Research Article

Insulin-like growth factor-1 levels in children with Beta-thalassemia minor

Beta-talasemi minörlü çocuklarda insülin-benzeri büyüme faktörü-1 seviyeleri

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Abstract

Objective: Growth retardation in children with β-thalassemia major is multifactorial. Some etiologies described for this condition are hemochromatosis, disturbed growth hormone (GH) / insulin growth factor-1 (IGF-1) axis, undernutrition and hypermetabolism. It has also been proven that growth retardation is present in β-thalassemia major children despite regular transfusion and chelation. Our aim was to evaluate the level of IGF-1 in β-thalassemia minor subjects and compare it with that in healthy children.

Material and Methods: Fifty children aged 6 months to 15 years with β-thalassemia minor (32 males, 18 females) and 50 age- and sex-matched normal healthy children were selected. Medical history was taken and complete physical examination was done in each case; IGF-1 level was checked in all cases. This study was done in Shiraz, southern Iran, during 2005.

Results: IGF-1 levels were significantly lower in β-thalassemia minor children than normal children (P = 0.015). This result demonstrates that some etiologies of growth failure in β-thalassemia major other than those described to date can exist, which may be shared with β-thalassemia minor in feature or may be transformed by genes that are either expressed or not.

Conclusion: We conclude that in addition to that observed in β-thalassemia major, IGF-1 level is also decreased in β-thalassemia minor, and these two may have similar etiologies. *(Turk J Hematol 2008; 25: 136-9)*

Key words: Thalassemia, insulin-like growth factor-1, growth retardation, β-thalassemia minor.

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Özet

Amaç: Beta-talasemi majörlü çocuklarda büyüme gecikmesi, hematokromatoz, büyüme hormonu (GH)/ insülin büyüme faktörü-1 (IGF-1) ekseninin bozulması, yetersiz beslenme ve hipermetabolizma gibi multifaktöriyel bir durumdur. Beta talasemi majörlü çocuklarda büyüme gecikmesinin düzenli transfüzyon ve şelasyona rağmen mevcut olduğu da kanıtlanmıştır. Amacımız β-talasemi minörlü olgularda IGF-1 seviyesini değerlendirmek ve bunu sağlıklı çocuklardakiyle karşılaştırmaktır.

Gereç ve Yöntemler: Erkek, 18 dişi ile yaş ve cinsiyet açısından eşleşmiş olan 50 normal çocuk bu çalışma için seçilmiştir. Her bir olgu için tıbbi özgeçmiş alınmış ve tam fizik muayene yapılmıştır; tüm vakalarda IGF-1 seviyesi kontrol edilmiştir. Bu çalışma, İran'ın güneyindeki Şiraz'da 2005 yılında yapılmıştır.

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Bulgular: IGF-1 seviyeleri β talasemi minörlü çocuklarda normallere nazaran önemli ölçüde düşüktür (P = 0,015). Bu sonuca göre, β talasemi majörde şu ana kadar tanımlananların yanı sıra başka büyüme yetersizliği etiyolojileri β-talasemi minörde mevcut olabilir ve eksprese edilen veya edilmeyen genlerle biçim değiştirebilir.
Sonuç: Bize göre, β talasemi majörün yanı sıra, β-talasemi minörde de IGF-1 seviyesi azalmıştır ve bu ikisi benzer etiyolojilere sahiptir. *(Turk J Hematol 2008; 25: 136-9)*
Anahtar kelimeler: Talasemi, insülin-benzeri büyüme faktörü-1, büyüme gecikmesi, β-talasemi minör.

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Introduction

Beta-thalassemia is one of the most common hereditary disorders in the world in which b-chain production is impaired. Sequelae of this disorder are hyperplastic bone marrow, increased iron storage and overload, cirrhosis of the liver, endocrine disturbances, skin hyperpigmentation, cardiac hemochromatosis, hypersplenism and shortened red cell life [1].

Growth delay is a striking feature of β-thalassemia major. Insulin-like growth factor-1 (IGF-1) and thyroid hormone appear to be the major mediators of skeletal growth [2]. Many of the effects of growth hormone are mediated by IGF-1, which circulates in the plasma bound to one of a series of binding proteins called IGF binding proteins (IGFBPs). These proteins circulate and modify IGF-1 action either as stimulators or inhibitors [3,4].

It has been shown that IGF-1 and IGFBP-3 response to growth hormone injection is significantly lower in thalassemia major patients than normal children, suggesting partial resistance to growth hormone in these children [5,6]. In general, there is no doubt that growth retardation in β-thalassemia major is multifactorial.

Beta thalassemia trait (BTT) is almost invariably asymptomatic and is characterized by mild anemia, a slightly reduced hemoglobin level and a marked reduction in mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH).

BTT is one of the most prevalent genetic disorders in Mediterranean countries. Close to 10% of the Iranian population has BTT according to the place of residence. BTT is most frequent (7-10%) in northern and southern Iran [7,8].

We observed that some of the patients that referred to the Pediatric Endocrinology Clinic due to short stature or poor weight gain were carriers of β-thalassemia. Therefore, we performed this study in order to investigate any correlation between IGF-1 level and growth retardation in β-thalassemia minor subjects and to compare its level with that in normal children.

Materials and Methods

In this case-control study, 50 children aged between 6 months and 15 years with β-thalassemia minor who had referred to our clinic were randomly selected within a period of six months during 2005. All of them had received breast milk for at least one year and none of them had splenomegaly or any other medical disorder except β-thalassemia minor. Thirty-two were male and 18 were female. The control group consisted of 50 age- and sex-matched healthy children who came for routine check-up and who had no nutritional deficiencies and no chronic or systemic disorders; their height and weight were between the 3rd and 95th percentile for age. Medical history was taken and complete physical examination was done in each case. We excluded all patients with familial short stature, constitutional growth delay, hormone deficiency, malnutrition, and chronic systemic disorders, and included healthy patients with thalassemia minor. We divided the thalassemia minor patients and controls in two subgroups as under 5 years and above 5 years.

Anthropometric parameters of weight and height were measured in both groups. Other data included hemoglobin (Hb), MCV, MCH, mean corpuscular hemoglobin concentration (MCHC), hemoglobin F (HbF) and hemoglobin A_2 (HbA_2). Their carrier state was established by complete blood count (CBC), MCH, MCV, Hb electrophoresis (by citrate agar), HbA2 (by column chromatography) and HbF (by alkaline denaturation).

In all cases, after obtaining an informed written consent from the subjects' parents, 5 ml of venous blood was withdrawn for measurement of IGF-1 and serum ferritin. We measured serum ferritin, serum iron and total iron binding capacity (TIBC) in order to rule out combined iron deficiency anemia and β-thalassemia minor. Human IGF-1 was measured by radioimmunoassay (RIA) employing reagents (Immunotech Co., France). Serum ferritin was also measured by RIA employing reagents (Orion Co., Orion Diagnostica Espoo, Finland).

Data of the 2000 Centers for Disease Control (CDC) growth chart was used to compare anthropometric measurements of β-thalassemia minor children with normally accepted weight and height for age.

Data were presented as mean SD. Statistical analyses were performed by Mann-Whitney U test to compare IGF-1 concentrations in these two groups and using correlation to determine the relationship between IGF-1 and other variants. P-values less than 0.05 were considered as significant. This study was done in Shiraz, southern Iran, and was approved by the medical ethics committee of Shiraz University of Medical Sciences.

Results

Beta-thalassemia minor subjects had a mean age of 6.5 ± 3.4 years (range: 6 months to 15 years) and the control group had a mean age of 6.8 ± 3.4 years (range: 4 months to 14.5 years).

Eight children had combined iron deficiency anemia and were therefore excluded from the study. Others had normal levels of serum ferritin, serum iron and TIBC.

IGF-1 level was 61.33 ± 67.64 ng/ml in the beta-thalassemia minor group and 126.93 ± 156.7 ng/ml in the control group. IGF-1 level was significantly higher in the control group (P=0.015). Table 1 shows the data of thalassemia minor patients

Table 1. Characteristics of the thalassemia minor subjects and controls (Mean±SD)

Factors	Patients	Controls
Age (yr)	6.5±3.4	6.8±34
Male	32	32
Female	18	18
IGF-1 (ng/ml)	61.33±67.64	126.93±156.7
HbA2 (%)	4.62±1.7	2.5±0.5
HbF (%)	3.17±3.2	1.6%±0.3
MCH (pg)	18.8±1.8	27±1.2
MCHC (g/dl)	31.5±1.7	32±1.4
MCV (fL)	59.6±4.7	80±2.9

Pg: Picogram. **g/dl:** Gram/deciliter. **fL:** Femtoliter

and controls. IGF-1 levels in thalassemia minor and control subjects under the age of 5 years were 37.3 ± 27.5 ng/ml and 44.5 ± 36.1, respectively. This difference was not statistically significant (P=0.7). However, the levels of IGF-1 in thalassemia minor and control subjects in the subgroup above 5 years of age were 77.7 ± 81.4 ng/ml and 188.7 ± 183 ng/ml, respectively, and this difference was statistically significant (P< 0.05). We found no effect of sex on hormonal level.

In comparison with CDC data, height for age was below the 3rd percentile in 10% of thalassemia minor children, while it was below the 25th percentile in 52% and below the 50th percentile in 78%. Low IGF-1 was seen in thalassemia minor subjects both below and above the 3rd percentile, and height below 3rd percentile was seen in thalassemia minor subjects both below and above 5 years of age. Weight for age was below the 3rd percentile in 4% of the thalassemia minor patients, while it was below the 25th percentile in 50% and below the 50th percentile in 78%.

Discussion

To the best of our knowledge, this is the first report on IGF-1 levels in β-thalassemia minor cases. In our study, we observed that IGF-1 was decreased in β-thalassemia minor patients in comparison with normal children. Previous reports have shown that children with β-thalassemia major frequently have growth retardation in the presence of low serum IGF-1 and abnormal growth hormone [9,10].

It has been proven that growth retardation in children with β-thalassemia major is multifactorial [5,11] and that despite regular blood transfusions and desferrioxamine treatment, these patients have growth delay and bone alteration [10-12]. However, there is a state of partial growth hormone insensitivity at the post-receptor level that can be overcome by supra-physiological doses of exogenous growth hormone [11,13].

In general, β-thalassemia major patients have growth retardation due to the contribution of lack of pubertal growth spurt and decreased synthesis of IGF-1, which might be secondary to a disturbed growth hormone/IGF-1 axis and/or undernutrition, probably due to the hypermetabolic status of these children [14,15].

In this study, we showed that IGF-1 levels are low in carriers of β-thalassemia gene when compared with normal children. The limitation of this study is that we could not measure IGFBP-3 because of unavailability of the IGFBP-3 kit. All of the selected thalassemia minor children were healthy without any medical disorder. Ten percent of these children had short stature (height for age below 3rd percentile) and 4% had weight for age below the 3rd percentile. Similar results obtained here have also been reported in thalassemia major patients [6,9-11]. This may be due to some genetic impairment that it shares with β-thalassemia major [16].

Additionally, in another study performed on thalassemia minor subjects, short stature was significantly more prevalent, which is similar to that observed in patients with thalassemia major [16]. There was no difference between IGF-1 levels in both groups under 5 years of age. Serum IGF-1 concentrations are highly age-dependent. They are lowest in young children (<5 years of age), the age at which one most wishes to have a single diagnostic test 2.

We think that some etiologies other than those described to date for growth retardation in β-thalassemia major may exist that can be transformed by genes, whether expressed or not.

In conclusion, similar to patients with thalassemia major, IGF-1 levels in β-thalassemia minor children are also lower than in normal children.

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