Insulin-Like Growth Factor-I (IGF-I) Screening For the Diagnosis of Growth Hormone (GH) Deficiency†

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Abstract

Growth hormone deficiency (GHD) is a common cause of growth retardation in children and adolescents. Gold standard for the diagnosis of GHD is based upon two standard growth hormone (GH) provocative tests demonstrating a peak serum GH of less than 7 ng/mL. These tests, besides requiring multiple blood samplings, are time-consuming and costly. GH primarily mediates its growth-promoting effect through insulin-like growth factor-I (IGF-I). Hence, basal serum IGF-I level reflects GH status. We studied 47 prepubertal children with or without short stature. Aged ranged between 4.3 and 15.6 years. They were divided into 2 groups based upon 2 standard GH provocative tests. Seventeen children were classified as having GHD. The remaining 30 were non-GHD. Basal serum IGF-I was obtained before GH testing. The means±SE (range) of serum IGF-I concentration were 44.26±3.19 (19.10-75.63) ng/mL in GHD and 118.42±10.03 (60.65-235.91) ng/mL in non-GHD which were significantly different ($P<0.001$). 88.2 per cent of GHD had serum IGF-I concentration less than 60 ng/mL whereas 100 per cent of non-GHD had serum IGF-I greater than 60 ng/mL. There was no correlation between serum IGF-I and either bone age or chronologic age in children with GHD. These data indicate that serum IGF-I level is a useful screening test to exclude GHD with high sensitivity. We suggest that if serum IGF-I is less than 80 ng/mL in prepubertal children, GH provocative tests should be performed to diagnose GHD. If serum IGF-I is greater than 80 ng/mL, growth rate monitoring is recommended. If growth rate is decreased despite normal IGF-I, GH provocative tests should be obtained to rule out GHD.

Growth hormone deficiency (GHD) is a common cause of growth retardation in children and adolescents. The prevalence of GHD is about 1:3480 to 1:8464[1,2]. Conventionally, the diagnosis of GHD is based upon two standard GH provocative tests demonstrating a peak serum GH of less than 7 ng/mL[3]. GH is synthesized by the anterior pituitary gland and secreted in a pulsatile fashion. Therefore, random blood tests for GH in normal children are highly variable and frequently low or undetectable.

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Insulin-like growth factor-I (IGF-I) is secreted primarily by the liver under the stimulation of GH[4,5]. The growth-promoting effect of GH is mainly mediated by IGF-I. Unlike GH, levels of IGF-I exhibit little fluctuation over 24 hour[6]. Hence, in a normal situation, basal serum IGF-I level reflects GH status[7-9]. Previous studies showed that basal serum IGF-I concentration is almost always low in GHD and elevated in gigantism[10,11]. However, it is low in other conditions despite adequate GH secretion such as normal neonates and infants, protein energy malnutrition, prolonged starvation, liver disease, chronic renal failure and hypothyroidism[4,12-14]. Thus, low serum IGF-I is relatively sensitive for screening short children with GHD but somewhat non-specific for the diagnosis of GHD. While GH provocative tests are the gold standard for the diagnosis of GHD, they require multiple blood samplings, consume several hours and are costly. Therefore, single blood test for serum IGF-I concentration which reflects GH secretion may be useful for the screening of short children with suspected GHD[15-18].

The objective of this study is to differentiate between prepubertal Thai children with GHD and non-GHD by measuring serum IGF-I compared with standard GH provocative tests. Our data indicate that serum IGF-I is almost always low in children with GHD. Thus, it is reasonable to measure serum IGF-I as a parameter to screen short children with suspected GHD.

SUBJECTS AND METHOD

Forty seven children (35M, 12F) were studied. All were prepubertal without secondary sexual characteristics. The height standard deviation scores (SDS) ranged between -7.67 and -0.64 with mean ± S.D. of -2.65±1.38. This study was carried out at the Division of Endocrinology, Department of Pediatrics and Research Center, Faculty of Medicine, Ramathibodi Hospital, Mahidol University. Heights were expressed in SDS in comparison to those of standard Thai reference[19]. Blood chemistries for electrolytes, renal and liver function tests and complete blood count were obtained to rule out systemic illnesses. Hormonal tests included serum total thyroxine, free thyroxine, thyrotropin, 8AM cortisol and GH provocative tests.

To diagnose GHD, we performed 2 standard GH provocative tests which include clonidine test (4 μg/kg) orally and insulin hypoglycemia test (0.1 u of regular insulin/kg) intravenously. Children aged between 10 and 15 years who were prepubertal received estrogen prior to perform GH provocative tests.

Heights were measured in duplicate by SECA stadiometer.

X-ray bone age was obtained and compared with Gruelich and Pyle standard[20].

Method

Serum IGF-I concentrations were measured by a double antiboby radioimmunoassay kit purchased from Bioclone, Australia. The standard for IGF-I was obtained from the International Reference Reagent for IGF-I for radioimmunoassay (IRR IGF-I 87/518). All samples were assayed in duplicate and in the same run. The method includes an acid-ethanol extraction step in which IGF-I is first separated from IGF binding proteins[21]. The intraassay coefficient of variation was 7 per cent.

Serum GH concentrations were determined using a double antibody radioimmunoassay kit purchased from Diagnostic Product Corporation, U.S.A. The intraassay coefficient of variation was 6 per cent.

Satistics

The comparison of serum IGF-I concentrations was calculated by using Student's *t* test.

Relations between IGF-I concentrations and all other variables in both groups were determined by Pearson's correlation.

RESULTS

Subjects were divided into two groups according to GH provocative tests (Table 1).

Table 1. Clinical characteristics of children with GHD and non-GHD.

	GHD	Non-GHD	P-value
n	17	30	
Age X±S.D. (yr)	10.53 ± 2.84	8.97 ± 3.18	0.065
range (yr)	5.50 - 15.58	4.33 - 14.08	-
Sex	9M, 8F	26M, 4F	0.32
Height SDS (X±S.D.)	-3.9 ± 1.32	-1.9 ± 0.83	0.002
BMI (kg/m^2) (X±S.D.)	14.9 ± 2.06	15.1 ± 1.92	0.56

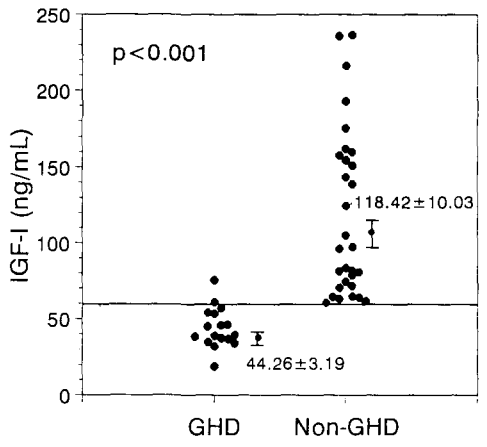

Fig. 1. Distribution of serum IGF-I concentrations in prepubertal children with GHD and non-GHD (mean±SE).

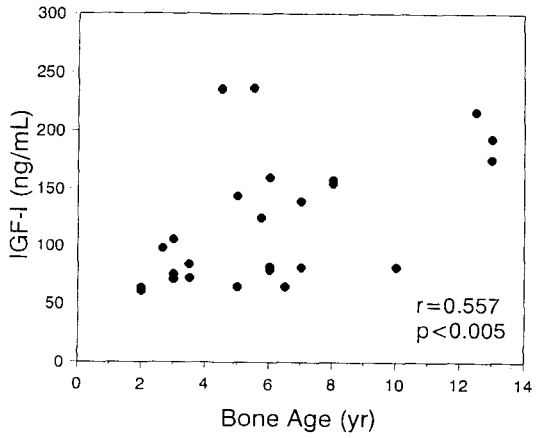

Fig. 2. Serum IGF-I concentrations *vs* bone age in prepubertal children with non-GHD (n=30, r=0.557, P<0.005).

1. GHD (n = 17 ; 9M, 8F) Subjects were classified as having GHD based upon the height of less than -2SD and the GH peaks of < 7 ng/mL following 2 standard GH provocative tests. The mean age±S.D. was 10.53±2.84 years and mean height SDS was -3.9±1.32.

2. Non-GHD (n = 30 ; 26M, 4F) Subjects were classified as having non-GHD based upon the GH peaks of ≥ 7 ng/mL in at least 1 standard GH provocative test. The mean age±S.D. was 8.97±3.18 years and mean height SDS was -1.9± 0.83. The mean height SDS in this group was low despite normal GH secretion because most of the children were familial short stature and constitutional delayed growth and puberty.

The clinical characteristics of children with GHD and non-GHD are presented in Table 1. The means±SE (range) of serum IGF-I concentrations were 44.26±3.19 (19.10-75.63) and 118.42± 10.03 (60.65-235.91) ng/mL in GHD and non-GHD group, respectively (Fig. 1). The mean serum IGF-I concentration in GHD was significantly less than that in non-GHD (P<0.001).

In GHD, 88.2 per cent had serum IGF-I concentrations less than 60 ng/mL whereas in non-GHD 100 per cent had IGF-I levels greater than 60 ng/mL (Fig. 1). Hence in prepubertal children, serum IGF-I of 60 ng/mL is a good cut-off level for differentiating between GHD and non-GHD. There was no correlation between serum IGF-I and either bone age or chronologic age in GHD (data not shown). In contrast, in non-GHD there was slight correlation between serum IGF-I and either bone age (r=0.557, P<0.005) (Fig. 2) or chronologic age (r=0.626, P<0.0001) (Fig. 3).

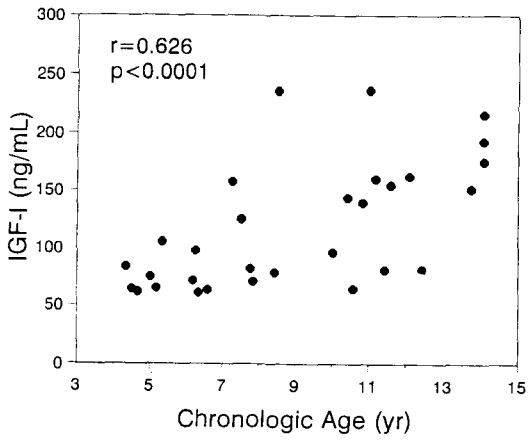

Fig. 3. Serum IGF-I concentrations *vs* chronologic age in prepubertal children with non-GHD (n=30, r=0.626, P<0.0001).

DISCUSSION

The measurement of serum IGF-I levels has been proposed as a useful tool for the evaluation of GH secretion[17]. Previous studies[17,18] showed that IGF-I levels had a significant correlation to spontaneous 24-hour GH secretion expressed as area under the curve. Since IGF-I level is age-dependent therefore interpretation of IGF-I levels requires age-related normal ranges. In addition, marked elevation of IGF-I levels during puberty was observed due to an increase of sex steroids and GH secretion[17]. In contrast, IGF-I levels are low in nutritional deficit and prolonged starvation despite elevated GH levels[22]. Hence, to reduce false positive low IGF-I in non-GHD, improvement of nutritional status should be accomplished prior to the blood test for IGF-I.

Our current study in prepubertal Thai children older than 4 years of age demonstrated that the single measurement of serum IGF-I by using 60 ng/mL as a cut-off point can differentiate between GHD and non-GHD with high sensitivity (88.2%). Since the level of IGF-I in non-GHD was greater than 60 ng/mL, therefore for screening purposes, we suggest that if serum IGF-I is less than 80 ng/mL in prepubertal Thai children, GH provocative tests should be performed to diagnose GHD. About 12 per cent of children with GHD can have low normal serum IGF-I. Hence, we recommend monitoring growth rate closely. If growth rate is decreased despite normal IGF-I, GH provocative tests should be obtained to rule out GHD.

We conclude that single measurement of serum IGF-I level is a sensitive and cost-effective screening test for the diagnosis of GHD.

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REFERENCES

1. Lindsay R, Feldkamp M, Harris D, Robertson J, Rallison M. Utah growth standards and the prevalence of growth hormone deficiency. J Pediatr 1994; 125: 29-35.
2. Bao XL, Shi YF, Du YC, Liu R, Deng JY, Gao SM. Prevalence of growth hormone deficiency in children in Beijing. Chin Med J Engl 1992; 105: 401-5.
3. Frasier SD. A review of growth hormone stimulation tests in children. Pediatrics 1974; 53: 929-37.
4. Hall K, Sara VR. Somatomedin level in childhood, adolescence and adult life. Clin Endocrinol Metab 1984; 13: 91-112.
5. Furlanetto RW, Underwood LE, Van Wyk JJ, D' Ercole AJ. Estimation of somatomedin C levels in normals and patients with pituitary disease by radioimmunoassay. J Clin Invest 1977; 60: 648-57.
6. Blum WF, Ranke MB. Insulin-like growth factor binding protein 3 for the evaluation of growth disorders. Horm Res 1990; 34 (Suppl.): 31-7.
7. Zapf J, Walter H, Froesch ER. Radioimmunological determination of insulin-like growth factors I and II in normal subjects and in patients with growth disorders and extrapancreatic tumor hypoglycemia. J Clin Invest 1981; 61: 1321-30.
8. Baxter RC, Brown AS, Turtle JR. Radioimmunoassay for somatomedin C : comparison with radioreceptor assay in patients with growth hormone disorders, hypothyroidism and renal failure. Clin Chem 1982; 28: 488-94.
9. Baxter RC. Measurement of somatomedins (insulin-like growth factors) by radioligand assay. Clin Biochem 1983; 3: 104-10.
10. Hasegawa Y, Hasegawa T, Aso T, et al. Clinical utility of insulin-like growth factor binding protein-3 in the evaluation and treatment of short children with suspected growth hormone deficiency. Eur J Endocrinol 1994; 131: 27-32.
11. Cianfarani S, Boemi S, Spagnoli A, et al. Is IGF binding protein-3 assessment helpful for the diagnosis of GH deficiency? Clin Endocrinol 1995; 43: 43-7.
12. Giudice LC, Zegher F, Gargosky SE, et al. Insulin-like growth factors and their binding proteins in the term and preterm human fetus and neonate with normal and extremes of intrauterine growth. J Clin Endocrinol Metab 1995; 80: 1548-55.
13. Pucilowska JB, Davenport ML, Kabir I, et al. Regulation of IGFBPs in young undernourished children. J Clin Endocrinol Metab 1993; 77: 1516-21.
14. Furanetto RW. Insulin-like growth factor measurements in the evaluation of growth hormone secretion. Horm Res 1990; 33 (Suppl. 4): 25-30.
15. Clemmons DR, Van Wyk JJ. Factors controlling blood concentration of somatomedin C. Clin

Endocrinol Metab 1984; 13: 113-43.
16. Rosenfeld RG, Wilson DM, Lee PDK, Hintz RL. Insulin-like growth factors I and II in evaluation of growth retardation. J Pediatr 1986; 109: 428-43.
17. Blum WF, Albertsson-Wikland K, Rosberg S, Ranke MB. Serum levels of Insulin-like growth factor-I (IGF-I) and IGF binding protein 3 reflect spontaneous growth hormone secretion. J Clin Endocrinol Metab 1993; 76: 1610-6.
18. Saggese G, Cesaretti G, Cioni C, Cinquanta L, Criannessi N. Relationship between plasma somatomedin C levels and 24-hour spontaneous growth hormone secretion in short children. J Pediatr Endocrinol 1991; 4: 159-66.
19. Weight, height standard and the assessment of the nutritional status of the Thai population aged 1 day - 19 years by the Division of Health, Ministry of Public Health, 1987.
20. Greulich WW, Pyle SI. Radiographic atlas of skeletal development of the hand and wrist. 2nd ed. Standford, Standford University Press, 1959
21. Baxter RC. The somatomedin: insulin-like growth factors. Adv Clin Chem 1986; 25: 49-115.
22. Soliman AT, Hassan AE, Aref MIC, Hintz RL, Rosenfeld RG, Rogol AD. Serum insulin-like growth factors I and II concentrations and growth hormone and insulin responses to arginine infusion in children with protein-energy malnutrition before and after nutritional rehabilitation. Pediatr Res 1986; 20: 1122-30.

การตรวจระดับ Insulin-like growth factor-I (IGF-I) ในการคัดกรองภาวะขาด growth hormone (GH)

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ได้ทำการศึกษาภาวะการขาด GH ในเด็กตัวเตี้ยที่ยังไม่เข้าสู่ความเป็นหนุ่มสาว (prepuberty) จำนวน 47 ราย อายุระหว่าง 4.3 ถึง 15.6 ปี ได้แบ่งเด็กออกเป็น 2 กลุ่ม โดยอาศัยการทดสอบ GH มาตรฐาน (GH provocative test) 2 วิธี กลุ่มแรกมีจำนวน 17 คนเป็นกลุ่มที่ขาด GH (GHD) ซึ่งมีระดับ GH สูงสุดทั้งสองวิธี ต่ำกว่า 7 นาโนกรัม/มล. กลุ่มที่สองมีจำนวน 30 คนเป็นกลุ่มที่ไม่ขาด GH (non-GHD) คือมีระดับ GH สูงสุด มากกว่า 7 นาโนกรัม/มล. จากการทดสอบหนึ่งหรือสองวิธี ได้ทำการตรวจวัดระดับ IGF-I ในเด็กทุกรายก่อนการทดสอบดังกล่าว พบว่าในกลุ่ม GHD ค่าเฉลี่ย $\pm$ ความคลาดเคลื่อนมาตรฐาน (พิสัย) ของระดับ IGF-I เท่ากับ 44.26 ± 3.19 (19.10-75.63) นาโนกรัม/มล. และในกลุ่ม non-GHD ค่าดังกล่าวเท่ากับ 118.42 ± 10.03 (60.65-235.9) โดยกลุ่ม GHD มีค่าเฉลี่ยของระดับ IGF-I ต่ำกว่ากลุ่ม non-GHD อย่างมีนัยสำคัญทางสถิติ ($P<0.001$). ร้อยละ 88.2 ของกลุ่ม GHD มีระดับ IGF-I ต่ำกว่า 60 นาโนกรัม/มล. ในขณะที่ร้อยละ 100 ของกลุ่ม non-GHD มีระดับ IGF-I มากกว่า 60 นาโนกรัม/มล. ในกลุ่ม GHD ระดับ IGF-I ไม่มีความสัมพันธ์กับอายุกระดูกและอายุจริง ข้อมูลนี้แสดงให้เห็นว่าระดับ IGF-I ใช้เป็นดัชนีในการคัดกรองภาวะขาด GH ได้ดี ถ้าระดับ IGF-I น้อยกว่า 80 นาโนกรัม/มล. ควรทดสอบ GH provocative tests เพื่อวินิจฉัยโรค GHD แต่ถ้ามีระดับ IGF-I มากกว่า 80 นาโนกรัม/มล. ควรเฝ้าติดตามดูอัตราการเจริญเติบโต ถ้าต่ำกว่าเส้นโค้งมาตรฐานควรทำ GH provocative tests เพื่อยืนยันให้แน่ใจว่าไม่ใช่โรค GHD

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