพบว่า ITT สามารถให้การวินิจฉัยโรคขาดฮอร์โมนเจริญเติบโตได้ โดยมี true positive 57% และ false positive 43% สำหรับ clonidine test ให้ผล true positive 67% และ false positive 33% โดยที่อายุจริง อายุกระดูก HtSDS WtSDS IGF-ISDS และ IGFBP-3 SDS ไม่แตกต่างกันระหว่างกลุ่ม true positive และ false positive ขนาดของฮอร์โมนที่ใช้รักษาเฉลี่ย 29.3 $\pm$ 4.6 ไมโครกรัม/กก./วัน อัตราการเพิ่มความสูงเพิ่มจาก 3.9 $\pm$ 2.5 เป็น 9.3 $\pm$ 2.5, 8.1$\pm$ 1.5, 7.2 $\pm$ 2.2, 6.8 $\pm$ 2.2, 7.6 $\pm$ 2.4 และ 6.5 $\pm$ 1.8 ซม./ปี หลังให้การรักษา 6 เดือน, 1, 2, 3, 4 และ 5 ปี และสามารถทำให้ HtSDS กลับขึ้นมาปกติภายใน 3 ปีหลังให้การรักษา หลังให้การรักษาครบ 1 ปี ระดับการเปลี่ยนแปลงของ IGF-I SDS มากกว่าหรือเท่ากับ 1 สามารถทำนายการตอบสนองของการรักษาโดยดูจากการเปลี่ยนแปลงของ Ht SDS ที่มากกว่าหรือเท่ากับ 0.5 โดยมี sensitivity เท่ากับ 88.9% และ specificity เท่ากับ 60% ในทำนองเดียวกันสามารถทำนายผลการรักษาโดยมี sensitivity 100% และ specificity 29% ในปีที่สองของการรักษา*

สรุป: *จากผลการศึกษาแสดงให้เห็นถึงประสบการณ์การวินิจฉัยและการรักษาเด็กโรคขาดฮอร์โมนเจริญเติบโต โดยพบว่าขนาดของฮอร์โมนเจริญเติบโตที่ใช้ในการรักษาน้อยกว่าขนาดที่แนะนำทั่วไปและผลของการรักษาเป็นที่น่าพอใจ นอกจากนั้นการใช้ซีรัม IGF-I และ IGFBP-3 ไม่สามารถนำมาใช้ในการวินิจฉัย แต่สามารถช่วยทำนายผลของการรักษาในระยะสองปีแรกได้ อย่างไรก็ตามคงต้องมีการติดตามผลในระยะยาวต่อไป*