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Use of Insulin-Like Growth Factor One Level in the Diagnosis of Ideopathic Short Stature in Growth Hormone Unit in AL-Diwaniya Maternity and Children Hospital

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Abstract: Background: the diagnosis of idiopathic growth hormone deficiency remains a challenge for the clinician. The uncertainties in the cut-off values to describe growth hormone deficiency and reference data for growth hormone secretion in normally growing children, differences in growth hormone assays over the time, problems in reproducibility of growth hormone test results all contribute to this vagueness. However, diagnosing growth hormone deficiency is important to identify children who will benefit most from the GH treatment. GH dependent peptides, insulin-like growth factor I (IGF-I) and insulin-like growth factor-binding protein 3, (IGFBP-3) are good markers of growth hormone status and are useful in diagnosing GH deficiency as well as monitoring efficacy of growth hormone treatment.

Objective: The aim of this study was to evaluate the role of IGF-1level in diagnosed short stature children without clear cause and had one of the following criteria.

Patients and method: cross sectional study comprised all short children seen in our Pediatric Endocrinology Unit in AL-Diwaniya maternity and children hospital from October 2021 to October 2022. IGF1-deficient children were defined as children without GH deficiency and with IGF1 levels below or equal to -2 SDS

Results: Among 37 children with isolated SS, 7 (18.91%) had low IGF-1 levels and normal GH level, consistent with a diagnosis of primary IGFD and 9(24.32%) non -growing, GHD children had normal IGF-1 levels

Conclusion: IGF-1 level has important clinical role in non-GHD, non-growing SS children.

Key words: Insulin, Growth Factor, Ideopathic Short Stature, Growth Hormone.

Introduction

Idiopathic short stature (ISS) constitutes the predominant category of individuals assessed for short height in pediatric endocrine clinics (1).

An expanding array of studies consistently underscores the existence of various messengers that possess functional significance concerning the growth hormone (GH)/insulin-like growth factor 1 (IGF-1) axis, including the GH receptor, JAK2, STAT5b, STAT5a, MAPK, PI3K, SOCS 1, 2, 3, and several other pertinent substances (2). Malfunction of one or more of these messengers appears to

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have a role in the clinical presentation of partial GH or IGF-1 resistance or diminished blood IGF-1 levels in certain individuals, resulting in a heterogeneous characteristic of ISS (3-7).

The subsequent impairments or a combination thereof may manifest in individuals with ISS: 1) Heterozygosity of genes within the GH/IGF-1 axis leading to inadequate transcription of IGF-1; 2) Polymorphisms affecting the transcription or translation of genes in the GH/IGF-1 axis; and 3) Dysfunction of unidentified genes (8). Individuals with ISS exhibit diminished hunger relative to healthy counterparts, and a lower body mass index (BMI) is posited as a contributing reason to shortened stature. Weight is recognized as a regulator of the GH/IGF-1 axis (9).

Lower GH sensitivity in IGF-I-producing tissues, particularly at the growth plate, may contribute to poor responses. Data from the study that used titration of the GH dose to individual IGF-I SDS [10] suggest that circulating IGF-I may to some extent reflect the generation of IGF-I in target tissues, like the growth plate, and determine linear growth. Treatment with IGF-I or IGF-I in combination with GH may, hypothetically, circumvent resistance to GH and stimulate growth. However, this approach assumes that the lack of GH responsiveness is not due to IGF-I resistance. In severe primary IGF deficiency (IGFD), treatment with IGF-I im- proves height velocity from approximately 3 cm per year up to 8 cm per year during the first year; height velocity attenuates in the following years, but remains above the pretreatment level [11].

A similar pattern of rapid, first-year catch-up growth is also observed following GH treatment. In severe, primary IGFD there is complete resistance to GH, at least in patients with identified GH receptor or STAT5b mutations [12] . However, in children with ISS and a relative insensitivity to GH, negative feedback on GH secretion by administration of IGF-I may affect the outcome of this treatment. In particular, proposed IGF-I-independent effects of GH on stem cell recruitment at the growth plate may be affected.(13)This study aims to examine the varying effects of GH on IGF-1 and IGF-binding protein 3 (IGFBP-3) levels in individuals with ISS compared to healthy people.

Methodology

This is a cross sectional descriptive study comprised all short children seen in our growth hormone Unit in AL-Diwaniya maternity and children hospital from October 2011 to October 2012.

From a total of 183 children 65 (35.52%) were females and 118 (64.48%) were males; thirty seven children were enrolled in this study27 (72.97%) of them were males and 10 (27.03%) were females.

For each child, the family history and parental heights were recorded, with calculation of the target height as absolute value and SDS to exclude familial causes of short stature.

1. Weight and height, were expressed as absolute values and SDS with reference to chronological age according to the WHO growth charts .weight measurement done by platform weighting scale, height measured by Stadiometer and followed each 2 months.for at least 6 months and plotted on height velocity charts.
2. Bone age was assessed by specialist radiologist in our hospital.
3. laboratory testing include CBC , ESR , CRP , liver function test , BUN Antigliadin and Transglutaminase antibodies , Thyroid function tests and Growth hormone level basal and after provocation by clonidine or exercise .
4. Three ml of blood was drawn, put in a plain serum tube to clot, centrifuged at 3000 cycle/minute for 5 minutes and the supernatant serum separated in another plain serum tube and kept frozen at -20º centigrade until it was analyzed were it was let to melt down for analysis. Analysis was made using enzyme linked immunosorbent assay (ELISA) method &the levels are expressed as nanograms per milliliter (ng/ml), the DEMEDITEC IGF-1 ELISA Kit (Germany) is a solid phase ELISA, based on the principle of competitive binding. All reagents and specimens must be allowed to come to room temperature before use. All reagents must be mixed without foaming. Once the test has been started, all steps should be completed without interruption. Patient sample

(standards and controls) are acidified and neutralized prior to the assay procedure. The pre-treated sample is incubated at room temperature with Conjugate (biotinylated IGF-1). After addition of the substrate solution, the intensity of color developed is reverse proportional to the concentration of IGF-1 in the patient sample.IGF-1 values referenced to chronological age in absolute value according to Reference Interval.

Statistical analysis:

Statistical analysis was done by using SPSS (statistical package for social sciences) version 17. In which we use chi square(X^2) for categorical data and independent sample T-test for measurement data. We set P value<0.05 as significant.

Result

Table (1) the Association between gender and IGF-1 level

Sex	IGF-1(ng/ml)		Total
	Normal	Low	
Male	23(85.2%)	4(14.8%)	27(100%)
Female	6(60.0%)	4(40.0%)	10(100%)
Total	29(78.4%)	8(21.6%)	37(100%)
P value	0.098		

Table (1) demonstrates the Association between gender andIGF-1 level, there is no statistical significant difference between gender and IGF-1 level, where there are no significant differences (P value =0.098)

Table (2) comparison between those with normal and low IGF-1 in different characteristics

characteristics	IGF-1 ng/mL	Mean of characteristics	Std. Deviation	P value
Chronological age (years)	Normal	8.286	3.255	0.198
	low	10.125	4.389	
Bone age delay (years)	Normal	2.4	1.496	0.002
	Low	4.56	2.128	
Height(cm)	Normal	110.0172	19.19053	0.275
	Low	118.0000	12.30853	
Weight(kg)	Normal	18.7448	6.54755	0.108
	Low	22.9375	5.54487	
GH basal level (µg/l)	Normal	2.1555	3.16898	0.26
	Low	3.8375	5.24811	
Peak GH level (µg/l)	normal	18.4600	16.60438	0.274
	low	8.9250	4.28437	

Table (2) demonstrates the Association among IGF-1 level and Chronological age, bone age delay, height, weight, basal GH, peak GH levels. There is statistical significant difference only between bone age delay and IGF-1 level P value (0.002).

Table (3) Classification and frequency of GH–IGF-1 axis abnormalities

Peak GH level	IGF-1 status	IGF-1mean (ranges ng/ml)	Patients % (n)	Diagnosis
Normal	Normal	124.37 (75-180)	54.05%(20)	Normal GH-IGF1 axis(ISS)
	Low	67.49 (26.4-99.5)	18.91%(7)	Primary IGFD

Low	Normal	126.27 (70-175).	24.32%(9)	(GHD)Lower normal GH
	Low	40.2	2.70%(1)	(GHD) lower normal IGF-1

The number of children undergoing a GH stimulation test (normal peak GH >7 µg/l) and an IGF-1 measurement falling into each diagnostic category is shown in Table (3).

Discussion

The diagnosis of idiopathic growth hormone deficiency remains a challenge for the clinician. The uncertainties in the cut-off values to describe growth hormone deficiency and reference data for growth hormone secretion in normally growing children, differences in growth hormone assays over the time, problems in reproducibility of growth hormone test results all contribute to this challenge. However, diagnosing growth hormone deficiency is important to identify children who will benefit most from the GH treatment. GH dependent peptides, insulin-like growth factor I (IGF-I) and insulin-like growth factor-binding protein 3, (IGFBP-3) are good markers of growth hormone status and are useful in diagnosing GH deficiency as well as monitoring efficacy of growth hormone treatment[14,15].

The percentage of primary IGFD was 18.91% as shown in table(3), in comparing with T Edouard et al (France) which showed that the prevalence was 20% in prepubertal children with isolated short stature[16], InAttieKM, et al acohort of 4663 short children [17] and Clayton PE,et alstudy in 190 short children[18] primary IGFD represents 25%.

Also there were no statistical significant difference, between gender and level of IGF-1 (p value >0.05) table 1.

In our study, when compared IGFDchildren with non-IGFD children, IGFD children had satistical significant more delayed bone age (4.56vs.2.4years,p=0.002) table 2,these data confirm the relationship between maturational delay and IGFD. The same result found in T Edouard, et al [16].

There were no statistical significant difference, among chronological age, height, weight, basal GH, peak GH levels and IGF-1 level (p > 0.05) table 2.this mean in our study basal and peak GH level not useful for prediction ofIGF-1 level. The same results found in France T Edouard, et al (2009) [16].

The number of patients underwent a GH stimulation test (normal peak GH >7µg /l) and an IGF-1 measurement falling into each diagnostic category table 3 which shows:

Seven of 27 (18.91%) non-GHD children had low IGF-1 level mean67.49 ng/ml range between (26.4-99.5) ng/ml, and those children diagnosed as primary IGFD.

Children with primary IGFD should be further analyzed in terms of GHI syndrome. Low serum levels ofIGFBP-3 suggestive of GHI. In patients with IGFD, theIGF1 generation test could be helpful in differentiating between low serum levels of IGF1 that are responsive, or partially responsive to rhGH, from low serum levels ofIGF1 that do not respond to rhGH administration with an increase in IGF1 levels and would not be expected to respond to rhGH treatment with an improvement in linear growth and adult height. However, because of controversies regarding the optimal protocol, diagnostic interpretation, lack of assay standardization, and nearly no correlation of test results with the clinical response to rhGH [19].so those children treated with rhGH and they need long term follow up which is beyond may field to recognize those children who not respond to rhGH and so they can benefit from rhIGF-1.

Twenty of 27(74.07%) non-GHD children had normal IGF-1 level mean = 124.37 ng/ml, range (75-180) ng/ml which indicate normal GH-IGF-1 axis. This goes with Rosenfeld RG, et al. who found IGF-1 level to be within normal limits in 68% of short children with no GH deficiency [20]. And those patients regarded as idiopathic short stature (The common definition of idiopathic short stature is height that is more than -2 SD below the mean for that age, sex and population group. And sufficient

growth hormone as documented by a growth hormone stimulation test [21])and can be treated according to the United States and seven other countries guidelines, the regulatory authorities have approved GH treatment for children shorter than2.25 SDS (1.2 percentile). Among this working consensus group, opinions regarding the appropriate height below which GH treatment could be considered ranged from2to3 SDS. Age should be taken into account when deciding to initiate treatment. It is felt that the optimal age for initiating treatment is 5 years to early puberty [22, 21].

Nine of 10GHDchildrenand growing had normal IGF-1 level mean 126.27 ng/ml, and range between (70-175) ng/ml. The normal growth (height velocity> 5th percentile) in spite of low GH peak is explain by normal IGF-1 level, In 25-44% of the individuals with the diagnosis of GH deficiency during childhood found to have normal GH levels on spontaneous GH secretion during sleep or on pharmacological testing when retested at adulthood [23].also in children younger than 10 years, IGF-I estimation is more useful than estimation of GH in pointing to subnormality in GH stimulation tests [24].

One child of 10 had low both GH and IGF-1 level 40.2 ng/ml and clinically he was growing this may be due to in spite of low IGF-1level it still has clinical effect. In T Edouard, et al low IGF-1levels were found in9% of the prepubertal children with isolated short stature with GH deficiency [16].Rosenfeld RG, et al found IGF-I levels were low for respective age in 82%of patients with GH deficiency [21].

Conclusion

Measuring IGF-1 level has important role in Help in the diagnosis of idiopathic short stature and Help in the decision of treating children with short stature and normal growth hormone level and low height velocity.

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