Growth Retardation in β-Thalassemia Major

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ABSTRACT:

BACKGROUND:
Thalassemia is an inherited autosomal recessive blood disease caused by genetic defects result in reduced rate of synthesis of one of the globin chains that make up hemoglobin. The combination of transfusion and chelating therapy has dramatically extended the life expectancy of thalassemic patients.

OBJECTIVE:
The objective of this study is to determine the factors associated with short stature in thalassemic patients and main endocrine complications.

PATIENTS AND METHODS:
A case-control study was performed prospectively in Ibn-Al Balady hospital in (Al- Sader city- Baghdad- Rasafa) for the period extended from the 1st of January to 31st of May (2013). Data were collected from 181 thalassemic patients, their ages were 10 to 20 years old being attended the hospital for regular follow up and blood transfusion. The control in this research work was one of the patients’ relatives with the same age after thalassemia was ruled out in the control. Data collected in this study included: age, sex, height and weight were assessed by the National Center of Health statistics (NCHS) growth curves, history of splenectomy, times of blood transfusion, hepatitis infection, type of chelating agent. Serum ferritin, hormones level, fasting and random blood sugar and serum calcium were estimated.

RESULT:
It was founded that 79% of the β-thalassemic patients had short stature (their height equal or less than 5th percentile) with significant relation with high serum ferritin (P-value=0.006). Delayed puberty was the commonest endocrine complication in thalassemic patients (83.9%).

CONCLUSION:
High serum ferritin is associated with growth retardation and many endocrine complications. Aggressive iron-chelating therapy and regular measurement of hormones concentration are necessary for thalassemic patients mainly during puberty to avoid growth retardation.

KEY WORDS: β-thalassemia major, short stature, endocrine complications, growth retardation.

INTRODUCTION:
Beta-thalassemia major is a severe early-onset form of Beta-Thalassemia characterized by severe anemia requiring regular red blood cell transfusions (1), it is consider a serious health problem in Iraq due mainly to the non availability of equipments and drugs during different periods of turmoil and war (2).

Beta-Thalassemia major is an inherited autosomal recessive blood disease due to genetic defect results in reduced rate of synthesis of Beta globin chains that make up hemoglobin (1). Beta-thalassemia is particularly prevalent among Mediterranean people, North Africa, West and South Asia. The annual incidence of symptomatic cases is estimated at 1/100,000 worldwide and 1/10,000 in the Europe (3). Beta-Thalassemia major usually cause severe anemia with several health problems like enlarged spleen, bone deformities, short stature, diabetes, hepatitis infection and requires regular life-long transfusion, therapy and medical supervision (4).

The child with Thalassemia major has a particular growth pattern, which is relatively normal until age of 9–10 years; after this age a slowing down of growth velocity and a reduced or absent pubertal growth spurt are observed. The pathogenesis of growth failure is multifactorial (4), as shown below.
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- Chronic anemia, hypersplenism, chronic liver disease (HBV, HCV)
- Zinc and folic acid deficiency, skeletal dysplasia
- Desferrioxamine (Desferal) toxicity
- Iron overload
- Emotional disturbance
- Endocrinopathies: hypothyroidism, delayed puberty, hypogonadism, dysfunction of the growth hormone (GH) – IGF 1 axis

A close monitoring of growth may lead to early identification and treatment of these complications to ensure that patients achieve near normal adult height[5]. The beneficial effects of regular transfusions on growth in patients with thalassemia were first reported in 1965 (Weatherall and Clegg 1981) and have been subsequently confirmed by additional studies (Johnson et al. 1966; Logothetis et al. 1972; Bronspiegel-Weintrob et al. 1990) (6).

AIMS OF THE STUDY:
The aim of this study is to assess height, weight and to determine the factors associated with short stature in thalassemic patients and main endocrine complications.

PATIENTS AND METHODS:
A case-control study was performed prospectively in Ibn-Al Balady hospital in (Al- Sader city-Baghdad-Rasafa) for the period extended from the 1st of January to 31st of May (2013). Data were collected from 181 thalassemic patients, their ages were 10 to 20 years old being attending the hospital for regular follow up and blood transfusion. The control in this research was one of the patients' relatives with the same age after thalassemia was ruled out in the control. Cases of thalassemia intermedia, thalassemia minor and other hemoglobinopathies were excluded from the study.

The collected data were taken from parents of the participants and included: age, sex, history of splenectomy, times of blood transfusion , type of chelating agent. A clinical examination was performed for both patients and controls which included: height measurement using stadiometer, weight measurement using accurate scale.

Weight and height measurement were compared with the normal values on children growth chart of NCHS percentile. The National Center of Health statistics (NCHS) growth curves are used as reference standards because the National Center of Health statistics growth charts can be used continuously from ages 2-19 years while WHO growth charts provide information on children up to 5 years of age(7). Sexual maturation assessed by Tanner staging system. Investigations done for the patients only by collecting venous blood samples which included: screening for hepatitis Bs antigen and anti-hepatitis C antibody, serum ferritin level, growth hormone assay and thyroid function test, fasting and random blood sugar standardized according to WHO diagnostic criteria for diabetes (8) and serum calcium level.

Statistical Methods:
Data were entered into Statistical Package for Social Science (SPSS) program for Windows version 20 to generate the general characteristics of the study. Quantitative variables were summarized by finding mean ± SD. Statistical analysis Differences between patients with and without growth retardation and between patients and control were tested with the independent t-test, x2 test and C-test to identify the potential risk factors. A two-tailed P-value of less than 0.05 was considered to be statistically significant.

RESULTS:
Figure 1 shows that one hundred thirteen patients were males (62.4%) and sixty eight patients (37.6%) were females. 128 (70.7%) of the control were males and 53 (29.3%) were females.
Table 1 shows that 79% of the thalassemic patients' heights were equal or less than 5th percentile, 21% more than 5th to 50th percentile and none of the patients were more than 50th percentile. Heights of 81.4% male patients were equal or less than 5th percentile and 75% of the female patients' heights were equal or less than 5th percentile with no significant sex predication (P value=0.09 > α=0.05).

Table 1 shows that there were significant differences between the heights of the thalassemic patients and control (P value= 0.0004 < α=0.05).

Table 2 shows that 73.5% of the thalassemic patients' weights were equal or less than 5th percentile and 26.5% their weights were more than 5th to 50th percentile. 76.1% of the male thalassemic patients' weights were equal or less than 5th percentile and 69.1% of the female thalassemic patients' weights were equal or less than 5th percentile with no significant sex effect (P value=0.1 > α=0.05).

Table 2 shows that there were significant differences between the weights of the thalassemic patients and control (P value= 0.0007 < α=0.05).
Table 3 shows that 34.5% of the male and 38.2% of the female patients were splenectomized. 30.4% of the male patients with heights equal or less than 5th percentile were splenectomized and 52.4% of patients with heights more than 5th to 50th percentile were splenectomized. There was no relationship between splenectomy and heights of male patients (P-value=0.1 > α=0.05). There were no relationship between splenectomy and heights of female patients (P-value=0.23 > α=0.05). Table 3 shows no significant sex predilection regarding splenectomy (P-value=0.45 > α=0.05).

Table 4 shows that none of the male and female thalassemic patients had hepatitis B infection, 13.2% of the male and 7.4% of the female patients had hepatitis C infection with no significant difference with patients heights (P value= 0.29 in male patients and 0.4 in female patients).

Table 5 shows that 71.7% of male and 69.1% of female patients received blood more than 1 time per month with no significant relation with patients heights (P value = 0.07 in male and 0.08 in female patients). Table 6 shows that mean serum ferritin was 6338±925µg/l in the males and 5924±865 µg/l in the females with their heights equal or less than 5th percentile while mean serum ferritin in those patients with their height more than 5th -50th percentile was 3514±1095µg/l in the males and 4119±657µg/l in the females patients. So mean serum ferritin where higher in those patients with their height equal or less than 5th percentile(P-value=0.006).
Table 7 shows that 61.9% of the male patients and 85.3% of the female patients use exjade (Deferasirox) tablets, 38.1% of the male patients and 14.7% of the female patients use desferal (Desferrioxamine) with no significant relation with patients heights (P value= 0.06 in the male patients and 0.3 in female patients).

Table 7: Chelating agents used in male and female thalassemic patients.

<table>
<thead>
<tr>
<th>Height percentile</th>
<th>Patients on Exjade</th>
<th>Patients on Desferal</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male No.</td>
<td>%</td>
<td>Male No.</td>
</tr>
<tr>
<td>≤5th</td>
<td>58</td>
<td>63.1</td>
<td>42</td>
</tr>
<tr>
<td>&gt;5th-50th</td>
<td>12</td>
<td>57.2</td>
<td>16</td>
</tr>
<tr>
<td>Total</td>
<td>70</td>
<td>61.9</td>
<td>58</td>
</tr>
</tbody>
</table>

Table 8 shows that 152 thalassemic patients (83.9%) had delayed sexual maturation, 122 patients (67.4%) had growth hormone deficiency, 19 patients (10.5%) had hypothyroidism, 13 patients (7.2%) had diabetes mellitus and 11 patients (6.1%) had hypocalcaemia. Forty three patients (36.5%) had more than one endocrine complication.

Table 8: Endocrine complications in thalassemic patients.

<table>
<thead>
<tr>
<th>Endocrine complication</th>
<th>Female No.</th>
<th>Male No.</th>
<th>Total No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delayed sexual maturation</td>
<td>59</td>
<td>93</td>
<td>152</td>
<td>83.9</td>
</tr>
<tr>
<td>Growth hormone deficiency</td>
<td>43</td>
<td>79</td>
<td>122</td>
<td>67.4</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>8</td>
<td>11</td>
<td>19</td>
<td>10.5</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>4</td>
<td>9</td>
<td>13</td>
<td>7.2</td>
</tr>
<tr>
<td>Hypocalcaemia</td>
<td>3</td>
<td>8</td>
<td>11</td>
<td>6.1</td>
</tr>
</tbody>
</table>

DISCUSSION:
Thalassemia affect the growth of the thalassemic patients. Regarding height, 81.4% of the males' and 75% of the females' heights were equal or less than 5th percentile. Thalassemic patients were shorter than control (P-value=0.0004). Regarding weight, 76.1% of the males and 69.1% of the females' weights were equal or less than 5th percentile. Weights of thalassemic patients were less than of the control (P-value=0.0007). In Iran, 65.7% of thalassemic patients their heights were under the 5th percentile and 54.2% their weights were under 5th percentile[9]. In Chinese thalassemic patients, 48% of the patients were of short stature with height under the 3rd percentile and 43.7% were their weight under 3rd percentile[10]. In Thalassemia Center in Erbil City –Iraq, weight and height were less than 5th percentile in 61% and 79% of patients respectively[11]. In this study, there was no relation between sex and physical growth retardation as in study done in Jordan[12] while in Thailand the female children had lower weight (p < 0.0001) and height (p < 0.02) compared to males[13]. In this study, there were no relation between heights of the patients and splenectomy in males and females patients (P-value=0.1 and 0.23 respectively) and this is in concordance with study done in America in 1960[14]. In Saudi Arabia, a study done in 1990 shows improvement in the height of thalassemic patients after splenectomy because of good control on hemoglobin level[15]. Number of blood transfusions per year not affect heights of thalassemic patients in our study (P-value in males=0.07 and in females=0.08). In India, more blood transfusion lead to more risk of growth retardation which may be due to iron deposition in the pituitary gland[16]. In table, hepatitis infection had no relation with heights of thalassemic patients (P-value= 0.4 in males and 0.07 in females). No study was founded shows any relation between hepatitis infection and growth of thalassemic patients. In this study, there were no relation between chelating agents (whether Desferal or Exjade) and height of thalassemic patients (P-value=0.06 in males and 0.3 in females) but there were reports of abnormal linear growth and metaphysial dysplasia observed in children treated with deferoxamine before the age of 3 years[17]. The exact mechanism of growth retardation in children with thalassemia major, who are regularly transfused and are on chelation therapy with...
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desferrioxamine is unclear and seems to be multifactorial but growth retardation was not reported with exjade. In this study, delayed sexual maturation was the commonest endocrine complication. While growth hormone deficiency, hypothyroidism, diabetes mellitus and hypopcalcaemia were found but with less frequency. As in our study, in Iran hypogonadism was the most common endocrine complication (46.8%), followed by growth hormone deficiency (33.8%), hypothyroidism (18.8%), diabetes mellitus (16.8%), hypoparathyroidism (7.7%) and 13% of the patients had more than one endocrine complication. An Italian working group reported delayed puberty in 47% of females and 51% of males, growth hormone deficiency (33.8%), diabetes mellitus (16.8%), hypothyroidism (15.9%) and hypoparathyroidism (6.3%). The prevalence of delayed sexual maturation and GH deficiency were considerably lower in Iran and Italy compared with our data and this is maybe caused by serum ferritin level, genetic factors or other unknown conditions may play a role in the genesis of these complications. In Erbil-Iraq, as in our study, short stature (height less than 5th percentile) was found in 79% of the thalassemic patients and delayed Sexual maturation was found in 97% of the patients.

CONCLUSION:
It was found that 79% of multi-transfused beta-thalassemic patients with their ages 10-20 years old had short stature which is occurring because of decrease growth hormone, thyroid hormones, parathyroid hormone, sex hormones secretion and other hidden causes related to iron overload. So aggressive iron chelating regime, regular measurement of height to detect short stature early, screening of thalassemic patients for hormonal deficiency and effective treatment of hormonals deficiency accordingly were warranted.

REFERENCES: