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Original Research Paper

Growth Disorders in Polytransfused Beta-Thalassemia Patients

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ABSTRACT:

Introduction: Beta-thalassemia is a chronic hereditary haemolytic anaemia characterized by a defect in the synthesis of beta-globin chains, which is particularly common in the Mediterranean region, South Asia, and the Middle East. Transfusion programs and chelation therapy have significantly extended the life expectancy of patients. This has led to an increase in the prevalence of complications related to iron overload. Growth retardation is extremely common in patients with transfusion-dependent thalassemia. **Objectives**: To describe the frequency of growth retardation and to evaluate the GH-IGF-I axis in a group of patients with transfusion-dependent beta-thalassemia. To study the relationship between growth retardation, ferritin levels, average transfusion volume, duration of transfusion therapy, splenectomy, and compliance with chelation therapy. **Methods**: This is a cross-sectional, descriptive, analytical, and monocentric study conducted in the pediatric department of Mustapha Bacha university hospital centre. The study involved 87 patients (46 girls and 41 boys) most of whom were regularly followed up for several years and treated with a transfusion regimen (more than 10 transfusions) combined with chelation therapy. All patients were assessed through clinical history, physical examination, measurement of height and weight, followed by blood tests for biochemical analysis, IGF1 assay, and a hand X-ray. Afterwards, we performed a dynamic test for patients with growth retardation. **Results**: Short stature (height <-2SD) was detected in 16 patients (18.4%). Among the 16 patients with short stature, 6 (37.5%) had severe growth retardation (<-3SD). 8 girls (50%) and 8 boys (50%) were affected by growth retardation. The mean age of patients with growth retardation was 16.3±5.6 years. Among the patients with short stature, three patients were diagnosed with growth hormone deficiency (GHD). There was a statistically significant correlation between serum ferritin levels and growth retardation (P=0.012), (OR=4.2). **Conclusion**: This study confirms the need to screen for short stature and the GH/IGF-I axis status in this group of patients. The presence of short stature does not seem to be correlated with the efficacy parameters of transfusion and chelation therapy. Therefore, other mechanisms, in addition to iron overload, may play a role in the pathogenesis of this clinical condition.

Keywords: Growth retardation, transfusion-dependent beta-thalassemia.

INTRODUCTION:

Beta-thalassemia is a chronic hereditary hemolytic anemia characterized by a defect in beta-globin chain synthesis and is particularly common in the Mediterranean region, southern Asia, and the Middle East (1). Transfusion programs and chelation therapy have significantly prolonged the lifespan of patients (2), which has led to an increase in the prevalence of cardiac, hepatic, and endocrine complications related to iron overload (3). Delayed growth is one of the most common complications in children and adolescents with thalassemia and a significant cause of poor body image. The prevalence of short stature in children with thalassemia ranges from 30 to 50% in most studies (4). The causes are multifactorial, and the relative contribution of various factors may vary depending on age. Chronic anemia, hypoxia, and nutritional factors are generally incriminated before the age of 5, particularly in children who do not receive regular transfusions. Between 5 and 10 years old, the adverse effects of transfusion induced iron overload on linear growth (GH-IGF-1 axis) become apparent in the absence of adequate chelation. Beyond 10 years old, the absence or reduction of pubertal spurt due to the involvement of the hypothalamic-pituitary-gonadal axis contributes significantly (5). The objective of our study is to describe the frequency of delayed growth and evaluate the GH-IGF-I axis in a group of patients

with polytransfused beta-thalassemia, and to study the relationship between delayed growth and ferritin levels, mean transfusion volume (MTV), duration of transfusion treatment, splenectomy, and compliance with chelation therapy.

MATERIAL AND METHODS:

This is a descriptive, analytical, and monocentric cross-sectional study conducted in the pediatrics department of Mustapha Bacha UHC, which included 87 patients with beta-thalassemia major (46 girls and 41 boys), most of whom were regularly followed up for several years and treated with a transfusion regimen (more than 10 transfusions) combined with chelation therapy. All patients were on a transfusion program, with the aim of maintaining the hemoglobin level above 9g/dL, associated with chelation therapy. In our department, before 2008, Deferoxamine (DFO) was the only chelator available, used intravenously at a dose of 40 mg/kg/day, then replaced between 2008 and 2011 by Deferiprone (DFP) orally, and since 2011, we have been using Deferasirox (DFX) orally. DFX is prescribed when serum ferritin exceeds 1000 µg/L at a dose of 20 mg/kg/day, which is maintained as long as serum ferritin is controlled (< 2500 µg/L). For patients whose ferritin exceeds 2500 µg/L, an increase in DFX dose to 40 mg/kg/day is recommended. After 3 months of treatment, if ferritin remains above 2500 µg/mL, we add DFO subcutaneously at a dose of 40 mg/kg/day, 5 days a week until ferritin values are below 2500 µg/mL. The availability of chelation therapy is ensured by the central pharmacy of the hospital, and we have not noted any interruptions in the distribution of the medication. Hematological data, including markers of iron overload, were collected from patient records. These included the total amount of blood units received, type of chelation treatment, pre-transfusion hemoglobin, comorbidities, serum ferritin, and liver function test.

All patients underwent clinical history, physical examination, height and weight measurement, BMI calculation (body mass index = weight in kg/height² in m), and calculation of the target height ([mother's height + father's height/2] + 6.5 for boys, -6.5 for girls). All these parameters were compared with reference growth charts (WHO). Secondly, we took blood samples for a biochemical assessment, IGF1 assay, and a hand X-ray (bone age) for all patients. We performed a dynamic test for patients with growth retardation (glucagon test and insulin test) and a pituitary MRI for patients with growth hormone deficiency (GHD). Short stature was defined as height below 2 standard deviations from the mean height for age and sex on the WHO charts, with a discrepancy between the patient's height and the target height greater than 1.5 SD. Growth hormone deficiency (GHD) was diagnosed in cases of insufficient GH secretion, suspected if the peak was less than 10 ng/mL during two successive stimulation tests done a few days apart. A serum ferritin level > 2500 g/L was considered an indicator of severe iron overload, and poor compliance with chelation therapy was defined by repeated treatment omissions and/or treatment interruption for more than one week. Statistical analysis was performed using SPSS 23 software. Descriptive analysis was conducted (mean ± standard deviation and/or median for quantitative variables, and percentages for qualitative variables). Statistical tests, such as khi2, Fisher, Student, Wilcoxon-Mann-Whitney, ANOVA, were used for comparisons of 2 or more variables, and the analysis was supplemented by logistic regression. The significance threshold was set at 0.05. The bibliography was automatically generated by Zotero using the Vancouver style.

RESULTS: (Table 1)

Our study included 87 cases of β-thalassemia, all of whom were enrolled at Mustapha University Hospital; over 50% of them came from different regions of the country, namely 31% from the east, 25% from the west, and 2.3% from the south. The mean age was 11.2±5.8 years with a range of 2 to 25.7 years, 25% of patients were older than 15 years. Both sexes were equally represented in our series, with 46 females and 41 males and a sex ratio of 0.9. The average duration of blood transfusion in our population (which reflects the duration of follow-up of these patients) was 10 years with extremes of 6 months to 24.7 years; 77% of patients had a transfusion frequency of less than 4 weeks, and 31% had a mean transfusion volume (MTV) greater than 250 ml/kg/year. Splenectomy was performed in 40% of our patients. The mean ferritin level was 1653.16±1272 µg/l; 38% of patients had a mild iron overload (<1000 µg/l), 41.3% had a moderate overload (1000-2500), and 20.7% of patients had a severe overload (ferritin > 2500 µg/l). Treatment compliance with iron chelation therapy was considered poor in 15% of our patients.

In our sample, the mean BMI was -0.79±1.31 SD; 50% of patients had a BMI < -0.94 SD. Underweight (BMI<-2SD) was observed in 14 cases (16.1%); overweight (BMI between +1SD and +2SD) was found in 9 patients (10.3%); and eutrophic patients (BMI between +1SD and -2SD) numbered 64 (73.6%); no obesity (BMI > +2SD) was found. Short stature (height <-2SD) was detected in 16 patients (18.4%); delayed bone age greater than 02 years was present in all these patients with growth retardation. Among the 16 patients with short stature, 6 (37.5%) had severe growth retardation (<-3SD). Eight girls (50%) and 8 boys (50%) were affected by growth retardation, and no statistically significant difference was found between boys and girls (P = 0.79) in growth retardation. The mean age of patients with growth retardation was 16.3±5.6 years, while the mean age of

patients with normal height was 10.1±5.28 years. There was a statistically significant relationship between age and growth retardation (p=0.00), (OR=44.16). IGF1 levels, which were measured in all patients, showed 51 (58.6%) patients with decreased IGF1 levels (<-2SD), and the levels were normal in 36 (41.4%) cases. (The IGF norms used were age- and sex-specific). A decreased IGF1 level was associated with short stature in 14 cases (87.5%), while a normal IGF1 level was found in two patients with short stature, and there was a significant correlation between IGF1 levels and growth retardation. Among the 16 patients with short stature, investigation of the somatotropic axis was performed on 13 patients, with 3 patients who had a contraindication to the tests. Out of the 13 glucagon tests performed, 7 tests were positive (GH peak > 10ng/ml), while the remaining 6 patients had a negative test (GH < 10ng/ml). For these patients with a negative test, another test with insulin was performed, resulting in 3 positive tests (GH > 10ng/ml) and 3 negative tests (GH < 10ng/ml). The three patients who were diagnosed with growth hormone deficiency (GHD) had severe growth retardation (<-3SD). All patients with GHD had normal pituitary MRI. The 3 patients with GHD had hypogonadism, hypothyroidism, low IGF1, and significant delay in bone age. Seven (43.8%) patients with short stature had a serum ferritin level greater than 2500 µg/l, while 9 patients had a level below 2500µg/l. There was a statistically significant correlation between serum ferritin level and growth retardation (P=0.012), (OR=4.2). Eight patients had a transfusion volume greater than 250 ml/kg/year, but there was no significant relationship between transfusion volume and growth retardation (p=0.069). Fourteen (87.5%) patients with short stature had a transfusion treatment duration of more than 10 years, and there was a statistically significant correlation (OR=17.85), (p=0.000) between these two parameters. Among the patients who underwent splenectomy, 11 (68.8%) had short stature, which was highly significant (p=0.005), (OR=4.9). Fourteen (87.5%) patients who had good adherence to chelation therapy had growth retardation, but no significant relationship was observed between treatment compliance and growth retardation (p=0.76).

		Growth Retardation		**OR**	**P**
		Yes	No		
Mean age		(16) 16,32	(71) 10 years		
>10 years		15(93,8)	32(45,1)	18,28	0,00
<10 years		1(6,3)	39(54,9)		
Gender	Male	8(50)	33(46,5)		0,79
	Female	8(50)	38(53,5)		
Ferritinemia	>2500	7(43,8)	11(15,5)	4,2	0,012
	<2500	9(56,3)	60(84,5)		
Splenectomy	Yes	11(68,8)	22(31)	4,9	0,05
	No	5(31,3)	49(69)		
MTV Ml/kg/year	>250	8(50)	19(26,8)		0,069
	<250	8(50)	52(73,2)		
Transfusion duration	>10an	14(87,5%)	20(28,2%)	17,85	0,000
	<10an	2(12,5%)	51(71,8%)		
IgF1	Low	14(87,5%)	37(52,1%)	7	0,009
	Normal	2(12,5%)	34(47,9%)		
Treatment compliance	Yes	14(87,5)	60(84,5)		0,76
	No	2(12,5)	11(15,5)		

Table I: Characteristics of the sample according to growth status

DISCUSSION:

The prevalence of underweight (BMI <-2SD) observed in 16.1% of cases in our population is consistent with previous studies of Hashemi who reported underweight in 18.6% of their 46 patients aged 2 to 28 years (6), and Jain who found 20% of underweight (<-2SD) in a series of 25 patients with a mean age of 10.3 years (7). The frequency of short stature was 18.4%, which is lower than the results of previous studies. Vogiatzi found 25% of short stature in a series with a mean age of 23 years (8), while De Sanctis reported short stature in 30% of patients in their series with a mean age of 13 years (9), and Sharma found that 55% of thalassemic patients had short stature with a mean age of 14 years (10). All previous reports suggest that the incidence of growth deficits in beta-thalassemia varies from 20% to 65% (11). The low frequency of short stature in our study is related to the younger age of our sample (mean age of 11 years) compared to the previously cited studies.There was no gender predominance among patients with short stature in our population, which is similar to the findings of De Sanctis (12). The mean age of patients with short stature was over 16 years, which is significantly different from the mean age of children with normal height of 10 years (p=0.00, OR=44.16).

In our study, severe iron overload (serum ferritin > 2500 µg/L) was significantly associated with short stature, Similar results are reported by Hamidah in 26 patients, by Shalitin in 39 patients with growth retardation (13.14). These results confirm the findings of Wonke and De Sanctis, who showed that iron deposits in the pituitary and thyroid glands, pancreas, liver, and growth plate cartilage, as well as the toxic free radical-induced damage of iron on these endocrine glands, are one of the main causes of growth retardation in thalassemics (15,16). However, this correlation between short stature and severe iron overload is not always found, as in the study by Grundy (17), suggesting that growth retardation in thalassemia is multifactorial. Other discussed causes include chronic anemia (18), increased energy expenditure due to high erythropoiesis and increased cardiac work (10), nutritional deficiencies especially in calories, folic acid, zinc, and vitamin A (19), disruption of calcium homeostasis, bone diseases (11), liver and pancreatic dysfunction, psychosocial stress (20), and the toxicity of chelation therapy (desferrioxamine) (21).

In our series, the serum IGF1 level was low in 51 patients (58.6%), which is consistent with the results of cross-sectional studies conducted by Scacchi and Giovannucci in beta-thalassemia patients of different ages who found low serum levels of IGF1 and IGFBP3 (22,23). Among the 16 patients who had short stature in our population, 14 (87.5%) had a lower-than-normal IGF1 level. This higher frequency of a low IGF1 level in children with short stature compared to the rest of the population is statistically significant (p=0.009, OR=7). Only 3 (3.4%) patients with short stature had growth hormone deficiency, and these three patients also had hypogonadism and significant delay in bone age. This discrepancy between the high number of children with low IGF-1 levels and the low number of patients with GHD has been observed in different studies (24, 25, 26) in which many thalassemic children show a normal GH response to stimulation tests with a low IGFI level. This could be explained by a degree of neurosecretory dysfunction due to reduced nocturnal spontaneous secretion because of disturbed pulsatile properties of GH or by liver resistance to GH action (24, 25, 26). The frequency of GHD in our series is similar to that reported in a North American study (n=262) (27), in which the rate is 3%, while an Italian study (28) (n=1861) reports a higher frequency of 12.4%. Pituitary MRI performed in our three patients did not find any morphological abnormalities of the pituitary gland, and treatment with growth hormone was initiated at a dose of 0.03 mg/kg/day. The evaluation of growth after treatment of these patients is not yet possible because we do not have sufficient follow-up. It is reported that these patients often require higher doses due to their partial insensitivity to GH as well as in children with delayed puberty; the best results are observed with concomitant replacement of sex steroids (29). In our sample, there is a correlation between the duration of transfusion treatment and short stature (OR=17, P=0.000), which is similar to the results of Delevecchio and Cavallo (30). There is a statistically significant relationship in our population between growth delay and splenectomy (p=0.05); among the 16 patients with short stature, 11 had undergone splenectomy. The same results have been found by others (31). This is because splenectomised subjects are more exposed to toxic free radicals of iron and therefore more vulnerable to the destruction of endocrine glands. There is no relationship in our series between compliance with chelation therapy and growth delay; this may be explained by the fact that chelation therapy remains insufficient. In addition, data on regular chelation treatment compliance in our study relied entirely on questioning parents and/or guardians. After logistic regression, only ferritinemia and transfusion duration were retained as prognostic factors for short stature (ORa=5, p=0.038 for a threshold of 2500 ug/ml, ORa=18.3, p=0.000 for a threshold of 10 years).

CONCLUSION:

This study confirms the need to screen for short stature and the status of the GH/IGF-I axis in this group of patients. The presence of short stature does not seem to be correlated with the efficacy parameters of transfusion and chelation therapy. Other mechanisms,

in addition to iron overload, could therefore play a role in the pathogenesis of this clinical condition.

Conflicts of interest: No conflicts of interest.

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