Insulin like Growth Factor 1 as an Indicator of Growth Hormone Deficiency

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ABSTRACT

Objective: Insulin like growth factor 1 is a protein produced by the liver under the effect of Growth hormone. It is used as a screening test in the evaluation of patients suspected to have growth hormone deficiency. The aim of the study was to determine the value of Insulin like growth factor 1 level as an Indicator of growth hormone deficiency.

Methods: This is a retrospective simple analytical study of 103 files of clinically diagnosed patients with short stature, was conducted in the period between June 2010 to November 2012 in the endocrine clinic at Queen Rania Al-Abdullah Hospital for Children. Seventy Patients were males while 33 patients were females, age ranged between 2 and 19 years. Al of these patients were evaluated clinically, height recorded using a stadiometer. Baseline routine laboratory studies, thyroid function test, celiac disease screening, and bone age were done for the patients. Insulin like growth factor 1 level and growth hormone stimulation test were performed for every patient. Patients with celiac disease, primary hypothyroidism, Turner syndrome, achondroplasia, Chronic liver diseases and malnutrition were excluded from the study.

Results: of the total 103 patients, 70 (68%) were males, 33 (32%) were females. Mean age was 9.6 years. There was significant correlation between Insulin like growth factor 1 Level and weight, chronological age, bone age. While there was no correlation between sex and insulin like growth factor 1. There was no correlation between Insulin like growth factor 1 and maximum growth hormone level response by growth hormone stimulation test, the correlation r = 0.56, the p value >0.05.

Conclusion: Insulin like growth factor 1 level is not a reliable indicator of growth hormone deficiency and lacks specificity. It can support the diagnosis of growth hormone deficiency, but growth hormone stimulation test is still the gold standard test in highly suspected cases of growth hormone deficiency even with normal level of Insulin like growth factor 1.

Key words: Growth hormone (GH), Growth hormone stimulation test (GHST), Growth hormone deficiency (GHD), Insulin like growth factor (IGF1).

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Introduction

Short stature is the most common problem encountered in pediatric endocrine clinic.

Although growth hormone deficiency (GHD) contributes to a minority of these patients, the diagnosis of GHD in children with short stature is very important because GHD might be

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accompanied with other pituitary hormone deficiency and /or central nervous system tumors.[1] Early diagnosis and treatment are mandatory for proper management and final height achievement.

Growth hormone (GH) is a polypeptide hormone produced in the anterior pituitary gland.[2] GHD should be suspected in patients with history of neonatal hypoglycemia, prolonged neonatal jaundice, male infants with bilateral undescended testicles and micropenis, patients with doll faces, small hands and feet, less mature voice and patients with midline defects that can cause hypothalamic -pituitary dysfunction.[3] IGF-1 level is a screening test used for suspected cases of GHD. It is a basic peptide hormone with 70 amino acids that mediates most of the biological actions of growth hormone. It is produced from the liver under GH stimulation.[3-6] Its role in the diagnosis of GHD in children and adults is controversial.[4]

Methods

A retrospective study of 103 patients' files were analyzed, there were 70 males and 33 females. Their age ranged between 2 and 19 years (mean=9.6 years). Data regarding date of birth, age, and sex were recorded for the patients. Heights of the patients and their parents were recorded in centimeters using a stadiometer. Proper standing positioning, head in Frankfurt plane, no hair do, and bare feet were considered in height measurement.

Height percentile and target height were plotted on growth charts using the normal growth data for age and sex, 2 to 20 years provided by the Centers for Disease Control and Prevention (CDC) http://www.cdc.gov/growthcharts/percentile_data_files.htm).[7] All patients' heights were below 3rd percentile according to the definition of short stature Weight was recorded for all patients in kilograms using digital scale. Weight percentile was plotted on CDC growth charts for age and sex. Bone age was recorded in years and months for left wrist X-ray reported by pediatric radiologist using Greulich and Pyle Atlas. All patients were tested for IGF1 level using serum samples collected in plain tubes and sent to the laboratory within 30 to 60 minutes. These samples were analyzed immediately using Immulite2000XPi –Siemens analyzer. IGF1 values were interpreted as normal or low for age and sex if the value was above or below 2 SD from the mean,[8] according to the lab reference in Princess Iman Center for Research and Laboratory Sciences at King Hussein Medical Center.

All of these patients underwent growth hormone stimulation test either by Insulin tolerance test (for patients' weight more than 20 kg) or Glucagon stimulation test (for patients' weight less than 20 kg or had a history of convulsions or cardiac diseases). Out of 103 patients who underwent growth hormone stimulation test there were 95 patients (92%) stimulated by Insulin tolerance test, and 8 patients (8%) by Glucagon stimulation test.

Serum samples in plain tubes were sent to the laboratory at the end of the test within 30 minutes. Samples were analyzed directly by Immulite2000XPi-Siemens analyzer.

Normal GH response was interpreted as maximum GH response of ≥ 7 ng/ml and GHD for patient with maximum response <7ng/ml.[7,8] earson correlation test and chi square test were used in the analysis of data. The results were considered significant if the (p-value <0.05).

Results

Of the total 103 patients, 70 (68%) were males and 33 (32%) were females. Mean age was 9.6 years. 73 (71%) had delayed bone age (2 SD below the mean) and 30 (29%) had normal bone age. 55 (53%) had low IGF1 and 48(47%) had normal IGF1. 47 (46%) had low GH level and 56 (54%) had normal GH response to stimulation test.

There was significant correlation between weight and IGF1 level. The more the weight of the patient, the higher the value of IGF1 (r = 0.35 and p value <0.05). There was also significant correlation between bone age, chronological age and level of IGF1. The older the age, the higher the value of IGF1 (r =0.32, r =0.25 respectively, both p value <0.05). While there was no correlation between sex and IGF1.

Table I: Patients data

Age (years)	No. of patients	Sex		Bone age		IGF1		GH (max)	
		Male	Female	Normal	Delayed	Normal	Low	Normal	Low
2-5	12	8	4	4	8	4	8	8	4
5.1-10	32	20	12	7	25	17	15	15	17
10.1-15	58	41	17	15	43	27	31	33	25
15.1-19	1	1	0	0	1	0	1	0	1
Total	103	70	33	26	77	48	55	56	47

There was no significant correlation between IGF1 and maximum GH value by stimulation tests, Chi squire test =0.56 and p value >0.05. Sensitivity of IGF1 is 47% in detecting GHD while the specificity is 65%.

Table 1 summarizes patients' data regarding age groups, sex, bone age and results of IGF-1 and GH maximum values.

Discussion

GH is synthesized in the anterior pituitary gland and stored in secretory granules. It is the most abundant hormone in the pituitary (25% of the gland's hormones). GH is a single polypeptide chain of 191 amino acids and it is coded by two genes on Chromosome 17.[6] It is secreted in a pulsatile manner (usually 6 pulses in 24 hours and mainly during the night),[9,10] so random GH level is not reliable and several methods have been recommended to assess the adequacy of GH secretion.[10] The diagnosis of GHD in childhood is a multifaceted process requiring comprehensive clinical and auxological assessment combined with biochemical tests of GH, IGF1 and radiological evaluation.[11] The presence of hypoglycemia in the neonatal period, septo-optic dysplasia and midline facial defects such as cleft palate and solitary central incisor will suggest the possibility of hypopituitarism. Cranial irradiation, histiocytosis X and hypothalamic pituitary tumors will support the probable diagnosis of GHD in poorly growing child.[12] Typically GH-deficient child has increased subcutaneous fat especially around the trunk, the face is immature with prominent forehead and depressed midfacial development, and dentation is delayed. Males may have micropenis, while puberty is delayed in both boys and girls.[12] GH stimulation tests are invasive, expensive and have the risk of hypoglycemia.[13]

Among classical provocative tests Insulin tolerance test (ITT), Arginine and Glucagon have been demonstrated to be the most reliable.[14,15] ITT and Glucagon stimulation tests (GST) should be undertaken by experienced staff working in a specialized endocrine unit.[16,17] ITT should not be used in children aged less than 5 years, in whom GST may be more appropriate.[17] In our patients we did ITT for patients older than 5 years and GST for those younger than 5 years of age. No complications were reported other than symptoms and signs of hypoglycemia. A cutoff GH peak response ≥ 7ng/ml was considered as sufficient GH response.[7,8] GH induces the generation of Insulin-like growth factor 1 (IGF-1 also called somatomedin 1) in the liver and regulates the paracrine production of IGF-1 in many other tissues.[18] Serum level of IGF-1 reflects the endogenous GH secretion in healthy children. In the circulating system, IGF-1 forms a ternary complex with IGF-1 binding protein-3 (IGF-BP3) and the acid-labile subunit. This complex serves as a circulatory reservoir for IGF-1.[19] The lack of any major diurnal variation in circulating IGF1 levels combined with the long half life of ternary bound IGF-1 and the absence of any major seasonal variation make IGF-1 a potential candidate for screening of GH deficiency.[20] GH and IGF-1 are both prerequisites for optimal longitudinal growth of bone; they have synergistic effect on growth and anabolic metabolism.[21] Deficiency of circulating IGF-1 can be caused by other conditions than GHD such as malnutrition, hypothyreosis, renal insufficiency, and liver insufficiency.[12,21] All patients with these conditions were excluded from the study. The IGF-1 level is influenced markedly by age, sex and pubertal development. Low levels of IGF-1 occur in normal children younger than 5 years of age. Therefore, the use of IGF-1 estimation to distinguish between normal

and GH-deficient children is less successful in this age group.[8,12,19,22] In our study we depended on age related values for interpretation of the IGF-1 levels. Serum IGF-1 were shown to have a positive correlation with Body Mass Index (BMI).[19] In our study there was significant correlation between weight and IGF-1 (r=0.35 and p value <0.05).

The value of IGF-1 as an indicator of growth hormone deficiency is controversial.

According to a survey conducted on 387 citations on most recent guidelines and recommendations for diagnosis of GHD, 82% answered that a low level of serum IGF-1 in the absence of malnutrition and chronic illness was equivalent to (45%) or better than (37%) growth hormone stimulation test (GHST).[23] Multiple studies exist that indicate that serum IGF-1 concentration does not correlate perfectly with GH status, as determined by provocation GH testing,[12,24-28] while other people still consider IGF-1 concentration may be a reliable test to some degree in diagnosing GHD as the result of GHST.[20,29-31] The diagnostic sensitivity of IGF1 is 83.87% and the diagnostic specificity is 76.2% in some studies,[32] but in our study the sensitivity of IGF-1 was 47% and the specificity was 65%. This may be due to small sample size in our study. Moreover we have 12 patients out of the total 103 (12%) aged <5 years ,the IGF-1 level is less sensitive and specific in this age group as it was mentioned previously in our discussion . Furthermore the biological variability in IGF-1 measurements is up to 32% in the same subject when tested on different days.[32]

Conclusion

IGF-1 level is not a reliable indicator of growth hormone deficiency and lacks specificity. It can support the diagnosis of growth hormone deficiency, but growth hormone stimulation test is still the gold standard test in highly suspected cases of growth hormone deficiency even with normal level of IGF-1.

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