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ORIGINAL RESEARCH
ORJİNAL ARAŞTIRMA

Short stature, insufficient annual height growth and back bone age: Nutritional growth retardation or growth hormone deficiency?

Boy kısalığı, yetersiz yıllık boy uzaması ve kemik yaşı geriliği birlikteliği: Nutrisyonel boy kısalığı mı büyüme hormonu eksikliği mi?

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ABSTRACT

Background/Aim: Serum insulin-like growth factor 1 (IGF-1) concentrations are affected both by nutritional status and serum growth hormone levels therefore IGF-1 is useful as an indicator of growth and nutritional status. The aim of this study is to determine the cut off level of IGF-1 to differentiate nutritional growth retardation (NGR) from growth hormone deficiency (GHD) in children with insufficient annual height growth and back bone age.

Methods: The study group included 57 children who had been diagnosed with NGR due to malnutrition and 36 children with similar age and sex, who had been diagnosed with short stature due to GHD. Serum IGF-1 concentrations were determined by chemiluminescent immunometric assay in all children.

Results: There was no significant difference in serum IGF-1 levels between NGR and GHD groups. We could not find an IGF-1 cut off level to differentiate NGR from GHD in children with NGR.

Conclusion: We suggest that examination of IGF-1 levels in children with NGR to exclude GHD is not useful.

Keywords: Insulin-like growth factor-1, short stature, malnutrition, children

ÖZET

Amaç: Serum insülin benzeri growth faktörü 1 (IGF-1) düzeyleri beslenme ve serum büyüme hormonu düzeyleriyle etkileşir, bu nedenle IGF-1 büyüme ve beslenmeyi gösteren bir parametre olabilir. Bu çalışmada, yetersiz boy uzaması ve kemik gelişimi olan çocuklarda nutrisyonel büyüme geriliğinin (NBG) büyüme hormon eksikliğinden (BHE) ayırımda kullanılabilecek serum IGF-1 kesim seviyeleri araştırıldı.

Gereç ve Yöntem: Çalışmaya malnutrisyon sonucu NBG saptanan 57 çocuk ve BHE'ye bağlı boy kısalığı olan benzer yaş ve cinsiyette 36 çocuk alındı. Tüm çocuklarda serum IGF-1 seviyesi immunometrik chemiluminescent yöntemiyle ölçüldü.

Bulgular: NBG ve GHD grupları arasında serum IGF-1 seviyeleri açısından anlamlı fark saptanmadı (p> 0.05). NBG'li çocukları GHD'li çocuklardan ayırmak için istatistiksel olarak anlamlı IGF-1 kesim seviyesi saptanmadı.

Sonuç: NBG'li çocukları BHE olan çocuklardan ayırmak için serum IGF-1 seviyesi incelemenin gereksiz bir yöntem olduğunu düşünüyoruz.

Anahtar kelimeler: İnsülin benzeri growth faktörü 1, kısa boy, malnutrisyon, çocuk

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INTRODUCTION

Short stature in children and adolescents may be due to variations in normal growth or to pathologic states. Accurate assessment and monitoring of growth in children is of critical importance for early identification of defects associated with treatable conditions versus growth variations. Growth deviations may be expressed as standard deviations (SD) from the normal population mean for children of comparable age and sex; children with heights >2 SD below the mean are generally classified as short stature (1). In this state, key parameters related to growth should be monitored, including length or height according to age, weight, body mass index (BMI) compared with the mean of the reference populations for boys and girls. In selected children, additional testing will be helpful, such as complete blood count, serum thyroid-stimulating hormone (TSH), free thyroxine (T4), growth hormone (GH), and insulin-like growth factor 1(IGF-1) levels and bone age (2).

IGF-1 is a hormone produced primarily by the liver and regulated by GH secretion by the somatotroph cells of the anterior pituitary gland. Serum IGF-1 concentrations are affected primarily by nutritional status and serum GH levels, therefore IGF-1 is a useful indicator of growth and nutritional status. In addition, age, gender, circadian variation, genetic factors, and chronic disease (i.e hepatic disease, diabetes mellitus, hypothyroidism) also have an important influence on IGF-1(3).

Children with protein-calorie malnutrition are generally referred to the pediatricians because of short stature so called nutritional growth retardation (NGR) and height below minus 2 SD from the mean height for age of the reference population. It is well known that nutritional status is an important determinant of the GH–IGF-1 axis. There is an inappropriate response to GH at the level of the liver therefore high blood levels of GH and low levels of IGF-1 in children with malnutrition. This state is an acquired GH resistance and an adaptive response to decreased energy intake (4,5). Therefore low IGF-1 levels lead to minimal anabolic effects thus energy can be used for acute needs and slowdown the catabolic process consequently to form aprotective mechanism for survival (6).

Growth hormone deficiency (GHD) is a rare disorder with a prevalence of approximately 1 in 4000 during childhood (7). The diagnosis of GHD is multifaceted and includes an assessment of the patient's auxology, a biochemical assessment of the GH-IGF-1 axis, bone age determination and imaging of the hypothalamo-pituitary axis (8). Growth hormone stimulates the liver and other body tissues to produce IGF-I, which then acts as the link between GH in the blood and inside cells that causes growth. The amount of IGF-1 in the blood provides an indirect measure of the amount of growth hormone present.

Apart from this study, there have been no other studies comparing serum IGF-1 levels in patients with NGR and GHD. The purpose in the present study is to determine the cut off level of IGF-1 to differentiate NGR from GHD in children with insufficient annual height growth and back bone age.

MATERIAL AND METHODS

This retrospective study included a total of 93 children with short stature, insufficient annual height growth and back bone age. Fifty seven patients aged 7–15 years had been diagnosed with NGR due to malnutrition in the Pediatric Gastroenterology Outpatient Clinic and 36 patients aged 7–15 years with similar age and sex had been diagnosed with short stature due to GHD in the Pediatric Endocrinology Outpatient Clinic at the Kecioren Training and Research Hospital.

In NGR group, the body weight and height percentiles of all patients were under the third percentile and less than –2 Z-score of weight-

for-age and height for-age. All children in this group had insufficient annual height growth and back bone age and they were investigated for GH deficiency by the same pediatric endocrinologist. The lack of GHD was shown according to the GH peak responses and GH stimulation tests (clonidine L-dopa) response.

The control group consisted of patients with GHD. Body weight of these patients were between 25th and 50th percentiles. Z-score of height-for-age were under the third percentile and less than –2 Z score. All children in this group had insufficient annual height growth and back bone age and insufficient GH peak levels and GH stimulation test (clonidine L-dopa, both of >10 ng/ ml) response considered GH deficiency. The brain magnetic resonance imaging done to exclude anatomic abnormalities was normal in all patients in this group.

Children born small for gestational age and children born prematurily (gestational age below 37 week) were excluded from study. and All patients with history of chronic disease (including chronic kidney disease, Crohn's disease, juvenile idiopathic arthritis, gluten enteropathy, cystic fibrosis, and hematologic or solid malignancies), hormone diseases (lack of thyroid hormones, Cushing's syndrome, congenital problems in the tissues where growth occurs (intrauterine growth restriction, chromosome abnormalities (Turner syndrome, Noonan syndrome), skeletal abnormalities (bone diseases or skeletal dysplasias) were excluded. To screen cytic fibrosis ,the sweat test measures of chloride concentration was used. Children whose sweat test outcomes 40mmol/L or greater were excluded. Patients taking an enteral nutrition or multivitamin drug or element treatment were also excluded.

All anthropometric measurements were recorded as the mean of two measurements. The child be weighed without shoes and wearing only light clothing. Z-score of weight-for-age and height for-age calculated according to the Turkish Standards (9). A BMI [body mass index = body weight (kg) / height (m2)] was calculated for all children. A radiograph of left hand and wrist were done in all patients for rickets and bone age estimation using published standards of Greulich and Pyle's Atlas of Skeletal Development.(10) The stage of puberty was assesed in each child by the Tanner's scale(11).

Blood samples were obtained after an overnight fasting and before initiation of the feeding. Serum and plasma samples were stored at −20 °C until assays of hormones. Baseline laboratory investigations included complete blood counts, serum urea, creatinine, glucose, alanine aminoteransferase (ALT), aspartate aminotransferase (AST), serum total protein and albumin, calcium, phosphore, alkaline phosphatase, zinc levels. Serum tissue transglutaminase IgA levels were determined using an enzyme-linked immunosorbent assay (Triturus automatic analyser, Grifols, Barcelona, Spain). The cut-off for defining a positive result was set at 20 U/ mL. Serum levels of IgA were also measured by enzyme linked immunosorbent assay (SPA-PLUS Binding site group Ltd, Birmingham, UK) to exclude immunuglobulin A deficiency. Serum IGF-1 concentrations were determined by a fully automated two-site, chemiluminescent immunometric assay (Immulite 2000, Siemens Healthcare Diagnostics, Malvern, USA). IGF-1 levels were expressed as IGF-1 Z scores according to appropriate reference data (12). Ferritine, 25-hydroxyvitamin D (25-OH vitamin D), TSH and T4 levels, cortisol, prolactine were measured by chemiluminescent immunometric assay (Architecht I 2000 Analyser, Abbott Diagnostics, IL, USA).

The study design was approved by the ethics committee of our hospital. Informed consent was obtained from the parents of children.

Statistical analysis was performed using SPSS 17.0 for Windows (SPSS Inc., Chicago, IL, USA). The Fisher exact test was applied to compare categorical data, and the Mann–Whitney U test was used to compare

RESULTS

In this study, 57 children with short stature due to malnutrition (40 male, 17 female) and 36 children with short stature due to GH deficiency (20 male, 16 female) were evaluated. The age of the subjects ranged from 7 to 15 years in the NGR group and from 5 to 15 years in the GHD group. There was no statistical difference in mean age or gender ratio between NGR and GHD groups (p= 0.06) (**Table 1**). In the NGR group we recognised prepubertal stage Tanner 1 in 15 children and tanner II/III stage in 42 (73.6%) children. In the GHD group we recognised prepubertal stage Tanner 1 in 10 children and tanner II/III stage in 26 (72.2%) children. We did not find any child who would have puberty stage IV/V. There was no statistical difference in tanner stages between NGR and GHD groups (p= 0.88).

Table 1. *Demographic features and laboratory results in study participants*

	NGR group(n=57)	GHD group (n=36)	p value
Age (years)	12.68 ±1.67	11.96±2.01	P=0.12
Gender (%female)	29 %	44%	P= 0.14
Weight	32.24±5.72	36.99±11.16	P=0.00
Height	139.10±10.02	133.80±12.45	P=0.06
BMI	15.77±0.90	20.27±3.09	P=0.00
Weight for age (SD score)	-2.19±0.62	-0.59±0.90	P=0.00
Height for age (SD score)	-2.28±0.40	-2.24±0.30	P=0.828
Annual height growth (cm)	3.97±0.73	3.77±0.73	P=0.226
Bone age	10.77±1.84	10.21±2.12	P=0.199
IGF-1	207.89±88.6	203.08±110.6	P=0.820
IGF-1 Z scores	-1.74±0.54	-1.62±0.46	P=0.515
Hemoglobin	13.31±0.82	13.26±0.87	P=0.917
Ferritin	23.87±9.19	28.72±13.19	P=0.112
Creatinine	0.61±0.06	0.69±0.10	**P=0.00**
ALT	21.33±9.18	20.20±8.10	P=0.878
AST	22.56±6.74	24.82±7.99	P=0.228
Albumin	4.33±0.29	4.56±0.19	**P=0.00**
Calcium	9.89±0.26	9.89±0.33	P=0.640
Phosphor	4.91±0.43	4.79±0.50	P=0.301
Zinc	67.44±8.45	70.84±9.42	P=0.07
Alkaline phosphatase	238.35±70.04	227.91±62.33	P=0.673
25-OH vitamin D	23.95±9.42	29.68±9.69	**P=0.002**
Cortisol	12.45±3.00	11.56±3.91	P=0.202
Prolactin	11.10±4.66	10.87±3.72	P=0.984
Free thyroxine	1.08±0.17	0.97±0.11	**P=0.005**
Thyroid stimulating hormone	2,26±0,94	2,56±0,89	P=0.150

On laboratory examinations, there were no statistically difference between NGR and GHD groups for serum IGF-1 levels (207.89 ±88.6 vs 203.08±110.6 p=0.820) and IGF Z scores (-1.74±0.54 vs -1,62±0.46, p=0.515). Blood T4, 25 OH vitamin D, creatinin and albumin levels were statistically lower in NGR group compared with GHD group. Blood

ferritine, TSH, cortisol, prolactin levels did not differ between these groups (p>0.05) (Table 1). All patients had normal Ig A and negative serum tissue transglutaminase antibodies for celiac disease.

A positive correlation was detected between IGF-1 and age (r =0.525, p< 0.001), height (r =0.537, p< 0.001), weight (r =0.528, p< 0.001), and bone age (r =0.604, p< 0.001) in NGR group. There was no significant correlation between IGF-1 and any parameters in GHD group.

DISCUSSION

Malnutrition is considered a leading cause of growth reatardation in children. When providing good nutrition, spontaneous catch-up growth usually occurs. However, in some cases (especially healthy children in appetite or refuse to eat), the catch-up growth is not complete, leading to a permanent growth deficit. Children with NGR may cease to gain appropriate weight and fail to grow in height, even without exhibiting body weight deficits for height. It may be difficult to differentiate NGR with annual height growth and back bone age from those with GHD in children.

There is an inappropriate response to GH at the level of the liver therefore high blood levels of GH and low levels of IGF-1 in children with malnutrition. This state is an acquired GH resistance and an adaptive response to decreased energy intake (4,5,13). Similar to those findings, low serum IGF-1 levels were found in our pediatric malnutrition group.

The serum IGF-1 levels in children with NGR and GHD are investigated in this study and mean serum IGF-1 were low in two groups but were not statistically different and there was not a cut off level for IGF-1 to differentiate NGR from GHD. Wan Nazaimoon et al. reported that the IGF-I concentration correlates strongly with height Z score in children with malnutrition, suggesting that it is a useful indicator of growth and nutritional status (14). We didn't find any correlations between IGF-1 and height Z score but we found a positive correlation between IGF-1 and age, height, weight, bone age in NGR group.

There are some limitations in our study. Firstly, sample size of this study was small. Secondly, we didn’t investigated IGFBP levels in this study. It is usually estimated by measurement of IGF-I immunoreactivity following extraction of IGFBP. Total serum IGF-I suffers from the drawback that its concentration does not necessarily reflect IGF-I bioactivity. Consequently, interest has increased in measurement of free IGF-I as a biologically and potentially more clinically relevant parameter. We measured of IGF-1 levels in this study.

In conclusion, to our knowledge, this is the first study to compare serum IGF-1 levels in children with NGR and GHD. We didn’t find cut off level for IGF-1 to differentiate NGR with insufficient annual height growth and back bone age from GHD in children. We suggest that examination of IGF-1 levels in children with NGR to exclude GHD is not useful.

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