Insulin-Like Growth Factor-1 (IGF-1) Predicte the Diagnosis of Growth Hormone Deficincy in Short Prepubertal Children[#]

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Abstract

To study the serum IGF-1 level for prediction of growth hormone deficiency and its role in the diagnosis of short stature in children and adolescents. A study was conducted on forty four (44) short children with growth hormone deficiency. Children were classified into Group I thirty five (35) prepubertal children and Group II (9) patients who entered puberty. In addition to forty (40) apparently healthy children as control group, also were divided into group I control(29) prepubertal &group II (11) pubertal . IGF-1,GH ,Thyroid function ,serology for celiac disease , Hb level ,bone age were done for all patients. IGF-1 and basal GH level (without provocative test) were done for control . There was a significant low difference between the serum IGF-1 level in the patients of group I in comparison to their serum level in control group I {(90.98±23.69) (121.83±23.69) ($p<0.05$)} . While there was no such difference between the serum IGF-1 level in the patients of group II in comparison to their serum level in control group II {(184.59±196.52) (285.91±68.89) ($p<0.05$)}. This study shows that IGF-1 level is low compared to control in short GH deficient children who did not enter puberty, while it is less significant in children and adolescents who entered puberty. So IGF-1 is a suitable parameter to predict GH deficiency in short prepubertal children in whom GH deficiency was found by GH provocative testing. But this test is less reliable in children who entered puberty.

Key Words: IGF-1, Growth Hormone Deficiency, Short Stature.

الخلاصة

هو دراسة مستوى هرمون في المصل IGF-1 للتحقق من نقص هرمون النمو وبيان دور هرمون IGF- 1 في تشخيص قصر القامة عند الأطفال والمراهقين . تم إجراء الدراسة على ٤٤ طفلا قصير القامة والذين لديهم نقص في هرمون النمو.حيث تم تصنيفها إلى مجموعتين الأولى وتضم ٣٥ طفلا في مرحلة ما قبل البلوغ والمجموعة الثانية و تضم ٩ أطفال دخلو مرحلة البلوغ بالإضافة إلى ٤٠ من الأطفال الأصحاء قسموا إلى مجموعة أولى لم يبلغوا (٢٩) ومجموعة ثانية دخلوا البلوغ(١١). وتم قياس هرمون IGF- 1 ,هرمون النمو, هرمونات الغدة الدرقية, اختبار حساسية الحنطة , مستوى الهيموغلوبين وعمر العظم لجميع المرضى.وقياس IGF-1 وهرمون النمو يدون فحص تحفيزي للأطفال الأصحاء. معدل مستوى هرمون IGF -1 في مصل مرضى المجموعة الأولى هو (٩٠.٩٨±٢٣.٩٦) نانوغرام/ ملليتر بينما معدل هرمون IGF- 1 في مصل المجموعة القياسية الأولى هو (١٢١,٨٣±٢٣,٦٩) نانوغرام /ملليتر والتي تظهر أن هناك فرقا ملحوظا بين المجموعتين ($p< 0.05$) في حين ان معدل مستوى هرمون IGF- 1 في مصل مرضى المجموعة الثانية هو(١٨٤,٥٩±١٩٦,٥٢) نانوغرام /ملليتر بينما معدل هرمون IGF- 1 في مصل المجموعة القياسية الثانية هو (٢٨٥,٩١±٦٨,٨٩) نانوغرام /ملليتر والتي تظهر أن هناك فرق غير ملحوظ بين المجموعتين($p> 0.05$). من خلال هذه الدراسة تبين أن نسبة هرمون IGF- 1 في مصل الأطفال قصار القامة الغير بالغين منخفض بشكل ملحوظ مقارنة مع المجموعة القياسية الأولى بينما لا يوجد فرق في نسبة الهرمون في مصل الأطفال والمراهقين مقارنة مع المجموعة القياسية الثانية.لذلك فان نسبة هرمون IGF-1 هو مقياس مناسب للتنبؤ بنقص هرمون النمو في الأطفال قصيري القامة الذين لم يصلوا البلوغ والذين تم الكشف عن نقص هرمون النمو لديهم بالفحص التحفيزي لهرمون النمو. ولكن هرمونIGF-1 يعتبر اقل اعتمادا للأطفال الذين وصلوا البلوغ.

Introduction

Growth hormone (GH) is secreted from the anterior pituitary gland. It binds to receptors on the surface of target cell, stimulates production of IGF -l (Insulin like growth factor-one) adding to growth of almost all tissues of the body[(1)]. Growth hormone deficiency (GHD) is suspected with short stature and a reduced growth velocity in whom other causes of poor growth have been excluded[(2)].The childhood component of human growth is determined by growth hormone[(3)]. The mitogenic actions of GH are mediated through the synthesis of IGF-1(4)GH secretion causes production and secretion of IGF-1 in many tissues of the body ,including the liver . Most of the effects of GH are the result of GH stimulated production of IGF-1 .

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Serum IGF-1 values are related to GH secretion ,rising in GH excess and decreasing in GH deficiency[5] .Circulating levels of IGF-I reflect the pulsatile GH secretion in prepubertal & pubertal children[6].The incidence of idiopathic GH deficiency in infants is about 1 in every 3800 live births[7]. The diagnosis is confirmed by a provocative test which identifies a subnormal response to a GH secretagogne such as insulin, clondine , glucagone, arginine, or L-dopa. This is generally viewed as more effective than measuring the spontaneous GH secretion[8]. Establishing a reasonable assessment of GH secretary ability or a firm diagnosis of GH deficiency can be difficult because of pulsatile ,and predominantly nocturnal nature of GH secretion and variability of GH assays (which recognize different circulating forms of GH to varying extents).All provocative tests may give false negative or positive responses . Screening tests are difficult to standarize and response is variable [4]. Serum level of IGF-I reflects the endogenous GH secretion in healthy children [6]. The lack of any major diurnal variation in circulating IGF-I levels (9) , combined with the long half-life of ternary bound IGF-1 and the absence of any major seasonal variation [10] , has led to the concept that single measurement of IGF-I is representative for an individual IGF-I level[11].This makes it potential candidate for screening of GH deficiency.

Patients and methods

Setting

Five months period(Sept.2009_Jan.2010) ,a prospective case control study for children and adolescents referred for evaluation and diagnosis of short stature to National Diabetes Center (NDC) \Al Mustansirya University, Baghdad ,Iraq, where the study was conducted.

Patients

During the study period (44)Patients with short stature and growth hormone deficiency who as well as their families accepted to participate in the study whilst they attend the National Diabetes Center ,seeking specialized medical service.They all were thoroughly interviewed by a consultant pediatrician , their height ,weight , head circumference, and sitting height was measured , stage of puberty was assessed for both girls and boys, also for boys testicular size and stretched penile length was measured. Since the diagnosis of growth hormone deficiency in short children requires the exclusion of other causes of short stature ; for this reason, our team tried in their design of limitations of the study to enroll only the patients whom thyroid function test ,renal function test , and hemoglobin level were normal and in whom celiac disease was excluded by at least two serological tests , Turner syndrome was excluded in short females by chromosomal study ,and skeletal dysplasia was excluded by comparing height to sitting height. Patients were classified into Group I (35) patients who did not enter puberty (prepubertal) , and Group II (9) patients who entered puberty (pubertal). For comparison control group of (40) normal children and adolescents with a comparable age to that of patients was also studied. These children were assessed by, height (found to be normal) .Basal serum growth hormone level, and IGF-1 level .These 40 children were subdivided into 2 groups comparable to the 2 patient groups that is group I control (29) who did not enter puberty and group II control (11) who entered puberty.

Radiology

Bone age assessed by Greulich and Pyle method using non dominant hand and wrist x-ray [12].

Laboratory analysis

Laboratory tests were done and included: Hemoglobin level, Renal function test (blood urea & serum creatinine levels),Thyroid function test (T3 ,T4 ,TSH), Serology for celiac disease (Antigliadin antibodies IgG and IgA , and Antiendomysim antibodies IgG and IgA tests.) , chromosomal study for short females to exclude Turner syndrome, growth hormone was measured ,basal level and after 1hr , 1.5hrs, and 2hrs of provocation (using Clonidine tablets 100 mg/m^2) by Hgh (I125) IRMA kit by Institute of Isotopes Co. ,Ltd Budapest,Hungary, and IGF-1 level (using kit by Immunotech- France (immunoradiometric assay).

Statistical analysis

Statistical analysis and reporting of obtained data were carried out by using Microsoft Excel - Windows XP professional program.Values were expressed as mean ± SD (standard deviation) Statistical tests were performed using unpaired student's t-test; the P values were ≤ 0.05, for the level of significance.

Ethical approval

All patients and their families were informed about the aim and the suspected benefit of the study before obtaining their agreements for participation according to the

medical research and ethical regulations, thus an oral consent was taken from all enrolled participants and their families .All the medical research ethics rules and instructions adopted in National Diabetes Center regarding patient s privacy ,humanity ,and security ,as well as the medical research ,laboratory data , and investigation results were strictly considered throughout all the steps of study.

Results

The male/female ratio was 2/1. The mean age of group I patients was(5.98 years), with age range (1.5-10.5) years .The mean age of the group II patients was 13 years, with age range (11.5-15) years. The height for both patients & control in both group I & group II were shown in table -1.Serum GH level for patients, both group I & group II basal & after provocation with clonidine, in addition to basal GH level to control groups were shown in table -2. Serum IGF-1 level for patients both group I & group II &control group I & group II were listed in table -2. Serum IGF-1 level in group I patients was significantly low compared to its level in group I control (P <0.05) (table -2) ,while no such significant difference between serum IGF-1 level in group II patients compared to its level in group II control was seen (table -2).Beside that serum IGF-1 level for both patients groups (I &II) (total) was(116.2. ±124.07 ng/ml) compared to both group I &II control (total) (166.95 ±84.41 ng/ml) with statistically significant difference (P <0.05) .

Table 1 : Height for patients groups and controls.

Groups	Patients height (cm)	Control height (cm)
Total	116.1±22.54	125.81±21.1
Group-I	108.226±16.409	115.655±14.202
Group-II	143.278±7.276	152.59±8.651

Values were expressed as mean ± SD.

Table 2 : Serum Levels of Growth hormone and IGF-1 in patients and controls.

Groups		Control		Patients	
		Group I	Group II	Group I	Group II
Growth Hormone (Basal)	Mean±SD ng/ml	7.41±0.322	7.327±0.3	0.324±0.511	0.117±0.158
Growth Hormone 1hr. provocation	Mean±SD ng/ml			2.945±2.764	4.228±4.264
Growth Hormone 1.5hr. provocation	Mean±SD ng/ml			2.559±2.319	2.779±2.222
Growth Hormone 2hr. provocation	Mean±SD ng/ml			1.291±1.335	0.826±0.636
IGF - 1	Mean±SD ng/ml	121.83±23.69	285.91±68.89	90.98*±85.78	184.59±196.52

Values were expressed as mean ± SD. , *Statistically different from control (P value < 0.05)

Discussion

In the present study , we found that serum IGF-1 can predict GH deficiency in short children as compared with healthy control ,but this is true in prepubertal children ,as these children enter puberty the value of IGF-1 level still lower than control but becomes less predictive, the average serum level of IGF-1 of group I patients (prepubertal children) was significantly low compared with control (P value <0.05) (as showed in table-3).Serum IGF-1 has proved to be a useful tool in evaluation of short prepubertal children, Juul A. in his study in Denmark found that subnormal IGF-1 level ,are highly predictive of a subnormal GH response to a GH provocative test in prepubertal children in whom GH deficiency is suspected , and the predictive value of IGF-1 in pubertal children is diminished in comparison with that in prepubertal children[13]. Serum IGF-1 levels in group II patients (pubertal children and adolescents) (184.59± 196.52) although were still lower than that of group II control (285.91± 68.89) but were not statistically

significantly low compared with IGF-1 serum level control (P value >0.05).Thus pubertal status plays a role on IGF-1 level independent to the GH deficiency . Kanbur- Oksus N. in a study found that in both sexes ,serum IGF-1 levels and IGF-1 / IGFBP-3 ratios were significantly correlated with sex steroid levels and this correlation indicates that increasing sex steroids with pubertal development increase the IGF-1 levels [(14)].The average IGF-1 level of both group I & group II patients was statistically significant compared with average IGF-1 level of both group I & group II control (P value <0.05).This is partly because the size of group I is larger than group II & also the IGF-1 level in group II although not statistically significant lower than control but it is still low compared to that of control , all this made the total IGF-1 level of patients statistically low compared with that of control.The usefulness of IGF-1 in the diagnosis of GH status was confirmed in short children. ,Jaruratanasirikul S. et al, in a study concluded that the serum concentrations of IGF-1 and IGFBP-3 could reflect endogenous GH secretion and could be used as a screening evaluation of GH status in short children [(15)]. Cianfarani S.et al, in a study in Italy found that combining the evaluation of growth velocity with IGF-I measurement , and implying that two subnormal values strongly suggest GH deficiency and two normal values strongly oppose the diagnosis of GH deficiency [(16)] .Federico G.et al, in a review of available data indicates that IGF-1 measurement in the diagnosis of childhood-onset isolated GH deficiency has a specificity of up to 100%, with a specificity ranging from about 70 to90%[(17)] . But this usefulness was disputed ,Wacharasindhu S, in a study in Bangkok, Thailand , suggest that the measurement of IGF-1 and IGFBP-3 cannot be used in diagnosing GH deficiency but still can predict the height outcome at least by the first 2 years of treatment[(18)] ,the reason for some of the discrepancy may be the number of studied patients and the absence of pubertal staging .

Conclusion

We concluded that IGF-1 is a suitable parameter to predict GH deficiency in short prepubertal children in whom GH deficiency was found by GH provocative testing. But this test is less reliable in children who entered puberty.

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