Kirkuk University Journal /Scientific Studies (KUJSS)
Volume 11, Issue 1, March 2016 , p.p(64-74)
ISSN 1992 – 0849

Growth Hormone and Some Other Parameters Estimation in Thalassemia major Patients

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Received date : 23 / 6 / 2014 **Accepted date : 17 / 11 / 2014**

ABSTRACT

This study is a cross-sectional study, included forty eight male subjects, during the period from the beginning of December 2013 to the beginning of April 2014 at Azadi teaching Hospital in Kirkuk City in Iraq. Questionnaire was administered, patients were examined, blood sample was collected and examined, data gathered and analysis (SD, T test & P value and Pearson correlation was employed for analysis of the relationship between variables).

Growth hormone (GH), Serum Ferritin(SF), Hemoglobin (Hb) and packed cell volume(PCV), also body weight &height as well as body mass index were evaluated in 33 male patients (aged 10–20 years old) with β thalassaemia & in 15 subjects at the same age and sex as a control group. This study revealed that there was highly significant decrease in all parameters in thalassemic patients (except serum ferritin was highly significant increase in patients) as compare with controls (P< 0.001). Positive correlation found between GH and both Hb and PCV, while negative correlation was found between GH and ferritin level.

Keywords: *Thalassemia, Iron Overload, Stunted Growth, Growth Hormone*

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قياس مستوى هرمون النمو و بعض المعايير الاخرى لمرضى الثلاسيميا الكبرى

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تاريخ استلام البحث: ٢٣ / ٦ / ٢٠١٤ تاريخ قبول البحث: ١٧ / ١١ / ٢٠١٤

الملخص

هذه الدراسة شملت ثماني و اربعين عنصرا من الذكور ، خلال الفترة منذ بداية شهر كانون الاول ٢٠١٣ و لغاية الاول من شهر نيسان ٢٠١٤ ، في مستشفى آزادي التعليمي في مدينة كركوك / العراق. تم جمع المعلومات مباشرة من الشتركين من خلال ملىء استمارة جمع المعلومات ، تم فحص المرضى و جمع عينات الدم من المرضى و مجموعة السيطرة . جمعت المعلومات و تم تحليلها احصائيا باستعمال : معدل الانحراف القياسي ، اختبار تي ، قيمة بي ، اختبارا.

تم حساب تركيز كل من : هرمون النمو ، حديدين المصل ، الهيموغلوبين و حجم الخلايا المضغوط. كذلك تم احتساب الوزن و الطول بالاضافة الى معيار كتلة الجسم لكل من مرضى الثلاسيميا(٣٣ عنصرا) و مجموعة السيطرة(١٥ عنصرا) من نفس العمر والجنس.

أظهرت الدراسة نقصانا معنويا عاليا في كل المعايير(عدا حديدين المصل ، زيادة معنوية عالية) لدى مرضى الثلاسيميا بالمقارنة مع مجموعة السيطرة ، كذلك بينت هذه الدراسة ان هنالك علاقة ايجابية بين هرمون النمو و كل من الهيموغلوبين وحجم الخلايا المضغوط و وجود علاقة سلبية بين هرمون النمو و نسبة الحديدين.

الكلمات الدالة: الثلاسيميا ، الحديد الزائد ، توقف النمو ، هرمون النمو.

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1. Introduction

Growth hormone (hGH, somatotropin),secreted from the anterior pituitary [1]. Of all the hormones produced by the hypophysis, GH is the most abundant. The pituitary gland contains an amount of GH that is 20 to 40 times greater than that of corticotropin and 50 to 100 times greater than that of PRL [2].

It's a polypeptide with two intra-chain disulfide bridges, which circulates free or bound to number of different GH-binding proteins [1]. About half of the GH in the plasma is bound to a protein that consists of a cleavage product of the GH receptor. This provides a reservoir that compensates for the wide fluctuations in the rate of secretion and the short half-life (6–20 minutes) of GH [3].

Several forms of growth hormone have been identified [1]with the major being of molecular weight 22,000 daltons [4] containing 191 amino acid residues . A 20,000-dalton variant, which posses all known biological actions of GH, has also shown to be important . The primary biological actions of the hormone are indirect growth promoting . GH exerts its effect directly on target organs such as bones and muscles; indirectly through the release of somatomedins ,a family of insulin like growth factor (IGF)hormones , produced in the liver . In particular somatotropin C (IGF-1) is essential for bone growth during childhood. [5]

The clinical usefulness of the measurement of growth hormone (GH) in children has been well established in ascertaining linear bone growth along the epiphyseal plate. Abnormally elevated levels lead to gigantism while complete absence slows the rate of growth one-third to one half of normal. In adults, the epiphyseal growth plates had fused so hGH excess gradually produces acromegaly, a cross thickening of the bones of the skull, hands and feet [6].

Growth retardation has been reported to occur in most patients with thalassemia major [7]. Defective somatomedin activity has been suggested [8, 9] as one of the causes of this growth failure, since endocrine studies did not show a significant suppression of GH secretion in all patients. Functional damage to the hypothalamic structure for GH control, with a markedly decreased GH response to GHRH, has also been reported recently [10]. The pathogenesis of growth failure is multifactorial. Key contributing factors to stunted growth in patients with Thalassemia Major may include chronic anemia, transfusional iron overload, hypersplenism, and

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chelation toxicity [11]. Other contributing factors include hypothyroidism, hypogonadism, GH deficiency/insufficiency, zinc deficiency, chronic liver disease, undernutrition and psychosocial stress [12].

The classic pattern of constitutional growth delay is normal birth weight and length. A subtle decrease in growth velocity occurs about second year of life. Thereafter, stature remains below the fifth percentile through childhood. However, growth velocity remains appropriate for the skeletal age. Linear growth is considered to be decreased when a child's height falls more than 2 standard deviation (SD) below the mean height for age [13].

The aim of the study is to evaluate the influence of age at the onset of blood transfusion, iron chelation therapy, and serum ferritin levels on growth and , and the prevalence of this endocrine complication with respect to pituitary somatotropic function among a group of male thalassemic patients in Kirkuk city.

2. Patients and Methods

Clinical information collected from 60 patients with β-thalassemia major who attended Azadi – teaching Hospital in Kirkuk city during the period from December 2013 till April 2014, and filled the questionnaires. The patients aged between 10 – 20 years (mean: 15.1 ± 4.8 years), and all were residents of Kirkuk city. The mean height value was 137.58 ±14.42 cm in male patients. All patients were homozygous for beta-thalassemia and were being treated with frequent transfusions to maintain the post transfusion hemoglobin level above 10g/dL, and long-term iron chelation therapy with desferoxamine (DFX) had been started in patients over 2.5-year-old, with serum ferritin concentrations greater than 1000 µg/L. The dose of DFX had been 30 – 50 mg/kg/day subcutaneously, 5 – 6 nights a week.

Thirty six age and sex matched patients without thalassemia constituted the control group. Blood was aspirated from all of the subjects in the early morning (8–10 AM) and separated into two aliquots, with one sample being stored in EDTA tubes for hematological estimations and the other in plain tubes for estimation of the other parameters in sera. Investigations were performed at the laboratory of the main blood bank of Azadi teaching Hospital in Kirkuk.

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The selection of reagents used in this study was based on accuracy, reliability, availability, and were purchased as kits. Growth Hormone estimated in serum by the ELISA technique using ready-for-use kits supplied by Monobind Inc., USA [14].

Serum Ferritin was measured by an enzyme linked assay method using a kit supplied by Biomerieux (France) by VIDAS technique [15].

3. Statistical analysis

All data were presented as the mean ± SD. The mean of variables was compared by using Un paired Student's *t* test. $P < 0.05$ was considered as statistically significant at the level of 0.05 [16]. In addition to Pearson correlation was used to correlate between measured variables [17].

4. Results

The results in the two groups are shown in Tables (1,2). There is a highly significant difference between thalassemia patients and healthy subjects in all parameters.

4.1. Anthropometric measurements results

Regarding body weight (BW): there is a high significant decrease (P=0.0001**) in thalassemic male BW (35.17±10.09 Kg) as compare with control subjects (60.59±13.7 Kg).

Regarding body height (BH): there is a high significant decrease (P=0.0001**) in thalassemic male BH (137.58±14.42 cm) as compare with control group (157.32±14.59 cm).

Also, there is a high significant decrease (P=0.0001**) in body mass index (BMI) of thalassemic male patients (18.64±2.15 Kg/m^2) as compare with control subjects (22.6±3.88 kg/m^2). As shown in Table (1).

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Table (1): Mean &SD of Thalassemic Patients and Control Group

Parameter	Thalassemic group(n=33)	Control group(n=15)	P-value
Body Weight (Kg)	٣٥.١٧±10.09	٦٠.٥٩±١٣.٧	٠.٠٠٠١**
Body Height (cm)	١٣٧.٥٨±١٤.٤٢	١٥٧.٣٢±١٤.٥٩	٠.٠٠٠١**
BMI(Kg/m^2)	**18.64±2.15**	٢٢.٦±٣.٨٨	٠.٠٠٠١**

4.2. Hematological results

Regarding hemoglobin (Hb): there is a high significant decrease (P=0.0001**) in Hb concentration of thalassemic male (7.970±0.888 gm/dl) as compare with that of control group (14.693±1.022 gm/dl).

Regarding packed cell volume (PCV): there is a high significant decrease (P=0.0001**)in thalassemic male PCV(24.836±2.613L/L) as compare with control group (45.040±3.143 L/L).

4.3. Serum analysis results

Regarding serum ferritin: there is a high significant increase (P=0.0001**) in thalassemic male patients serum ferritin(4505±2838 ng/ml) as compare with control group (55.07±7.22 ng/ml).

Regarding serum Growth Hormone (GH): there is a high significant decrease (P=0.001**) in thalassemic male patients serum GH (2.392±1.929 µIU/ml) as compare with that of control group (8.67±5.32 µIU/ml). As shown in Table (2).

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Table (2): Mean &SD of Thalassemic Patients and Control Group

parameter	Thalassemic group(n=33)	Control group(n=15)	P-value
Hemoglobin (g/dl)	٧.٩٧٠±٠.٨٨	14.69±1.02	٠.٠٠٠١**
PCV(L/L)	٢٤.٨٣±٢.٦١	٤٥.٠٤±٣.١٤	٠.٠٠٠١**
Ferritin(ng/ml)	٤٥٠٥±٢٨٣٨	٥٥.٠٧±٧.٢٢	٠.٠٠٠١**
Growth Hormone (µIU/ml)	٢.٣٩٢±١.٩٢٩	٨.٦٧±٥.٣٢	٠.٠٠١**

**mean highly significant

5. Discussion

Endocrine dysfunctions have been well described in patients with thalassemia major. [18-27] Results of this study show a high prevalence of stunted growth (62%) in a sample of male thalassemic patients in Kirkuk city.

Short stature has been reported as a common complication in transfusion dependent thalassemia [28]. Many factors are involved in the growth retardation of patients with thalassemia, the main ones are chronic anemia , iron overload, hypersplenism, folate deficiency, endocrine disorders secondary to iron overload (hypogonadism, hypothyroidism), and bone dysplasia secondary to DFX toxicity. [24, 27, 29] GH secretion is also operative.

Studies on GH secretion in patients with thalassemia have shown both normal and reduced GH response to stimulation tests, and reduced spontaneous secretion (neurosecretory dysfunction). [20].

Both Soliman et al and Borgna-Pignatti et al reported short stature in 49% and 40.6% of the patients with thalassemia ، respectively [28,36].

Results of this study show that short stature and hypogonadism are very common in our thalassemic patients, mainly in those who have serum ferritin levels above 2000 µg/L. Some studies suggest that iron chelation therapy has an important role in gonadic function and growth

in patients with thalassemia major and most of the patients who start treatment in the first years of life and have constantly good compliance may show normal growth and sexual maturation. [27, 37].

6. Conclusions

In conclusion ،poor compliance with chelating therapy is the main reason for low growth hormone level, which is the main cause of stunted growth.

7. Recommendations

Timing of regular blood transfusion and iron chelation therapy influence the growth in these patients. We recommend new chelating therapy that insures good compliance of patients with the drug. Also early detection of low GH level to be treated early.

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